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VOLUMETRIC AND ULTRAACOUSTIC APPROACH TO INTERACTION OF SODIUM SALICYLATE AND 4-AMINOANTIPYRINE DRUGS IN AQUEOUS GLYCINE/L-PROLINE SOLUTION AT DIFFERENT TEMPERATURES

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ABSTRACT

Major drugs are small organic molecules with the purpose to inhibit and activate the function of biomolecules such as lipids, carbohydrates and proteins. Drug design and development process involves the design of molecules to facilitate the drug mechanism and their action. Studies of thermophysical and biological properties play a vital role to understand the pattern of molecular interactions of drug with the biomolecules. Present article, reports the density, ultrasonic velocity and refractive index of sodium salicylate and 4-aminoantipyrine in aqueous solution of glycine/L-proline at T = (303.15, 308.15 and 313.15) K and atmospheric pressure. Apparent molar properties such as apparent molar volume ($V_{2,\phi}$) and apparent molar compressibility ($\kappa_{S,2,\phi}$) have been calculated from ρ, u and n data. The standard partial molar volumes ($V^{o}_{2,\phi}$) and compressibilities ($\kappa^{0}_{S,2,\phi}$) of solute in aqueous glycine/L-proline solution have also been obtained by extrapolating the plots. These properties have been interpreted in terms of hydration behaviour and solute-solute/solute-solvent interactions of sodium salicylate and 4-aminoantipyrine drugs in studied solution.

KEYWORDS: Molecular interaction, NSAID, Amino acid, Aqueous solution, Thermodynamic properties.

1. INTRODUCTION

Molecular interactions between drugs and significant biopolymer components i.e. proteins, lipids and sugars are the important phenomenon and complex mechanism as for as biological and physiochemical point of view.[1] Drug-biomolecules interactions give an idea about drug actions i.e. drug reaching to the blood stream, its extent of distribution, its binding to receptor and produce physiological action.[2] These interactions are of different types may includes ion-dipole, ionic bonding, covalent bonding, charge transfer, hydrophobic interactions, metal complexation, cation-π interaction and hydrogen bonding[3-5] which are useful for understanding the pharmacokinetics and pharmacodynamics of drugs. Drug molecule affects the folding/unfolding behaviour, stability and solubility of proteins due to their different types of molecular interactions.[6] Drug-protein interactions plays a key role in many biological and chemical processes and the way organic molecules/drug molecule interact with the protein is vital process to drug formulation, screening, development and protein engineering application.[7-8]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most clinical significant medicine which are used to treatment of inflammation associated diseases such as anti-inflammatory, analgesic, antipyretic, asthma, arthritis and cardiovascular disease.[9-10] Ampyrone/4-aminoantipyrine and sodium salicylate drugs are the class of NSAIDs. Anti-inflammatory, analgesic and antipyretic, anthelmintic activity and anticonvulsive properties are shown by 4-aminoantipyrine and its derivatives.[11-13] Sodium salicylate inhibits the activity of both type of cyclooxygenase-1 (COX-1) and cyclooxygenase-1 (COX-2) and prostaglandin production.[14]

In biophysical chemistry, drug-protein interaction is an important biochemical process having complex mechanism.[15] Due to complex three-dimensional structure of proteins includes multiple functional groups; direct study of drug action with protein is difficult[16], therefore, investigation of thermodynamic solution behavior of drugs in aqueous solution of amino acids as a basic unit of peptides/proteins. Thermodynamic techniques are important tools to better understanding the molecular interactions and solution behaviour of drug in binary/ternary solution.

Thermophysical properties of drugs in aqueous amino acids solutions will be helpful for obtaining important information regard with different types of molecular interactions occurs

in these solutions. These interactions give an idea about drugs behaviour in solutions and folding/unfolding state of proteins. S. P. Zodape et al[17] have studied acoustic and volumetric properties procainamide·HCl in aqueous solutions of L-alanine/L-valine. Density and ultrasonic velocity of streptomycin sulphate in aqueous solutions of L- asparagine acid/L-glutamine have measured by J. Gupta and A. K. Nain.[18] Ultraacoustic and volumetric properties of derivatives of 4-amino antipyrene in 1,4-dioxane/DMF have evaluated by S. Baluja and A. Shah.[19] S. D. Deosarkar et al[20] have carried out the thermodynamic properties of ibuprofen/diclofenac drugs in aqueous solutions of β-cyclodextrin. Furthermore, there are extensive ultraacoustic and volumetric properties of biologically active drug molecules in aqueous solution[21] and also different aqueous media; hydrotropic agents[22], carbohydrates[23], β-cyclodextrin[24], salt[25] and organic solvent[26] have been carried out earlier, but still the data on thermodynamic properties of 4-aminoantipyrene and sodium salicylate in aqueous solution of amino acids are lack.

To the best of our knowledge, there is no data on thermodynamic behaviour of sodium salicylate and 4-aminoantipyrine drugs in aqueous amino acid solutions have been reported until now. This promoted us to estimate the interactions of nonsteroidal anti-inflammatory sodium salicylate and 4-aminoantipyrene drugs in aqueous solutions of amino acids at different temperatures. In continuation to our work on thermodynamic properties of drugs and amino acids,[27-29] in different aqueous media have been studied. Therefore in the present work, we have reports density, ultrasonic velocity and refractive index of sodium salicylate and 4-aminoantipyrene drugs in aqueous solutions of 0.02, 0.05 and 0.10 mol·kg^{-1} glycine/L-proline at T = (303.15, 308.15 and 313.15) K and atmospheric pressure. These measured values have been used to calculate the derived properties such as standard molar volumes and standard molar compressibility of ternary solution system (drugs + water + amino acids) are reported. The results are interpreted in terms of different types of molecular interactions and solution behaviour of drugs in aqueous solution of amino acid at different temperatures. Present study will explore the drug–amino acid molecular interactions to understand the phenomena like drug action, drug absorption and drug transport across the biological membrane.

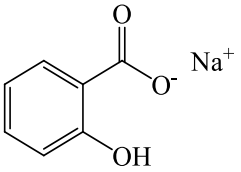
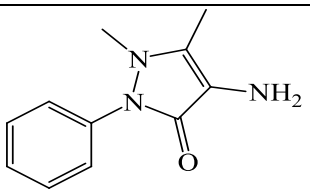
2. MATERIALS AND METHODS

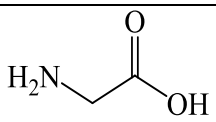
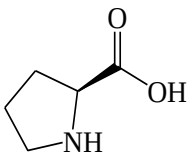
The non-steroidal anti-inflammetory drugs, sodium salicylate was obtained from the SD Fine Chem. Ltd., 4-aminoantipyrine was obtained from the Merck Life Sci. Pvt. Ltd., both drugs

AR grade. Glycine and L-proline of AR grade were procured from HiMedia Laboratories Pvt. Ltd.; specifications of all these chemicals are reported in Table 1. Three stock solution of cosolutes glycine/L-proline (0.02, 0.05 and 0.10 mol·kg^{-1}) were prepared in triple distilled water and used as solvent for all the preparation of drugs solution using an analytical grade balance (Anamed electronic balance, Model AA-2200 (with precision ±0.0001 g). The estimated uncertainty in the molality of drugs solutions is found within u(m) ±5 × 10^{-4} mol·kg^{-1}. The solution were prepared so carefully and stored in airtight bottle to avoid contamination and evaporation.

