Influence of External factors on Self-Aggregation of Amphiphilic Antidepressant Drug: A Thermodynamic Study

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Summary: Apparent molar volumes, (V_ϕ), adiabatic compressibilities, (K_ϕ), and thermal expansivities (E^0) of venlafaxine hydrochloride, an amphiphilic antidepressant drug, have been determined in water and aqueous 0.01 mol/kg $CaCl_2.2H_2O$ solutions. The densities and ultrasound velocities were measured at 298.15 and 303.15 K by using an Anton Paar density sound analyzer (DSA 5000M). The critical micelle concentrations (cmc) of this drug were obtained from ultrasound velocity (u) measurement by using recently developed least square fitting algorithm. Negative deviations from Debye-Huckel limiting law of apparent molar volume for this drug was obtained at 298.15 and 303.15 K in water and 0.01 mol/kg $CaCl_2.2H_2O$ solutions showing no pre-association below the critical micellar concentration. The volumetric parameters indicating the interactions of venlafaxine hydrochloride with $CaCl_2.2H_2O$ and in water have been obtained by using transfer molar volume and the resulting values are in good agreement within each other within experimental error. The Partial molar expansivity, (E^0), and second derivative values, ($\partial^2 V^0/\partial T^2$), have also been estimated.

Keywords: Venlafaxine hydrochloride, Partial molar compressibilities, Serotonin specific reuptake inhibitor, Critical micelle concentration.

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. Venlafaxine hydrochloride is a selective serotonin reuptake inhibitor with no activity at muscarinic, histaminergic or adrenergic receptors [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]. Under normal physiological conditions, the rate of uptake of venlafaxine hydrochloride from blood into brain is completely flow-limited, thus the study of volumetric behavior of this drug is of great significance.

The Micelles are the most prevalent aggregates in surfactant solutions and form over a narrow range of concentration known 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, the solution behaviour of venlafaxine hydrochloride has been investigated in order to obtain a comprehensive description of its aggregation process in aqueous solution to analyze how the temperature affects the thermodynamics of the aggregation. For this purpose, the apparent molar volumes and expansibilities of venlafaxine hydrochloride were obtained by using density and sound velocity data at 298.15 and 303.15 K. In addition, the critical micelle concentration for the aggregation of this drug in aqueous solution has been calculated by using Philip's definition [6] of the critical micelle concentration (*cmc)*, the concentration that corresponds to the maximum change in the gradient of a plot of the magnitude of any physical quantity against concentration.

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Results and Discussions

The apparent molar volume, V_ϕ, in water and 0.01 mol/kg $CaCl_2.2H_2O$ solutions results are illustrated in Fig. 1 and 2 respectively. The apparent molar volume, V_ϕ, of the drug in water and 0.01 mol/kg $CaCl_2.2H_2O$ 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, 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]. Figures 1 and 2 shows that V_ϕ vary linearly and this data was fitted to the recently developed algorithm [12] based on Levenberg-Marquardt least square fitting algorithm:

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

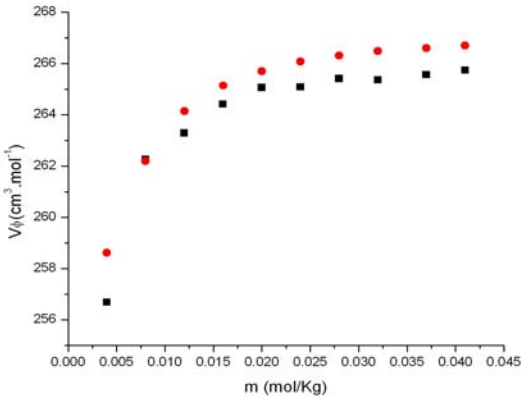

Fig. 1: The apparent molar volumes, V_ϕ, of venlafaxine hydrochloride vs. concentration in Water at (■) 298.15 K and (●) 303.15K.

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 [13-15] and 'm' is molality of the solution. The calculated values of V^0 with their standard errors of the venlafaxine hydrochloride at different temperatures are summarized in Table-1.

The partial molar volume data at different temperatures are used to calculate the partial molar Expansivity (E^0) using the following equation [16]

$$E^0 = [\partial V^0 / \partial T]_p \quad (3)$$

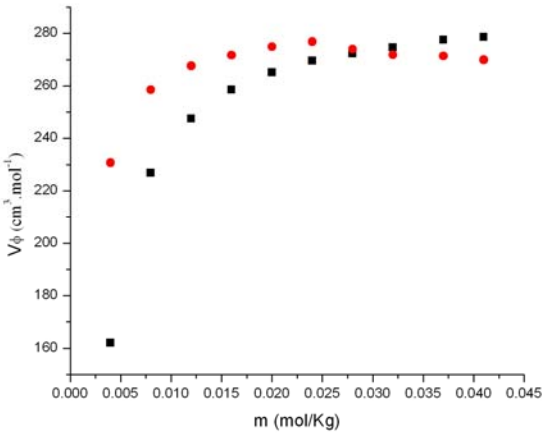

Fig. 2: The apparent molar volumes, V_ϕ of Venlafaxine hydrochloride vs concentration (0.01 mol/kg $CaCl_2.2H_2O$) at (■) 298.15 K and (●) 303.15K.

