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ANALYSIS OF MOLECULAR INTERACTION IN TRAMADOL DRUG WITH ALCOHOLS UNDER ULTRASONIC TECHNIQUE AT TEMPERATURE T= 278.15 K

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ABSTRACT: The prime aim of this research paper is to find out the various kinds of intermolecular interactions in the alcoholic tramadol below the room temperature. Study of molecular interaction in the mixture of alcohols namely ethanol,1-propanol,1-butanol with tramadol drug at T = 278.15 K have been examined under the ultrasonic technique at 2MHz. Ultrasonic data of drug solutions has been evaluated at various desired acoustical parameters e.g. Free length, adiabatic compressibility, relative association, molar sound velocity, adiabatic compressibility, internal pressure etc. In this research, investigation is carrying out the various types of possible molecular interaction in the solution. These parameters have been thoroughly analyzed and eventually interpreted at the possible molecular interactions such as structure making and structure breaking effect and also solute-solvent, ionic interaction, H-bonding effect in the alcoholic tramadol drug solution. It can be concluded that there is associative behavior in the alcoholic tramadol solution at desired concentration.

INTRODUCTION: The effect of the drugs in pharmacodynamics and pharmacokinetics is physiological and bio-chemical and their action of mechanism on organ system level or subcellular level or macromolecular level. It also refers to movement of drug in and altercation by the body includes absorption and distribution by binding or localization or storage or biotransformation or excretion of the drug. [1, 3] Ultimately it provides physicochemical properties of the drugs and functional group of molecule in the living organism.

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Most of the drugs are organic molecules with both hydrophilic and hydrophobic group and these drugs intend towards the specific as well as electrostatic interactions. The information of physicochemical properties of the drugs deals with the physiological action which direct depends on the behavior of solution.[4, 5] Ultrasonic wave are propagated in the liquid and it is directed to evaluate the properties of liquid which is highly focus on the physical and chemical properties or behavior of the solution and their molecular interactions examine by ultrasonic parameters. Such a particular data is very helpful to carrying out the various acoustical parameters which are more supportive to interpret the molecular interactions at micro level in the drug solutions.[6, 10]

In the present trend, ultrasonic studies are exclusively carried out and examined the thermodynamics properties and also predict various

types of interaction occurred in the solution.[11,12] Alcohols are highly self-associated through H-bonding and aprotic than other.[13, 15] Tramadol is extensively metabolized after oral administration. The inhibition of one or both types of the enzymes involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.[16] Tramadol and its metabolites are excreted mainly by the kidneys, with a cumulative renal excretion (tramadol and metabolites) of approximately 95%. You should avoid or limit the use of alcohol while being treated with tramadol. Using tramadol together with ethanol can increase nervous system side effects such as dizziness, drowsiness, and difficulty concentrating.

In the present paper ultrasonic velocity, density, viscosity, relative association and other related parameters of the mixture of tramadol and ethanol, propanol, butanol are reported at low temperature range i.e. 278.15K over a range of 0.01- 0.1 molar concentration. In order to investigate various kinds of interactions and their subsequent effect on transport properties. The interpretation of physicochemical behavior of drug can be the great interest from academic as well as physiological sense.[17, 22]

MATERIALS AND METHODS:

The solvents alcohols like ethanol, 1-propanol, 1-butanol and analgesic drug tramadol were used AR grade (E-Merck chemicals, Germany) without further purification. The purity of chemicals has been checked out by comparing the ultrasonic velocity, densities data with standard literature value.[23,25] All the measurement of ultrasonic velocity of the solution by using ultrasonic interferometer supplied by Vi-Micro system, Chennai (Model VCT: 71) having frequency 2 MHz with on overall accuracy of 0.0001 m/s. The densities of solutions are measured using 10 ml specific gravity bottle. Specific gravity bottle having accuracy of $\pm$ 2 X10^{-2} kg/m^3.

Automatic temperature controller water bath supplied by Lab-Hosp Company Mumbai having accuracy ±1K temperature. Viscosities were measured at desired temperature using Oswald's viscometer; the viscometer has been calibrated using doubled distilled water with literature value. The time flow of doubled distilled water and experimental solutions are measured with digital stop clock having accuracy of 0.01 sec (Model: RACER- 10W).Weights were measured with an electronic digital balance (Contech CA-34) having accuracy 0.0001gm. By the above experimental set up utilized to determine the ultrasonic and thermo-acoustic parameters in mixtures of alcohols and tramadol at T=278.15K at various molar concentrations.

