Correlation between Surface Tension on Aqueous Solution of 5-Fluorouracil with Heterocyclic Compound at Various Temperatures

Ubagaramary D[1], Enoch VMV[2], Mullainathan S[3], Abishek S[4], kumar VP[4] and Jagan K[4*]

[1]Department of Chemistry, Adhiyamaan College of Engineering, Hosur-635109, Tamil Nadu, India

[2]Nanotoxicology Research Lab, Karunya Institute of Technology & Sciences, Coimbatore-641114, Tamil Nadu, India

[3]Department of Physics, Thiru. Vi. Ka. Government Arts and Science College, Thiruvarur, Tamil Nadu, India

[4*,]Department of Biotechnology, Adhiyamaan College of Engineering, Hosur-635109, Tamil Nadu, India

[*]Corresponding author: Jagan K, Department of Biotechnology, Adhiyamaan College of Engineering, Hosur-635109, Tamil Nadu, India, Tel: 04344 261 002; E-mail: jegankannan312@gmail.com

Abstract

The speed of sound (U), density (ρ) and viscosity (η) of aqueous solution of 5-Fluorouracil with tetrahydrofuran (THF) are measured at various mole fractions at various temperatures at 295.15 K and 300.15 K. From the experimental data, the adiabatic compressibility (β), free volume (VF), internal pressure (πi) and acoustic impedance (Z) are established. The observed results are examined in terms of structural changes around the ion and effect of the solvent.

Keywords: Ultrasonic spectroscopy; 5-Fluorouracil; Tetra hydro furan (THF); Surface tension

Introduction

Tetrahydrofuran (THF) is a color-less, low-viscous, water-miscible heterocyclic ether. It is a versatile solvent in industrial process involving the acid-catalyzed dehydration of butan-1, 4-diol. It is more basic than diethyl ether and forms stronger complexes with Li^+, Mg^{2+} and boranes. THF is a popular solvent for hydroboration reactions and for organometallic compounds such as organ lithium and Grignard reagent [1-3]. The present investigation is on the compositions involving of 5-Fluorouracil.

Fluorouracil (5-FU), sold under the brand name Adrucil among others, is a medication used to treat cancer. By injection into a vein it is used for colon cancer, esophageal cancer, stomach cancer, pancreatic cancer, breast cancer and cervical cancer. AS a cream it is used for actinic keratosis and basal cell carcinoma.

When used by injection most people develop side effects, Common side effects include inflammation of the mouth, loss of appetite, low blood cell counts, hair loss and inflammation of the skin. When used as a cream, irritation at the site of

application may occur. Use of either form in pregnancy may harm the baby. Fluorouracil is in the antimetabolite and pyrimidine analog families of medications.

Fluorouracil has been given systemically for anal, breast, colorectal, esophageal, stomach, pancreatic and skin cancers (especially head and neck cancers. It has also been given topically (on the skin) for actinic keratosis, skin cancers and Bowen's disease and as eye drops for treatment of ocular surface squamous neoplastic.

It is contraindicated in patients that are severely debilitated or in patients with bone marrow suppression due to either radiotherapy or chemotherapy. It is likewise contraindicated in pregnant or breastfeeding women. It should also be avoided in patients that do not have malignant illnesses such as Nausea, Vomiting, Diarrhea, Mucositis, Headache, Myelosuppression, Alopecia (hairloss), Photosensitivity, Hand-foot syndrome, Macula popular eruption, Itch, Cardiotoxicity Persistent hiccups Mood disorders (irritability, anxiety, depression) Uncommon (0.1–1% frequency) Oesophagitis, GIulcerationandbleeding, Proctitis, Naildisorders, Veinpigmentation, Confusion, Cerebellar syndrome, Encephalopathy, Visual changes, Photophobia, Lacrimation, Fever without signs of infection.

Diarrhea is severe and may be dose-limiting and is exacerbated by co-treatment with calcium folinate. Neutropenia tends to peak about 9-14 days after beginning treatment. Cardio toxicity is a fairly common side effect, but usually this cardio toxicity is just angina or symptoms associated with coronary artery spasm, but in about 0.55% of those receiving the drug will develop life-threatening cardiotoxicity. Life-threatening cardio toxicity includes: arrhythmias, ventricular tachycardia and cardiac arrest, secondary to trans mural is chaemia.

