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Density & viscosity studies of Fluoxetine hydrochloride in mixed binary solvent in presence of additives

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ABSTRACT

The densities and viscosities of Fluoxetine hydrochloride are determined in binary solvent ethanol-water containing salt NaCl, KCl, $NiCl_2$, $CuCl_2$ and a non electrolyte Glucose. The values are used to calculate excess viscosities, excess molar volume, excess Gibbs free energy of viscous flow and d_{12}, T_{12} and H_{12} parameters. The viscosity results are used to calculate the Jones Dole viscosity B-coefficient. These results indicate that fluoxetine HCl act as structure making compounds due to hydrophobic hydration.

Keywords: Fluoxetine hydrochloride; excess properties; thermodynamic properties; binary solvent.

INTRODUCTION

The physical properties of solution such as density, viscosity, refractive index etc. mostly depend on the solvent and solute present in the system. These parameters are related with molecular interactions among the solute and solvent. Drug also interacts with solvent media. These interactions are important to understand mechanism of processes such as drug transport, protein binding, anesthesia [1] diffusion and dissolution rate control [2] of the drug. The binary solvent mixture is used as medium for study of complexation, electrochemical oxidation and ion solvation [3]. Therefore we decided to study the density and viscosity parameters of fluoxetine HCl (ft-HCl) in ethanol-water binary solvent system.

MATERIALS AND METHODS

2.1 *Materials*:-The salts KCl, NaCl, $NiCl_2$, $CuCl_2$ and nonelectrolyte glucose used were of AR grade. Water used was double distilled over alkaline $KMnO_4$ in quick fit glass assembly (Conductance=$2x10^{-6}$ mhos) Commercial alcohol was refluxed with lime for two hours and then distilled using long fractionating column. The purity of water and ethanol was checked by comparing their measured densities and viscosities with those reported in the literature.

2.2 *Apparatus and procedure*: The density of different solution mixtures were measured with a set of three pyknometers and single pan electronic balance (Contech CA, Mumbai) with a precision of 0.0001g. The weighing was repeated thrice to ensure the accuracy in weights with a little interval of time. The reproducibility of the result was close to 100%. Viscosity measurements were performed by using Ostwald's viscometer. The viscometer was clamped vertically in a thermostatistically controlled waterbath, whose temperature was maintained constant at 301.15K (± 0.02). The measurement of flow time of the solution between the two points on the viscometer was performed at least five times for each solution and the result was averaged.

RESULTS AND DISCUSSION

3.1 Drug profile: The drug ft-HCl is an antidepressant and its molecular formula is $C_{17}H_{18}F_3NO$-HCl. The molecular weight of ft-HCl is 347.79, and mp is 158° C. Its IUPAC name is (RS)-N-methyl-3-phenyl-3-[4- (trifluoromethyl) phenoxy] propan-1- amine, (±)-N-Methyl-3-phenyl-3[(α, α, α-trifluro-ρ-toluil) oxy] propylamine (fig 1)

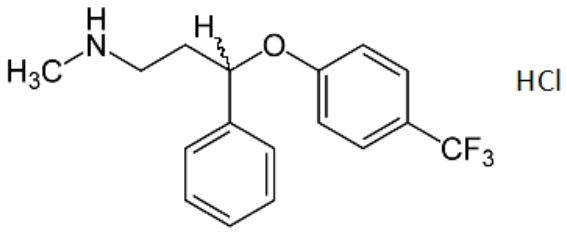

Fig 1 Fluoxetine hydrochloride

3.2 Excess parameters: The densities and viscosities of the drug in binary solvent system in presence of additives were measured and represented in table-1. These are used to calculate excess molar volumes, excess viscosities and excess free energy change. The excess properties are analyzed because of their importance for inferring which type of interaction predominates in solution. The excess volume of binary solvent, in presence of drug and salt solution was calculated by equation,

$$V^E = V_{mix} - x_1 V_1 - x_2 V_2 \quad \text{..... (1)}$$

Over entire range of concentration for binary system V^E values are found to be negative and changes in parabolic manner with mole fraction of ethanol.(fig 2a & 2b). The V^E depend on the drug, its size, shape and the number of non polar groups attached to it [4]. Liquid mixtures containing hydrogen bonded molecules such as water, alcohols, phenols etc., show

pronounced non ideal thermodynamic behavior. The negative values of V^E indicate the packing effect and/or strong interactions between unlike components.

