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Effect of Temperature on the Volumetric, Compressibility and Viscometric Properties of Paracetamol in Aqueous Methanol Solution

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Abstract: The values of density(ρ), ultrasonic speed(u) and viscosity(η) of paracetamol are measured in aqueous methanol solution at different temperature T=(298.15, 303.15, 308.15, 313.15, 318.15)K. Using the values of density, apparent molal volume V_φ, partial molal volume V_φ^0, molar expansivity E_2^0, isobaric thermal expansion coefficient(α_2) and second derivative of infinite dilution of partial molal volume with temperature $\partial^2 V_\varphi^0/\partial T^2$ are calculated. Using the values of density with ultrasonic speed isentropic compressibility β_s, change in isothermal compressibility $\Delta\beta_s$, relative change in isentropic compressibility ($\Delta\beta_s/\beta_s^0$), apparent molal compressibility K_φ and partial molal compressibility K_φ^0 are calculated. Using the viscosity data, viscosity B-coefficient, variation of B-coefficient with temperature dB/dT, free energy of activation per mole solvent $\Delta\mu_1^{0*}$ and solute $\Delta\mu_2^{0*}$ are calculated. In addition to this the hydration numbers H_n are also estimated. These calculated parameters are used to predict the solute-solute, solute-solvent interactions, structure making / breaking ability of the drug and hydration property of the drug in aqueous methanol solution.
Keywords: Paracetamol, Aqueous methanol, Apparent molal volume, Apparent molal compressibility, Viscosity B-coefficients, Hydration number.

1. Introduction

Physico chemical properties of drugs in aqueous, protic solvents and aqueous - protic solutions are of great importance to understand drug action at the molecular levels. Most of the drugs are organic molecules with both hydrophilic and hydrophobic groups and its action viz. drug reaching the blood stream, its extent of distribution, its binding to the receptors and finally producing the physiological actions, all depend upon the intermolecular interactions that include ionic or covalent, hydrogen bonding, hydrophilic interactions etc[1,2]. In biophysical chemistry, drug macromolecular interaction is an important phenomenon involving a complex mechanism. Since most of the biochemical process occur in water and in water since the polar groups are hydrated, the intermolecular aggregations of drug molecules through their hydrophobic parts is expected to occur in a way analogous to miscillization[3] favouring their limited aqueous solubilization. Some authors have reported the thermodynamical study of drugs in aqueous media[4-9]. Since alcohols are often present in drug delivery formulation, few authors have reported the thermodynamical study of drugs in alcohols at different temperatures[10-13]. Since some aprotic solvents like dimethyl sulphoxide is widely used as cryoprotectant of biological structures such as membranes and proteins[14] some reports are available in literature on thermodynamical study of drugs in aprotic solvents. For example, Iqbal and Chaudhry[15] have reported the

thermodynamical study of a nervous system depressant and intestional antiseptic drug, phenyl salicylate in some aprotic solvents like acetonitrile, dimethyl sulphoxide, tetrahydrofuran and 1,4-dioxane. Baluja et al.,[16] reported ultrasonic study of some drugs in dimethyl formamide. Similarly some authors have reported the thermodynamical study of drugs in aqueous alcoholic mixtures[17-20]. Thus the thermodynamical and transport properties of drugs in aqueous, protic solvent and aqueous protic solutions provide useful information about absorption of drugs and transport of drugs across biological membranes and these data are used in the field of pharmaceutical and medicinal chemistry. In continuation of our previous study of a drug, Salbutamol sulphate which is used in the control of Chronic bronchial asthma, in aqueous methanol solution[21], in this paper we report the values of density, ultrasonic speed and viscosity of paracetamol in various aqueous methanol solutions (V/V-90%W + 10%M), (V/V-80%W + 20%M), (V/V-70%W + 30%M), (V/V-60%W + 40%M) and (V/V-50%W + 50%M) at different temperatures. In literature few authors have reported volumetric, viscometric and acoustical studies of paracetamol in aqueous solution and aqueous alcohol solutions. For example Meshram et al.,[22] have reported the acoustical behaviour of Paracetamol in 70% methanol solution only at different temperatures in the concentration range 0.002M to 0.01M. These authors have evaluated parameters like adiabatic compressibility, viscous relaxation time, relative association, acoustical impedance and intermolecular free length and discussed the results in terms of solute-solvent interactions and structure making / breaking ability of the solute in 70% methanol solvent. Aswale et al.,[23] have reported adiabatic compressibility, free length and acoustical impedance of paracetamol in aqueous solution at different ultrasonic frequencies and temperatures and discussed the result interms of molecular interactions. Shaikh et al.,[24] have reported density and viscosity of paracetamol in ethanol + water system at 301.5K. Md.M.Huque et al.,[25] have reported physico-chemical properties of paracetamol and aspirin in water, ethanol systems and the results have been discussed on the basis of structure modifying properties of the drugs in water ethanol solution. Aswale Sunanda et al.,[26] have evaluated free volume, relaxation time of paracetamol in aqueous solution at three different temperatures and at different ultrasonic frequencies. Iqbal and Malik et al.,[27] have reported the partial molar volume of paracetamol in water at four different temperatures under 101.325 kPa. Thus, the reports that are available in literature with paracetamol in aqueous and in aqueous alcoholic solutions are totally different from what we are reporting for the first time in literature. This paper deals with the new data and results of volumetric, compressibility and viscometric properties of paracetamol in aqueous methanol solution at different concentrations of the drug, different volume/volume of water and methanol at five different temper tures. Paracetamol also known as N-acetyl P-aminophenol, is white in colour widely used as an analgesic (pain reliever) and antipyretic (fever reducer) drug. The molecular formula is $C_8H_9NO_2$. The thermodynamic data have been obtained in the range of 298.15K to 318.15K insteps of 5K provide relevance to drug macromolecules behaviour near physiological temperature. From the data on density, ultrasonic speed and viscosity several thermodynamical and transport parameters such as apparent molal volume V_φ, partial molal volume V_φ^0, molal expansivity E_2^0, isobaric thermal expansion coefficient(α_2), second derivative of infinite dilution of partial molal volume with temperature $\partial^2 V_\varphi^0/\partial T^2$, isentropic compressibility β_s, change in isothermal compressibility $\Delta\beta_s$, relative change in isentropic compressibility($\Delta\beta_s/\beta_s^0$), apparent molal compressibility K_φ and partial molal compressibility K_φ^0, viscosity B-coefficient, variation of B-coefficient with temperature dB/dT, free energy of activation per mole solvent $\Delta\mu_1^{0^*}$ and solute $\Delta\mu_2^{0^*}$, Hydration number H_n are estimated and discussed interms of drug-solvent interaction and structure making ability of the drug is studied in the aqueous methanol solution.

