

# Ultrasonic Studies Of Alanine in Aqueous Paracetamol Solutions at Different Temperatures

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## Abstract:

Ultrasonic velocity and density data of alanine in 0.025, 0.05, 0.075, and 0.1 M concentration of aqueous paracetamol solutions are measured and reported at 298.15, 303.15, 308.15, 313.15 and 318.15 K to compute several thermodynamic parameters like isentropic compressibility ( $\beta_s$ ), the change in isentropic compressibility ( $\Delta\beta_s$ ), the relative change in isentropic compressibility ( $\Delta\beta_s/\beta_s^0$ ), the apparent molal compressibility ( $k_\phi$ ), the limiting apparent molal compressibility ( $k_\phi^0$ ), the limiting apparent molal compressibility of transfer ( $\Delta_{tr}k_\phi^0$ ), the hydration number ( $n_H$ ), and the pair and triplet interaction parameters ( $k_{AH}$ ,  $k_{AHH}$ ). These parameters are used to interpret the solute-solute and solute-solvent interactions of alanine in aqueous paracetamol solutions.

**Keywords:** Hydration number · Isentropic compressibility · Limiting apparent molal compressibility · Paracetamol · Ultrasonic speed

## INTRODUCTION

Drugs are biologically supreme macromolecules which have been in use for a long time for the treatment of various diseases and to provide immunity to the living system. By examining the physico-chemical properties of drugs in aqueous, protic solvents and aqueous-protic solutions, one can understand the interaction of drugs at the molecular levels. Interaction studies of drugs with biomolecules will provide vital data about physiological media such as blood, membranes and cellular fluids. Since drugs are organic molecules with both hydrophilic and hydrophobic groups, these molecules show specific as well as electrostatic interactions.

Drug transport, protein binding, and anesthesia are some of the processes where drugs and biomolecules appear to interact in an important and noteworthy manner. However the mechanisms of these molecular processes are not yet to be clearly understood [1]. In protein binding, particular conduct has been noted regarding certain medications. The actions of the drug like drug reaching the blood stream, its expanse of giving out, its binding to the receptors, and eventually producing physiological action, all depend on various physicochemical properties primarily noticed by diverse interactions of the compounds [2,3]. Pharmacokinetics is the study of the use of drugs involving physiological and biochemical effects and their mechanism of action at macromolecular/subcellular/organ system levels [4,5]. Pharmacokinetic process involves the transport of drugs across biological membranes which can be well understood by transport property measurements, like ultrasonic speed, viscosity, diffusion, and thermal conductivity [4]. Thus, knowledge of the physicochemical and thermodynamic properties of drugs plays an important part to perceive their physiological actions showing that they are highly dependent on the solution to respond. Literature survey shows that many authors prefer the model compound amino

acids in place of proteins as proteins are highly complex molecules in the determination of thermodynamic parameters in aqueous media [6,7]. Recently [8] we have reported the volumetric and viscometric studies of alanine in aqueous paracetamol and confirmed the presence of strong solute-solvent interactions in addition to the presence of weak solute-solute interactions. As Compressibility is being a more sensitive parameter to elucidate the interaction studies in solutions [9], in this paper we report thermodynamic parameters such as adiabatic compressibility ( $\beta_s$ ), change in adiabatic compressibility ( $\Delta\beta_s$ ), the relative change in adiabatic compressibility ( $\Delta\beta_s/\beta_s^0$ ), the apparent molal compressibility ( $k_\phi$ ), the limiting apparent molal compressibility ( $k_\phi^0$ ), the transfer limiting apparent molal compressibility ( $\Delta_{tr}k_\phi^0$ ), the hydration number ( $n_H$ ), and the pair and triplet interaction parameters ( $k_{AH}$ ,  $k_{AHH}$ ) using the measured density and ultrasonic velocity data. These parameters are used to interpret the solute-solvent and solute-solute interactions of alanine in aqueous paracetamol solutions. The data at temperatures T = (298.15, 303.15, 308.15, 313.15 and 318.15) K provide insight into the drug macromolecular behavior near physiological temperatures.

## MATERIALS AND METHODS

Paracetamol and the amino acid, L-alanine of full cleanness has been procured from S.D. Fine. Chem. Ltd. Mumbai and Loba Chemie Pvt Ltd (assemble fraction cleanness > 0.990), has been used after drying over P<sub>2</sub>O<sub>5</sub> in a desiccator for 72 hrs before utility. L-alanine of different molality (0.02, 0.04, 0.06, 0.08 and 0.1) M has been added as solutes in four different molal (0.025, 0.05, 0.075 and 0.1) concentration of aqueous paracetamol solvents, made with doubly distilled deionized water of  $1.5 \times 10^{-4} \Omega^{-1} \text{m}^{-1}$  conductivity. The density of the solutions and speed of

ultrasound in the solutions have been measured using single stem pycnometer and single-crystal variable-path multi-frequency ultrasonic interferometer (M-05, Mittal Enterprises, India) operated at 2 MHz whose procedures have been discussed in detail elsewhere [10].