This may attributed to the specific interaction as well as structural combinations arising from the geometrical fitting of one component molecule into the other, due to difference in the molar volume and free volumes between the components. Alcohols are highly self-associated through H-bonding & dipole-dipole interactions to affect the properties of alcohol solutions [5]. The mixing of ethanol with water and the drug molecule can expect to show changes hydrogen bonding equilibrium and electrostatic interactions, giving different resultant contribution to the molar volumes of the mixtures. The values of V^E are negative and increases with the percentage of ethanol, maximum at 60-70% aq. ethanol and then changes non-linearly.

The excess viscosity was determined by following equation and is shown graphically (fig 3a & 3b).

$$\eta^E = \eta - \exp\,(x_1 ln\eta_1 + x_2 \ln \eta_2) \quad \text{..... (2)}$$

There are several semi-empirical relations used to correlate the viscosity of binary liquid mixtures. The Grunberg-Nissan interactions parameter, d_{12}, which is regarded as a measure of the strength of interactions between two dissimilar molecules were calculated as

$$d_{12} = \left[\frac{\ln \eta - x_1 \ln \eta_1 - x_2 \ln \eta_2}{x_1 \; x_2}\right] \quad \text{..... (3)}$$

Tamura and Kurata developed the following equations for the viscosity of binary liquid mixtures.

$$\eta = \sum_{i=1}^{2} x_i \phi_i \eta_i + 2T_{12} \prod_{i=1}^{2} \sqrt{x_i \phi_i} \quad \text{..... (4)}$$

ϕ_i is the volume fraction. Hind suggested following equation for the viscosity of binary liquid mixtures.

$$\eta = \sum_{i=1}^{2} x_i^2 \eta_i + 2H_{12} \prod_{i=1}^{2} x_i \quad \text{..... (5)}$$

H_{12} is the interaction parameter. Among these three parameters, the Grunberg-Nissan parameter provides the best measure to ascertain the strength of interaction for any binary mixture.

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We observed positive values for d_{12}. (Fig 4) The positive values of Grunberg-Nissan interaction parameter, d_{12}, may be attributed to the dominance of specific interaction between unlike molecules leading to the complex formation [6].

The Tamura-Kurata parameter (fig 5) and Hind parameter (fig 6) are also positive and decrease with increase in percentage of ethanol. We observed that d_{12}, T_{12} and H_{12} values decrease with increase in concentration of KCl / NaCl / glucose and then become constant. In case of $NiCl_2$ it increases and becomes constant. No specific trend is observed in the case of $CuCl_2$.The trend for d_{12} ,T_{12} and H_{12} for the additives at a specific mole fraction solvent system and at specific (same) concentration of additives followed the order glucose < $NiCl_2$ < NaCl < $CuCl_2$ < KCl . Among

these excess thermodynamic parameters, the trend in presence of all the additives was $d_{12} < T_{12} < H_{12}$.

The excess free energy is related with viscosity of the solution by following equation,

$$\eta = \frac{hN}{M} e^{\frac{\Delta G^{E*}}{RT}} \quad \text{…….. (6)}$$

The maximum values of ΔG^{*E} are at 50 to 60% aq. Ethanol (fig 7). The Gibbs free energy of ft-HCl was found to increase up to 60% alcohol and then decreases. It ranges from ~ 20 to ~63 KJ/mole. The values are observed to be positive. Large positive ΔG^{E} values indicate the specific interaction leading to complex formation through intermolecular hydrogen bonding between unlike molecules compared to like molecules [7]. Comparing the atomic radius of K ($2.27A^0$) and Na ($1.537A^0$), the ΔG^{*E} value is high for K^+ than Na^+. Similarly when the atomic radius of Cu ($1.278A^0$) and Ni ($1.246\ A^0$) is co-related, the ΔG^{*E} value is in the same order, but we cannot compare alkali metals ions with transition metal ions

