Study Of Physico-Chemical Properties Of Paracetamol As Pharmaceutical Waste In Water: An Analysis Of Molecular Interactions

Malabika Talukdar, Sulochana Singh

Abstract: The presence of pharmaceutical wastes has been detected in various water environments. These pharmaceutical pollutants may lead to serious problems to human and animal health. Various molecular interactions existing in aqueous drug systems may be considered responsible for these health hazards. Physico-chemical properties of aqueous paracetamol have been experimentally determined and other derived parameters are calculated from the experimental data. Analysis of various physico-chemical parameters led to an understanding of intra and intermolecular interaction of the drug solution.

Keywords: molar conductance, paracetamol, pharmaceutical wastes, surface tension, viscosity

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1. INTRODUCTION

Pharmaceutical wastes are expired, unused, contaminated, damaged or residual medicinal drugs those are no longer needed. These wastes can be proved to be extremely harmful to the environment if not stored and disposed of properly. Pharmaceutical wastes those are excreted with urine and faecal matters find their way to sewage water, ground water and even in fresh water bodies. As most of these drugs adapt resistance to biochemical degradation inside the body retain their physical and chemical properties in the environment. Extensive investigations have been carried out to detect the presence of pharmaceutical pollutants in water systems and in other environment [1]. Though a very low level of these micropollutants are found in water bodies, endocrine disruption in aquatic life is evidenced from research work carried out by Liney and coworkers [2]. The effect of these pharmaceutical wastes to the environment and to human and animal health can clearly be understood with the knowledge of different molecular interactions existing in aqueous drug systems. Studies of various physico-chemical properties of these drugs are necessary to interpret different intra and intermolecular interactions in drug solutions. In the present article physico-chemical properties of a commonly used analgesic and antipyretic drug Paracetamol in aqueous solutions are studied. Paracetamol is generally used in mild dose. Higher doses may lead to serious liver failure and skin rashes [3]. Residual paracetamol is found in sewage outfall, river water and river sediment and at a very low level in ground water [4]. Conductance (Λ) and viscosity (η) and Surface tension (γ) of aqueous solutions of

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Paracetamol have been measured at different temperatures ranging between 298.15- 313.1K. Surface tension values were also calculated from density and ultrasonic velocity data [5]. The experimentally obtained data have been used to derive other physico-chemical parameters necessary to interpret molecular interactions. With the help of viscosity and conductance data thermodynamic parameters like ΔG^0, ΔH^0, ΔS^0 were calculated. Various other physicochemical parameters such as molar conductance (Λ_m), limiting molar conductance ($\Lambda_m{}^0$), association constant (K_A), activation energy (E_S) and Walden product ($\Lambda_m^0 \eta^0$) were evaluated from conductance values. Measurement of viscosity helped in calculating relative viscosity (η_r), Jone-Dole's coefficients (B_J), and chemical potential (μ). Surface tension values were used to determine mean ionic activity ($a_\pm$) and surface excess (Γ).

2. EXPERIMENTAL

2.1 CHEMICALS
The drug paracetamol was procured from ORISSA DRUGS & CHEMICALS LTD (ODCL) and LABORATORY CHEMICALS, Bhubaneswar, Odisha and used as such. All chemicals were of GR, BDH or AnalaR grades. All solutions were made with Conductivity water (Sp.cond.~$10^{-6} Scm^{-1}$).

2.2 METHODS

2.2.1 PREPARATION OF SOLUTIONS
Molal concentration of aqueous paracetamol solution was calculated first and that was converted to molar concentrations by using the standard expression [6] considering different density values at the respective temperatures. Solutions of four successive concentrations were made by dilution of the stock solution.

2.2.2 VISCOMETRIC STUDIES
A calibrated Ostwald viscometer of 25mL capacity was used to measure the viscosity at the required temperatures controlled to ±0.05 K by keeping it in a water thermostat. A digital stop watch with accuracy of 0.01s was used to measure the flow time of water and that of the solutions.The viscosity values thus obtained are within a range of ± 0.3×10^{-3} cP. The reference values of viscosity of water at

different experimental temperatures are collected from the literature [7].

$$\frac{\eta_1}{\eta_2} = \frac{d_1 t_1}{d_2 t_2} \qquad (1)$$

where η_1 is the coefficient of viscosity of water
η_2 is the coefficient of viscosity of solution
d_1 is the density of water
d_2 is the density of the solution
t_1 is the time of flow of water
t_2 is the time of flow of solution

