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VISCOSITIES OF L - PROLINE AND L- THREONINE IN (0.05, 0.10, 0.15, AND 0.20) MOL·KG^{-1} AQUEOUS METFORMIN HYDROCHLORIDE SOLUTIONS AT DIFFERENT TEMPERATURES

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ABSTRACT
viscosity (η) measurements of amino acids L-Proline and L-Threonine in aqueous solutions of metformin hydrochloride (an antidiabetic drug) (0.05, 0.10, 0.15 and 0.20 mol·kg^{-1}) have been carried out in the concentration range (0.025−0.15 mol·kg^{-1}) at 298.15, 303.15, 308.15, 313.15 and 318.15 K. Viscosity B-coefficients of Jones-Dole equation, B- coefficients transfer (ΔB), temperature dependent of B- coefficient, free energy of activation per mole of solvent ($\Delta\mu_1^{0*}$) and solute ($\Delta\mu_2^{0*}$) are estimated using viscosity data. Our study concludes the existence of strong solute solvent interaction in the studied systems. Furthermore, structure making and breaking behaviour of both amino acids have also been assessed in aqueous metformin hydrochloride solutions. The thermodynamics of viscous flow has also been discussed.

KEYWORDS: L-proline, L-threonine, Metformin Hydrochloride, B- coefficients, Free energy of activation per mole of solvent ($\Delta\mu_1^{0*}$) and solute ($\Delta\mu_2^{0*}$).

INTRODUCTION
To understand the structure and function of proteins, it is essential to study the interactions responsible for stabilizing the native state of proteins in aqueous solutions. The study of these interactions provides an important insight into the conformational stability and unfolding behaviour of proteins. The study of these characteristics of proteins has proved quite challenging due to its complex structure and still remains a subject of extensive investigations.

The thermodynamic properties of a completely unfolded protein system can be estimated by adding together the thermodynamic property contributions of the small structural units that constitute its molecular sequence. Therefore, protein model compounds such as amino acids and peptides, which are basic components of proteins, have been investigated in detail with respect to their thermodynamic properties in aqueous and mixed aqueous solutions.[1-7] Recently, researchers have evoked a lot of interest on the model of proteins such as amino acids, peptides, amides and their derivatives.[8-13]

Amino acids are the building blocks of proteins which can be used for studies expected to set impact on the solvation and conformation of proteins and often regarded as the ideal model for the studies of proteins. The thermodynamic properties and transport properties of amino acids in a variety of media can provide valuable information for the stability and denaturation of proteins, which could promote the progresses of medicine(drugs) and human science.[14,15] Since the living organism is a complex system, it is of immense significance to study the thermodynamic properties of amino acids with functionally important biomolecule in aqueous drug solutions.[16,17]

Among the various thermodynamic properties, attempts have been made to study the interaction of amino acids and peptides in aqueous drug solutions[18] with viscometric properties as viscosity is an important parameter that affects the permeation of drug through biological membrane. The Viscosity B-coefficient is considered to be a measure of the effective hydrodynamic volume of the solvated ion/solute, and used to denote the order or disorder introduced by the ions or solute into the solvent structure.[19] Viscosity B

coefficient is a very good parameter to describe the kosmotropic and chaotropic nature of solute in different solvents which are obtained by Jones-Dole equation.[20]

As the amino acids and peptides in vivo are not involved in pure aqueous medium, their studies in various aqueous drug solutions will yield the thermodynamic transfer functions of amino acids and peptides from water to aqueous drug solutions. These transfer functions can be interpreted in terms of mutual interactions between amino acids/peptides and cosolute molecules.

There are extensive investigations of amino acids in aqueous and aqueous additive solutions, such as sugar, polyols and urea[21-24], but to our best knowledge, only limited reports are available (other than our work) on the viscometric properties of aminoacids in metformin hydrochloride aqueous solutions as discussed below.

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[25] and confirmed the structure promoting tendency of both the amino acids investigated through their volumetric and viscometric studies.