The densities of drugs in aqueous solutions of glycine/L-proline have been measured using standard graduated pycnometer. It has with graduated marks, standardized bore and closed by well-fitting Teflon white cap and having bulb volume of ~10 cm^3. The calculated standard uncertainty in the density measurements was within ± 0.08 kg·m^{-3}. Density measurements of drugs solutions were carried out in triplicate for each solution. The quartz crystal ulrasonic interferomer (M-F05, Mittal Enterprises) with stainless steel samle cell and digitial micrometer was used for ultrasonic velocity mesurment at operating frequency 2±0.0001MHz. The ultrasonic interferometer was calibrated with triple distilled water. Temperature of solution was controlled by thermostatic water bath (±0.1 K, Mittal Enterprises). Uncertainty in measurement of ultrasonic velocity is found to be within u(m)= ± 1.12 m·s^{-1}. Averge of 30 times digital micrometer reading were mesured and it consider for calculation of ultrasonic velocity. The thermostatic Cyber LAB-Cyber Abbe Refractometer (Amkette Analytics, ±0.0002) was used for mesurment of refractive indices of solutions. Standared uncertianty in refractive index, n mesurment was ± 0.000.

Table 1: Specifications of chemicals.

Name of the chemical	Molar mass, g·mol^{-1}	Source	Chemical structure	CAS number	Mass fraction purity
Sodium salicylate (SS) $C_7H_5NaO_3$	160.11	S.D. Fine-Chem Ltd		$C_7H_5NaO_3$	≥98.00%
4-aminoantipyrine (4-AA) $C_{11}H_{13}N_3O$	203.24	Merck Life Sci. Pvt.Ltd		$C_{11}H_{13}N_3O$	99.00%

Glycine (Gly) $C_2H_5NO_2$	75.07	S.D. Fine-Chem Ltd.		56-40-6	99.00%
L-proline (L-pro) $C_5H_9NO_2$	115.13	Hi Media Laboratories Pvt. Ltd		147-85-3	≥99.00%

3. RSULTS AND DISCUSSION

3.1 Volumetric properties

The experimental dnsities, ρ values of sodium salicylate (SS) and 4-aminoantipyrine (4-AA) drugs in aqueous and aqueous solutions of glycine/L-proline at different temperatures are reported in Table 2. It is seen from Table 2 shows that, ρ values are increases with increase in concentration of drugs as well as concentration of glycine/L-proline. ρ values are decrease with increases in the temperatures. The obtaining ρ trends indicates that molecular interactions among the solute and solvent molecules. Further, ρ data used to calculate $V_{2,\phi}$ apparent molar volume using following equation.[30]

$$V_{2,\phi} = \frac{M_2}{\rho} + \frac{1000}{m\rho\rho_0}(\rho_0 - \rho) \qquad (1)$$

Where, ρ_0, ρ, M_2 and m are the densities (kg·m^{-3}) of solvent and solution, molar mass (kg·mol^{-1}) of solutes and molality (mol·kg^{-1}) of solutes respectively. $V_{2,\phi}$ is apparent molar volume (m^3·mol^{-1}) and the calculated $V_{2,\phi}$ as function of molalities of SS and 4-AA in aqueous solutions of glycine/L-proline are reported in Table 2. It is clear from Table 2 shows that, $V_{2,\phi}$ values of SS are increases with increase in the concentrations of solutes as well as concentration of glycine/L-proline, but $V_{2,\phi}$ values of 4-AA are decrease with increases the concentration of 4-AA due to effect of electrostriction[31] and $V_{2,\phi}$ values of both drugs are increase with rise in the temperatures. This suggests that solute-solute interactions are decreases and solute-solvent interactions are increases with increase in temperatures. Apparent molar volumes are sum of the geometrical volume of the solute and change in the solvent molecule due to different types of interactions with solutes.

Table 2: Densities, ρ and apparent molar volumes, $V_{2,\phi}$ of anti-inflammatory drugs (SS & 4-AA) in aqueous- Glycine/L-Proline solutions at different temperatures and pressure 101 kPa±2 kPa.

C mol·kg^{-1}	ρ ,kg·m^{-3}			$V_{2,\phi} \times 10^{-6}$ m^3·mol^{-1}		
	T=303.15 K	T= 308.15 K	T= 313.15 K	T=303.15 K	T= 308.15 K	T= 313.15 K
SS+ 0.02 mol·kg^{-1} glycine						
0.02	997.08	996.33	994.29	86.53	89.06	90.11
0.04	998.53	997.72	995.66	86.91	89.70	90.75
0.06	1000.05	999.17	997.08	86.99	89.98	91.19
0.10	1001.48	1000.52	998.40	87.18	90.44	91.73
0.12	1002.88	1001.86	999.78	87.55	90.77	92.09
SS + 0.05 mol·kg^{-1} glycine						
0.02	998.66	997.37	995.88	88.52	90.05	92.10
0.04	1000.06	998.72	997.21	89.15	91.19	92.74
0.06	1001.40	1000.13	998.56	90.28	91.62	93.64
0.10	1002.82	1001.46	999.86	90.64	91.91	93.82
0.12	1004.15	1002.70	1001.12	91.02	92.95	94.93
SS + 0.10 mol·kg^{-1} glycine						
0.02	1000.48	999.20	997.40	90.49	91.52	94.08
0.04	1001.85	1000.54	998.68	90.87	92.15	94.97
0.06	1003.18	1001.86	999.98	91.58	92.62	95.92
0.10	1004.58	1003.23	1001.23	91.84	92.99	96.15
0.12	1005.88	1004.50	1002.36	92.27	93.50	97.45
SS+ 0.02 mol·kg^{-1} L-proline						
0.02	997.28	996.09	993.84	88.04	90.08	92.15
0.04	998.69	997.46	995.18	88.67	90.71	92.53
0.06	1000.16	998.88	996.56	88.97	91.15	93.03
0.10	1001.56	1000.18	997.84	89.05	91.94	93.63
0.12	1002.90	1001.58	999.20	89.65	92.04	93.79
SS + 0.05 mol·kg^{-1} L-proline						
0.02	998.25	996.64	994.91	90.04	92.09	94.15
0.04	999.62	997.96	996.19	90.67	92.97	95.04
0.06	1001.03	999.34	997.50	91.26	93.29	95.83
0.10	1002.36	1000.62	998.67	91.64	93.80	97.11
0.12	1003.70	1001.86	999.89	91.72	94.47	97.95
SS + 0.10 mol·kg^{-1} L-proline						
0.02	999.33	997.74	996.24	93.03	94.08	96.14
0.04	1000.64	999.04	997.50	93.66	94.46	96.52
0.06	1001.93	1000.38	998.80	94.12	94.91	96.95
0.10	1003.28	1001.65	1000.00	94.35	95.14	97.56
0.12	1004.55	1002.86	1001.21	94.59	95.83	98.40
***4-AA* + 0.02 mol·kg^{-1} glycine**						
0.02	996.17	995.44	993.40	176.08	177.69	179.00
0.04	996.75	995.98	993.92	175.55	177.41	178.79
0.06	997.34	996.53	994.45	175.18	177.17	178.53

