Thermodynamic and Solution Properties of Amphiphilic Anti-Allergic Drug Cetirizine HCl

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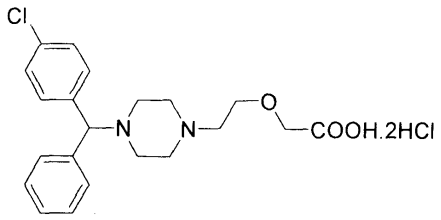
Summary: This article describes the thermodynamic and solution properties of amphiphlic drug Cetirizine HCl in the temperature range of 20-50 °C in aqueous solution. Densities, conductivities, viscosities and surface tension were measured to calculate critical micelle concentration (cmc) and in this way its surface and bulk properties have been estimated. Various fundamental parameters such as area per molecule at air/water interface and surface excess concentration have been calculated and thermodynamics of micellization has been monitored. Our results show that Cetirizine HCl micellises through closed association process and micellization is found to be entropy driven. The solution viscosities have been used to estimate the micellar density, partial specific volume and Intermicellar interaction parameter, K_H of micelle over temperature range of 20-50 °C. From cmc we have calculated ΔH_{mic}, ΔG_{mic} and ΔS_{mic}.

Introduction

Colloidal behavior is exhibited by a large number of amphiphilic drugs. Although these drugs show pharmacological activities at low concentration but, if administered for the long period, they may get accumulated at certain sites of organism and form aggregates. These aggregates are unable to pass through membrane thus decreasing transport rate and consequently leading to adverse effects on health. It is important to study the physico-chemical properties of amphiphilic drugs from chemical, physical, biological and pharmacological point of view [1]. Most of the surfactants have hydrocarbon based hydrophobic groups which join each other during micellization giving rise to spheroidal aggregates. A large number of drugs with diphenyl methane structure also have flexible hydrophobic groups similar to that of surfactants and lead to close or micellar association. But some drugs having rigid aromatic or heterocyclic ring system to which an ester or charge bearing nitrogen (N) atom is directly attached or which include pyridine like nitrogen (N) atom display an open or continuous association which may, in no way be called micellization and there is no equivalent to cmc in this case. Amphiphilic drugs lie in between these two extremes. They may resemble to typical surfactants in their association behavior because they have aromatic ring with high degree of flexibility [2].

Cetirizine HCl has following chemical structure.



Cetirizine is a second-generation H1-anti-histamine especially valuable in physical and delayed pressure urticarias [3]. Cetirizine like some other antihistamines is a piperazine derivative, on the structural basis of an ethylenediamine [4]. It is non-sedating drug and its levorotatory enantiomer has been found to exhibit better pharmacological profile than racemic mixture and currently marketed as Xyzal™ in Europe [5]. In our previous article, we have discussed thermodynamic properties of the amphiphilic drug thioradazine HCl in water/ethanol solvent [6]. In this article we intend to discuss the thermodynamic and solution properties of this amphiphilic drug cetirizine HCl at different concentrations and temperatures using different techniques.

Results and Discussion

Surface tension, specific conductivities, viscosities and densities have been used to study the surface and bulk properties of Cetirizine hydrochloride in water.

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Fig. 1 shows the plot of surface tension, γ, *versus* log m for Cetirizine HCl in water at 20°C. From this figure it is clear that surface tension remains constant above clear inflection in data, indicating the formation of full Gibbs monolayer at air /solution interface. The inflection in surface tension curve is observed at 0.075 mol Kg^{-1} and is taken as cmc. It is in reasonable agreement with that detected by conductivity (0.0758 $molKg^{-1}$) and density (0.087 $molKg^{-1}$). Although cmc values obtained from all three techniques are somewhat different but it is generally accepted that values of cmc vary to a certain extent according to what physical properties are considered for the determination of the critical micelle concentration [6]. The slope of plot of γ against log m in premicellar region was used to calculate the approximate value of area per molecule in full surface monolayer, A, from the surface excess concentration, Γ. A value of area of 1.25 nm^2/molecule was calculated in this manner. The values of surface excess concentration and area per molecule are given in Table-1. The standard Gibbs free energy of micellization, ΔG_m°, at 293 K, was calculated by using equation 3 giving a value of -25.51 KJ/ mol while the value of standard Gibbs free energy of adsorption at the same temperature was -73.1 KJ/mol. The values of ΔG_m° and ΔG_{ads}° are also given in Table-1. The value of ΔG_{ads}° is more negative than that of ΔG_m° showing that migration of drug molecules in the monomer state to air-water interface is more spontaneous than its micellization.