H Kumar et al[26] reported the interactions of L-serine and L-threonine with the drug metformin hydrochloride at low concentrations (0.03, 0.06 and 0.09 $mol.kg^{-1}$) as a function of temperature (305.15, 310.15 and 315.15K) through the volumetric and acoustic studies However, to the best of our knowledge, they have not reported the viscometric studies of L-threonine in aqueous metformin hydrochloride. In continuation of our earlier work on metformin hydrochloride with homologous amino acids such as glycine, L-leucine, L-alanine and L-valine[1, 27-30], in this paper, we report the viscometrtic studies of L-threonine and L-proline in aqueous metformin hydrochloride solutions of higher concentrations which are different from H kumar et al's work. As we feel that depending on the intensity of type 2 diabetes, higher dosage of metformin hydrochloride has to be used by the diabetic patients, it is reasonable to study and report the viscometric parameters at slightly higher concentrations of metformin hydrochloride in this paper. We further reported the viscometric properties of L-proline in the said concentrations of metformin hydrochloride for the first time in the literature. Metformin hydrochloride is an anti hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes,[31,32] lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral anti hyperglycemic agents. Metformin hydrochloride decreases both the hepatic glucose production and intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Chemical structure of L-threonine and L-proline are as shown in figure (1) and (2) respectively. L-proline is a non-essential or dispensable amino acid out of the 10 amino acids[33] which are used to synthesize proteins by the human body. This amino acid is encoded in the human genetic code with the codons CCA, CCC, CCG and CCU. L-proline is the only proteinogenic amino acid that is a secondary amine, meaning that its amine nitrogen is bound to two alkyl groups. Virtually all of the proteins in the human body contain L-proline. It is especially important in the production of collagen, which is a primary component in skin, cartilage and bone.

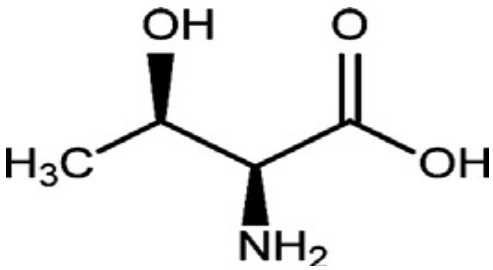

Figure (1)

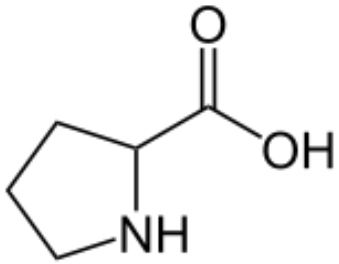

Figure (2)

L-threonine is a polar amino acid and one of the two proteinogenic amino acids that contain alcohol groups. L-threonine is an essential amino acid which is biologically active in humans, however, cannot be synthesized by the human body. It is primarily found in animal protein such as beef, poultry and fish. Dairy products also contain significant levels of L-threonine, especially cottage cheese. Vegetable sources of L-threonine include black beans, lentils and sesame seeds. L-threonine is often used to support the production of connective tissue. Additional benefits of L-threonine supplements include the support of bone and liver health as well as the immune system.

In this present study, we report the viscosity, η, of L-Proline and L-Threonine in aqueous Metformin Hydrochloride solutions at different temperatures T = (298.15, 303.15, 308.15, 313.15 and 318.15) K. Using the viscosity, η, data, the Jones-Dole viscosity B-coefficient, Temperature dependence of B- coefficient, B- coefficients transfer (ΔB), free energy of activation per mole of solvent ($\Delta\mu_1^{0*}$) and solute ($\Delta\mu_2^{0*}$) are estimated. Our study concludes the existence of strong solute solvent interaction in the studied systems. Furthermore, structure making and breaking behaviour of L-Proline and L-threonine have also been assessed in

aqueous Metformin Hydrochloride solutions. The thermodynamics of viscous flow has also been discussed.

MATERIALS AND METHODS

L-Proline (CAS no.147-85-3) with mass fraction of purity > 0.99 procured from SDFCL Pvt. Ltd., Mumbai, India and L-Threonine (CAS no. 80-68-2) purchased from NICE chemicals, Kerala, India have been used as such. Metformin-HCl with mass fraction purity > 0.985 purchased from Accumen Pharmaceuticals Pvt. Ltd., India has been 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 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-Proline and L-Threonine solutions of five different molal concentrations (ranging from 0.025 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 viscosity measurements have been carried out using a suspended Ubbelohde type viscometer, which has been calibrated with triply distilled water at five temperatures between 298.15 K and 318.15 K. A thoroughly cleaned and perfectly dried viscometer filled with the test solution has been placed vertically in the glass walled thermopath (EURO therm – INSCIN) maintained at a desired temperature (±0.01 K). A thermostatted water bath used for measurements of viscosity values has been maintained at a particular temperature for about 30 min prior to recording of readings at each temperature of study. After attainment of thermal equilibrium, efflux times of flow have been recorded with an electronic watch with the resolution 0.01 s. The average of at least four readings reproducible within 0.1 s has been used as final efflux time**.** The viscosity of a solution η, is calculated by using the following expression.[34]

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

Where ρ is the density of the solution, t is the flow time, and L and K are the viscometer constants obtained by measuring the flow time for water at five different temperatures.

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 glass cap. A standard microscope is used to calibrate the volume of solution in the pycnometer. The calibrated standard values have been used to calculate the volume of the solution and its density. The reproducibility of density measurements has been ± 2.5 $\times 10^{-4}$ $kg\cdot m^{-3}$. The viscosity values of water at different temperatures have been taken from the literature for calibration purpose.[35] Our experimental values of viscosity measured at different temperatures have been compared with the literature values.

