

Elucidation of Molecular Interactions of Non-Steroidal Anti-Inflammatory Drug Diclofenac Potassium in Aqueous and Aqueous Urea Solutions: Acoustic and Viscometric Approach

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Abstract: In this work, the physicochemical approach is proposed to reproduce the ultrasonic velocity and viscosity of diclofenac potassium over a range of temperature and concentration in aqueous and aqueous solutions of urea. Ultrasonic velocity (U) is measured at 298.15 K only. Using U values acoustic parameters like apparent molar compressibility ($K_{s,\phi}$), isentropic compressibility (K_s), molar compressibility (W), acoustic impedance (Z), internal pressure (π_i), free volume (V_f), relative association (R_A), molar sound velocity (R) and free length (L_f) have been evaluated. The relative viscosity data are analyzed at (298.15- 313.15) K using Jones-Dole relation and A_F and B_j coefficients are derived and discussed. Using the viscosity data Gibbs free energy of activation of viscous flow per mole of the solvent $\Delta\mu_1^{0*}$ And of solute $\Delta\mu_2^{0*}$ were obtained. The results were discussed in terms of solute-solute and solute-solvent interactions in the studied systems.

Keywords: Diclofenac potassium; ultrasonic velocity; acoustic parameters; viscosity; molecular interactions.

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1. Introduction

The influence of a substance's different physical and chemical properties on the biomolecule is directly related to that compound's capability to extract therapeutic or pharmacological effects. Such properties are called physicochemical properties [1-4]. The study of these properties in the field of medicine and pharmacy has attended great importance, particularly for the poorly water-soluble drug entities. Human pharmaceutical compounds have gained wide attention from health and environmental agencies due to their inherent biological activity and pervasive environmental occurrence. Even from wastewater treatment plants, the direct discharge of treated and untreated wastewater pollutes the aquatic environment and aquatic life; their toxic effects are more dangerous in soluble and aggregated solutions. Estimation shows more than 40% of pharmaceutically potent compounds are water-insoluble bearing variable bioavailability [5, 6]. Poor aqueous solubility of drug compounds gained prime attention in the pharmaceutical field. Numerous research groups have previously undertaken different techniques like co-solvency, hydrotropy, use of a buffer, changing pH, complexation, emulsions, microemulsions, percolation, etc. [7, 8]. Diclofenac is claimed to

increase the chance of cardiovascular side effects and gastrointestinal bleeding. DP sparingly dissolves in water but is soluble in organic solvents [9]. There were found adequate examples to adopt various approaches for increasing the aqueous solubility of DP, as noted above. Amongst those techniques use of hydrotropes or chaotropes, which increase the aqueous solubility of drug solute, is an easy and error-free method. The compound that stabilizes hydrophobic compounds in water is called hydrotrope, and it consists of a small hydrophobic part and a big hydrophilic part.

Aqueous urea has gained special attention being the basis of divergent studies for various researchers cause of stimulating properties of higher concentrations of aqueous urea. Aqueous urea is a crucial mixed solvent. For the concentration above 6 to 8 mol. L⁻¹, urea acts as a strong protein denaturant. While a drug is taken to change the protein concentration, it will bind with receptor proteins inside the body. Hence, in this paper, we have investigated the interactions of urea and DP in an aqueous medium for 1M urea concentration under its denaturation concentration.

To the best of our knowledge, it is one of the new studies to investigate and analyze various physicochemical properties in terms of the molecular interactions for the drug DP solution in binary and ternary mixtures of DP, water, and urea. This article continues our research, where we investigated the solubility and different molecular interactions of drug solutes in aqueous, organic, and aqueous hydrotropic agent solvents at experimental temperatures and atmospheric pressure. Here in this paper, we report various experimental as well as derived parameters from the ultrasonic and viscosity studies. From the U values, apparent molar compressibility ($K_{s,\phi}$), isentropic compressibility (K_s), molar compressibility (W), acoustic impedance (Z), internal pressure (π_i), free volume (V_f), and relative association (R_A), molar sound velocity (R) and free length (L_f), and from the viscosity data A_F and B_J coefficients are derived using the Jones-Dole relation and discussed in the light of molecular interactions. Using the viscosity data Gibbs free energy of activation of viscous flow per mole of the solvent $\Delta\mu_1^{0*}$, and of solute $\Delta\mu_2^{0*}$ were also obtained.

In the present work, the studied temperature in the range of 298.2 K to 318.2 K was selected. Knowing all such physicochemical properties is crucial to understanding hydrophobic-hydrophobic, hydrophilic-hydrophilic, ion-hydrophobic, and ion-hydrophilic types of interactions prevailing in the binary and ternary mixtures of the drug solute under investigation [10].

2. Materials and Methods

2.1. Materials and sample preparation.

Diclofenac potassium (DP) and urea having molecular weights 334.24 and 60.06 g/mol purity $\geq 99\%$ were obtained from Orissa Drugs & Chemicals Ltd. (ODCL), Bhubaneswar, Odisha, and Laboratory Chemicals Bhubaneswar, Odisha, respectively, and used as received. To do the whole experimental work, double distilled water was used to prepare the DP solutions of different concentrations in molality. To make the stock solutions of 1M urea (solvent) for the different concentrations of DP, urea was weighed on a digital weighing machine with a precision of ± 0.001 mg. In the same way, DP was weighed to make its aqueous solution as well as solutions in 1M urea solvent for seven different concentrations to do the experimental work. Then the experiments were carried out at four different temperatures (298.15 – 313.15 K).

