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TEMPERATURE-DEPENDENT VOLUMETRIC AND VISCOMETRIC PROPERTIES OF L-PHENYLALANINE IN AQUEOUS METFORMIN HYDROCHLORIDE SOLUTIONS

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ABSTRACT

Densities and viscosities of L-Phenylalanine in (0.05, 0.10, 0.15 and 0.20) mol kg^{-1} aqueous solutions of Metformin-HCl have been measured at T = (298.15, 303.15, 308.15, 313.15 and 318.15) K and experimental pressure p = 0.1 MPa to study nature of the interactions of Phenylalanine with aqueous metformin hydrochloride (Metformin-HCl) as a function of temperature. Several thermodynamical parameters such as partial molal volume $V\varphi$, standard partial molal volume $V\varphi^0$, transfer volume $\Delta V\varphi^0$, hydration number n_H, the second derivative of infinite dilution of partial molal volume with respect to temperature, viz., $\partial^2 V\varphi^0 / \partial T^2$, viscosity B-coefficient, transfer B-coefficient ΔB, variation of B with temperature (dB/dT), free energies of activation of viscous flow $\Delta\mu 1^{0*}$ and $\Delta\mu 2^{0*}$ per mole of solvent and solute are reported. The dependence of these parameters upon concentration and temperature clearly show the presence of strong solute - cosolute interactions. Furthermore the pair and triplet interaction coefficient have also been calculated and reported.

KEYWORDS: Standard partial molal volume, transfer volume, hydration number, viscosity B-coefficient, activation energy, L-Phenylalanine, Metformin hydrochloride.

1. INTRODUCTION

Proteins are large organic compounds consisting of different kinds of amino acids arranged in a linear form and joined together by peptide bonds between the carboxyl and amino groups of adjacent amino acid residues. They are essential for the structure, function and regulation of the body's tissues and organs. Proteins are the biomolecules, which play a vital role in all the biochemical processes occurring in living organisms. In aqueous media in the presence of cosolutes, proteins behaviour have been governed by their interactions with the surrounding environment which play an important role in their conformational characteristics. These interactions that include the non-covalent interactions such as hydrogen bonding, electrostatic interactions, hydrophobic interactions, etc., stabilize the proteins. The study of these interactions provides important insight into the conformational stability of proteins.[1]

Due to the structural complexity of these biological macromolecules, direct thermodynamic study of proteins in aqueous media is somewhat difficult. Thus, amino acids are being extensively used by many authors as model compounds as they are structural units of proteins.[2-5] Thermodynamic properties of these model compounds in aqueous drug medium provide information about solute–cosolute and solute–solvent interactions, which in turn help to understand biochemical processes of absorption of drugs and transport of drugs across biological membranes[6] that are vital in the field of medicine and drug design. It is to be added that drug macromolecular interactions involved in drug transport, protein binding and anesthesia are important phenomena in physiological media.[7] The mechanisms of these molecular processes are however yet to be clearly understood.

To understand the macromolecule aqueous drug interactions a few researchers have reported the interactions of amino acids in some aqueous drug solutions at different temperatures as mentioned herewith. Rajagopal and Jayabalakrishnan (2010) have reported the effect of temperature on volumetric and viscometric properties of homologous amino acids in aqueous Metformin Hydrochloride solutions[8] and concluded that second derivative of V_{φ}^{o} with respect to temperature shows the structure making property of the studied amino acids in aqueous metformin hydrochloride solutions which has also been substantiated by their viscosity B coefficients, dB/dT values. Furthermore Volumetric and Viscometric studies of 4-Aminobutyric acid in aqueous solutions of Metformin Hcl have been reported by Rajagopal and Jayabalakrishnan (2011).[9] Ultrasonic studies of 4- Aminobutyric acid in aqueous Metformin Hcl at different temperatures have been reported by Rajagopal and

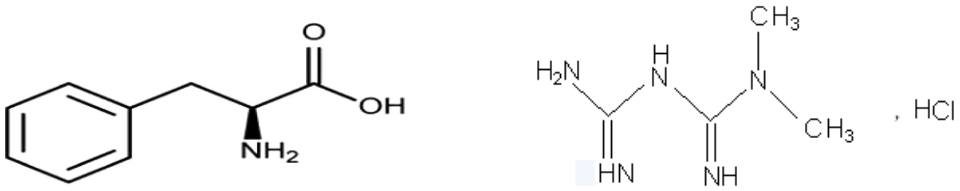
Jayabalakrishnan(2010)[10] and confirmed the presence of strong solute–solvent interactions. Rajagopal and Edwin (2010) studied Partial Molar volume and partial molar compressibility of four homologous α – amino aicds in aqueous sodium fluoride solutions at different temperatures.[11] Similarly, studies on volumetric and viscometric properties of valine in aqueous paracetamol solutions at different temperatures have been investigated by Rajagopal, Richi Renold and Mohamed Roshan (2017)[12] and have concluded that valine is a structure maker in aqueous paracetamol solutions which has also been substantiated by their viscometric studies. Furthermore Ultrasonic studies of Valine and Alanine in aqueous paracetamol solutions over a range of temperatures from 298.15 to 318.15K have been reported by Rajagopal, Richi Renold and Mohamed Roshan (2017).[13,14] Density (ρ), speed of sound (u) and viscosity (η) measurements of amino acids L-glutamine and L-histidine in aqueous solutions of metformin hydrochloride have been carried out by Suvarcha Chauhan et al[15] and confirmed the structure promoting tendency of both the amino acids. H Kumar et al[16] have reported the interactions of L-serine and L-threonine with the aqueous drug metformin hydrochloride as a function of temperature (305.15, 310.15 and 315.15K) through the volumetric and acoustic studies and have indicated structure promoter nature of these solutes.

