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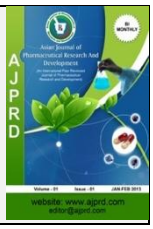

Open Access Research Article

Acoustical Studies& Molecular Interactions of Antiepileptic Drug Levitiracetam in DMSO-Water Mixtures at Different Temperatures

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A B S T R A C T

The densities and speeds of sound have been measured of ternary mixtures of Levitiracetam drug in aqueous dimethyl sulfoxide (DMSO) mixtures at 25% interval of the solvent at 303K,308 K,313 K and frequency 2MHz .The experimental data has been used to determine acoustic parameters like intermolecular free length (L_f),Specific acoustic impedence (z) etc.The changes in these properties with composition and temperature are used to interpret the nature of solute-solvent, solute-solute interactions in the system.

Keywords- Acoustical Properties, Antiepileptic, DMSO, Molecular interactions, Ultrasonic velocity.

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INTRODUCTION

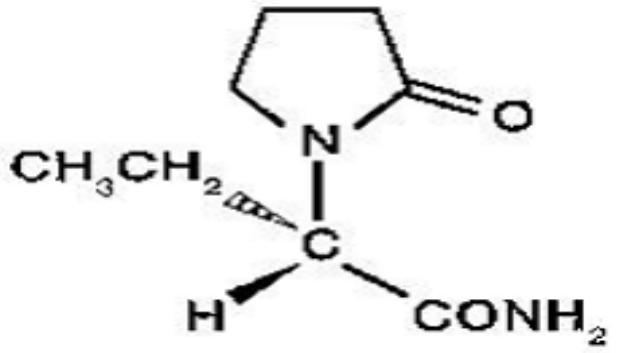
For industrial advancement, the development in thermophysical studies is going parallel. It contributes to the designing and output of the processes. Since the experimental determination of the values of thermophysical properties leads to quick and reliable results and economic establishment of innovative models that facilitate the determination of the points necessary for the industry. The experimental determination of thermophysical properties also gives the important information about the intermolecular interaction and molecular level structure of different solvent systems. This is also helpful to understand the macroscopic properties of fluids[1-3].

The elucidation of fluid structure has to be done by combining the experimental result and theoretical models due to complex intermolecular interaction[4] .Due to the differences in molecular size, shape and structure various solvent mixtures exhibit considerable deviations from ideal behavior as far as the thermodynamic properties are concerned[5].Many researchers studied the volumetric and acoustical properties by measuring density and ultrasonic velocity of electrolytic as well as nonelectrolytic solutions[6,7],various aqueous and non aqueous systems [8,9]at different temperatures, different concentrations of solute and in different percentage of organic solvents which was proved useful in elucidating solute-solute and solute-solvent interactions.

Dimethyl sulfoxide (DMSO) is colorless, stable hygroscopic organic liquid having exceptional solvent properties. It is a polar aprotic solvent miscible with water, lipids [10].and organic solvents and holds the ability to dissolve an enormous catalogue of polar and non polar small molecules[11] and an extraordinary variety of inorganic and organic chemicals. It's cryoprotective effects on biological systems[12-14] this polyfunctional molecule with highly polar S=O group and two group and two hydrophobic CH group has a potential for wide applications[15,16]

The drug used in present study is Levitiracetam an antiepileptic drug. Pyrrolidine anticonvulsant levetiracetam drug is used in the treatment of epilepsy.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidineacetamide.It has the following structural formula.



The study found each of the nitrogen atoms of the free base to be a proton donor in intermolecular hydrogenbonds with the oxygen atoms of the sulfate anion. With the presence of the hydroxyl group and water being the solvent interesting results regarding molecular interactions are expected between these component molecules in the present ternary system.

By detailed study of literature and in the view of the pharmaceutical and medical significance of Levitiracetam, some extensive studies regarding their ultrasonic and volumetric behavior of present ternary system, are planned in this work to examine the intermolecular interactions between the unlike molecules by investigating the acoustic, volumetric and spectroscopic properties.