0.10	997.95	997.08	994.98	174.77	177.04	178.38
0.12	998.56	997.64	995.52	174.51	176.84	178.21
***4-AA* + 0.05 mol·kg^{-1} glycine**						
0.02	997.79	996.51	995.04	175.70	177.03	178.25
0.04	998.36	997.05	995.57	175.49	176.93	177.97
0.06	998.93	997.60	996.10	175.40	176.80	177.90
0.10	999.50	998.15	996.64	175.37	176.72	177.72
0.12	1000.08	998.70	997.18	175.24	176.66	177.63
***4-AA* + 0.10 mol·kg^{-1} glycine**						
0.02	999.57	998.29	996.52	179.42	180.62	182.02
0.04	1000.06	998.76	996.97	179.15	180.40	181.74
0.06	1000.55	999.24	997.42	179.08	180.15	181.63
0.10	1001.05	999.72	997.88	178.90	180.00	181.46
0.12	1001.55	1000.20	998.34	178.81	179.95	181.31
4-AA + 0.02 mol·kg^{-1} L-proline						
0.02	996.37	995.19	992.90	177.55	179.23	180.59
0.04	996.91	995.70	993.40	177.20	178.95	180.06
0.06	997.46	996.22	993.90	176.94	178.67	179.90
0.10	998.03	996.75	994.42	176.55	178.42	179.52
0.12	998.60	997.28	994.93	176.32	178.26	179.41
4-AA + 0.05 mol·kg^{-1} L-proline						
0.02	997.36	995.78	994.08	178.27	179.14	179.90
0.04	997.88	996.29	994.58	178.05	178.79	179.62
0.06	998.40	996.80	995.08	177.92	178.70	179.51
0.10	998.93	997.32	995.60	177.74	178.55	179.22
0.12	999.45	997.85	996.12	177.73	178.34	179.06
4-AA + 0.10 mol·kg^{-1} L-proline						
0.02	998.46	996.88	995.41	180.10	180.96	181.69
0.04	998.95	997.35	995.87	179.63	180.63	181.42
0.06	999.44	997.83	996.33	179.45	180.37	181.31
0.10	999.94	998.32	996.80	179.23	180.13	181.14
0.12	1000.45	998.81	997.28	178.98	179.97	180.93

Standard uncertainties, u are u(T)=0.1 K, u(p)=±2.0 kPa, u(ρ)=0.08 kg·m^{-3}and u(m)=0.0005 mol·kg^{-3}.

The positive $V_{2,\phi}$ value of solutes indicates strong solute-solvent interactions and found to be varying linearly with molality of solutes at all concentration of cosolutes and temperatures. Thus, standard molar volume, $V_{2,\phi}^{o}$ could be calculated by using following known standard relation.[32]

$$V_{2,\phi} = V_{2,\phi}^{o} + S_v m^{1/2} \qquad (2)$$

Where, intercept, $V_{2,\phi}^{o}$ is standard partial molar volume and it provides information regarding solute-solvent interactions.[33] S_v is experimental slope corresponds to ion-ion/solute-solute

interactions in the solutions.[34] At infinite dilutions, solvent molecules are present around the solute molecules and negligible solute-solute interactions. Thus, two volumes are equal.[35] The $V_{2,\phi}^{o}$ and S_v values of drugs (SS & 4-AA) are reported in Table 4. From the Table 4 which reveals that, $V_{2,\phi}^{o}$ values are positive for both drugs at all concentration of glycine/L-proline and studied temperatures which suggests presence of effective solute-solvent interactions and obtained $V_{2,\phi}^{o}$ trends due to solvation behavior of solutes.[36] The ion-ion and ion-solvent interactions can be elucidated in terms of structural changes that occur due to hydrogen bonding among the different components of solvent/solution systems.

$V_{2,\phi}^{o}$ values of SS are increases with increase with concentration of glycine/L-proline as well as it increase increases with temperature. On the other hand $V_{2,\phi}^{o}$ values of 4-AA decrease firstly and then increases with the concentration of glycine/L-proline. $V_{2,\phi}^{o}$ values are also increases with rise in temperatures. The reported[37] $V_{2,\phi}^{o}$ values of SS at (298.15, 303.15, 308.15 and 313.15) K are (93.26, 94.31, 95.29 and 95.95) $\times 10^{-6}$ $m^3 \cdot mol^{-1}$ respectively. The observed $V_{2,\phi}^{o}$ values SS at (303.15, 308.15 and 313.15) K are (93.31, 94.65 and 95.70) $\times 10^{-6}$ $m^3 \cdot mol^{-1}$ respectively. The $V_{2,\phi}^{o}$ values of SS in aqueous solutions at selected temperatures are in good agreement with reported values. The $V_{2,\varphi}^{o}$ values increases with rise in temperatures for the both drugs in aqueous solution of cosolutes and this can be explained by considering the size of hydration layer around the ionic (COO^-/Na^+) and hydrophilic (-NH_2, C=O, –N–N– and OH) groups of drugs molecules; at high temperature the loose solvent molecule from hydration layer of solutes (ionic/hydrophilic groups) are released into bulk solvent or decreasing electrostriction with an increasing temperatures as result, expansion of solution. Similar trends were also observed in literatures.[38-40]

Furthermore, $V_{2,\varphi}^{o}$ values of SS are increase with increase in concentration of cosolutes is due to effective drug-solvent interactions may due to hydration of ion/hydrophilic sites of drugs. In case of 4-AA the $V_{2,\varphi}^{o}$ values are firstly decrease then increase in cosolutes concentration. The concentration of cosolutes affects molecular interactions of studied drugs in water + glycine/L-proline system which are confirmed from the change in partial molar volume with increase in the concentration of cosolutes.