Table-1: Various Parameters calculated from surface tension measurements.

Surface Excess Concentration (Γ) (Mol/m^2)	Area per molecule (A) nm^2	Free Energy of Adsorption (ΔG_{ads})	Free Energy of Micellization (ΔG_m)
1.32969×10^{-6}	1.25	-73.1KJ/mol	-25.51KJ/mol
1.33×10^{-6}			

Fig. 2 shows the concentration dependence of electrical conductivity of cetirizine HCl at various temperatures and inflection points were made visible by employing Origin program. The typical plot is shown at 20 °C in Fig. 3. The value of cmc increases with increase in temperature due to increase in solubility and decrease in hydration of hydrophilic groups which enhances repulsion between them making micellization difficult and thus increasing cmc value. The thermodynamic parameters

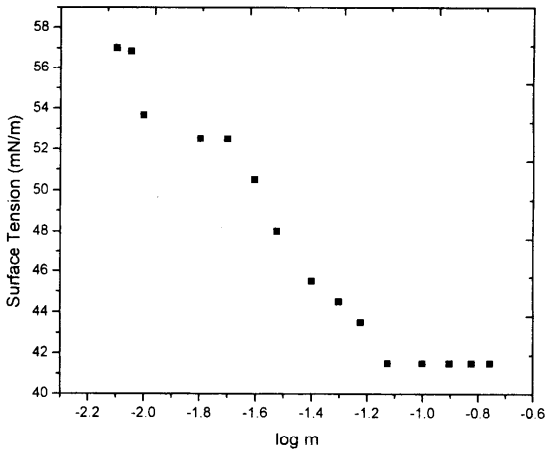

Fig. 1: A typical plot of Surface tension, γ, versus logarithm of molality, m, (mol/Kg), for aqueous solution of Cetirizine HCl at 20 °C.

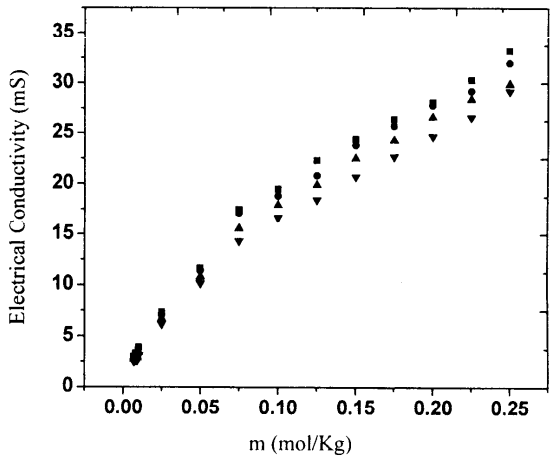

Fig. 2: The plot of Specific Conductivity (mS) versus molality, m, (mol/Kg), for aqueous solution of cetirizine HCl at 20°C (■), 30°C (●), 40°C (▲) and 50°C (▼).

calculated from cmc value are given in Table-2. The degree of counter ion binding (α) decreases with temperature, as shown in Table-2, suggesting the shift of equilibrium toward dissociation.

Fig. 4 shows the plots of density of Cetirizine HCl as a function of concentration at various temperatures and again the cmc is indicated in Fig. 5 by using Origin Program. The values of various parameters calculated from viscosity and density are shown in Table-3.

Table-2: Various parameters calculated from specific conductivity measurements.

Temp (K)	CMC (mol/Kg)	ΔH_m (KJ/mol)	ΔG_m (KJ/mol)	ΔS_m (J/Kmol)	Degree of Counter ion Binding (α)
293	0.0758	-20.2	-25.47	17.9	0.585
303	0.0761	-21.6	-26.292	15.4	0.583
313	0.0763	-23.07	-26.835	12.02	0.570
323	0.0766	-24.6	-26.95	7.36	0.560

Table-3: Partial specific volume, Micellar density, Interaction parameter and intrinsic viscosity at four different temperatures.