2.2. Methods.

The density measurements were carried out per the procedure given elsewhere [11]. The standard uncertainties in density measurements were estimated as $\pm 0.01 \text{ kg} \cdot \text{m}^{-3}$. The ultrasonic velocity measurement was done using an Ultrasonic Interferometer (Mittal Enterprises, New Delhi, India) at a frequency of 2 MHz at 298.15 K only. The accuracy of the ultrasonic velocity measurement is within $\pm 0.5 \text{ m/s}$ [12]. Ultrasonic velocity can be treated as thermodynamic property since the ultrasonic absorption is small due to the acoustic waves' low amplitude and low frequency (2 MHz). A calibrated Ostwald viscometer of 25mL capacity was used to measure the viscosity of the drug solutions at the experimental temperatures ($T = 298.15\text{-}313.15\text{K}$) and the atmospheric pressure. The densities, speed of the sound, and viscosity values are extremely sensitive to temperature, so it was controlled to $\pm 0.01 \text{ K}$ by keeping it in a water thermostat.

3. Results and Discussion

3.1. Ultrasonic velocity study.

Ultrasonic velocity is one of the most important physical properties of liquids that are of great interest in pure and applied sciences. Ultrasonic or sound waves are a series of expansions and compressions in the medium surrounding them. Though we are imaging these ultrasonic or sound waves like traveling through the air, these also propagate through other mediums like liquid. For a sound wave, the propagation velocity can be obtained by multiplication of wave frequency with the measured wavelength of sound wave [13, 14].

The velocity of a sound wave is strongly dependent on the medium's temperature, pressure, density, chemical structure, etc. This velocity for the ultrasonic waves in liquids varies from 700 to 2500 m/s. The ultrasonic technique is a dynamic and useful tool in the investigation of molecular interactions in the solution. Thus to understand the effect of concentration, temperature, and nature of solvent on the existing molecular interactions in the drug solution, the ultrasonic technique is used to find the acoustic parameters like apparent molar compressibility ($K_{s,\phi}$), isentropic compressibility (K_s), free volume (V_f), acoustic impedance (Z), internal pressure (π_i) molar compressibility (W), relative association (R_A), molar sound velocity (R) and free length (L_f). The ultrasonic velocity as well as all its derived parameters have been evaluated only at 298.15K.

Table 1. Ultrasonic velocity U ($\text{m} \cdot \text{s}^{-1}$), isentropic compressibility K_s ($\text{m}^3 \cdot \text{mol}^{-1}$), isentropic molar compressibility $K_{s,\phi}$ ($\text{m}^3 \cdot \text{mol}^{-1} \cdot \text{Pa}^{-1}$), free length L_f (m), vander Waals constant b ($\text{m}^3 \cdot \text{mol}^{-1}$), molar sound velocity R ($\text{m}^{\frac{-8}{3}} \cdot \text{s}^{\frac{-1}{3}}$), relative association (R_A) and molar compressibility (W) for DP in water and water + 1M urea as a function of molality at 298.15 K.

m ($\text{mol} \cdot \text{kg}^{-1}$)	U ($\text{m} \cdot \text{s}^{-1}$)	$K_s \times 10^{10}$ $\text{m}^3 \cdot \text{mol}^{-1}$	$K_{s,\phi} \times 10^7$ ($\text{m}^3 \cdot \text{mol}^{-1} \cdot \text{Pa}^{-1}$)	$L_f \times 10^3$ (m)	$b \times 10^5$ ($\text{m}^3 \cdot \text{mol}^{-1}$)	$R \times 10^5$ ($\text{m}^{\frac{-8}{3}} \cdot \text{s}^{\frac{-1}{3}}$)	$R_A \times 10^2$	$W \times 10^5$
Water								
0.0000	1496.8							
0.0266	1502.4	4.43	-7.07	4.33	2.64	20.77	100.28	39.33
0.0399	1505.2	4.40	-5.61	4.31	2.66	20.82	100.43	39.45
0.0531	1509.6	4.36	-5.06	4.30	2.69	20.89	100.55	39.57
0.0663	1513.2	4.33	-4.69	4.28	2.71	20.94	100.71	39.69
0.0795	1516.4	4.31	-4.23	4.27	2.74	21.03	100.72	39.85
0.0928	1519.2	4.29	-3.87	4.26	2.77	21.11	100.73	40.02
0.1059	1523.2	4.26	-3.76	4.25	2.79	21.18	100.83	40.15

Water + 1M urea

m (mol. kg ⁻¹)	U (m.s ⁻¹)	K _s × 10 ¹⁰ m ³ . mol ⁻¹	K _{s,φ} × 10 ⁷ (m ³ . mol ⁻¹ . Pa ⁻¹)	L _f × 10 ³ (m)	b × 10 ⁵ (m ³ . mol ⁻¹)	R × 10 ⁵ (m ⁻⁸ . s ⁻¹)	R _A × 10 ²	W × 10 ⁵
0.0000	1507.0							
0.0239	1512.0	4.07	-17.01	4.15	2.48	19.34	106.24	36.99
0.0356	1515.2	4.04	-12.31	4.14	2.50	19.39	106.35	37.09
0.0474	1519.2	4.02	-9.89	4.12	2.52	19.45	106.37	37.21
0.0592	1522.0	4.00	-8.32	4.11	2.54	19.51	106.42	37.33
0.0709	1525.6	3.98	-7.29	4.10	2.56	19.58	106.41	37.46
0.0827	1529.2	3.95	-6.55	4.09	2.58	19.65	106.39	37.60
0.0943	1532.8	3.93	-6.04	4.08	2.61	19.71	106.43	37.72

U_o (Ultrasonic velocity of water = 1496.63 [16])

K_s⁰(water) = 4.59 × 10⁻¹⁰ m³. mol⁻¹, K_s⁰ (water + 1M urea) = 4.21 × 10⁻¹⁰ m³. mol⁻¹

K_{s,φ}⁰(water) = -9.79 × 10⁻⁷(m³. mol⁻¹. Pa⁻¹), K_{s,φ}⁰ (water + 1M urea) = -2.31 × 10⁻⁷. (m³. mol⁻¹. Pa⁻¹)

Standard uncertainties are, u (m) = 0.1(10⁻³mol. kg⁻¹), u (U) = ± 0.1(m.s⁻¹).

