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Self aggregation of a selective serotonin reuptake inhibitor drug paroxetine hydrochloride: A thermodynamic study

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ABSTRACT

Paroxetine HCl is an amphiphilic serotonin specific reuptake inhibitor antidepressant drug. The association characteristics, thermodynamic behavior and sonochemical behavior of this drug in ethanol have been determined from density and ultrasound velocity data at 298.15 K and 308.15 K using an Anton Paar density sound analyzer (DSA 5000). The critical micelle concentrations of this drug were obtained from ultrasound velocity measurement by using recently developed least square fitting algorithm. The compressibility data have been used to discuss solvent-aggregate interaction.

KEYWORDS

Apparent molar volume;
Partial molar volume;
Antidepressant drugs;
Self-aggregation;
Paroxetine HCl.

INTRODUCTION

The selective serotonin reuptake inhibitors (SSRIs) have become important tools in basic and clinical brain research. They were the first drugs to establish beyond doubt a pathophysiological role for serotonin (5-HT) in affective illnesses and in the broad spectrum of anxiety disorders[1]. Many drugs of pharmacological importance show colloidal behavior and it is possible that they may form aggregates in the body decreasing the transport rate of the drug consequently deteriorating the health[2]. A large number of antidepressant drugs act as amphiphiles and forms colloids in solutions. Although the activities of these drugs are evident at very low concentration yet they may form aggregates. Thus the study of self aggregation of these antidepressant drugs is important from the physical, chemical, biological and pharmacological point of view for their implications because these drugs exert their activity by interaction with the biological membranes[3].

The micelles are the most prevalent aggregate structure in surfactant solutions and form over a narrow range of concentration know as critical micelle concentration which is used to study the self-aggregation of amphiphilic molecules. The critical micelle concentration can be detected by discontinuity of the concentration dependence of the physiochemical properties of the solution. A better understanding of the volumetric behavior of these antidepressant drugs requires information on a variety of thermodynamic properties[4,5].

In the present work, we report the volumetric behavior of a selective serotonin reuptake inhibitor antidepressant drug, Paroxetine HCl in order to obtain a comprehensive description of their aggregation process in ethanol to analyze how the temperature and solvent affect the thermodynamics of the aggregation.

For this purpose, the apparent molar volumes and expansibilities of Paroxetine HCl were obtained by using density and sound velocity data at 298.15 K and 308.15 K. In addition the critical micelle concentration for the aggregation of this drug in ethanol has been calculated by using Philips definition[6] of the critical micelle concentration.

RESULTS AND DISCUSSION

The apparent molar volume, V_ϕ, of the drug in ethanol was calculated by means of the following equation[7].

$$V_\phi = (1000 / mdd_0)(d_0 - d) + (M / d) \quad (1)$$

where M, represents the molar mass of the antidepressant drug, m is molality, and d and d_0 are densities of solution and pure solvent, respectively.

Apparent molar volume data for these compounds in water was checked for the structural transformation of the primary aggregates, dimerization and association at concentration below the critical micelle concentration etc by many researchers[8-11]. Apparent molar volume (V_ϕ) data was found to vary linearly and was fitted to the recently developed algorithm[12] based on Levenberg-Marquardt least square fitting algorithm:

$$V_\phi = V^0 + S_v\, m \quad (2)$$

Values of, V^o, i.e. the apparent molar volume at infinite dilution were taken as the partial molar volume (V^o), S_v, is the limiting slope which is considered to be the volumetric pair wise interactions coefficient[13-16] and 'm' is molality.

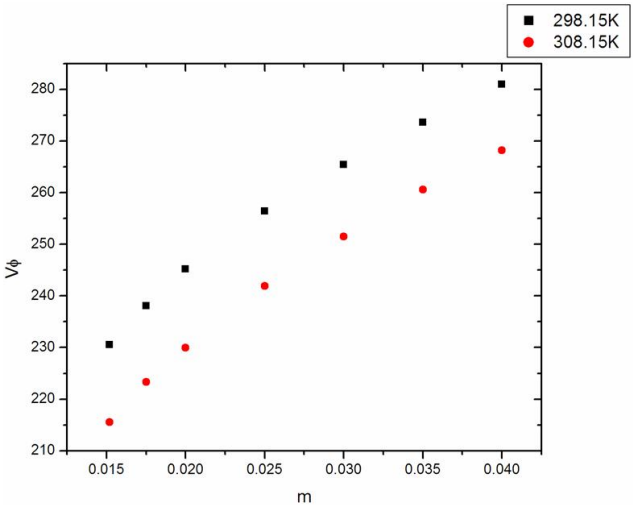

Figure 1 : The apparent molar volumes, V_ϕ of Paroxetine HCl in ethanol at T = (298.15 and 308.15K)

The apparent molar volumes of Paroxetine HCl in ethanol at 298.15 K and 308.15 K have been shown in Figure 1. The increase in the values of the apparent molar volume show hydrophilic interactions with the increase of temperature and concentration.