For instance, the measured values of the viscosity of water have been found to be 10^3 η/Pa.s = 0.8900, 0.7967, 0.7189, 0.6521, 0.5958 at T = (298.15, 303.15, 308.15, 313.15 and 318.15) K, respectively in comparison to the corresponding literature values[40] of 10^3 η/Pa.s = 0.8902, 0.7973, 0.7191, 0.6527, 0.5961. The uncertainties in viscosity measurements have been found to be within ±0.001 mPa .s. A close agreement with literature values substantiates our experimental procedure.

RESULTS AND DISCUSSIONS

The experimental densities and viscosities L-proline and L-threonine in (0.05, 0.10, 0.15 and 0.20) mol. Kg^{-1} aqueous metformin hydrochloride the solutions at 298.15, 303.15, 308.15, 313.15 and 318.15 K are shown in Table 1 and Table 2.

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

M	ρ/kg·m^{-3}					η/m Pa s				
mol·kg^{-1}[b]	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
	L-proline+0.05 mol·kg^{-1} $m_{Mfm\text{-}HCl}$[c]									
0	0.99889	0.99746	0.99583	0.99399	0.99201	0.9086	0.8111	0.7303	0.6611	0.6026
0.025	0.99962	0.99822	0.99660	0.99477	0.99280	0.9159	0.8167	0.7346	0.6644	0.6046
0.05	1.00038	0.99900	0.99738	0.99557	0.99360	0.9223	0.8224	0.7395	0.6689	0.6093
0.075	1.00117	0.99979	0.99819	0.99638	0.99443	0.9285	0.8281	0.7448	0.6734	0.6134
0.1	1.00198	1.00061	0.99902	0.99722	0.99526	0.9369	0.8350	0.7510	0.6790	0.6181
0.125	1.00279	1.00144	0.99985	0.99807	0.99613	0.9440	0.8416	0.7567	0.6842	0.6227
	L-proline+0.10 mol·kg^{-1} $m_{Mfm\text{-}HCl}$[c]									
0	1.00077	0.99932	0.99767	0.99582	0.99383	0.9206	0.8222	0.7407	0.6697	0.6109
0.025	1.00149	1.00007	0.99841	0.99659	0.99466	0.9288	0.8287	0.7456	0.6736	0.6134
0.05	1.00224	1.00084	0.99919	0.99737	0.99546	0.9367	0.8357	0.7521	0.6791	0.6184
0.075	1.00302	1.00163	0.99999	0.99818	0.99627	0.9450	0.8428	0.7583	0.6844	0.6225
0.1	1.00382	1.00243	1.00081	0.99902	0.99712	0.9502	0.8477	0.7624	0.6886	0.6267
0.125	1.00462	1.00326	1.00161	0.99983	0.99796	0.9572	0.8538	0.7680	0.6935	0.6313

	L-proline+0.15 mol·kg^{-1} $m_{Mfm\text{-}HCl}$ [c]									
0	1.00266	1.00121	0.99956	0.99769	0.99569	0.9319	0.8335	0.7513	0.6804	0.6207
0.025	1.00337	1.00194	1.00030	0.99845	0.99647	0.9411	0.8410	0.7568	0.6847	0.6243
0.05	1.00412	1.00270	1.00107	0.99922	0.99726	0.9477	0.8465	0.7622	0.6895	0.6288
0.075	1.00489	1.00348	1.00185	1.00002	0.99806	0.9559	0.8539	0.7679	0.6946	0.6330
0.1	1.00566	1.00427	1.00265	1.00084	0.99891	0.9622	0.8601	0.7731	0.6991	0.6371
0.125	1.00648	1.00509	1.00346	1.00167	0.99975	0.9686	0.8649	0.7788	0.7041	0.6418
	L-proline+0.20 mol·kg^{-1} $m_{Mfm\text{-}HCl}$ [c]									
0	1.00460	1.00312	1.00146	0.99959	0.99760	0.9439	0.8437	0.7606	0.6890	0.6291
0.025	1.00530	1.00384	1.00219	1.00033	0.99837	0.9548	0.8527	0.7678	0.6947	0.6337
0.05	1.00603	1.00458	1.00294	1.00110	0.99916	0.9628	0.8595	0.7737	0.6998	0.6380
0.075	1.00677	1.00535	1.00371	1.00189	0.99997	0.9684	0.8644	0.7781	0.7039	0.6418
0.1	1.00757	1.00614	1.00451	1.00267	1.00079	0.9754	0.8709	0.7838	0.7089	0.6461
0.125	1.00839	1.00695	1.00532	1.00350	1.00162	0.9829	0.8770	0.7895	0.7140	0.6506

M – molality of Amino acids $m_{Mfm\text{-}HCl}$ - molal concentrations of metformin hydrochloride.