3.3 Jone-Dole parameter: The viscosity data was used to calculate Jones-Dole parameters.

$$\eta_r - 1 = A\sqrt{C} + B \quad \text{…….. (7)}$$

In the equation 7, B is called as B-viscosity coefficient. This coefficient is a measure of the effective hydrodynamic volume of the solvated ions and it denote the order or disorder introduced by the ions into solvent structure. In the present study B-Coefficient was found to maximum for 40-50% water-ethanol mixture and decreases in ethanol rich region of the system. The Jones-Dole parameters are given in table (2). The A- coefficient values are negative. These are indicative of solute-solute interaction in the system [8].

3.4 Apparent molar volume: The apparent molar volume of ft-HCl in 0.002, 0.004, 0.006, 0.008 and 0.01M salt, prepared in binary solvent, have been calculated from density data by using equation 8.

$$\phi_v = \frac{M_2}{\rho^o} - \frac{1000\,(\rho - \rho^o)}{m\rho\rho^o} \quad \text{…….. (8)}$$

Where ρ^o is the density of binary solvent, ρ is the density of solution, m is the molality of solution and M_2 is the molecular weight of ft-HCl. These values are used to calculate the limiting apparent volume. (table3)

$$\phi_v = \phi_v^o + S_v\sqrt{C} \text{……. (9)}$$

Where ϕ^o_v and S_v are calculated from the intercept and slope of the extrapolation of ϕ_v versus $C^{1/2}$ (not shown) The S_v in above equation can be attributed to be as a measure of ion-ion or solute-solute interactions.

[1] Table:1 Density and viscosity values of fluoxetine in presence of additives

[2]

%	**0.002M KCl**		**0.004M KCl**		**0.006M KCl**		**0.008M KCl**		**0.01M KCl**	
EtOH	ρ	η	ρ	η	ρ	η	ρ	η	ρ	η
10	0.9659	11.5831	0.9655	11.3491	0.9651	11.1303	0.9655	11.1349	0.9664	11.1453
20	0.9545	14.8186	0.9546	14.8201	0.9536	14.4874	0.9533	14.8	0.9533	14.588
30	0.9429	16.9388	0.9417	16.3951	0.9422	16.8218	0.9409	16.5899	0.9411	16.5934
40	0.9354	19.916	0.9336	19.2565	0.9341	19.6811	0.9338	19.5713	0.934	19.5755
50	0.9196	21.5172	0.9171	20.9502	0.917	20.3377	0.9165	20.7332	0.9165	20.7332
60	0.8987	21.3271	0.8968	20.9837	0.8975	20.3034	0.8977	20.1088	0.8971	19.9959
70	0.8725	19.0605	0.8741	18.9986	0.8699	18.7143	0.8708	18.8303	0.8705	18.7272
80	0.8469	16.7169	0.8461	16.7011	0.846	16.6991	0.8462	16.8907	0.8456	16.6912
90	0.8257	14.6748	0.8247	14.3751	0.8228	14.1545	0.8217	14.1356	0.8287	14.9169

	0.002M NaCl		**0.004M NaCl**		**0.006M NaCl**		**0.008M NaCl**		**0.01M NaCl**	
	ρ	η	ρ	η	ρ	η	ρ	η	ρ	η
10	0.9656	11.029	0.9658	11.0313	0.966	11.1407	0.9658	10.9242	0.9656	10.8149
20	0.9547	14.8217	0.9534	15.1187	0.9536	14.5931	0.9532	14.7984	0.9535	14.9088
30	0.9423	17.2416	0.9414	17.3295	0.9409	17.3203	0.9411	17.5327	0.9412	17.1171
40	0.935	19.2854	0.9352	19.2895	0.9335	19.1509	0.9335	19.0474	0.9328	18.9297
50	0.917	21.0496	0.9169	20.5389	0.9165	20.6316	0.9172	20.3422	0.9178	20.4573
60	0.8986	20.7268	0.8966	19.8853	0.8973	20.0998	0.8983	19.7238	0.8979	19.715
70	0.8714	18.9399	0.8704	18.7251	0.8702	19.1068	0.8708	18.8303	0.8688	18.6907
80	0.8481	16.3644	0.8463	16.0481	0.8469	16.3412	0.8477	16.7327	0.8472	16.2531
90	0.8189	13.7142	0.8214	14.3176	0.822	14.328	0.8212	14.4077	0.8254	15.1396

