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Volumetric and Acoustical Study of Antimalarial Hydroxychloroquine Sulfate Drug in DMSO-Water mixtures at different temperatures

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Abstract*: The densities and speeds of sound have been measured for ternery mixtures of hydroxychloroquine sulfate in aqueous-dimethyl sulfoxide(DMSO) mixtures at 20 vol% interval of the cosolvent at 303.15, 308.15 and 313.15 K and frequency 2MHz. The experimental data has been used to determine various acoustic/thermodynamic parameters viz. isentropic compressibility (k_s), intermolecular free length (L_f), relative association (R_A) and specific acoustic impedance (Z). 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, Antimalarial, DMSO, Molecular interactions, Ultrasonic velocity*

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I. INTRODUCTION

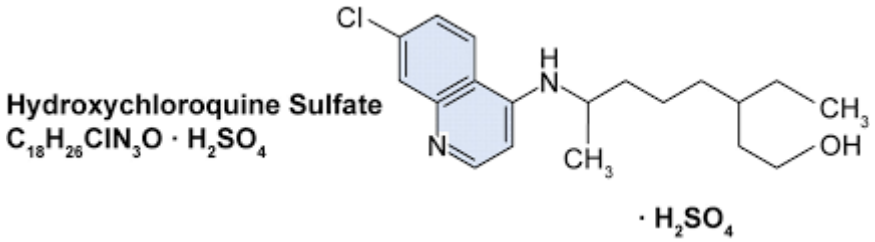
The development of thermophysical studies is parallel to industrial advances, which contributes to the designing as well as the output of the processes. This is due the increasing interest for industrial multicomponent process. The experimental determination of the values of thermophysical properties leads to the fast, reliable and economical establishment of innovative models that facilitate the determination of the properties necessary for the industry. Important information about the intermolecular interactions and the molecular level structure of different solvent systems is also obtained from the experimental determination of thermophysical properties. This knowledge helps to understand macroscopic properties of fluids [1-5].

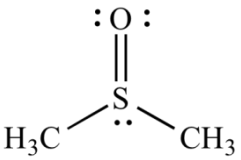
Intermolecular interactions being very complex, the elucidation of fluid structure has to be done by combining the experimental results and theoretical models [6]. Various solvent mixtures, due to the differences in molecular size, shape and structure exhibit considerable deviations from ideal behavior as far as the thermodynamic properties are concerned. [7]

The study of volumetric and acoustical properties was done by many workers by measuring density and ultrasonic velocity of electrolytic as well as nonelectrolytic solutions [8–13], different aqueous and non-aqueous systems [14-21] at different temperatures, different concentrations of solute and in varied 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, lipoids [22] and organic solvents and holds the ability to dissolve an enormous catalog of polar and non polar small molecules [23] and an extraordinary variety of inorganic and organic chemicals . Much known for its cryoprotective effects on biological systems [24–26] this polyfunctional molecule with highly polar S=O group and two hydrophobic CH groups has a potential for broader applications [27,28]

The drug used in present study, hydroxychloroquine sulfate (HCS) [2-({4-[(7-chloroquinolin-4-yl)amino]pentyl}(ethyl)amino)ethan-1-ol,sulfuric acid] which initially was developed as an antimalarial agent, is often used as slow-acting antirheumatic drug in the treatment of disorders of connective tissue [29-31]. The crystal structure projection and intermolecular interactions of the monocrystal drug was demonstrated by Semeniuk and coworkers (2008) [32] using X-ray diffraction and crystallography The study found each of the nitrogen atoms of the free base to be a proton donor in intermolecular hydrogen bonds with the oxygen atoms of the sulfate anion. Also 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.





Dimethyl Sulfoxide

L. Pikkarainen has measured the excess molar volume for the binary solvent of N,N-diethylmethanesulfonamide with aliphatic alcohols at different temperatures and found that the excess molar volume increases on increasing the length of the alkyl chain of aliphatic alcohols [33]. The importance of steric factors for molecular interactions in binary liquid mixtures is shown by Yadava and co-workers who have measured the excess molar volume for binary mixture of nitro-alkanes and 4-methyl-2-pentanone with hydrocarbons. [34,35]. Volumetric and viscometric studies of binary mixtures of methanol with chlorobenzene and bromobenzene over the complete composition range at three different temperatures was carried out by Shukla et al [36] assessment of effect of the ion association on the volumetric properties of NaOH(aq), the density measurements with different temperatures at 0 MPa was done by Corti and Simonson [37].

