Study of Physico–Chemical Properties of Paracetamol & Aspirin in Water - Ethanol System

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Abstract

The aqueous solutions of paracetamol and aspirin in presence of ethanol were studied through the measurement of viscosity and density at different temperatures $(10\text{-}18)^0$C and the results were discussed on the basis of the structure-modifying properties of aspirin and paracetamol in water and ethanol. The calculated values of the β co-efficient of the Jone-Dole equation, intrinsic viscosity, apparent specific volume and thermodynamic parameter of flow phenomena, indicate that the structure-making and -breaking properties of aspirin and paracetamol in water were retained in presence of ethanol under experimental conditions. But the structure-intensifying and -rupturing properties of aspirin and paracetamol were modified differently in presence of ethanol.

Keywords: β co-efficient, paracetamol, aspirin, Jone-Dole equation.

Introduction

The development of solution chemistry is still far from being adequate to account for the properties of solution in terms of the properties of the constituent molecules. It is clear that if the solute and the solvent are interacting, as indeed they do, then the chemistry of the solute in a solvent must be different and the presence of a solvent can modify the properties of a solute. Interactions of drugs with their surrounding environment play an important role in their characteristic properties. There are several experimental procedures, which can in principle be used to obtain information on the solvation of molecules (Bhat and Ahluwalia, 1985; Vadi and Goyal, 1992; Owaga, Mizutani, and Yasuda, 1984; Lilley and Tasker, 1982). The thermodynamic and transport properties are sensitive to the solute-solvent, solute-solute and solvent-solvent interactions (Huque and Saad, 1988). In solution systems, these three types of interactions are possible but solute-solute interactions are considerably negligible in dilute solutions. The concentration dependence of the thermodynamic properties is a measure of solute-solute interaction and in the limit of infinite dilution these parameters serve as a measure of solute-solvent interactions (Nikam, Ansari and Hasan, 1999). In solution, the solute changes the water structure, as a result it also changes the solution viscosity. The variation of viscosity of solution with solute concentration is related to the size of the solute, nature of the solute as well as solute-solvent interaction (Yan *et al*, 2004).

On the basis of above points, the measurement of density and viscosity are thought to be powerful tools to investigate the intermolecular interactions between these two commonly used drugs with water and ethanol which was focused in this study.

Materials and Methods

Materials

Ethanol and water were used as solvents. Ethanol was obtained from E. Mark and its purity was 99.5%. Paracetamol and aspirin were used as solute, obtained from Gonosastha Pharmaceutical Ltd., Bangladesh. Double distilled water of high purity (Specific conductance $\approx 1.05 \times 10^{-6}$ ohm^{-1}cm^{-1}) was prepared in the laboratory using small amount of potassium permanganate.

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Freshly prepared double distilled water and ethanol in different proportion (20:80 – 80:20 in volume) were used as mixed solvent to prepare stock solutions of paracetamol and aspirin of different compositions (4.9×10^{-3} mol / lit – 9.9×10^{-3} mol / lit for paracetamol and 2.27×10^{-4} mol / lit – 4.16×10^{-3} mol / lit for Aspirin).

Specifications of Paracetamol: It is a white, odorless crystalline powder, sparingly soluble in water, freely soluble in ethanol, mp-169°C, LOD-0.06% w/w, Batch no. PAR 910124, Manufacturer-Square Pharmaceuticals Ltd. (manufacturing date-October 10, 2007, expiry date- October 10, 2010).

Specifications of Aspirin: It is a white crystalline powder, sparingly soluble in water, freely soluble in ethanol, mp-143°C, LOD-0.9% w/w, Batch no. 0606601, Manufacturer-Rhobia Thai Industries Ltd. (manufacturing date-March 07, 2007, Expiry date- March 07, 2010).

Each solution of paracetamol and aspirin was prepared by dissolving the appropriate quantities in required amount of mixed solvents using a high precision (resolution 10^{-2} mg, accuracy $\pm$ 0.1 mg) analytical balance (Shimadzu, Japan). All solutions were freshly prepared prior to their use.