2.2.3 CONDUCTOMETRIC STUDIES
An Elico make conductivity meter with sensitivity of 0.1% and cell constant $1\mathrm{Scm}^{-1}$was used to measure conductance of aqueous paracetamol solutions of five different concentrations. The measurements of specific conductance (S m⁻¹) and molar conductance (S $m^2 mol^{-1}$) were made over the temperature range of 298.15- 313.15 K (±0.05K) upto three digits. The ionic strengths of the solutions were $\sim 10^{-4}$ to 10^{-2} mol. m^{-3} . Appropriate corrections for the conductance of the solutions were made with respect to the conductance of the solvent (water) [8].

2.2.4 SURFACE TENSION STUDIES
Using experimental values of density and ultrasonic velocity of aqueous ibuprofen, the surface tension (γ) values were calculated at 298.15 K over the entire concentration range.

These derived γ values were compared with the experimental γ values obtained by the drop count method using a Stalagmometer [9]. These values were proved to be helpful to study different intermolecular interactions in these systems.

3. RESULTS AND DISCUSSION

3.1 VISCOMETRIC ANALYSIS
It is well understood that viscosity, which is resulted by the all possible intermolecular forces, regulates the fate of transportation of water. Hence to understand the structural aspects of the studied solutions their viscosity (η) measurements were made at four temperatures such as at 298.15, 303.15, 308.15 and 313.15 K. Jones and Doles equation (2) is followed to determine the relative viscosity (η_r) values. The viscosity (η) and relative viscosity (η_r) of different concentrations of paracetamol in pure water at different temperatures is listed in Table 1.

$$\eta_r = \eta/\eta_0 = 1 + A_F c^{1/2} + B_J c \qquad (2)$$

where η_r = relative viscosity (η/η_0)
η = viscosity coefficient of solution
η_0 = viscosity coefficient of solvent
A_F= Falken-Hagen coefficient
B_J = Jones-Dole coefficient
and c = molar concentration [10]

Table 1 - *Values of η ($kg.m^{-1}s^{-1}$) and η_r($kg.m^{-1}s^{-1}$) at different concentrations for paracetamol in water (c) at different temperatures (T).*

C mol. m^{-3}	298.15 K		303.15 K		308.15 K		313.15 K	
	$\eta \times 10^3$ kg. $m^{-1} s^{-1}$	η_r kg. $m^{-1} s^{-1}$	$\eta \times 10^3$ kg. $m^{-1} s^{-1}$	η_r kg. $m^{-1} s^{-1}$	$\eta \times 10^3$ kg. $m^{-1} s^{-1}$	η_r kg. $m^{-1} s^{-1}$	$\eta \times 10^3$ kg. $m^{-1} s^{-1}$	η_r kg. $m^{-1} s^{-1}$
10.0	0.909	1.020	0.810	1.015	0.744	1.025	0.665	0.001
30.0	0.921	1.034	0.822	1.030	0.750	1.032	0.671	0.001
50.0	0.927	1.040	0.834	1.045	0.755	1.039	0.676	0.001
70.0	0.932	1.047	0.840	1.052	0.761	1.048	0.682	0.001
90.0	0.939	1.054	0.845	1.059	0.767	1.056	0.688	0.001

From Table 1, it can be noticed that the viscosity as well as relative viscosity of paracetamol solutions decrease with increase in temperature from which it can be ascribed that the pulling capacity of molecules towards each other became weaker when the temperature is increased, by the virtue of the obstruction of thermal energy [11]. From Fig 1, it is also seen that viscosity is increased with increase in concentrations of the pharmaceutical drug paracetamol. It may be due to the molecular association between drug and water molecules and hence producing a solution of strong intermolecular forces in the solvent.
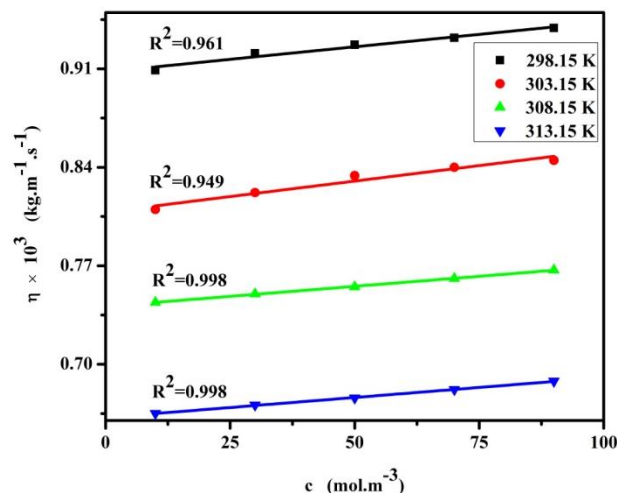
Fig. 1 *Viscosity η ($kg.m^{-1}s^{-1}$) vs conc. c ($mol.m^{-3}$) of paracetamol in water at different temperatures.*