### RESULTS

The experimental measured densities and ultrasonic velocities of alanine in aqueous paracetamol solutions are given in Tables-1 and 2, respectively. The Newton-Laplace expression given by equation (1) has been used to calculate adiabatic compressibility ( $\beta_S$ ) and the uncertainty associated with  $\beta_S$  [11] has been calculated using equation (2) and are listed in Table-3.

$$\beta_S = 1/(\rho u^2) \quad (1)$$

$$\delta\beta_S = \beta_S [(2\delta u/u)^2 + (\delta\rho/\rho)^2]^{1/2} \quad (2)$$

The change in isentropic compressibility [12] ( $\Delta\beta_S$ ) and relative change in isentropic compressibility

( $\Delta\beta_S/\beta_S^0$ ) [13] have been calculated using the following equations:

$$\Delta\beta_S = \beta_S^0 - \beta_S = A + Bm \quad (3)$$

$$\beta_S = \beta_S^0 - \alpha\beta_S^0 \quad (4)$$

$$\alpha = (\beta_S^0 - \beta_S) / \beta_S^0 = \Delta\beta_S / \beta_S^0 \quad (5)$$

$$\Delta\beta_S / \beta_S^0 = A' + B'm \quad (6)$$

where  $\beta_S^0$  and  $\beta_S$  are the adiabatic compressibilities of the solvent and solution, respectively.  $A$  and  $B$  are the intercept and slope values of  $\Delta\beta_S$  versus  $m$  plot (see Figure 1), respectively. Similarly  $A'$  and  $B'$  stand for the intercept and slope values of ( $\Delta\beta_S/\beta_S^0$ ) versus  $m$  plot (see Figure 2), respectively. The values of  $\Delta\beta_S$  and ( $\Delta\beta_S/\beta_S^0$ ) are listed in Tables-4 and 5.

The apparent molal compressibility  $k_\phi$  values of alanine in aqueous paracetamol solution are obtained using the following equation [14] and are listed in Table-6.

$$k_\phi = M\beta_S/\rho - 1000(\beta_0\rho - \beta_S\rho_0)/m\rho\rho_0 \quad (7)$$

where  $M$  and  $m$  are the molar mass and molality of alanine;  $\rho$  and  $\rho_0$  are the densities of the solute and solvent, respectively.

**Table-1 Density ( $\rho$ ) of alanine in aqueous paracetamol solutions at different Temperatures**

$m_A$ (mol·kg <sup>-1</sup> )	$\rho \times 10^{-3}$ (kg·m <sup>-3</sup> )				
	$m_p = 0.00$ M	$m_p = 0.025$ M	$m_p = 0.05$ M	$m_p = 0.075$ M	$m_p = 0.1$ M
<b>T = 298.15 K</b>					
0.00	0.99706	0.99769	0.99837	0.99904	0.99973
0.02	0.99763	0.99830	0.99900	0.99969	1.00040
0.04	0.99819	0.99889	0.99962	1.00033	1.00106
0.06	0.99874	0.99947	1.00023	1.00095	1.00170
0.08	0.99927	1.00004	1.00083	1.00156	1.00233
0.10	0.99978	1.00059	1.00141	1.00215	1.00295
$\delta\rho =$	$4.16 \times 10^{-4}$	$4.43 \times 10^{-4}$	$4.65 \times 10^{-4}$	$4.75 \times 10^{-4}$	$4.92 \times 10^{-4}$
<b>T = 303.15 K</b>					
0.00	0.99560	0.99621	0.99689	0.99756	0.99824
0.02	0.99616	0.99681	0.99752	0.99820	0.99890
0.04	0.99670	0.99739	0.99812	0.99882	0.99955
0.06	0.99723	0.99797	0.99872	0.99942	1.00018
0.08	0.99771	0.99853	0.99931	0.99998	1.00080
0.10	0.99818	0.99907	0.99989	1.00055	1.00140
$\delta\rho =$	$3.95 \times 10^{-4}$	$4.37 \times 10^{-4}$	$4.57 \times 10^{-4}$	$4.56 \times 10^{-4}$	$4.83 \times 10^{-4}$
<b>T = 308.15 K</b>					
0.00	0.99403	0.99463	0.99530	0.99596	0.99663
0.02	0.99458	0.99521	0.99591	0.99658	0.99727
0.04	0.99512	0.99577	0.99650	0.99719	0.99790
0.06	0.99565	0.99633	0.99709	0.99778	0.99852
0.08	0.99616	0.99687	0.99768	0.99835	0.99910
0.10	0.99666	0.99740	0.99825	0.99891	0.99969
$\delta\rho =$	$4.02 \times 10^{-4}$	$4.23 \times 10^{-4}$	$4.50 \times 10^{-4}$	$4.51 \times 10^{-4}$	$4.67 \times 10^{-4}$
<b>T = 313.15 K</b>					
0.00	0.99228	0.99286	0.99354	0.99419	0.99485
0.02	0.99282	0.99342	0.99412	0.99480	0.99547
0.04	0.99335	0.99397	0.99470	0.99538	0.99608
0.06	0.99387	0.99450	0.99527	0.99595	0.99668
0.08	0.99438	0.99500	0.99582	0.99653	0.99723
0.10	0.99489	0.99550	0.99636	0.99709	0.99781
$\delta\rho =$	$3.98 \times 10^{-4}$	$4.03 \times 10^{-4}$	$4.32 \times 10^{-4}$	$4.42 \times 10^{-4}$	$4.51 \times 10^{-4}$
<b>T = 318.15 K</b>					
0.00	0.99032	0.99089	0.99156	0.99221	0.99287
0.02	0.99083	0.99142	0.99212	0.99278	0.99346
0.04	0.99133	0.99194	0.99266	0.99334	0.99404
0.06	0.99183	0.99245	0.99320	0.99390	0.99461
0.08	0.99232	0.99294	0.99374	0.99444	0.99517
0.10	0.99280	0.99341	0.99426	0.99498	0.99572
$\delta\rho =$	$3.79 \times 10^{-4}$	$3.86 \times 10^{-4}$	$4.12 \times 10^{-4}$	$4.24 \times 10^{-4}$	$4.35 \times 10^{-4}$

$m_A$  molality of alanine       $m_p$  molality of paracetamol

$\delta\rho$  uncertainty in density values

**Table-2 Ultrasonic velocity ( $u$ ,  $m \cdot s^{-1}$ ) of alanine in aqueous paracetamol solutions at different temperatures**