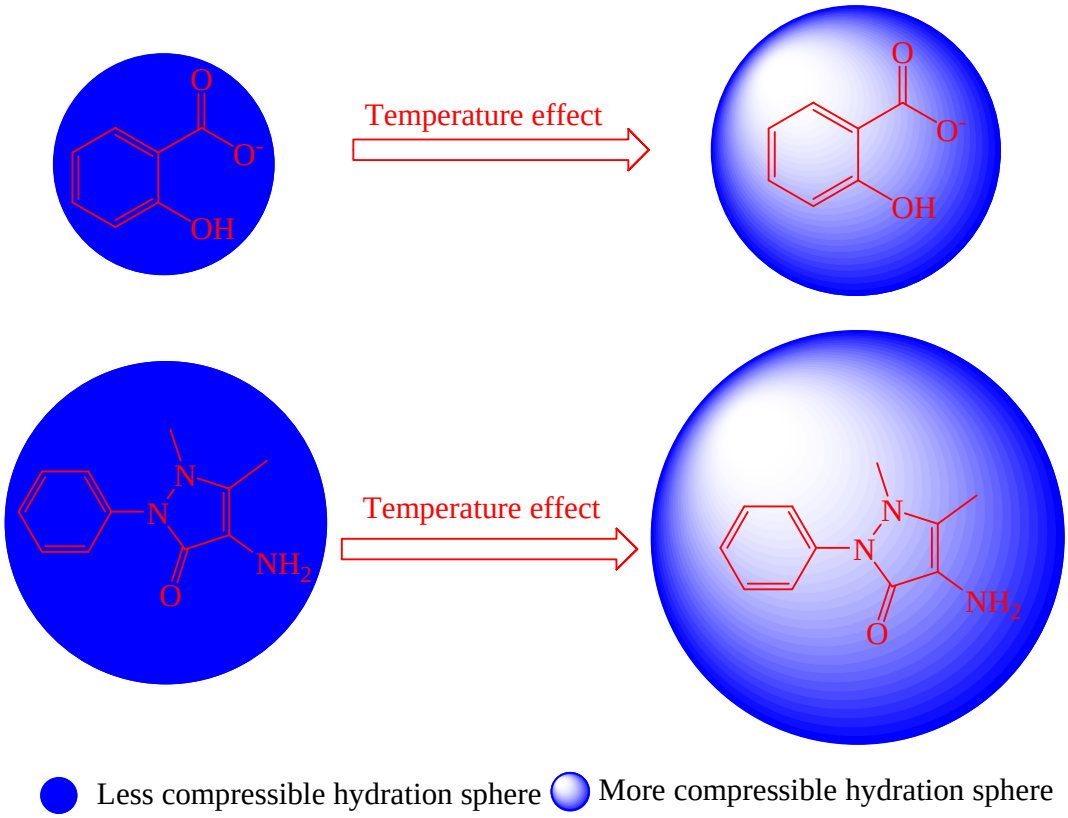
Generally $V_{2,\varphi}^{o}$ values increases with increases in molecular weight/mass.[41] The $V_{2,\varphi}^{o}$ increases from SS to 4-AA and due to increases in molecular weight/mass, same trend were found in case of dimetridazole (DMZ) and metronidazole (MNZ)[42] the $V_{2,\varphi}^{o}$ values are greater for MNZ (due to high molar mass) than DMZ and also found in citrate salt.[43] Present investigation the $V_{2,\varphi}^{o}$ values of 4-AA is greater than the SS due to molar mass of 4-AA is greater than the SS. The S_v values of SS are found positive but less than $V_{2,\phi}^{o}$ values indicates that, weak ion-ion interaction than ion-solvent interaction. Huaji et al[44] has also reported the similar type of interactions. S_v values of 4-AA are negative due to very weak solute-solute/ion-ion interactions.

3.2 Acoustical properties

Ultrasonic velocities, u values of drugs in aqueous glycine/L-proline solution at different temperatures are reported in Table 3. It is seen from Table 3 that the u values of drugs (SS and-AA) increase with increase in the concentrations of drugs as well as cosolutes and it is also increase with temperatures. Increasing u trends with increasing in the concentration solute and cosolute and also rises with temperature which suggests that cohesion of molecules.[45] The isentropic compressibility, κ_s values of studied drugs in aqueous cosolute solutions at different temperatures were calculated by using well-known Newton−Laplace equation

$$\kappa_s = \frac{1}{u^2 \rho} \qquad (3)$$

The calculated κ_s values of all drugs in water + glycine/L-proline at different temperatures are reported in Table 3. κ_s values are decrease with increasing in solutes concentrations which described that solvent molecule around the ionic (COO^-/Na^+) and hydrophilic ($-NH_2$, C=O, –N–N– and OH) groups of solute molecules are less compressible than bulk.[46] The decrease in κ_s values may due to (i) introduction of SS/4-AA drugs molecules into solution which reduce the cavities in solution and (ii) increase in ionic-ionic/hydrophilic and hydrophilic-hydrophobic interactions.[47-49]



Scheme 1: Effect of increase in temperature on hydration spheres of SS and 4-AA in relation with the volume and compressibility.

Further, decrease κ_s values with an increase in temperature may attribute to rapture the hydrogen bonded structure of water molecules around ionic/hydrophilic groups of solutes and zwitter ionic end ($–NH_3^+$, $–COO^–$) groups of co-solutes. The effect of temperature which shown in scheme 1.

Table 3: Ultrasonic velocities, u, adiabatic compressibility, κ_s and apparent molar isentropic compressibility, $\kappa_{S,2,\phi}$ of anti-inflammatory drugs (SS & 4-AA) in aqueous glycine/L-Proline at different temperatures and pressure 101 kPa±2 kPa.