5-FU injection and topical application, even in small doses, cause both acute central nervous system (CNS) damage and progressively worsening delayed degeneration of the CNS in mice. This latter effect is caused by 5-FU-induced damage to the oligo dendrocytes that produce the insulating myelin sheaths.

The United States package insert warns that acute cerebellar syndrome has been observed following injection of fluorouracil and may persist after cessation of treatment. Symptoms include ataxia, nystagmus and dysmetria.

There is very little difference between the minimum effective dose and maximum tolerated dose of 5-FU and the drug exhibits marked individual pharmacokinetic variability. Therefore, an identical dose of 5-FU may result in a therapeutic response with acceptable toxicity in some patients and unacceptable and possibly life-threatening toxicity in others. Both overdosing and under dosing are of concern with 5-FU, although several studies have shown that the majority of colorectal cancer patients treated with 5-FU are under dosed based on today's dosing standard, body surface area. The limitations of BSA-based dosing prevent oncologists from being able to accurately titer the dosage of 5-FU for the majority of individual patients, which results in sub-optimal treatment efficacy or excessive toxicity.

It's should be avoided in patients receiving drugs known to modulate dihydropyrimidine dehydrogenase. It may also increase the INR and prothrombin times in patients on warfarin. Fluorouracil's efficacy is decreased when used alongside allopurinol,

which can be used to decrease fluorouracil induced stomatitis through use of allopurinol mouthwash. The structure of 5-FU and THF are given by:
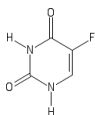
This paper was discussed about the densities, speeds of sound and viscosities of THF with 5-Fluorouracil in water system of ternary mixtures over the entire composition range at T=(303.15–313.15) K. The values of the pure components generally have been decided with the available literature data. From the experimental data, various physicochemical parameters, of the components at infinite dilution have been analyzed [4,5]. The results are studied in terms of the molecular interactions through the dipole-induce-dipole interactions between the components of the mixtures, resulting in the formation of electron donor-acceptor complexes.

Materials and Methods

Density measurement

All the binary liquid mixtures were prepared by weighing suitable amount of pure liquids on an electric balance by means of stoppered bottle. The uncertainty of electronic balance was ± 0.01 mg but the accuracy of the mole fraction was ± 1 × 10-4. An electronically operated constant temperature bath was used to circulate water through the double walled measuring cell made up of steel containing the experimental solution at the desired temperature, the accuracy in the temperature measurement is 0.01 K.

The density of the pure liquids and their mixtures and electrolytic solution were measured using a 5 ml corning specific gravity bottle by relative measurement method. The volume of specific gravity bottle was ascertained by weighing it with doubled distilled water at the experimental temperatures. By using the following relation, the density of the unknown mixture at any temperature can be determined.

$$\rho_s = (W_s/W_w \times \rho_w) \tag{1}$$

Where, ρ_w is the density of water, W_s and W_w are the weight of unknown solution and water respectively. The densities of pure liquids thus obtained are found to be in good agreement with the standard values.

Viscosity measurement

An Ostwald's viscometer (10 ml) was used for the determination of viscosity for the pure liquid, liquid mixtures and electrolytes by relative method. The viscometer was filled with conductivity water and then immersed in the water bath, which was kept at the experimental temperature. The time of flow of water was noted after the liquid inside the viscometer attained temperature. The water was replaced by the mixture whose viscosity is to be determined. The time of flow of the mixture was

measured with digital stop clock having accuracy after the liquid inside the viscometer attained the temperature of the bath. By knowing the flow time of the reference liquid and liquid mixture, the viscosity of the mixture can be determined using the relation,

$$\eta_s = \eta_w \frac{\rho_s t_s}{\rho_w t_w} \qquad (2)$$

Where η_s and ρ_s are viscosity and density of the solution respectively. $\llbracket \eta \rrbracket\_w$ and ρ_w are the corresponding values for water. The time of flow was measured with an accuracy of the density and viscosity measurements were carried out in a well-stirred water bath whose temperature can be controlled [6,7]. All measurements were made at a constant temperature with an accuracy of since viscosity is highly temperature sensitive.