The formulation of ultrasonic and thermo-acoustic parameters as follows:

Adiabatic Compressibility $(\beta) = 1 / U^2\rho$ ..... (1)
Specific Acoustic Impedance $(Z) = U\rho$..... (2)
Intermolecular Free Length $(L_f) = K_T \beta^{1/2}$ ..... (3)
Relaxation Time $(\tau) = (4/3)^*\beta^*\eta$..... (4)
Relative association $(Ra) = (\rho/\rho_0)(U_0/U)^{1/3}$ ..... (5)
Classical Absorption $(\alpha/f^2) = (8\pi^2\eta)/(3\,U\,\rho)$ ..... (6)
Internal Pressure $(P) = bRT\,(K\eta/U)^{1/2} x\,(\rho^{2/3}/M^{7/6}eff)$. (7)
Free Volume $(V_f) = (M_{eff}\,U/\eta\,K)^{3/2}$ .....(8)
Molar volume $(Vm) = Meff/\rho$..... (9)
Molar Sound Velocity or Rao Constant $(R) = Meff/\rho\,(U)^{1/3}$. (10)
Molar compressibility or Wada constant $(W) = V\,\beta^{-1/7}$..... (11)
Isothermal Compressibility $(\beta i) = \gamma\,\beta$..... (12)
Surface Tension $(\sigma) = (6.3 x10^{-4})\,\rho U^{3/2}$ ..... (13)

RESULTS AND DISCUSSION: The Experimental evaluation in terms of Ultrasonic Velocity (U), Density (ρ), Viscosity (η) and allied parameters with increase in concentration of Tramadol with ethanol, propanol, butanol at temperature T=278.15K are presented in **Table 1** to **3** and it has been shown graphically. Ultrasonic velocity increases nonlinearly with increase in mole fraction of Tramadol **(Fig.1).** Dipole-dipole interaction or hydrogen bonded complex formation between unlike molecules which leads to increase in sound velocity and decreases compressibility **(Fig.4).** At low concentration, the number of hydrogen bonds formed may be less and at higher concentration it may be more due to solute-solute interactions.

The behavior of increase in velocity and decrease in compressibility forms a tightly bounded system.[26] Adiabatic compressibility is a measure of intermolecular association or dissociation or repulsion. Free length of solution decreases as the concentration increases; this indicates significant interactions between solute and solvent molecules

[27, 30] **(Fig.6).** Ultrasonic velocity increases on decrease in free length and vice-versa. A sudden decrease in molecular free length shows a tightly packing molecules or strong interaction. Increase behavior of acoustic impedance with increase concentration may asses the strength of inter molecular interaction in the solution, and this may be on the basis of the interaction between solute and solvent molecules **(Fig.5).** Relative association varies linearly with concentration which reveals the specific interaction exists in the solution and relatively it is strong in nature **(Fig.8).**

TABLE 1: TRAMADOL + ETHANOL AT T = 278.15 K

Mol-arity	U (m/s)	ρ (kg/m^3)	η(Ns/m^2) E-03	B(m^2/N) E-10	Z (kg/sm^2) E+05	Lf(Å) E-11	τ(sec)E-12	Ra	(α/f2) E-14	P (pascal) E+09	Vf * E-08	Vm * E-05	R *E-04	W* E-03	βi* E-09	σ * E+03
0.01	1233.968	793.3565361	1.753717	8.27797	9.78976 5782	5.4608	1.9356	0.9904438	3.093	1.1182112	2.09038	5.81809	6.2404	1.154038	1.2417	21.665304
0.02	1232.138	791.3767444	1.849932	8.32335	9.75085 3591	5.4757	2.0530	0.9884610	3.285	1.1440402	1.93245	5.84740	6.2687	1.158945	1.2485	21.563182
0.03	1232.830	793.8564835	1.740632	8.28804	9.78690 0886	5.4641	1.9235	0.9913728	3.076	1.1084745	2.12709	5.84382	6.2661	1.158939	1.2432	21.648974
0.04	1233.286	797.236128	1.774 96	8.2468	9.83220 1553	5.4505	1.9517	0.9954706	3.120	1.1190395	2.07462	5.83366	6.2559	1.157749	1.2370	21.753203
0.05	1233.736	799.735865	1.805144	8.21503	9.86662 9271	5.4400	1.9772	0.9984704	3.160	1.1273738	2.03151	5.82998	6.2528	1.157657	1.2322	21.833355
0.06	1234.886	800.7657566	1.824963	8.18919	9.88854 4222	5.4314	1.9926	0.9994458	3.181	1.1306996	2.00880	5.83700	6.2622	1.159573	1.2283	21.892045
0.07	1236.532	804.1753979	1.859087	8.13277	9.94388 6132	5.4127	2.0159	1.0032559	3.214	1.1404235	1.96488	5.82655	6.2538	1.15864	1.2199	22.029232
0.08	1238.980	807.5750403	1.911054	8.06656	10.0056 9323	5.3906	2.0554	1.0068332	3.271	1.1549899	1.89799	5.81654	6.2472	1.158002	1.2099	22.188088
0.09	1241.333	812.5745143	1.972913	7.98657	10.0867 556	5.3638	2.1009	1.0124257	3.337	1.1738737	1.8213	5.79502	6.2280	1.155362	1.1979	22.389077
0.10	1245.214	817.5139947	2.036863	7.88891	10.1797 9871	5.3309	2.1424	1.0175207	3.392	1.1922848	1.7508	5.77418	6.2121	1.153232	1.1833	22.630895