Methods

Viscosity of each solution at different temperature (10-18°C) was measured by using an Ostwald viscometer (SILVER BRAND NO.2). During measurement, temperature was kept constant (with an accuracy of $\pm$ 0.05^{o}C) by placing the viscometer in a thermostatic water bath. A digital stop watch (with an accuracy $\pm$ 0.01sec) was used to record the flow time. The flow time measurement was repeated for at least five times and the average value was taken. The density of each solution was determined at different temperature by Hydrostatic method using a plumate of 2.0cm^{3}. An ultra thermostat (Polish made) was used to control the temperature by water circulation. The temperature co-efficient of the volume of plumate (glass made) at low range of temperature (10-18°C) was assumed to be negligible. The experimental solutions were allowed to equilibrate for 10 minutes before the reading was taken at each temperature. The apparatus for density measurement was calibrated using redistilled water on the basis of the data

available in the literature. The reproducibility of the result was checked by repeating the measurement three times. The accuracy of density values was $\pm$ 10^{-4} gm cm^{-3}. From the measurement of time flow the viscosity coefficient ή was calculated by using the Poiseuille equation:

$$\acute{\eta} = Apt$$

Here A = r^{4}hg/8vl is the viscometer constant and was determined by measuring efflux time of double distilled water.

Preparation of solution: The solutions under investigation were prepared by dissolving required amount of aspirin, and paracetamol in different proportion of ethanol and water. Caution was taken to prevent evaporation and precipitation.

β co-efficient of Jone Dole Equation: To interpret the viscosity data of aqueous solution, Falkenhagen and Jone Dole use an empirical equation (Yan *et al*, 2004):

$$\eta_{rel} = 1 + A\sqrt{C} + \beta C$$

Here β is an empirical co-efficient which correspond to the solute-solvent interaction and has positive or negative values depending upon the nature of interaction between the solute and the solvent which intensity the structure of solution will have positive value. The negative value of β co-efficient corresponds to the disorder in molecular arrangement of the solution. Experimental value of relative viscosity (ή) at different molar concentration of drugs was fitted into above equation by the method of least square. The slope of straight lines was taken as β co-efficient.

Apparent Specific Volume: The interaction between particles in liquid solution can also be explained by the change of apparent specific volume. The apparent specific volume of solutions under study was calculated from the density data by using the formula (Basumallick and Mohanti, 1986):

$$\Psi = 1/\rho_o[1 + \rho_o - \rho/C]$$

Where ρ_o and ρ are the density of water:ethanol in different proportion without drug and with drug respectively and C is the molar concentration of drug in moles/lit.

Enthalpy of activation: The enthalpy of activation of flow process is obtained from the temperature

dependence of viscosity which is expressed mathematically by the linear equation.

$$\eta = A\, e^{-\Delta H/RT}$$

This equation is known as eyring equation and is used to evaluate the enthalpy change of flow of different solutions under study. The enthalpy of activation and other related thermodynamic quantities were determined from the diagram ln η Vs 1/T and using the equation:

$$\Delta H_\eta^\# = \Delta E_\eta^\# = R\frac{d\ln}{d/T}$$

Free energy change of activation $\Delta G_\eta^\#$ is calculated by the equation:

$$\Delta G_\eta^\# = RT\ln\frac{V\eta}{hN_A}$$

From the values of free energy change and enthalpy change of activation, the value of change of entropy $(\Delta S_\eta^\#)$ is calculated by using the equation:

$$\Delta G_\eta^\# = \Delta H_\eta^\# - T\Delta S_\eta^\#$$

$$\Delta S_\eta^\# = (\Delta H_\eta^\# - \Delta G_\eta^\#)/T$$

Therefore, $\Delta S_\eta^\# = \Delta H_\eta^\#/T + RT\ln\dfrac{hN_A}{V\eta}$

Results and Discussion

The viscosity co-efficient of paracetamol in different composition of mixed solvents at different temperature (10^0C, 12^0C, 14^0C, 16^0C, 18^0C) are presented in Table 1. It is observed from the table that, in the presence of paracetamol in general, the values of viscosity co-efficient increases with the increase of percentage of water (up to 60% water) in mixed solvent. With further increase of percentage of water, the value decreases. This may be due to the positive interaction between water and ethanol molecules through H-bonds (Badarayani and Kumar, 2002). However, it is evident from the result present in Table-1 that at higher percentage of water, the value of viscosity co-efficient decreases. From this result, it may be said that, positive interaction between water and ethanol was favored when the percentage of water and ethanol was 50:50.