Table 2 shows the viscosity parameter values, that is A_F, B_J, $\overline{V}_1^0$, $\overline{V}_2^0$, $\Delta\mu_1^0$ and $\Delta\mu_2^0$. If is found that the A_F values are positive at all the temperature studied, which indicates a

strong solute-solute interaction. The B_J coefficient is understood as a measure of effective solvodynamic volumes of the solvated ions and is supervised by the solute-solvent interactions which have structural effect on the solvent, i.e. it can cause an increase in viscosity of the solutions. Also it is seen from the Table 2 that the values of B_J are mostly positive, such contribution of B_J values caused an increase in the viscosity of the studied solutions.

The viscosity is also interpreted on the basis of transition state theory for relative viscosity of the solution as suggested by Feakins [12] by using the following equation:

$$\Delta\mu_2^{0*} = \Delta\mu_1^{0*} + \left(RT/\overline{V}_1^0\right)\left[1000B_J - \left(\overline{V}_1^0 - \overline{V}_2^0\right)\right] \qquad (3)$$

where

$\overline{V}_1^0$ = partial molar volume of the solvent

$\overline{V}_2^0$ = partial molar volume of the solute

B_J = Jones-Dole parameter

$\Delta\mu_2^{0*}$ = contribution per mole of the solvent to free energy of activation for viscous flow of the solution

$\Delta\mu_1^{0*}$ = contribution per mole of the solute to free energy of activation for viscous flow of the solvent [13] and given by

$$\Delta\mu_1^{0*} = RT \ln \left(\frac{\eta_0 \overline{V}_1^0}{hN}\right) \qquad (4)$$

$$\overline{V}_1^0 = M_{solvent}/d \qquad (5)$$

and

$$\overline{V}_2^0 = V_\phi^0 \qquad (6)$$

h = Planck's constant.

N = Avogadro number.

Table 2- *Values of parameters A_F $\left(m^{3/2}.mol^{-1/2}\right)$, B_J $\left(m^{3/2}.mol^{-1/2}\right)$, $\overline{V}_1^0$ $((m^3.mol^{-1})$, $\overline{V}_2^0$ $((m^3.mol^{-1})$, $\Delta\mu_1^0$ $(kJ.mol^{-1})$ and $\Delta\mu_2^0$ $(kJ.mol^{-1})$ for paracetamol in water at different temp (T).*

T (K)	A_F $(m^{3/2}.mol^{-1/2})$	B_J x 10^2 $(m^{3/2}.mol^{-1/2})$	$\overline{V}_1^0$ x 10^3 $(m^3.mol^{-1})$	$\overline{V}_2^0$ x 10^{-1} $(m^3.mol^{-1})$	$\Delta\mu_1^0$ x 10^{-3} $(kJ.mol^{-1})$	$\Delta\mu_2^0$ x 10^{-5} $(kJ.mol^{-1})$
298.15	0.007	-0.013		-0.192	3.167	0.030
303.15	0.004	0.027	18.15	-0.149	3.218	0.036
308.15	0.008	-0.028		-0.160	3.268	0.029
313.15	0.005	0.000		-0.159	3.318	0.033

A perusal of Table 2 indicates that $\Delta\mu_1^0$ and $\Delta\mu_2^0$ values are positive at all the temperatures. $\Delta\mu_1^0$ increased with an increase in temperature. Such behavior of $\Delta\mu_1^0$ and $\Delta\mu_2^0$ is in fact similar to that of B_J in the solution with stronger solute-solvent interactions. Substantially, the positive values of $\Delta\mu_2^0$ indicate the formation of the transition state accompanied by the rupture and distortion of the intermolecular forces in the solvent structure.

