Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2015, 7(1):174-183
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Ultrasonic studies of hyberdised drug molecules synthesized from nicotinamide in 70% DMF-Water at 300.15K

Ujjwala D. Chapke[1*], Bhushan P. Meshram[2], Pratibha S. Agrawal[3] and Baliram N. Berad[4]

[1]Post Graduate Teaching Department of Chemistry,RashtrasantTukadojiMaharaj Nagpur University, Nagpur
[2]Department of Chemistry, Hislop College, Nagpur
[3]Department of Chemistry, Laxminarayan Institute of Technology, Nagpur

---

ABSTRACT

The hybrid drugs have been synthesized by the condensation of nicotinamide and acid chlorides of salicylic acid, 5-nitro salicylic acid and ibuprofen as well as salicylaldehyde and vanillin in chloroform medium. The structures of all hyberdised drugs are confirmed on the basis of their spectral data. The ultrasonic velocity (U), viscosity(η) and density (ρ) have been reported for these drug molecules within the concentration range 0.001M – 0.005M drug in 70% DMF-Water at 300K.From thesemeasured datadifferent acoustical parameters, such as adiabatic compressibility (β), relative association (R_A), acoustic impedance (Z), relaxation time (τ) and intermolecular free length (L_f) were computed. The result have been analyzed and interpreted in terms of molecular interactions.

Keywords: Hybrid drugs, Nicotinamide, Ultrasonic Velocity, Density and Viscosity.

INTRODUCTION

Nicotinamide (3-pyridine carboxylic acid amide)commonly known as Niacin or vitamin B3 is a water soluble vitamin, required for cell respiration[1-5]. It helps in release of energy and the metabolism of carbohydrates, fats and proteins, proper circulation and healthy skin, functioning of the nervous system and normal secretion of bile and stomach fluid and so it is a pharmacologically important compound. A deficiency of nicotinamide causes pellagra. Considering that nicotinamide is present in tissues of nearly all living organisms, its complexes with transition metals and biological ligands could play a very important role in oxidation–reduction processes of metabolic pathways, could help the body get rid of toxic and harmful chemicals, and help treat osteoarthritis and rheumatoid arthritis, insulin-dependent diabetes, insomnia, and migraine headaches. People with cancer are more likely to have vitamin B_3 deficiency. It is a reactive moiety of the coenzyme nicotinamideadenin dinucleotide (NAD).On decomposition NAD and NADP give a small amount of nicotinamide[6-10].

Ultrasonic is a versatile non-destructive and feasible technique hence readily available and have wide range of applications in various field like chemistry, physics, engineering, biology, food industry, medicine, dentistry, oceanography, seismology, geophysics, geosciences, agriculture, metallurgy, cleaning bath, textile, cement, paper industry etc.[11-15]. In chemistry, ultrasonic velocity with related acoustical parameters have been extensively used to study molecular interactions in binary, ternary, quaternary liquid mixtures and solute-solvent interactions and

transport properties of alkali halides, hydrocarbons, alcohols, polymers, proteins, amines, amino acids, drugs etc[16-20].

The newly synthesized drug molecules are important organic compounds which have application in the field of medical sciences which developed our interest in the study of their physico-chemical behavior. The growing interest in the study of the thermodynamic properties and intermolecular interactions of drug in various organic compounds solutions is due to the fact that these interactions are the key to understand the structural and characteristicpropertyof drug molecules. The acoustical studies are extensively used to estimate the thermodynamic properties and predict the intermolecular interactions. The sound velocity is one of the physical properties that help in understanding the nature of liquid state. Ultrasonic velocity and viscosity measurement have been widely used in the field of interaction and structural aspect.

To our knowledge no work has been reported on acoustical properties of hybrid drugs of nicotinamide. In our laboratory, we have reported the density, ultrasonic velocity and viscosity of hyberdised drugs namely N-[(2-hydroxyphenyl)carbonyl]pyridine-3-carboxamidehydrochloride (I), N-[(E)-(2-hydroxyphenyl)methylidene]pyridine-3-carboxamide (II), N-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]pyridine-3-carboxamide (III) and N-{2-[4-(2-methylpropyl)phenyl]propanoyl}pyridine-3-carboxamide hydrochloride (IV) within the concentration range 0.001M – 0.005M drug in 70% DMF-Water at 300K. From the density (ρ), viscosity (η) and ultrasonic velocity (U) of solutions, the different acoustical parameters, such as adiabatic compressibility (β), relative association (R_A), acoustic impedance (Z), relaxation time (τ) and intermolecular free length (L_f)have been calculated.

