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Volumetric, ultrasonic and conductance behaviour of metformin hydrochloride (MH) in water and aqueous sorbitol at different temperatures

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The behaviour of metformin hydrochloride (MH) in water and aqueous sorbitol solutions was studied to explore molecular interactions at different temperatures. The volumetric, ultrasonic and conductance studies were used to investigate the interactions of drug MH in water and aqueous sorbitol system. The density (ρ), ultrasonic velocity (*u*) and molar conductance of MH in water and in (2, 4 and 6 wt.%) aqueous solutions of sorbitol have been measured at 305.15, 310.15 and 315.15 K temperatures. The density data was analysed with the help of Masson's equation and (Φ_V^0) and Masson's coefficient, (S_V) were determined. The ultrasonic velocity data of MH in water and water-sorbitol system were used to determine adiabatic compressibility (β), intermolecular free length (L_f), and specific acoustic impedance (*Z*). The structure making/breaking behaviour of MH in water and water-sorbitol system was determined on the basis of Hepler's reasoning and from temperature dependence of Walden's product.

Keywords: Partial molar volume, adiabatic compressibility, intermolecular free length, specific acoustic impedance, Walden product.

Introduction

The solvation of solute in various solvents or the mixing effect of chemical mixtures widely used in industry is difficult to know; therefore, an understanding of thermodynamic properties such as densities, ultrasonic velocities, apparent molar and partial apparent molar properties is of significant importance[1]. During the formation of liquid mixtures, a change in molecular interactions occurs, and the difference in component packing becomes apparent[2,3]. The physicochemical interactions between a drug and functionally important molecules in a living organism may include ionic, covalent, charge transfer, hydrogen bonding, ion-dipole interactions are of great benefit to understand the pharmacodynamics and pharmacokinetics[4–6] of drugs. Pharmacodynamics is the study of how a drug affects an organism, whereas pharmacokinetics is the study of how the organism affects the drug. Both together influence dosing, benefit, and adverse effects of drugs. The studies on the physicochemical interactions in the aqueous phase by the volumetric and ultrasonic methods provide useful information in pharmaceutical[7,8] and medicinal chemistry. The drug-water molecular interactions and their temperature dependence play an important role in understanding drug action[9,10] at the molecular level. Such results are also helpful for predicting the absorption of drugs, transport of drugs across biological membranes, and investigating the presence, migration, and transformation of the drugs in the environment[11–13]. Drug action, i.e. drug reaching the blood stream, its extent of distribution, its binding to the receptors, and finally producing physiological action, all depend on various physicochemical properties mainly detected by various interactions[14,15]. The polyhydroxy compound, sugar alcohol is usually used as sugar replacer due to its low calorie and little effect on blood sugar level[16], has been used widely in the pharmaceutical and food industries. Sugar alcohols are a kind of "low-digestible carbohydrate", a group that comprises fiber and resistant starch. Sorbitol is one of the sugar alcohols, having six OH groups due to which hydrogen-bond formation occurs when the substance is dissolved with water. It is often used as a substitute to sugar in various diet foods (including soft drinks and ice cream), cough syrups, mints, and sugar-free chewing gum[17–19]. In addition, it can be used as a building block for many value-added derivatives. On the basis of the broad range of its applications, estimated annual production of sorbitol is over 500,000 tons,

and it is about 50% of the polyol market[20]. Sorbitol have potential applications as building blocks for producing various value-added derivatives[21].

Metformin hydrochloride (MFHCl), a white crystalline powder, has a molecular formula of ($C_4H_{11}N_5HCl$). It is an antidiabetic and antihyperglycemic agent[22,23] that lowers both basal- and postprandial-elevated blood glucose in patients with non-insulin-dependent diabetes mellitus (Type-2 diabetes)[24], where hyperglycemia cannot be satisfactorily managed by diet alone. It is frequently referred to as an "insulin sensitizer" because in settings of insulin resistance and hyperinsulinemia, it lowers circulating insulin levels[25]. Recent studies show that metformin can reduce cancer risk and/or improve cancer prognosis. The study is also important whether the metformin hydrochloride will be safer for the patient suffering from hypertension i.e. high blood pressure. If the drug behaviour is structure maker in water-carbohydrate system then free water molecules will be less available for the solvation of sodium ions present in the blood stream and thus the medicine will be safer for the patient suffering from high blood pressure[26]. If the drug act as structure breaker in any studied system containing water then the drug will not be safe due to high solvation of sodium ions present in the blood. Despite numerous applications of mixtures containing sorbital, much less work has been done on their thermodynamic study[27–29].

The main focus in the present paper is to study the interactions of antidiabatic drug metformin hydrochloride (MH) in water and water-sorbitol systems in 2, 4 and 6 wt.% aqueous sorbitol at 305.15 K, 310.15 K and 315.15 K. A change in temperature or concentration significantly affects the charge distribution in molecules, which also influence the different type of molecular interactions (H-bonding, ion-dipole and dipole-dipole etc.)[30]. The present study include the molecular interactions of MH in different concentrations of sorbitol at different temperatures. Recent literature on the volumetric properties of drugs and other materials of biological importance show increasing interest in this area of research[31–33].