$m_A$ ( $mol \cdot kg^{-1}$ )	$u$ ( $ms^{-1}$ )				
	$m_p = 0.00$ M	$m_p = 0.025$ M	$m_p = 0.05$ M	$m_p = 0.075$ M	$m_p = 0.1$ M
T = 298.15 K					
0.00	1496.60	1498.90	1500.95	1502.70	1504.15
0.02	1497.86	1500.16	1502.22	1503.99	1505.45
0.04	1499.04	1501.34	1503.40	1505.18	1506.65
0.06	1500.15	1502.47	1504.54	1506.34	1507.82
0.08	1501.15	1503.44	1505.51	1507.32	1508.81
0.10	1502.15	1504.45	1506.53	1508.37	1509.87
$\delta u =$	$8.46 \times 10^{-4}$	$8.46 \times 10^{-4}$	$8.50 \times 10^{-4}$	$8.63 \times 10^{-4}$	$8.70 \times 10^{-4}$
T = 303.15 K					
0.00	1509.00	1511.32	1513.37	1515.10	1516.62
0.02	1510.25	1512.57	1514.63	1516.38	1517.91
0.04	1511.43	1513.74	1515.81	1517.57	1519.10
0.06	1512.56	1514.87	1516.96	1518.75	1520.29
0.08	1513.65	1515.91	1517.99	1519.82	1521.33
0.10	1514.63	1516.87	1518.95	1520.82	1522.34
$\delta u =$	$8.62 \times 10^{-4}$	$8.49 \times 10^{-4}$	$8.54 \times 10^{-4}$	$8.75 \times 10^{-4}$	$8.74 \times 10^{-4}$
T = 308.15 K					
0.00	1519.68	1522.02	1524.07	1525.82	1527.38
0.02	1520.92	1523.27	1525.33	1527.10	1528.68
0.04	1522.10	1524.45	1526.50	1528.28	1529.85
0.06	1523.22	1525.58	1527.64	1529.45	1531.02
0.08	1524.20	1526.57	1528.62	1530.46	1532.06
0.10	1525.14	1527.50	1529.55	1531.43	1533.04
$\delta u =$	$8.36 \times 10^{-4}$	$8.39 \times 10^{-4}$	$8.39 \times 10^{-4}$	$8.58 \times 10^{-4}$	$8.65 \times 10^{-4}$
T = 313.15 K					
0.00	1528.92	1531.26	1533.30	1535.06	1536.65
0.02	1530.17	1532.53	1534.58	1536.35	1537.96
0.04	1531.35	1533.70	1535.76	1537.54	1539.15
0.06	1532.47	1534.84	1536.90	1538.72	1540.32
0.08	1533.51	1535.92	1537.95	1539.77	1541.43
0.10	1534.38	1536.84	1538.87	1540.70	1542.37
$\delta u =$	$8.40 \times 10^{-4}$	$8.56 \times 10^{-4}$	$8.54 \times 10^{-4}$	$8.66 \times 10^{-4}$	$8.77 \times 10^{-4}$
T = 318.15 K					
0.00	1536.47	1538.80	1540.85	1542.60	1544.25
0.02	1537.73	1540.07	1542.13	1543.89	1545.55
0.04	1538.91	1541.26	1543.33	1545.11	1546.77
0.06	1540.04	1542.41	1544.48	1546.26	1547.95
0.08	1541.07	1543.47	1545.53	1547.34	1549.04
0.10	1541.99	1544.43	1546.48	1548.30	1550.02
$\delta u =$	$8.46 \times 10^{-4}$	$8.62 \times 10^{-4}$	$8.63 \times 10^{-4}$	$8.73 \times 10^{-4}$	$8.84 \times 10^{-4}$

$m_A$  molality of alanine       $m_p$  molality of paracetamol       $\delta u$  uncertainty in ultrasonic velocity values

By drawing a linear plot of  $k_\phi$  versus  $m$  (see the representative plot in Figure 3) the limiting apparent molal compressibility ( $k_\phi^0$ ) of alanine is evaluated [14] using the least-squares method of the following general equation:

$$k_\phi = k_\phi^0 + S_K m \quad (8)$$

where  $S_K$  is the experimental slope that is a measure of solute-solute interactions and  $k_\phi^0$  is the partial molal parameter at infinite dilution is a measure of solute-solvent interactions. The calculated values of  $k_\phi^0$  and  $S_K$  are listed in Table-7.

The number of water molecules ( $n_H$ ) hydrated to alanine are calculated using a method given by Millero et al. [15]

$$n_H = -k_\phi^0 (\text{elec}) / \beta_s^0 V_b^0 \quad (9)$$

where  $\beta_s^0$  is the adiabatic compressibility of the aqueous paracetamol solution and  $V_b^0$  is the molar volume of bulk water which is taken to be the molar volume of water in the

paracetamol solution. The calculated  $n_H$  values are given in Table-8.

The partial molal compressibilities of transfer ( $\Delta_{tr} k_\phi^0$ ) from water to aqueous paracetamol solutions are calculated using the following equation and are listed in Table-9.

$$\Delta k_\phi^0 = k_\phi^0 (\text{alanine in solution}) - k_\phi^0 (\text{alanine in water}) \quad (10)$$

McMillan-Mayer theory of solutions proposed by Kozak et al. [16] and further discussed by Friedman and Krishnan [17], Franks et al. [18] and Rajagopal et al. [19-23] has been used to analyse the solute-cosolute interactions in the solvation sphere. According to this theory, at infinite dilution,  $\Delta_{tr} k_\phi^0$  can be expressed as

$$\Delta_{tr} k_\phi^0 = 2K_{AP} m_P + 3K_{APP} m_P^2 \quad (11)$$

where A stands for alanine, P stands for paracetamol, and  $m_P$  is the molality of paracetamol. The constants  $K_{AP}$  and  $K_{APP}$  are pair and triplet interaction coefficients, respectively, and are given in Table-10.