Ultrasonic velocity measurement

Ultrasonic velocity measurements were working an ultrasonic interferometer (Model M 84, inform by M/S Mittal Enterprises, New Delhi), at T=303.15–313.15 K with the accuracy of ± 0.1 ms−1. The measuring cell of interferometer is a specially designed double-walled vessel with provision for temperature constancy. An electronically operated digital constant temperature bath (Model SSI-03 Spl, supplied by M/S Mittal Enterprises, New Delhi), operating in the temperature range of −10°C to 85°C with an accuracy of ± 0.1°C has been used to circulate water through the outer jacket of the double-walled measuring cell containing the experimental liquid.

Results and Discussion

The density, speed of sound and viscosity for pure liquid mixtures of various mole fractions of 5-FU are presented in TABLE 1. Molar volumes and excess calculated values of isentropic compressibility, free volume, internal pressure, free length and relaxation time are presented in TABLE 2, 3. These are graphically represented by FIG. 1. Respectively. Molar volume data are influenced by (i) break up of hydrogen bonds and loss of dipolar association, owing to differences in size and shape of unlike molecules and (ii) The possible intermolecular interactions like hydrogen bonding or donor-acceptor interactions between unlike molecules [8-10]. The former effect leads to positive excess molar volumes, whereas the latter effect results in negative values. The experimental results suggest that the negative values are dominant in the present investigation for all binary mixtures over the entire composition range at T=(295.15 to 300.15) K.

TABLE 1. **Measured values of density (ρ) of the pure liquids at 300.15 K.**

Components	Density (ρ) Kgm⁻³		References
	Observed values	**Literature values**	
THF	870	877.1	Rathnam et al. (2013). [5]
5-Fluorocil	993	1001.4	FU et al. (2006). [6]

TABLE 2. **Measured values of density (ρ), ultrasonic velocity (U), viscosity (η) and molar volume (V_m) for 5-Fluorouracil+THF+water at 295.15 K and 300.15 K.**

Mole fraction (X_2)	Density (ρ) Kgm^{-3}	Viscosity (η) $\times 10^3$ Nsm^{-2}	Ultrasonic velocity (U) ms^{-1}	Molar volume (V_m) m^3
System: 5-Fluorouracil+THF+water at 295.15 K				
0.1033	936.4	0.7142	943.2	0.0828
0.1136	916.1	0.7465	965.2	0.0853
0.1263	898.9	0.7592	975.2	0.0877
0.1420	879.7	0.7674	983.2	0.0907
0.1623	868.6	0.7698	991.2	0.0932
System: 5-Fluorouracil+THF+water at 300.15 K				
0.1033	936.0	0.7139	950.2	0.0829
0.1136	914.9	0.7455	954.3	0.0854
0.1263	900.3	0.7503	962.6	0.0876
0.1420	882.1	0.7794	971.8	0.0905
0.1623	868.8	0.7860	993.6	0.0932

TABLE 3. **Calculated values of excess free volume, internal pressure, adiabatic compressibility, acoustical impedance and relaxation time of 5-Fluorouracil+THF+water at 295.15 K and 300.15 K.**

Mole fraction (X_2)	Excess free volume (V_F^E) $\times 10^5$ m^3 mol^{-1}	Excess internal pressure (π_i^E) $\times 10^{10}$ Nm^{-2}	Excess adiabatic compressibility (β^E) $\times 10^8$ Pa^{-1}	Excess free length (L_F^E) $\times 10^{10}$ m	Excess relaxation time (τ^E) $\times 10^{-5}$ S
System: 5-Fluorouracil+THF+water at 295.15 K					
0.1033	0.1547	-0.1238	1.5706	-0.4177	0.1116
0.1136	0.1704	-0.1362	1.7304	-0.4594	0.1227
0.1263	0.1893	-0.1515	1.9224	-0.5103	0.1363
0.1420	0.2127	-0.1706	2.1616	-0.5741	0.1534
0.1623	0.2428	-0.1952	2.4703	-0.6560	0.1752
System: 5-Fluorouracil+THF+water at 300.15 K					
0.1033	0.1140	-0.3602	5.0480	-0.4190	0.1184
0.1136	0.1253	-0.3964	5.5520	-0.4608	0.1302
0.1263	0.1391	-0.4406	6.1682	-0.5120	0.1446
0.1420	0.1564	-0.4958	6.9384	-0.5759	0.1627