Table 1: Viscosity co-efficient (η) of different solution of paracetamol and aspirin at different temperatures

Solvent composion H₂O: C₂H₅OH	Conc. of Paracetamol (m mol/liter)	Viscosity Co-efficient (η) at different temperature (^{0}C)					Conc. of Aspirin (m mol/liter)	Viscosity Co-efficient (η) at different temperature (^{0}C)				
		10	12	14	16	18		10	12	14	16	18
20 ml : 80 ml	0.496	1.17	1.05	1.03	1.01	0.99	0.027	1.24	1.21	1.14	1.12	1.09
	0.661	1.12	1.11	1.08	1.06	1.05	0.416	1.19	1.17	1.14	1.12	1.10
	0.992	1.19	1.17	1.15	1.13	1.10	0.138	1.16	1.14	1.14	1.09	1.07
30 ml : 70 ml	0.496	1.17	1.16	1.04	1.03	1.01	0.027	1.34	1.29	1.25	1.23	1.18
	0.661	1.20	1.15	1.13	1.09	1.07	0.416	1.27	1.24	1.21	1.18	1.15
	0.992	1.25	1.22	1.18	1.15	1.12	0.138	1.23	1.20	1.18	1.16	1.14
40 ml : 60 ml	0.496	1.21	1.18	1.15	1.13	1.10	0.027	1.36	1.32	1.26	1.22	1.19
	0.661	1.27	1.23	1.20	1.16	1.14	0.416	1.39	1.33	1.28	1.23	1.19
	0.992	1.24	1.21	1.15	1.14	1.11	0.138	1.19	1.17	1.12	1.10	1.08
50 ml : 50 ml	0.496	1.22	1.16	1.14	1.11	1.08	0.027	1.46	1.44	1.38	1.30	1.26
	0.661	1.27	1.24	1.22	1.18	1.16	0.416	1.43	1.38	1.30	1.24	1.20
	0.992	1.23	1.20	1.17	1.11	1.10	0.138	1.25	1.21	1.15	1.14	1.13
60 ml : 40 ml	0.496	1.23	1.21	1.18	1.16	1.13	0.027	1.44	1.38	1.33	1.29	1.26
	0.661	1.21	1.19	1.18	1.15	1.12	0.416	1.43	1.38	1.33	1.28	1.24
	0.992	1.24	1.21	1.19	1.17	1.14	0.138	1.24	1.23	1.20	1.17	1.16
70 ml : 30 ml	0.496	1.10	1.09	1.07	1.05	1.04	0.027	1.50	1.26	1.23	1.20	1.17
	0.661	1.17	1.16	1.14	1.11	1.09	0.416	1.14	1.11	1.11	1.08	1.06
	0.992	1.18	1.15	1.14	1.12	1.12	0.138	1.17	1.15	1.13	1.11	1.10
80 ml : 20 ml	0.496	1.07	1.05	1.04	1.03	1.01	0.027	1.31	1.27	1.2	1.21	1.18
	0.661	1.10	1.06	1.05	1.04	1.03	0.416	1.06	1.03	1.02	1.01	1.00
	0.992	1.10	1.09	1.06	1.04	1.03	0.138	1.12	1.11	1.08	1.07	1.05

The results presented in Table 1 also show that the value of viscosity co-efficient decreases with the increase of temperature for all solution. This is the normal trend for all liquids. It is also evident from the table that the value of viscosity co-efficient initially increases with the increase of concentration of paracetamol then decreases almost at all temperatures. This indicates that, there is positive interaction between the molecules of paracetamol and the solvent (water and ethanol). This may be due to the presence of hydroxyl group in all the three different molecules (water and ethanol and paracetamol) (Huque and Uddin, 2005). However, the interaction decreases at higher concentration of paracetamol. This might be due to the presence of large nucleophilic (electro hating) benzene ring in the paracetamol molecule. Similar trend is also observed in this case of aspirin in change of viscosity co-efficient. This may be due to similar structure of aspirin and paracetamol.