Standard error of K_s⁰(water) = 0.008, K_s⁰ (water + 1M urea) = 0.01075 and K_{s,φ}⁰ (water) = 0.54538,

K_{s,φ}⁰ (water + 1M urea) = 0.15262.

For ultrasonic velocity, the experimental values of the solvent and solutions are given in Table 1, which shows the ultrasonic velocity increases with an increase in the concentration of DP in water as well as water + 1M urea medium, that may be due to the increase in mass of the DP as concentration increases. A similar trend is also reported by Sulochana Singh *et al.* for DP in higher compositions of urea in solution [15]. It is also clear from this plot that ultrasonic velocity for DP is more in water + 1M urea solvent than water which may be due to the increased mass of the former solvent and hence more interactions.

Isentropic compressibility, K_s is $-\frac{1}{V} \left(\frac{\partial V}{\partial P} \right)_S$ [17], where V, P, and S represent the volume, pressure, and entropy of the system. K_s can be obtained by using the Newton-Laplace equation, which is represented as equation (1) [18].

$$K_s = \frac{1}{U^2 d} \tag{1}$$

Values of K_s decreased with an increase in the concentration of DP in both the solvent [15]. The limiting isentropic compressibility K_s⁰ is obtained from the intercept of the plot of K_s as a function of \sqrt{m} (Fig. 1a).

$$K_s = K_s^0 + A^I m + B^I m^{3/2} + C^I m^2 \tag{2}$$

where A^I, B^I and C^I are the empirical constants. It can be seen that the values of K_s for DP is higher in water than water +1M urea solvent. This decline of K_s values with m demonstrate a pattern of Zwitter ion - water dipoles as well as Zwitter ions-ions indenture in both the solvents [18, 19]. Ultrasonic velocity also depends upon the intermolecular free length in the solution. Because the molecules get perplexed in the presence of ultrasonic waves in the solution. By virtue of some elastic nature of the solution, perplexed molecules return to the equilibrium positions of their own. As we know, the solute molecules attract and get attracted by the solvent molecules when added into it; such practice is called compression or limiting compressibility. This gathering of solvent molecules around solute molecules strongly reinforces the influential solute-solvent interactions for which the structure of the medium is altered to a reasonable extent. Thus isentropic compressibility and intermolecular free path length, as observed from Table 1, decrease from those of pure solution, implying considerable solute (DP)-solvent interactions. A model recommended by Kincaid and Eyring in 1938 supports the fact that ultrasonic velocity increases with the decrease of free path length and vice versa [21]. Intermolecular free length is calculated using equation (3).

$$L_f = K^I K_s^{1/2} \tag{3}$$

where $K^I = (93.875 \pm 0.375T) \times 10^{-8}$ is the Jacobson temperature-dependent constant.

The apparent molar isentropic compressibility, $K_{s,\phi}$ has been computed from the equation,

$$K_{s,\phi} = 1000K_s m^{-1} - K_s^0 \rho_0^{-1}(1000m^{-1}\rho - M). \tag{4}$$

The measured $K_{s,\phi}$ data were fitted to the following equation to get the limiting apparent molar compressibility, $K_{s,\phi}^0$.

$$K_{s,\phi} = K_{s,\phi}^0 + F'm^{1/2} + G'm \tag{5}$$

Here F' and G' are the empirical constants. Table 1 imparts that the values of $K_{s,\phi}$ are negative in both the solvents chosen for all the concentrations of DP. The presence of an active solute-solvent interaction is indicated by these negative values of $K_{s,\phi}$ since the molecules of water are restricted more in the bulk of the solution than the molecules of water encompassing the primary as well the secondary solvation layers of DP, which again holds the fact of being substantial interactions between Zwitterionic form of DP and ions of the solvent system (H_2O and 1M urea) [21]. A visual representation of the variation of $K_{s,\phi}$ with the square root of concentration of DP is shown in Figure 1b.