It is assumed that the amphiphilc compounds in solutions behave as a single dispersed system in premicellar region so the apparent molar volume at concentration below the critical micelle concentration may be described by the following equation [17].

$$V_\phi = V^0 + A_v m^{1/2} + B_v m \quad (4)$$

Where, V^0, is the apparent molar volume at infinite dilution. A_v is Debye-Huckel limiting law coefficient and B_v is the pair interaction co-efficient [3]. Except for hydrogen-bonding, this coefficient is negative [3]. Values obtained for V^0 and B_v are shown in Table-1. The uncertainty of the data in the region of high dilution does not allow obtaining very accurate values of B_v, however, some qualitative conclusions can be drawn. At high temperatures this parameter assumes positive values [18]. For this compound, in aqueous 0.01 mol/kg $CaCl_2.2H_2O$ slightly large negative value of B_v are obtained. As it has already been pointed out that B_v is related with non-electrostatic solute–solute interactions, so it could be expected that the value would decrease with solute concentration. The positive B_v values have been normally described in literature due to the presence of dimers in the premicellar region [19], although in some cases compounds with small negative B_v, values also showed dimerization [11]. Aggregation at concentrations below the critical concentration has important implications for the transport of the drug molecules through biological membranes since this may occur at the low concentrations prevalent *in vivo*.

Table-1 Partial molar volume V^0, Pair interaction Co-efficient, B_v, of Venlafaxine hydrochloride in water and 0.01 mol/kg $CaCl_2.2H_2O$ at 298.15 and 303.15 K.

Temp(K)	V^o(cm^3 mol^{-1}) inWater	V^o(cm^3 mol^{-1}) in$CaCl_2.2H_2O$	B_v(cm^3 kgmol^{-2}) in Water	B_v(cm^3 kg mol^{-2})in$CaCl_2.2H2O$	ΔV_{tr}(cm^3 mol^{-1})
298.15	256.83± 1.430	201.68± 15.19	-0.18	-2.27	55.15
303.15	257.29± 1.831	251.48± 7.595	-0.16	-1.21	5.81

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 that physical property against concentration corresponds to the critical micelle concentration in accordance with Philip's definition [6].The Plots of ultrasound velocity, *u,* as a function of molality, *m,* for venlafaxine hydrochloride in water and 0.01 mol/kg $CaCl_2.2H_2O$ systems at 298.15 and 303.15 K gave the critical micelle concentrations. The plot for self-aggregation is shown in Fig. 3.

$$(d^3u/dm^3)_{m=cmc} = 0 \qquad (5)$$

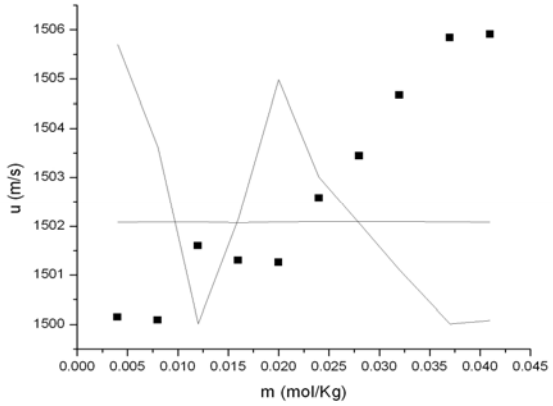

Fig. 3: Ultrasound velocity (u) vs. concentration m for Venlafaxine hydrochloride in 0.01 mol/kg $CaCl_2.2H_2O$ at (■) 298.15 K. The line indicates the Gaussian fit of the second derivative of the ultrasound velocity against molality.

Cheema et al used Runge-Kutta numerical integration and Levenberg-Marquardt least square fitting algorithm [3] for numerical analysis of data. The precise values of the critical micelle concentration (*cmc*) of Venlafaxine hydrochloride is shown in Table-3.

The apparent molar compressibility K_ϕ can be calculated by using the following relation [3]

$$K_\phi = (10^3(k_s\text{-}k^0_s)/(mdd_0)) + k_s\, V_\phi$$

Where, *ks* and k^0s are the coefficients of compressibility of the solution and solvent, respectively.

The positive values of the partial molar volume, V^0, (Table-1) show strong solute-solvent interactions which have implications for their transport rate in the organisms. The positive value of partial molar expansivity, E^0, (Table-2) indicates the predominance of hydrophobic hydration over the electrostriction of ethanol molecules around the solute molecules. The positive values of ΔV_{tr} (Table-1) 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 leads to decrease to structure breaking tendency of the ion and then enhance the electrostriction of the water.