TABLE 2: TRAMADOL + PROPANOL AT T = 278.15

Mola-rity	U (m/s)	ρ (kg/m^3)	η(Ns/m^2) E-03	β(m^2/N) E-10	Z(kg/sm^2) E+05	Lf(Å) E-11	τ(sec)E-12	Ra	(α/f2) E-14	P (pascal) E+09	Vf * E-08	Vm * E-05	R *E-04	W* E-03	βi* E-09	σ * E+ 03
0.01	1297.682	796.8861648	3.762023	7.45190	10.341 04832	5.1811	3.7379	0.9804109	5.680	1.1739927	1.06986	7.55993	8.2459	1.522227	1.1177	23.468712
0.02	1296.32	794.8663773	3.593831	7.48654	10.304 01182	5.1932	3.5873	0.9782683	5.457	1.1429269	1.14813	7.59724	8.2837	1.528726	1.1229	23.372383
0.03	1296.888	796.1562416	3.577526	7.46787	10.325 25476	5.1867	3.5622	0.9797127	5.416	1.1381546	1.16088	7.60297	8.2912	1.530427	1.1201	23.425699
0.04	1297.334	797.0661459	3.768413	7.45422	10.340 61011	5.1820	3.7454	0.9807200	5.692	1.1655888	1.07818	7.61230	8.3023	1.532704	1.1181	23.464570
0.05	1297.545	799.2759134	3.828 07	7.43119	10.370 96465	5.1739	3.7929	0.9833856	5.764	1.1736182	1.05706	7.60918	8.2993	1.532755	1.1146	23.535363
0.06	1298.78	800.7857545	3.873472	7.40308	10.400 44522	5.1641	3.8234	0.9849309	5.805	1.1782452	1.04369	7.61272	8.3058	1.534296	1.1104	23.613495
0.07	1300.096	802.8555368	3.932117	7.36905	10.437 89272	5.1523	3.8634	0.9871433	5.859	1.1853294	1.02558	7.61090	8.3066	1.534 94	1.1053	23.710520
0.08	1302.752	805.8752191	3.998123	7.31154	10.498 55553	5.1321	3.8976	0.9901823	5.899	1.1937541	1.00687	7.60010	8.3005	1.534479	1.0967	23.872668
0.09	1306.896	809.3748509	4.065317	7.23383	10.577 68755	5.1048	3.9210	0.9934301	5.916	1.2020438	0.99014	9 7.58487	8.2926	1.533742	1.0850	24.090831
0.10	1311.656	811.6746097	4.140544	7.16107	10.646 37871	5.0790	3.9534	0.9950462	5.943	1.2099273	0.97192	9 7.58093	8.2984	1.535162	1.0741	24.291393