After a detailed search in the literature and in the view of the pharmaceutical and medical significance of hydroxychloroquine sulfate, 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.

II. EXPERIMENTAL

2.1. Materials:

All the chemicals used were of AR grade. DMSO purchased from SD fine (minimum assay by volume 99.9%), purified sample of the drug hydroxychloroquine sulfate was provided by Ajanta pharmaceuticals, Mumbai. Deionized distilled water (HPLC grade, pH=6.91) obtained from Millipore prefiltration kit (Direct-Q ™ system series) 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.

2.2. 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. The volume of pycnometer was corrected for 30°C. 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-F05, Mittal Enterprises, New Delhi, 2 ± 0.0001 MHz). The ultrasonic speeds were reproducible within ±0.03 %. The temperature was maintained by an electronically controlled thermostated water bath (accuracy of ±0.01 K). Refractive index measurements were performed on thermostatically controlled Cyber LAB-Cyber Abbe refractometer (Amkette Analytics, ±0.0002). Refractometer was calibrated using standard specimen (n=1.5167). Experimental temperature was maintained by water circulation system surrounding the prism box using water bath. All the measurements of densities and speeds of sound of the ternary mixtures were determined at 303.15, 308.15 and 313.15 K.

III. THEORY

Various physical parameters [38-40], isentropic compressibility [k_s], intermolecular free length [L_f], relative association[R_A] and acoustic impedance [Z] for ternary mixtures of HCS with 30%, 50% and 70% DMSO-Water were calculated from ultrasound velocities (u) and densities (ρ) by using following relations:

Isentropic compressibility: $k_s = \frac{1}{\rho u^2}$ (1)

Intermolecular free length: $L_f = K\,(k_s)^{\frac{1}{2}}$ (2)

Where K is temperature dependent constant which is known as Jacobson's constant,
K= (93.875+0.375T) x$10^{-8,}$ taken from the work of Thanuja et al[41].

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

Relative association: $R_A = \frac{\rho}{\rho_0} \times \left(\frac{u_0}{u}\right)^{\frac{1}{3}}$ (4)

IV. 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 [3, 42]. 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 HCS 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 HCS in 30% DMSO-Water at different temperatures

c	ρ	u	κ_s	Z	R_A	L_f	N
303.15K							
0.0000	1.03539	1647.22	3.5595	1.706	1.00000	0.3916	1.3750
0.0097	1.03747	1649.55	3.5424	1.711	1.00154	0.3906	1.3760
0.0194	1.03950	1651.75	3.5260	1.717	1.00305	0.3897	1.3771
0.0292	1.04155	1653.99	3.5096	1.723	1.00458	0.3888	1.3779
0.0390	1.04355	1656.33	3.4930	1.728	1.00603	0.3879	1.3786
0.0488	1.04562	1658.55	3.4767	1.734	1.00758	0.3870	1.3793
308.15K							
0.0000	1.03215	1645.33	3.5789	1.698	1.00000	0.3962	1.3745
0.0097	1.03415	1647.16	3.5641	1.703	1.00157	0.3954	1.3752
0.0195	1.03612	1649.01	3.5493	1.709	1.00310	0.3946	1.3760
0.0293	1.03812	1650.85	3.5346	1.714	1.00466	0.3937	1.3769
0.0391	1.04012	1652.55	3.5205	1.719	1.00625	0.3930	1.3775
0.0490	1.04214	1654.44	3.5057	1.724	1.00782	0.3921	1.3783
313.15K							
0.0000	1.03129	1630.33	3.6481	1.681	1.00000	0.4036	1.3730
0.0097	1.03321	1632.55	3.6314	1.687	1.00141	0.4027	1.3736
0.0195	1.03507	1634.44	3.6165	1.692	1.00282	0.4018	1.3744
0.0292	1.03698	1636.55	3.6006	1.697	1.00424	0.4010	1.3750
0.0391	1.03880	1638.55	3.5855	1.702	1.00559	0.4001	1.3758
0.0490	1.04068	1640.33	3.5713	1.707	1.00705	0.3993	1.3763