The β co-efficient of different solutions containing paracetamol and aspirin at different temperature are presented in Table 2. It is evident from these results that there is no systematic trend of change of value of β co-efficient in case of solution containing paracetamol. From this observation, it may be said that Jone Dole equation is not applicable to the non-ionizable solute like paracetamol. Similar comments were made by Falkenhangen (Water and Kay, 1970).

Table 2: β co-efficient of paracetamol and aspirin at different temperature in different proportion of water-ethanol

Solvent composition H_2O: C_2H_5OH	Temperature ^{O}C (Paracetamol)					Temperature ^{O}C (Aspirin)				
	10	12	14	16	18	10	12	14	16	18
20 ml : 80 ml	-216.83	-214.72	-230.11	-243.47	-199.83	101.84	75.978	-13.00	87.646	87.646
30 ml : 70 ml	-155.32	-214.07	0.0204	-209.84	1875.7	114.11	134.19	98.201	59.956	30.862
40 ml : 60 ml	81.84	49.454	135.94	84.342	96.062	618.35	510.0	493.18	437.93	374.31
50 ml : 50 ml	121.96	21.88	171.32	227.25	172.08	548.83	531.38	485.4	310.47	237.07
60 ml : 40 ml	-78.942	-0.053	-35.114	-52.043	-59.515	585.99	0.4704	411.79	357.8	271.13
70 ml : 30 ml	-27.189	208.304	12.894	-27.189	208.304	-96.67	-106.92	-64.472	-107.44	-136.57
80 ml : 20 ml	-14.00	-115.2	-87.166	-13.536	-17.227	-222.42	-253.43	-211.21	-199.66	-189.5

The results presented in table show that the positive values were obtained for the solution of aspirin in mixed solvents up to the composition 60:40 water–ethanol. However, at higher composition of water-ethanol negative values are obtained. From these positive and negative values, it can be said that unlike paracetamol, aspirin is ionizable in water–ethanol solvents mixtures. This is due to the ionizable -COOH group present in aspirin molecule (Murthy and Subrahmanyam, 1980). It is observed that in general the positive values of β co-efficient increases with the increase in amount of water in solvent mixture up to 60:40 (water–ethanol). At higher proportion of water negative values of β co-efficients are obtained.

The results of apparent specific volume are presented in Table 3. It is evident from the result that in general the values of apparent specific volume decrease with the increase of concentration of aspirin. This may be due to structure intensification of solvent mixture by aspirin molecules. Similar effect is also observed in the case of β co-efficient values. It is also evident from the results that the values of apparent specific volume in case of paracetamol are not changed in a regular order.

It is also observed from the results that the values of apparent specific volume increase with the increase of temperature for all the solutions. This is usual characteristic for all liquid system. If there is no chemical interaction between the particles in solution, the measurement of viscosity data and its corresponding result of flow process are related to the change in size and interaction between the hydrodynamic groups, which characterize the flow process. The increase or decrease of enthalpy of

Table 3: Apparent Specific Volume (ψ) of paracetamol and aspirin at different concentration and temperature of water-ethanol