MATERIALS ANDMETHODS

In the present study, thesolutes were used which were synthesized by

1) The condensation of 1.22g nicotinamide (CAS No. 98-92-0, mass fraction purity > 0.990, Merck) with 1.14ml 2-hydroxybenzoyl chloride(acid chlorides of salicylic acid)and 2.14ml 2-[4-(2- methylpropyl)phenyl]propanoyl chloride (chloride of ibuprofen) by shaking in the presence of chloroform medium for about 2hr and 3-4hrs respectively has resulted in the formation of N-[(2-hydroxyphenyl)carbonyl]pyridine-3-carboxamide hydrochloride (I) and N-{2-[4-(2-methylpropyl)phenyl]propanoyl}pyridine-3-carboxamide hydrochloride (IV).

2) The 1.22g of nicotinamide refluxed with 1.06ml salicylaldehyde(CAS No.69-72-7, mass fraction purity > 0.990 , Merck) and 1.52g vanillin(CAS No. 121-33-5, mass fraction purity > 0.990, Merck)in the presence of chloroform medium for about 1.5hrs and 2-3hrs respectively has resulted in the formation of N-[(E)-(2-hydroxyphenyl)methylidene]pyridine-3-carboxamide (II) and N-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene] pyridine-3-carboxamide (III).

All the synthesized solutes were crystallized using suitable solvent and characterized by IR, ^{1}H NMR and Mass Spectra.

N-[(2-hydroxyphenyl)carbonyl]pyridine-3-carboxamide hydrochloride (I):
Yield 63%;mp 134^0-135^{0}C (Chloroform); R_f = 0.625, FT-IR (KBr) cm^{-1}: 3380 (br, OH), 3200 (-NH), 2380 (Ar-CH), 1700-1400 (C=O, C=C, C=N). ^{1}H NMR ($CDCL_3$) δ: 10.367 (s, 1H, OH), 7.504-7.947 (4H, pyridyl), 6.918-7.028 (4H, aromatic), 7.255 (1H, -NH).

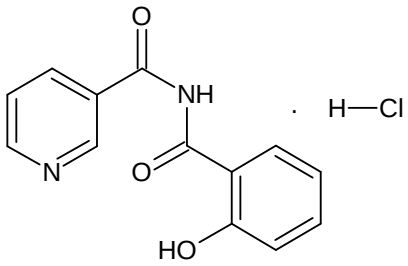

Fig. 1: Str. of N-[(2-hydroxyphenyl)carbonyl]pyridine-3-carboxamide hydrochloride

N-[(E)-(2-hydroxyphenyl)methylidene]pyridine-3-carboxamide (II):
Yield 60%; mp 129^0-130^0C (Ethanol); R_f = 0.732, FT-IR (KBr) cm^{-1}: 3367.71 (br,OH), 3167.12—2729.27 (aromatic ring, str.), 1700-1400 (C=O, C=C, C=N). ^{1}H NMR ($CDCL_3$) δ:9.825 (s, 1H, OH), 8.157-8.773 (4H, pyridyl), 6.164-7.446 (4H, aromatic), 5.868 (1H, CH). MS: m/z (%) = 227.05 [M^+]

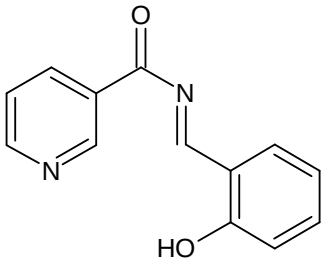

Fig. 2: Str. of N-[(E)-(2-hydroxyphenyl)methylidene]pyridine-3-carboxamide

N-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]pyridine-3-carboxamide (III):
Yield 66%;mp 89^0-90^0C (Benzene); R_f = 0.617, FT-IR (KBr) cm^{-1}: 3400 (br, OH), 2358.93 (Ar-CH), 1060 (C-O-C), 1700-1400 (C=O, C=C, C-N). ^{1}H NMR ($CDCL_3$) δ = 9.824 (s, 1H, OH), 7.027-7.434 (3H, aromatic), 6.373 (1H, CH), 3.966 (3H, -OCH_3). MS: m/z (%) = 256 [M^+]

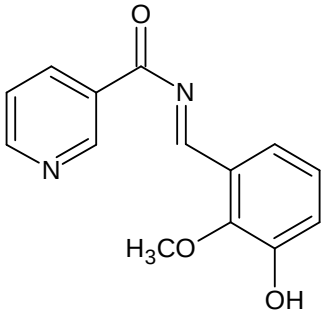

Fig. 3:Str. of N-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]pyridine-3-carboxamide

N-{2-[4-(2-methylpropyl)phenyl]propanoyl}pyridine-3-carboxamide hydrochloride (IV):
Yield 69%;mp 92^0-93^0C (Ethanol:Water 1:1); R_f = 0.534, FT-IR (KBr) cm^{-1}: 3180 (-NH),), 1700-1400 (C=O, C=C, C=N) . ^{1}H NMR ($CDCL_3$) δ = 7.402-9.038 (4H, pyridyl), 7.088-7.256 (4H, aromatic), 6.604 (1H, NH), 3.696-3.766 (4H, Ar-CH), 2.432-2.455 (2H, Ar-CH_2), 1.506-1.885 (7H, aliphatic). MS: m/z (%) = 347.85 [M^+]