3.2 CONDUCTANCE MEASUREMENTS
3.2.1 MOLAR CONDUCTANCE
The molar conductance values, Λ_m calculated from the specific conductance values (eq.7) for paracetamol in water at different temperatures are recorded in Table -3 [14].

$$\Lambda_m = 1000\text{k}_{corr}/c \qquad (7)$$

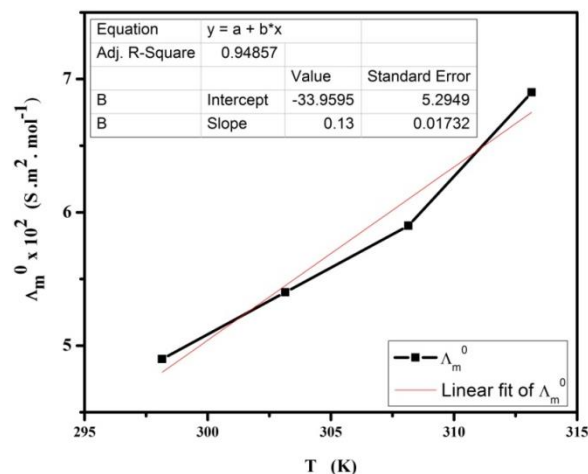where $\text{k}_{correct} = \text{k}_{solution} - \text{k}_{solvent}$

where Λ_m is the molar conductance, k is the specific conductance and c is the concentration of the solution.

Table 3- *Values of $\Lambda_m (S.m.^2 mol^{-1})$ for paracetamol in different concentrations in water at different temp T (K)*

Conc. (mol.m^{-3})	Λ_m (S.m.^{2} mol^{-1})x 10^3			
	298.15K	303.15K	308.15K	313.15K
10.0	38.18	45.06	42.49	54.93
30.0	11.28	12.40	13.11	14.10
50.0	2.28	6.61	6.68	7.88
70.0	1.35	1.42	4.38	4.77
90.0	0.75	0.82	1.85	2.60
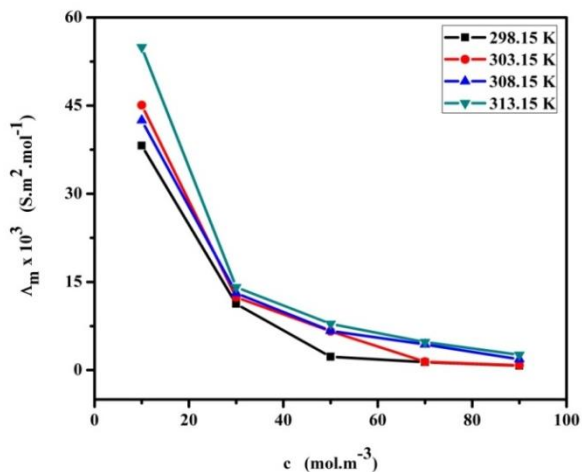
Fig 2 *Molar conductance, Λ_m (S m^2 mol^{-1}) vs concentration, c (mol.m^{-3}) at different temperatures (T)*

As observed Λ_m of aqueous paracetamol varied directly with temperature (Table 3) and inversely with its concentrations in water. The variation in Λ_m with increasing concentration (Fig 2) may be due to the solvation of paracetamol by water (called hydration) and hence reduces number of free ions to move. Increase in Λ_m with temperature may be due to the fact that increased thermal energy results in greater bond breaking and variation in rotational, vibrational, and translational energy of parcetamol units in water and that leads to higher frequency and higher mobility of the ions [15]. The derived Λ_m values were further utilized to calculate the Walden product , $\Lambda_m^0 \eta^0$.

Then approximate limiting molar conductance (Λ_m^0) is obtained from the intercept of the plot between Λ_m and $c^{1/2}$ by following least squares method using the equation (eq. 8).

$$\Lambda_m = \Lambda_m^0 - S\, c^{1/2} \tag{8}$$

where S is the slope and Λ_m^0 is the intercept of the plot of Λ_m vs. $c^{1/2}$.