2. Experimental

Paracetamol drug in powder form, procured from S.D. Fine Chemicals, Mumbai (minimum Assay mass fraction purity 0.998) and dried in a vacuum oven before use. Methanol (Analar grade, Himedia, Mumbai) has been used in the experiments without further purification. Doubly distilled deionised water having conductivity of 1.49×10^{-4} $\Omega^{-1}m^{-1}$ has been degassed prior to use for making solutions. The densities of the solutions have been measured using a single stem pycnometer (Borosil glass) of bulb capacity of 11×10^{-3} dm^{-3} having a graduated stem with 5×10^{-7} dm^{-3} division. The graduation on the stem has been calibrated with doubly distilled water. The weighing has been done by taking the samples in air tight bottles in a high precision and electronic balance (AUY 220model, Japan) with a precision of ±0.1 mg. The reproducibility of density measurements is $\pm2.8\times10^{-4}$ g cm^{-1}. The ultrasonic speeds in solvents and in solutions have been measured using a single crystal variable path multi frequency ultrasonic interferometer [M-05, Mittal Enterprises, India] operated at 2 MHz. The reproducibility in ultrasonic speed measurements is within ±0.03%. Viscosity has been measured by means

of a suspended level Ubbelhode viscometer with a flow time of approximately 173 s for distilled water at T = 303.15 K. The time of flow has been measured with a stopwatch capable of recording ±0.01 s. An average of three sets of flow times for each solution has been taken for the calculation of viscosity. The overall experimental reproducibility is estimated to be ±2 x 10^{-3} mPa . s. As the flow times were greater than 100 s, the kinetic energy corrections are not necessary[28]. The pycnometer filled with air bubble free solutions and the Ubbelhode viscometer filled with test solutions have been allowed to stand for about 30 min in a thermostatic water bath(Eurotherm, Chennai), to reduce thermal fluctuations. The temperature of the solution has been maintained to an uncertainty of ±0.01 K in an electrically controlled thermostatic water bath. The values of density, ultrasonic speed and viscosity for the doubly distilled water and methanol at the temperatures studied are compared with the literature values (see table 1). A reasonably good agreement between the measured values with the literature values validates our experimental procedures.

Table 1. Comparison of experimental density, ρ, viscosity, η, and ultrasonic speed, u, of water and methanol with literature values

T/K	10^3ρ/(Kg.m^{-3})		η/(mPa.s)		u/(ms^{-1})	
	Present Work	Litrerature	Present Work	Litrerature	Present Work	Litrerature
Water						
298.15	0.99707	0.997045[a]	0.8878	0.8903[d]	1496.7	1496.68[a]
303.15	0.99565	0.995650[b]	0.7938	0.7970[b]	1509.0	1509.00b
308.15	0.99401	0.994030[c]	0.7150	0.7190[c]	1519.8	1519.83[e]
		0.994032[a]				1519.808[a]
313.15	0.99202	0.992217[c]	0.6483	0.6526[c]	1528.9	1528.88[e]
318.15	0.99014	0.990216[c]	0.5909	0.5916[c]	1536.4	1536.42[e]
		0.990213[a]				
Methanol						
298.15	0.78682	0.786710[i]	0.5406	0.5444	1105.1	1107.00[k]
303.15	0.78195	0.782400	0.5032	0.5041[j]	1088.9	1088.00[b]
308.15	0.77701	0.777689[f]	0.4699	0.4786[g]	1072.6	1076.30[f]
		0.778500[g]				1078.03
313.15	0.77211	0.774700[g]	0.4397	0.4373[g]	1056.6	1060.00[g]
318.15	0.76792		0.4120		1041.2	

[a] Ref 29. [b] Ref 30. [c] Ref 31. [d] Ref 32. [e] Ref 33. [f] Ref 34.
[g] Ref 35. [h] Ref 36. [i] Ref 37. [j] Ref 38. [k] Ref 20.

3. Results

The experimental values of aqueous methanol solution densities listed in Table 2 have been used to calculate the apparent molal volumes V_φ of Paracetamol in aqueous methanol solution by using the following equation[39]:

$$V_\varphi = (M/\rho) - 1000\,(\rho - \rho_0)\,/m\,\rho\,\rho_0 \qquad (1)$$

where ρ and ρ_0 are the densities of the drug solution and solvent, respectively. M is the molal mass, and m is the molal concentration of the drug. The values of V_φ are listed in Table 3. The partial molal volume V_φ^0 of Paracetamol is evaluated using Masson's equations[5] from the linear plot of V_φ against m (See the representative plots shown in Figure 1) using the least squares method of the following general equation:

$$V_\varphi = V_\varphi^0 + S_v m \qquad (2)$$

where S_v is the experimental slope and is a measure of solute–solute interactions while V_φ^0, the partial molal parameter at infinite dilution, is a measure of solute–solvent interactions.

Table 2. Density, ρ, and Apparent molal volume, V_φ, of Paracetamol in aqueous methanol solution at different temperatures