Temp.(K)	Partial specific volume, $\bar{v}$ (mL/g)	Miceller density (g/mL)	Intermicellar Interaction Parameter K_H	Intrinsic Viscosity, $[\eta]$ (mL/g)
293	0.760	1.317	-6.414	4.55
303	0.77	1.302	-6.045	2.92
313	0.77	1.30	13.28	1.81
323	0.762	1.31	24.2	1.62

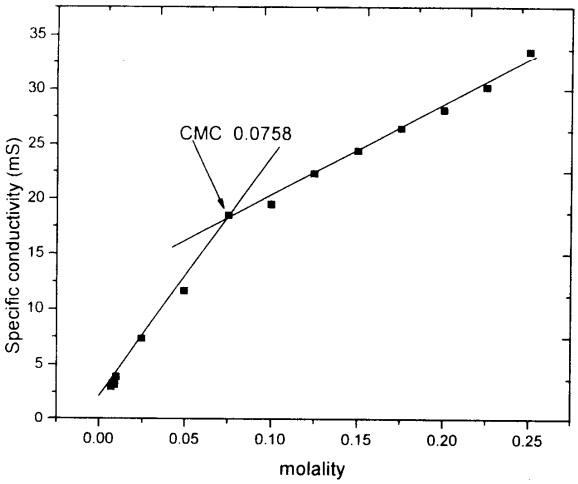

Fig. 3: The plot of specific Conductivity (mS) versus molality, m, (mol/Kg), for aqueous solution of cetirizine HCl at 20°C.

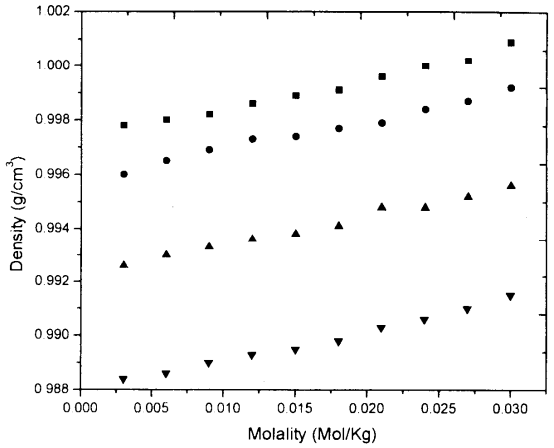

Fig. 4: The plot of density versus concentration for aqueous solution of Cetrizine HCl at 20°C (■), 30°C (●), 40°C (▲) and 50°C (▼).

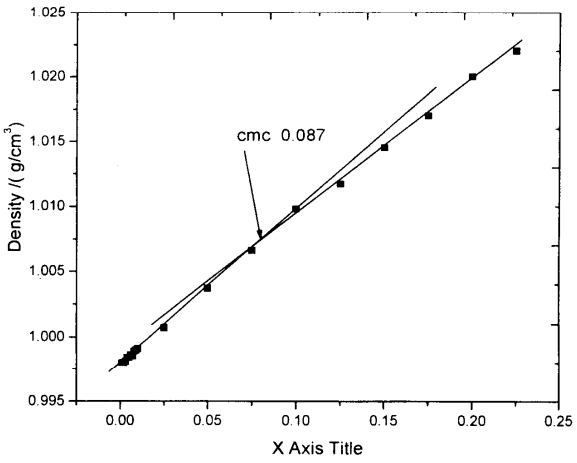

Fig. 5: The plot of density versus molality for aqueous solution of Cetrizine HCl at 20°C.