Solvent composion H$_2$O: C$_2$H$_5$OH	Conc. of Paracetamol (m mol/liter)	Apparent specific volume (ψ) at different temperature (°C)					Conc. of Aspirin (m mol/liter)	Apparent specific volume (ψ) at different temperature (°C)				
		10	12	14	16	18		10	12	14	16	18
20 ml : 80 ml	0.496	228.42	112.14	180.21	26.70	77.35	0.027	4285.24	2228.2	688.9	349.33	648.00
	0.661	62.36	57.52	0.32	-7.87	44.21	0.416	120.81	-18.17	-204.6	-284.45	-240.9
	0.992	15.25	11.57	-10.98	-24.51	-20.15	0.138	324.71	80.05	19.76	-7.36	6.32
30 ml : 70 ml	0.496	33.52	32.58	8.55	-30.29	9.92	0.027	1467.58	1484.6	1807.3	2014.1	1846.5
	0.661	28.59	24.35	28.50	-22.28	28.47	0.416	56.49	362.95	422.48	579.01	25.92
	0.992	-12.54	-15.23	-8.61	-16.31	-10.85	0.138	368.04	54.34	60.90	47.86	58.68
40 ml : 60 ml	0.496	18.55	-14.74	-9.14	-34.88	-20.38	0.027	94.85	1282.7	1031.2	1202.1	1563.3
	0.661	18.98	16.3	30.88	17.42	23.43	0.416	59.69	90.62	203.81	59.50	162.91
	0.992	-7.90	15.08	-2.08	-15.57	-7.73	0.138	106.38	51.56	-48.61	-90.88	-69.65
50 ml : 50 ml	0.496	163.24	190.41	91.74	28.15	24.27	0.027	1470.77	788.6	741.56	891.69	878.53
	0.661	13.65	18.78	15.23	15.35	16.19	0.416	-76.08	-330.5	-388.5	-264.06	-315.9
	0.992	60.92	80.06	61.19	68.74	62.82	0.138	-35.61	-62.24	-72.61	-72.73	-69.21
60 ml : 40 ml	0.496	12.55	-2.42	0.21	-0.13	16.44	0.027	1671.87	1649.3	2248.4	2259.7	2812.1
	0.661	0.33	-2.80	-10.90	-2.06	14.59	0.416	-60.54	43.47	-64.39	-42.63	598.70
	0.992	67.35	69.43	69.14	76.71	85.25	0.138	61.35	-65.32	-72.24	-63.92	-35.15
70 ml : 30 ml	0.496	50.41	64.05	-0.47	-6.34	-9.21	0.027	-60.39	0.91	-1197.3	-1195.1	-1219.2
	0.661	20.85	16.22	-8.39	-12.25	-9.15	0.416	22.23	184.55	24.74	-35.89	-318.47
	0.992	89.43	87.82	71.94	77.19	73.64	0.138	209.59	-14.79	-57.27	-61.12	-42.75
80 ml : 20 ml	0.496	229.17	-290.25	-244.45	30.49	30.40	0.027	4975.61	-3834.80	-2878.7	1890.6	1942.9
	0.661	166.17	-217.20	-185.68	24.26	21.66	0.416	268.24	-984.05	400.29	1241.5	1206.98
	0.992	185.25	-109.55	-87.68	44.63	40.83	0.138	802.30	-314.37	-284.18	71.71	64.35

Table 4: Value of Enthalpy of activation (ΔH$_n^O$) for different concentration of paracetamol and aspirin in different proportion of water-ethanol

Solvent composition (H$_2$O : C$_2$H$_5$OH)	Concentration of Paracetamol (m mol/lit)	Value of ΔH$_n^O$ (K.Cal/mol)	Concentration of Aspirin (m mol/liter)	Value of ΔH$_n^O$ (K.Cal/mol)
20 ml : 80 ml	0.49	5283.04	0.027	7573.13
	0.66	4946.41	0.138	8762.12
	0.99	4853.46	0.416	6760.77
30 ml : 70 ml	0.49	6814.98	0.027	8913.43
	0.66	6094.24	0.138	6235.16
	0.99	5505.69	0.416	8629.93
40 ml : 60 ml	0.49	6586.60	0.027	9199.44
	0.66	6481.67	0.138	6417.90
	0.99	6604.14	0.416	9199.44
50 ml : 50 ml	0.49	6877.50	0.027	10051.62
	0.66	5952.74	0.138	5519.24
	0.99	6602.97	0.416	9859.57
60 ml : 40 ml	0.49	6311.32	0.027	9626.78
	0.66	6522.41	0.138	6232.17
	0.99	5448.16	0.416	9532.83
70 ml : 30 ml	0.49	5048.67	0.027	8058.84
	0.66	5309.07	0.138	5185.44
	0.99	5464.21	0.416	5045.68
80 ml : 20 ml	0.49	3220.26	0.027	8276.75
	0.66	3914.06	0.138	4438.51
	0.99	3220.26	0.416	4248.20

Table 5: Energy of activation (ΔG_η^0) of different concentration of paracetamol and aspirin at different temperature and proportion of water-ethanol