EXPERIMENTAL

Materials:- All the chemicals used were of AR grade. DMSO purchased from Merck (minimum assay by volume 99.9%), Distilled water was used in present work. The purity of the chemicals was further assessed by comparison of the experimental density values with literature densities wherever available. All the liquid mixtures were prepared by volume and were stored in glass stoppered flasks to avoid contamination and evaporation. All the glassware was cleaned and dried before and after the use.

Methods:-Density measurements were performed by pycnometric method. The thermal equilibrium was attained by keeping the experimental liquids in the constant temperature water bath for 15 min. The reported values are the average values obtained after repeating the density measurements at least three times for each measurement. The accuracy of pycnometer was 0.0003 g $cm^{-3.}$ Weighing was done on single pan electronic balance (±0.001 g). Ultrasonic velocity (u) measurements in the liquid mixtures were done using commercial ultrasonic interferometer (Model- No.84S) Mittal Enterprises, New Delhi. All the measurements of densities and speeds of sound of the ternary mixtures were determined at 303K, 308K and 313K.

THEORY

Various physical parameters [17-19] isentropic compressibility [k_s], intermolecular free length [L_f], relative association[R_A] and acoustic impedance [Z]for ternary mixtures of Levitiracetam with 25%, 50% and 75% DMSO-Water were calculated from ultrasound velocities (u) and densities (ρ) by using following relations:

Isentropic compressibility: $k_s=1/\rho u^2$(1)

Intermolecular free length: $L_f=K(k_s)1/2$ (2) Where K is temperature dependent constant which is known as Jacobson's constant,

K= (93.875+0.375T) $x10^{-8}$, taken from the work of Thanuja et al[20]

Specific acoustic impedance: $Z= \rho u$ (3)

Relative association: $RA= \rho/\rho_0 \times u_0/u$ 1/3 (4)

RESULTS AND DISCUSSION

The experimental values of density (ρ), ultrasonic velocity (u) and refractive index (n) along with derived acoustical parameters such as isentropic compressibility (k_s), intermolecular free length (L_f), specific acoustic impedance (Z), and relative association (R_A) have been listed in Tables 1, 2 and 3 for various mole fractions of DMSO. The values of ρ and u of solution increase with the drug concentration and gradually decrease with increase in temperature for all the three solvent compositions. The variation of ρ and u (Fig.1 and Fig.2) with concentration and temperature indicates increase in molecular interaction with increasing concentration of drug. Increasing thermal energy causes the weakening of the molecular forces which tends to decrease the ultrasonic velocity [2, 21]. The increasing values of density and ultrasonic velocity with the solute concentration show that there is an effective interaction between solute and solvent molecules and greater association. A noticeable rise in sound velocity values has been observed for 50% DMSO-Water solvent system, which suggest maximum solute-solvent interaction at equal percentage of solvent and cosolvent. The isentropic compressibility (k_s) and intermolecular free length (L_f) both have an inverse relationship with ultrasonic velocity ((1) and (2)). This is supported by the values of u and k_s in Table-1, 2 and 3, where k_s decreases gradually with increase in concentration and increases with increase in temperature. This trend is reverse to that of ultrasonic velocity (Fig.3) The decrease in values of k_s suggests significant association of solute and solvent molecules that results in close packing and clinging of molecules. This makes the solution less compressible and hence values of adiabatic compressibility decrease. L_f depends on k_s and the

values of L_f show similar trend to that of k_s and inverse to that of u. L_f decreases with increasing concentration and increases with rise in temperature. This prevails that specific strong intermolecular interaction exists between solute and solvent molecules and indicates structure promoting behavior of Levitiracetam molecule. There is an increase in the Z values with the increase in concentration of the drug which indicates strong ion-solvent interactions. The values decrease with increase in temperature thus showing similar behavior to that of u. The values of R_A for the studied solvent mixtures, suggest that R_A increases with an increase of drug concentration. However, there is no appreciable variation in the R_A values with rise in temperature. The values of n (Fig. 4) increase with concentration and decrease with temperature for every system similar to those of ρ and u. However, the value of n increases with increase in the volume percentage of DMSO.