**Table-3 Adiabatic Compressibility ( $\beta_S$ ) of alanine in aqueous paracetamol solutions at different temperatures**

$m_A$ (mol·kg <sup>-1</sup> )	$\beta_S \times 10^{11}$ (pa <sup>-1</sup> )				
	$m_p = 0.00$ M	$m_p = 0.025$ M	$m_p = 0.05$ M	$m_p = 0.075$ M	$m_p = 0.1$ M
<b>T = 298.15 K</b>					
0.00	44.78 (0.054)	44.61 (0.054)	44.46 (0.054)	44.33 (0.055)	44.21 (0.056)
0.02	44.68 (0.054)	44.51 (0.054)	44.36 (0.054)	44.22 (0.055)	44.11 (0.055)
0.04	44.58 (0.054)	44.41 (0.054)	44.26 (0.054)	44.12 (0.055)	44.01 (0.055)
0.06	44.49 (0.054)	44.32 (0.054)	44.17 (0.054)	44.03 (0.055)	43.91 (0.055)
0.08	44.41 (0.053)	44.24 (0.054)	44.08 (0.054)	43.95 (0.054)	43.82 (0.055)
0.10	44.33 (0.052)	44.16 (0.053)	44.00 (0.054)	43.86 (0.054)	43.74 (0.055)
<b>T = 303.15 K</b>					
0.00	44.11 (0.053)	43.95 (0.053)	43.80 (0.053)	43.67 (0.054)	43.55 (0.054)
0.02	44.01 (0.053)	43.85 (0.053)	43.70 (0.053)	43.57 (0.054)	43.45 (0.054)
0.04	43.92 (0.053)	43.76 (0.053)	43.60 (0.053)	43.47 (0.054)	43.35 (0.054)
0.06	43.83 (0.053)	43.66 (0.053)	43.51 (0.053)	43.38 (0.054)	43.26 (0.054)
0.08	43.75 (0.053)	43.58 (0.052)	43.43 (0.053)	43.29 (0.054)	43.17 (0.054)
0.10	43.67 (0.053)	43.50 (0.052)	43.35 (0.053)	43.21 (0.054)	43.09 (0.054)
<b>T = 308.15 K</b>					
0.00	43.56 (0.051)	43.40 (0.051)	43.25 (0.052)	43.13 (0.052)	43.01 (0.053)
0.02	43.47 (0.051)	43.30 (0.051)	43.16 (0.051)	43.03 (0.052)	42.91 (0.053)
0.04	43.37 (0.051)	43.21 (0.051)	43.07 (0.051)	42.94 (0.052)	42.82 (0.052)
0.06	43.29 (0.051)	43.12 (0.051)	42.98 (0.051)	42.84 (0.052)	42.72 (0.052)
0.08	43.21 (0.051)	43.05 (0.051)	42.90 (0.051)	42.76 (0.052)	42.64 (0.052)
0.10	43.14 (0.05)	42.97 (0.051)	42.82 (0.051)	42.69 (0.052)	42.56 (0.052)
<b>T = 313.15 K</b>					
0.00	43.11 (0.05)	42.96 (0.051)	42.81 (0.051)	42.69 (0.052)	42.57 (0.052)
0.02	43.02 (0.05)	42.86 (0.051)	42.72 (0.051)	42.59 (0.052)	42.47 (0.052)
0.04	42.93 (0.05)	42.77 (0.051)	42.62 (0.051)	42.50 (0.051)	42.38 (0.052)
0.06	42.84 (0.05)	42.68 (0.051)	42.54 (0.051)	42.41 (0.051)	42.29 (0.052)
0.08	42.76 (0.05)	42.60 (0.051)	42.46 (0.051)	42.33 (0.051)	42.20 (0.052)
0.10	42.69 (0.05)	42.53 (0.05)	42.38 (0.051)	42.25 (0.051)	42.13 (0.052)
<b>T = 318.15 K</b>					
0.00	42.77 (0.05)	42.62 (0.051)	42.48 (0.051)	42.35 (0.051)	42.23 (0.052)
0.02	42.68 (0.05)	42.53 (0.05)	42.38 (0.051)	42.26 (0.051)	42.14 (0.052)
0.04	42.59 (0.05)	42.44 (0.05)	42.29 (0.05)	42.17 (0.051)	42.05 (0.052)
0.06	42.51 (0.05)	42.35 (0.05)	42.21 (0.05)	42.08 (0.051)	41.96 (0.051)
0.08	42.43 (0.05)	42.27 (0.05)	42.13 (0.05)	42.00 (0.051)	41.88 (0.051)
0.10	42.36 (0.05)	42.20 (0.05)	42.05 (0.05)	41.93 (0.051)	41.80 (0.051)

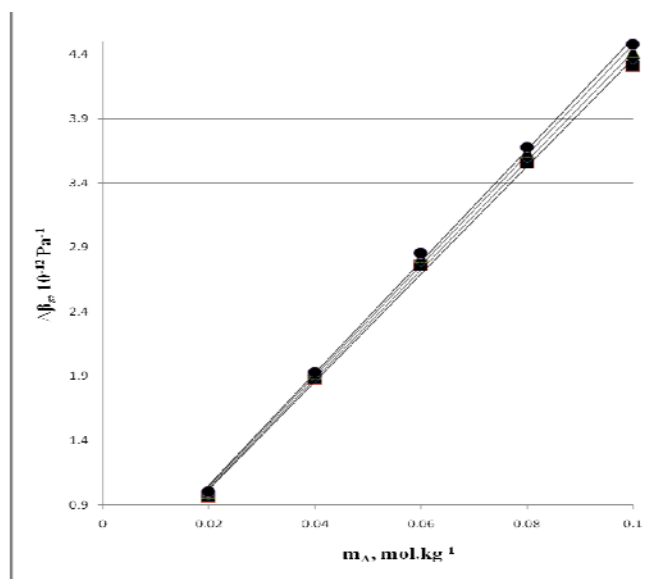
Paranthesis indicates uncertainty in  $\beta_S$  values

