Volumetric and Ultrasonic Studies of an Antidepressant Drug in Aqueous and Alcoholic Medium over Temperature Range 298.15-313.15 K

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(Received on 18th June 2012, accepted in revised form 10th December 2012)

Summary: Escitalopram oxalate is an amphiphilic serotonin specific reuptake inhibitor-antidepressant drug. Ultrasonic velocity (u) and density (d) measurements were carried out for Escitalopram oxalate in aqueous and alcoholic systems as a function of concentration in a range of molality, m = (0.0075-0.04) mol.Kg^{-1} at 298.15-313.15 K using an Anton Paar density sound analyzer (DSA 5000M). Using these experimental values, the acoustical parameters such as apparent molar adiabatic compressibility (K_ϕ), apparent molar volume (V_ϕ) and partial molar volume (V^0) was computed for all the systems. The Partial molar expansivity (E^0) and second derivative values, ($\partial^2V^0/\partial T^2$), have also been estimated. The critical micelle concentrations of this drug were obtained from ultrasound velocity measurement by using recently developed least square fitting algorithm. The results are interpreted in the light of structure-making or structure-breaking effects of escitalopram oxalate in the mixtures.

Keywords: Partial molar volume, Adiabatic compressibility, and Escitalopram oxalate.

Introduction

In bio-physical chemistry, drug interaction is an application of demanding studies, involving complex molecular mechanisms. Despite years of investigations, many important drug actions and their mechanisms are still not fully understood. Structure activity relationship is one of the most common factors presented for explaining drug action. In cases such as certain hormones, an antibiotic and peptide action, amphiphilicity in molecular structure is considered to be a key factor in the overall drug mechanism [l, 2]. The selective serotonin reuptake inhibitors (SSRIs) have become important tools in basic and clinical brain research. These were the first drugs to establish beyond doubt a pathophysiological role for serotonin (5-hydroxytryptamine, 5-HT) in effective illnesses and in the broad spectrum of anxiety disorders [3]. Many drugs of pharmacological importance show colloidal behavior and considered that they may form aggregates in the body decreasing the transport rate of the drug consequently deteriorating the health [4]. 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 [5, 6]. Such drug self-association depends upon the nature and concentration of additives. The alcohols are usually present in amphiphilic drug delivery formulations since they are of low toxicity and also they affect the inter-ionic attraction and the solute–solvent interactions in aqueous medium [6, 15]. The presence of alcohol in the drug formulation can modify the adsorption of drug from alcohol/water solution which can increase drug uptake. This needs a deep investigation about the drug behaviour in alcohol/water solutions.

The role of density and ultrasonic velocity, however, is considered important in connection with the explanation of molecular interactions in biological membranes. Volumetric and ultrasonic data of drugs, lipid bilayers, and membrane proteins can provide evidences to the interactions occurring in cellular fluids. Recent literature on the volumetric and acoustical properties of drugs and other materials of biological importance shows increasing interest by a number of workers in this area of study [5-15].

In present work, the study of molecular interactions on drug-substrate system using thermodynamic methods has been carried out. Partial molar volume and compressibility are calculated from experimental density and ultrasonic velocity in aqueous and alcoholic media at various temperatures (293.15 – 318.15 K) by using of density sound analyzer (DSA-5000M). The data are discussed in terms of relative solvation of this antidepressant in

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both solvents. Relative hydrophobicity of solute and aspects of structural characteristics in relation to drug actions are also discussed.

Results and Discussion

The apparent molar volume, V_ϕ, of the drug in water and ethanol was calculated by means of the following equation [9].

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

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

V_ϕ data was found to vary linearly and was fitted to the recently developed algorithm [10] based on Levenberg-Marquardt least square fitting algorithm:

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

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 [12] and 'm' is molality of the solution.

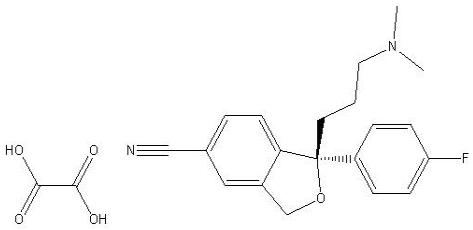

Fig.1: Structure of Escitalopram Oxalate.