Experimental

Materials:

1,1-Dimethylbiguanide hydrochloride molecular formula: $C_4H_{11}N_5HCl$, molecular weight: 165.62 g/mol (CAS:24390-14-5; Alfa Aesar, mass fraction ≥98.0%) and analytical grade, sorbitol, $C_6H_{14}O_6$ molecular weight: 182.17 g/mol (CAS:50-70-4; s d fine chemical Mumbai, mass fraction ≥98.0%) and analytical grade was used for the investigation of the effect of temperature and concentration of MH in aqueous sorbitol solutions. These chemicals were used as such without any further purification. Both these chemicals were vaccum dried over anhydrous $CaCl_2$ in dessicator for 48 h. The specifications of the chemicals used in this study are given in Table 1.

Methods:

Triply distilled and deionised water with specific conductance less than 10^{-6} Scm^{-1} was used for the preparation of solutions. Three different concentrations of sorbitol (2, 4 and 6 wt.%) were used as solvent to prepare ternary solutions of MH. The molal aqueous solutions of MH were prepared by using Shimadzu electronic balance (Model No. D432613208, Japan) with an accuracy of ±0.1 mg. The solutions were prepared by weight method and the conversion of molality into molarity was done with the help of standard expression (1)[34].

$$C = \frac{1000\, m\rho}{1000 + mM} \qquad (1)$$

where ρ, m stands for density and molality of solution and M is the molecular mass of MH.

The densities (ρ) and ultrasonic velocities (u) of the solutions was measured with the help of a vibrating-tube density meter (DSA 5000, Anton Parr, Austria). The DSA was cali-

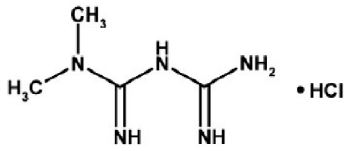


Fig. 1. Chemical structure of metformin hydrochloride.

Table 1. Specification of chemicals

Chemical name	Molecular mass	Provenance	Mass fraction purity	CAS No.
Metformin hydrochloride	165.62	Alfa Aesar	≥ 98%	24390-14-5
Sorbitol	182.17	SD Fine Chem. India	≥ 98%	50-70-4

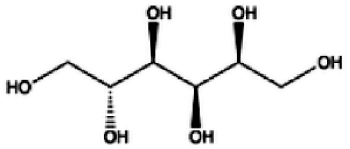


Fig. 2. Chemical structure of sorbitol.

brated at the experimental temperatures with triply distilled water and dry air at atmospheric pressure as directed in user manual. The density and sound velocity measurements were accurate to 5×10^{-6} g cm^{-1} and 0.5 ms^{-1}, respectively. Pure water is not a good conductor of electricity. Ordinary water generally has a specific conductivity of about 3.5×10^{-3} Ω^{-1} cm^{-1}. Most of this conductivity is due to impurities and very little of it is, due to ionization of water. Elaborate precautions are required in order to produce water of conductivity less than 10^{-4} Ω^{-1} cm^{-1} by distillation. For the determination of electrical conductance, conductivity cell has been used. The cell consists of two electrodes of platinum fused in pyrex glass. Connection to the electrode is made through mercury. To determine the cell constant of the conductivity cell the following procedure is used. The cell used for the conductivity measurements is not of accurately known dimensions, and consequently it needs to be calibrated before it is possible to reduce values of specific conductance from measurement of cell resistance. This is done by means of accurately known specific conductance. Suppose a given cell, when filled with a solution of known specific conductance, *K* is found to have a resistance *R*, then the cell constant is equal to *KR*. The cell constant may therefore be thought of as the resistance that the cell would exhibit when filled with liquid of unit conductivity. In the present study, the conductivity cell was calibrated with the solution of potassium chloride in conductivity water. The potassium chloride of AR grade was dried over P_2O_5 in a vacuum dessicator for 24 h.

The conductivity cell before each reading was washed thoroughly with distilled water and then was rinsed four times with 10 ml of the sample solution under study. Solutions of metformin hydrochloride in water and in 2, 4 and 6% aqueous solution of sorbitol was made by weight. After filling the solution, the cell was suitably placed inside the water thermostat where it was allowed to attain a constant temperature before conductance measurements were made. Conductance measurements were carried out with a calibrated Digital Conductivity Meter (ELICO CM 183EC-TDS ANALYSER) at 50 Hz. The measured conductance remained stationary with time. The cell was removed from the water thermostat and the conductance was determined once again.

Results and discussion

The density (ρ), ultrasonic velocity (*u)* and conductance values measured for different concentrations (0.001–0.01 mol.kg^{-1}) of metformin hydrochloride in 2, 4 and 6 wt.% aqueous sorbitol at 305.15, 310.15 and 315.15 K temperatures have been used to calculate various important parameters such as apparent molar volume, adiabatic compressibility, intermolecular free length, specific acoustic impedance and Walden's product etc.

The apparent molar volume[35] (reported in Table 2) was obtained by using experimental data according to the eq. (2),

$$\Phi_v = (M/\rho) + (1000(\rho_0 - \rho)/m\rho\rho_0) \quad (2)$$

where Φ_v, *m*, ρ, ρ_0 and *M* are the apparent molar volume, molality, density of the solution, density of pure solvent and molar mass of MH, respectively.