Fig. 6 shows the plots of apparent molal volume, V_Φ, against the molal concentration of Cetirizine HCl at different temperatures. There are two critical concentrations, cc_1 and cc_2 as shown in Fig. 7 at 20 °C. The cc_1 is regarded as premicellar aggregation while cc_2 as cmc. V_Φ increases till cc_1 and then becomes constant till cc_2. The values of V_Φ increase from 20 °C to 30 °C and then decrease. This is due to the fact that with the increase in temperature the hydrophilic heads are dehydrated and the degree of counter ion binding also decreases. These two factors result in repulsion between ionic heads, which increases the size of aggregates. But above 30°C water molecules surrounding the hydrophobic moieties in the core are also removed making hydrophobic attraction stronger and thus making micelles more compact. Positive value of ΔV_ϕ^m is due to release of structured water from hydration shell of the monomer when micelles are formed, which allows greater freedom of monomer within micelles and, consequently, higher volume per monomer within aggregate than in solution [7].

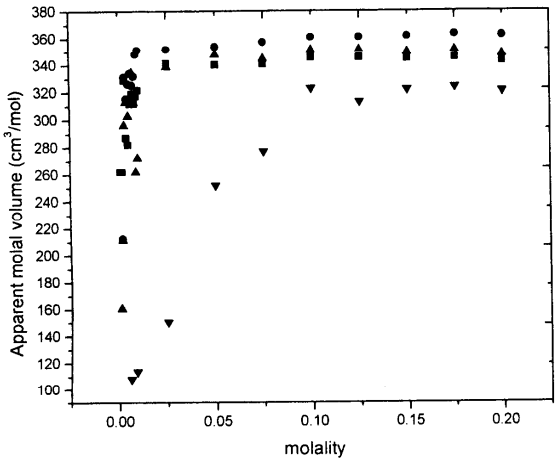

Fig. 6: The plot of apparent molal volume versus molality for aqueous solution of Cetrizine HCl at 20°C (■), 30°C (●), 40°C (▲) and 50°C (▼).

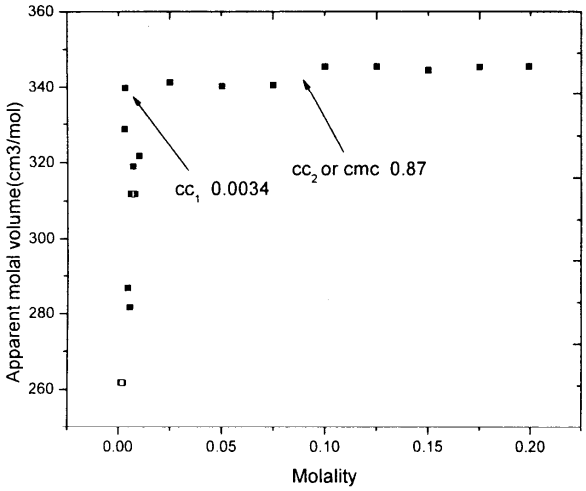

Fig. 7: The plot of apparent molal volume versus molality for aqueous solution of Cetrizine HCl at 20 °C.

Fig. 8 shows the plot of reduced viscosity as a function of concentration as described by equation 8. The intrinsic viscosity, [η] was determined by extrapolating the data to zero concentration using linear regression while the value of intermicellar interaction parameter, K_H was calculated from slope. The partial specific volume, ύ was calculated from equation 9. Table-3 shows variation of partial specific volume (ύ), Miceller density, Intermicellar

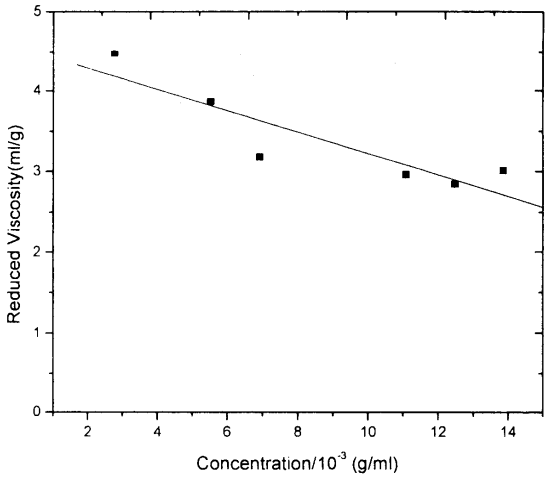

Fig. 8: The plot of reduced viscosity versus concentration for aqueous solution of Cetrizine HCl at 20°C.