Table 1: Experimental density, ultrasonic velocity and derived isentropic compressibility, specific acoustic impedance, relative association, intermolecular free length and refractive index of Levitiracetam in 25 % DMSO-Water at different temperatures.

c	ρ	U	ks	Z	RA	Lf	N
303 K							
0.0000	1.03640	1747.22	3.6595	1.806	1.00000	0.4017	1.3850
0.0098	1.03848	1749.55	3.6425	1.810	1.00156	0.4007	1.3860
0.0195	1.04051	1751.74	3.6259	1.813	1.00307	0.3996	1.3870
0.0293	1.04256	1754.89	3.6095	1.817	1.00459	0.3987	1.3878
0.0391	1.04456	1757.43	3.5929	1.823	1.00604	0.3976	1.3885
0.0487	1.04563	1759.55	3.5765	1.827	1.00759	0.3970	1.3892
308K							
0.0000	1.03314	1745.32	3.3965	1.795	1.00000	0.4061	1.3845
0.0098	1.03514	1747.17	3.2700	1.800	1.00025	0.4052	1.3851
0.0195	1.03711	1749.02	3.2545	1.811	1.00055	0.4045	1.3859
0.0294	1.03911	1751.83	3.2365	1.813	1.00075	0.4036	1.3868
0.0392	1.04111	1753.46	3.2120	1.815	1.00110	0.4030	1.3876
0.0489	1.04313	1755.43	3.1725	1.830	1.00149	0.4020	1.3881
313 K							
0.0000	1.03229	1730.31	3.7380	1.780	1.00000	0.4135	1.3820
0.0098	1.03420	1732.54	3.7211	1.786	1.00151	0.4125	1.3835
0.0195	1.03605	1733.42	3.7164	1.792	1.00296	0.4115	1.3841
0.0293	1.03797	1735.45	3.7056	1.798	1.00454	0.4108	1.3849
0.0391	1.03979	1737.55	3.6854	1.801	1.00596	0.4100	1.3857
0.0490	1.04168	1739.31	3.6711	1.804	1.00703	0.3991	1.3861

Footnote: ρ= $g.cm^{-3}$, u= $m.s^{-1}$, k_s = × $10^{-10}m^{-2}N^{-1}$, Z=× $10^{6}kgm^{-2}s^{-1}$, L_f= Å

Table 2: Experimental density, ultrasonic velocity and derived isentropic compressibility, specific acoustic impedance, relative association, intermolecular free length and refractive index of Levitiracetam in 50%DMSO-Water at different temperatures

c	*ρ*	*u*	k_s	Z	R_A	L_f	*N*
303 K							
0.0000	1.06735	1790.55	3.2532	1.908	1.00000	0.3850	1.4165
0.0095	1.06990	1800.09	3.2334	1.817	1.00020	0.3831	1.4175
0.0199	1.07061	1804.65	3.2165	1.825	1.00059	0.3815	1.4185
0.0280	1.07425	1811.12	3.1775	1.835	1.00086	0.3800	1.4195
0.0379	1.07595	1817.45	3.1595	1.842	1.00125	0.3785	1.4105
0.0470	1.07559	1821.79	3.1351	1.855	1.00171	0.3769	1.4119
308K							

0.0000	1.06261	1780.51	3.2865	1.798	1.00000	0.3901	1.4045
0.0095	1.06410	1795.05	3.2695	1.803	1.00026	0.3885	1.4065
0.0190	1.06559	1798.60	3.2445	1.808	1.00058	0.3880	1.4080
0.0294	1.06710	1800.10	3.2160	1.811	1.00081	0.3850	1.4085
0.0392	1.06857	1811.43	3.1915	1.815	1.00112	0.3845	1.4090
0.0487	1.07113	1818.75	3.1665	1.819	1.00150	0.3840	1.4108
313 K							
0.0000	1.06150	1774.50	3.3485	1771	1.00000	0.3870	1.4045
0.0099	1.06130	1787.61	3.3305	1.782	1.00106	0.3860	1.4061
0.0196	1.06320	1780.10	3.3108	1.787	1.00215	0.3855	1.4075
0.0290	1.06512	1784.40	3.2950	1.799	1.00330	0.3840	1.4080
0.0385	1.06700	1787.51	3.2735	1.801	1.00441	0.3825	1.4085
0.0490	1.06882	1790.87	3.2650	1.805	1.00551	0.3815	1.4100