However, to the best of our knowledge volumetric and viscometric studies of L-Phenylalanine in aqueous Metformin hydrochloride solution have not been reported so far and the objective of this paper is to report the experimental density and viscosity values of L-Phenylalannine in aqueous metformin hydrochloride solutions at different temperatures.

The present study is a continuation of our earlier work on metformin hydrochloride.[7,8,9] Metformin hydrochloride belongs to a group of medicines called biguanide anti−hyperglycaemic agents. It works by lowering human blood−sugar level, i.e. lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral anti hyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin is used to treat non−insulin dependent diabetes (also called type 2 diabetes) where diet and exercise alone have failed to control blood sugar levels, particularly if overweight.

Phenylalanine is one of the common amino acids in proteins and a nutritionally essential, aromatic amino acid. Phenylalanine occurs naturally in many protein-rich foods, such as

milk, eggs and meat. There are three forms of phenylalanine: D-phenylalanine, L-phenylalanine and the mix made in the laboratory called DL-phenylalanine. L-phenylalanine is an essential amino acid and is the only form of phenylalanine found in proteins which has been investigated in this study. Chemical structure of L-Phenylalanine & Metformin Hydrochloride are as shown in figure 1.



1 (a) **1 (b)**

Figure 1. Chemical structure of L-Phenylalanine (1 (a)) and Metformin Hydrocloride (1(b)).

Thus in this paper, we report the density (ρ) and viscosity (η) of L-Phenylalanine in four aqueous molal concentrations of metformin hydrochloride solutions. Since hydration effects are sensitive to temperature[17], both volumetric and viscometric studies are reported over a range of temperatures from 298.15 to 318.15 K which includes human body temperature. The temperatures are chosen carefully as pointed out by Iqbal et al.[18], such that significant relevance can be achieved by studying compounds of biological importance (amino acids) over a range of temperatures which is close to the optimum temperature of several living species rather than only at 298.15K as reported by many researchers in the literature. From the measured values of density and viscosity, different physical parameters are estimated, such as partial molal volume $V\varphi$, standard partial molal volume $V\varphi^0$, transfer volume $\Delta V\varphi^0$, hydration number n_H, the second derivative of infinite dilution of partial molal volume with respect to temperature, viz., $\partial^2 V\varphi^0 / \partial T^2$, viscosity B-coefficient, transfer B-coefficient ΔB, variation of B with temperature (dB/dT) free energies of activation of viscous flow $\Delta\mu_1^{0*}$ and $\Delta\mu_2^{0*}$ per mole of solvent and solutes of the amino acids. Pair and triplet coefficients V_{AB}, V_{ABB} and η_{AB}, η_{ABB} have also been calculated from transfer parameters. All these parameters are used to discuss the solute-cosolute and solute-solvent interactions occurring in the ternary (amino acids + metformin hydrochloride + water) system and the structure making/breaking tendency of the solutes in the given solvent.

2. MATERIALS AND METHODS

Phenyl Alanine (CAS no.63-91-2) with mass fraction of purity > 0.99 procured from Avra Synthesis Pvt. Ltd. India, has been used as such. Metformin-HCl with mass fraction purity > 0.99 purchased from Accumen Pharmaceuticals Pvt. Ltd., India used without further purification. Doubly distilled deionized water with a conductivity of 1 $\mu\Omega^{-1}\cdot cm^{-1}$ has been used in our experiments and degassed prior to preparation of solutions. The densities of the solutions have been measured using a single stem pycnometer (Borosil glass) of bulb capacity of ~ 10mL. The Capillary, with graduated marks, had a uniform bore and could be closed by a well-fitting airtight glass cap. A standard microscope is used to calibrate the volume in the pycnometer. Once the Pycnometer is calibrated, then the calibrated standard values may be used to calculate the volume of the solution[19] and its density in turn.

The solutions of metformin hydrochloride (0.05, 0.10, 0.15 and 0.20) $mol\cdot kg^{-1}$ have been prepared in double distilled water and used as solvents to prepare the L-Phenylalanine solutions of five different molal concentrations (ranging from 0.05 to 0.15 $mol\cdot kg^{-1}$). The solutions so prepared have been gently stirred on a magnetic stirrer before being subjected to measurements. The weighing has been done on a high precision SHIMADZU electronic balance (model TXC623L, Philiphines) with a precision of ±0.1 mg. The reproducibility of density measurements has been ± 2.5 $\times 10^{-4}$ $kg\cdot m^{-3}$.

Viscosity has been measured by means of a suspended level Ubbelohde viscometer with a flow time of approximately 162 seconds for double distilled water at 303.15 K. The time of flow has been measured with a stopwatch capable of recording ±0.01 s. Viscometer has been calibrated using the flow time of water for a temperature range from 298.15 to 318.15 K. An average of three or four sets of flow time for each solution has been taken for the calculation of viscosity. The viscosity of a solution η, is calculated by using the following expression.[20]

$$\eta/\rho = Lt - K/t \qquad (1)$$

Where ρ is the density of the solution, t is the flow time and L and K are the viscometer constants. The uncertainties in viscosity measurements have been found to be within ±0.001 mPa.s.[21] As the flow time was greater than 100 s, the kinetic energy corrections are not necessary.[17] The pycnometer filled with solutions without bubbles and Ubbelhode viscometer filled with test solutions have been allowed to stand for about 30 minutes in a thermostatic water bath so as to minimize thermal fluctuations. The temperatures of the solutions have been maintained to an accuracy of ±0.01 K in an electronically controlled

thermostatic water bath (Eurotherm, INSCIN, Chennai). The standard partial molal volumes (V_φ^0) and viscosity B-coefficients that are calculated using the experimentally measured density and viscosity values (see table 2 and table 6 respectively) for phenylalanine in water at the studied temperatures agree very well with the literature values[22] thus validating our experimental procedures.