It is further seen from Table 1 and Table 2, that viscosity values increase with increase in concentration of metformin hydrochloride. Generally, when a solute is dissolved in a solvent some of the solvent molecules are attracted to the solute as the result of solute-solvent interaction and thus increase the solution viscosity. Thus, the increase in viscosity of the solution on addition of solute indicates the structure-making aspects of solutes.[36]

The relative viscosities η_r of the amino acids in water and in co-solute solutions are calculated using the following equation,

$$\eta_r = \eta / \eta_0 \qquad (2)$$

Where η and η_0 are the viscosities of the solution (water+MfmHcl+amino acids) and solvent(water+ MfmHcl), respectively.

The relative viscosity values (shown in the table 3) of the solutions decrease with an increase in temperature. The increase in temperature may have caused the increase in the kinetic energy of molecules and ions present in the solution, which in turn, decreases, the solute-solvent interactions.[37]

Table 2: Density and viscosity values of L-Threonine in aqueous Metformin Hydrochloride at different temperatures.

M	**ρ/kg·m^{-3}**					**η/m Pa s**				
mol·kg^{-1} [b]	**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**
	L-threonine+0.05 mol·kg^{-1} $m_{Mfm\text{-}HCl}$									
0	0.99889	0.99746	0.99583	0.99399	0.99201	0.9086	0.8111	0.7303	0.6611	0.6026
0.05	1.00098	0.99955	0.99790	0.99605	0.99405	0.9266	0.8257	0.7426	0.6715	0.6118
0.075	1.00201	1.00057	0.99892	0.99706	0.99506	0.9340	0.8331	0.7492	0.6775	0.6170
0.1	1.00303	1.00159	0.99994	0.99807	0.99607	0.9425	0.8408	0.7550	0.6827	0.6215
0.125	1.00404	1.00260	1.00094	0.99907	0.99707	0.9511	0.8476	0.7622	0.6885	0.6265
0.15	1.00504	1.00360	1.00194	1.00006	0.99804	0.9601	0.8542	0.7671	0.6927	0.6304
	L-threonine+0.10 mol·kg^{-1} $m_{Mfm\text{-}HCl}$									
0	1.00077	0.99932	0.99767	0.99582	0.99383	0.9206	0.8222	0.7407	0.6697	0.6109
0.05	1.00281	1.00135	0.99969	0.99783	0.99583	0.9376	0.8369	0.7532	0.6809	0.6206
0.075	1.00380	1.00235	1.00069	0.99882	0.99681	0.9484	0.8463	0.7619	0.6868	0.6261
0.1	1.00480	1.00334	1.00168	0.99980	0.99779	0.9564	0.8523	0.7667	0.6925	0.6310
0.125	1.00578	1.00432	1.00266	1.00077	0.99876	0.9653	0.8613	0.7747	0.6988	0.6366
0.15	1.00675	1.00529	1.00362	1.00174	0.99972	0.9735	0.8672	0.7795	0.7031	0.6401
	L-threonine+0.15 mol·kg^{-1} $m_{Mfm\text{-}HCl}$									
0	1.00266	1.00121	0.99956	0.99769	0.99569	0.9319	0.8335	0.7513	0.6804	0.6207
0.05	1.00465	1.00319	1.00153	0.99965	0.99764	0.95050	0.84963	0.7646	0.6918	0.6308
0.075	1.00563	1.00416	1.00250	1.00062	0.99860	0.96065	0.85806	0.7727	0.6993	0.6368
0.1	1.00659	1.00512	1.00346	1.00157	0.99955	0.96917	0.86451	0.7785	0.7037	0.6412
0.125	1.00755	1.00608	1.00441	1.00252	1.00049	0.97929	0.87485	0.7866	0.7110	0.6474
0.15	1.00850	1.00703	1.00536	1.00346	1.00143	0.98740	0.88068	0.7919	0.7156	0.6515
	L-threonine+0.20 mol·kg^{-1} $m_{Mfm\text{-}HCl}$									
0	1.00460	1.00312	1.00146	0.99959	0.99760	0.9439	0.8437	0.7606	0.6890	0.6291

0.05	1.00654	1.00505	1.00338	1.00150	0.99950	0.9646	0.8614	0.7758	0.7024	0.6408
0.075	1.00749	1.00600	1.00433	1.00244	1.00044	0.9734	0.8692	0.7829	0.7084	0.6459
0.1	1.00843	1.00694	1.00527	1.00338	1.00137	0.9825	0.8769	0.7895	0.7140	0.6510
0.125	1.00936	1.00786	1.00620	1.00429	1.00229	0.9941	0.8867	0.7983	0.7217	0.6575
0.15	1.01028	1.00878	1.00711	1.00521	1.00320	1.0031	0.8944	0.8045	0.7272	0.6626

M – molality of Amino acids $m_{Mfm\text{-}HCl}$ - Concentrations of metformin hydrochloride.