Footnote: ρ= g.cm^{-3}, u= m.s^{-1}, k_s = × 10^{-10}m^{-2}N^{-1}, Z=× 10^{6}kgm^{-2}s^{-1}, L_f= Å

Table 3: Experimental density, ultrasonic velocity and derived isentropic compressibility, specific acoustic impedance, relative association, intermolecular free length and refractive index of Levitiracetamin 75%DMSO- Water at different temperatures

c	*ρ*	*u*	k_s	*Z*	R_A	L_f	*N*
303 K							
0.0000	1.08525	1665.80	3.3021	1.811	1.00000	0.3770	1.4370
0.0094	1.08735	1670.70	3.2760	1.822	1.00095	0.3750	1.4376
0.0189	1.09152	1672.10	3.2530	1.831	1.00205	0.3740	1.4380
0.0275	1.09365	1680.60	3.2190	1.839	1.00315	0.3725	1.4385
0.0375	1.09582	1685.80	3.2065	1.845	1.00425	0.3715	1.4395
0.0467	1.09700	1690.30	3.1835	1.847	1.00535	0.3702	1.4400
308K							
0.0000	1.08170	1655.00	3.3605	1.790	1.00000	0.3850	1.4355
0.0095	1.08370	1660.11	3.3430	1.801	1.00070	0.3825	1.4360
0.0190	1.08570	1655.45	3.3060	1.805	1.00155	0.3810	1.4365
0.0276	1.08670	1670.80	3.2885	1.815	1.00255	0.3790	1.4370
0.0377	1.08975	1675.75	3.2635	1.825	1.00315	0.3780	1.4372
0.0469	1.09075	1680.75	3.2380	1.835	1.00400	0.3765	1.4380
313 K							
0.0000	1.07654	1635.54	3.4560	1.765	1.00000	0.3930	1.4350
0.0095	1.07883	1640.40	3.4240	1.775	1.00101	0.3915	1.4351
0.0193	1.08230	1645.90	3.3935	1.784	1.00210	0.3890	1.4355
0.0277	1.08375	1655.40	3.3595	1.795	1.00305	0.3870	1.4365
0.0378	1.08520	1660.20	3.3280	1.805	1.00415	0.3850	1.4367
0.0470	1.08865	1665.55	3.2960	1.815	1.00515	0.3835	1.4375

Footnote: ρ= g.cm^{-3}, u= m.s^{-1}, k_s = × 10^{-10}m^{-2}N^{-1}, Z=× 10^{6}kgm^{-2}s^{-1}, L_f= Å