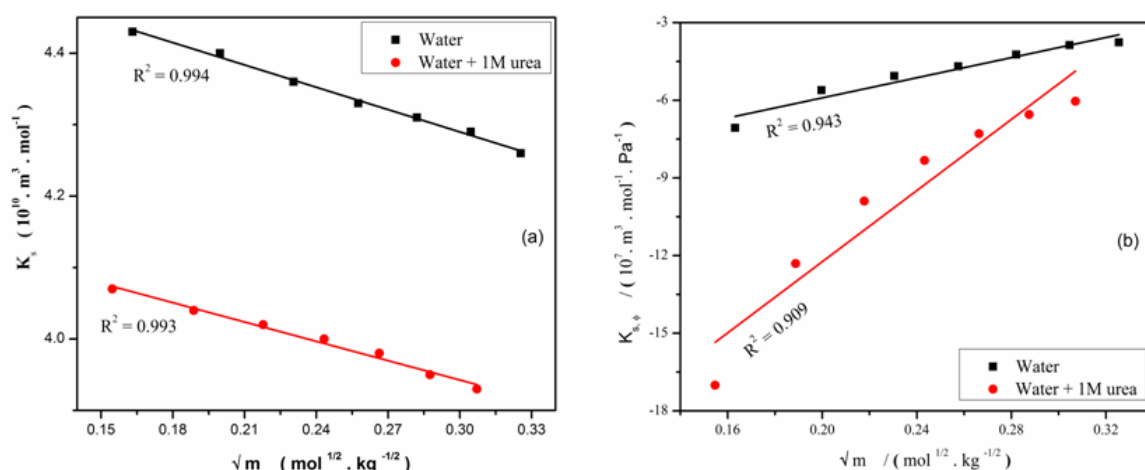


Figure 1. Variation of (a) isentropic compressibility, K_s and (b) apparent molar isentropic compressibility, $K_{s,\phi}$ with the square root of molality, \sqrt{m} of DP solutions in water and water + 1M urea system at 298.15 K.

The property relative association, which is a function of ultrasonic velocity and density, is evaluated by the following equation [22],

$$R_A = (\rho/\rho_0)(U_0/U)^{1/3} \tag{6}$$

Disruption of solvent molecules on the addition of solute and solvation of solute molecules combining describes this property. It is observed from Table 1 that R_A is more for DP in water +1M urea solvent than water. It may be due to the presence of greater interaction of DP with H_2O + 1M urea.

Acoustic impedance (Z) is defined as the product of the velocity of the sound wave and porous media density which through the sound wave passes (Eq. 7). Usually this acoustic impedance is a complex quantity. For the wave traveling in a finite medium, it has an absolute value which is known as wave resistance, i.e., $U \rho$. This is an estimation of the opposition that the medium offers to the acoustic flow [23].

$$Z = U \rho \tag{7}$$

In this study Z values increase with an increase in the concentration of DP in water and water + 1M urea (higher) at the studied temperature. Such variation illustrates a distinctive molecular interaction in the solution. As observed, the plot of Z vs. c is almost linear [15] (Fig. 2), which is in good agreement with the theoretical concern that the density and ultrasonic velocity increase with an increase in the concentration of solution at a particular temperature suggesting an effective solute (DP)- solvent interactions [24, 25].

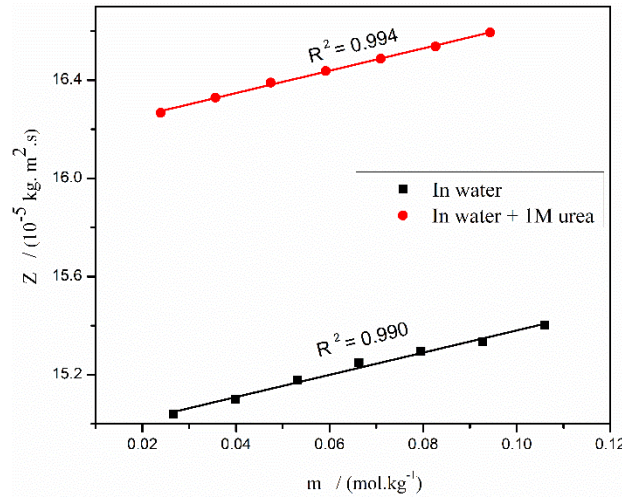


Figure 2. Variation of Acoustic impedance, Z with concentration, m for DP solutions in water and water + 1M urea system at 298.15 K.

A number of intermolecular forces can enrich solvation like ion-dipole interaction, dipole-dipole interaction, hydrogen bonding, van der Waals forces, etc. We know that van der Waals constant b depends on pressure, temperature and volume. For the present study, the values of b are calculated using equation (12). It is observed that b increases with an increase in the concentration of DP in the solution, which intends stronger binding forces between the solvent and solute molecules. Hence, a strong interaction is persisting in the system (Table - 1) [20, 26, 27].

$$b = \bar{M}/\rho [1 - (RT/\bar{M} U^2)\{(1 + \bar{M}U^2/3RT)^{1/2} - 1\}] \quad (8)$$

For the thermodynamic and physicochemical study of binary and ternary systems, perception of molar sound velocity, R , and molar compressibility, W are very important. In this study, R and W (calculated using equation (9) and (10) for DP in water and water + 1M water indicates a decrease in their values, with an increase in the concentration of DP indicating an active presence of molecular interactions in the solution.

$$R = \bar{M} \rho^{-1} U^{1/3} \quad (9)$$

$$W = \bar{M}/K_s^{1/7} \rho \quad (10)$$

The firmness of intermolecular forces brought into play by molecules in a liquid atmosphere is also identified by other two pivotal properties, i.e., internal pressure, π_i and free volume, V_f . Conversely, these two components control the entropy of the solution. These two factors are responsible for keeping the liquid molecules well organized. Internal pressure from the physical point of view gives an overview of the dispersion as well as repulsion forces and diversifies instantly with intermolecular separation. Nonetheless, the interactions like hydrogen bonding appreciably shrink the free volume of molecules in a liquid system. π_i and V_f are calculated using the following relations [28].

$$\pi_i = (K_s^0 - K_s) \quad (11)$$

$$V_f = V_m - b \tag{12}$$

where $V_m = \bar{M}/\rho$ (13)