	0.002M NiCl		**0.004M NiCl**		**0.006M NiCl**		**0.008M NiCl**		**0.01M NiCl**	
	ρ	η	ρ	η	ρ	η	ρ	η	ρ	η
10	0.9664	10.931	0.9666	11.362	0.967	11.3667	0.967	11.4739	0.9674	11.586
20	0.955	14.1909	0.9547	13.9747	0.9548	14.188	0.9544	14.0762	0.9548	14.188
30	0.9415	16.9137	0.9412	16.4908	0.9417	17.1261	0.9428	17.4598	0.9418	16.9191
40	0.9359	18.8888	0.9341	18.4381	0.935	18.7669	0.9348	18.7629	0.9355	18.6732
50	0.9172	20.1388	0.9161	20.1146	0.9159	20.0086	0.916	19.9093	0.9157	19.6996
60	0.8983	20.3215	0.898	19.7172	0.8991	20.539	0.9003	20.5664	0.9009	20.7799
70	0.8745	19.0072	0.8759	18.8434	0.8725	18.6735	0.8749	19.21	0.8745	19.3952
80	0.848	16.5505	0.8484	16.6524	0.8482	16.6485	0.849	15.8169	0.8478	15.7005
90	0.8211	13.3849	0.8213	13.4793	0.8212	13.6598	0.8218	13.6697	0.8268	14.2113
	0.002M $CuCl_2$		**0.004M $CuCl_2$**		**0.006M $CuCl_2$**		**0.008M $CuCl_2$**		**0.01M $CuCl_2$**	
	ρ	η	ρ	η	ρ	η	ρ	η	ρ	η
10	0.9653	11.2397	0.9659	11.3538	0.9664	11.2525	0.9673	11.3702	0.967	11.2595
20	0.9549	15.0366	0.9537	15.0177	0.9547	14.7158	0.9543	14.9213	0.9557	15.0492
30	0.9512	17.5099	0.95	17.4878	0.9502	17.4915	0.9496	17.0592	0.9498	17.3788
40	0.9358	19.8207	0.9355	19.7106	0.9347	19.2792	0.9346	19.4844	0.9338	19.6748
50	0.9162	19.9136	0.9171	20.34	0.9167	20.6361	0.9166	21.0404	0.9169	21.2506
60	0.897	20.5905	0.8972	20.6946	0.897	20.6899	0.8974	20.8982	0.8974	21.0972
70	0.8753	18.9297	0.874	18.8995	0.8746	18.9124	0.8755	19.1261	0.8694	18.5108
80	0.8417	16.1475	0.8522	17.1995	0.8535	18.6455	0.8523	16.729	0.852	17.101
90	0.8244	14.6161	0.8215	14.4129	0.8231	14.441	0.8198	14.0099	0.8249	14.3786
	0.002M Glucose		**0.004M Glucose**		**0.006M Glucose**		**0.008M Glucose**		**0.01M Glucose**	
	ρ	η	ρ	η	ρ	η	ρ	η	ρ	η
10	0.9748	11.4453	0.9751	11.3881	0.9753	11.3306	0.9765	10.8783	0.9778	10.8928
20	0.9618	13.849	0.9631	13.6396	0.964	14.2807	0.9651	14.1602	0.9657	14.5077