Using the value of Λ_m^0, Λ_m^I was calculated as

$$\Lambda_m^I = \Lambda_m^0 - S\, c^{1/2} \tag{9}$$

The plot of Λ_m^I vs $c^{1/2}$ gives a new value of $\Lambda_m^{0\,I}$ which is used to get a new value of Λ_m^{II}. Thus the final constant value of Λ_m^0 was obtained by following re-iteration process. The values of limiting molar conductance (Λ_m^0) is listed in Table 4. As presented in Fig 3, the values of Λ_m^0 increased with increase in temperature for paracetamol in water. The reason behind it may be that more number of hydrogen bonds are broken due to increase in thermal energy, hence, increases the speed of ionic species [16]. The degree of association and thermodynamic parameters were calculated using the following relations.

Fig 3. *Limiting molar conductance, Λ_m^0 (S m^2 mol^{-1}) vs temperature, T (K) for aqueous paracetamol.*

From Ostwald's dilution law, for weakly soluble drugs, say MA,

$$\mathbf{MA \leftrightarrow M^+ + A^-}$$
$$\mathbf{(1-\alpha)c \quad \alpha c \quad \alpha c}$$
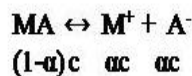
where $\alpha = {\Lambda_m}/{\Lambda_m^0}$, is the degree of dissociation of the solute and c is the molar concentration of the solution.

The dissociation constant $K_d = {\alpha^2 c}/{(1-\alpha)}$, considering the activity coeffiient term and taking the mean activity coefficient $\gamma_\pm$, K_d becomes K_d^I

$$K_d^I = \left[{\alpha^2 c}/{(1-\alpha)} \right] \cdot \gamma_\pm^2 \tag{10}$$

By using Debye-Huckel limiting equation for $\gamma_\pm$, at 298.15 K, K_d^I can be written as

$$\log K_d^I = \log K_d - 1.018\, c^{1/2} \tag{11}$$

From the plot of $\log K_d^I$ vs $c^{1/2}$ the value of $\log K_d$ is obtained from the intercept. The reciprocal of K_d (dissociation constant) gives the association constant K_A.

The free energy change, ΔG^0 for the association process was calculated from the following relation,

$$\Delta G^0 = -2.303\, RT \log K_A \tag{12}$$

where $R = 8.314\ J\ K^{-1} mol^{-1}$ and $T = 298.15 K$

The entropy change, ΔS^0 was calculated from the relation,

$$\Delta S^0 = - \left({\partial(\Delta G^0)}/{\partial T} \right)_p \tag{13}$$

Finally, the enthalpy change was calculated by using the Gibb's Helmholtz relation as,

$$\Delta G^0 = \Delta H^0 - T \Delta S^0 \tag{14}$$

Also from Table 4, it is marked that the association constant, K_A values of aqueous paracetamol show an irregular variation with increase in temperature. This may be attributed to the varying degree of exothermic ion-pair association resulted from the difference in ionic stability, specific ion-solvent and solvent-solvent interactions.

3.2.2 WALDEN PRODUCT

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A solute may be classified as a structure maker or breaker depending on its Walden product. i.e a product of limiting molar conductance and viscosity of the solvent. We may say Walden product can give an idea of the water-structuring activity of the solute. The values of Walden product for aqueous paracetamol at all the studied temperatures are presented in Table 4. The positive values of Walden product indicate towards the structure making properties of paracetamol in water [17].

Table 4 - *Values of limiting molar conductance, Λ_m^0 ($S.m.^2\, mol^{-1}$), association constant, K_A ($m.^3\, mol^{-1}$) and Walden product, $\Lambda_m^0 \eta^0$ for paracetamol in water at different temp (K)*

Temp (K)	Λ_m^0 (S. m.^{2} mol^{-1})	K_A (m.^{3} mol^{-1})	$\Lambda_m^0 \eta^0 \times 10^3$
298.15	4.90 ±0.02	126.18±1.10	0.044
303.15	5.40 ±0.03	218.27±1.02	0.047
308.15	5.90 ±0.01	43.75±0.11	0.039
313.15	6.90 ±0.05	38.11±1.14	0.045

Table 5 - *Thermodynamic parameters ΔG^0 ($kJ\, mol^{-1}$), ΔH^0 ($kJ\, mol^{-1}$), ΔS^0 ($J\, mol^{-1}$), and E_S ($kJ\, mol^{-1}$) for paracetamol in water at 298.15 K.*

ΔG^0 (kJ mol^{-1})	ΔH^0 (kJ mol^{-1})	ΔS^0 (J mol^{-1})	E_S (kJ mol^{-1})
31.82	1.80	0.50	1.45

As displayed in Table 5, the values of ΔG^0 are positive. The preference of the association process over the dissociation process is clearly indicated. The positive values of ΔH^0 show that the endothermic association processes are more energy consuming. The positive value of ΔS^0 indicates the randomness of ions in water medium. From the plot of log Λ_m^0 vs. $1/T$ the activation energy E_a value has been computed from the slope ($= -E_a/2.303R$) and is given in Table 5 for aq paracetamol solution. The positive values of E_a are pointing towards the favourable solubilisation process.