m mol·kg^{-1}	u m·s^{-1}			κ_s ×10^{-10} Pa^{-1}			$\kappa_{S,2,\phi}$ ×10^{-15} m^3·mol^{-1}·Pa^{-1}		
	T=303.15K	T=308.15K	T=313.15K	T=303.15K	T=308.15K	T=313.15K	T=303.15K	T=308.15K	T=313.15K
SS + 0.02 mol·kg^{-1} glycine									
0.02	1515.54	1520.68	1527.82	4.367	4.340	4.309	-6.141	-5.813	-5.505
0.04	1517.82	1523.00	1530.07	4.347	4.321	4.290	-6.061	-5.798	-5.477
0.06	1520.20	1525.42	1532.46	4.327	4.301	4.271	-6.012	-5.761	-5.464
0.10	1522.42	1527.73	1534.75	4.308	4.282	4.252	-5.933	-5.711	-5.430
0.12	1524.59	1530.00	1537.12	4.290	4.264	4.233	-5.830	-5.648	-5.383
SS + 0.05 mol·kg^{-1} glycine									
0.02	1517.73	1520.69	1528.95	4.347	4.336	4.295	-5.706	-5.418	-5.418
0.04	1520.00	1522.94	1531.16	4.328	4.317	4.277	-5.692	-5.405	-5.405
0.06	1522.29	1525.28	1533.50	4.309	4.298	4.259	-5.616	-5.365	-5.365
0.10	1524.63	1527.49	1535.68	4.290	4.280	4.241	-5.543	-5.318	-5.318
0.12	1526.90	1529.84	1538.08	4.272	4.261	4.222	-5.504	-5.290	-5.290
SS + 0.10 mol·kg^{-1} glycine									
0.02	1521.28	1530.96	1536.29	4.319	4.270	4.248	-5.315	-5.032	-4.818
0.04	1523.47	1533.10	1538.44	4.301	4.252	4.231	-5.282	-4.965	-4.730
0.06	1525.65	1535.22	1540.77	4.283	4.235	4.213	-5.202	-4.893	-4.703
0.10	1527.85	1537.40	1542.92	4.264	4.217	4.196	-5.100	-4.807	-4.654
0.12	1529.89	1539.60	1545.28	4.248	4.200	4.178	-4.983	-4.796	-4.638
SS + 0.02 mol·kg^{-1} L-proline									
0.02	1508.68	1516.95	1530.94	4.405	4.363	4.293	-5.735	-5.337	-5.018
0.04	1510.86	1519.08	1533.04	4.387	4.345	4.276	-5.664	-5.267	-4.944
0.06	1513.10	1521.28	1535.18	4.367	4.326	4.258	-5.574	-5.180	-4.818
0.10	1515.08	1523.28	1537.24	4.350	4.309	4.241	-5.419	-5.013	-4.737
0.12	1517.14	1525.36	1539.20	4.332	4.291	4.224	-5.319	-4.927	-4.587
SS + 0.05 mol·kg^{-1} L-proline									

0.02	1512.13	1522.80	1532.45	4.381	4.327	4.280	-5.354	-5.116	-4.811
0.04	1514.30	1524.98	1534.60	4.363	4.309	4.263	-5.342	-5.083	-4.764
0.06	1516.60	1527.27	1536.86	4.343	4.290	4.244	-5.315	-5.062	-4.701
0.10	1518.80	1529.45	1539.11	4.325	4.272	4.227	-5.293	-5.013	-4.655
0.12	1521.00	1531.64	1541.36	4.307	4.255	4.210	-5.287	-4.954	-4.558
SS + 0.10 mol·kg^{-1} L-proline									
0.02	1516.46	1525.10	1536.55	4.351	4.309	4.252	-4.822	-4.501	-4.101
0.04	1518.54	1527.10	1538.46	4.334	4.292	4.236	-4.783	-4.456	-4.003
0.06	1520.60	1529.18	1540.48	4.317	4.275	4.219	-4.721	-4.386	-3.950
0.10	1522.78	1531.18	1542.45	4.298	4.258	4.203	-4.695	-4.360	-3.918
0.12	1524.86	1533.22	1544.55	4.281	4.242	4.187	-4.669	-4.315	-3.873
4-AA + 0.02 mol·kg^{-1} glycine									
0.02	1515.96	1521.25	1528.47	4.368	4.341	4.309	-1.638	-1.558	-1.485
0.04	1518.78	1524.11	1531.37	4.349	4.322	4.290	-1.665	-1.577	-1.508
0.06	1521.60	1527.00	1534.27	4.331	4.304	4.272	-1.677	-1.599	-1.519
0.10	1524.43	1529.90	1537.19	4.312	4.285	4.253	-1.691	-1.608	-1.530
0.12	1527.28	1532.80	1540.13	4.293	4.266	4.235	-1.704	-1.616	-1.541
4-AA + 0.05 mol·kg^{-1} glycine									
0.02	1518.34	1521.39	1529.67	4.347	4.335	4.295	-1.721	-1.680	-1.624
0.04	1521.21	1524.27	1532.59	4.328	4.317	4.276	-1.742	-1.689	-1.643
0.06	1524.10	1527.19	1535.54	4.310	4.298	4.258	-1.756	-1.698	-1.649
0.10	1527.02	1530.12	1538.50	4.291	4.279	4.239	-1.763	-1.701	-1.661
0.12	1529.94	1533.07	1541.50	4.272	4.260	4.220	-1.769	-1.708	-1.674
4-AA + 0.10 mol·kg^{-1} glycine									
0.02	1521.94	1531.68	1537.03	4.319	4.270	4.248	-1.337	-1.246	-1.166
0.04	1524.81	1534.60	1539.96	4.301	4.252	4.230	-1.385	-1.310	-1.227
0.06	1527.75	1537.52	1542.93	4.282	4.233	4.211	-1.440	-1.336	-1.274
0.10	1530.66	1540.48	1545.92	4.264	4.215	4.193	-1.448	-1.368	-1.302
0.12	1533.68	1543.52	1548.92	4.245	4.197	4.175	-1.498	-1.405	-1.337
4-AA + 0.02 mol·kg^{-1} L-proline									
0.02	1509.25	1517.62	1531.67	4.406	4.363	4.293	-1.351	-1.311	-1.279

0.04	1511.98	1520.42	1534.51	4.388	4.345	4.275	-1.354	-1.317	-1.293
0.06	1514.73	1523.22	1537.38	4.370	4.326	4.257	-1.362	-1.324	-1.299
0.10	1517.46	1526.04	1540.22	4.351	4.308	4.239	-1.366	-1.332	-1.307
0.12	1520.22	1528.87	1543.10	4.333	4.290	4.221	-1.369	-1.337	-1.310
4-AA + 0.05 mol·kg^{-1} L-proline									
0.02	1512.80	1523.50	1533.19	4.381	4.327	4.279	-1.429	-1.381	-1.334
0.04	1515.63	1526.33	1536.07	4.362	4.308	4.261	-1.453	-1.398	-1.368
0.06	1518.46	1529.20	1538.97	4.344	4.290	4.243	-1.467	-1.414	-1.387
0.10	1521.31	1532.10	1541.87	4.325	4.272	4.225	-1.478	-1.433	-1.398
0.12	1524.20	1535.00	1544.78	4.307	4.253	4.207	-1.493	-1.447	-1.412
4-AA + 0.10 mol·kg^{-1} L-proline									
0.02	1517.22	1525.95	1537.47	4.351	4.308	4.250	-1.275	-1.214	-1.155
0.04	1520.05	1528.79	1540.35	4.333	4.290	4.232	-1.292	-1.231	-1.175
0.06	1522.89	1531.65	1543.24	4.314	4.272	4.214	-1.297	-1.243	-1.181
0.10	1525.73	1534.53	1546.16	4.296	4.254	4.196	-1.303	-1.254	-1.196
0.12	1528.57	1537.42	1549.07	4.278	4.236	4.179	-1.309	-1.260	-1.202

Standard uncertainties, u are u(T)=0.1 K, u(p)=±2.0 kPa, u(*m*)=0.0005 mol·kg^{-3} and u(*u*)=1.09 m·s^{-1}.