0.1623	0.1786	-0.5667	7.9286	-0.6581	0.1859

The excess volume has positive value for system of 5-FU+THF+water at T=(303.15 to 313.15) K over the whole composition range and at all experimental temperatures. The positive values of VE values indicated that the absence of specific interactions such as hydrogen bond interaction between the mixing components, dipole-dipole or dipole-dipole induced interaction leading to electron donor-donor complexes. There was a more ability for hydrogen bond interaction (O-H…) between 5-FU and THF with water. Furthermore, there was chance of electron donor-donor interactions between the electron donating atom of 5-FU and THF and water. In such electron donor-acceptor interactions, 5-FU acts as an electron donor and THF act as electron acceptor [11-13]. In the present study, interactions between 5-FU and THF may be attributed to dipole-induced-dipole interactions between the components of the mixtures resulting the formation of electron donor-acceptor complexes [14]. When oxygen atom of the Tetra hydro furan with 5-FU in water was transferred the charges in the bond away from the ring to oxygen (mesmeric effect>inductive effect) leaving a positive charge in the ring. However, it was also donor in a donor-acceptor action [15-19]. As result of these two opposite effects, there might be a net transfer of negative charge from the ring to the oxygen atom as well as an enhancement of the acceptor character of the THF. Therefore, the interaction between THF with 5-FU in water must be increased when Oxygen and hydroxyl atom was attached to the ring.

VE data in the TABLE 3. for the ternary systems of Tetra hydro furan with 5-FU in water showed more positive VE values for the later than the former. Hydroxyl group in 5-FU ring is (negative inductive effect) electron withdrawing and tries to attract the oxygen of the THF ring and hence, the electron density of the THF ring decreases. As a result, the THF becomes relatively electron donor towards electron seeking proton of any group [20,21]. The experimental results in the present investigation supported this contention.

The more positive VE data for the ternary system of Tetra hydro furan with 5-FU in water may be due to less dipole moment and dielectric constant. THF is supposed to be a relatively complex molecule and its non-ideality arises due to rotation of oxygen group freely along the C–N axis where it gives more flexibility to the interaction with 5-FU in water.

The increase in VE values with increasing temperature may be due to factors (i) de clustering of components at higher temperature, (ii) weakening of dipole-dipole interactions due to decreases in polarizabilities and (iii) increase in kinetic energy at higher temperature [22].

The excess isentropic compressibility data were given in TABLE 3. and graphically presented in FIG. 1. An examination of data in the TABLE 3. Suggests that the excess isentropic compressibility data for these systems are positive over the entire composition range at T=295.15 K and 300.15 K. The observed values of can be qualitatively explained by considering the factors (i) disruption of associated structures/molecular order in the pure liquids, (ii) the formation of strong bonds by dipole-induced-dipole interaction between unlike molecules and (iii) free volume changes from mixing of components of different sizes. The first factor contributes positive values, whereas the remaining two factors led to negative values [23]. The resultant