The apparent molar volumes of Escitalopram Oxalate in ethanol and aqueous systems at temperatures 298.15, 303.15, 308.15 and 313.15 K have been shown in Fig. 2 and 3 respectively. The increase in the values of the apparent molar volume show hydrophilic interactions with the increase of temperature and concentration. The positive values of the partial molar volume (Table 1 & Table 2) show strong solute-solvent interactions which have implications for their transport rate in the organisms.

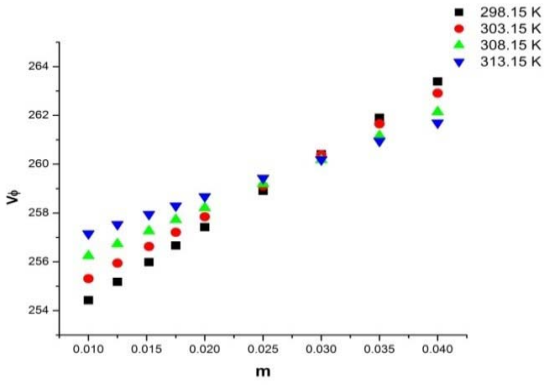

Fig. 2: V_ϕ against m (molality) for Escitalopram Oxalate in Ethanol from T = (298.15-313.15 K)

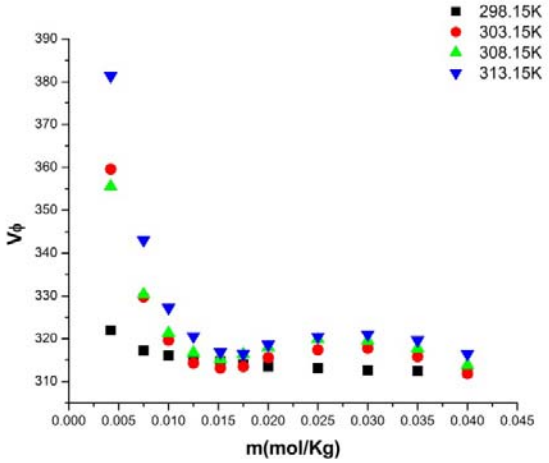

Fig. 3: V_ϕ against m for Escitalopram Oxalate in Water from T = (298.15-313.15 K).

Table-1: Partial molar volume, V^0, Expansivity, E^0, Hepler's constant, $(\partial^2 V^o/\partial T^2)$ and cmc of Escitalopram Oxalate in ethanol from T = (298.15-313.15 K).

Sr. No.	T (K)	V^o ($cm^3.mol^{-1}$) in Ethanol	E^0 ($cm^3.mol^{-1}K^{-1}$) in Ethanol	$(\partial^2 V^o/\partial T^2)$ ($cm^6/mol^2.K^2$) in ethanol	cmc
1	298.15	251.92 ± 0.432	0.80	1.6	0.011
2	303.15	252.50 ± 0.745			0.014
3	308.15	253.55 ± 0.534			0.020
4	313.15	254.26 ± 0.321			0.021

The apparent molar adiabatic compressibility K_ϕ, can be calculated by using the following relation [5]

$$K_\phi = \frac{10^3(\beta_s - \beta^0_s)}{mdd_0} + \beta_s V_\phi \qquad (3)$$

$$\beta^0_s = 1 / u^2 d \qquad (4)$$

where, β_s and β^0_s are the coefficients of compressibility of the solution and solvent, respectively. The adiabatic compressibility (K_ϕ) values showed (Fig. 5) a decreasing trend in case of water with the increase in the concentration of escitalopram oxalate and also with the rise of temperature. Escitalopram oxalate molecules in the neutral solutions exit in the dipolar form and have a strong interaction with the surrounding water molecules. The increasing electrostrictive compression of water around the molecules results in larger decrease in the compressibility of the solution. However the reverse is observed in alcoholic medium, which has been shown in Fig. 4.