m/ (mol.kg^{-1})	T = 298.15K		T = 303.15K		T = 308.15K		T = 313.15K		T = 318.15K	
	10^3 ρ / (kg.m^{-3})	10^6 V_φ / (m^3.mol^{-1})	10^3 ρ / (kg.m^{-3})	10^6 V_φ / (m^3.mol^{-1})	10^3 ρ / (kg.m^{-3})	10^6 V_φ / (m^3.mol^{-1})	10^3 ρ / (kg.m^{-3})	10^6 V_φ / (m^3.mol^{-1})	10^3 ρ / (kg.m^{-3})	10^6 V_φ / (m^3.mol^{-1})
(V/V – 90%W + 10%M)										
0.000	0.98162		0.97999		0.97821		0.97619		0.97401	
0.025	0.98234	124.25	0.98069	125.21	0.97888	126.25	0.97685	127.15	0.97465	128.12
0.050	0.98307	123.77	0.98140	124.70	0.97959	125.62	0.97752	126.67	0.97531	127.62
0.075	0.98382	123.28	0.98213	124.24	0.98030	125.20	0.97823	126.12	0.97599	127.06
0.100	0.98460	122.69	0.98290	123.59	0.98104	124.60	0.97896	125.48	0.97671	126.39
(V/V – 80%W + 20%M)										
0.000	0.97053		0.96858		0.96639		0.96416		0.96170	
0.025	0.97131	122.32	0.96935	123.26	0.96713	124.30	0.96489	125.20	0.96242	126.21
0.050	0.97212	121.71	0.97014	122.75	0.96791	123.64	0.96564	124.72	0.96315	125.67
0.075	0.97294	121.35	0.97094	122.29	0.96869	123.27	0.96641	124.17	0.96391	125.12
0.100	0.97379	120.75	0.97178	121.63	0.96951	122.63	0.96722	123.52	0.96470	124.43
(V/V – 70%W + 30%M)										
0.000	0.95545		0.95288		0.95023		0.94745		0.94455	
0.025	0.95631	120.35	0.95372	121.31	0.95106	122.28	0.94826	123.25	0.94534	124.23
0.050	0.95720	119.77	0.95459	120.77	0.95190	121.72	0.94909	122.75	0.94616	123.71
0.075	0.95809	119.38	0.95546	120.30	0.95276	121.32	0.94994	122.21	0.94699	123.15
0.100	0.95901	118.77	0.95637	119.67	0.95366	120.66	0.95082	121.54	0.94786	122.44
(V/V – 60%W + 40%M)										
0.000	0.94266		0.93959		0.93655		0.93334		0.93008	
0.025	0.94360	118.08	0.94051	119.05	0.93746	119.95	0.93423	120.99	0.93095	122.02
0.050	0.94455	117.52	0.94145	118.51	0.93838	119.46	0.93514	120.51	0.93184	121.45
0.075	0.94552	117.13	0.94240	118.04	0.93932	119.06	0.93606	119.95	0.93275	120.90
0.100	0.94650	116.69	0.94338	117.42	0.94029	118.39	0.93702	119.29	0.93370	120.19
(V/V – 50%W + 50%M)										
0.000	0.92341		0.91994		0.91639		0.91275		0.90901	
0.025	0.92444	115.56	0.92095	116.51	0.91739	117.51	0.91373	118.45	0.90998	119.40
0.050	0.92548	114.93	0.92198	115.96	0.91840	116.77	0.91473	117.95	0.91096	118.92
0.075	0.92653	114.59	0.92302	115.47	0.91942	116.51	0.91574	117.42	0.91196	118.33
0.100	0.92761	113.97	0.92408	114.84	0.92047	115.88	0.91678	116.74	0.91299	117.62

m stands for molality of Paracetamol. W stands for water. M stands for methanol.

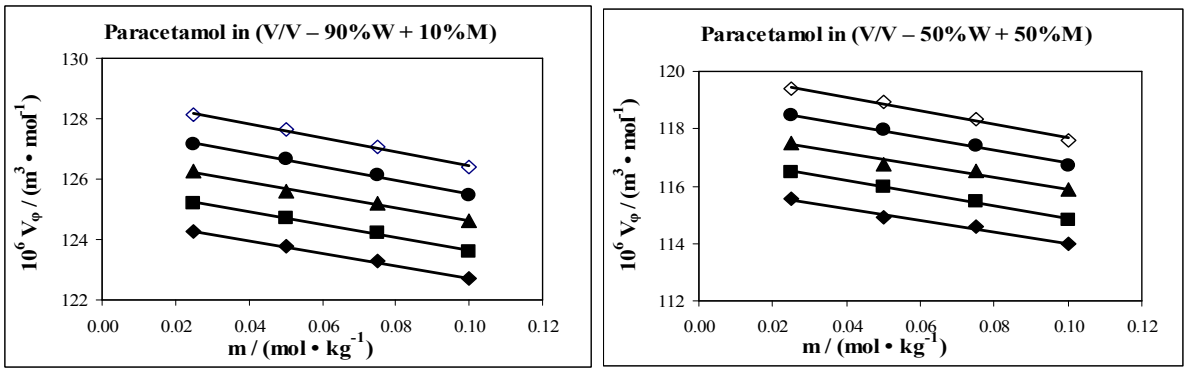

Figure 1. Plot of apparent molar volume (V_φ) against molal concentration(m) of paracetamol at T = (◆) 298.15K, (■)303.14K, (▲) 308.15K, (●) 313.15K,(◇) 318.15K of (V/V – 90%W + 10%M) and (V/V – 50%W + 50%M)

The evaluated values of V_φ^0 and S_v are listed in Table 3. The values of molal expansivity are calculated[40] from the partial molal volume using the relation (3) as follows:

$$E_2^0 = (\partial V_\varphi^0/\partial T)_p \quad (3)$$

The values of E_2^0 are included in Table 3. From the partial molal volume V_φ^0, the values of the isobaric thermal expansion coefficients of the solute at infinite dilution α_2 are also determined using the following equation (4)[11] and are given in Table 3:

$$\alpha_2 = (1/ V_\varphi^0) (\partial V_\varphi^0/\partial T)_p = E_2^0/ V_\varphi^0 \quad (4)$$

Table 3. Partial molal volume, V_φ, experimental slope, S_V, limiting molal expansivity, E_2^0, isobaric thermal expansion coefficient, α_2, and Hepler's constant ($\partial^2 V_\phi^0 / \partial T^2$)of Paracetamol in aqueous methanol solution at different temperatures

T/K	10^6 V_ϕ^0 / ($m^3.mol^{-1}$)	10^6 S_V / ($m^3.l^{1/2}.mol^{-3/2}$)	10^6 E_2^0 / ($m^3..mol^{-1}.k^{-1}$)	10^3 α_2 / k^{-1}	$\partial^2 V_\phi^0 / \partial T^2$ / ($m^6.mol^{-2}.k^{-2}$)
(V/V – 90%W + 10%M)					
298.15	124.792	-20.714	0.1976	0.001378	0.0001
303.15	125.761	-21.280		0.001368	
308.15	126.756	-21.752		0.001357	
313.15	127.743	-22.227		0.001346	
318.15	128.742	-23.110		0.001336	
(V/V – 80%W + 20%M)					
298.15	122.803	-20.342	0.2007	0.001401	0.0002
303.15	123.816	-21.327		0.001389	
308.15	124.800	-21.889		0.001378	
313.15	125.796	-22.355		0.001367	
318.15	126.830	-23.587		0.001356	
(V/V – 70%W + 30%M)					
298.15	120.848	-20.531	0.2005	0.001423	0.0003
303.15	121.861	-21.575		0.001411	
308.15	122.810	-22.032		0.001401	
313.15	123.847	-22.583		0.001389	
318.15	124.868	-23.778		0.001377	
(V/V – 60%W + 40%M)					
298.15	118.497	-18.256	0.206	0.001452	0.0004
303.15	119.598	-21.473		0.001438	
308.15	120.480	-22.252		0.001428	
313.15	121.597	-22.620		0.001415	
318.15	122.648	-24.130		0.001402	
(V/V – 50%W + 50%M)					
298.15	116.046	-20.513	0.2002	0.001723	0.0005
303.15	117.069	-21.977		0.001708	
308.15	117.961	-22.485		0.001695	
313.15	119.057	-22.701		0.001680	
318.15	120.057	-23.837		0.001666	

W stands for water. M stands for methanol.