positive values for this system indicates the non-dominance of net combination of factors (ii) and (iii) and this system is more compressible.
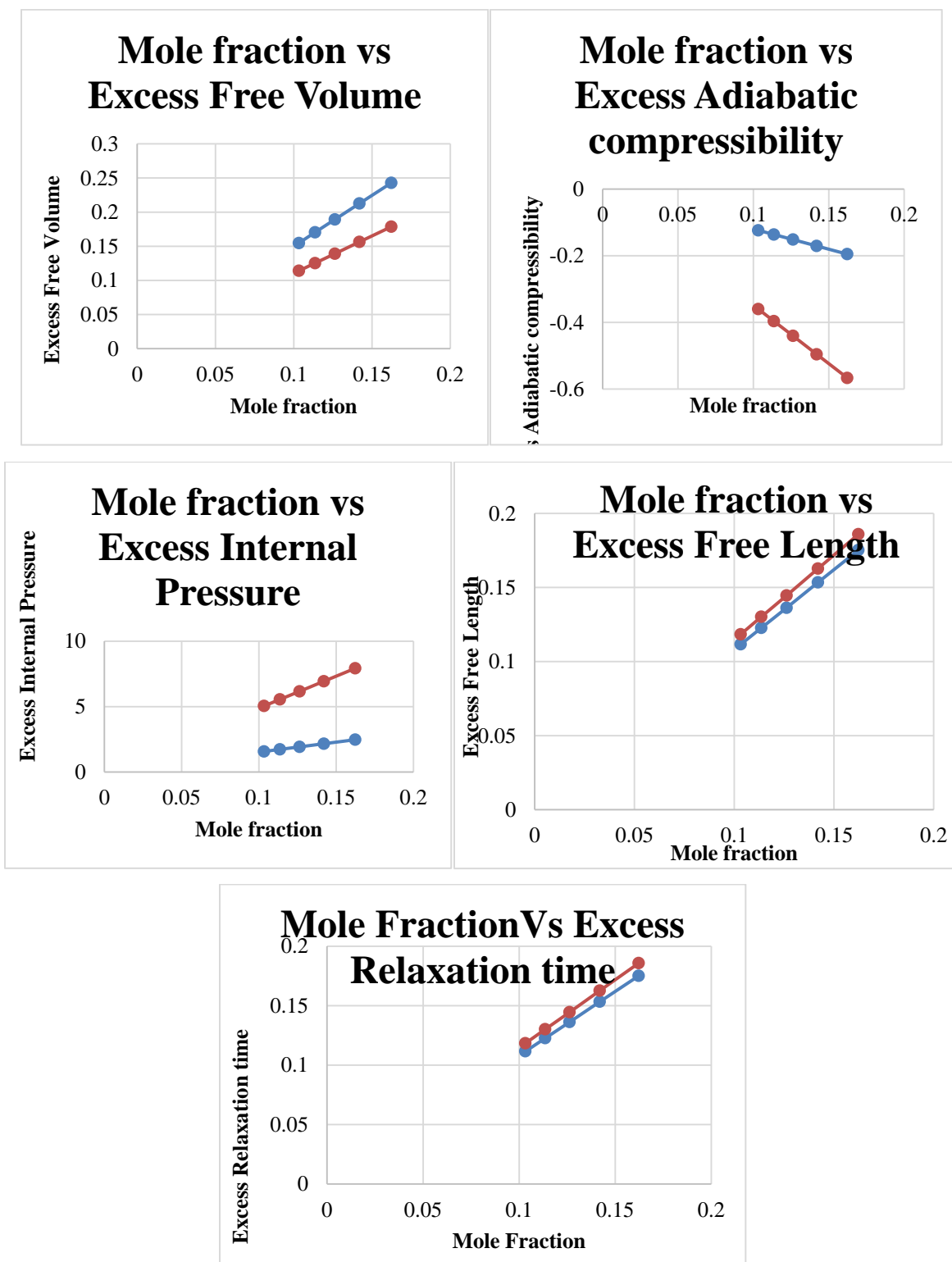

FIG. 1. **Plots of excess volume of free volume, adiabatic compressibility, internal pressure, free volume and relaxation time**

for various mole fractions of 5-FU+THF+water at 295.15 K and 300.15 K.

The sign and magnitude of viscosity depend on the combined effect of the factors such as molecular size, shape and intermolecular forces [24]. The positive data for Tetra hydro furan with 5-FU in water system suggests that the viscosity of the mixture is higher than that of the pure components and hence the fluidity of the mixture is low. This indicates the presence of specific interaction such as electron donor-acceptor interactions between unlike molecules. The viscosity deviation values are found to be similar to the molar volumes for this system. This suggests that the molar volumes of each component in the mixture are less than their respective molar volume in the pure state, i.e., there is a contraction in volume on the mixtures on mixing, which may be attributed to the dipole-induced-dipole interactions leading to electron donor-acceptor complexes. However, as the temperature increases and becomes more negative, there are enhanced solute-solvent type interactions between component molecules in THF with 5-FU in water.