The apparent molar volume (Φ_v) of a solute is defined as the difference between the volume of the solution and the volume of the pure solvent per mole of solute[36–38]. Table 2 shows that the apparent molar volume of MH increases with

Table 2. Densities (ρ) and apparent molar volume (Φ_v) of MH in water and in aqueous sorbitol system at different temperatures

m (mol.kg^{-1})	*C* (mol.L^{-1})	Density (ρ) (g cm^{-3})			Φ_v (cm^3 mol^{-1})		
		305.15 K	310.15 K	315.15 K	305.15 K	310.15 K	315.15 K
		Metformin hydrochloride in water					
0.000	0.000000	0.994988	0.993380	0.991483			
0.001	0.031543	0.995132	0.993435	0.991537	114.82	117.25	119.73
0.002	0.044606	0.995180	0.993481	0.991582	116.80	119.23	121.20
0.003	0.054628	0.995225	0.993525	0.991625	118.45	120.54	122.34

Table-2 (contd.)

0.004	0.063075	0.995269	0.993567	0.991666	119.52	121.69	123.41
0.005	0.070516	0.995311	0.993607	0.991705	120.56	122.77	124.44
0.006	0.077241	0.995351	0.993645	0.991743	121.58	123.82	125.29
0.007	0.083425	0.995390	0.993685	0.991781	122.45	124.29	125.90
0.008	0.089179	0.995428	0.993721	0.991816	123.23	125.14	126.72
0.009	0.094583	0.995465	0.993758	0.991852	123.94	125.68	127.25
0.010	0.099692	0.995500	0.993795	0.991887	124.71	126.12	127.77
			Metformin hydrochloride in 2% sorbitol				
0.000	0.000000	0.995652	0.994072	0.992212			
0.001	0.031656	1.002284	1.002205	1.002141	115.76	119.94	123.97
0.002	0.044766	1.002322	1.002243	1.002174	119.73	123.46	127.99
0.003	0.054823	1.002355	1.002276	1.002202	122.73	126.30	131.00
0.004	0.063300	1.002384	1.002305	1.002227	125.23	128.73	133.26
0.005	0.070767	1.002410	1.002330	1.002249	127.33	130.99	135.22
0.006	0.077515	1.002432	1.002352	1.002267	129.40	132.99	137.19
0.007	0.083720	1.002450	1.002370	1.002283	131.46	135.00	138.89
0.008	0.089494	1.002467	1.002385	1.002297	133.12	136.89	140.41
0.009	0.094915	1.002480	1.002398	1.002308	134.87	138.57	141.94
0.010	0.100042	1.002494	1.002412	1.002315	136.16	139.82	143.55
			Metformin hydrochloride in 4% sorbitol				
0.000	0.000000	0.996340	0.994786	0.992956			
0.001	0.029416	1.008535	1.006834	1.004818	115.28	126.97	141.48
0.002	0.041602	1.008573	1.006862	1.004848	120.37	131.48	145.01
0.003	0.050952	1.008605	1.006885	1.004860	124.09	134.74	147.57
0.004	0.058836	1.008629	1.006903	1.004868	127.99	137.51	149.84
0.005	0.065781	1.008650	1.006918	1.004873	130.94	139.84	151.82
0.006	0.072060	1.008668	1.006929	1.004875	133.42	142.07	153.53
0.007	0.077834	1.008682	1.006935	1.004878	135.76	144.39	154.75
0.008	0.083209	1.008698	1.006944	1.004881	137.27	145.75	155.62
0.009	0.088257	1.008710	1.006950	1.004882	138.90	147.14	156.52
0.010	0.093031	1.008720	1.006960	1.004884	140.40	147.85	157.13
			Metformin hydrochloride in 6% sorbitol				
0.000	0.000000	0.997014	0.995494	0.993704			
0.001	0.031823	1.012890	1.010582	1.010255	119.28	129.86	140.35
0.002	0.045002	1.012922	1.010605	1.010272	124.92	135.22	143.51
0.003	0.055112	1.012949	1.010623	1.010283	128.51	138.58	146.43
0.004	0.063633	1.012970	1.010635	1.010291	131.85	141.81	148.76
0.005	0.071139	1.012990	1.010643	1.010295	134.05	144.57	150.96
0.006	0.077923	1.013007	1.010648	1.010296	136.04	146.92	152.93
0.007	0.084160	1.013022	1.010653	1.010297	137.74	148.59	154.34
0.008	0.089964	1.013031	1.010654	1.010297	139.80	150.36	155.55
0.009	0.095414	1.013038	1.010656	1.010298	141.62	151.63	156.33
0.010	0.100567	1.013049	1.010650	1.010299	142.67	153.45	156.98

m is the molality of MH in aqueous sorbitol solutions. The standard uncertainty in molality as per stated purities is $u(m)= \pm 1\times10^{-3}$ mol.kg^{-1}. Standard uncertainties in $u(\rho)$ density measurements are $\pm 5\times10^{-6}$ g cm^{-3}. Standard uncertainties in $u(T)$ temperatures are $\pm 1\times10^{-2}$. Standard uncertainties in $u(P)$ pressures are 0.1 MPa.

rise in temperature and with increase in concentration of sorbitol in water-sorbitol system.