Footnote: ρ= g.cm^{-3}, u= m.s^{-1}, $k_{s=} \times 10^{-10} m^{-2} N^{-1}$, $Z= \times 10^{6} kgm^{-2} s^{-1}$, $Lf= Å$

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

c	ρ	u	κ_s	Z	R_A	L_f	N
303.15K							
0.0000	1.06838	1693.55	3.2635	1.809	1.00000	0.3750	1.4066
0.0094	1.06998	1700.11	3.2335	1.819	1.00021	0.3732	1.4080
0.0188	1.07162	1705.88	3.2067	1.828	1.00061	0.3717	1.4086
0.0283	1.07326	1712.33	3.1778	1.838	1.00088	0.3700	1.4096

0.0378	1.07497	1718.55	3.1498	1.847	1.00127	0.3684	1.4102
0.0474	1.07660	1723.99	3.1252	1.856	1.00173	0.3669	1.4117
308.15K							
0.0000	1.06363	1688.77	3.2966	1.796	1.00000	0.3803	1.4050
0.0094	1.06512	1694.44	3.2700	1.805	1.00028	0.3787	1.4069
0.0189	1.06660	1699.88	3.2446	1.813	1.00060	0.3772	1.4084
0.0284	1.06810	1706.11	3.2164	1.822	1.00079	0.3756	1.4090
0.0380	1.06958	1711.44	3.1920	1.831	1.00113	0.3742	1.4094
0.0476	1.07112	1716.88	3.1672	1.839	1.00152	0.3727	1.4111
313.15K							
0.0000	1.06051	1675.55	3.3587	1.777	1.00000	0.3873	1.4048
0.0095	1.06231	1678.66	3.3406	1.783	1.00108	0.3862	1.4065
0.0189	1.06420	1682.11	3.3210	1.790	1.00217	0.3851	1.4068
0.0285	1.06613	1685.44	3.3019	1.797	1.00333	0.3840	1.4076
0.0381	1.06800	1688.55	3.2840	1.803	1.00447	0.3829	1.4090
0.0477	1.06983	1691.88	3.2655	1.810	1.00553	0.3818	1.4101

Footnote: ρ= g.cm^{-3}, u= m.s^{-1}, $k_{s=} \times 10^{-10} m^{-2} N^{-1}$, $Z = \times 10^{6} kgm^{-2} s^{-1}$, $Lf = Å$

Table 3: Experimental density, ultrasonic velocity and derived isentropic compressibility, specific acoustic impedance, relative association, intermolecular free length and refractive index of HCS in 70%DMSO- Water at different temperatures

c	ρ	u	κ_s	Z	R_A	L_f	N
303.15K							
0.0000	1.08725	1668.88	3.3023	1.814	1.00000	0.3772	1.4371
0.0092	1.08939	1673.77	3.2766	1.823	1.00099	0.3757	1.4377
0.0185	1.09153	1678.11	3.2533	1.832	1.00209	0.3744	1.4383
0.0278	1.09368	1682.66	3.2294	1.840	1.00316	0.3730	1.4390
0.0371	1.09583	1686.88	3.2069	1.849	1.00430	0.3717	1.4394
0.0465	1.09800	1691.33	3.1838	1.857	1.00540	0.3703	1.4401
308.15K							
0.0000	1.08180	1656.00	3.3708	1.791	1.00000	0.3845	1.4358
0.0093	1.08375	1661.22	3.3436	1.800	1.00075	0.3830	1.4362
0.0186	1.08578	1666.55	3.3161	1.810	1.00156	0.3814	1.4368
0.0279	1.08774	1671.88	3.2890	1.819	1.00230	0.3798	1.4372
0.0373	1.08978	1676.77	3.2637	1.827	1.00320	0.3784	1.4375
0.0467	1.09175	1681.77	3.2385	1.836	1.00402	0.3769	1.4382
313.15K							
0.0000	1.07754	1638.55	3.4566	1.766	1.00000	0.3929	1.4350
0.0093	1.07994	1644.44	3.4242	1.776	1.00103	0.3910	1.4355
0.0186	1.08236	1649.95	3.3938	1.786	1.00215	0.3893	1.4360
0.0280	1.08477	1656.44	3.3598	1.797	1.00307	0.3873	1.4366
0.0374	1.08723	1662.22	3.3289	1.807	1.00418	0.3855	1.4369
0.0468	1.08967	1668.56	3.2963	1.818	1.00516	0.3836	1.4376