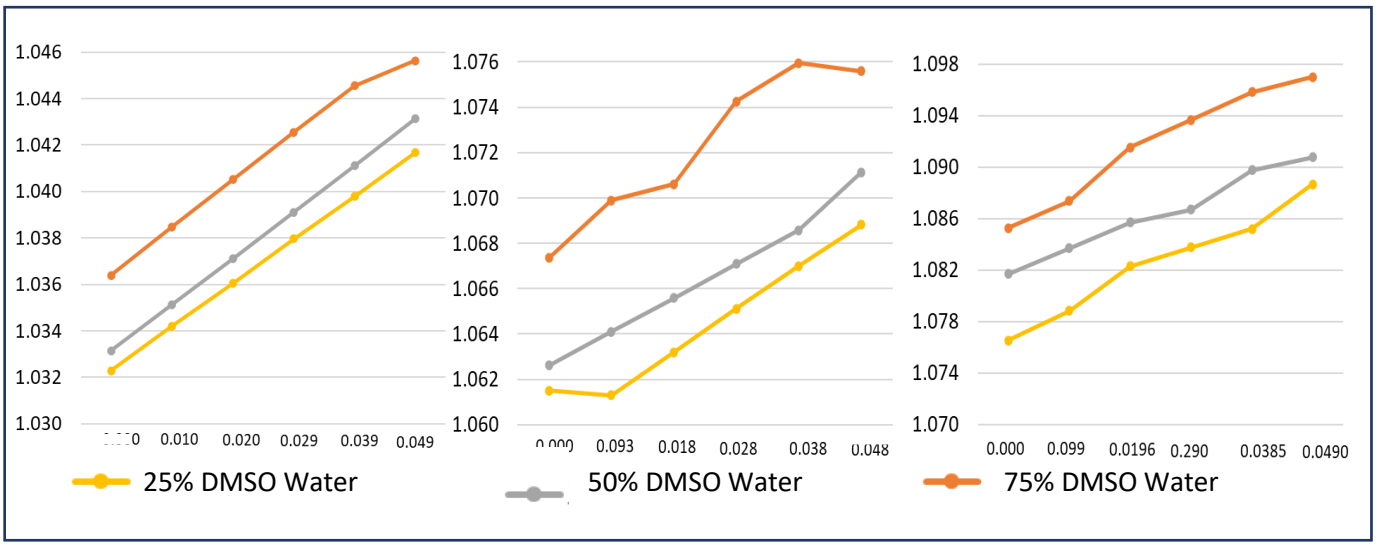


Figure 1: Variation in densityof Levitiracetam in 25%,50% and 70% DMSO -water mixture at different temperatures.

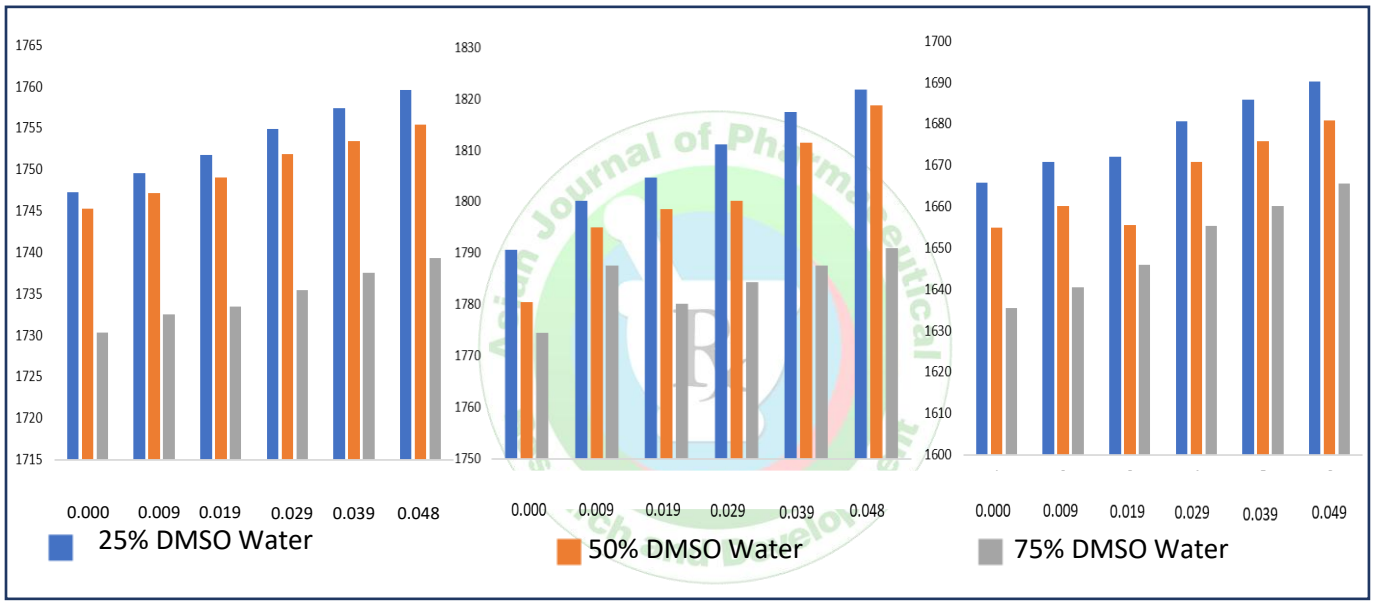


Figure 2 : Variation in Ultrasonic velocity in Levitiracetam in 25 % , 50% and 75 % DMSO -water mixtures at different temperatures.