The apparent molar volume occupied by one mole of a solute at infinite dilution is called partial molar volume of a solute in solution[39]. The partial molar volume also called limiting apparent molar volume is calculated by least square fitting of Φ_v vs $\sqrt{c}$ by the Masson's eq. (3)[40].

$$\Phi_v = \Phi_v^0 + S_v \sqrt{c} \quad (3)$$

The intercept gives partial molar volume (Φ_v^0) which signifies solute-solvent interactions independent of solute-solute interactions and the slope S_v called Masson's coefficient is a measure of solute-solute interactions[41]. The values of Φ_v^0 and S_v for MH in different aqueous sorbitol solutions at the experimental temperatures are reported in Table 3.

The Φ_v^0 is a measure of solute-solvent interaction. The value of Φ_v^0 (Table 3) are positive, which signifies that there exist strong solute-solvent interactions for MH in water and water-sorbitol system at different temperatures. The value of Φ_v^0 increases with rise in temperature may be due to decrease in hydrogen bonding in water-sorbitol system with rise in temperature and thus free molecules of water will be available for the solvation of MH. The plots showing the variation of Φ_v with concentration for metformin hydrochloride in water and water-sorbitol system at different temperatures are given in Fig. 3(a-d).

The value of Masson's coefficient, S_v is positive for MH in water and water-sorbitol system suggests strong solute-solute interactions which are due to electrostatic force of attraction between drug molecules.

The temperature dependence[42] of Φ_v^0 is given by the following eq. (4)

$$\Phi_v^0 = a + bT + cT^2 \quad (4)$$

where *a*, *b* and *c* are constants for a given system and *T* is temperature expressed in Kelvin. The values of constants *a*, *b* and *c* are calculated by using eq. (4) at different temperatures and are given in Table 3.

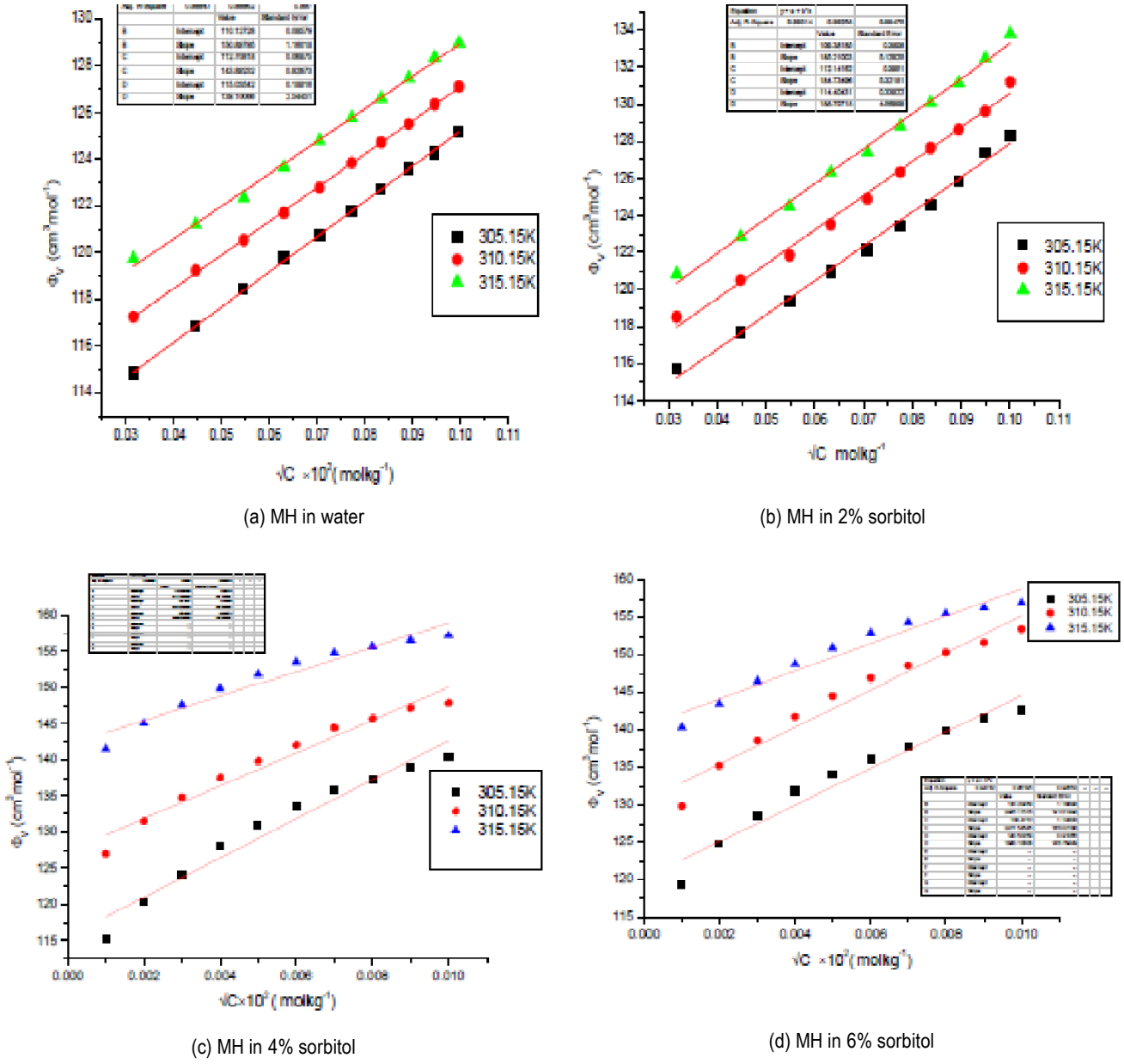
The values of partial molar volume expansion, (Φ_E^0), of MH was obtained from the temperature dependence of partial molar volume[43], Φ_v^0 given by eq. (5)

$$\Phi_E^0 = [\partial \phi_v^0 / \partial T] = b + 2cT \quad (5)$$

The importance of Φ_E^0 lies in the fact that it helps in the elucidation of the long range structure making or structure breaking effects of solutes[44–46]. The values of Φ_E^0 and $\alpha°$ obtained for MH in different water-sorbitol system at different