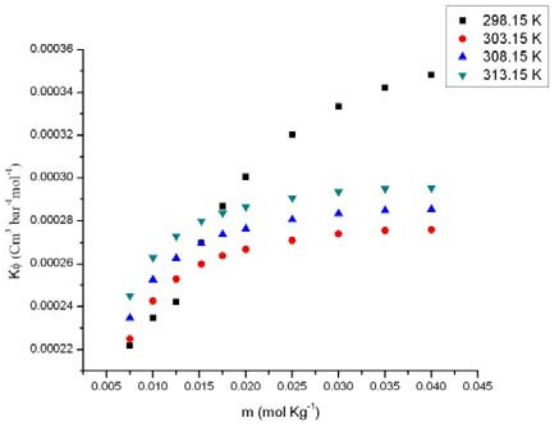

Fig. 4: Adiabatic compressibility, K_ϕ versus molality of Escitalopram Oxalate in ethanol from T = (298.15-313.15 K).

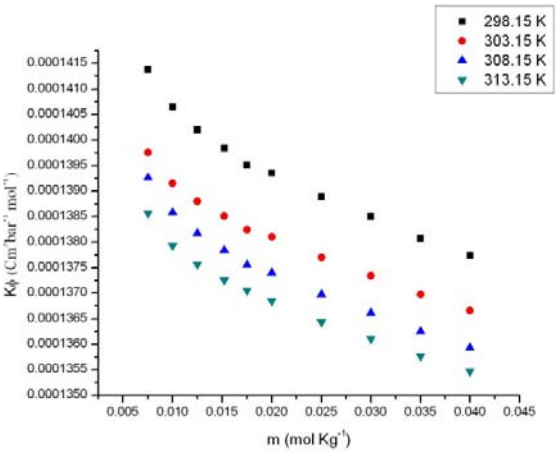

Fig. 5: Adiabatic compressibility, K_ϕ versus molality of Escitalopram Oxalate in water from T = (298.15-313.15 K).

Table-2: Partial molar volume V^0, Expansivity E^0, cmc and Hepler's constant, $(\partial^2 V^o/\partial T^2)$, of Escitalopram Oxalate in water from T = (298.15-313.15 K).

Sr. No.	T K	V^o ($cm^3.mol^{-1}$) in Water	E^0 ($cm^3.mol^{-1}K^{-1}$) in Water	$(\partial^2 V^o/\partial T^2)$ ($cm^6/mol^2.K^2$) in water	ΔV_{tr}	cmc
1	298.15	319.08 ± 0.60	9.15	18.3	67.16	0.016
2	303.15	335.67 ± 0.458			83.17	0.033
3	308.15	335.95 ± 0.588			82.40	0.033
4	313.15	349.49 ± 0.554			95.23	0.032

The apparent molar expansivities were calculated by using following equation [12].

$$E^0 = [\partial V^0 / \partial T]_p \qquad (5)$$

The positive value of partial molar expansivity E^0 indicates the predominance of hydrophobic hydration over the electrostriction of ethanol molecules around the solute molecules. The transfer molar volume, ΔV_{tr}, was calculated by the following equation [13]:

$$\Delta V_{tr} = V^o \text{ (in water)} - V^o \text{ (in ethanol)} \qquad (6)$$

The positive values of ΔV_{tr} (Table 2) indicate that the hydration shell of the solute molecule increases in volume with the change of solvent due to increase in hydrogen bonding with the water molecules. This also implies a hydrophobic character for this compound despite some of apparent hydrophilic properties. Although there are certain polar sites present in this molecule (Fig. l), this also contain alkyl chain, aromatic rings, and other hydrophobic groups. The net assets of the molecule as a result of complex interactions of different locations seems almost hydrophobic molecule.The temperature dependence of V^0 can be expressed by the following relationship [13].

$$V^0 = a + bT + cT^2 \qquad (7)$$

We estimated the coefficients a, b, and c by plotting partial molar volume data at different temperatures by the least-square fitting method. Qualitative information on the hydration of the solute molecules can be retrieved from the values of the Hepler's constant ($\partial^2 V^o/\partial T^2$). Inspection of Table 1 and Table 2 reveals that positive value of ($\partial^2 V^o/\partial T^2$), in case of both ethanol and water, is associated with the structure-making nature of the drug molecules because of their hydrophobicity[14].