Cohesive data are given in TABLE 4. and graphically presented in FIG. 2. The Cohesive values are found to be increased over the entire composition range at T=295.15 K and 300.15 K Tetra hydro furan with 5-FU in water system. The observed values of can be qualitatively explained by considering the cohesive forces between THF molecules down in to a water liquid are shared with all neighboring molecules of 5-FU. Those one of the surface have no neighboring atoms above and exhibit stronger attractive forces up on their nearest neighbor on the surface. This enhancement of the intermolecular attractive at the surface of Tetra hydro furan with 5-FU in water system is shown in FIG. 3.
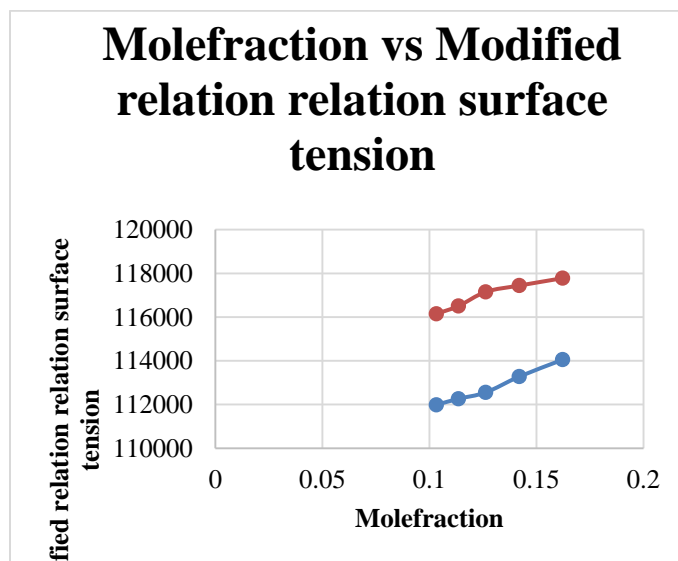
Molefraction vs Modified relation relation surface tension
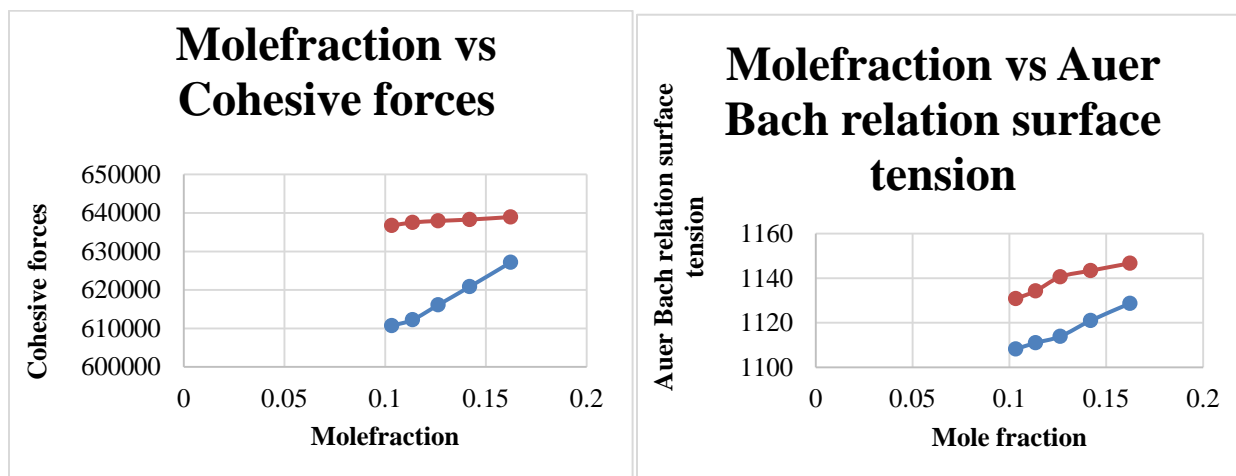
FIG. 2. **Plots of cohesive force, surface tension of Auer Bach relation and surface tension of modified relation, for various mole fractions of 5-FU+THF+water at 295.15 K and 300.15 K.**
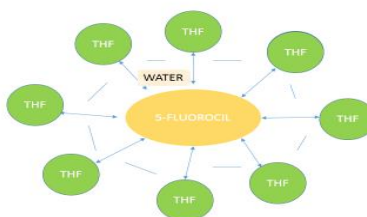