The temperature dependence of V_φ^0 [41] for the drug studied can be expressed by the equation

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

where a, b, and c may be estimated by the least squares fitting of partial molal volume data in the above equation. To obtain the qualitative information of hydration of solutes, the value of $\partial^2 V_\varphi^0/\partial T^2$ [42] has been

calculated and listed in Table 3. For structure making solutes $\partial^2 V_\varphi^0/\partial T^2$ value is positive and for structure breaking solute the $\partial^2 V_\varphi^0/\partial T^2$ value is negative. The experimental values for ultrasonic speeds are given in Table 4. These values along with the results for density are used to calculate the following thermodynamic parameters. The isentropic compressibility of the Paracetamol in aqueous methanol solutions is calculated using the Newton–Laplace expression[43].

$$\beta_s = 1/(\rho u^2) \quad (6)$$

The β_s-values as functions of concentration and temperature are also listed in Table 4 and a representative plot of β_s versus m is shown in Figure 2. The change $\Delta \beta_s$ [44] and relative change $\Delta\beta_s/\beta_s^0$ [45] in isentropic compressibility are calculated by using the following equations:

$$\Delta \beta_s = \beta_s^0 - \beta_s = A + B\,m \quad (7)$$

$$\beta_s = \beta_s^0 - \alpha \beta_s^0 \quad (8)$$

$$\alpha = (\beta_s^0 - \beta_s)/\beta_s^0 = \Delta \beta_s/\beta_s^0 \quad (9)$$

$$\Delta \beta_s/\beta_s^0 = A' + B'm \quad (10)$$

where β_s^0 and β_s are the isentropic compressibility of solvent and solution, respectively. The A and B are the values of the intercept and slope from the $\Delta \beta_s$ versus m plot, respectively; α represents the relative change in isentropic compressibility, i.e., $\Delta \beta_s/\beta_s^0$ while A' and B` stand for the intercept and slope values from the $\Delta \beta_s/\beta_s^0$ versus m plot, respectively. The values of $\Delta \beta_s$ and $\Delta \beta_s/\beta_s^0$ are listed in Table 5.

Table 4. Ultrasonic Speed, u, Isentropic compressibility, β_s of Paracetamol in aqueous methanol solution at different temperatures

m/ (mol.kg^{-1})	T = 198.15K		T = 303.15K		T = 308.15K		T = 313.15K		T = 318.15K	
	u / (m.s^{-1})	$10^{10}\beta_s$ / (pa^{-1})	u / (m.s^{-1})	$10^{10}\beta_s$ / (pa^{-1})	u / (m.s^{-1})	$10^{10}\beta_s$ / (pa^{-1})	u / (m.s^{-1})	$10^{10}\beta_s$ / (pa^{-1})	u / (m.s^{-1})	$10^{10}\beta_s$ / (pa^{-1})
(V/V – 90%W + 10%M)										
0.000	1533.9	4.33	1540.5	4.30	1545.8	4.27	1550.6	4.26	1554.1	4.25
0.025	1536.6	4.31	1543.2	4.28	1548.5	4.26	1553.3	4.24	1556.8	4.23
0.050	1539.1	4.29	1545.7	4.26	1550.9	4.24	1555.7	4.23	1559.2	4.22
0.075	1541.4	4.27	1548.0	4.25	1553.1	4.23	1557.9	4.21	1561.4	4.20
0.100	1543.5	4.26	1549.5	4.23	1555.1	4.22	1559.9	4.20	1563.4	4.19
(V/V – 80%W + 20%M)										
0.000	1557.5	4.25	1559.1	4.25	1560.8	4.25	1559.5	4.27	1558.7	4.28
0.025	1560.5	4.23	1562.0	4.23	1563.6	4.23	1562.1	4.25	1561.3	4.26
0.050	1563.1	4.21	1564.5	4.21	1565.9	4.21	1564.3	4.23	1563.5	4.25
0.075	1565.2	4.20	1566.5	4.20	1567.8	4.20	1566.1	4.22	1565.3	4.23
0.100	1567.0	4.18	1568.1	4.19	1569.4	4.19	1568.0	4.21	1567.2	4.22
(V/V – 70%W + 30%M)										
0.000	1571.0	4.24	1567.2	4.27	1562.7	4.31	1557.7	4.35	1551.8	4.40
0.025	1574.0	4.22	1570.0	4.25	1565.4	4.29	1560.2	4.33	1554.2	4.38
0.050	1576.5	4.20	1572.4	4.24	1567.7	4.27	1562.4	4.32	1556.2	4.36
0.075	1578.5	4.19	1574.2	4.22	1569.4	4.26	1564	4.30	1558.0	4.35
0.100	1580	4.18	1575.8	4.21	1571	4.25	1565.5	4.29	1559.7	4.34
(V/V – 60%W + 40%M)										
0.000	1561.4	4.35	1555.8	4.40	1547.8	4.46	1537.5	4.53	1529.2	4.60
0.025	1564.4	4.33	1558.6	4.38	1550.4	4.44	1539.9	4.51	1531.5	4.58
0.050	1566.9	4.31	1560.9	4.36	1552.5	4.42	1541.9	4.50	1533.3	4.57
0.075	1569.0	4.30	1562.8	4.35	1554.2	4.41	1543.4	4.49	1534.8	4.55
0.100	1570.7	4.28	1564.3	4.33	1555.8	4.40	1545.2	4.47	1536.3	4.54
(V/V – 50%W + 50%M)										
0.000	1522.1	4.67	1511.0	4.76	1499.2	4.86	1487.4	4.95	1478.4	5.03
0.025	1524.9	4.65	1513.7	4.74	1501.9	4.83	1490.0	4.93	1480.9	5.01
0.050	1527.1	4.63	1515.8	4.72	1503.8	4.82	1491.9	4.91	1482.8	4.99
0.075	1529.20	4.62	1517.80	4.70	1505.80	4.80	1493.80	4.89	1484.6	4.98
0.100	1531.00	4.60	1519.40	4.69	1507.40	4.78	1495.40	4.88	1486.2	4.96