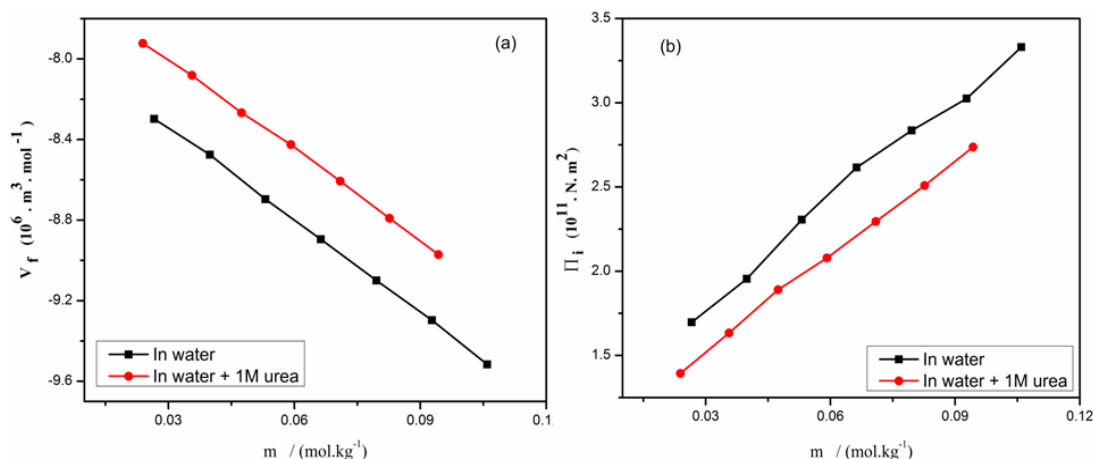


Figure 3. Variation of (a) free volume, V_f and (b) internal pressure, π_i concentration, c for DP solutions in water and water + 1M urea system at 298.15 K.

The free volume, V_f decrease with an increase in the concentration of DP in both the solvents chosen for the study (Figure 3a). It has maximum values for DP in water + 1M urea than DP in water. On account of the relationship that free volume and intermolecular interactions are inversely proportional to each other, the lower and negative values of V_f suggests a substantial molecular interaction that increases with the presence of a hydrotropic agent (1M urea) in the system. For both the solvents (water and water + 1M urea), when the concentration of DP increases the internal pressure, π_i rises which are again supported by the decrease in free volume and free length (Table 1). The result of π_i is shown graphically in Figure 3b. Such tendency reveals the presence of active molecular interaction in the solution under investigation.

Analysis of viscosity data

The experimental viscosity, η data for different concentrations of DP in water and aqueous 1M urea solutions are obtained by using equation (14) at four different temperatures (298.15, 303.15, 308.15, and 313.15 K). The values are listed in Table 2.

$$\frac{\eta_1}{\eta_2} = \frac{\rho_1 t_1}{\rho_2 t_2} \tag{14}$$

where η_1 = coefficient of viscosity of the solvent

η_2 = coefficient of viscosity of solution = η

ρ_1 = density of the solvent

ρ_2 = density of solution

t_1 = flow time of solvent

t_2 = flow time of solution

The relative viscosity η_r of DP solution can be obtained as $\eta_r = (\eta/\eta_0)$ and analyzed by using the Jones-Dole equation(15), where η = viscosity of the solution and η_0 = viscosity of solvent [28].

$$\eta_r = \eta/\eta_0 = 1 + A_F m^{1/2} + B_J m \tag{15}$$

The solute-solute interaction, as well as the electrostatic interactions manifesting interionic forces between existing ions, is expressed by A_F values, whereas the influence of ions on the structure of hydrogen bonds is explained by B_J accounting for the solute-solvent interactions

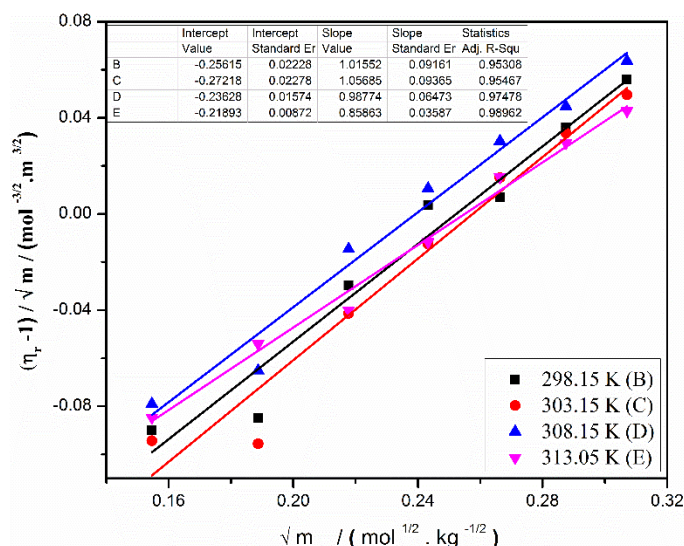


Figure 4. Variation of $[(\eta_r - 1)/\sqrt{m}]$ vs \sqrt{m} of DP in water +1M urea system at different temperatures.

From the intercept and slope of the plot of $[(\eta_r - 1)/\sqrt{m}]$ vs \sqrt{m} , A_F and B_J are obtained and are tabulated in Table 3. A visual presentation is shown for DP in water +1M urea system at different temperatures in Figure 4.

Table 2. Values of η ($\text{kg. m.}^{-1} \text{s}^{-1}$) for DP in water and aqueous urea system at different temperatures.