TABLE 3: TRAMADOL + BUTANOL AT T = 278.15 K

Molarity	U (m/s)	ρ(kg/m^3)	η(Ns/m^2) E-03	β(m^2/N) E-10	Z(kg/sm^2) E+05	Lf(Å) E-11	τ(sec) E-12	Ra	(α/f2) E-14	P(pascal) E+09	Vf * E-08	Vm * E-05	R * E-04	W* E-03	βi* E-09	σ * E+ 03
0.01	1328.932	797.87 60607	4.35 9352	7.09 674	10.603 23029	5.0562	4.1249	0.971 3464	6.120	0.978 7936	1.21 71	9.31 062	10.2 36	1.88 7862	1.0645	24.35 1746
0.02	1327.190	796.78 61753	4.30 1571	7.12 512	10.574 86644	5.0663	4.0865	0.970 4437	6.071	0.969 4943	1.24 345	9.34 431	10.2 68	1.89 3613	1.0687	24.27 0682
0.03	1328.245	797.17 61343	4.25 7762	7.11 032	10.588 45214	5.0610	4.0365	0.970 6616	5.992	0.961 9628	1.26 844	9.36 065	10.2 89	1.89 7488	1.0665	24.31 1520
0.04	1328.465	797.97 60501	4.32 5824	7.10 084	10.600 83253	5.0576	4.0956	0.971 5819	6.079	0.967 6702	1.24 308	9.37 213	10.3 02	1.90 0177	1.0651	24.34 1962
0.05	1328.781	800.75 57577	4.52 299	7.07 283	10.640 29036	5.0476	4.2653	0.974 8891	6.329	0.989 0904	1.16 698	9.36 035	10.2 90	1.89 8861	1.0609	24.43 5472
0.06	1330.432	802.17 56083	4.62 5007	7.04 28	10.672 40099	5.0369	4.3430	0.976 2136	6.437	0.998 1641	1.13 445	9.36 448	10.2 99	1.90 0853	1.0564	24.52 4435
0.07	1332.342	804.67 53453	4.76 008	7.00 08	10.721 02759	5.0219	4.4432	0.978 7875	6.576	1.011 4060	1.09 245	9.35 598	10.2 95	1.90 0752	1.0501	24.65 3854
0.08	1335.672	807.57 50403	4.89 8328	6.94 093	10.786 55369	5.0004	4.5331	0.981 4976	6.692	1.024 5407	1.05 392	9.34 288	10.2 89	1.90 0421	1.0411	24.83 5514
0.09	1339.540	810.97 46826	5.03 8942	6.87 197	10.863 33026	4.9755	4.617	0.984 6798	6.796	1.037 8984	1.01 784	9.32 409	10.2 78	1.89 9306	1.0308	25.04 8479
0.10	1343.890	816.47 41041	5.23 1217	6.78 157	10.972 51384	4.9426	4.7301	0.990 2863	6.940	1.057 8762	0.97 01	9.28 150	10.2 42	1.89 421	1.0172	25.34 1280

Internal pressure provides an excellent basis for examining the solution phenomenon and studying various properties of the liquid state **(Fig.10).** Observing the changes in the internal energy of liquid or liquid mixtures, it has seen that it undergoes a very small isothermal change. It is a measure of cohesive or binding forces between the solute and solvent molecules. The internal pressure may provide information regarding the nature and strength of forces existing between the molecules. Free volume decreases with increase in molar concentration implies molecular binding between solute and solvent molecules that implies structure making in nature **(Fig.11).** Molar sound velocity and molar compressibility increases with increasing concentration that shows there is strong interaction between solute and solvent molecules and vice-versa **(Fig.13, 14).** The variation of surface tension also supports the significant associative interaction in the solution **(Fig.16).**

Data interpretation by graphical tactic as follows: Following figures are of various ultrasonic and thermo-acoustic parameters V/S molarity