Table 3. Partial molar volume (Φ_v^0), Masson's coefficient (S_v), partial molar expansibility (Φ_E^0), isobaric thermal expansion coefficient ($\alpha°$), *a*, *b*, *c* and Hepler's constant values for MH in water and water-sorbitol system

	Φ_v^0 (cm^3 mol^{-1})			S_v		
Solvent	305.15 K	310.15 K	315.15 K	305.15 K	310.15 K	315.15 K
Water	110.43	113.36	115.71	143.84	131.31	120.55
2% Sorbitol	106.25	110.25	115.35	299.83	295.70	281.52
4% Sorbitol	107.96	117.52	133.79	401.36	336.61	250.93
6% Sorbitol	109.62	119.88	134.53	335.78	339.63	252.51
	Φ_E^0 (cm^3 mol^{-1}.K^{-1})			$\alpha°$ (K^{-1})		
Water	0.622	0.544	0.464	0.005649	0.004826	0.004034
2% Sorbitol	0.706	0.906	1.402	0.006647	0.008221	0.012159
4% Sorbitol	2.440	3.160	3.180	0.022613	0.026893	0.023784
6% Sorbitol	1.780	2.290	2.810	0.016240	0.019115	0.020892
	a	*b*	*c*	$\left(\frac{\partial^2 \Phi_v^0}{\partial T}\right)_p = 2c$		
Water	826.61	–5.504	0.008	0.016		
2% Sorbitol	5509.57	–23.8	0.020	0.040		
4% Sorbitol	6063.26	–41.5	0.072	0.148		
6% Sorbitol	4363.03	–29.6	0.051	0.102		



(a) MH in water

(b) MH in 2% sorbitol

(c) MH in 4% sorbitol

(d) MH in 6% sorbitol

Fig. 3. Plots showing the variation of Φ_v with concentration for metformin hydrochloride in water and water-sorbitol system at different temperatures.

temperatures are recorded in Table 3. The value of Φ_E^0 for MH in water and water-sorbitol system increases with rise in temperature indicates that caging effect is present. The isobaric thermal expansion coefficient ($\alpha°$) for MH in water and water sorbitol system is obtained from the values of Φ_E^0 and Φ_v^0 using the following eq. (6)

$$\alpha° = \Phi_E^0/\Phi_v^0 \quad (6)$$

The $\alpha°$ value increases with increase in concentration of sorbitol in water-sorbitol system. This may be due to structure making of MH in water and water-sorbitol system. The plots showing the variation of Φ_E^0 with temperature for MH in water, 2, 4 and 6 wt.% aqueous sorbitol are shown in Fig. 4(a, b, c and d).