3.3 SURFACE TENSION STUDIES

The surface tension (γ), mean ionic activity ($a_\pm$) and surface excess (Γ_2) data for paracetamol have been derived from the usual relations (15-19) using the experimentally determined data of density and ultrasonic velocity at 298.15 K in water and the values are listed in Table 6 [18,19]. The γ values are also evaluated from drop number method (eq.20) using Stalagmometer at 298.15 K. The results are correlated with the derived γ data from U values.

(i) SURFACE TENSION FROM DENSITY AND ULTRASONIC VELOCITY MEASUREMENT

The surface tension (γ) values were computed from the sound velocity and density values at 298.15 K by using equation as given below,

$$\gamma = 6.3 \times 10^{-4} \times d \times U^{3/2} \qquad (15)$$

The stoichiomolalities (m) were converted to mean ionic activities ($a_\pm$) using the mean ionic activity coefficients ($\gamma_\pm$) given in the following equation.

$$a_\pm = (Q\alpha m\gamma_\pm) \qquad (16)$$
$$\text{where} Q = (v_+^{v+}v_-^{v-})^{1/v}, \qquad (17)$$

$\gamma_\pm$ is the mean ionic activity co-efficient as given by Debye-Huckel limiting law [20] and $v = (v_+ + v_-)$ is the total number

of moles of ions [21] produced from one mole of solute. α is the degree of dissociation ($\alpha = \Lambda_m/\Lambda_m^0$).

$$\log \gamma_\pm = -A\, |z^+||z^-|\, I^{1/2} \qquad (18)$$

z_+ and z_- = the valences of positive and negative ions, respectively

A = the Debye-Huckel constant, i.e.

$A = 1.823 \times 10^6/(\acute{\varepsilon}\, T^{3/2})$

$\acute{\varepsilon}$ = dielectric constant and I = ionic strength of the solution.
where, $I = \frac{1}{2} \Sigma m_i z_i^2$, where m_i is m_+ or m_-.

The surface excess Γ_2 can be obtained from the Gibbs equation [22]

$$\Gamma_2 = -(a_\pm/2RT) \times (d\gamma/da_\pm) \qquad (19)$$

where the $d\gamma/da_\pm$ is the slope obtained from the plot of γ vs. $a_\pm$.

(ii) SURFACE TENSION FROM DROP NUMBER METHOD USING STALAGMOMETER

Since surface tension (γ) illustrates itself in various effects, it offers so many paths to its measurement. Use of Traube's Stalagmometer [23] is one of the most important techniques to measure surface tension of a liquid. It is an instrument for estimating surface tension by measuring exact number of drops in a known quantity of liquid.
Thus, surface tension (γ) of the solution was by using the following equation,

$$\gamma_1/\gamma_2 = (n_2/n_1) \times (d_1/d_2) \qquad (20)$$

where γ_1 = surface tension of water
γ_2 = surface tension of the aqueous solution
d_1 = density of water
d_2 = density of the aqueous solution
n_1 = number of drops of water falling
n_2 = number of drops of aqueous solution falling

The principle of the drop number method is that a fixed volume of solution freely falling from a capillary tube which is held vertically and the number of drops were counted carefully.