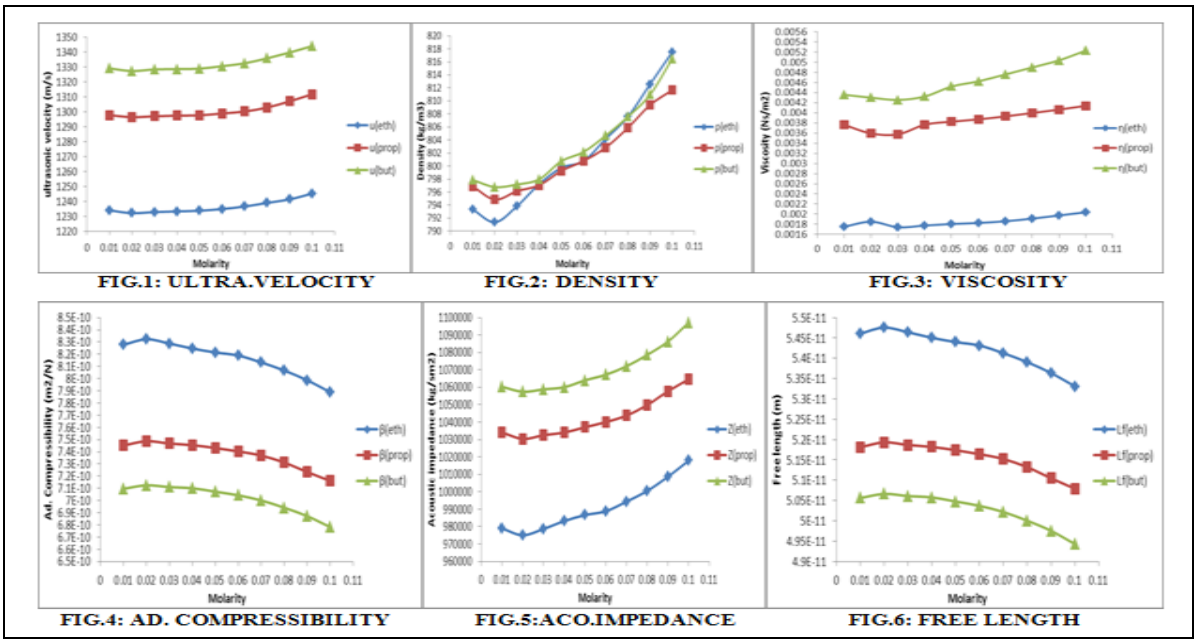

FIG.1: ULTRA.VELOCITY FIG.2: DENSITY FIG.3: VISCOSITY

FIG.4: AD. COMPRESSIBILITY FIG.5:ACO.IMPEDANCE FIG.6: FREE LENGTH

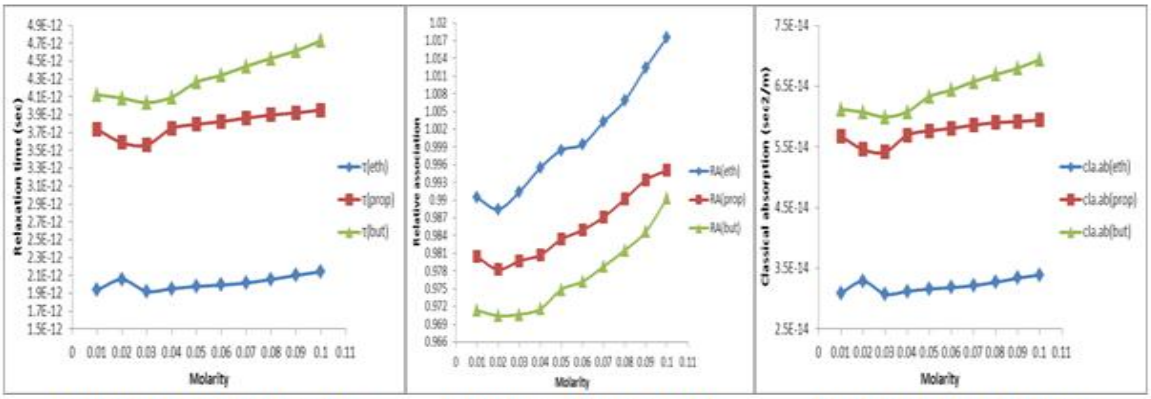

FIG.7: RELAXATION TIME FIG.8:REL.ASSOCIATION FIG.9:CLA.ABSORPTION

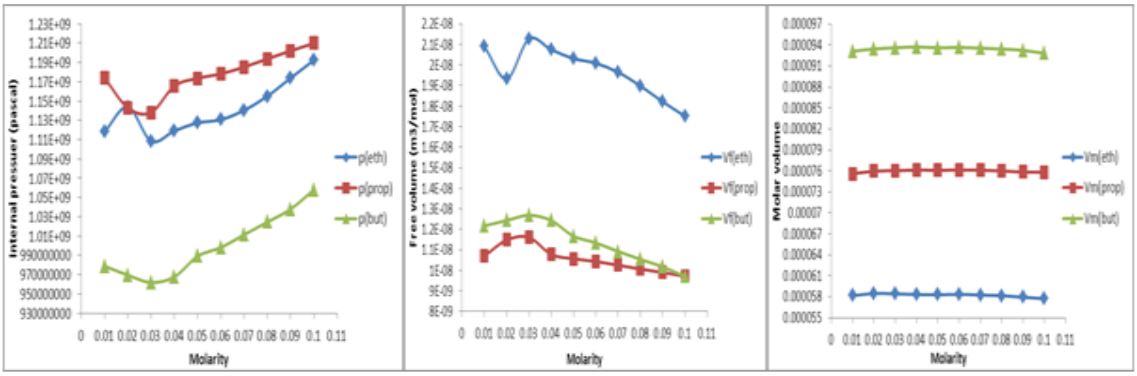

FIG.10:INT.PRESSURE FIG.11: FREE VOLUME FIG.12: MOLAR VOLUME

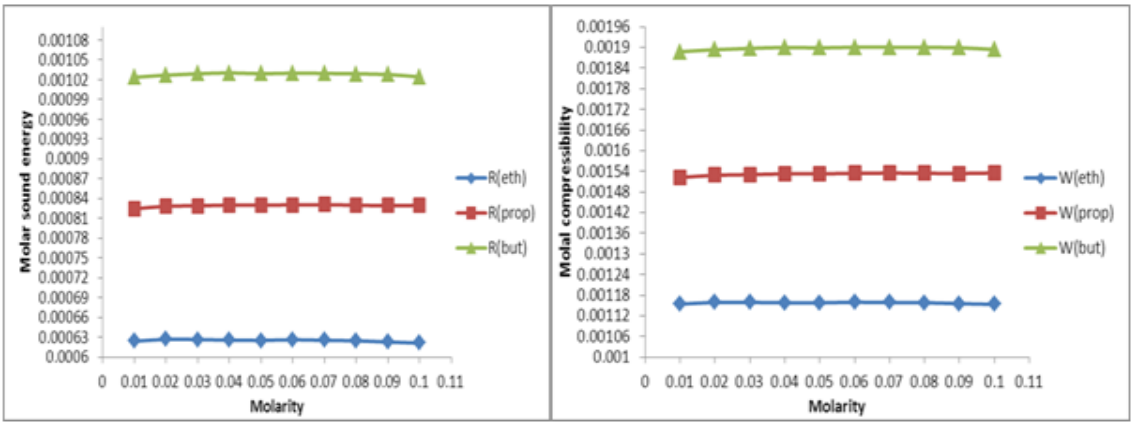

FIG.13: MOLAR SOUND ENERGY FIG.14: MOLAR COMPRESSIBILITY