30	0.9499	17.4354	0.9518	17.1364	0.9513	17.4611	0.9447	17.8922	0.9439	17.3253
40	0.9275	19.669	0.9273	19.6648	0.9297	19.8258	0.9317	19.6477	0.9319	19.2103
50	0.9104	19.6299	0.9115	19.7077	0.9135	20.8641	0.9132	20.4359	0.9157	20.4918
60	0.8936	19.1726	0.8935	19.7889	0.8937	20.618	0.8977	21.1245	0.8971	20.9034
70	0.9728	19.4311	0.8652	18.0144	0.8669	18.5998	0.8637	18.2082	0.868	18.6234
80	0.8414	16.7909	0.8387	16.4468	0.8408	16.8759	0.8432	17.6049	0.8413	16.0125
90	0.8121	14.0516	0.8125	13.7773	0.8256	15.0471	0.8265	16.2933	0.862	15.4355

(ρ is density and η is viscosity)

Table 2: A- and B-Coefficient Value

Glucose % B	KCl		NaCl		$NiCl_2$		$CuCl_2$		
	A	B	A	B	A	B	A	B	A
10	-110.597	14.3961	-89.5625	12.243	-70.061	11.2796	-90.5794	12.8393	-111.4274
14.326									
20	-110.1872	15.4074	-112.7102	15.7266	-95.1455	13.3428	-116.323	16.1507	-74.2937
11.6264									
30	-72.6654	9.8127	-75.9092	10.7386	-63.1538	9.3787	-84.8151	11.5314	-75.123
10.823									
40	-125.4733	17.231	-118.967	16.229	-106.3746	14.7663	-127.6942	17.1927	-124.7819
17.1793									
50	-123.2885	16.1229	-113.2647	15.0857	-97.8299	13.2589	-77.7483	12.0867	-70.6701
11.3228									
60	-125.6207	15.809	-108.3063	13.9463	-81.7399	12.1508	-62.3926	11.5415	-55.0515
9.7709									
70	-93.2414	12.6262	-87.9166	12.1939	-81.8966	11.8753	-89.0965	12.3039	-100.9272
12.9557									
80	-60.1415	8.529	-51.5473	7.4435	-72.3057	9.0286	-42.7633	7.5731	-62.2199
8.7033									
90	-33.881	4.5566	-2.0519	1.9367	-1.7916	1.1785	-38.634	4.8467	-9.3395
1.5926									

Table 3: Limiting apparent molar volumes in ethanol

Conc. (M)	KCl		NaCl		$NiCl_2$		$CuCl_2$		Glucose	
	ϕ_v^0	S_v	ϕ_v^0	S_v	ϕ_v^0	S_v	ϕ_v^0	S_v	ϕ_v^0	S_v
0.002	49.3969	0.2660	49.8688	0.2717	49.3142	0.2859	48.7543	0.3389	45.1823	
0.7214										
0.004	49.6953	0.2545	49.575	0.2841	49.3287	0.2857	49.0128	0.2937	44.645	
0.7891										
0.006	49.7786	0.2622	49.6377	0.2779	49.0771	0.3130	48.8505	0.2990	44.9034	
0.7052										
0.008	49.7924	0.2647	49.7115	0.2668	49.1113	0.2962	48.5431	0.3384	44.8551	
0.7041										
0.01	49.7378	0.2503	49.8654	0.2467	49.1369	0.2815	48.5799	0.3341	44.3728	
0.7394										

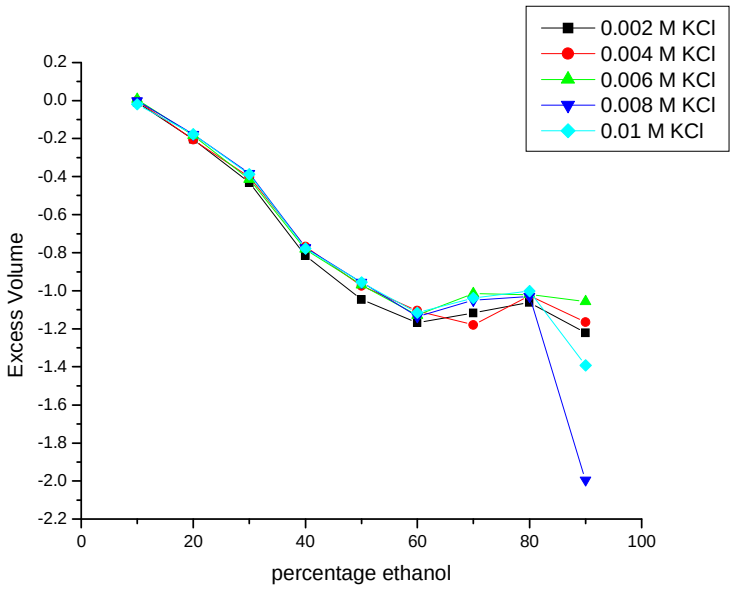

Fig 2a Excess volume of ethanol-water in presence Fluoxetine and various concentration of KCl