Footnote: ρ= g.cm^{-3}, u= m.s^{-1}, $k_{s=} \times 10^{-10} m^{-2} N^{-1}$, $Z = \times 10^{6} kgm^{-2} s^{-1}$, $Lf = Å$

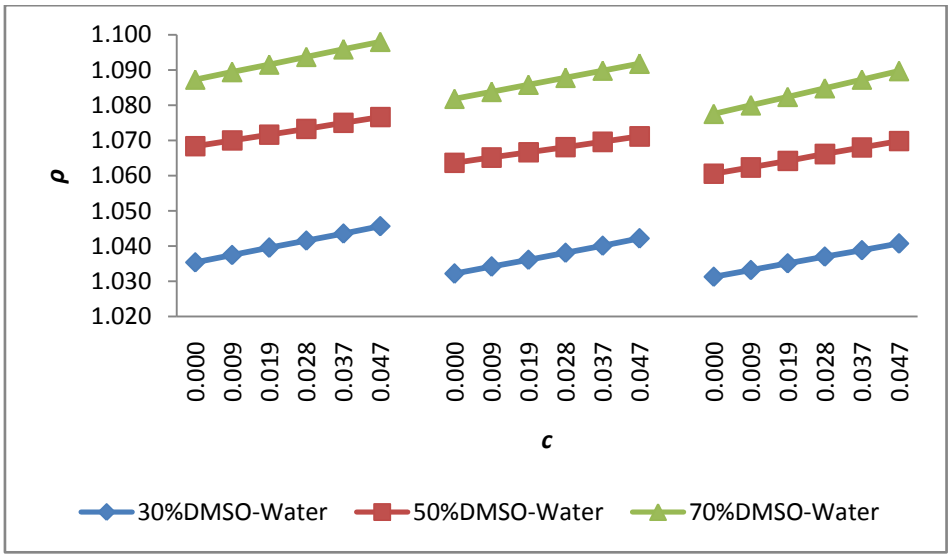


Figure 1: Variation in density of HCS in 30%, 50% and 70% DMSO-Water mixture at different temperatures

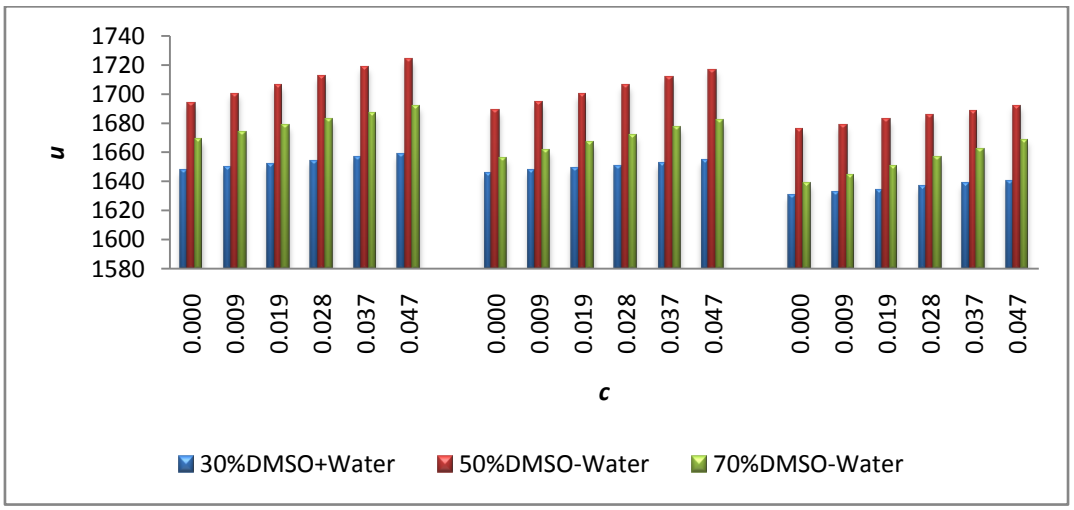


Figure 2: Variation in ultrasonic velocity of HCS in 30%, 50% and 70% DMSO-Water mixtures at different temperatures