3. RESULTS AND DISCUSSIONS

3.1. Apparent Molal Volume and Partial Molal Volume

The experimental densities and viscosities of the solutions at 298.15, 303.15, 308.15, 313.15 and 318.15 K are shown in Table 1. The Apparent molal volume V_φ of amino acids is calculated using the following equation.

$$V_\varphi = (M/\rho)\text{-}1000\ (\rho - \rho_0)\ /m\ \rho\ \rho_0 \qquad (2)$$

Where *M*, *m*, ρ and ρ_0 are the molar mass of solute (amino acid), the molality of solute, densities of solution and solvent (aqueous metformin hydrochloride solutions), respectively.

The values of partial molal volume for the amino acids are generally represented[23] by a linear equation,

$$V_\varphi^{\circ} = V_\varphi + S_v\, m \qquad (3)$$

Where V_φ^0 is the infinite dilution value that is equal to the partial molal property at infinite dilution and S_v is the experimental slope. The V_φ^0 values of Phenylalanine in water at the studied temperatures agree fairly well with literature values (Table 2) thus validating our experimental procedures.

The value of V_φ^0 is by definition free from solute-solute interaction and therefore provides information regarding solute- solvent interactions.[24] Table (2) shows that the V_φ^0 values increase with increase in temperature for phenylalanine in aqueous metformin hydrochloride solution. It indicates that the strength of solute /cosolute–solvent interactions are increasing with increase in temperature.

Table 1: Density and viscosity of L-Phenyl Alanine in aqueous Metformin Hydrochloride at different temperatures.

M	ρ/kg·m^{-3}					η/m Pa s				
mol·kg^{-1b}	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K	298.15 K	303.15 K	308.15K	313.15 K	318.15 K
	m_H / mol·kg^{-1} = 0.05									
0	0.99889	0.99746	0.99583	0.99399	0.99201	0.9086	0.8111	0.7303	0.6611	0.6026
0.05	1.00121	0.99977	0.99812	0.99627	0.99427	0.9391	0.8377	0.7525	0.6805	0.6191
0.075	1.00228	1.00082	0.99916	0.99729	0.99530	0.9528	0.8496	0.7623	0.6891	0.6262
0.1	1.00330	1.00183	1.00014	0.99828	0.99624	0.9650	0.8585	0.7697	0.6943	0.6315
0.125	1.00422	1.00270	1.00106	0.99919	0.99718	0.9785	0.8700	0.7792	0.7028	0.6383
0.15	1.00507	1.00360	1.00190	1.00002	0.99799	0.9880	0.8777	0.7872	0.7096	0.6437
	m_H / mol·kg^{-1} = 0.10									
0	1.00077	0.99932	0.99767	0.99582	0.99383	0.9206	0.8222	0.7407	0.6697	0.6109
0.05	1.00307	1.00161	0.99994	0.99808	0.99608	0.9482	0.8480	0.7649	0.6890	0.6277
0.075	1.00414	1.00266	1.00098	0.99910	0.99709	0.9633	0.8583	0.7724	0.6966	0.6347
0.1	1.00512	1.00367	1.00196	1.00006	0.99802	0.9764	0.8700	0.7814	0.7046	0.6409
0.125	1.00606	1.00453	1.00285	1.00095	0.99895	0.9911	0.8789	0.7896	0.7110	0.6463
0.15	1.00689	1.00539	1.00367	1.00179	0.99975	0.9944	0.8878	0.7992	0.7179	0.6526
	m_H / mol·kg^{-1} = 0.15									
0	1.00266	1.00121	0.99956	0.99769	0.99569	0.9319	0.8335	0.7513	0.6804	0.6207
0.05	1.00495	1.00347	1.00181	0.99993	0.99791	0.9638	0.8584	0.7724	0.6985	0.6366
0.075	1.00599	1.00452	1.00283	1.00094	0.99891	0.9746	0.8683	0.7800	0.7056	0.6433
0.1	1.00696	1.00548	1.00378	1.00189	0.99986	0.9883	0.8775	0.7880	0.7122	0.6480
0.125	1.00788	1.00636	1.00466	1.00276	1.00072	1.0000	0.8873	0.7977	0.7197	0.6548
0.15	1.00873	1.00720	1.00550	1.00359	1.00152	1.0109	0.8985	0.8063	0.7276	0.6620
	m_H / mol·kg^{-1} = 0.20									
0	1.00460	1.00312	1.00146	0.99959	0.99760	0.9439	0.8437	0.7606	0.6890	0.6291
0.05	1.00685	1.00536	1.00369	1.00181	0.99980	0.9757	0.8709	0.7840	0.7086	0.6459
0.075	1.00791	1.00639	1.00469	1.00279	1.00079	0.9900	0.8833	0.7924	0.7169	0.6529
0.1	1.00885	1.00734	1.00563	1.00373	1.00170	1.0013	0.8917	0.8007	0.7235	0.6584
0.125	1.00976	1.00822	1.00650	1.00460	1.00258	1.0134	0.9015	0.8098	0.7319	0.6663
0.15	1.01057	1.00903	1.00732	1.00541	1.00336	1.0238	0.9114	0.8180	0.7373	0.6705

m_H – molality of metformin hydrochloride/mol.kg^{-1}.