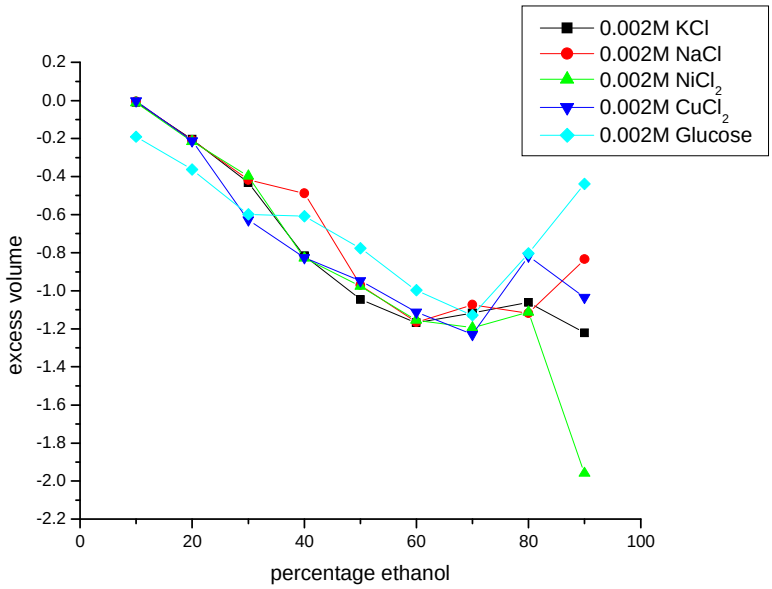

Fig 2b Excess volume of ethanol-water in presence fluoxetine and various additives

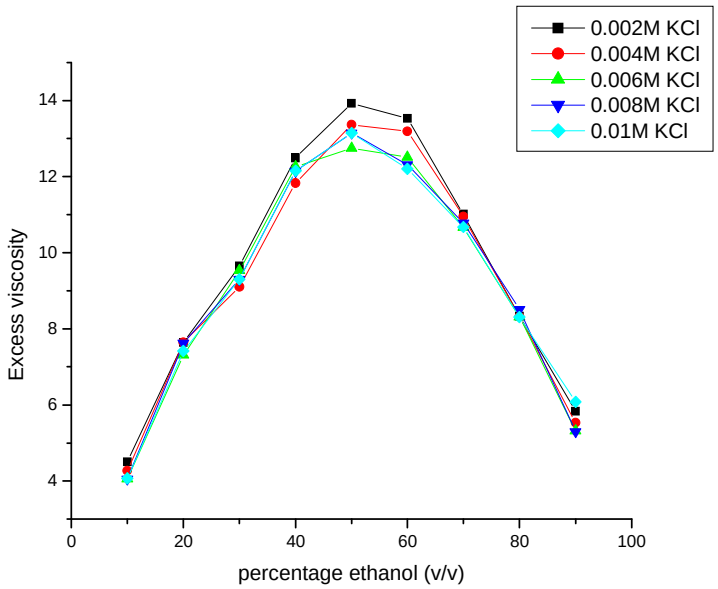

Fig 3a Variation of excess viscosity of ethanol-water in presence of fluoxetine at various concentration of KCl