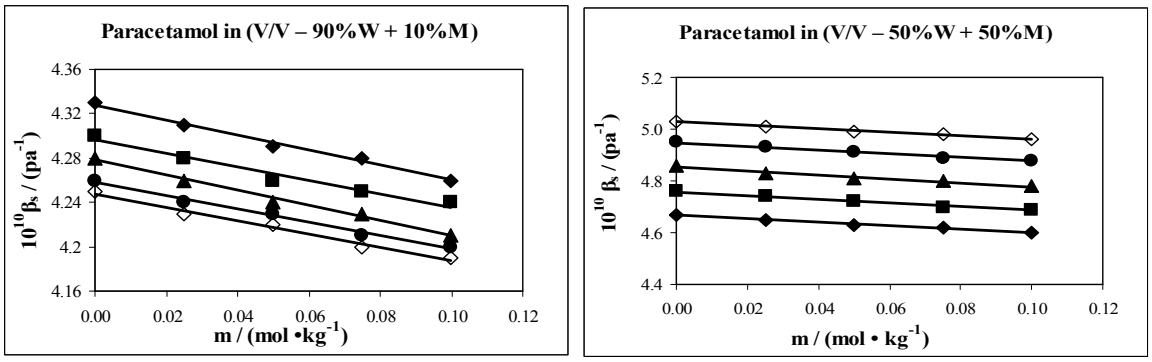

Figure 2. Plot of Isentropic compressibility (β_s) against molal concentration (m) of Paracetamol at T = (◆) 298.15K, (■) 303.14K, (▲) 308.15K, (●) 313.15K, (◇) 318.15K of (V/V – 90%W + 10%M) and (V/V – 50%W + 50%M)

Table 5. $\Delta\beta_s$-Change in Isentropic compressibility and $\Delta\beta_s / \beta_s^0$-Relative change in Isentropic compressibility of Paracetamol in aqueous methanol solution at different temperatures

m/ (mol.kg^{-1})	T = 198.15K		T = 303.15K		T = 308.15K		T = 313.15K		T = 318.15K	
	$10^{11}\Delta\beta_s$/ pa^{-1}	$10^{-3}\Delta\beta_s/\beta_s^0$	$10^{11}\Delta\beta_s$/ pa^{-1}	$10^{-3}\Delta\beta_s/\beta_s^0$	$10^{11}\Delta\beta_s$/ pa^{-1}	$10^{-3}\Delta\beta_s/\beta_s^0$	$10^{11}\Delta\beta_s$/ pa^{-1}	$10^{-3}\Delta\beta_s/\beta_s^0$	$10^{11}\Delta\beta_s$/ pa^{-1}	$10^{-3}\Delta\beta_s/\beta_s^0$
(V/V – 90%W + 10%M)										
0.025	1.834	4.236	1.807	4.203	1.784	4.171	1.777	4.170	1.751	4.120
0.050	3.554	8.208	3.502	8.145	3.406	7.960.	3.356	7.876	3.312	7.792
0.075	5.162	11.922	5.085	11.827	4.914	11.486	4.851	11.385	4.795	11.280
0.100	6.664	15.3918	6.239	14.5093	6.321	14.775	6.227	14.617	6.204	14.594
(V/V – 80%W + 20%M)										
0.025	1.974	4.646	1.911	4.498	1.847	4.349	1.741	4.082	1.713	4.004
0.050	3.747	8.823	3.603	8.482	3.426	8.065	3.264	7.653	3.264	7.626
0.075	5.211	12.267	5.024	11.829	4.785	11.265	4.573	10.724	4.572	10.683
0.100	6.539	15.395	6.223	14.652	5.994	14.112	5.944	13.939	5.944	13.888
(V/V – 70%W + 30%M)										
0.025	1.996	4.706	1.900	4.447	1.832	4.251	1.764	4.056	1.726	3.926
0.050	3.721	8.775	3.582	8.382	3.499	8.119	3.361	7.728	3.227	7.340
0.075	5.176	12.206	4.939	11.559	4.782	11.096	4.630	10.643	4.619	10.507
0.100	6.374	15.031	6.197	14.504	6.075	14.098	5.852	13.452	5.965	13.569
(V/V – 60%W + 40%M)										
0.025	2.098	4.821	2.007	4.565	1.923	4.315	1.842	4.064	1.780	3.872
0.050	3.915	8.998	3.732	8.487	3.558	7.984	3.448	7.608	3.293	7.162
0.075	5.480	12.594	5.231	11.897	4.963	11.136	4.767	10.516	4.660	10.135
0.100	6.881	15.815	6.515	14.818	6.323	14.1866	6.267	13.827	6.007	13.066
(V/V – 50%W + 50%M)										
0.025	2.231	4.772	2.217	4.656	2.236	4.605	2.223	4.489	2.231	4.432
0.050	4.094	8.758	4.055	8.517	4.023	8.287	4.046	8.170	4.052	8.050
0.075	5.888	12.597	5.829	12.243	5.831	12.011	5.836	11.785	5.809	11.542
0.100	7.509	16.065	7.361	15.462	7.396	15.233	7.438	15.019	7.441	14.783

Furthermore the values of the apparent molal compressibility K_φ are evaluated using the following equation [39] and are listed in Table 6:

$$K_\varphi = M\beta_s / \rho - 1000\,(\beta_0\rho - \beta_s\rho_0)/ m\,\rho\rho_0 \qquad (11)$$

The limiting molal compressibility K_φ / of Paracetamol is evaluated using Masson's equations [5] from the linear plot of K_φ against m (See the representative plot figure 3), using the least squares method of the following equation:

$$K_\varphi = K_\varphi^0 + S_k m \quad (12)$$

where S_k is the experimental slope and is a measure of solute–solute interactions, K_φ^0 is the partial molal parameter at infinite dilution, which is a measure of solute–solvent interactions. The calculated values of K_φ^0 and S_k are listed in Table 7.

Table 6. Apparent molal compressibility, $-K_\varphi$ of Paracetamol in aqueous methanol solution at different temperatures

m/ (mol.kg^{-1})	10^{15} ($-K_\varphi$) / (m^3.mol^{-1}.pa^{-1})				
	T = 298.15K	T = 303.15K	T = 308.15K	T = 313.15K	T = 318.15K
(V/V – 90%W + 10%M)					
0.025	21.16	20.15	19.18	18.86	17.69
0.050	19.26	18.29	16.31	15.21	14.18
0.075	17.37	16.40	14.03	13.13	12.24
0.100	15.58	11.29	12.10	11.11	10.75
(V/V – 80%W + 20%M)					
0.025	29.63	26.79	23.89	1905	1747
0.050	25.98	22.70	18.80	1492	1450
0.075	20.67	17.84	14.25	1086	1042
0.100	16.88	13.35	10.67	09.71	09.29
(V/V – 70%W + 30%M)					
0.025	32.76	28.15	24.65	21.10	18.69
0.050	27.55	24.01	21.62	17.98	14.34
0.075	22.23	18.30	15.39	12.56	11.63
0.100	17.11	14.65	12.67	09.60	10.06
(V/V – 60%W + 40%M)					
0.025	37.87	33.35	28.91	24.33	20.68
0.050	32.39	27.77	23.17	19.69	15.37
0.075	27.19	22.95	18.18	14.30	11.77
0.100	23.03	18.48	15.49	13.83	10.05
(V/V – 50%W + 50%M)					
0.025	42.87	41.17	40.80	39.01	38.32
0.050	35.41	33.42	31.58	30.72	29.78
0.075	32.13	30.18	28.96	27.79	26.34
0.100	28.90	26.19	25.30	24.55	23.53