The apparent molar isentropic compressibility, $\kappa_{S,2,\varphi}$ values of solutes in aqueous solution of L-proline/glycine have been calculated using standard relation

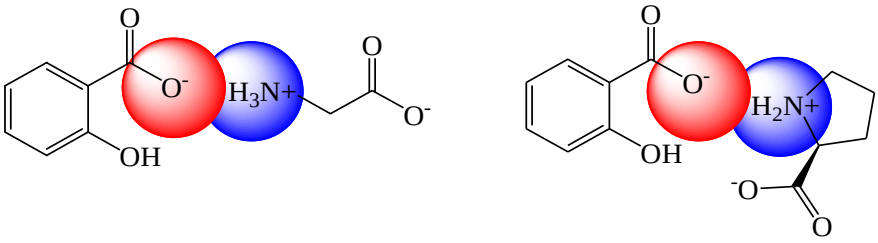
$$\kappa_{S,2,\phi} = \frac{1000(\kappa_s \rho_o - \kappa_o \rho)}{m\rho\rho_o} + \frac{M \times \kappa_s}{\rho} \quad (4)$$

Where, m is the molality (mol·kg^{-1}) of solution, ρ_0 and ρ are the densities (kg·m^{-3}) of solvent and solutions respectively, M is molar mass (kg·mol^{-1}) of drug, κ_{s0} and κ_s are isentropic compressibilities of solvent and solution (Pa^{-1}), $\kappa_{S,2,\phi}$ is apparent molar isentropic compressibility (m^3·mol^{-1}·Pa^{-1}) of solution. The calculated $\kappa_{S,2,\phi}$ values of drugs are listed in Table 3. It is seen from Table 3 that, $\kappa_{S,2,\phi}$ values of both drugs are negative at all concentration of cosolute and temperature. $\kappa_{S,2,\phi}$ values of SS are increase with increase in concentration of cosolutes as well as temperature but in 4-AA the $\kappa_{S,2,\phi}$ values are firstly decrease then increase in both cosolutes concentration. $\kappa_{S,2,\phi}$ increase for both drugs with rise in temperatures which suggest that release of water molecule from solvation shell of drugs molecule due to different types of interactions between ionic/hydrophilic groups of solutes and zwitterionic end ($-NH_3^+$, $-COO^-$) groups of amino acids.

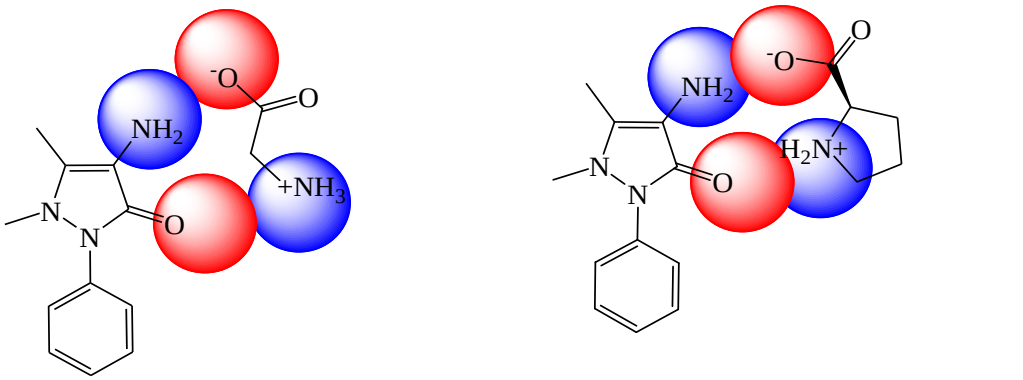
Further, $\kappa_{S,2,\varphi}$ values of drugs have been fitted by least-squares method with following standard relation.[50]

$$\kappa_{S,2,\phi} = \kappa^0_{S,2,\phi} + S_k m^{1/2} \quad (5)$$

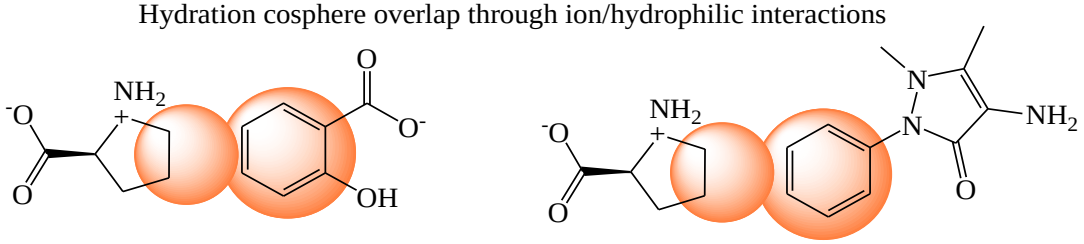
Where, $\kappa^0_{S,2,\phi}$ is the apparent molar isentropic compressibility at infinite dilution, which is free from solute-solute interactions and it measure the solute-solvent interaction, S_k is experimental slope which represents the ion-ion/solute-solute interactions. The calculated $\kappa^0_{S,2,\phi}$ values of studied drugs in aqueous solution of glycine/L-proline are reported in Table 5. $\kappa^0_{S,2,\phi}$ values of SS in aqueous solution at selected temperatures are in good agreement with literature values.[37] The $\kappa^0_{S,2,\phi}$ values (from Table 5) are more negative at low temperature due to effective interactions between the drug-solvent, and it becomes less negative with increasing in temperature.



Hydration cosphere overlap through ion-ion/hydrophilic interactions



Hydration cosphere overlap through ion/hydrophilic interactions



Hydration cosphere overlap through hydrophobic-hydrophobic interactions

Scheme 2: Plausible schematic representation of different interactions between SS/4-AA and Glycine/L-proline in aqueous medium (these interactions are due to hydration cosphere overlap of solute and cosolute).

Negative $\kappa^0_{S,2,\phi}$ values suggests that the solvent molecules around the ionic/hydrophilic groups of SS/4-AA are less compressible than the water molecules present in the bulk solution[51] and decrease in magnitude of $\kappa^0_{S,2,\phi}$ values at high temperatures, which may described that rapture the compact hydration structure in the region of SS/4-AA drugs molecule.[52] The ion-ion/hydrophilic interactions between (COO^-/Na^+) and hydrophilic (-NH_2, C=O, –N–N– and OH) of drugs and (–NH_3^+, –COO^-) groups of amino acids which increase the compressibility and hydrophobic-hydrophilic/hydrophobic interactions decrease the compressibility. The observed values of $V^o_{2,\varphi}$ and $\kappa^0_{S,2,\phi}$ are due to ion-ion/hydrophilic interactions, which dominates over hydrophobic-hydrophilic/hydrophobic interactions. The different possible interactions due to solute-cosolute interactions and overlap of hydration spheres are shown in Scheme 2.