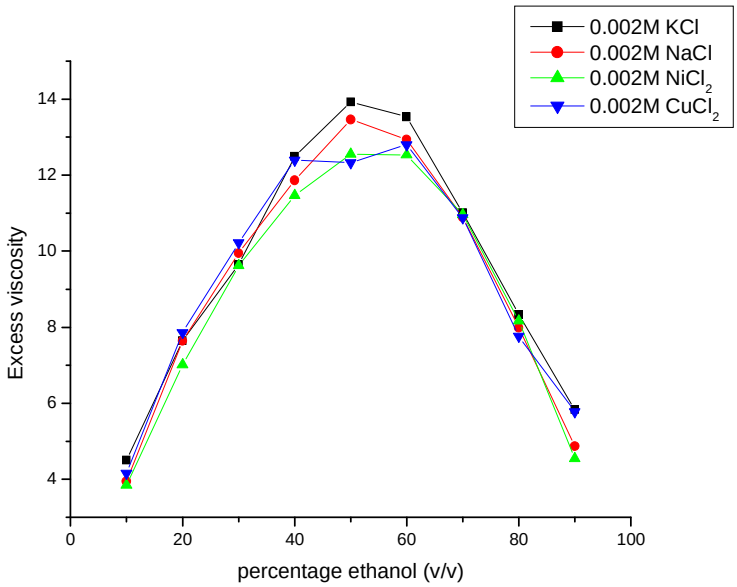

Fig 3b Variation of excess viscosity of ethanol-water in presence of fluoxetine and additives

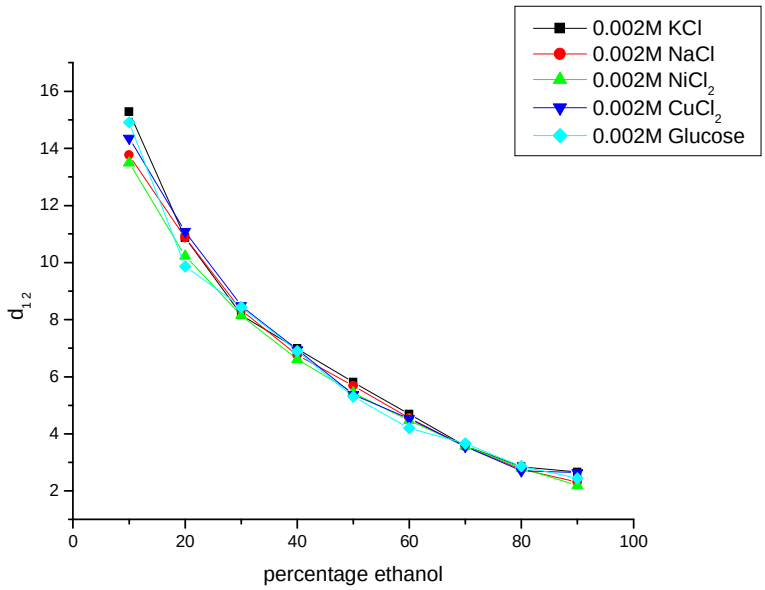

Fig 4 Variation of d_{12} for fluoxetine with percentage ethanol (v/v) in presence of additives

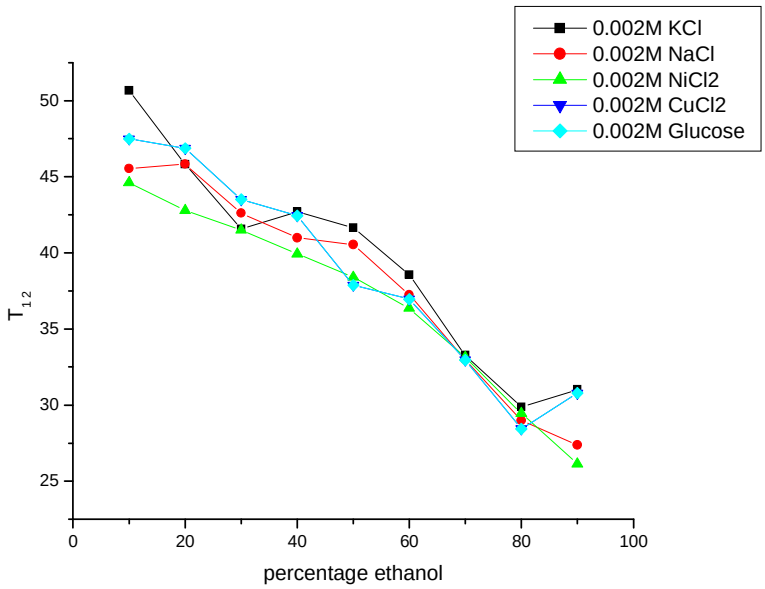

Fig 5 Variation of T_{12} for fluoxetine with percentage ethanol (v/v) in presence of additives