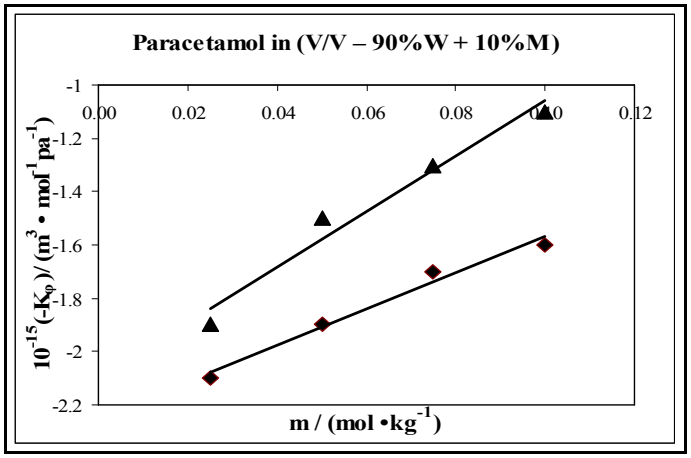

Figure 3. Plot of apparent molar compressibility ($-K_\varphi$) against molal concentration(m) of paracetamol at T = (◆)303.15K and (▲)313.15K of (V/V – 90%W + 10%M)

Table 7. Partial molal compressibility, ($-K_\varphi^0$) and Experimental slope, S_K, Paracetamol in aqueous methanol solution at different temperatures

K	$10^{15}(-K_\varphi^0)$ / ($m^3.mol^{-1}pa^{-1}$)	$10^{17} S_k$ / ($m^3.mol^{-2}.kg.pa^{-1}$)	$10^{15}(-K_\varphi^0)$ / ($m^3.mol^{-1}pa^{-1}$)	$10^{17} S_k$ / ($m^3.mol^{-2}.kg.pa^{-1}$)
(V/V – 90%W + 10%M)			(V/V – 80%W + 20%M)	
298.15	2.3	7.45	3.41	17.41
303.15	2.36	11.3	3.14	18.07
308.15	2.12	9.4	2.79	17.69
313.15	2.09	10.1	2.16	12.8
318.15	1.94	9.1	2.007	11.4
(V/V – 70%W + 30%M)			(V/V – 60%W + 40%M)	
298.15	3.79	20.9	4.25	19.89
303.15	3.28	18.48	3.79	19.77
308.15	2.91	16.86	3.27	18.09
313.15	2.52	15.96	2.72	14.76
318.15	2.08	11.44	2.33	14.19
(V/V – 50%W + 50%M)				
298.15	4.61	18.06		
303.15	4.47	19.27		
308.15	4.39	19.65		
313.15	4.21	18.53		
318.15	4.14	19.12		

Furthermore the solute–solvent interaction may be discussed through the change of dynamic property such as viscosity. The viscosity data given in Table 8 may be analyzed using the Jones–Dole equation[46]

$$\eta_r = \eta / \eta_0 = 1 + B \cdot c \qquad (13)$$

where $\eta_r = \eta/\eta_0$. η and η_0 represent the viscosity of the mixed solution and solvent, respectively, where c is the molarity of the drug solution. Using the linear plots of η_r against c (See a representative plot Figure 4), the viscosity B-coefficients are valuated by the least squares method of equation (13). The evaluated values of B-coefficients are given in Table 9.

Table 8. Viscosity η of Paracetamol in aqueous methanol solution at different temperatures

m/ ($mol.kg^{-1}$)	η/(mPa.s)				
	T = 298.15K	T = 303.15K	T = 308.15K	T = 313.15K	T = 318.15K
(V/V – 90%W + 10%M)					
0.000	1.1276	0.9947	0.8818	0.7896	0.7117
0.025	1.1355	1.0012	0.8871	0.7940	0.7153
0.050	1.1460	1.0103	0.8950	0.8010	0.7215
0.075	1.1550	1.0180	0.9015	0.8064	0.7259
0.100	1.1625	1.0240	0.9062	0.8096	0.7289
(V/V – 80%W + 20%M)					
0.000	1.3091	1.1473	1.0071	0.8969	0.8046
0.025	1.3191	1.1555	1.0138	0.9024	0.8091
0.050	1.3315	1.1662	1.0231	0.9105	0.8162
0.075	1.3425	1.1756	1.0308	0.9171	0.8216
0.100	1.3512	1.1824	1.0365	0.9212	0.8253
(V/V – 70%W + 30%M)					
0.000	1.5186	1.3094	1.1461	1.0142	0.8995
0.025	1.5307	1.3198	1.1543	1.0211	0.9051
0.050	1.5458	1.3319	1.1653	1.0303	0.9132
0.075	1.5592	1.3430	1.1747	1.0382	0.9196
0.100	1.5695	1.3512	1.1813	1.0439	0.9240
(V/V – 60%W + 40%M)					
0.000	1.5910	1.3798	1.2073	1.0649	0.9471
0.025	1.6050	1.3917	1.2166	1.0727	0.9535
0.050	1.6209	1.4046	1.2287	1.0826	0.9623

0.075	1.6353	1.4169	1.2385	1.0917	0.9695
0.100	1.6463	1.4255	1.2460	1.0978	0.9742
(V/V – 50%W + 50%M)					
0.000	1.3876	1.3876	1.2195	1.0780	0.9605
0.025	1.4001	1.4001	1.2299	1.0865	0.9675
0.050	1.4132	1.4132	1.2422	1.0969	0.9767
0.075	1.4258	1.4258	1.2529	1.1066	0.9845
0.100	1.4352	1.4352	1.2604	1.1130	0.9893

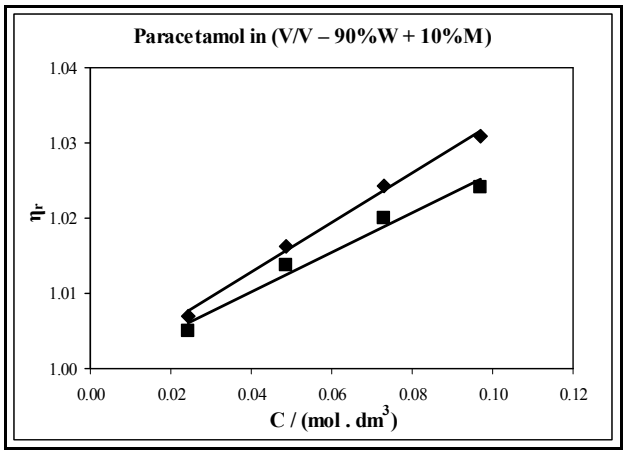

Figure 4. Plot of relative viscosity (η_r) against molarity (c) of paracetamol at T =(◆) 298.15K and (■)318.15K of (V/V – 90%W + 10%M)