Solvent composition H$_2$O: C$_2$H$_5$OH	Conc. of Paracetamol (m mol/liter)	Energy of activation (ΔG_η^0) at different temperature (^{O}C) X10^3					Conc. of Aspirin (m mol/liter)	Energy of activation (ΔG_η^0) different temperature (^{O}C) X10^3				
		10	12	14	16	18		10	12	14	16	18
20 ml : 80 ml	0.496	66.67	66.70	66.96	67.20	67.41	0.027	66.81	67.06	67.21	67.45	67.64
	0.661	66.55	66.98	67.23	67.48	67.68	0.416	66.64	66.92	67.21	67.40	67.61
	0.992	66.69	66.83	67.07	67.31	67.54	0.138	66.71	66.97	67.21	67.47	67.67
30 ml : 70 ml	0.496	66.67	66.95	67.20	67.43	67.64	0.027	67.00	67.23	67.46	67.70	67.87
	0.661	66.72	67.07	67.30	67.54	67.73	0.416	66.79	67.04	67.30	67.55	67.77
	0.992	66.82	66.93	67.18	67.39	67.60	0.138	66.87	67.13	67.36	67.59	67.79
40 ml : 60 ml	0.496	66.75	67.00	67.23	67.47	67.67	0.027	67.04	67.28	67.47	67.68	67.87
	0.661	66.86	67.06	67.24	67.50	67.70	0.416	66.71	66.96	67.17	67.40	67.62
	0.992	66.81	67.09	67.34	67.56	67.76	0.138	67.11	67.30	67.50	67.70	67.88
50 ml : 50 ml	0.496	66.76	66.95	67.21	67.43	67.64	0.027	67.23	67.51	67.70	67.86	68.04
	0.661	66.87	67.03	67.27	67.44	67.69	0.416	66.82	67.06	67.22	67.50	67.75
	0.992	66.79	67.11	67.38	67.60	67.81	0.138	67.17	67.40	67.55	67.71	67.91
60 ml : 40 ml	0.496	66.80	67.05	67.29	67.56	67.74	0.027	67.19	67.40	67.61	67.84	68.03
	0.661	66.75	67.05	67.31	67.57	67.76	0.416	66.81	67.09	67.35	67.58	67.81
	0.992	66.81	67.01	67.29	67.54	67.72	0.138	67.18	67.39	67.61	67.81	67.99
70 ml : 30 ml	0.496	66.51	66.79	67.05	67.29	67.52	0.027	67.30	67.16	67.40	67.65	67.84
	0.661	66.66	66.93	67.20	67.46	67.67	0.416	66.66	66.92	67.18	67.44	67.69
	0.992	66.68	66.95	67.21	67.44	67.66	0.138	66.59	66.59	67.140	67.37	67.59
80 ml : 20 ml	0.496	66.43	66.70	66.97	67.24	67.46	0.027	66.95	67.19	67.42	67.66	67.86
	0.661	66.51	66.80	67.03	67.27	67.51	0.416	66.56	66.83	67.08	67.34	67.57
	0.992	66.51	66.71	66.99	67.26	67.50	0.138	66.40	66.64	66.92	67.19	67.19

activation is related to increase or decrease of energy of interaction between solute molecules and the solvent. This is due to the possibilities of change in dimension of cluster structures of solvent molecules which are formed through H-bonds.

The enthalpy of activation of flow process is obtained from the temperature dependence of viscosity which is presented in Table 4. The value of enthalpy of activation increases with the increase of percentage of water in solvent mixture up to 50:50%. However, at higher percentage of water in solvent mixture, the value of enthalpy of activation decreases. This indicates the positive interaction of solute solvent at lower percentage of water in the solvent mixture.

It is also evident from the results that with increase of concentration paracetamol, entropy of activation decreases at lower percentage of water.

However, at higher percentage of water in solvent mixtures opposite trend is observed. The structure intensifying properties is almost similar to that of paracetamol. This may be due to the fact that paracetamol and aspirin both have almost similar structure (Yang, Zhao and Dai, 1993). Ortho and Para substituted benzene molecule do have much effect on the structure modifying properties of mixed solvents.

The calculated value of free energy of activation is presented in Table 5. From these data, there is no appreciable change in the value of free energy change. This may be due to the use of very dilute solution of paracetamol and aspirin. The calculated values of entropy of activation of flow process are presented in Table-6 where most of the values are negative which indicate intensified structure of liquid solution.