Solvent	m (mol. kg ⁻¹)	$\eta \times 10^4$ (kg. m. ⁻¹ s ⁻¹)			
		298.15K	303.15K	308.15K	313.15K
Water	0.0000	8.909 [Expt]	7.982 [Expt] 8.007 [27]	7.262 [Expt]	6.540 [Expt] 6.559 [27]
	0.0266	8.964	8.082	7.335	6.590
	0.0399	8.997	8.118	7.360	6.614
	0.0531	9.061	8.214	7.462	6.695
	0.0663	9.061	8.210	7.475	6.691
	0.0795	9.122	8.222	7.532	6.710
	0.0928	9.157	8.307	7.557	6.757
0.1047	9.215	8.326	7.620	6.778	
1M urea	0.0000	8.700	7.789	7.199	6.291
	0.0239	8.777	7.868	7.225	6.358
	0.0356	8.758	7.841	7.224	6.376
	0.0474	8.843	7.913	7.291	6.386
	0.0592	8.909	7.960	7.333	6.424
	0.0709	8.917	8.017	7.373	6.468
	0.0827	8.992	8.062	7.409	6.497
0.0943	9.053	8.106	7.457	6.527	

Standard uncertainties $u(m) = \pm 1.0 \times 10^{-4} \text{ mol. kg}^{-1}$, $u(T) = \pm 0.01 \text{ K}$, $u(\eta) = 0.002 \times 10^{-4} \text{ (kg. m.}^{-1} \text{ s}^{-1})$.

Table 3. Values of parameters A_F ($\text{kg}^{1/2} \cdot \text{mol}^{-1/2}$), B_J ($\text{kg} \cdot \text{mol}^{-1}$), $\Delta\mu_1^{0*}$ (kJ. mol^{-1}) and $\Delta\mu_2^{0*}$ (kJ. mol^{-1}) for DP in water and water + 1M urea at temperatures ($T = 298.15 - 313.15\text{K}$).

T (K)	A_F	B_J	$\Delta\mu_1^{0*} \times 10^3$	$\Delta\mu_2^{0*} \times 10^3$
DP + Water				
298.15K	-0.029	0.405	2.96	215.40
303.15K	-0.003	1.000	3.01	536.70
308.15K	-0.031	0.569	3.06	312.19
313.15K	-0.014	0.402	3.11	224.80
DP + water +1M urea				
298.15K	-0.256	1.016	2.94	1341.82
303.15K	-0.272	1.057	2.99	1416.82

T (K)	A _F	B _J	Δμ ₁ ^{0*} × 10 ³	Δμ ₂ ^{0*} × 10 ³
308.15K	-0.236	0.988	3.04	1343.95
313.15K	-0.219	0.859	3.08	1185.01

Standard uncertainties u (T) = 0.01 K, u (A_F) = 0.003 (kg^{1/2} . mol^{-1/2}), u (B_J) = 0.004 (kg . mol⁻¹), u (Δμ₁^{0*}) = 0.017 × 10³(kJ . mol⁻¹), u (Δμ₂^{0*}) = 0.072 x10³(kJ . mol⁻¹).

It is observed from Table 3 that A_F coefficient values are negative and B_J coefficient values are positive. Even if the values of A_F are quite smaller than B_J in magnitude. This suggests a presence of weakly solute-solute and actively solute-solvent interaction in the studied systems. One can say because of higher hydrophilic-ionic interactions for DP in water +1M urea system B_J values have higher values than DP in water, i.e., when urea molecules replace the water, the friction is increased, which opposes the flow of water. Hence 1M urea is a water structure maker by H-bonding.

3.3 Thermodynamics of viscous flow

Various other parameters are also analyzed based on Eyring transition state theory [29]. As per this theory B_J the coefficient is also expressed as

$$B_J = \frac{[(\bar{V}_1^0 - \bar{V}_2^0) + \bar{V}_1^0 (\Delta\mu_2^{0*} - \Delta\mu_1^{0*}) / RT]}{1000} \quad (16)$$

where \bar{V}_1^0 is the partial molar volume of the solvent and $\bar{V}_2^0 (= V_\phi^0)$ is the limiting apparent molar volume of the solute. $\Delta\mu_1^{0*}$ is the partial molar Gibbs energy of activation per mole of the solvent and $\Delta\mu_2^{0*}$ is that of the solute. $\Delta\mu_1^{0*}$ can be calculated as per Eyring viscosity relation (17) [30, 31].

$$\Delta\mu_1^{0*} = 2.303 RT \log \left(\frac{\eta_0 \bar{V}_1^0}{hN} \right) \quad (17)$$

where $\bar{V}_1^0 = M_{\text{solvent}}/d$, $V_2^0 = V_\phi^0$, h = Planck's constant and N = Avogadro number.

By rearranging the equation (16) to (18) $\Delta\mu_2^{0*}$ can be calculated using relation (18) and the values of $\Delta\mu_1^{0*}$ and $\Delta\mu_2^{0*}$ are given in Table - 3.

$$\Delta\mu_2^{0*} = \Delta\mu_1^{0*} + (RT/\bar{V}_1^0) [1000B_J - (\bar{V}_1^0 - \bar{V}_2^0)] \quad (18)$$

An observation of Table 3 reveals that $\Delta\mu_2^{0*}$ values are positive and more than $\Delta\mu_1^{0*}$ (also positive) and also increased with an increase in temperature. $\Delta\mu_2^{0*}$ positive values indicate that the viscous flow phenomenon is crucial when the temperature rises and the solute (DP) - solvent interaction is stronger in the ground state than in the transition state. The higher and positive values of $\Delta\mu_2^{0*}$ is also supported by positive values of B_J. This is supported by Feakins *et al.* (in 1993), who reported that the presence of active solute-solvent interactions in the ground state than in the transition state is revealed by the positive values of B_J for solutes with $\Delta\mu_2^{0*} > \Delta\mu_1^{0*}$. A distortion and puncture of the intermolecular forces prevailing in the solvent structure signify the formation of the transition state [28].