Table 9. Viscosity B-coefficients, mean volume of solvent, $\bar{V}_1^0$, activation free energy of solvent , $\Delta\mu_1^{0*}$, and solute , $\Delta\mu_2^{0*}$, of Paracetamol in aqueous methanol solution at different temperatures

T/K	10^3 B/ ($m^3.mol^{-1}$)	10^6 $\bar{V}_1^0$ / ($m^3.mol^{-1}$)	10^6 $\Delta\mu_1^{0*}$ / ($kJ.mol^{-1}$)	10^3 $\Delta\mu_2^{0*}$ / ($kJ.mol^{-1}$)
(V/V – 90%W + 10%M)				
298.15	0.330	19.02	9.877	66.66
303.15	0.317	19.06	9.731	65.78
308.15	0.300	19.09	9.587	64.30
313.15	0.275	19.13	9.461	61.68
318.15	0.265	19.17	9.343	61.03
(V/V – 80%W + 20%M)				
298.15	0.343	20.45	10.426	64.42
303.15	0.329	20.60	10.287	63.18
308.15	0.316	20.64	10.128	62.28
313.15	0.296	20.69	9.997	60.47
318.15	0.283	20.64	9.863	59.73
(V/V – 70%W + 30%M)				
298.15	0.363	21.83	10.956	63.42
303.15	0.342	21.99	10.785	61.43
308.15	0.336	22.05	10.629	61.37
313.15	0.322	22.12	10.491	60.36
318.15	0.301	22.12	10.341	58.62
(V/V – 60%W + 40%M)				
298.15	0.374	23.38	11.242	60.98
303.15	0.355	23.58	11.093	59.31
308.15	0.352	23.65	10.941	59.56
313.15	0.344	23.73	10.801	59.28
318.15	0.319	23.69	10.659	57.32
(V/V – 50%W + 50%M)				
298.15	0.394	25.17	11.428	59.19
303.15	0.374	25.40	11.294	57.51
308.15	0.370	25.50	11.160	57.63
313.15	0.368	25.60	11.030	57.97
318.15	0.339	25.62	10.903	55.65

In addition to this, the data of the B-coefficient of the solutions are used to estimate the free energy of activation per mole of the solute $\Delta\mu_2^{0*}$ and solvent $\Delta\mu_1^{0*}$ using the following equations given by transition state theory suggested by Feakins et al.[47] and Eyring et al[48].

$$B=(\bar{V}_1^0 - \bar{V}_2^0)/1000 + (\bar{V}_1^0/1000)(\Delta\mu_2^{0*} - \Delta\mu_1^{0*})/RT \quad (14)$$

$$\Delta\mu_1^{0*} = RT\ln(\eta_0 \bar{V}_1^0/hN_A) \quad (15)$$

Equation (14) can be rearranged as

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

where $\bar{V}_1^0 = (\Sigma x_i m_i / \rho)$ is the mean volume of the solvent and $\bar{V}_2^0 = \bar{V}_\phi^0$ is the partial molal volume at infinite dilution of the solute. The terms x_i and M_i denote the mole fraction and molar mass of water (1) and Paracetamol (2) and ρ is the density of solvent mixture (Paracetamol + aqueous methanol), h is the Planck's constant, N_A is Avogadro's number, η_0 is the viscosity of the solvent and R is the gas constant.

The calculated values of $\bar{V}_1^0$, $\Delta\mu_2^{0*}$ and $\Delta\mu_1^{0*}$ are also given in Table 9.

The hydration of any solute can be judged from the magnitude of the hydration number H_n which can be calculated using the following equation[49].

$$H_n = B/V_\phi^0 \quad (17)$$

The ratio of B/V_ϕ^0 is an important indicator through which the property of hydration or unhydration of a drug molecule in a solvent may be obtained. A value of B/V_ϕ^0 Is within 0 – 2.5 it indicates the unhydrated nature while a value higher than 2.5 is an indication of solvated nature[5]. The evaluated values of hydration number are given in Table 10.

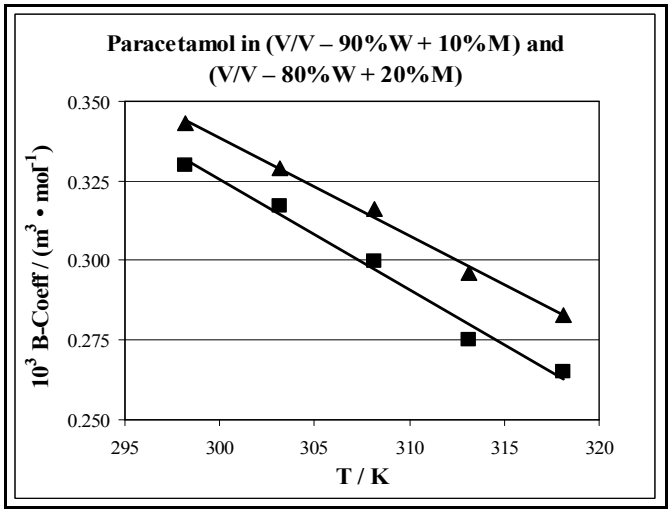

Figure 5. Plot of Viscosity B-coefficient against temperature (T/K) of paracetamol (■ V/V – 90%W + 10%M) and (▲ V/V – 80%W + 20%M)

Table 10. B/V_φ^o and dB/dT of Paracetamol in aqueous methanol solution

T/K	(V/V – 90%W + 10%M)		(V/V – 80%W + 20%M)		(V/V – 70%W + 30%M)		(V/V – 60%W + 40%M)		(V/V – 50%W + 50%M)	
	B/V_φ^o	dB/dT	B/V_φ^o	dB/dT	B/V_φ^o	dB/dT	B/V_φ^o	dB/dT	B/V_φ^o	dB/dT
		$m^3\ mol^{-1}\ k^{-1}$		$m^3\ mol^{-1}\ k^{-1}$		$m^3\ mol^{-1}\ k^{-1}$		$m^3\ mol^{-1}\ k^{-1}$		$m^3\ mol^{-1}\ k^{-1}$
298.15	2.64		2.79		3.00		3.15		3.39	
303.15	2.52		2.65		2.81		2.96		3.19	
308.15	2.37	-0.0034	2.53	-0.0031	2.73	-0.0029	2.92	-0.0024	3.13	-0.0023
313.15	2.15		2.35		2.60		2.83		3.09	
318.15	2.06		2.23		2.41		2.60		2.82	