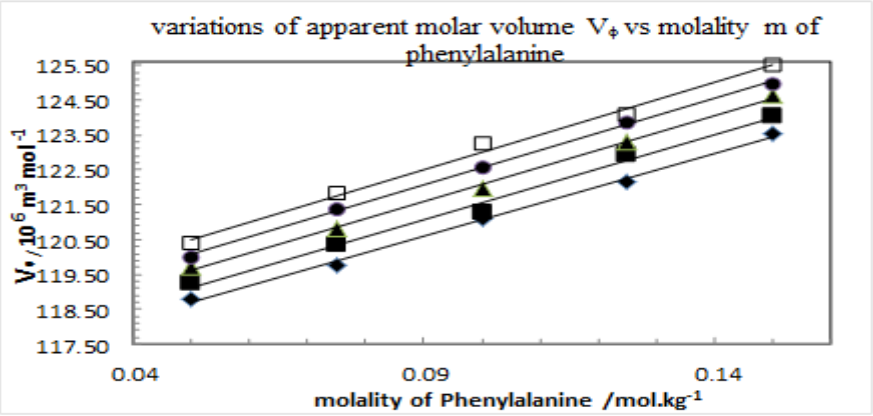


Figure 2. Representative plots of V_φ versus concentration for Phenylalanine in 0.05 mol.kg^{-1} aqueous metformin hydrochloride at 298.15K(◆), 303.15K(■), 308.15K(▲), 313.15K(●) 318.15K (□).

Table 2: Standard Partial Molal Volumes (V_φ^0) of L-PhenylAlanine in aqueous Metformin Hydrochloride solutions at different temperatures.

Temperature	Standard Partial Molal Volume $V_\varphi^0 \times 10^6/m^3 \cdot mol^{-1}$					
T/K	m_H = 0 (water)		m_H = 0.05	m_H = 0.10	m_H = 0.15	m_H = 0.20
Temperature	Present work	Literature [25]	mol·kg^{-1}	mol·kg^{-1}	mol·kg^{-1}	mol·kg^{-1}
298.15	121.590	121.544, 121.551, 121.608	116.086	116.311	116.659	116.987
303.15	122.140		116.521	116.690	117.022	117.331
308.15	122.740	122.821, 122.881, 122.770	116.951	117.139	117.501	117.77
313.15	123.460		117.352	117.560	117.824	118.195
318.15	123.990	123.994, 123.977, 123.984	117.846	118.000	118.320	118.61

m_H – molality of metformin hydrochloride/mol.kg^{-1}.

3.2 Partial molal volume of transfer

The V_φ^0 values in water and in aqueous drug solutions have been used to calculate the partial molal volume of transfer at infinite dilution using equation (4).

$\Delta V_\varphi^0 = V_\varphi^0$ (amino acids in aqueous drug solution) - V_φ^0 (amino acid in water) (4)

The resultant values of ΔV_φ^0 has been given in table (3). These trends of ΔV_φ^0 values can be justified by the Co-sphere model suggested by Friedman and Krishnan [8, 26]. The properties of water molecules in the hydration co-spheres around amino acids and metformin hydrochloride molecules depend on the nature of the intermolecular interactions. The interactions between the Phenylalanine and metformin hydrochloride can be classified into four types as discussed below.[27,28]:

(i) (ion+ hydrophilic) interactions (between zwitterionic centres of amino acids and polar groups of Metformin-HCl)

(ii) (hydrophilic + hydrophilic) interactions (between polar groups of amino acids and polar groups of Metformin-HCl)

(iii)(ion + hydrophobic) interactions (between zwitterionic centres of amino acids and nonpolar groups of Metformin-HCl) and

(iv)(hydrophobic + hydrophobic) interactions (between non-polar groups of amino acids and non-polar groups of Metformin-HCl).

According to co-sphere overlap model, (ion + hydrophobic) interactions and (hydrophobic + hydrophobic) interactions contribute negatively whereas (ion + hydrophilic) and (hydrophilic + hydrophilic) interactions contribute positively to the ΔV_φ^0 values. In our present study of phenylalanine+water+metformin hydrochloride the ΔV_φ^0 values are negative indicating the predominance of the type (iii & iv) interactions over type (i) & (ii) interactions.[8,29]

Table 3. Partial Molal Volumes of transfer (ΔV_φ^0) and Hydration Number (n_H) of L-Phenyl Alanine in aqueous Metformin Hydrochloride solutions at different temperatures.

Temperature	Partial Molal Volume Transfer $\Delta V_\varphi^0 10^6/m^3 \cdot mol^{-1}$				Hydration Number n_H			
T/K	m_H=0.050.05	m_H = 0.10	m_H = 0.15	m_H = 0.20	m_H = 0.05	m_H = 0.10	m_H = 0.15	m_H = 0.20
	mol·kg^{-1}	mol·kg^{-1}	mol·kg^{-1}	mol·kg^{-1}	mol·kg^{-1}	mol·kg^{-1}	mol·kg^{-1}	mol·kg^{-1}
298.15	-5.504	-5.279	-4.931	-4.603	6.33	6.27	6.18	6.10
303.15	-5.619	-5.450	-5.118	-4.809	6.22	6.17	6.09	6.01
308.15	-5.789	-5.601	-5.239	-4.970	6.11	6.06	5.97	5.90
313.15	-6.108	-5.900	-5.636	-5.265	6.01	5.96	5.89	5.80
318.15	-6.144	-5.990	-5.670	-5.380	5.89	5.85	5.77	5.69

m_H – molality of metformin hydrochloride/mol.kg^{-1}.

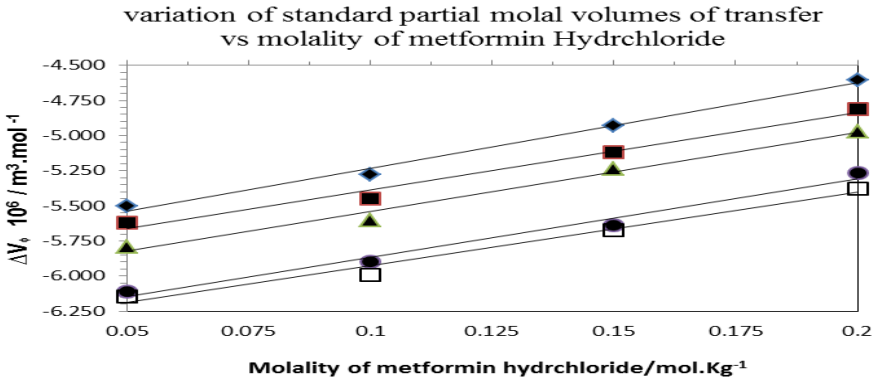


Figure 3. Representation plots of ΔV_φ^0 versus concentration of metformin hydrochloride at different temperatures 298.15K(◆), 303.15K(■), 308.15K(▲), 313.15K(●) 318.15K (□).