Table 4: Standard molar volumes, $V_{2,\phi}^{o}$ and experimental slope, S_v for SS and 4-AA in aqueous- Glycine/L-Proline at different temperatures and pressure 101 kPa±2 kPa.

Drugs	*m* ***mol·kg^{-1}***	***303.15 K***		***308.15 K***		***313.15 K***	
		$V_{2,\phi}^{o}$ **×10^{-6} m^3·mol^{-1}**	S_v **×10^{-6} m^3·mol^{-1}·kg^{-1}**	$V_{2,\phi}^{o}$ **× 10^{-6} m^3·mol^{-1}**	S_v **× 10^{-6} m^3·mol^{-1}·kg^{-1}**	$V_{2,\phi}^{o}$ **× 10^{-6} m^3·mol^{-1}**	S_v **× 10^{-6} m^3·mol^{-1}·kg^{-1}**
SS	0.02 glycine	85.80	05.19	87.74	09.45	88.52	11.16
	0.05 glycine	86.40	14.83	88.03	14.78	89.85	15.07
	0.10 glycine	88.97	10.25	89.97	10.88	91.47	17.81
	0.02 L-proline	86.93	08.18	88.41	11.66	90.68	09.85
	0.05 L-proline	88.68	10.01	90.32	12.63	90.88	21.54
	0.10 L-proline	91.86	08.79	92.67	09.31	94.20	12.21
		$V_{2,\phi}^{o}$ ×10^{-6} m^3·mol^{-1}	S_v ×10^{-6} m^3·mol^{-1}·kg^{-1}	$V_{2,\phi}^{o}$ ×10^{-6} m^3·mol^{-1}	S_v ×10^{-6} m^3·mol^{-1}·kg^{-1}	$V_{2,\phi}^{o}$ ×10^{-6} m^3·mol^{-1}	S_v ×10^{-6} m^3·mol^{-1}·kg^{-1}
4-AA	0.02 glycine	177.35	-8.91	178.35	-4.70	179.66	-4.50
	0.05 glycine	176.00	-2.39	177.34	-2.16	178.71	-3.40
	0.10 glycine	179.88	-3.38	181.18	-3.99	182.56	-3.88
	0.02 L-proline	178.59	-7.03	180.04	-5.60	181.48	-6.64
	0.05 L-proline	178.71	-3.21	179.71	-4.19	180.58	-4.67
	0.10 L-proline	180.92	-6.05	181.76	-5.64	182.27	-4.06

Standard uncertainties, u are u(T)=0.1 K, u(p)=±2.0 kPa.

Table 5: Standard compressibilities, $\kappa^0_{S,2,\phi}$, experimental slope, S_k for SS and 4-AA in aqueous- Glycine/L-Proline at different temperatures and pressure 101 kPa±2 kPa.

Drugs	m mol·kg^{-1}	303.15 K		308.15 K		313.15 K	
		$\kappa^0_{S,2,\phi}\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}	$S_k\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}·kg^{-1}	$\kappa^0_{S,2,\phi}\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}	$S_k\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}·kg^{-1}	$\kappa^0_{S,2,\phi}\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}	$S_k\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}·kg^{-1}
SS	0.02 glycine	-6.393	1.670	-5.964	0.912	-5.604	0.640
	0.05 glycine	-5.905	1.231	-5.540	0.761	-5.391	1.214
	0.10 glycine	-5.619	1.867	-5.240	1.436	-4.949	1.008
	0.02 L-proline	-6.111	2.389	-5.711	2.376	-5.386	2.371
	0.05 L-proline	-5.417	0.414	-5.252	0.868	-5.022	1.360
	0.10 L-proline	-4.952	0.898	-4.656	1.061	-4.265	1.240
		$\kappa^0_{S,2,\phi}\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}	$S_k\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}·kg^{-1}	$\kappa^0_{S,2,\phi}\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}	$S_k\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}·kg^{-1}	$\kappa^0_{S,2,\phi}\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}	$S_k\times10^{-15}$ m^3·mol^{-1}·Pa^{-1}·kg^{-1}
4-AA	0.02 glycine	-1.589	-0.361	-1.511	-0.336	-1.444	-0.306
	0.05 glycine	-1.686	-0.271	-1.658	-0.155	-1.587	-0.266
	0.10 glycine	-1.212	-0.878	-1.128	-0.856	-1.033	-0.956
	0.02 L-proline	-1.334	-0.109	-1.288	-0.151	-1.256	-0.175
	0.05 L-proline	-1.381	-0.350	-1.325	-0.375	-1.277	-0.428
	0.10 L-proline	-1.252	-0.183	-1.178	-0.262	-1.119	-0.262

Table 6: Refractive indices (n) and derived atomic polarization (P_a) of SS and 4-AA) in different concentration of glycine/L-proline at different temperatures.