4. Discussion

It is seen from Table 2 that density of the ternary system increases with an increase in concentration of drug in the aqueous methanol mixtures at studied temperatures indicating the enhanced structure of the mixed solvent due to the presence of the Paracetamol[17]. The values of the partial molal volume V_φ^o are positive and show an increasing trend with increase in temperature attributing the presence of strong drug–solvent interactions in the studied systems[17]. The variation in partial molal volumes may be explained using scaled particle theory[50] as follows

$$V_\varphi^o = V_{cavity} + V_{interactions} + \beta_s^0 RT \qquad (1)$$

Here V_{cavity} is related to the contribution of the formation of cavity while $V_{interactions}$ represents the intermolecular interactions. β_s^0 is the isothermal compressibility of the mixed solvent, R is the gas constant and T is the absolute temperature. Generally creation of the cavity is by definition a positive contribution to the partial molal volume while presence of strong interactions between solute and solvent molecules reduces the values of V_φ^o by shrinking the cavity. The trend of V_φ^o with temperature may be viewed interms of the geometrical fit of the drug molecules in an ordered methanol-water solution. It is difficult to accommodate a complex drug molecule like paracetamol in an ordered solvent like aqueous methanol solution. As the temperature increases cavities are produced in the ordered solution environment resulting in the better fit of the drug solute molecules in the solvent. The increase of V_ϕ^0 with temperature may also be attributed to reduction of electrostriction and release of some solvent molecules from the loose hydration layers of the drug in the aqueous methanol solution[5]. The negative values of S_v (See Table 3) indicate the presence of weak solute–solute interaction in the solution[51, 52].

The values of partial molal expansivity E_0^2 (See Table 3) are positive indicating that paracetamol acts as a structure maker in aqueous methanol solution[4]. Further they indicate the predominance of hydrophobic hydration over the electrostriction of water methanol molecules around the paracetamol molecules. From Table 3, it is seen that that the values of isobaric thermal expansion coefficient (α_2) are positive and decrease with increase of temperature substantiates its linear dependence on density values[11].

The positive values of Hepler's constant, i.e., $\partial^2 V_\varphi^0/\partial T^2$ (See Table 3) further supports structure making capacity of paracetamol in aqueous methanol solution[53].

From Table 4, it is seen that the ultrasonic speed increases with concentration of paracetamol and indicating the presence of strong solute – solvent interactions[54]. Isentropic compressibility β_s decreases with increase in concentration of the drug and temperature

The decrease in compressibility values may be discussed in view of the following model for water [55, 56]. Water is regarded as an equilibrium mixtures of two structures such as an ice like structure and a close – packed structure. Compressibility of liquid water is given by

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

Where β_α is an instantaneous part of compressibility and β_{relax}, a relaxational part of compressibility[31]. The relaxation time τ is of the order of 10^{-11} S corresponding to β_{relax}. Thus in the present case $\omega\tau << 1$; ω being the angular frequency.

Thus the isentropic compressibility $\beta_s = (\beta_\alpha + \beta_{relax})$. With rise in temperature, β_α increases due to thermal expansion while β_{relax} decrease due to thermal rupture of the ice-like structure. Thus any decrease in β_s values with concentration and temperature may be attributed to the corresponding decrease in β_{relax} values which is dominant over the corresponding increase in β_α [57].

The change in isentropic compressibility ($\Delta\beta_s$) and relative change in isentropic compressibility ($\Delta\beta_s / \beta_s^0$) with concentration of drug (See Table 5) may be related to an increase in the incompressible part in the aqueous methanol solution. However the decrease in the above values with temperature may be attributed to thermal rupture of water structure. The intercept values of the plots of $\Delta\beta_s$ and $\Delta\beta_s / \beta_s^0$ versus Paracetamol concentration for all the (% methanol) solutions are zero or close to zero which indicates the strong solute-solvent intermolecular / interionic interactions. The same results were reported in electrolyte systems[58].

Partial molar compressibility K_φ^0 is a sensitive measure of solute solvent interactions existing in a solution[59]. When K_φ^0 have positive values it indicates weak interaction and negative values vice versa. The negative values for K_φ^0 in the studied system (See Table 7) indicates the presence of solute-solvent interaction and compliments the volumetric results. The decrease of K_φ^0 with temperature may be attributed to the thermal rupture of water structure as discussed earlier. The small positive values of S_k indicate the weak solute-solute interactions.

From Table 8, it is clear that viscosities increase with increase in concentration of the drug. Usually when a solute is dissolved in a solvent some of the solvent molecules are attracted to the solute molecules as a result of solute solvent interaction which will be reflected in the increase in viscosity values. This may also be attributed to the structure making ability of the solute[12], thus compliments the volumetric and compressibility results. With increase in temperature the kinetic energy of the molecules increases there by showing a decrease in viscosity values. The viscosity B coefficient is also an indicator of solute solvent interaction and structure making ability of a solute in a solvent/solution. The positive values of the viscosity B-coefficients further substantiate the presence of strong solute solvent interactions between drug and aqueous methanol solution and structure making ability of the paracetamol in the studied solutions[60]. The values of B coefficient decrease with the increase in temperature (See Figure 5) may be attributed to the structure promoting tendency of the compound. Generally the sign of dB/dT values (See Table 10) give the important information regarding the structure-making and structure-breaking roles[61, 62] of the solute in the solvent media rather than simply the B coefficient. In the present study the B value decreases with temperature indicating structure making properties. These are in excellent agreement with the conclusions drawn from $\partial^2 V_\varphi^0 / \partial T^2$ discussed earlier. It is also seen from Table 9 that the values of $\Delta\mu_2^{0^*}$ are positive and larger than $\Delta\mu_1^{0^*}$ indicating the stronger solute solvent interactions and structure making ability of the solute[63]. In other words the formation of the transition state is less favoured in the presence of the solute due to rupture and distortion of the intermolecular forces in the aqueous methanol solution[64].

In the present study, the values of H_n is higher than 2.5 for all concentrations of aqueous methanol solutions and also at low temperatures, which reveals the indication of hydrated nature of drug molecule[10, 49] .However at high temperature for few cases, the values of H_n is less than 2.5 indicating the effect of temperature on the hydration properties of the drug molecule.

5. Conclusions

In this work, the volumetric, ultrasonic speed, and viscometric properties of Paracetamol in aqueous methanol solution have been reported for different temperatures. The values of apparent molal volumes and apparent molal compressibility indicate the presence of strong solute–solvent interactions in the drug solution. Further, the volumetric studies conclude that the drug, Paracetamol acts as a structure maker in the aqueous methanol solutions. The values of viscosity B-coefficient and other activation parameters compliments the results obtained from volumetric studies.

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