Table 6: Entropy of $(T\Delta S_\eta^0)$ of different concentration of paracetamol at different temperature and proportion of water-ethanol

Solvent composion H_2O: C_2H_5OH	Conc. of Paracetamol (m mol/liter)	Energy of activation (ΔG_η^0) at different temperature (^{O}C) X10^3					Conc. of Aspirin (m mol/liter)	Energy of activation (ΔG_η^0) different temperature (^{O}C) X10^3				
		10	12	14	16	18		10	12	14	16	18
20 ml : 80 ml	0.496	-61.39	-61.42	-61.67	-61.92	-62.13	0.027	-59.24	-9.48	-59.64	-5.88	-60.073
	0.661	-61.69	-62.03	-62.28	-62.53	-62.74	0.416	-57.88	-8.158	-58.45	-58.64	-58.85
	0.992	-61.75	-61.98	-62.22	-62.46	-62.69	0.138	-59.95	-60.21	-60.45	-0.711	-60.91
30 ml : 70 ml	0.496	-59.85	-60.13	-60.39	-60.61	-60.82	0.027	-58.09	-8.32	-8.54	-8.79	-58.96
	0.661	-61.21	-60.98	-61.21	-61.44	-61.64	0.416	-60.56	-60.80	-61.06	-61.31	-61.53
	0.992	-60.73	-61.43	-61.67	-61.88	-62.10	0.138	-58.24	-58.50	-8.73	-58.96	-59.16
40 ml : 60 ml	0.496	-60.17	-60.42	-60.64	-60.89	-61.08	0.027	-57.84	-8.08	-8.27	-8.48	-58.68
	0.661	-60.26	-60.58	-60.76	-61.02	-61.22	0.416	-60.29	-60.54	-6.07	-60.98	-61.20
	0.992	-60.32	-60.49	-60.73	-60.95	-61.16	0.138	-57.91	-58.10	-8.30	58.50	-58.68
50 ml : 50 ml	0.496	-59.89	-60.08	-60.34	-60.55	-60.76	0.027	-57.17	-7.45	-7.65	-7.80	-57.99
	0.661	-60.26	-61.08	-61.31	-61.48	-61.73	0.416	-61.31	-6.15	-1.71	-6.19	-62.23
	0.992	-60.83	-60.51	-60.78	-61.00	-61.21	0.138	-57.31	-57.54	-7.69	-57.86	-58.05
60 ml : 40 ml	0.496	-60.48	-60.74	-60.98	-61.25	-61.43	0.027	-57.56	-7.77	-7.98	-8.21	-58.41
	0.661	-61.30	-60.53	-60.79	-61.05	-61.24	0.416	-60.58	-0.86	-61.11	-61.34	-61.58
	0.992	-60.28	-61.56	-61.84	-62.09	-62.27	0.138	-57.65	-7.86	-8.08	-8.28	-58.46
70 ml : 30 ml	0.496	-61.47	-61.74	-62.00	-62.24	-62.47	0.027	-59.24	-9.11	-9.34	-9.59	-59.78
	0.661	-61.20	-61.62	-61.89	-62.15	-62.36	0.416	-61.48	-1.73	-2.00	-2.26	-62.50
	0.992	-61.37	-61.48	-61.75	-61.98	-62.19	0.138	-61.55	-61.78	-2.09	-62.32	-62.54
80 ml : 20 ml	0.496	-63.21	-63.48	-63.75	-64.02	-64.24	0.027	-58.67	-8.92	-9.14	-9.38	-59.58
	0.661	-63.29	-62.88	-63.11	-63.35	-63.60	0.416	-62.12	-2.39	-2.64	-62.90	-63.13
	0.992	-62.60	-63.49	-63.77	-64.04	-64.28	0.138	-62.15	-2.40	-62.67	-62.94	-63.18

Conclusion

From the results presented in this study, following conclusions may be drawn:

i) There is positive interaction between paracetamol/aspirin & water-ethanol mixture.

ii) The extent of positive interaction decreases at higher concentration of paracetamol and aspirin.

iii) Jone-Dole equation is not applicable for the mixture containing paracetamol because of its non-ionizable character.

iv) Jone-Dole equation is applicable for aspirin. This is due to the presence of –COOH group where aspirin ionizes like other salt in solution.

v) Since some positive interactions are observed between paracetamol/ aspirin & water-ethanol mixture, people should not take alcoholic drinks while taking parametamol or aspirin.

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