Table-4: The change in apparent volume of Cetirizine HCl with temperature during micellization in aqueous solution

Temp(K)	V_ϕ° (cm³mol⁻¹)	V_ϕ^{cm} (cm³mol⁻¹)	ΔV_ϕ^{cm} (cm³mol⁻¹)
293	254.05	354.51	91.46
303	301.22	360.7	59.48
313	227.3	347	120
323	158.5	321	221.7

Interaction parameter, K_H and Intrinsic Viscosity, [η] with temperature. Micellar density decreases from 20 °C to 30 °C and remains almost constant from 30 °C to 40°C while at 50 °C its value again slightly increases. It is because micellar size first increases due to increase in aggregation number and due to dehydration of hydrophilic heads while at 50°C it decreases due to increase in dehydration of hydrophobic ends which enhances hydrophobic interaction causing decrease in size and increase in micellar density. Partial specific volume is reciprocal of micellar density therefore change in its value shows opposite trend. The value of K_H is negative at 20 °C and 30 °C becomes positive at 40 °C and 50 °C. The reason is that the solubility increases with increase in temperature for ionic surfactant and hence due to greater solute-solvent interaction, the K_H shows positive value at high temperature. The negative slope of Huggin's Equation for surfactants is also shown by M. A. Abed *et al.* for alpha olefin sulphonate in aqueous solution at 25 °C [8]. The increase in K_H shows increase in solute-solvent interaction with temperature.

Experimental

Material

Cetirizine HCl ([2-[4-[(4-chlorophenyl)phenyl-methyl]-1-piperazinyl] ethoxy]acetic acid, dihydro-chloride of molar mass 461.82, was obtained from Sigma Chemical Co. and was used as received. Solutions were made by weight using Shimadzu AUW220D analytical balance with precision of 0.0001 mg. The experiments were carried out from 20-50 °C with 10 °C increment, in distilled and deionised water.

Surface Tension

Surface tension of aqueous solutions of Cetirizine HCl was determined using Torsion balance (White Elect. Inst. Co. Ltd) equipped with Platinum ring (4.0 cm circumferences) along with water circulator (Irmeco I-1800) to control temperature at 20 °C. A home made glass cell with a special hollow space for water circulation was used to ensure the constant temperature. The molal solutions were prepared and carefully diluted. It is well known that cmc derived from surface tension is particularly sensitive to impurities [9].

Specific Conductivities

Conductivities were measured with Jenway 4310 from 20-50 °C with 10 °C increment. The electrode was calibrated using KCl over the appropriate concentration range.

Densities and Viscosities

Measurements of densities and viscosities were performed using Anton Paar SVM 3000 at 20-50 °C with 10° rise in temperature. The instrument was calibrated by using deionized water whose density and viscosity were taken from the literature. The instrument gives us the values of density and viscosity directly and simultaneously.

Theory and Data Evaluation

Surface Tension

On the basis of plot of the surface tension, as a function of concentration of drug in water, the amount of drug at air/water interface, Γ_2, can be determined by the application of Gibbs Adsorption Equation [9].

$$\Gamma_2 = -\frac{1}{2.303RTx}\left(\frac{d\gamma}{d\log m}\right)_T \qquad (1)$$

where R is the gas constant, T the temperature in Kelvin. The variable x is introduced to allow for the simultaneous adsorption of cations and anions. The expressions used is:

$$x = 1 + \frac{m}{m + m_s} \qquad (2)$$

Calculations of x were proposed by Mateejavic and Pathica [9], where m_s are concentration of added electrolyte, if any. The value of x is 2 in water and approaches to 1 in presence of excess inert electrolyte. The area per molecule was calculated from equation 1 using formula $A = 1/N_A\Gamma_2$ where N_A is the Avogadro's constant. The values of the Gibbs energy change per mole of monomer on aggregation was calculated from expression:

$$\Delta G_m^0 = (1+\alpha)RT \ln X_{cmc} \qquad (3)$$

where α is degree of counter ion binding given as $\alpha = 1-\beta$ and β is degree of ionization. The degree of ionization (β) was calculated by the ratio of slope of micellar and premicellar phases following Evans [10] as $\beta = S_2/S_1$, where S_2 and S_1 are the slopes of micellar and premicellar phases, respectively. In equation 3, X_{cmc} is critical micelle concentration expressed in mole fraction unit. The standard Gibbs Energy of Adsorption, ΔG_{ads}, in water for this drug was calculated from standard Gibbs Energy of micellization and surface tension data through the equation;

$$\Delta G_{ads}^{\circ} = \Delta G_m^{\circ} - \frac{\pi_{cmc}}{\Gamma_2} \qquad (4)$$

where π_{cmc} is surface pressure at critical micelle concentration calculated as; $\pi_{cmc} = \gamma_{\circ} - \gamma_{cmc}$ where γ_{cmc} and $\gamma_{\circ}$ is the surface tension of drug at the cmc and of water, respectively.

Specific Conductivities

The self aggregation of amphiphilic molecules are studied by a fundamental quantity, the

critical micelle concentration. The experimental determination of specific conductivities provides more scientific technique to detect cmc. The concentration dependence of electrical conductivities shows a gradual increase of slope at each temperature. According to William *et al.* [11] the cmc can be determined by intersection of two straight lines of concentration-conductivity plot, above and below cmc. The precision of measurement depends on the width of concentration range over which the change in physical properties are observed. The thermodynamic parameters e.g. Gibbs free energy of micellization, ΔG_m° was calculated from equation 3, while Enthalpy of micellization, ΔH_m° and Entropy of micellization, ΔS_m° are calculated from conductivity data using equation 5 and 6, respectively;

$$\Delta H_m = -2.3RT^2\left[\frac{\partial(1+\alpha)(\log X_{cmc})}{\partial T}\right]_P \quad (5)$$

$$\Delta S_m^\circ = \frac{\Delta H_m^\circ - \Delta G_m^\circ}{T} \quad (6)$$

Density

The apparent molal volume, Vφ, was calculated from density which tells us about change in properties of a solution with concentration. The apparent molal volume, Vφ, of Cetirizine HCl was calculated by means of equation 7;

$$V_\phi = \frac{M}{\rho} - \frac{10^3(\rho-\rho_\circ)}{m\rho\rho_\circ} \quad (7)$$

where m and M are molality and molar mass of drug, ρ is the density of solution and $\rho_\circ$ is that of pure solvent. In order to obtain reliable volume data, it is necessary to measure densities with great precision [12].

Viscosity

The Huggin's Equation [13] has been used to calculate intrinsic viscosity;

$$\eta_{red} = [\eta] + K_H[\eta]^2 c \quad (8)$$

where K_H is intermicellar interaction parameter, η_{red} is reduced viscosity and [η], the intrinsic viscosity [14]. Partial Specific Volume, ύ was calculated from equation 9;

$$\rho = \rho_\circ + (1 - ύ\,\rho^\circ)\,C \quad (9)$$

The slope of plot between density (ρ) and concentration(C) gives the value of ύ [14].

Conclusion

Surface and bulk properties of Cetrizine Hydrochloride have been studied from surface tension, specific conductivity, density and viscosity measurements. The value of cmc obtained by Surface tension is 0.075 mol Kg^{-1} while the conductivity and density data show 0.0758 mol Kg^{-1} and 0.087 molKg^{-1}, respectively as cmc at the same temperature. Free energy of adsorption is more negative than that of micellization which means that adsorption is more spontaneous process and hence occurs before micellization. The cmc increases with temperature because solubility of drug increases and also due to dehydration of hydrophilic groups the repulsion between them increases causing the cmc to increase. Free energy of micellization becomes more negative with temperature which indicates process of micellization becomes more spontaneous at high temperature. The apparent molal volume shows two critical concentrations *i.e.* cc_1 and cc_2. The cc_1 indicates pre-miceller aggregation and cc_2 indicates micellization therefore cc_2 may be regarded as equivalent to cmc which is in agreement with the cmc obtained from surface tension and conductivity. The apparent molal volume and specific molal volume increase from 20 to 30°C and then decrease while micellar density shows opposite trend. The value of Intermicellar interaction Parameter, K_H, increases while that of intrinsic viscosity decreases with temperature.

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