3.3 Hepler's constant, partial molal expansivity and isobaric thermal expansion coefficient

The structure making/breaking property of the solute (AA) in aqueous metformin hydrochloride may be determined from the temperature dependence of the standard partial molal volume at infinite dilution. This study has been further used to interpret the effect of the hydrocarbon chain on the structure of water using the general hydrophobicity criteria proposed by Hepler.[30] According to the criteria, the behaviour of the second derivative of the infinite dilution standard partial molal volume with temperature is related to the hydrophobic or hydrophilic character of the solute. When $\partial V_\varphi^0/\partial T > 0$ and $\partial^2 V_\varphi^0/\partial T^2 < 0$, the solute has hydrophilic character. However when $\partial V_\varphi^0/\partial T < 0$ and $\partial^2 V_\varphi^0/\partial T^2 > 0$, the solute has hydrophobic character.[31] In order to obtain the hydrophilic or hydrophobic character of Phenylalanine in aqueous metformin hydrochloride solutions, the experimental values of V_φ^0 have been related to the temperature dependence of V_φ^0[32] by the equation (5).

$$V_\varphi^0 = a + bT + cT^2 \qquad (5)$$

Where a, b and c may be estimated by the least squares fitting of partial molal volume in the above equation.

Table 4. Partial molal expansivity E_2^0, Temperature derivative of B-coefficient, dB/dT, and Hepler's constants ($\partial^2V_\varphi^0/\partial T^2$), of L-Phenylalanine in aqueous Metformin Hydrochloride solutions for a range of temperatures from 298.15 to 318.15K.

m_H/ (mol·kg^{-1})	10^6 E_2^0/ (m^3 ·mol^{-1}·K^{-1})	$\partial^2V_\varphi^0/\partial T^2$ / (m^6. mol^{-2} · k^{-2})	dB/dT / (m^3 ·mol^{-1}·K^{-1})
0	0.12000	0.00023	-0.00774
0.05	0.08800	0.00025	-0.00672
0.1	0.08445	0.00027	-0.00588
0.15	0.08305	0.00031	-0.00546
0.2	0.08115	0.00037	-0.00524

m_H – molality of metformin hydrochloride/mol.kg^{-1}

In the present case the following equations (6) at four concentrations of metformin hydrochloride are obtained.

$V_\varphi^0 = 114.27 - 0.0697\ T + 0.00025\ T^2$ (for $m_H = 0.05$ mol.kg^{-1})

$V_\varphi^0 = 116.45 - 0.0806\ T + 0.00027\ T^2$ (for $m_H = 0.10$ mol.kg^{-1}) (6)

$V_\varphi^0 = 121.88 - 0.1121\ T + 0.00031\ T^2$ (for $m_H = 0.15$ mol.kg^{-1})

$V_\varphi^0 = 127.16 - 0.1432\ T + 0.00037\ T^2$ (for $m_H = 0.20$ mol.kg^{-1})

It is clear that the values of $\partial^2V_\varphi/\partial T^2$ are positive for all four concentrations of metformin hydrochloride (see Table4), indicating the structure-making ability of Phenylalanine in aqueous metformin hydrochloride solutions.[30,32]

The values of partial molal expansivity[32] have been calculated from the partial molal volume using the relation (5) and are included in table 4.

$E_2^0 = (\partial V_\varphi^0/\partial T)_P$ (7)

The values of partial molar expansivity E_2^0 are considered to be an important and sensitive indicator of solute-solvent interactions and the structure making or breaking properties of solute.[33] Positive values of E_2^0 (see table 4) indicate that the studied amino acid (L-Phenylalanine) is a structure maker in aqueous Metformin hydrochloride solvent.

The results of the partial molar volume V_φ^0 have been used for the calculation of the isobaric thermal expansion coefficient α_2 of drugs as follows:

$\alpha_2 = E_2^0 / V_\varphi^0$ (8)

Table 5. Isobaric Thermal Expansion Coefficient α_2 of L-Phenylalanine in aqueous Metformin Hydrochloride solutions at different temperatures.

	Isobaric Thermal Expansion Coefficient $\alpha_2 = (E_2^0 / V_\varphi^o) / K^{-1}$				
T/K	m_H = 0 (water)	m_H = 0.05	m_H = 0.10	m_H = 0.15	m_H = 0.20
	mol•kg−1	mol•kg−1	mol•kg−1	mol•kg−1	mol•kg−1
298.15	0.00098692	0.00075806	0.00072607	0.00071190	0.00069367
303.15	0.00098248	0.00075523	0.00072371	0.00070970	0.00069163
308.15	0.00097768	0.00075245	0.00072094	0.00070680	0.00068905
313.15	0.00097197	0.00074988	0.00071836	0.00070486	0.00068658
318.15	0.00096782	0.00074674	0.00071568	0.00070191	0.00068418

m_H – molality of metformin hydrochloride/mol.kg^{-1}.

The values of isobaric thermal expansion coefficient (α_2) for the system investigated (see table 5) are found to decrease with increase in temperature thereby showing the predominance of hydroxyl group interactions in the reported systems.