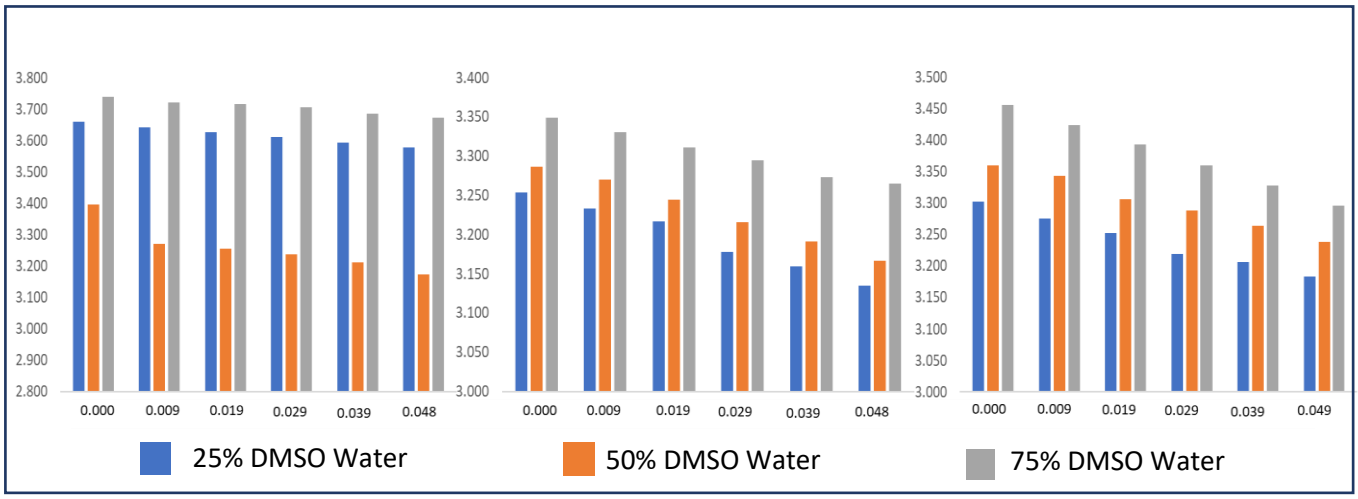


Figure 3: Variation in isentropic compressibility of Levitiracetam in 25% ,50% and 75% DMSO-water mixtures at different temperatures.

CONCLUSION

The drug molecules occupy the available free space upon addition in the medium and hence the density increases with increase in drug concentration. Increase in ultrasonic velocity with concentration supports the structure making property of the drugs and strong interactions between solute components. The addition of the drug to water or the aqueous solution of co-solutes makes the overall system compact and this structural framework makes the entire system less compressible, which is why the adiabatic compressibility decreases with increasing concentration. This suggests the strong solvent–solute interaction. The present study of aqueous DMSO mixtures of Levitiracetam in different composition of solvent systems at different temperatures, gives us a satisfactory understanding about the specific behavior of acoustical parameters that reflect remarkable drug-solvent interactions in studied drug solutions.