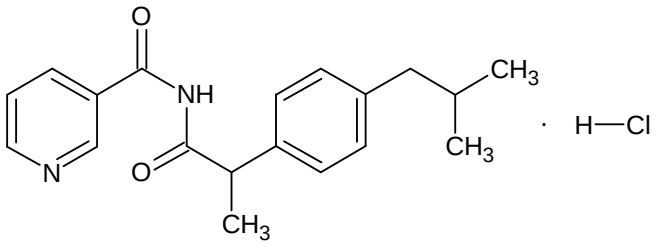

Fig. 4:Str. of N-{2-[4-(2-methylpropyl)phenyl]propanoyl}pyridine-3-carboxamide hydrochloride

Before use, these compounds were dried in vacuum oven and were kept in vacuum desiccator over anhydrous fused calcium chloride for more than two days. It was then used for present investigation. N, N-DMF used was of Analytical grade. All the mixtures were prepared in freshly prepared, 70% DMF-Water on a molarity basis by using one pan balance Dhona 200D with an accuracy ±0.001gm.Theviscometricmeasurement were made by Ostwald's Viscometer with an accuracy 0.001Ns m^{-2}. The density of the solution was measured at 300.15 K by using Digital Densitimeter (Model-DDM 2910, Rudolph Research analytical, USA.). The accuracy in density measurement was found to be ±0.00001gm. Ultrasonic sound velocity measurement were made by variable path single crystal

interferometer (Mittal Enterprises, Model F-81S) at 2MHz with accuracy of 0.03%. The temperature was maintained with an accuracy of 0.1^0C. Electronically digital operated constant temperature bath (Plasto Craft Industries) for low temperature bath model, LTB-10 was used to circulate water through the double walled measuring cell made up of steel containing the experimental solution at the desired temperature with accuracy in temperature measurement -10^0C to 90^0C.

Using the measured data, the acoustical parameters such as adiabatic compressibility (β), relative association (R_A), acoustic impedance (Z), relaxation time (τ) and intermolecular free length (L_f) have been calculated by using following expression and represent in Table.1.

$\beta = 1/U^2\rho$ …(1)

$R_A = (\rho / \rho o)\,(Uo/U)^{1/3}$ ...(2)

$Z = U.\rho$ …(3)

$\tau = 4\eta / 3\rho U^2$ …(4)

$Lf = K(\beta)^{1/2}$ ...(5)

where K is a Jacobson Constant.

RESULTS AND DISCUSSION

The variation density, viscosity, ultrasonic velocity, adiabatic compressibility, acoustic impedance, relative association, relaxation time and intermolecular free length with concentration in figures 5-12.

Table 1:Density (ρ), viscosity (η), ultrasonic velocity (U), adiabatic compressibility (β), acoustic impedance (Z), relative association (R_A), relaxation time (τ) and intermolecular free length (L_f) of solutes in 70% DMF-Water at 300.15K

Conc. (M)	ρ g.cm^{-3}	η. 10^3 poise	U 10^{-5}cm.s^{-1}	β. 10^{-10} (cm^{2}dyn^{-1})	Z. 10^{-5} g.cm^{-2}	R_A	L_f Å	τ. 10^{-6} s
N-[(2-hydroxyphenyl)carbonyl]pyridine-3-carboxamide hydrochloride (I)								
0.001	0.987329	16.15294	1.6524	3.709436	1.631462	1.000195	1.256473	7.989105
0.002	0.987605	16.34424	1.6568	3.688729	1.636263	0.999588	1.252961	8.038597
0.003	0.987998	16.63105	1.6598	3.673943	1.639879	0.999384	1.250447	8.146872
0.004	0.988142	17.00726	1.6641	3.654448	1.644367	0.998667	1.247125	8.286954
Conc. (M)	**ρ g.cm^{-3}**	**η. 10^3 poise**	**U 10^{-5}cm.s^{-1}**	**β. 10^{-10} (cm^{2}dyn^{-1})**	**Z. 10^{-5} g.cm^{-2}**	**R_A**	**L_f Å**	**τ. 10^{-6} s**
0.005	0.988339	17.29105	1.6687	3.633604	1.649241	0.997948	1.243564	8.377175
N-[(E)-(2-hydroxyphenyl)methylidene]pyridine-3-carboxamide (II)								
0.001	0.986688	13.99635	1.6492	3.726262	1.627246	1.000192	1.259319	6.953877
0.002	0.987181	14.28341	1.6517	3.713135	1.630527	1.000187	1.257099	7.071499
0.003	0.987276	14.47151	1.6546	3.699777	1.633546	0.999698	1.254836	7.138847
0.004	0.987533	14.84883	1.6597	3.676117	1.639008	0.998933	1.250817	7.278139
0.005	0.987773	15.22609	1.6631	3.660211	1.642765	0.998494	1.248108	7.430761
N-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]pyridine-3-carboxamide (III)								
0.001	0.98696	15.02689	1.6512	3.716216	1.629669	1.000064	1.257621	7.445758
0.002	0.987351	15.40633	1.6537	3.703521	1.632783	0.999956	1.255471	7.607691
0.003	0.987692	15.59845	1.6572	3.686623	1.636803	0.999596	1.252603	7.667416
0.004	0.987746	15.87955	1.6617	3.66648	1.641338	0.998748	1.249177	7.762937
0.005	0.987883	16.162	1.6657	3.648388	1.645516	0.998086	1.246091	7.862034
N-{2-[4-(2-methylpropyl)phenyl]propanoyl}pyridine-3-carboxamide hydrochloride(IV)								
0.001	0.988076	18.31428	1.6561	3.690088	1.636352	1.000206	1.253192	9.010842
0.002	0.988441	18.50801	1.6611	3.66655	1.6419	0.999571	1.249189	9.048072
0.003	0.988833	18.8894	1.6652	3.64707	1.646605	0.999146	1.245866	9.185461
0.004	0.988972	19.07909	1.6687	3.631278	1.650297	0.998587	1.243166	9.237534
0.005	0.989154	19.36323	1.6734	3.610244	1.65525	0.997835	1.23956	9.320801