Hepler devised a method to account for structure making

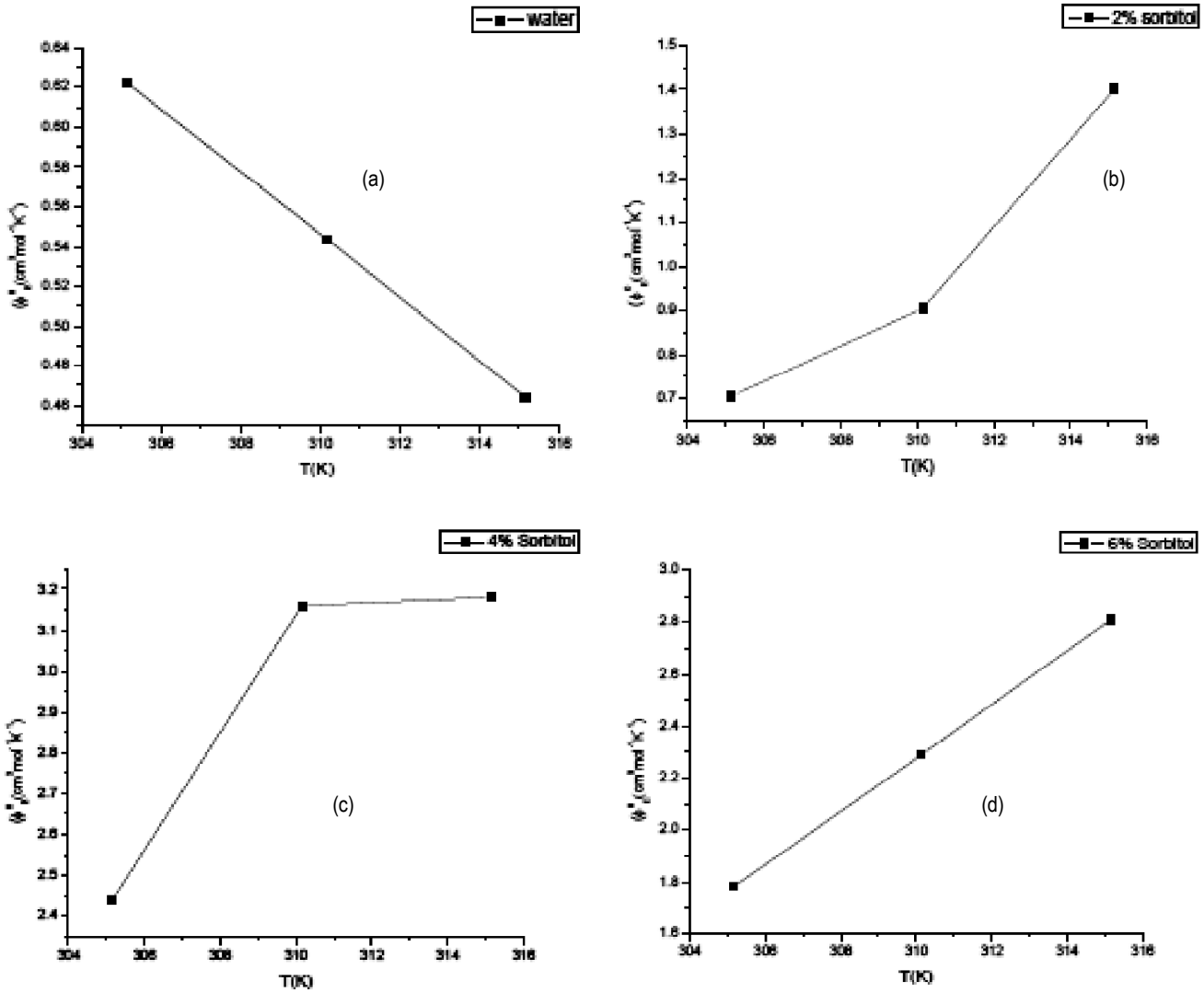


Fig. 4. Plots showing the variation of Φ_E^0 with temperature for MH in water, 2, 4 and 6 wt.% aqueous sorbitol.

and breaking capacity of solutes in aqueous solutions on the basis of sign of $(\partial^2\Phi_v^0/\partial T^2)_P$. The Hepler's constant gives the qualitative details on hydration of solutes. The positive value of[47] $(\partial^2\Phi_v^0/\partial T^2)_P$] indicates that solute is structure maker and negative value of Hepler's constant indicates structure breaking behaviour of solute. The values of $(\partial^2\Phi_v^0/\partial T^2)_P$ calculated

$$(\partial^2\Phi_v^0/\partial T^2)_P = 2c \quad (7)$$

for MH in water and in different solutions of aqueous sorbitol are listed in Table 3.

The positive values of $(\partial^2\Phi_v^0/\partial T^2)_P$ for MH in water and water sorbitol system suggests that MH acts as a structure maker in water, 2, 4 and 6 wt.% water-sorbitol system. The structure making ability of MH is also confirmed by the variation of Φ_E^0 with temperature.

Ultrasonic studies:

The density and ultrasonic velocity data for MH in water and water-sorbitol system are given in Table 4 have been used to calculate acoustical parameters like adiabatic compressibility (β), intermolecular free length (L_f) and specific acoustic impedance (Z) which are useful in elucidating the nature of solute-solute and solute-solvent interactions occurring in the solutions.

The Adiabatic compressibility (β) was obtained by apply-

Table 4. Ultrasonic velocity (u), adiabatic compressibility (β), intermolecular free length (L_f), and specific acoustic impedance (Z) values for MH in water and water-sorbitol system at different temperatures and atmospheric pressure