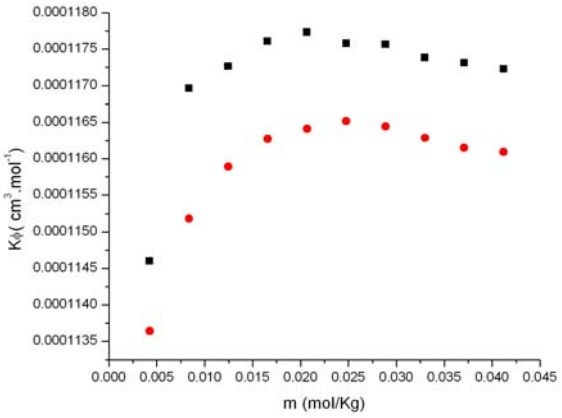

Fig. 4: The apparent molar compressibility, K_ϕ of Venlafaxine hydrochloride in Water at (■) 298.15 K and (●) 303.15K.

Table-2: Thermal Expansivity coefficient, α, Hepler's Constant, $(\partial^2V^o/\partial T^2)$, Partial molar Expansivity, E^0, of venlafaxine hydrochloride in water and 0.01 mol/kg $CaCl_2.2H_2O$ at 298.15 and 303.15 K.

Temp(K)	α (K)		$(\partial^2V^o/\partial T^2)$(cm^{6}mol^{-2}K^{-2})		E^0(cm^{3}mol^{-1}K^{-1})$^{in\ Water}$	E^0(cm^{3}mol^{-1}K^{-1})$^{in\ CaCl_2.2H_2O}$
	in Water	in $CaCl_2.2H_2O$	in Water	in $CaCl_2.2H_2O$		
298.15	0.00179	0.246	0.92	99.6	0.46	49.8
303.15	0.00178	0.198				

Table-3: Critical micelle concentrations, *cmc,* of venlafaxine hydrochloride in water and 0.01 mol/kg $CaCl_2.2H_2O$ at 298.15 and 303.15 K.

Temperature K	cmc in $CaCl_2.2H_2O$(mol/kg)	cmc in Water(mol/kg)
298.15	0.0313	0.0280
303.15	0.0314	0.0282

The temperature dependence of V^0 can be expressed by the following relationship [17].

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

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 ($\partial^2V^o/\partial T^2$). Inspection of Table-2 reveals that positive values of ($\partial^2V^o/\partial T^2$) in case of both water and 0.01mol/kg $CaCl_2.2H_2O$ are associated with the structure-making nature of the drug molecules because of their hydrophobicity.

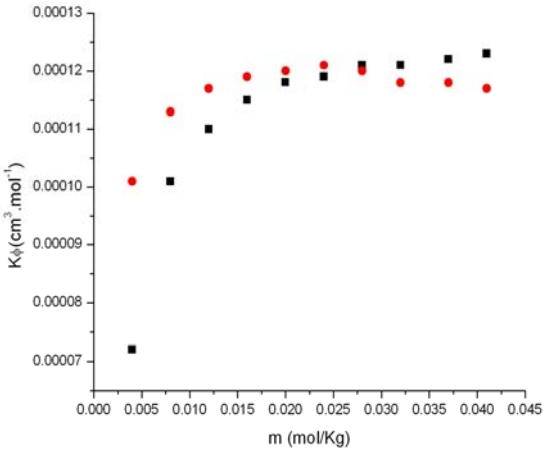

Fig. 5: The apparent molar compressibility, K_ϕ of venlafaxine hydrochloride in 0.01 mol/kg $CaCl_2.2H_2O$ at (■) 298.15 K and (●) 303.15K.

Experimental

The antidepressant drug, venlafaxine hydrochloride (1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexan-1-ol) was obtained from Sigma®. The water used was triply distilled and degassed. 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 density sound analyzer (DSA 5000M). The uncertainty in temperature measurement was ± 0.01 K and sound velocity measurements were ± 0.5 ms^{-1}. All of the experiments were repeated thrice.

Conclusions

We have used density and sound velocity data to calculate the apparent molar volume, partial molar volume and adiabatic compressibilities of venlafaxine hydrochloride. The solvents were water and 0.01 mol/kg $CaCl_2.2H_2O$ over temperature range (T= 298.15-303.15) K. The values of apparent molar volume increase with the increase in concentration. The positive values of partial molar volumes indicate strong solute-solvent interactions which have implication 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 venlafaxine hydrochloride aggregates is indicated by the positive values of the apparent molar adiabatic compressibility. The values of compressibility for this drug are much greater than those of surfactants. The values of compressibility in $CaCl_2.2H_2O$ are greater than those of in water. These high compressibilities in $CaCl_2.2H_2O$ 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.

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