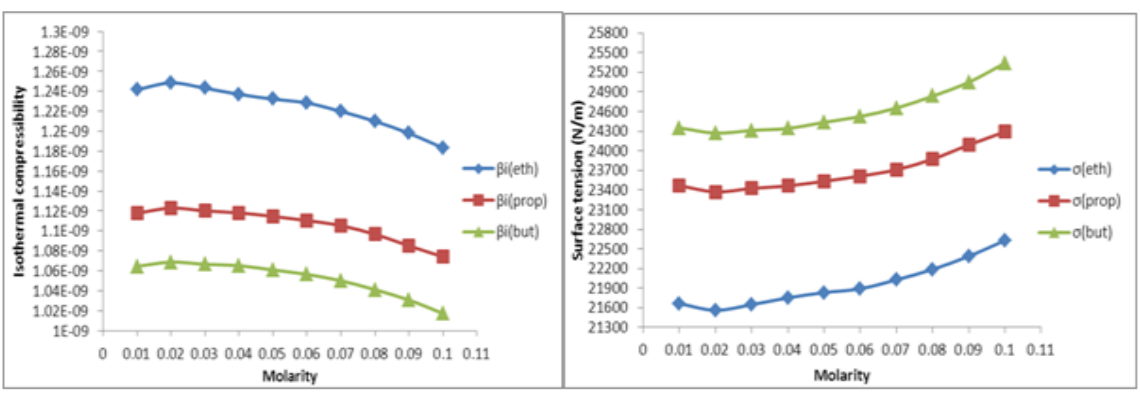

FIG.15: ISOTHERMAL COMPRESSIBILITY FIG.16: SURFACE TENSION

CONCLUSION: The estimation of alcoholic tramadol solution, mentioned in research paper, accomplish towards the strong intermolecular interaction that revealed the structure making property in the solution. The solute-solvent interaction interpreted in terms of structural re-arrangement due to hydrogen bond interaction between solute and solvent system.

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