^{c}m (mol.kg^{-1})	Ultrasonic velocity (u) (m.s^{-1})			β (10^{-10} Pa^{-1})			L_f (10^{-11} m)			Z (10^6 kg m^{-2} s^{-1})		
	305.15 K	310.15 K	315.15 K	305.15 K	310.15 K	315.15 K	305.15 K	310.15 K	315.15 K	305.15 K	310.15 K	315.15 K
Metformin hydrochloride in water												
0.001	1513.84	1523.75	1532.13	4.3848	4.3354	4.2963	4.3593	4.3763	4.3980	1.5064	1.5066	1.5191
0.002	1513.98	1523.95	1532.38	4.3838	4.3341	4.2947	4.3588	4.3756	4.3972	1.5066	1.5067	1.5194
0.003	1514.12	1524.14	1532.64	4.3828	4.3328	4.2931	4.3583	4.3750	4.3963	1.5068	1.5069	1.5198
0.004	1514.19	1524.21	1532.7	4.3822	4.3322	4.2926	4.3580	4.3747	4.3960	1.5070	1.5071	1.5199
0.005	1514.26	1524.27	1532.76	4.3816	4.3317	4.2921	4.3577	4.3744	4.3958	1.5071	1.5073	1.5200
0.006	1514.36	1524.34	1532.82	4.3809	4.3311	4.2915	4.3573	4.3741	4.3955	1.5073	1.5075	1.5201
0.007	1514.41	1524.4	1532.88	4.3804	4.3306	4.2910	4.3571	4.3739	4.3953	1.5074	1.5078	1.5202
0.008	1514.59	1524.59	1533.03	4.3792	4.3294	4.2900	4.3567	4.3733	4.3948	1.5076	1.5079	1.5204
0.009	1514.71	1524.71	1533.44	4.3783	4.3285	4.2876	4.3561	4.3728	4.3944	1.5078	1.5081	1.5206
0.010	1514.82	1524.83	1533.25	4.3775	4.3277	4.2885	4.3557	4.3724	4.3940	1.5080	1.5083	1.5208
Metformin hydrochloride in 2% sorbitol												
0.001	1521.58	1531.26	1539.38	4.3094	4.2554	4.2487	4.3216	4.3357	4.3565	1.5251	1.5345	1.5425
0.002	1521.67	1531.29	1539.43	4.3087	4.2551	4.2475	4.3213	4.3355	4.3555	1.5253	1.5346	1.5427
0.003	1521.73	1531.31	1539.48	4.3082	4.2548	4.2467	4.3210	4.3353	4.3549	1.5254	1.5348	1.5428
0.004	1521.77	1531.33	1539.53	4.3079	4.2546	4.2459	4.3208	4.3351	4.3546	1.5256	1.5349	1.5429
0.005	1521.80	1531.36	1539.58	4.3076	4.2543	4.2452	4.3206	4.3349	4.3544	1.5258	1.5351	1.5431
0.006	1521.83	1531.39	1539.62	4.3073	4.2541	4.2446	4.3205	4.3347	4.3541	1.5259	1.5353	1.5433
0.007	1521.85	1531.41	1539.67	4.3071	4.2539	4.2440	4.3203	4.3345	4.3538	1.5261	1.5355	1.5435
0.008	1521.88	1531.45	1539.71	4.3069	4.2535	4.2433	4.3202	4.3342	4.3533	1.5262	1.5356	1.5437
0.009	1521.90	1531.50	1539.77	4.3067	4.2532	4.2427	4.3200	4.3344	4.3521	1.5264	1.5358	1.5438
0.010	1521.93	1531.55	1539.83	4.3065	4.2529	4.2422	4.3198	4.3342	4.3526	1.5265	1.5359	1.5439
Metformin hydrochloride in 4% sorbitol												
0.001	1527.65	1537.05	1545.01	4.2487	4.2040	4.1691	4.3323	4.3095	4.2915	1.5406	1.5475	1.5524
0.002	1527.83	1537.19	1545.19	4.2475	4.2031	4.1680	4.3317	4.3090	4.2910	1.5409	1.5477	1.5526
0.003	1527.95	1537.3	1545.3	4.2467	4.2024	4.1674	4.3313	4.3086	4.2907	1.5410	1.5478	1.5528
0.004	1528.08	1537.39	1545.41	4.2459	4.2018	4.1668	4.3309	4.3084	4.2903	1.5412	1.5480	1.5529
0.005	1528.20	1537.47	1545.49	4.2452	4.2013	4.1663	4.3305	4.3081	4.2901	1.5414	1.5481	1.5530
0.006	1528.29	1537.55	1545.57	4.2446	4.2009	4.1659	4.3302	4.3078	4.2899	1.5415	1.5482	1.5531
0.007	1528.39	1537.63	1545.65	4.2440	4.2004	4.1654	4.3299	4.3076	4.2896	1.5416	1.5482	1.5531
0.008	1528.49	1537.71	1545.73	4.2433	4.1999	4.1650	4.3296	4.3074	4.2894	1.5417	1.5483	1.5532
0.009	1528.60	1537.79	1545.81	4.2427	4.1995	4.1645	4.3292	4.3071	4.2892	1.5419	1.5484	1.5533
0.010	1528.68	1537.85	1545.89	4.2422	4.1991	4.1641	4.3290	4.3069	4.2890	1.5420	1.5485	1.5534

Table-4 (contd.)

Metformin hydrochloride in 6% sorbitol											
0.001	1534.19	1542.15	1551.12	4.1949	4.1607	4.1141	4.3048	4.2872	4.2631	1.5538	1.5576	1.5670
0.002	1534.21	1542.21	1551.23	4.1942	4.1603	4.1134	4.3044	4.2870	4.2628	1.5540	1.5579	1.5671
0.003	1534.29	1542.27	1551.34	4.1937	4.1599	4.1128	4.3042	4.2868	4.2625	1.5541	1.5581	1.5672
0.004	1534.37	1542.33	1551.43	4.1931	4.1595	4.1123	4.3039	4.2866	4.2622	1.554	1.5583	1.5673
0.005	1534.45	1542.38	1551.51	4.1926	4.1592	4.1119	4.3036	4.2865	4.2620	1.5543	1.5584	1.5674
0.006	1534.52	1542.45	1551.59	4.1922	4.1588	4.1114	4.3034	4.2863	4.2617	1.5544	1.5585	1.5675
0.007	1534.59	1542.51	1551.67	4.1917	4.1588	4.1110	4.3032	4.2861	4.2615	1.5545	1.5587	1.5676
0.008	1534.66	1542.59	1551.75	4.1913	4.1581	4.1106	4.3029	4.2859	4.2613	1.5546	1.5589	1.5677
0.009	1534.73	1542.65	1551.83	4.1909	4.1577	4.1101	4.3027	4.2857	4.2611	1.5547	1.5590	1.5678
0.010	1534.81	1542.71	1551.89	4.1905	4.1574	4.1098	4.3022	4.2855	4.2609	1.5548	1.5591	1.5678