Jone-Dole equation may be used to analyze the relative viscosity data using the relation.

$$\eta_r = 1 + AC^{1/2} + BC \quad (3)$$

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 viscosity *B*-coefficient originally introduced as an empirical term, has been found to depend upon solute-solvent interactions and on the relative size of the solute and solvent molecules.[38]

Table 3: Relative viscosity values of L-Proline and L-Threonine in aqueous Metformin Hydrochloride at different temperatures.

M	**Relative Viscosity (η_r) of L-Proline in aqueous metformin hydrochloride solutions**									
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**
	$m_{Mfm\text{-}HCl}$/mol·kg^{-1} = 0.05 / 0.10									
0.025	1.0080	1.0069	1.0060	1.0050	1.0032	1.0089	1.0079	1.0067	1.0059	1.0041
0.05	1.0150	1.0140	1.0127	1.0118	1.0110	1.0175	1.0164	1.0154	1.0140	1.0124
0.075	1.0219	1.0210	1.0199	1.0187	1.0179	1.0265	1.0250	1.0238	1.0220	1.0190
0.1	1.0311	1.0295	1.0284	1.0272	1.0256	1.0321	1.0310	1.0294	1.0283	1.0260
0.125	1.0389	1.0376	1.0362	1.0350	1.0333	1.0397	1.0384	1.0369	1.0355	1.0335
	$m_{Mfm\text{-}HCl}$/mol·kg^{-1} = 0.15 / 0.20									
0.025	1.0099	1.0089	1.0073	1.0063	1.0057	1.0116	1.0106	1.0095	1.0083	1.0074
0.05	1.0170	1.0156	1.0145	1.0134	1.0130	1.0200	1.0187	1.0172	1.0157	1.0141
0.075	1.0258	1.0245	1.0220	1.0208	1.0198	1.0260	1.0245	1.0231	1.0216	1.0202
0.1	1.0326	1.0319	1.0290	1.0275	1.0264	1.0334	1.0322	1.0305	1.0289	1.0271
0.125	1.0394	1.0377	1.0365	1.0348	1.0339	1.0413	1.0395	1.0380	1.0363	1.0342
M	Relative Viscosity (η_r) of L-Threonine in aqueous metformin hydrochloride solutions									
mol·kg^{-1b}	$m_{Mfm\text{-}HCl}$/mol·kg^{-1} = 0.05 / 0.10									
0.05	1.0198	1.0180	1.0169	1.0158	1.0152	1.0185	1.0178	1.0169	1.0167	1.0160
0.075	1.0279	1.0272	1.0260	1.0249	1.0239	1.0302	1.0293	1.0287	1.0256	1.0249
0.1	1.0373	1.0367	1.0339	1.0328	1.0312	1.0389	1.0365	1.0351	1.0340	1.0329
0.125	1.0467	1.0450	1.0437	1.0415	1.0395	1.0485	1.0475	1.0460	1.0435	1.0421
0.15	1.0566	1.0532	1.0505	1.0479	1.0460	1.0574	1.0547	1.0524	1.0499	1.0478
	$m_{Mfm\text{-}HCl}$/mol·kg^{-1} = 0.15 / 0.20									
0.05	1.0200	1.0193	1.0177	1.0168	1.0162	1.0219	1.0209	1.0200	1.0194	1.0186
0.075	1.0309	1.0295	1.0284	1.0278	1.0259	1.0313	1.0302	1.0294	1.0281	1.0268
0.1	1.0400	1.0372	1.0362	1.0343	1.0329	1.0409	1.0393	1.0380	1.0363	1.0349
0.125	1.0509	1.0496	1.0470	1.0450	1.0429	1.0532	1.0510	1.0496	1.0474	1.0451
0.15	1.0596	1.0566	1.0540	1.0518	1.0495	1.0627	1.0601	1.0578	1.0555	1.0533

To obtain information about solute-solvent interactions in ternary systems rather than solute-solute interactions, many researchers[39-41] used the relative viscosity data η_r in the modified equation,

$$\eta_r = 1 + BC \quad (4)$$

Thus the measured relative viscosity is used to obtain information on B only (solute-solvent interactions) rather than A (solute-solute). The above Eq. (4) is used in this study and the evaluated values of viscosity B-coefficient are summarized in Table 4 and 5 which shows that the values of viscosity B coefficients are positive for both L-proline as well as L-threonine in all concentrations of metformin hydrochloride at all temperatures.Larger and positive *B* values indicates structure making tendency of (hydrophobic and hydrogen bonded actions) L-proline and L-threonine with metformin hydrochloride.[39]