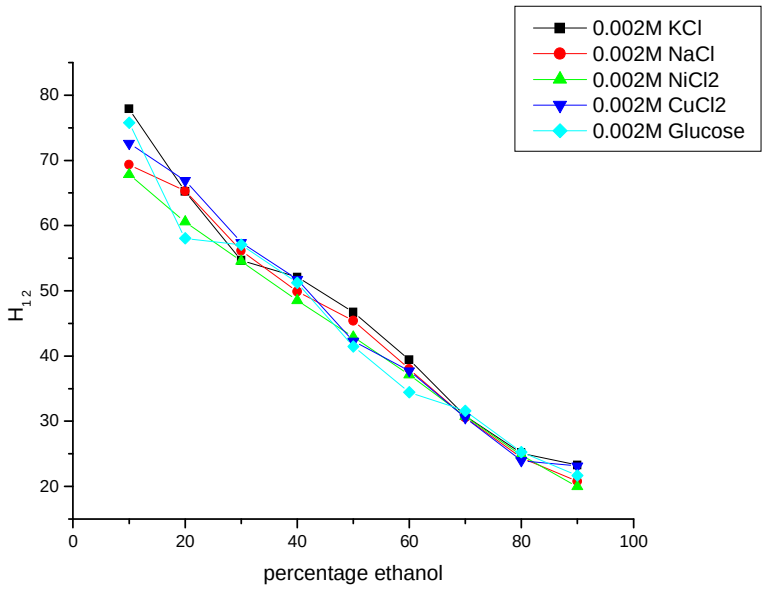

Fig 6 Variation of H_{12} for fluoxetine with percentage ethanol (v/v) in presence of additives

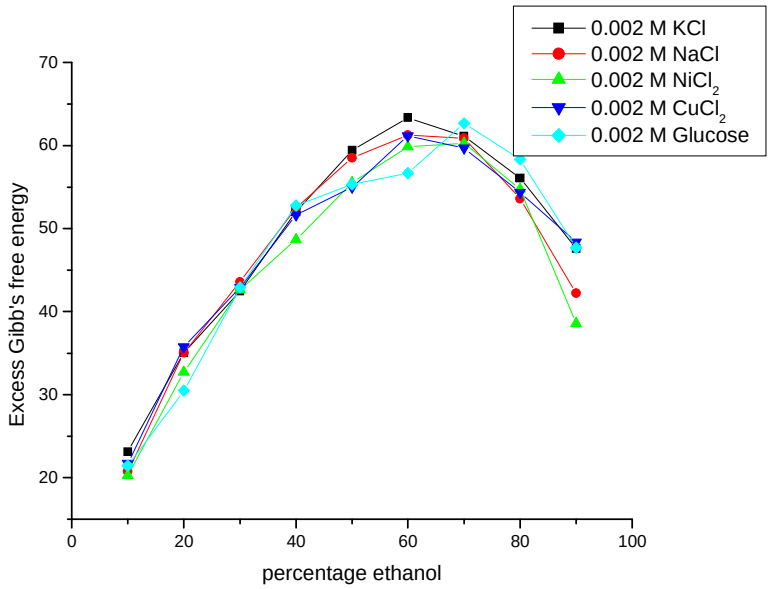

Fig 7 Variation of excess Gibbs free energy for fluoxetine with percentage ethanol (v/v) in presence of additives

CONCLUSION

From the present study we can conclude that ft HCl molecule interact solvent ethanol or water through hydrogen bonding. There may be complex formation between metal ion and ft-HCl which leads in the change in the density, viscosity and excess parameters of the binary solvent system.

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