FIG. 3. **Intermolecular attractive at the surface of Tetra hydro furan with 5-FU in water system.**

The surface tension data were given in TABLE 4. and graphically presented in FIG. 2. The surface tension are found to be increased over the entire composition range at T=295.15 K and 300.15 K, THF with 5-FU in water system by using Auerbauch relation and modified relations. The observed values of can be explained the surface tension of Tetra hydro furan with 5-FU in water system increases significantly with temperature at T=295.15 K and 300.15 K. The surface tension arises from the polar nature of Tetra hydro furan with 5-FU in water system. Molecule liquid state experience strong intermolecular attractive forces [25]. When those forces are between like molecules, they are referred to as cohesive forces. The molecules of a water droplet are held together by cohesive force and the especially strong cohesive forces at the surface of THF with 5-FU in water system. When the attractive forces are between unlike molecules, that molecules are said to be adhesive forces. The adhesive forces between water molecules with THF and walls of the 5-FU are stronger than cohesive force leads to contribute capillary actions. These attractive forces between 5-FU with THF in water system can be viewed residual electrostatic forces and van der Waal's forces.

TABLE 4. **Calculated values of cohesive forces, Auerbach relation (σ_{auer}) modified relation (σ_{mod}) of 5-Fluorouracil+THF+water at 295.15 K and 300.15 K.**

Mole fraction X_2	Cohesive forces 10^6 kJ mol^{-1}	Auer Bach relation (σ) $_{Auer}$ m N/m	Modified relation $(\sigma)_{Mod}$ m N/m
System: 5-Fluorouracil+THF+water at 295.15 K			
0.1033	610715.90	1108.2	111988.6
0.1136	612254.70	1111.0	112266.2
0.1263	616102.84	1113.9	112555.8
0.1420	620849.39	1121.0	113280.0
0.1623	627159.78	1128.7	114053.5
System: 5-Fluorouracil+THF+water at 300.15 K			
0.1033	636731.42	1130.8	116150.9
0.1136	637518.34	1134.3	116508.0
0.1263	637930.02	1140.6	117154.7
0.1420	638276.95	1143.4	117443.6
0.1623	638940.85	1146.7	117780.8

List of Symbols

K_T: Temperature dependent constant;

M: Molality;

ρ: Density;

η: Viscosity;

U: Ultrasonic velocity;

V_m: Molar volume;

β^E: Excess adiabatic compressibility;

V_F^E: Excess free volume;

L_F^E: Excess free length;

π_i^E: Excess internal pressure;

σ_{Auer}: Surface tension of Auer bauch Relation;

σ_{Mod}: Surface tension of Modified Relation;

5-FU: 5-Fluorouracil.

Conclusion

This paper reports the densities, speeds of sound and viscosities of THF with 5-FU in water system of ternary mixtures over the entire composition range at T=295.15 K and 300.15 K. The values of the pure components generally agree with the available literature data. From the experimental data, various physicochemical parameters, of the components at infinite dilution have been calculated. The results are analyzed in terms of the molecular interactions through the dipole-induce-dipole interactions between the components of the mixtures, resulting in the formation of electron donor-acceptor complexes. 5-FU having higher molecular mass (long hydrophobic tail) diffuses less to the interface of THF in water and are tightly adsorbed at the interface causing a cohesive force act on the surface, thereby increasing the surface tension of Tetra hydro furan with 5-FU in water system. There is strong molecular interaction between adjacent molecules causing strong surface film face at higher concentration of THF with 5-FU in water system.

REFERENCES

1. Uvarani R, Sivaprakasam. Acoustical studies on molecular interactions in binary liquid mixtures at 303 K. J Chem. 2009;6:1150-52.

2. Mehra, Sajnami. Acoustical studies in ternary electrolytic mixtures at 25, 30, 35, 40 and 45°C. Ind J Pure Appl Phys. 2000;38:762-765.

3. Mehra R, Gupta A, Isran iR. Methyl-tertiary-butyl-ether (MTBE) misclassified. Ind J Chemistry Section A. 2001;40:505-508.