Table 4: 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, $\Delta\mu_1^{0*}$, free energy of activation of solute, $\Delta\mu_2^{0*}$ for L-Proline 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-Proline in water						Literature values of L-Proline in water [a] [42][a], [43][b], [44][c]				
$10^3.B/(m^3\cdot mol^{-1})$	0.268	0.284	0.297	0.308	0.314		0.268[a]		0.296[b]		0.321[c]
$\bar{V}^0_1\cdot10^6\ (m^3\cdot mol^{-1})$	18.07	18.09	18.12	18.16	18.19						
$\bar{V}^0_2.\ 10^6\ (m^3\cdot mol^{-1})$	82.421	82.854	83.286	83.624	83.997						
B/V_φ^0	3.25	3.43	3.56	3.68	3.74						
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.16	9.04	8.93	8.83	8.74						
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	54.77	57.62	60.07	62.40	63.96						
	L-Proline in 0.05 / 0.10 m_p /($mol\cdot kg^{-1}$) aqueous Metformin Hydrochloride										
$10^3.B/(m^3\cdot mol^{-1})$	0.316	0.312	0.309	0.307	0.305		0.309	0.306	0.302	0.299	0.295
$\Delta B.10^3/(m^3\cdot mol^{-1})$	0.048	0.028	0.013	-0.0010	-0.009		0.040	0.022	0.006	-0.009	-0.019
$\bar{V}^0_1\cdot10^6\ (m^3\cdot mol^{-1})$	18.17	18.19	18.22	18.26	18.29		18.27	18.29	18.32	18.36	18.39
$\bar{V}^0_2.\ 10^6\ (m^3\cdot mol^{-1})$	86.347	85.344	84.858	84.485	84.233		86.724	85.691	85.264	84.877	84.419
B/V_φ^0	3.67	3.66	3.65	3.64	3.62		3.58	3.57	3.54	3.52	3.49
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.23	9.10	8.99	8.88	8.78		9.27	9.15	9.04	8.92	8.83
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	61.62	61.65	61.85	62.12	62.46		60.43	60.64	60.65	60.75	60.80
	L-Proline in 0.15/0.20 mMfm HCl /($mol\cdot kg^{-1}$) aqueous Metformin Hydrochloride										
$10^3.B/(m^3\cdot mol^{-1})$	0.301	0.299	0.295	0.289	0.284		0.293	0.288	0.284	0.280	0.270
$\Delta B.10^3/(m^3\cdot mol^{-1})$	0.033	0.015	-0.001	-0.019	-0.030		0.025	0.004	-0.012	-0.028	-0.044
$\bar{V}^0_1\cdot10^6\ (m^3\cdot mol^{-1})$	18.36	18.39	18.42	18.46	18.49		18.46	18.49	18.52	18.55	18.59
$\bar{V}^0_2.\ 10^6\ (m^3\cdot mol^{-1})$	87.096	86.187	85.841	85.314	84.596		87.470	86.641	86.292	85.835	84.757
B/V_φ^0	3.47	3.46	3.44	3.38	3.35		3.35	3.32	3.30	3.27	3.18
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.32	9.20	9.09	8.98	8.89		9.36	9.24	9.13	9.03	8.93
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	59.28	59.43	59.55	59.17	58.95		58.02	57.76	57.84	57.82	56.81