Figure 1. Plot of change in adiabatic compressibility ( $\Delta\beta_S$ ) versus molality of amino acid ( $m_A$ ) at various molal concentrations of aqueous paracetamol solutions at  $T = 308.15$  K: 0.025 M, ■, 0.05M, ◆, 0.075 M, ▲, 0.1 M, ●.

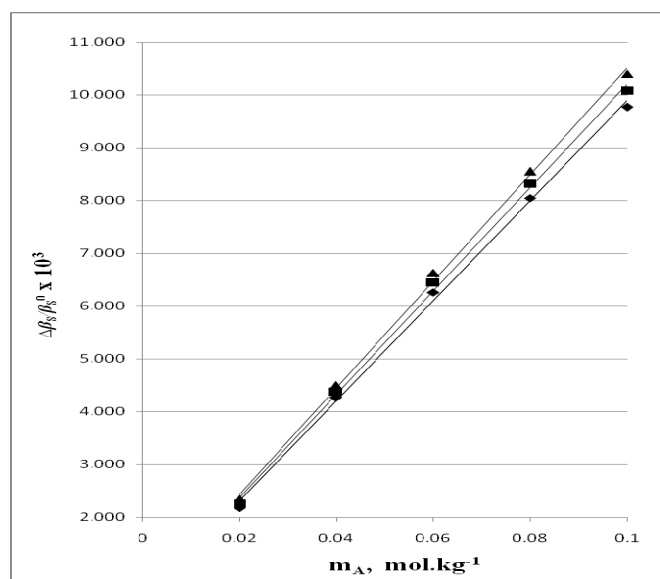


Figure 2. Plot of relative change in adiabatic compressibility ( $\Delta\beta_S/\beta_S^0$ ) versus molality of amino acid ( $m_A$ ) at various molal concentrations of aqueous paracetamol solutions at  $T = 308.15$  K: 0.00 M, ●, 0.05 M, ◆, 0.1 M, ▲.

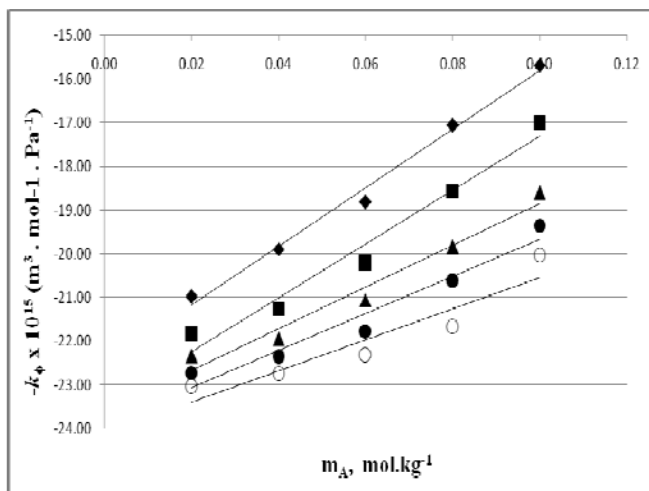


Figure 3. Plot of apparent molal compressibility ( $-k_{\phi}$ ) versus molality of amino acid ( $m_A$ ) at various molal concentrations of aqueous paracetamol solutions at  $T = 308.15$  K: 0.00 M,  $\blacklozenge$ , 0.025 M,  $\blacksquare$ , 0.05 M,  $\blacktriangle$ , 0.075 M,  $\bullet$ , 0.1 M,  $\circ$ .

### DISCUSSION

The effectiveness of solute-solvent interactions [24] leads to the indication of greater association of molecules that is substantiated by an increase in the ultrasonic speed in any solution with the addition of a solute (see Table-2). With an increase in the concentration of alanine, paracetamol and the temperature of the solution, the adiabatic compressibility ( $\beta_S$ ) decreases [25].

The decrease in adiabatic compressibility with an increase in concentration of alanine may be attributed to (i) an increase in the number of incompressible

molecules/zwitterions in (ternary system) solution and (ii) the formation of the compact structure of zwitterions-aquatic dipoles and zwitterions-ions structures in solutions. The changes occurring in the water structure around zwitterions-ions [26] leads to the decrease in adiabatic compressibility values with increasing temperature. Water is considered to be an equilibrium medley of two structures such as an ice-like structure and a close-packed structure [19,20]. The compressibility of liquid water is given by

$$\beta_S = \beta_{\alpha} + \beta_{\text{relax}}/(1 + \omega^2\tau^2),$$

where  $\beta_{\alpha}$  is an instantaneous part of the compressibility and  $\beta_{\text{relax}}$  is a relaxational part of the compressibility.

$\omega$  is the angular frequency

$\tau$  is the relaxation time and is of the order of  $10^{-11}$  s corresponding to  $\beta_{\text{relax}}$ .