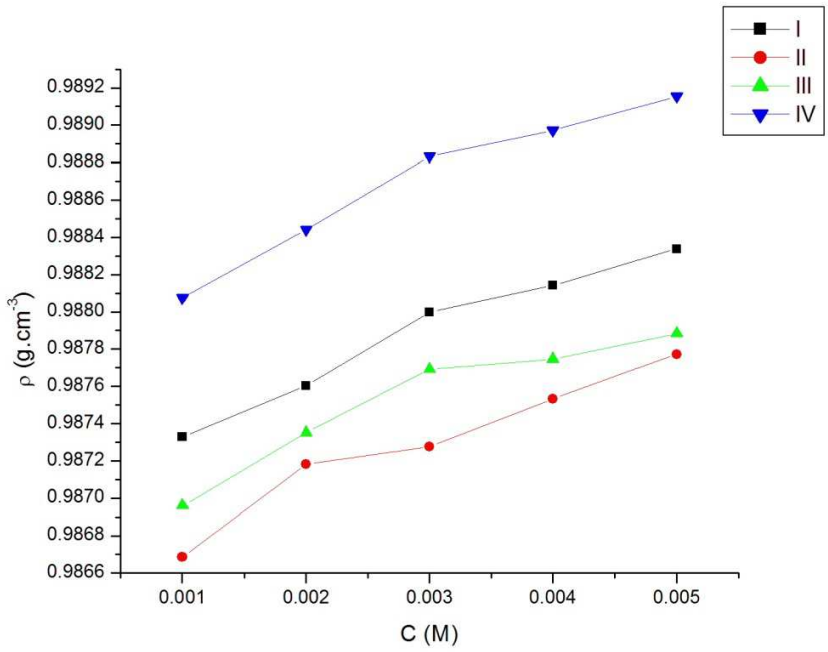

Figure 5: Variation of Density with Concentration

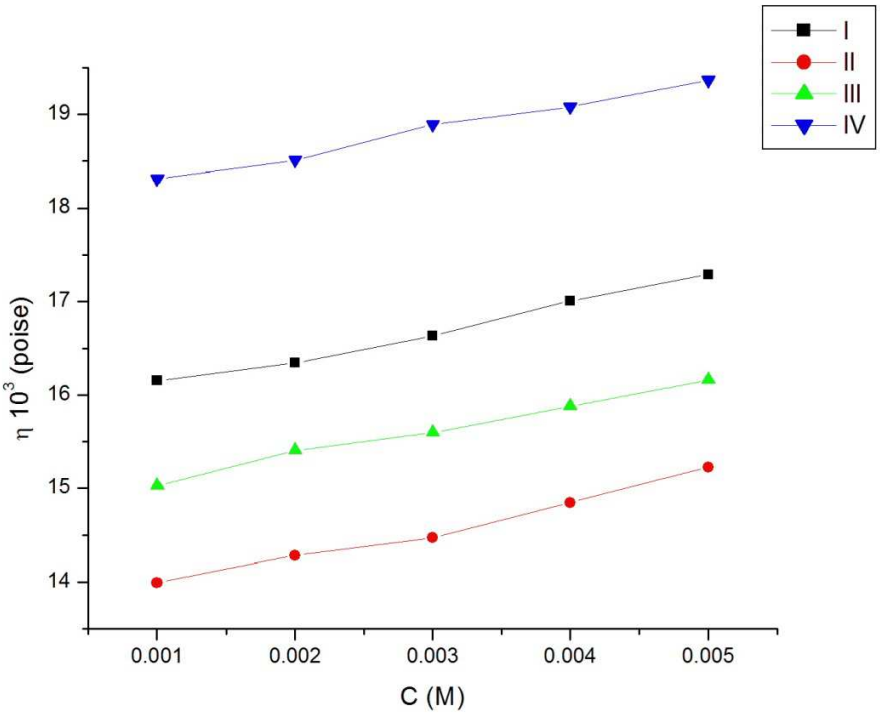

Figure 6: Variation of Viscosity with Concentration

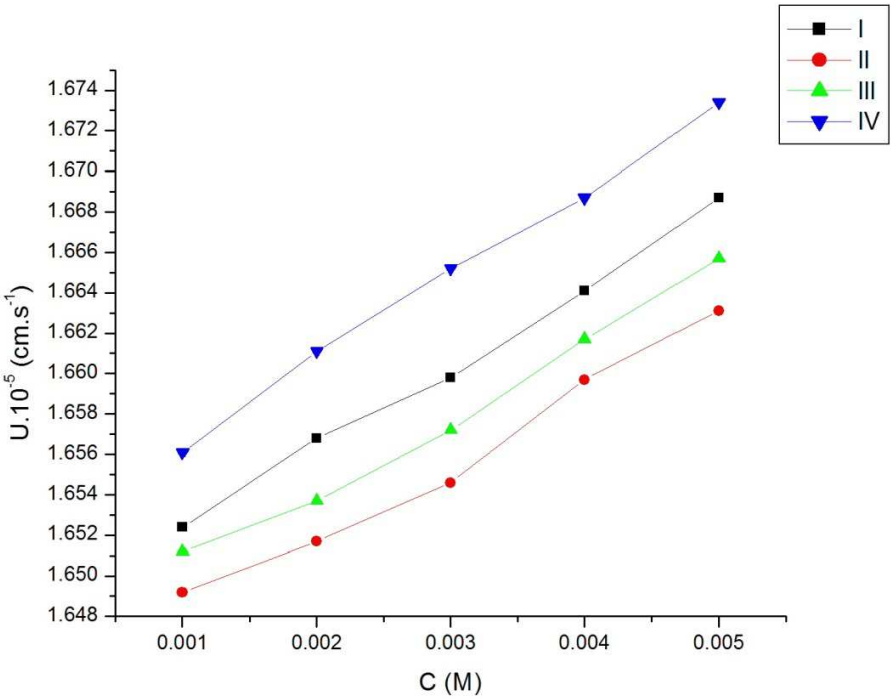

Figure 7: Variation of Ultrasonic Velocity with Concentration

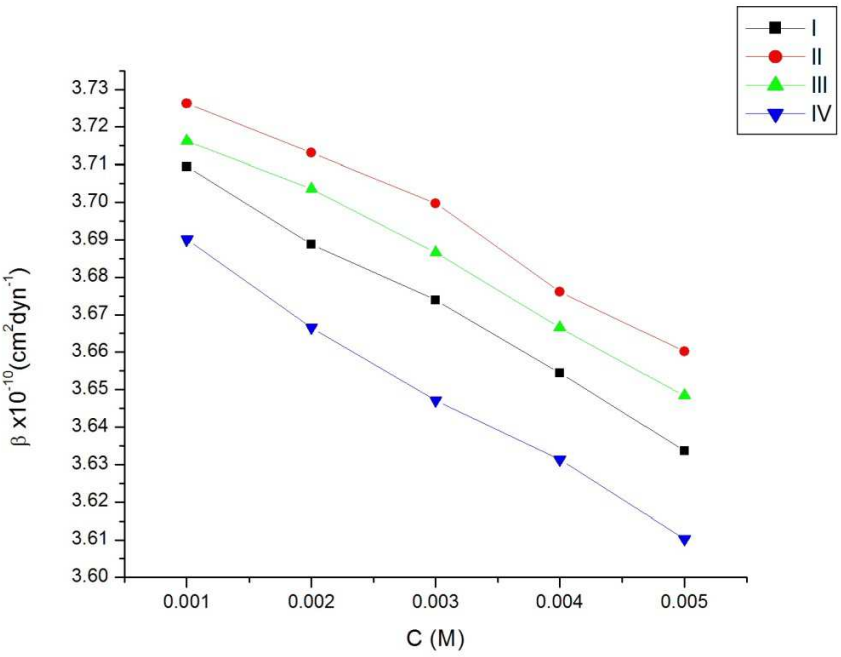

Figure 8: Variation of Adiabatic Compressibility with Concentration

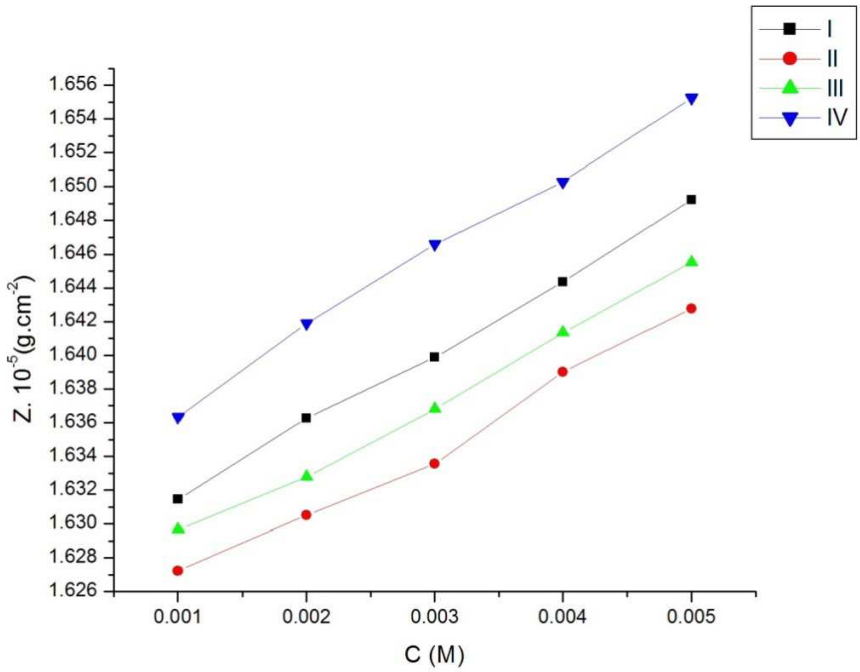

Figure 9: Variation of Acoustic Impedance with Concentration

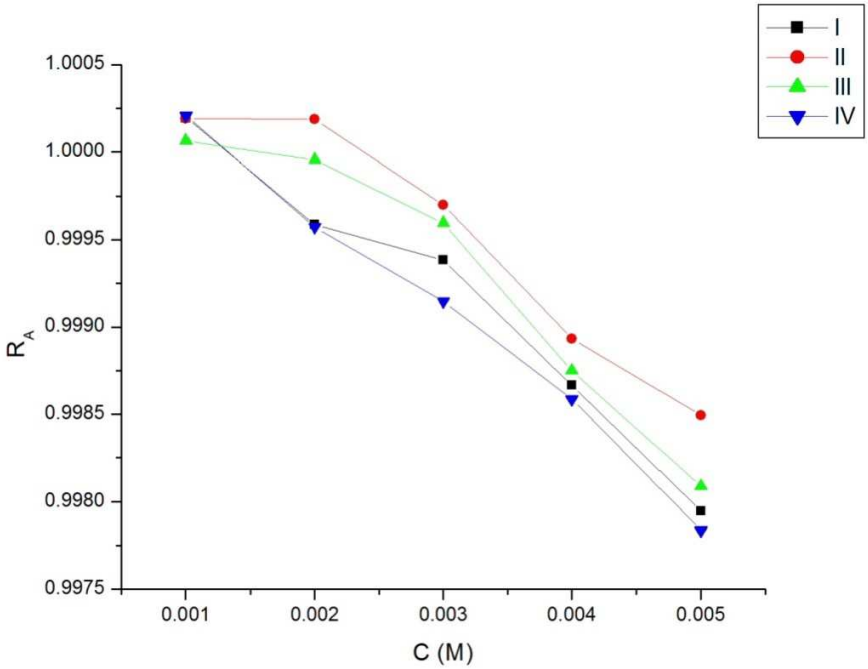

Figure 10: Variation of Relative Association with Concentration

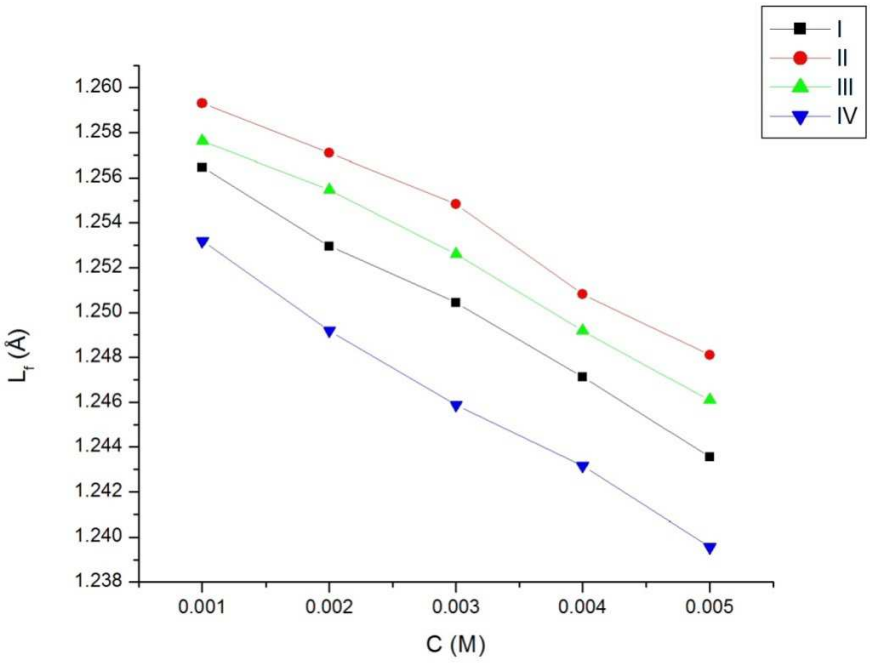

Figure 11: Variation of Intermolecular Free Length with Concentration

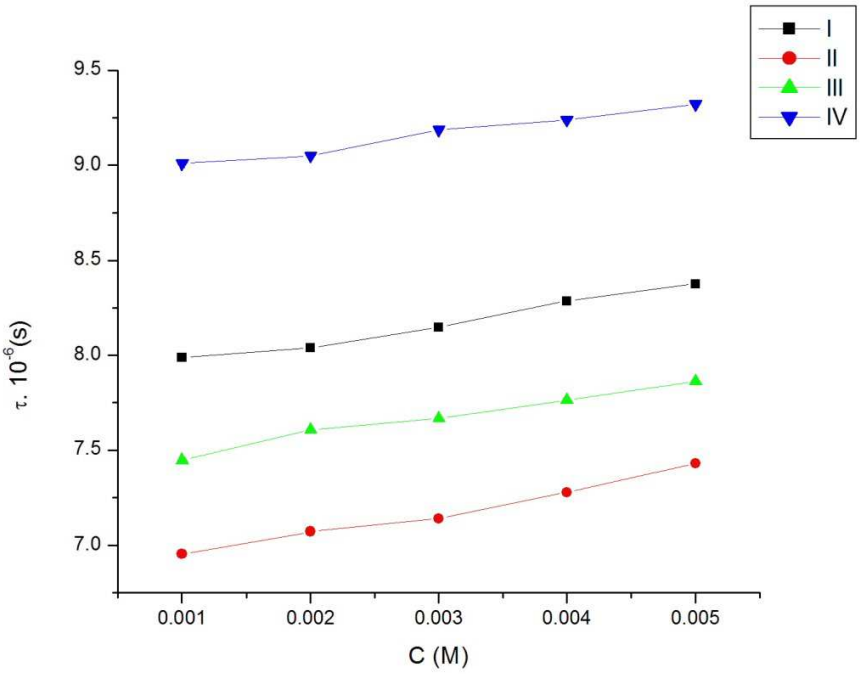

Figure 12: Variation of Relaxation Time with Concentration