Table 5: 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, $\Delta\mu_1^{0*}$, free energy of activation of solute, $\Delta\mu_2^{0*}$ for L-Threonine 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-Threonine in water						Literature values of L-Threonine in water [39][a], [45][b], [46][c]				
$10^3.B/(m^3\cdot mol^{-1})$	0.344	0.329	0.317	0.302	0.289		0.342[a]		0.315[b]	0.296[c]	0.284[c]
$\bar{V}^0_1\cdot10^6\ (m^3\cdot mol^{-1})$	18.07	18.09	18.12	18.16	18.19						
$\bar{V}^0_2.\ 10^6\ (m^3\cdot mol^{-1})$	75.668	76.066	76.401	76.768	77.145						
B/V_φ^0	4.55	4.33	4.15	3.93	3.75						
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.16	9.04	8.93	8.83	8.74						
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	64.26	62.95	61.98	60.54	59.33						
	L-Threonine in 0.05 / 0.10 m_p /($mol\cdot kg^{-1}$) aqueous Metformin Hydrochloride										
$10^3.B/(m^3\cdot mol^{-1})$	0.376	0.359	0.346	0.330	0.316		0.390	0.374	0.360	0.344	0.330
$\Delta B.10^3/(m^3\cdot mol^{-1})$	0.032	0.030	0.029	0.028	0.027		0.046	0.045	0.043	0.042	0.041
$\bar{V}^0_1\cdot10^6\ (m^3\cdot mol^{-1})$	18.17	18.19	18.22	18.26	18.29		18.27	18.29	18.32	18.36	18.39
$\bar{V}^0_2.\ 10^6\ (m^3\cdot mol^{-1})$	76.884	77.207	77.492	77.828	78.160		77.949	78.267	78.469	78.797	79.111
B/V_φ^0	4.89	4.65	4.47	4.24	4.05		5.01	4.78	4.59	4.37	4.17
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.23	9.10	8.99	8.88	8.78		9.27	9.15	9.04	8.92	8.83
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	68.50	67.04	66.02	64.47	63.16		70.33	68.96	67.76	66.29	65.02
	L-Threonine in 0.15/0.20 mMfm HCl /($mol\cdot kg^{-1}$) aqueous Metformin Hydrochloride										
$10^3.B/(m^3\cdot mol^{-1})$	0.402	0.384	0.371	0.355	0.341		0.419	0.402	0.389	0.372	0.358
$\Delta B.10^3/(m^3\cdot mol^{-1})$	0.058	0.055	0.054	0.053	0.052		0.075	0.073	0.072	0.070	0.069
$\bar{V}^0_1\cdot10^6\ (m^3\cdot mol^{-1})$	18.36	18.39	18.42	18.46	18.49		18.46	18.49	18.52	18.55	18.59
$\bar{V}^0_2.\ 10^6\ (m^3\cdot mol^{-1})$	78.870	79.132	79.382	79.665	79.976		79.752	80.061	80.192	80.524	80.808
B/V_φ^0	5.10	4.86	4.67	4.46	4.27		5.25	5.02	4.85	4.62	4.42
$\Delta\mu_1^{0*}/(kJ\cdot mol^{-1})$	9.32	9.20	9.09	8.98	8.89		9.36	9.24	9.13	9.03	8.93
$\Delta\mu_2^{0*}/(kJ\cdot mol^{-1})$	71.76	70.19	69.15	67.74	66.50		73.83	72.44	71.47	69.94	68.66

It is observed from the tables 4 and 5 that values of B – coefficients are higher for L-threonine than L-proline which means L-threonine has a greater kosmotropic effect than L-proline in metformin hydrochloride solutions. It is also observed from the tables 4 and 5 that the magnitude of B – coefficients for both the amino acids decreases with the increase in temperature. The sign of derivative of B-coefficient with the temperature, that is dB/dT will give the structure making/breaking ability of the solute in the ternary solutions.[38,47,48] Generally, the negative dB/dT values indicates structure-making ability of solute, while positive dB/dT values indicate structure-breaker characteristics of the solute. In the present case (see figure 3) for both the amino acids, the values of dB/dT are negative thus indicating the structure making ability of solutes.

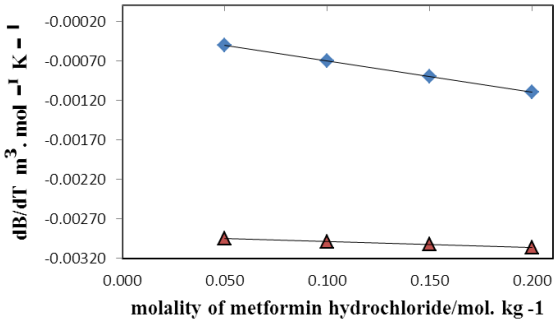

Figure: 3 The ratio of B with the temperature (dB/dT) Vs molality of metformin hydrochloride.

The values of L-proline in aqueous metformin hydrochloride solutions at different molalities shown with (◆) and the values of L- threonine in aqueous metformin hydrochloride solutions at different molalities shown with (▲).

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

$$\Delta B = B_{\text{in aq.-Metformin Hydrochloride}} - B_{\text{in water}} \quad (5)$$

The ΔB values for L-proline and L-threonine as a function of molality of the solute at all the studied temperatures are given in tables 4 and 5.

As per the co-sphere overlap model[49], a change in thermodynamic property is accomplished when the solute particles come relatively close together, so that co-spheres overlap takesplace and hence some co-sphere material is displaced. In ternary systems (amino acid+metformin hydrochloride+water), the interactions can be classified into two types.[50]

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. Similar conclusions have been drawn by banipal et al[50] for the amino acids L-serine and L-threonine in aqueous solutions of sodium acetate and magnesium acetate. In the present systems studied, for L-threonine, as ΔB values (shown in table 5) are observed to be positive, the type I interactions are stronger than the type II interactions. However in the case of L-proline while type I dominate at lower temperatures (298.15, 303.15, 308.15K), type II interactions seems to dominate over type I at higher temperatures (313.15 and 318.15K).