4. Conclusions

This article studied the interaction of DP with water and aqueous 1M urea medium using the measured density data from the experimental method at (298.15 -313.15K). The presence of a reasonable solute-solvent interaction was identified between DP-water and DP-aqueous 1M urea solvents. Strong solute (DP) –solvent interactions is confirmed by the increase in U, Z, π_i, R_A and decrease in K_S, L_f, V_f, R, W with an increase in the concentration of DP. The coactions of Zwitterionic form of DP with ions of the solvent system

(H₂O and 1M urea) giving negative values of $K_{s,\phi}$ suggests greater molecular interaction in the solution. Active solute-solvent interaction is also confirmed by the negative values of A_F coefficient. A stronger solute-solvent interaction in the ground state than in the transition state is revealed by the positive values of B_j for solutes with $\Delta\mu_2^{0*} > \Delta\mu_1^{0*}$. Higher B_j coefficients in water + 1M urea solutions suggest the structure-making behavior. Overall, the obtained results justify the presence of molecular interactions controlling the studied system and could be used as an effective tool to improve the bioavailability of poorly soluble drugs.

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Conflicts of Interest

The author declares no conflict of interest.

References

1. da Silva, A. E.; Abreu Pedro, M. B.; Geraldles, D.C.; Nascimento, L. O. Hydroxychloroquine: Pharmacological, physicochemical aspects and activity enhancement through experimental formulations. *J. Drug Deliv. Sci. and Tech.* **2021**, *63*, 102512, <https://doi.org/10.1016/j.jddst.2021.102512>.
2. Singh, S.; Dash, U.N. Volumetric and Viscometric Studies on Aqueous Ibuprofen Solutions at Temperatures. *Int. J. Pharm. Sci. Rev. Res.* **2015**, *35*, 25-29, <https://doi.org/10.1016/j.jct.2013.05.012>.
3. Dickens, J.E.; Chen, R.; Bareford, L.; Talreja, G.; Kolwyck, D. Colorimetric and Physico-Chemical Property Relationships of Chemically Defined Media Powders Used in the Production of Biotherapeutics. *J. Pharma. Sci.* **2021**, *110*, 1635-1642, <https://doi.org/10.1016/j.xphs.2020.10.032>.
4. Singh, S.; Dash, U.N. An environmental remediation: study of molecular interactions of the poorly soluble pharmaceutical drug ibuprofen in aqueous media. *Biointerface Res. Appl. Chem.* **2020**, *10*, 5061–5067, <https://doi.org/10.33263/BRIAC101.061067>.
5. Liu, Z.; Smart, J. D.; Pannala, A.S. Recent developments in formulation design for improving oral bioavailability of curcumin: A review *J. Drug Deliv. Sci. Tech.* **2020**, *60*, 102082, <https://doi.org/10.1016/j.jddst.2020.102082>.
6. Singh, S.; Dash, U.N.; Talukdar, M.. Solubility enhancement and study of molecular interactions of poorly soluble ibuprofen in presence of urea, a hydrotropic agent. *Mater. Today: Proc.* **2020**, *30*, 246-253, <https://doi.org/10.1016/j.matpr.2020.01.289>.
7. Chen, X.; Zhao, B.; Tang, T.; Yin, X.; Li, R., Han, D. The co-solvency and thermodynamic properties of camptothecin in mixtures of (ethyl acetate + methanol/ethanol). *J. Chem. Thermodyn.* **2021**, *163*, 106592, <https://doi.org/10.1016/j.jct.2021.106592>.
8. Talukdar, M.; Singh, S. Study of Physico-Chemical Properties Of Paracetamol As Pharmaceutical Waste In Water: An Analysis Of Molecular Interactions. *Int. J. Sci. Tech. Res* **2020**, *9*, 2802-2808.
9. Nugrahani, I.; Komara, S. W.; Horikawa, A.; Uekusa, H. Composing Novel Diclofenac Potassium and L-Proline Salt Cocrystal as a Strategy to Increase Solubility and Dissolution. *J. Pharma. Sci.* **2020**, *109*, 3423-3438, <https://doi.org/10.1016/j.xphs.2020.08.002>.
10. Talukdar, M.; Singh, S.; Dehury, S. K. A review on conductometric studies of electrolytes in mixed solvent systems to understand ion-ion and ion-solvent interactions. *Biointerface res. Appl.Chem.* **2020**, *10*, 5332, <https://doi.org/10.33263/BRIAC102.332337>.
11. Singh, S.; Talukdar, M.; Dash, U.N. Ultrasonic studies on paracetamol in aqueous solutions of sodium salicylate and nicotinamide. *J. Mol. Liq.* **2018**, *249*, 815–824, <https://doi.org/10.1016/j.molliq.2017.11.099>.