In our case the relation,  $\omega\tau < 1$ . Thus,

$$\beta_S = \beta_{\alpha} + \beta_{\text{relax}}$$

When the temperature increases,  $\beta_{\alpha}$  increases due to thermal expansion and  $\beta_{\text{relax}}$  decreases due to thermal burst of the ice-like structure. Thus, the decrease in compressibility with increase in temperature may be ascribed to the corresponding decrease in  $\beta_{\text{relax}}$  which is dominant over the corresponding increase in  $\beta_{\alpha}$ . The values of  $\Delta\beta_S$  and  $(\Delta\beta_S/\beta_S^0)$  (see Table-4 and 5) show an increasing trend of variation with an increase in concentration of solute(alanine) which may be attributed to an increase in the incompressible part in a solution and the variation with temperature may be attributed to the thermal rupture of the water structure.

Table-4 Change in adiabatic compressibility ( $\Delta\beta_S$ ) of alanine in aqueous paracetamol solutions at different temperatures

$m_A$ (mol·kg <sup>-1</sup> )	$\Delta\beta_S \times 10^{12}$ (pa <sup>-1</sup> )				
	$m_p = 0.00$ M	$m_p = 0.025$ M	$m_p = 0.05$ M	$m_p = 0.075$ M	$m_p = 0.1$ M
<b>T = 298.15 K</b>					
0.02	1.01	1.02	1.03	1.05	1.06
0.04	1.96	1.98	2.00	2.03	2.05
0.06	2.87	2.91	2.94	2.98	3.01
0.08	3.69	3.73	3.78	3.82	3.87
0.10	4.51	4.57	4.63	4.69	4.75
<b>T = 303.15 K</b>					
0.02	0.98	0.99	1.00	1.02	1.03
0.04	1.90	1.92	1.95	1.97	1.99
0.06	2.79	2.83	2.87	2.90	2.94
0.08	3.63	3.67	3.71	3.76	3.80
0.10	4.40	4.46	4.52	4.57	4.63
<b>T = 308.15 K</b>					
0.02	0.95	0.96	0.98	0.99	1.01
0.04	1.86	1.88	1.89	1.92	1.93
0.06	2.73	2.76	2.79	2.83	2.85
0.08	3.51	3.55	3.60	3.64	3.68
0.10	4.25	4.31	4.36	4.42	4.48
<b>T = 313.15 K</b>					
0.02	0.94	0.95	0.97	0.98	0.99
0.04	1.83	1.84	1.87	1.88	1.91
0.06	2.68	2.71	2.75	2.78	2.80
0.08	3.48	3.52	3.56	3.60	3.65
0.10	4.19	4.24	4.30	4.35	4.41
<b>T = 318.15 K</b>					
0.02	0.92	0.93	0.94	0.95	0.96
0.04	1.79	1.81	1.83	1.86	1.87
0.06	2.63	2.66	2.69	2.72	2.75
0.08	3.41	3.45	3.49	3.54	3.58
0.10	4.12	4.17	4.23	4.28	4.34

Table-5 Relative change in adiabatic compressibility( $\Delta\beta_s/\beta_s^0$ ) of alanine in aqueous paracetamol solutions at different temperatures

$m_A$ (mol·kg <sup>-1</sup> )	$\Delta\beta_s/\beta_s^0 \times 10^3$				
	$m_p = 0.00$ M	$m_p = 0.025$ M	$m_p = 0.05$ M	$m_p = 0.075$ M	$m_p = 0.1$ M
<b>T = 298.15 K</b>					
0.02	2.252	2.289	2.325	2.364	2.395
0.04	4.381	4.445	4.508	4.575	4.640
0.06	6.401	6.519	6.622	6.726	6.819
0.08	8.251	8.366	8.497	8.621	8.745
0.10	10.076	10.241	10.412	10.584	10.749
<b>T = 303.15 K</b>					
0.02	2.216	2.253	2.291	2.326	2.359
0.04	4.313	4.374	4.442	4.508	4.569
0.06	6.329	6.437	6.548	6.651	6.752
0.08	8.237	8.356	8.482	8.605	8.725
0.10	9.986	10.146	10.309	10.472	10.633
<b>T = 308.15 K</b>					
0.02	2.182	2.222	2.261	2.297	2.338
0.04	4.269	4.327	4.380	4.446	4.492
0.06	6.262	6.360	6.453	6.557	6.630
0.08	8.048	8.186	8.314	8.434	8.554
0.10	9.767	9.920	10.085	10.245	10.406
<b>T = 313.15 K</b>					
0.02	2.176	2.219	2.255	2.291	2.325
0.04	4.245	4.293	4.369	4.415	4.477
0.06	6.220	6.301	6.414	6.510	6.587
0.08	8.077	8.197	8.319	8.442	8.564
0.10	9.709	9.881	10.041	10.195	10.348
<b>T = 318.15 K</b>					
0.02	2.152	2.182	2.220	2.248	2.274
0.04	4.184	4.245	4.313	4.384	4.429
0.06	6.146	6.240	6.336	6.425	6.516
0.08	7.964	8.094	8.224	8.350	8.472
0.10	9.627	9.796	9.961	10.117	10.272

The apparent molal compressibility ( $k_\phi$ ) is related to the second pressure differential of the partial molal free energy of the solute and is known to be very sensitive to changes in solvation, hydrogen bonding, and structural changes of water in the watery medium. The estimations of  $k_\phi$  are negative (see Table-6) which indicates the strong interactions between solute–solvent molecules. By definition  $k_\phi^0$  values are free from solute–solute interactions and therefore furnish information about strong solute–solvent interactions. Generally, electrolytes in aqueous solution has negative limiting apparent molal compressibility ( $k_\phi^0$ ), and the magnitude depends upon the charges of cations(electrostriction).

The negative values are attributed to hydration of cations (water-losing compressibility due to coulombic attraction) [11]. The high negative values of  $k_\phi^0$  at low temperatures are attributed to the strong attractive interactions between the drug and water. With increase in temperature the  $k_\phi^0$  values become less negative. It suggests that electrostriction reduces and some water

molecules are released to the bulk water, rendering the solutions more compressible at higher temperatures [27-29].