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 [9].

$$\left(\frac{d^2u}{dm^2}\right)_{m=cmc} = 0. \qquad (8)$$

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

$$\frac{du}{dm} = \frac{1}{2}\left[\frac{ui+1 - ui}{mi+1 - mi} + \frac{ui - ui-1}{mi - mi-1}\right] \qquad (9)$$

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 9 was used to get second derivative i.e. d^2u / dm^2

The data obtained was fitted using Gaussian fit integrated with Levenberg-Maquardt nonlinear fitting to get fit of the curve.

$$y = y_0 + \frac{A}{w\sqrt{\pi/2}} e^{-2\frac{(x-x_c)^2}{w^2}} \qquad (10)$$

where y is the dependent variable and is the offset value which can be set to 0. x and x_o are the independent variables. x_o represents the mean value which is given by the center of the bell shaped Gaussian curve as shown in the Fig. 8. x corresponds to the molality and x_0 corresponds to the critical micelle concentration.

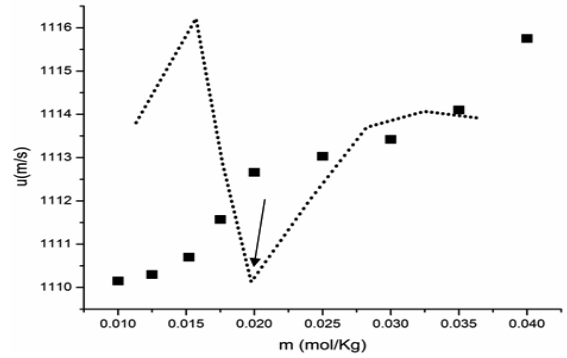

Fig.8: Ultrasound velocity u versus concentration m for Escitalopram in ethanol at (■) 298.15 K. The dotted line indicates the Gaussian fit of the second derivative of the ultrasound velocity against molality. The arrow indicates the critical micelle concentration.

Experiment

The antidepressant drug, Escitalopram Oxalate was obtained from Shaanxi Zhengbang International Trade Co., Ltd. and was used as received. The water used was triply distilled, deionized and degassed and the absolute ethanol was of purity 98%. Solutions were made by weight using Wiggen Hauser analytical balance with precision of ± 0.001mg. The density was measured with an uncertainty of ± 10^{-5} gcm^{-3} using Anton Paar (DSA 5000) density sound analyzer. The uncertainty temperature measurement was ± 0.01 K and in sound velocity measurements was ± 0.5 $m.s^{-1}$. All of the experiments were repeated thrice.

Conclusion

We have used density and sound velocity data to calculate the apparent molar volume, partial molar volume and adiabatic compressibilities of ecsitalopram oxalate in water and ethanol over temperature range 298.15-313.15K. The apparent molar volume value increases with the concentration while in water it decreases with the concentration due to the formation and structural rearrangement of the aggregates that have already been formed as ecsitalopram oxalate behaves as an amphiphilic molecule. 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. When the amphiphilic molecules form micelles, the hydrophobic hydration around the solute disappears and the compressibility of the aggregate becomes the dominant factor. The hydrophobic character of Escitalopram oxalate aggregates is indicated by the positive values of the apparent molar adiabatic compressibility. The values of compressibility of antidepressant drugs are much greater than those of surfactants. The values of compressibility in ethanol are greater (Fig. 4) than in water (Fig. 5). These high compressibilities in ethanol (Fig. 5) are due to van der Waals interactions between solute and solvent molecules giving rise to an aggregate interior resembling that of a bulk liquid phase.

Acknowledgement

The financial grant of Higher Education Commission, HEC Pakistan (project No. 20-1353/R&D/09/4539) for the purchase of density sound analyzer (DSA 5000 M) and chemicals is gratefully acknowledged by the authors.

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