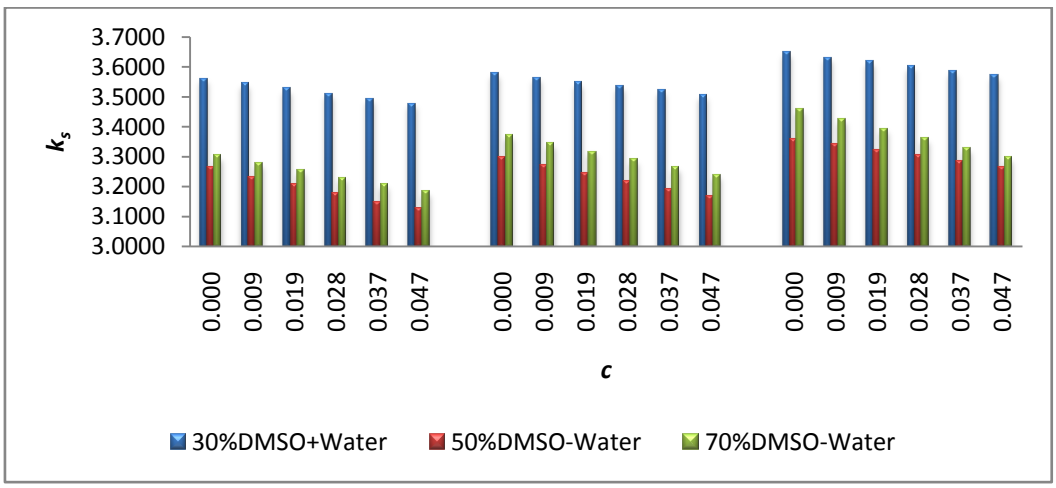


Figure 3: Variation in isentropic compressibility of HCS in 30%, 50% and 70% DMSO-Water mixtures at different temperatures

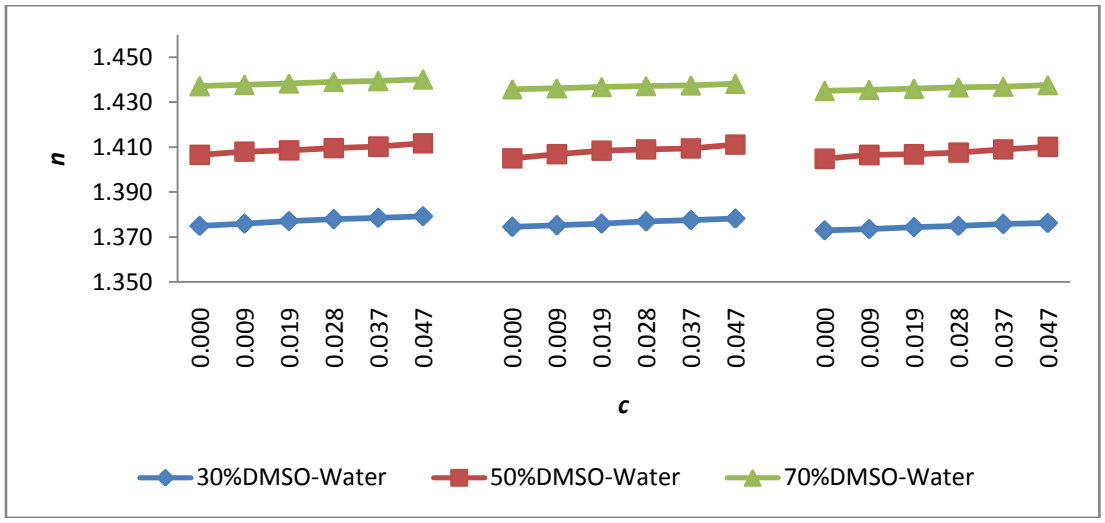


Figure 4: Variation in refractive index of HCS in 30%, 50% and 70% DMSO-Water mixtures at different temperatures

V. 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 aggregation of solvent molecules around solute molecules, in short, the strong solvent–solute interaction. The refractive index data shows linear dependence over the drug concentration at all the studied temperatures, which is well in accordance with the data obtained from volumetric and acoustical study. The present study of aqueous DMSO mixtures of HCS 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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