It is found that  $k_\phi^0$  decrease linearly with the concentration of paracetamol in solution (see Table-8). It indicates that the cosolute–solvent interactions decrease with increasing concentration of paracetamol in solution. A similar observation was made by Doyel M. Bhattacharya et al. [25] for antihelmintic drug in aqueous solutions.

On the basis of the continuum model [30] of a solution, the limiting apparent molal adiabatic compressibility,  $k_\phi^0$ , of a solute may be expressed as

$$k_\phi^0 = k_\phi^0(\text{int}) + n_H (k_{\phi_h}^0 + k_{\phi_b}^0) \quad (12)$$

where  $k_\phi^0(\text{int})$  is the intrinsic compressibility of a solute (alanine) molecule, and  $k_{\phi_h}^0$  and  $k_{\phi_b}^0$  are the apparent molal adiabatic compressibilities of water in the hydration shell and in the bulk state of a solution.

**Table-6 Apparent molal compressibility ( $k_\phi$ ) of alanine in aqueous paracetamol solutions at different temperatures**

$m_A$ (mol·kg <sup>-1</sup> )	$k_\phi \times 10^{15}$ (m <sup>3</sup> ·mol <sup>-1</sup> ·Pa <sup>-1</sup> )				
	$m_p = 0.00$ M	$m_p = 0.025$ M	$m_p = 0.05$ M	$m_p = 0.075$ M	$m_p = 0.1$ M
<b>T = 298.15 K</b>					
0.02	-23.47	-25.09	-26.33	-27.42	-28.45
0.04	-22.05	-23.45	-24.66	-25.69	-26.76
0.06	-20.74	-22.26	-23.56	-24.57	-25.60
0.08	-19.04	-20.38	-21.65	-22.56	-23.61
0.10	-17.85	-19.31	-20.63	-21.60	-22.73
<b>T = 303.15 K</b>					
0.02	-22.15	-23.75	-25.07	-25.98	-27.08
0.04	-20.69	-22.15	-23.31	-24.28	-25.42
0.06	-19.57	-21.23	-22.44	-23.33	-24.58
0.08	-18.17	-19.90	-21.04	-21.63	-22.98
0.10	-16.60	-18.47	-19.70	-20.30	-21.68
<b>T = 308.15 K</b>					
0.02	-20.97	-22.41	-23.76	-24.70	-25.86
0.04	-19.89	-20.97	-22.09	-23.07	-23.87
0.06	-18.81	-20.02	-21.25	-22.14	-23.07
0.08	-17.06	-18.34	-19.70	-20.34	-21.33
0.10	-15.69	-16.90	-18.32	-18.95	-20.04
<b>T = 313.15 K</b>					
0.02	-20.46	-21.74	-22.95	-24.17	-25.02
0.04	-19.26	-20.12	-21.45	-22.13	-23.14
0.06	-18.15	-19.01	-20.43	-21.22	-22.18
0.08	-16.93	-17.72	-19.08	-19.97	-20.76
0.10	-15.24	-16.05	-17.47	-18.38	-19.23
<b>T = 318.15 K</b>					
0.02	-19.19	-20.19	-21.49	-22.36	-23.19
0.04	-17.86	-18.86	-20.01	-21.10	-21.88
0.06	-16.95	-17.91	-19.07	-20.04	-20.93
0.08	-15.70	-16.60	-17.91	-18.81	-19.74
0.10	-14.25	-15.09	-16.49	-17.43	-18.35

**Table-7 Limiting apparent molal compressibility,  $k_\phi^0$ , and slope,  $S_K$ , of alanine in aqueous paracetamol solutions at various temperatures**

Temp (K)	$k_\phi^0 \times 10^{15} / (\text{m}^3 \cdot \text{mol}^{-1} \cdot \text{Pa}^{-1})$ & $S_K \times 10^{15} / (\text{m}^3 \cdot \text{mol}^{-2} \cdot \text{kg} \cdot \text{Pa}^{-1})$									
	$m_p = 0.00$ M mol·kg <sup>-1</sup>		$m_p = 0.025$ M mol·kg <sup>-1</sup>		$m_p = 0.05$ M mol·kg <sup>-1</sup>		$m_p = 0.075$ M mol·kg <sup>-1</sup>		$m_p = 0.1$ M mol·kg <sup>-1</sup>	
298.15	-24.910 (0.019)	7.133	-26.48 (0.033)	7.318	-27.68 (0.037)	7.201	-28.80 (0.042)	7.391	-29.80 (0.045)	7.296
303.15	-23.510 (0.021)	6.807	-24.94 (0.028)	6.410	-26.21 (0.033)	6.503	-27.30 (0.03)	6.997	-28.32 (0.032)	6.625
308.15	-22.490 (0.038)	6.687	-23.82 (0.031)	6.825	-25.00 (0.033)	6.633	-26.10 (0.034)	7.116	-27.09 (0.045)	7.099
313.15	-21.830 (0.031)	6.388	-23.06 (0.027)	6.894	-24.27 (0.027)	6.671	-25.29 (0.047)	6.869	-26.25 (0.036)	6.982
318.15	-20.390 (0.025)	6.043	-21.46 (0.026)	6.231	-22.62 (0.024)	6.048	-23.59 (0.015)	6.077	-24.36 (0.021)	5.910

Parantheses indicates the standard deviation.