3.4 Hydration number

The information on hydration effect may be obtained by evaluating the electrostriction partial molal volume $V_\varphi^{0}{}_{(elec)}$ from the experimentally measured V_ϕ^0 values as,

$$V_\varphi^{0}{}_{(elec)} = V_\varphi^{0} - V_\varphi^{0}{}_{(int)} \quad (9)$$

Where $V_\varphi^{0}{}_{(int)}$, the intrinsic partial molal volume has been calculated (Millero et al 1978, Pal and Kumar 2005)[17, 34] using the following expressions,

$$V_\varphi^{0}{}_{(int)} = (0.7/0.634)^{x} V_\varphi^{0}{}_{(cryst)} \quad (10)$$

$$\text{Where } V_\varphi^{0}{}_{(cryst)} = (M/\rho_{(cryst)}) \quad (11)$$

M and ρ being molecular weight and density values of amino acids respectively. In eqn (10) 0.7 is the packing density for molecules in the organic crystal and 0.634 is the packing density for random packing spheres. The decrease in volume due to electrostriction can be related to the number of water molecules n_H hydrated to the amino acids and are estimated (Millero et al 1974, Zhao et al 2005)[8,32,34-36] using the relation given by,

$$n_H = V_\varphi^{0}{}_{(elec)} / (V_E^{o} - V_B^{o}) \quad (12)$$

Where V_E^0 is the molal volume of the electrostricted water and V_B^0 is the molal volume of bulk water at T = 308.15 K (Lark 2006).

$$(V_E^{o} - V_B^{o}) = -4\text{cm}^2.\text{ mol} \quad (13)$$

This value of (V_E^0 - V_B^0) has been retained at the other studied temperatures following the work of Lark et al (2006)[37] and the evaluated values of n_H are included in Table 3.

It is seen from Table 3 that the hydration number n_H of Phenylalanine in aqueous metformin hydrochloride decreases with increasing concentration of metformin hydrochloride and temperature, which again substantiates the predominance of solute-co-solute interactions. Further this establishes the fact that metformin hydrochloride has a dehydration effect on the amino acids.

3.5 Viscosity B coefficient and transfer B coefficient

In order to support the results obtained from the volumetric data, the viscosity data are obtained for all ternary solutions at the reported temperatures and are given in Table 1. The relative viscosities η_r of the amino acids in water and in co-solute solutions are calculated using the following equation,

$$\eta_r = \eta / \eta_0 \qquad (14)$$

Where η and η_0 are the viscosities of the solution and solvent, respectively. The relative viscosity data may be analyzed by means of the Jones-Dole equation.[38]

$$\eta_r = 1 + AC^{1/2} + BC \qquad (15)$$

Where C is the molar concentration (evaluated from molal concentration ‘m’ using standard relation), A is the Falkenhagen coefficient that accounts for solute- solute interaction. The Jones-Dole coefficient B is an empirical parameter that measures the structural modi-fication induced by solute-solvent interactions.[39] As the focal point of interest is to obtain infor-mation about solute-solvent interactions in ternary systems rather than solute-solute interactions, many researchers[40,41] used the relative viscosity data η_r in the modified equation,

$$\eta_r = 1 + BC \qquad (16)$$

Thus the measured relative viscosity is used to obtain information on B only (solute-solvent interactions)[8] rather than A (solute-solute), Eq. (16) in this study and the evaluated values of viscosity B-coefficient are summarized in Table 6.

Table 6. Viscosity B coefficient, B and transfer B coefficients, ΔB, Ratio of B coefficient to partial molal volume, B/V_φ^0, free energy of activation of solvent, $\Delta\mu_1^{0*}$ and free energy of activation of solute, $\Delta\mu_2^{0}$* for L-PhenylAlanine in aqueous Metformin Hydrochloride solutions at different temperatures.

	T/K						T/K				
Property	298.15	303.15	308.15	313.15	318.15		298.15	303.15	308.15	313.15	318.15
	L-PhenylAlanine in water						Literature values of L-PhenylAlanine in water [a] [22], [b] [42]				
$10^3.B/(m^3\cdot mol^{-1})$	0.583	0.528	0.497	0.457	0.425		0.580[a]	0.513[b]			
B/V_φ^0	4.79	4.32	4.04	3.70	3.42						
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.16	9.04	8.93	8.83	8.74						
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	103.35	97.087	93.982	89.461	85.91						
	L-PhenylAlanine in 0.05/m_H mol.kg^{-1}						L-PhenylAlanine in 0.10/m_H mol.kg^{-1}				
$10^3.B/(m^3\cdot mol^{-1})$	0.558	0.509	0.486	0.449	0.420		0.535	0.500	0.476	0.444	0.416
$\Delta B.10^3/(m^3\cdot mol^{-1})$	-0.025	-0.019	-0.011	-0.008	-0.005		-0.048	-0.028	-0.021	-0.013	-0.009
B/V_φ^0	4.80	4.36	4.15	3.82	3.56		4.59	4.28	4.06	3.77	3.52
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.23	9.10	8.99	8.88	8.78		9.27	9.15	9.04	8.92	8.83
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	98.725	93.236	91.192	87.038	83.903		95.185	91.600	89.411	85.969	82.979
	L-PhenylAlanine in 0.15/m_H mol.kg^{-1}						L-PhenylAlanine in 0.20/m_H mol.kg^{-1}				
$10^3.B/(m^3\cdot mol^{-1})$	0.525	0.487	0.467	0.438	0.413		0.517	0.480	0.460	0.432	0.410
$\Delta B.10^3/(m^3\cdot mol^{-1})$	-0.058	-0.041	-0.030	-0.019	-0.012		-0.066	-0.048	-0.037	-0.025	-0.015
B/V_φ^0	4.50	4.16	3.97	3.71	3.49		4.41	4.09	3.90	3.65	3.45
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.32	9.20	9.09	8.98	8.89		9.36	9.24	9.13	9.03	8.93
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	93.456	89.460	87.820	84.792	82.243		92.020	88.159	86.508	83.637	81.510

m_H – molality of metformin hydrochloride/mol.kg^{-1}.