Figure 5 represents the variation of density (ρ) of solution as a function of molarity of solution for 70% DMF-Water of different hyberdised drugs at 300.15K. It can be observed from this figure that density of solution increases continuously with the increase in molarity of solution for all the systems of hyberdised drugs within the concentration range studied. Similar increase in density has also been reported in some glycol ethers[21]. Figure 6 represents the variation of viscosity with concentration. Variation in viscosity indicates the presence of

intermolecular interactions between the hyberdised drug molecules and solvent molecules. Viscosity of solution increases with the increase in concentration of solution. The increasing concentration of hyberdised drugs supports non rupturing of drug molecules and hence there is increase in viscosity.Similar increase in viscosity has also been reported by Sh. Baluja et.al in some drugs in methanol and DMF at 308.15K[22]. Figure 7 represents the variation of ultrasonic velocity (U) with concentration. It can be observed from this figure that velocity of solution increases with the increase in molarity of solution for all the systems. As density of solution increases the number of particles in a given region increases and this leads to quick transfer of sound energy and thus velocity also increases. This suggest the disruption of solvent structure with the addition of hyberdised drug. Similar increase in velocity has been found in case of glycine, L-alanine and β-alanine[23].

The ultrasonic velocity (U) depends on intermolecular free length (L_f). The velocity increases with decrease in L_f or vice versa. Table 1 show L_f decreases continuously which suggests that there is strong interaction between solvent and drug molecules. Figure 11 represents the variation of intermolecular free length (L_f) with concentration. Similar decrease in intermolecular free length has also been reported in Lamivudine: β-Cyclodextrin and polymer inclusion complexes[24]. Figure 8 represents the variation of adiabatic compressibility (β) with concentration. It can be depicted that adiabatic compressibility values decrease with the increase of solute concentration for all the drug solutions. The decrease of adiabatic compressibility with increasing concentration might be due to aggregation of solvent molecules around solute molecules indicating thereby the presence of solvent-solute interactions in all these systems. Similar decrease in adiabatic compressibilty has also been reported in aqueous solution of glycine and DL-alanine[25].