Table 6 - *Values of mean ionic activity ($a_\pm$), and derived and experimental values of surface tension (γ) $(N.m^{-1})$ and surface excess (Γ_2) at different concentrations for paracetamol in water at 298.15 K.*

Conc. (c) $mol.m.^{-3}$	$a_\pm \times 10^3$	Derived values from d and U		Experimental values	
		$\gamma \times 10^{-1}$	$\Gamma_2 \times 10^4$	$\gamma \times 10^{-1}$	$\Gamma_2 \times 10^4$
10.0	191.80	3662.65	805.88	3663.83	803.56
30.0	11.29	3679.36	47.44	3679.44	47.30
50.0	0.59	3694.10	2.47	3695.22	2.46
70.0	0.11	3706.38	0.47	3707.42	0.44
90.0	0.02	3722.18	0.10	3723.21	0.07
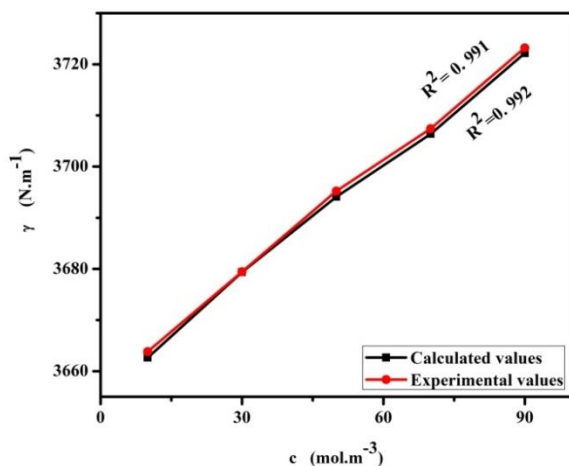
Fig 4 *Surface tension, γ (derived from density (d) and ultrasonic velocity (U) values, and experimental drop number method) vs concentration, c for aq paracetamol solutions at 298.15 K.*
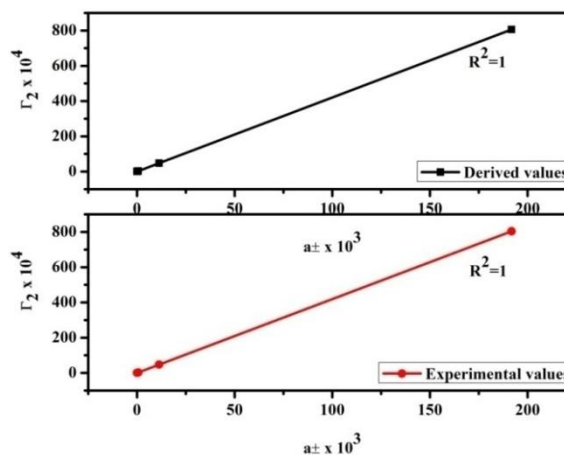
Fig 5 *Surface excess, Γ_2 (obtained from density (d) and ultrasonic velocity (U) values, and experimental drop number method) vs concentration, c for aqueous paracetamol at 298.15 K.*

From a perusal of Table 6, it is observed that the surface tension values for all the solutions increase with concentration. Model plots are presented in Fig 4 and Fig 5. The values of surface excess are positive. Since Γ_2 is a measure of the solute depleted out or collected in the inter phase region, the positive values indicates the adsorption at their inter phase [24]. A comparison of surface tension and surface excess between the two methods chosen reveals that the values are closer to each other. The results obtained using Stalagmometer are in agreement with the promising for the use of this counting drop method in the accurate measurement of surface tension.

4. CONCLUSION
In this study viscosity, conductance and surface tension of paracetamol in water was determined. In addition to this different derived parameters were also determined by established equations and then analysed to understand the molecular interactions in the studied system. It has been found that with increase in temperature viscosity of paracetamol solutions were decreased. Viscosity is also increased with concentration indicating molecular association or stronger solute-solvent interaction. The positive values of Falken-Hagen coefficient (A_F) and Jones-Dole coefficient (B_J) reveals strong solute-solute and solute-solvent interactions. From the conductance results it is understood that with an increase in temperature Λ_m^0 increased due to breaking of more hydrogen bonds and hence enhancing the speed of the ions. The positive values

of Walden product imply that paracetamol in water acts as a structure maker. Positive ΔG^0 value indicates the preference of association process over dissociation. Endothermic nature of such association processes is revealed by positive value of ΔH^0. The results of surface tension and surface excess using derived data of density and ultrasonic velocity, and as well by Stalagmometer are in good agreement with the use of such technique for the precise measurement of surface tension. A systematic study on physico-chemical properties of drugs present in pharmaceutical wastes focuses light on their effects on environment and human and animal health. Attempts are made by developing green technologies to reduce or remove the environmental hazards imposed by the pharmaceutical wastes that lead to a cleaner environment.

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