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REFERENCES

1. Marcus Y., Solvent mixtures: properties and selective salvation (Marcel Dekker: New York (NY); 2002
2. Awasthi .A, Awasthi.A, Intermolecular interactions in formamide + 2-alkoxyethanols: viscometric study, Thermochimica 2012, Acta.,537,57–64.
3. Awasthi .A, Awasthi.A., Intermolecular interaction in binary mixtures of formamide with 2-alkoxyethanol at different temperatures: optical and internal pressure study, Phys Chem Liqs., 2013,51, 112–123.
4. Murrell JN, Jenkins AD. Properties of liquids and solutions (1994, Chichester: Wiley;)
5. Radhamma M., VenkatesuP.,Rao. M. V. Prabhakara , Lee M-J., Lin H.M., Excess molar volumes and ultrasonic studies of dimethylsulphoxide with ketones at T = 303.15 K, J. Chem. Thermodyn, 2008, 40, 492–497.
6. Galan J.J, Del Castillo J.J, Gonzalez-Perez A., Czapkiewicz J., Rodriguez J.R., Density and sound velocity studies of aqueous solutions of tetradecyltrimethylammonium nitrate at different temperatures, J. Solution Chem.2003, 32, 919–927
7. Blandmer M.J., Davis M.I., DouheretG., ReisJ.C., Apparent molar isentropic compressions and expansions of solutions., Chem. Soc. Rev.,2001, 30, 8–15
8. KondaiahM., Sreekanth K., NayeemS. M., Rao D.K., Ultrasonic, volumetric and viscometric study of aqueous-electrolyte solutions, Journal Chemical, Biological & Physical Sciences,2014, 4(3), 2401–2415.
9. KumarD. S, RaoD. K., Study of molecular interactions and ultrasonic velocity in mixtures of some alkanols with aqueous propylene glycol, Indian Journal of Pure and Applied Physics, 2007, 45(3), 210–220.
10. KligmanA. M., Topical Pharmacology and Toxicology of Dimethyl Sulfoxide—Part 1, JAMA.1965,193(10), 796-804.
11. CapriottiK., CapriottiJ.A., Dimethyl Sulfoxide, History, Chemistry, and Clinical Utility in Dermatology, DermatolJ Clin Aesthet, 2012 , 5(9), 24–26.
12. JacobS. W., RosenbaumE. E., WoodD. C., Dimethylsulphoxide (Marcel Dekker, NewYork, 1971).
13. LalJ. T, LauF. W., RobbD., WesthP., NielseinG., TrandumC., HvidtA. and KogaY., Excess partial molar enthalpies, entropies, Gibbs energies, and volumes in aqueous dimethylsulfoxide, J. Solution Chem.1995, 24, 89-102.
14. ScadutoR. C., Oxidation of DMSO and methanesulfinic acid by the hydroxyl radical, Free Radical Biol. Med.,1995,18, 271-277.
15. ParkerA. J., The effects of solvation on the properties of anions in dipolar aprotic solvents. Quart. Rev. Chem. Soc.1962, 16, 163-87.
16. MartinD., HauthalHG, Dimethyl sulfoxide (John Wiley & Sons, New York, 1975)
17. OlsenN.J., SchleichM.Aand KarpD.R., Multifaceted effects of hydroxychloroquine in human disease, Semin Arthritis Rheum.,2013, 43(2), 264-72.
18. McLachlanA.J, TettS.E., CutlerD.J. and DayR.O., Disposition of the enantiomers of hydroxychloroquine in patients with rheumatoid arthritis following multiple doses of the racemate, PharmacolBr J Clin., 1993,36(1), 78-81.
19. TettS.E., CutlerD.J., DayR.O. and BrownK.F. Bioavailability of hydroxychloroquine tablets in healthy volunteers, PharmacolBr J Clin.,1989, 27(6), 771-79.
20. ThanujaB., NithyaG.,KanagamC.C., Ultrasonic studies of intermolecular interactions in binary mixtures of 4-methoxy benzoin with various solvents: excess molar functions of ultrasonic parameters at different concentrations and in different solvents, UltrasonicsSonochem., 2012.19, 1213–1220.
21. AwasthiA., RastogiM., ShuklaJ.P., Ultrasonic and IR study of molecular association process through hydrogen bonding in ternary liquid mixtures, Fluid Phase Equilibria,2004, 215, 119–127.