The values of viscosity B-coefficient in literature for the amino acids in water are also given in Table 6 for comparison. The fair agreement between the reported values with the literature values further supplement our experimental procedures.

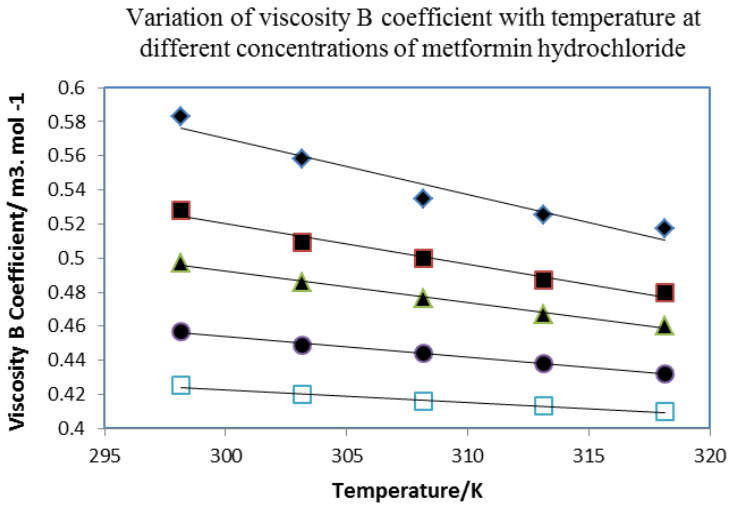


Figure 5. Representative plots of Viscosity B coefficient of Phenylalanine versus temperature in (water + metformin hydrochloride) solutions of (a) concentration 0.0 mol.kg^{-1} (◆), (b) concentration 0.05 mol.kg^{-1}(■), (c) concentration 0.10 mol.kg^{-1} (▲), (d) concentration 0.15 mol.kg^{-1} (●), (e) concentration 0.15 mol.kg^{-1} (□).

It is to be noted here that the viscosity B-coefficient is important for a number of reasons.[43] Its application in two research areas is interesting. First, viscosity B-coefficient provides information about the salvation of the solutes and their effects on the structure of solvent in the near environment of the solute molecules. Furthermore, some activation parameters of viscous flow may be obtained using viscosity B-coefficient.

The viscosity B-coefficients evaluated using equation (16) are shown in Table 6. Larger and positive B values of the reported systems (see table 6) indicate the structure making action (hydrophobic and hydrogen bonded actions) of the solute in the solutions.[44] However, many researchers prefer the temperature derivative of B Coefficient with temperature (dB/dT) to study the structure making/breaking property of the solute rather than using B values alone. As per the literature when dB/dT shows a negative value it indicates the structure making property of the solute and when dB/dT is positive, the solute has structure breaking property.[21,45] Thus the dB/dT values are calculated from figure 5 and are included in Table 4. It may be seen from Table 4 that (dB/dT) is negative for L- Phenylalanine in aqueous metformin hydrochloride showing the structure making ability of amino acids[7] complementing our volumetric results.

The B-coefficient data in aqueous metformin hydrochloride solutions have also been used to calculate the corresponding (ΔB) transfer function as follows:

$$\Delta B = B_{\text{in aq.-Metformin Hydrochloride}} - B_{\text{in water}} \qquad (17)$$

The ΔB values for L-phenylealanine as a function of molality of the solute at all the studied temperatures are given in table (6).

As per the co-sphere overlap model[46], a change in thermodynamic property is accomplished when the solute-cosolute particles come relatively close together, so that co-spheres overlap takesplace. In ternary systems (amino acid+metformin hydrochloride+water), the interactions can be classified into two types.[47]

Type I: Ion-charged/hydrophilic group interactions between ions of metformin hydrochloride ($C_4H_{11}N_5H^+$) and groups ($CH_3\ COO^-$) of amino acids.

Type II: Ion-hydrophobic group interactions between ions of metformin hydrochloride and non-polar parts of amino acids.

According to this model, the ion-charged/hydrophilic group interactions result in positive ΔB values, whereas ion-hydrophobic group interactions result in negative ΔB values.

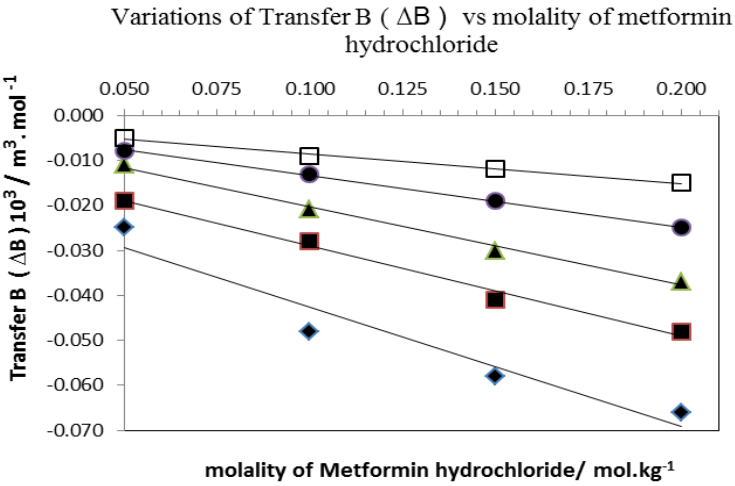


Figure 6. Variations of transfer B, ΔB vs molality of metformin hydrochloride for Phenylalanine in metformin hydrochloride solutions at temperatures T/K temperatures 298.15K(◆), 303.15K(■), 308.15K(▲), 313.15K(●) 318.15K (□).

Analysis of figure 6 shows that values of ΔB are negative and decreases with concentration and temperature in all cases. The nature of variation in ΔB may be attributed to the dominance of type (ii) i.e ion-hydrophobic interactions over the type (i) i.e ion charged/ hydrophilic interactions[48] thus validating our volumetric results.