It is very difficult to find the critical micelle concentration exactly, however if a graph is plotted for any physical property against the concentration, then the inflection point on the Gaussian fit of the second derivative of the ultrasound velocity against concentration corresponds to the critical micelle concentration in accordance with Philip's definition[6].

$$\left(\frac{d^3 u}{dm^3}\right)_{m=cmc} = 0 \quad (3)$$

Cheema et al used Runge-Kutta numerical integration and Levenberg-Marquardt least square fitting algorithm[3]

The derivative is taken by averaging the slopes of the two adjacent data points by following equation:

$$\frac{du}{dm} = \frac{1}{2}\left[\frac{ui+1-ui}{mi+1-mi} + \frac{ui-ui-1}{mi-mi-1}\right] \quad (4)$$

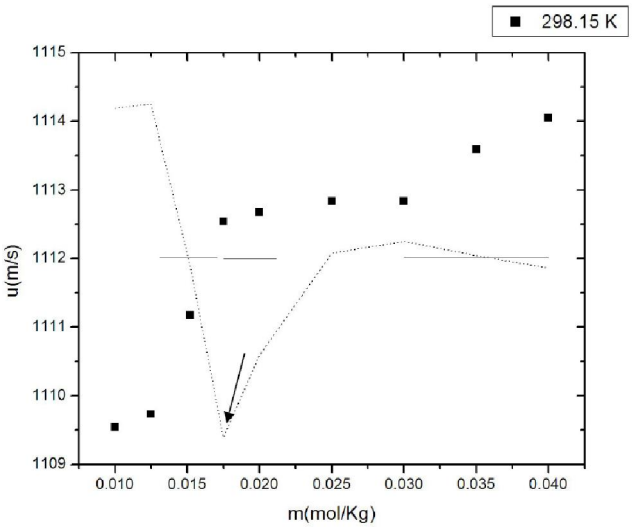

Figure 2 : Ultrasound velocity u versus concentration m for Paroxetine HCl in water at (■) 298.15 K. The dotted line indicates the Gaussian fit of the second derivative of the ultrasound velocity against molality. The arrow indicates the critical micelle concentration.

Where u is the sound velocity and m is the molality. The above equation gives the 1st order derivative data of sound velocities with respect to molality. The equation (4) was used to get second derivative i.e d^2u / dm^2

The data obtained was fitted using Gaussian fit in-

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tegrated with Levenberg-Maquardt non linear fitting to get fit of the curve.

$$y = y_0 + \frac{A}{w\sqrt{\pi/2}} e^{-2\frac{(x-x_c)^2}{w^2}} \quad (5)$$

Where y is the dependent variable and is the offset value which can be set to 0. x and x_c are the independent variables. x_c represents the mean value which is given by the center of the bell shaped Gaussian curve as shown in the Figure 2. x corresponds to the molality and x_c corresponds to the critical micelle concentration.

TABLE 1 : Molality, density and apparent molar volume, Vϕ, data of Paroxetine HCl at 298.15K and 38.15K

Molality	Density	Vϕ	Density	Vϕ
	298.15K		308.15K	
0.0152	0.791079	230.51	0.781700	215.56
0.0175	0.791326	238.03	0.781968	223.29
0.02	0.791587	245.16	0.782259	229.98
0.025	0.792089	256.36	0.782779	241.92
0.03	0.792557	265.38	0.783308	251.46
0.035	0.792985	273.61	0.783765	260.57
0.04	0.793388	280.95	0.784210	268.19

TABLE 2 : Partial molar volume, V^o, limiting slope, S_v, and critical micelle concentration, cmc, of Paroxetine HCl at 298.15 K and 308.15 K

Temperature K	V^o cm^3mol^{-1}	Sv	cmc mol kg^{-1}
298.15	221.05 ± 2.55	8.66	0.175
308.15	205.27 ± 2.37	9.07	0.014

EXPERIMENTAL

The antidepressant drug, Paroxetine HCl (3S,4R)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine hydrochloride was obtained Sigma 98% pure and was used as received. The absolute ethanol (Merck) was of purity 98%. Solutions were made by weight using Wiggen Hauser analytical balance with precision of ±0.001mg. Measurements were carried out using a commercial density and ultrasound velocity measurement apparatus (Anton Paar DSA 5000 density sound analyzer). The densimeter was calibrated with triply-distilled deionized and degassed water and with air.

CONCLUSION

We have used density and sound velocity data to calculate the apparent molar volume and partial molar volume of Paroxetine HCl in ethanol at 298.15 and 308.15K. The values of apparent molar volume increase with the concentration due to the structural rearrangement of the aggregates that have already been formed. The positive values of partial molar volumes indicate strong solute solvent interactions which have implications in the transport rate of this drug in the living organism.

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