Figure 9 represents the variation of acoustic impedance with concentration. It can be observed that acoustic impedance increases with increase in solute concentration. Theoretical requirement of Z is density and velocity which are increased with increase of concentration of solute in solution. The increase of Z with solute concentration can be attributed to the effective solvent-solute interactions. Similar increase in acoustic impedance has also been reported in methionine in aqueous electrolytic solutions[26]. Figure 10 represents the variation of relative association with concentration. The relative association depends on either the breaking up of the solvent molecules on addition of solute to it or the salvation of ions that are present. The relative association value shows increase with the increase of solute concentration. This increase is due to the solute-solvent interaction dominates over solvent-solvent interactions. Similar increase in relative association has also been reported in L-Threonine in aqueous and in mixed aqueous solution[27].Figure 12 represents the variation of relaxation time with concentration. It can be observed that relaxation time increases with increase in solute concentration which indicates the structure-making tendency of compound. Similar increase in relaxation time has been reported in Epoxy Oleate of 9, 9'-Bis(4-hydroxyphenyl) Anthrone-10 solutions[28]. This parameters is the cumulative effect of ultrasonic velocity, density and viscosity of solution under the given sets of conditions.

Acknowledgement
One of the author (UDC) is thankful to UGC for the award of JRF.Authors are thankful to The Head, Dept. of Chemistry, RTMNU, The Head, Dept. of Chemistry, Hislop College, Nagpur For providing laboratory facilities and also to the Q.C. Executive, Relief Lab, MIDC, Kalmeshwar for providing necessary drugs samples.

REFERENCES

[1] J.W. Park, Y.H. Paik,*Bull. Korean Chem. Soc.*,**1985**,6, 23.
[2] P.A. Thibodeau, B. Paquette,*Free Radic. Biol. Med.*, **1999**, 27, 1367.
[3] S. Mazzini, R. Monderelli, E. Ragg, L. Scaglioni,*J. Chem. Soc. Perk. T.*, **1995**, 2, 285.
[4] O. Carugo, P. Argos,*Proteins*, **1997**,28, 10.
[5] N. Shiomi, S. Hori,*Soil Sci. Plant Nutr.*,**1973**, 19(2), 133.
[6] M. Chatzopoulou, E. Kotsampasakou, V.J. Demopoulos,*Syn. Communications*, **2013**, 43, 2949.
[7] H.L. Gensler,*Nutrition & Cancer*, **1997**, 29(2), 157.
[8] H. Shekhar, V. Kant,*Mol. Cryst. Liq. Cryst.*, **2013**, 577, 103.
[9] W. Kamimura, T. Ooya, N. Yui,*J. Biomater. Sci. Polymer Edn.*,**2000**, 11(7), 747.
[10] E.J. Amigues, E. Armstrong, M. Dvorakova, M.E. Migaud, M. Huang; *Nucleosides, Nucleotides & Nucleic Acids*, **2009**, 28, 238.
[11] R. Gupta, M. Singh,*J. Chem. Sci.*, **2005**, 117, 275.
[12] S. Thirumaran, J.E. Jayakumar, *Ind. J. Pure & Appl. Phys.*,**2009**, 47, 265.

[13] A.N. Sonar, N.S. Pawar, *Rasayan J. Chem.*,**2010**, 3(1), 38.
[14] K. Rajagopal, S.S. Jayabalakrishnan, *Int. J.Thermophys.*,**2010**, 31, 2225.
[15] S.K. Thakur, S. Chauhan, *J. Chem. Pharm. Res.*,**2011**, 3(2), 657.
[16] S. Anuradha, S. Prema, K. Rajagopal, *J. Pure Appl.Ultrasonics*,**2005**, 27, 49.
[17] G. Arul, L. Palaniappan, *Ind. J. Pure & Appl. Phys.*,**2005**, 43, 755.
[18] S.S.B. Ambomase, S. Tripathy, M. Tripathy, U.N. Dash, *E-J. Chem.*,**2011**, 8(1), 63.
[19] S.K. Thakur, S. Chauhan, *Pel. Res. Lib.*, **2011**, 2(2), 208.
[20] S.S. Aswale, S.R. Aswale, R.S. Hajare, D.T. Tayade,*Golden Res. Thoughts*,**2011**, 1, 1.
[21] S.S. Dhondge, C.P. Pandhurnekar, S. Sheikh,D.W. Deshmukh, *J. Chem. Thermodynamics*,**2011**, 43, 1961.
[22] S. Baluja, A. Solanki, N. Kachhadia, *Rus. J.Phy. Chem. A*,**2007**, 81(5), 742.
[23] S.S. Dhondge, R.L. Paliwal, N.S. Bhave, C.P. Pandhurnekar, *J. Chem. Thermodynamics*,**2012**, 45, 114.
[24] A.P.Selvam, D. Geetha, *Pakistan J. Bio. Sci.*,**2008**, 11(4), 656.
[25] R.K. Wadi, P. Ramasami, *J. Chem. Soc., Faraday Trans.*, **1997**, 93(2), 243 .
[26] T. Sumathi, M. Varalakshmi, *Rasayan J. Chem.*,**2010**, 3(3), 550.
[27] Anjana, R.K. Bamezai, *Sch. Res. Lib.*, **2011**, 3(1), 370.
[28] B.D. Bhuva, P.H. Parsania,*J. Sol. Chem.*, **2011**, 40, 719.