C	n	P_a	n	P_a	n	P_a	c	n	P_a	n	P_a	n
	303.15K		**308.15K**		**313.15K**		**303.15K**		**308.15K**		**313.15K**	
SS + 0.02 mol·kg^{-1} glycine							**4-AA + 0.02 mol·kg^{-1} glycine**					
0.02	1.3322	1.8635	1.3315	1.8615	1.3308	1.8596	1.3322	1.8635	1.3315	1.8615	1.3310	1.8601
0.04	1.3328	1.8652	1.3321	1.8632	1.3314	1.8613	1.3332	1.8663	1.3322	1.8635	1.3318	1.8624
0.06	1.3335	1.8671	1.3330	1.8657	1.3324	1.8641	1.3342	1.8691	1.3330	1.8657	1.3326	1.8646
0.08	1.3340	1.8685	1.3335	1.8671	1.3330	1.8657	1.3352	1.8719	1.3340	1.8685	1.3334	1.8669
0.10	1.3345	1.8699	1.3340	1.8685	1.3335	1.8671	1.3362	1.8747	1.3350	1.8713	1.3342	1.8691
SS + 0.05 mol·kg^{-1} glycine							4-AA + 0.05 mol·kg^{-1} glycine					
0.02	1.3324	1.8641	1.3316	1.8618	1.3310	1.8601	1.3325	1.8643	1.3320	1.8629	1.3315	1.8615
0.04	1.3330	1.8657	1.3325	1.8643	1.3320	1.8629	1.3338	1.8680	1.3328	1.8652	1.3322	1.8635
0.06	1.3337	1.8677	1.3332	1.8663	1.3326	1.8646	1.3346	1.8702	1.3335	1.8671	1.3330	1.8657
0.08	1.3344	1.8697	1.3340	1.8685	1.3332	1.8663	1.3358	1.8736	1.3342	1.8691	1.3336	1.8674
0.10	1.3350	1.8713	1.3346	1.8702	1.3340	1.8685	1.3370	1.8769	1.3355	1.8727	1.3345	1.8699
SS + 0.10 mol·kg^{-1} glycine							4-AA + 0.10 mol·kg^{-1} glycine					
0.02	1.3330	1.8657	1.3325	1.8643	1.3316	1.8618	1.3335	1.8671	1.3330	1.8657	1.3320	1.8629
0.04	1.3335	1.8671	1.3330	1.8657	1.3320	1.8629	1.3342	1.8691	1.3335	1.8671	1.3325	1.8643
0.06	1.3342	1.8691	1.3336	1.8674	1.3328	1.8652	1.3350	1.8713	1.3342	1.8691	1.3333	1.8666
0.08	1.3355	1.8727	1.3343	1.8694	1.3335	1.8671	1.3360	1.8741	1.3350	1.8713	1.3345	1.8699
0.10	1.3364	1.8753	1.3350	1.8713	1.3342	1.8691	1.3375	1.8784	1.3360	1.8741	1.3355	1.8727
SS + 0.02 mol·kg^{-1} L-proline							4-AA + 0.02 mol·kg^{-1} L-proline					
0.02	1.3325	1.8643	1.3315	1.8615	1.3306	1.8590	1.3328	1.8652	1.3320	1.8629	1.3312	1.8607
0.04	1.3334	1.8669	1.3322	1.8635	1.3314	1.8613	1.3338	1.8680	1.3330	1.8657	1.3325	1.8643
0.06	1.3340	1.8685	1.3332	1.8663	1.3324	1.8641	1.3347	1.8705	1.3340	1.8685	1.3335	1.8671
0.08	1.3346	1.8702	1.3340	1.8685	1.3331	1.8660	1.3356	1.8730	1.3350	1.8713	1.3345	1.8699
0.10	1.3352	1.8719	1.3345	1.8699	1.3338	1.8680	1.3368	1.8764	1.3358	1.8736	1.3352	1.8719
SS + 0.05 mol·kg^{-1} L-proline							4-AA + 0.05 mol·kg^{-1} L-proline					
0.02	1.3330	1.8657	1.3324	1.8641	1.3320	1.8629	1.3330	1.8657	1.3320	1.8629	1.3315	1.8615

0.04	1.3339	1.8683	1.3330	1.8657	1.3327	1.8649	1.3345	1.8699	1.3328	1.8652	1.3327	1.8649
0.06	1.3346	1.8702	1.3340	1.8685	1.3334	1.8669	1.3355	1.8727	1.3336	1.8674	1.3339	1.8683
0.08	1.3352	1.8719	1.3348	1.8708	1.3345	1.8699	1.3368	1.8764	1.3346	1.8702	1.3352	1.8719
0.10	1.3360	1.8741	1.3355	1.8727	1.3350	1.8713	1.3385	1.8812	1.3358	1.8736	1.3369	1.8767
SS + 0.10 mol·kg^{-1} L-proline							4-AA + 0.10 mol·kg^{-1} L-proline					
0.02	1.3348	1.8708	1.3335	1.8671	1.3330	1.8657	1.3338	1.8680	1.3327	1.8649	1.3325	1.8643
0.04	1.3355	1.8727	1.3342	1.8691	1.3336	1.8674	1.3342	1.8691	1.3335	1.8671	1.3330	1.8657
0.06	1.3362	1.8747	1.3348	1.8708	1.3342	1.8691	1.3355	1.8727	1.3350	1.8713	1.3340	1.8685
0.08	1.3370	1.8769	1.3354	1.8725	1.3348	1.8708	1.3365	1.8755	1.3360	1.8741	1.3349	1.8711
0.10	1.3375	1.8784	1.3365	1.8755	1.3354	1.8725	1.3376	1.8786	1.3370	1.8769	1.3360	1.8741

Footnote 1: Standard uncertainties, u are u(T)=0.1 K, u(p)=±2.0 kPa, and u(*m*)=0.0005 mol·kg^{-1} and u(*n*)=0.0002.

Further, $\kappa^0_{S,2,\phi}$ values of 4-AA firstly decreases and then increases with increasing in the concentration of cosolutes and also $\kappa^0_{S,2,\phi}$ values of SS are increases with concentration of cosolutes. This is attributed to the dehydration effect may caused due to glycine/L-proline. The zwitterionic end ($–NH_3^+$, $–COO^–$) groups of amino acids interact with ionic/hydrophilic groups of drug molecules and it reduce the hydration at ionic/hydrophilic sites of drugs molecules result into an expansion of volume, therefore solution become more compressible. The experimental slope, S_k values of SS are positive in aqueous solution of glycine/L-proline and investigated temperatures and negative S_k values of 4 -AA which suggest that, the weak solute-solute interaction in SS+ water + glycine/L-proline solution and very negligible solute-solute interaction in 4-AA+ water + glycine/L-proline systems.

3.3 Optical properties

The refractive indices, n and atomic polarization, P_a values of studied drugs in water and water + glycine/L-proline solution at different temperatures were measured and listed in Table 6. It is seen from Table 6 shows that, n and values of drugs are increasing with increasing in the concentration of solutes as well as cosolutes which suggests that increasing compactness of the solution due strong solute-solvent interactions in solution. The P_a value increases with increase in the composition of drug as well as amino acid and decrease with increase in temperatures in each case. This observation of n and P_a are in good agreement with the conclusions drawn from the volumetric and acoustic studies. Further, decreasing trends of n and P_a with temperatures indicates that weakening solute-solvent interactions. Overall, n and P_a values are influenced by composition of drugs as well glycine/L-proline.

3. CONCLUSION

The density, ultrasonic velocity and optical properties of SS and 4-AA in aqueous glycine/L-proline solutions were measured at different temperatures. Positive $V^o_{2,\varphi}$ values and negative, $\kappa^0_{S,2,\phi}$ values of SS and 4-AA in glycine/L-proline solutions indicates that the existing effective solute-solvent interactions in this system, which increases with increase in the concentration of glycine/L-proline. The obtained $\kappa^0_{S,2,\phi}$ and $V^o_{2,\phi}$ values of solutes due to ion-ion/hydrophilic and hydrophilic-hydrophilic interactions occurs between drugs and solvent molecules. Increasing trends $\kappa^0_{S,2,\phi}$ and $V^o_{2,\phi}$ values with temperatures may due to dehydration

effect. Increasing tends of n with concentration of cosolutes due to strong drug-solvent interactions. Present study will have significance in pharmacokinetics, pharmacodynamics of drugs and also in protein chemistry.

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Conflict of interests

Authors declare that there is no conflict of interest regarding the publication of present research article.

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