12. Rajagopal, K.; Jayabalakrishnan, S.S. Volumetric, ultrasonic speed, and viscometric studies of salbutamol sulphate in aqueous methanol solution at different temperatures. *J. Chem. Thermodyn.* **2010**, *42*, 984–993, <https://doi.org/10.1016/j.jct.2010.03.016>
13. Singh, S.; Talukdar, M.; Dash, U.N. Studies on molecular interactions in aqueous and aqueous urea systems of paracetamol (N-(4-hydroxyphenyl) ethanamide). *J. Mol. Liq.* **2018**, *265*, 679–686, <https://doi.org/10.1016/j.molliq.2018.05.092>.
14. Singh, S.; Dhal, K.; Talukdar, M. A Comparative Study on the Effect of Temperature and Concentration on Density, Sound Velocity and their Derived Properties for Diclofenac Potassium in Aqueous Urea Media. *Biointerface Res. Appl. Chem.* **2020**, *10*, 6377 – 6388, <https://doi.org/10.33263/BRIAC105.63776388>.
15. Haiyun, H.; Baojuan, J.; Qingzhong, L.; Xinlu, L.; Yanping, D.; Jing, Y.; Songtao, L. Mass density, sound velocity, mixing enthalpy, ¹H NMR, Ab initio calculations and intermolecular interactions in binary mixtures of N-methylimidazole + water, +methanol, +ethanol, +1-propanol, +2-propanol. *J. Chem. Thermodyn.* **2019**, *132*, 174 – 205, <https://doi.org/10.1016/j.jct.2018.12.019>.
16. Harned, H.S.; Owen, B.B. Physical Chemistry of Electrolyte Solutions. New-York : Reinhold, **1958**, 3rd edition (Chapter 8).
17. Sajid, T. A.; Jamal, M. A.; Saeed, M.; Atta-ul-H.; Muneer, M. Elucidation of molecular interactions between amino acid and imidazolium based ionic liquid in an aqueous system: Volumetric and acoustic studies. *J. Mol. Liq.* **2021**, *335*, 116513, <https://doi.org/10.1016/j.molliq.2021.116513>.
18. Malik, S.; Darolia, P.J.; Sharma, D.; Sharma, V.K. Topological investigations of molecular interactions in binary and ternary mixtures at varying temperatures and atmospheric pressure: Excess molar volumes and excess isentropic compressibilities. *Chem. Data Collections* **2021**, *35*, 100771, <https://doi.org/10.1016/j.cdc.2021.100771>.
19. Nugrahani, I.; Utami, D.; Ibrahim, S.; Nugraha, Y. P.; Uekusa, H. Zwitterionic cocrystal of diclofenac and L-proline: Structure determination, solubility, kinetics of cocrystallization, and stability study. *Eur. J. Pharma. Sci.* **2018**, *117*, 168-176, <https://doi.org/10.1016/j.ejps.2018.02.020>.
20. Eyring, H.; Kincaid, J.F. Free volumes and free angle ratios of molecules in liquids. *J. Chem. Phys* **1938**, *6*, 620-629, <http://doi:10.1063/1.1750134>.
21. Singh, S.; Talukdar, M.; Dash, U.N. Solute-solvent and solute-solute interactions of ibuprofen in aqueous and in aqueous solutions of urea, sodium salicylate and nicotinamide by volumetric and interferometric techniques. *J. Mol. Liq.* **2017**, *241*, 934-945, <https://doi.org/10.1016/j.molliq.2017.06.112>.
22. Jamal, M.A.; Naseemb, B.; Khana, J.H.; Arif, I. Temperature dependent solution properties of amino acids in colloidal solutions. *J. Mol. Liq.* **2019**, *275*, 105–115, <https://doi.org/10.1016/j.molliq.2018.11.046>.
23. Khushboo, Devi, A.; Malik, P.; Kumar, H. Thermodynamic and acoustical study of zinc oxide-nematic liquid crystals mixtures. *J. Mol. Liq.* **2016**, *214*, 145-148, <https://doi.org/10.1016/j.molliq.2015.11.025>.
24. Naseem, B. Effect of alkyl chain length of 1-alkanols on solution behavior of bactericidal antibiotic in terms of thermo-acoustic parameters. *Journal of Molecular Liquids* **2020**, *307*, 112991, <https://doi.org/10.1016/j.molliq.2020.112991>.
25. Nithiyantham, S.; Mullainathan, S.; Jayalakshmi, R. Thermoacoustical studies on some electrolyte solvent mixtures at 303 K. *Orient. J. Chem.* **2009**, *25*, 759–761, <http://www.orientjchem.org/?p=23143>.
26. Mehra, R.; Sajnani, H. Acoustical parameters of CuCl-KCl systems in acetonitrile – water solvent mixture. *J. Phys. Chem. Liq.* **2001**, *39*, 581–588, <http://DOI:10.1080/00319100108030679>.
27. Franks, F. Water: A Comprehensive Treatise. Vol. 3 Aqueous Solutions of Simple Electrolytes, *Plenum Press, New York* **1973**, Chapter 1, <http://dx.doi.org/10.1007/978-1-4684-2955-8>.
28. Feakins, D.; Canning, F.M.; Waghorne, W.E.; Lawrence, K.G. Relative viscosities and quasi-thermodynamics of solutions of tert-butyl alcohol in the methanol–water system: a different view of the alkyl–water interaction. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 3381-3388, <https://doi.org/10.1039/FT9938903381>.
29. Glasstone, S.; Laidler, K.J.; Eyring, H. The Theory of Rate Processes. *J. Chem. Educ.* **1942**, *19*, 5, 249, <https://doi.org/10.1021/ed019p249.1>.
30. Joseph, A.; Radhakrishnan, N. P.; Mathew, S. Investigation of Iron Oxide-Based Ionanofluids and Ionic Liquids by Ultrasonic Sound Velocity Method. *Int J Thermophys.* **2020**, *41*, 168, <https://doi.org/10.1007/s10765-020-02748-y>.
31. Silva, A.C.A.; Silva, M.J.B.; Rocha, A. A.; Costa, M.P.C.; Marinho, J. Z.; Dantas, N.O. Synergistic effect of simonkolleite with zinc oxide: Physico-chemical properties and cytotoxicity in breast cancer cells. *Materials Chem. Phy.* **2021**, *266*, 124548, <https://doi.org/10.1016/j.matchemphys.2021.124548>.