**Table-8 Hydration number ( $n_H$ ) of alanine in aqueous paracetamol solutions at various temperatures**

$m_p$ (M) mol·kg <sup>-1</sup>	$n_H$				
	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
0.000	3.075	2.902	2.777	2.695	2.517
0.025	3.269	3.079	2.941	2.847	2.649
0.050	3.417	3.236	3.086	2.996	2.793
0.075	3.556	3.370	3.222	3.122	2.912
0.100	3.679	3.496	3.344	3.241	3.007

**Table-9** Transfer apparent molal compressibility ( $\Delta_{tr}k_{\phi}^0$ ) of alanine in aqueous paracetamol solutions at various temperatures

Temp (K)	$\Delta_{tr}k_{\phi}^0 \times 10^{15} (\text{m}^3 \cdot \text{mol}^{-1} \cdot \text{Pa}^{-1})$			
	$m_p = 0.025 \text{ M}$ $\text{mol} \cdot \text{kg}^{-1}$	$m_p = 0.05 \text{ M}$ $\text{mol} \cdot \text{kg}^{-1}$	$m_p = 0.075 \text{ M}$ $\text{mol} \cdot \text{kg}^{-1}$	$m_p = 0.1 \text{ M}$ $\text{mol} \cdot \text{kg}^{-1}$
298.15	-1.57	-2.77	-3.89	-4.89
303.15	-1.43	-2.70	-3.79	-4.81
308.15	-1.33	-2.51	-3.61	-4.60
313.15	-1.23	-2.44	-3.46	-4.42
318.15	-1.07	-2.23	-3.20	-3.97

**Table-10** Pair ( $K_{AP}$ ) and triplet ( $K_{APP}$ ) interactions of alanine in aqueous paracetamol solutions at various temperatures

Temp (K)	$K_{AP}$	$K_{APP}$
	$(\text{mol}^{-2} \cdot \text{Pa}^{-1} \cdot \text{kg})$	$(\text{mol}^{-1} \cdot \text{Pa}^{-1} \cdot \text{kg}^2)$
298.15	-33.025	60.31
303.15	-30.075	41.02
308.15	-27.650	31.56
313.15	-25.750	23.56
318.15	-22.625	14.98

The triplet interaction coefficients,  $K_{APP}$ , are positive and pair interaction coefficients,  $K_{AP}$ , are only negative shown in Table-10. The negative estimations of the pair interaction coefficients,  $K_{AP}$ , suggest that weak interactions occur due to the overlap of hydration spheres of solute-cosolute molecules. The large positive  $K_{APP}$  values propose the mastery of triplet interactions for the alanine over pair compressibility interaction parameters [35] which substantiates the results given by volumetric and transport properties [8].

The bulk water has an open structure when compared to electrostricted water and is therefore more compressible. When paracetamol is added the electrostricted water behaves like bulk water, and this depicts that the limiting apparent molal adiabatic compressibilities of amino acids in mixed solvents becomes smaller than the corresponding ones in water as given in Table-7. The positive values of  $S_K$  predicts weak solute-solute interactions. Hydration number reflects the changes in electrostriction. The  $n_H$  values calculated from compressibility data (see Table-8) are high in aqueous paracetamol solutions as compared to water and increase with increasing concentration and decrease with increase in temperature. The trend of  $n_H$  values from compressibility data shows weak solute-cosolute interactions.

The limiting apparent molal compressibilities of transfer,  $\Delta_{tr}k_{\phi}^0$ , from water to paracetamol at infinite dilution are found to be negative and increases with the rise in temperature and decreases with increase in paracetamol concentration. (see Table-9). The negative value  $\Delta_{tr}k_{\phi}^0$  for the alanine in aqueous paracetamol solutions result from the overlap of hydration co-spheres of hydrophobic - hydrophobic groups and ionic - hydrophobic / hydrophilic - hydrophobic groups leads to a net decrease in volume could be explained by the co-sphere overlap model developed by Friedman and Krishnan [31]. The types of the interaction occurring between alanine and aqueous paracetamol can be classified as follows [32,33].

- The hydrophilic-ionic interaction between OH groups of paracetamol and zwitterions of alanine.
- Hydrophilic-hydrophilic interaction the OH groups of paracetamol and NH groups in the side chain of acid alanine mediated through hydrogen bonding.
- Hydrophilic-hydrophobic/ionic-hydrophobic interaction between the OH groups/ $\text{H}^+$ ,  $\text{O}^-$  of paracetamol molecule and non-polar ( $-\text{CH}_3$ ) in the side chain of alanine molecule.
- Hydrophobic-hydrophobic group interactions between the non-polar groups (Benzene ring) of Paracetamol and non-polar ( $-\text{CH}_3$ ) in the side chain of alanine molecule.

The negative values for  $\Delta_{tr}k_{\phi}^0$  for the ternary system suggest that the increased hydrophobic interactions with the carbon skeleton of the paracetamol leads to the disruption of the hydration sphere of the charged centre of the drug and the positive contribution to the  $\Delta_{tr}k_{\phi}^0$  gets reduced. These negative values of transfer attributed to the interactions occurring indicates the dominance of hydrophobic-ionic interactions over those of the hydrophilic-ionic interactions which substantiates the results given by volumetric and transport properties [8]. These interactions contributed by the presence of paracetamol increases the electrostriction of neighboring water molecules around the charged centers of alanine(solute). Here in the neighborhood of the solute, water is not allowing the solute to enter the bulk due to the pressure [34], thus making a negative contribution to  $\Delta_{tr}k_{\phi}^0$ . This observation means that the dehydration of solute and cosolute is low. Doyel M. Bhattacharya et al. [25] also reported negative  $\Delta_{tr}k_{\phi}^0$  values for antihelmintic drug in aqueous NaCl solutions.



## CONCLUSION

The compressibilities studies of alanine in aqueous paracetamol have shown the presence of weak solute-solute interactions and strong solute-solvent interactions which substantiates the volumetric and viscometric studies [8].

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