4. Asghar, Khan, Subramani K. Thermodynamic studies of molecular interactions in ternary liquid mixtures at various temperatures. J Chem. 2010;3:697-704.

5. Rahman MVI, Uddin M. Viscometric behavior of binary mixtures of butan-2-one with benzene at T=(303.15, 313.15 and 323.15) K. Rasayan J Chem Eng. 2011;56:1718-21.

6. Gorgas TJ, Roy H, Wilkens B, et al. *In situ* acoustic and laboratory ultrasonic sound speed and attenuation measured in heterogeneous soft seabed sediments: Eel River shelf, California. Mar Geol. 2002;182:103-19.

7. Palani R, Geetha A. Physico-chemical behaviour of binary liquid mixtures of some monohydroxy alcohols with Dmso as common solvent. Rasayan J Chem. 2008;3:481.

8. Bhandakkar, Bedare, Muley, et al. Molecular interactions of acrylonitrile and methylmethacrylate in methanol, cyclohexane & P-dioxane. Advances in App Sci Res. 2011;2:338-347.

9. Ghael, Gardas, Oswal. Volumetric and transport properties of ternary mixtures containing 1-alkanol+ethyl ethanoate+cyclohexane at 303.15 K: Experimental data, correlation and prediction by ERAS model. Thermochemica Acta. 2009;491:44-57.

10. Ramasamy K, Ranganathan V. Ind J Pure Appl Phys. 1983;27:579.

11. Mehra, Israni. Ind J Chemistry Section A. 2001;43:743-747.

12. Fort RJ, Moore WR. Viscosities of binary liquid mixtures. Trans Farad Soc. 1966;62:1112.

13. Jain DVS, Dhar NS. Mit neuer Führungsstruktur zog Hüls Konsequenzen aus Wandel und Wachstum. Ind J Tech. 1992;310:620-621.

14. Ciler M, Kesanovil D. Hydrogen Bonding. Ed Ha Zi D Peragamon Press. London. 1957.

15. Largeman RJ, Dundbar WS. Relationships between the velocity of sound and other physical properties of liquids. J Phys Chem. 1945;49:428-436.

16. Maham Y, Liew CN, Mather AE. Viscosities and excess properties of aqueous solutions of ethanolamines from 25 to 80°C. J Sol Chem. 2002;31:743-756.

17. Nayeem, Kondaiah, Sreekanth K, et al. Ultrasonic investigations of molecular interaction in binary mixtures of cyclohexanone with isomers of butanol. J Appl Chem. 2014;1:1-12.

18. Ayasen Jermaine, Grace Agbizu Cookey. Volumetric behavior of binary mixtures of alkoxyethanols and some selected amines at 298.15 K. J Thermodyn. 2015;1:1-8.

19. Saleh Bagheri, Mshdi Rakhshi. J Iran Chem Res. 2010;3:245-256.

20. Umadevi M, Kesavasamy R, Rathina K, et al. Studies on liquid-liquid interactions of some ternary mixtures by density, viscosity and ultrasonic speed measurements. J Mol Liq. 2016;219:820-828.

21. Chhotaray KP, Shankar J, Gardas RL. Structural and compositional effect on the acoustic and volumetric properties of ammonium based ionic liquids with water and N-methyl-2-pyrrolidone. J Mol Liq. 2016;219:829.

22. Gowrishankar. J Chem Thermodyn. 2016;101:92-102.

23. Chadha C, Singla M, Kumar H. Interionic interactions of glycine, l-alanine, glycylglycine and phenylalanine in aqueous 1-hexyl-3-methylimidazolium chloride ionic liquid solutions at T=(288.15 to 308.15) K: Volumetric, speed of sound and viscometric measurements. J Mol Liq. 2016;218:68-82.

24. Reddy MS, Nayeem MSK. The study of solute-solvent interactions in 1-ethyl-3-methylimidazolium ethylsulfate+2-ethoxyethanol from density, speed of sound and refractive index measurements. J Mol Liq. 2016;218:83-94.

25. Andrzej B. Ultrasonic measurements of aqueous solutions of β-cyclodextrin with alkyl pyridinium bromides. Arch Acoust. 2008;33:413.