Furthermore, the solvation of any solute can be gauged from the magnitude of B/V_φ^0 and are listed in table 6. A value between 0 and 2.5 indicates the unsolvated spherical species; and any higher value (>2.5) is an indication of solvated ones. In the present case, the values of B/V_φ^0 is > 2.5 substantiating the presence of solvated spherical species in the reported systems.[22]

3.6 Free energy of activation per mole of the solvent and solute

The free energy of activation per mole of the solvent ($\Delta\mu_1^{0*}$) and solute ($\Delta\mu_2^{0*}$) are evaluated using the viscosity B-coefficient by making use of the following equation given by transition state theory suggested by Feakins et al (1993)[49] and Eyring et al (1941).[50]

$$B = \frac{\left[(\bar{V}_1^{\,0} - \bar{V}_2^{\,0}) + \bar{V}_1^{\,0}(\Delta\mu_2^{0*} - \Delta\mu_1^{0*})/RT\right]}{1000} \tag{18}$$

The free energy of activation per mole of the solvent $\Delta\mu_1^{0*}$ is calculated by the following relation,

$$\Delta\mu_1^{0*} = RT\ln\left(\frac{\eta_0 \bar{V}_1^{\,0}}{hN_A}\right) \tag{19}$$

The free energy of activation per mole of the solute $\Delta\mu_2^{0*}$ is calculated by the following relation,

$$\Delta\mu_2^{0*} = \Delta\mu_1^{0*} + \left(\frac{RT}{\bar{V}_1^{\,0}}\right)\left[1000B - (\bar{V}_1^{\,0} - \bar{V}_2^{\,0})\right] \tag{20}$$

$\bar{V}_2^{\,0} = V_\phi^0$ is the partial molal volume of the solute. h is the Plancks constant, N_A is Avogadros number, η_0 is the viscosity of the solvent and R is the gas constant. The evaluated values of $\Delta\mu_1^{0*}$ and $\Delta\mu_2^{0*}$ are given in Table 6.

It is also seen from Table 6 that the values of $\Delta\mu_2^{0*}$ are positive and larger than $\Delta\mu_1^{0*}$ indicating the stronger solute cosolute interactions and structure making ability of the solute.[49] It is further seen from the table 6 that $\Delta\mu_2^{0*}$ decreases with increase in concentrations of metformin hydrochloride solutions and temperature. This suggests that the process of viscous flow becomes difficult as the temperature as well as molality increases. Hence, the formation of transition state becomes less favorable in Gibbs free energy terms and thus supplements our earlier findings by $\partial^2 V_\varphi^{\,0}/\partial T^2$ and d*B*/d*T* studies. In other words, the formation of the transition state is less favoured in the presence of the solute due to rupture and distortion of the intermolecular forces in the aqueous metformin hydrochloride solution.[51]

3.7 Pair and Triplet interaction coefficients

Thermodynamic transfer functions of amino acids may be expressed by the Mc Millan-Mayer theory of solutions[31,52,53] which permits the formal separation of the effects due to the interaction between the pairs of the solute molecules and those due to interactions between three or more molecules by the equations (21) and (22).

$$\Delta V_{\varphi}^{0}{}_{\text{(water to aqueous Metformin Hydrochloride solution)}} = 2\, V_{AB}\, m_H + 3\, V_{ABB}\, m_H^2 + \text{----} \qquad (21)$$

$$\Delta B_{\text{(water to aqueous Metformin Hydrochloride solution)}} = 2\, \eta_{AB}\, m_H + 3\, \eta_{ABB}\, m_H^2 + \text{----} \qquad (22)$$

Where A stands for Phenylalanine and B stands for metformin hydrochloride and m_B is the molality of metformin hydrochloride in water (cosolute). The constants V_{AB} / η_{AB}, V_{ABB} / η_{ABB} are pair and triplet volumetric/viscometric interaction parameters obtained by fitting data to equation (20) & (21). The evaluated parameters V_{AB} / η_{AB}, V_{ABB} / η_{ABB} for volumes and viscosities are summarized in Table 7.

Table 7. Values of pair (V_{AB}, η_{AB}) and triplet (V_{ABB}, η_{ABB}) of L-Phenylalanine in aqueous Metformin Hydrochloride solutions at different temperatures.

T/K	V_{AB} x10^6 / $m^3.mol^{-2}.kg$	V_{ABB} x10^6 / $m^3.mol^{-3}.kg^2$	10^3 η_{AB}/ $m^3.mol^{-2}.kg$	10^3 η_{ABB}/ $m^3.mol^{-3}.kg^2$
	From volume		From viscosity	
298.15	-62.484	187.408	-0.288	0.402
303.15	-63.804	190.257	-0.200	0.284
308.15	-65.680	195.916	-0.116	0.077
313.15	-69.249	205.954	-0.081	0.072
318.15	-69.69	206.69	-0.054	0.057

The positive values of V_{ABB}/η_{ABB} indicate that the triplet interactions are stronger than the doublet interactions V_{AB}/η_{AB} in the studied system.

4. CONCLUSIONS

Density and viscosity measurements have been reported for L-Phenylalanine in aqueous metformin hydrochloride solutions in this study. The partial molal volumes of L-Phenylalanine increases apparently with the molal concentrations of metformin hydrochloride solutions. The second derivative of V_{φ}^{0} with respect to temperature shows the structure making property of Phenylalanine in aqueous metformin hydrochloride solutions. Our volumetric studies concludes that metformin hydrochloride has a dehydration effect on the amino acids. The positive values of Hepler's constant that account for the structure−making behavior of L-phenylalanine in aqueous metformin hydrochloride solutions, are further

substantiated by Viscosity B-coefficient, their negative dB/dT values and free activation energy values.

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