The solvation of any solute can be judged from the magnitude of B / V_φ^0.[42] The B / V_φ^0 values are calculated for both the amino acids in aqueous metformin hydrochloride solutions and shown in tables 3 & 4. It is observed from both the tables that B / V_φ^0 values of L-proline and L-threonine studied are greater than 2.5 and hence they are highly solvated.

The viscosity data are used to estimate the free energy of activation per mole of solvent ($\Delta\mu_1^{0*}$) and solute ($\Delta\mu_2^{0*}$) as suggested by Feakins et al[51] and Eyring et al[52] using the following equations,

$$B = \frac{\left[(\bar{V}_1^0 - \bar{V}_2^0) + \bar{V}_1^0(\Delta\mu_2^{0*} - \Delta\mu_1^{0*})/RT\right]}{1000} \quad (6)$$

Where $\bar{V}^0_1$ and $\bar{V}^0_2$ are the mean volume of the solvent and partial molar volumes of the solute at infinite dilution. The free energy of activation per mole of the solvent $\Delta\mu_1^{0*}$ is calculated by the following relation,

$$\Delta\mu_1^{0*} = RT \ln\left(\frac{\eta_0 \bar{V}_1^0}{hN_A}\right) \quad (7)$$

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

$$\Delta\mu_2^{0*} = \Delta\mu_1^{0*} + \left(\frac{RT}{\bar{V}_1^0}\right)\left[1000B - (\bar{V}_1^0 - \bar{V}_2^0)\right] \quad (8)$$

h is the planck's constant, N_A Avogadros number, η_0 is the viscosity of the solvent and R is the gas constant.

The calculated values of $\bar{V}^0_1$, $\bar{V}^0_2$, $\Delta\mu_1^{0*}$, $\Delta\mu_2^{0*}$, for both the amino acids in metformin hydrochloride solutions are given in the tables 4 and 5. In tables 4 and 5, the values of $\Delta\mu_2^{0*}$ are positive and larger than $\Delta\mu_1^{0*}$, indicating the structure making ability of both L-proline and L-threonine in aqueous metformin hydrochloride solutions, supplementing the findings through viscosity B – coefficient and dB/dT studies. Further, higher values of $\Delta\mu_2^{0*}$ shows the presence of stronger ion-solvent interactions[47] and suggests that the formation of

transition state is less favoured due to simultaneous breaking of intermolecular bonding in solvent molecules in the presence of amino acids.

Thermodynamic transfer functions of amino acids may be expressed by the Mc Millan-Mayer theory of solutions[53,54,55] 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 (9).

$$\Delta B_{tr\ (water\ to\ aqueous\ Metformin\ Hydrochloride\ \ solution)} = 2\,\eta_{AB}\,m_B + 3\,\eta_{ABB}\,m_B^{\,2} + \text{----} \quad (9)$$

Where A stands for Amino acid (L-proline /L- threonine) and B stands for metformin hydrochloride and m_B is the molality of metformin hydrochloride in water (co-solute). The constants η_{AB}, η_{ABB} are pair and triplet viscometric interaction parameters obtained by fitting data to equation (9). The evaluated parameters η_{AB}, η_{ABB} for viscosities are summarized in table 6.

Table 6. Values of pair (η_{AB}) and triplet (η_{ABB}) of L-proline and L-threonine in aqueous metformin hydrochloride solution at different temperatures.

T/K	$10^3\,\eta_{AB}$/ $m^3.mol^{-2}.kg$	$10^3\,\eta_{ABB}$/ $m^3.mol^{-3}.kg^2$	$10^3\,\eta_{AB}$/ $m^3.mol^{-2}.kg$	$10^3\,\eta_{ABB}$/ $m^3.mol^{-3}.kg^2$
	For L-proline		For L-threonine	
298.15	0.547	-1.777	0.339	-0.570
303.15	0.333	-1.175	0.324	-0.533
308.15	0.157	-0.677	0.311	-0.503
313.15	0.002	-0.263	0.300	-0.474
318.15	-0.080	-0.096	0.290	-0.448

From the table 6 it is seen that η_{AB} values are positive while η_{ABB} values are negative for both L-proline and L-threonine. The larger positive η_{AB} in comparison to η_{ABB} shows that the interactions between both the amino acids and metformin hydrochloride are mainly pair wise interactions due to the overlap of hydration spheres of solute and co-solute molecules.

CONCLUSION

Viscosity measurements have been reported for L-proline and L-threonine in aqueous metformin hydrochloride solutions in this study. The change in viscosity B coefficient with temperature i.e. (dB/dT) for both L-proline and L-threonine observed to be negative and proves the presence of structure making ability of solute in the solution. It is also observed that the values of η_{AB} and η_{ABB} predicts pair wise interactions between both the amino acids and aqueous solution of metformin hydrochloride. Furthermore, the solute−solvent interactions seem to be more effective in the presence of L-threonine as reflected by its higher B-coefficients compared to those in L-proline.

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