^{c}m is the molality of MH in aqueous glucose solutions. The standard uncertainty in molality as per stated purities is $u(m)$= ±1×10^{-3} mol.kg^{-1}. Standard uncertainties in $u(u)$ ultrasonic velocity measurements are ±5×10^{-2} ms^{-1}. Standard uncertainties in $u(T)$ temperatures are ±1×10^{-2}. Standard uncertainties in $u(P)$ pressures are 0.1 MPa.

ing Newton-Laplace eq. (8)[48], defined as

$$\beta = \left(-\frac{1}{V}\right)\left(\frac{\partial V}{\partial P}\right)_S .$$

$$\text{or } \beta = 1/u^2\rho \qquad (8)$$

where u is the ultrasonic velocity and ρ is the density of solution. The data Table 4 shows that adiabatic compressibility values for MH in water and water-sorbitol system decreases with increase in concentration of MH at different temperatures. This may be due to strong electric field (electrostriction), the solvent molecules within the primary solvation shell of electrolytic solution become incompressible moreover increasing concentration of ions results in more solvent molecules to engage in incompressible solvation spheres thereby decreasing the adiabatic compressibility[49]. The decrease in adiabatic compressibility with increase in concentration of MH in water and water-sorbitol system shows the predominance of drug solvent interactions in water-sorbitol systems. As the temperature increases, the attractive forces among solvent molecules decreases and thus there are more free solvent molecules available for solvation of drug molecules which is confirmed by the decreasing β values with increase in temperature.

The plots for the variation of β and L_f with concentration of MH in these systems are shown in Fig. (5)(a-b).

According to Jacobson's intermolecular free length theory for liquids[50], the molecules of liquid are assumed to be spherical and the average value of the distance that the ultrasonic waves travel between the two molecules is called the intermolecular free length.

The experimental values of ultrasonic velocity U are related to L_f [51] as

$$L_f = \frac{K}{U_{\exp}\sqrt{\rho_{\exp}}} = K\sqrt{\beta} \qquad (9)$$

where K is the temperature dependent constant = (93.875 + 0.375T)×10^{-8})[52].

The values for intermolecular free length show similar behaviour to that of adiabatic compressibility with concentration. The values of L_f (Table 4) increases with rise in temperature. These trends show the presence of drug solvent interactions i.e. MH in water-sorbitol systems.

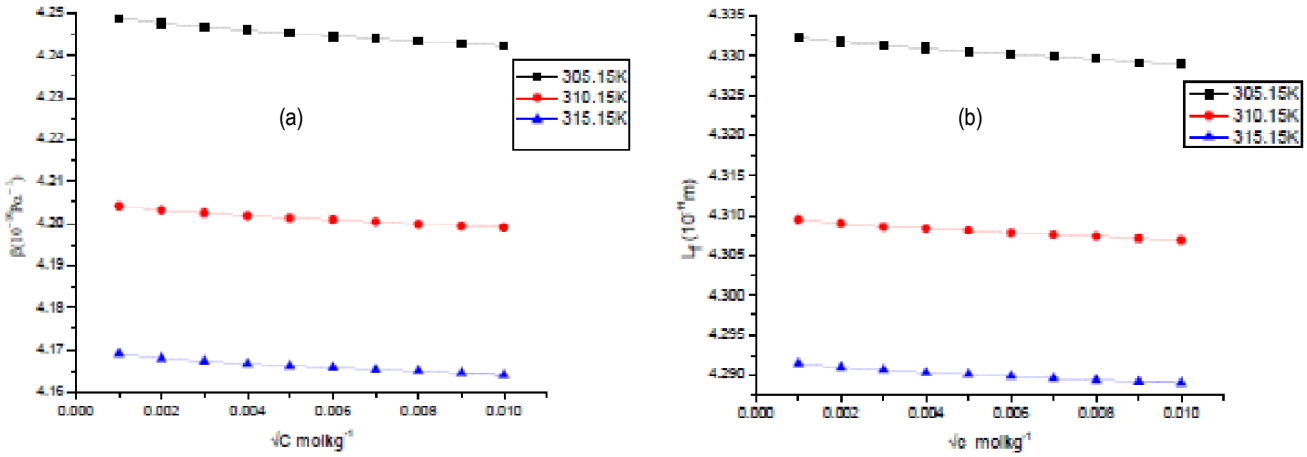


Fig. 5. Plots for (a) the variation of β and (b) the L_f for MH in 4% aqueous sorbitol at different temperature.

Specific acoustic impedance which is a measure of the resistance offered by the medium for the propagation of sound waves through it. The values of *Z* for MH in water and in different water-sorbitol system are reported in Table 4 by using eq. (8). The values of *Z* are compatible with the values of β and L_f indicating the presence of drug solvent interactions in the studied systems[53,54].

$$Z = u\rho \qquad (10)$$

where *u* and ρ are the ultrasonic velocity and densities of solution respectively.

Conductance study:

In the present investigation, the specific conductance, molar conductance and Walden product for metformin hydrochloride in water and in aqueous sorbitol systems at 305.15 K, 310.15 K and 315.15 K temperatures have been determined. The electrical conductance is an important parameter to understand degree of dissociation, nature of solute-solvent interactions, ion-association and dissociation constant and above all the structure making/breaking tendency. The measurement of conductance as a function of concentration gives the conductance at infinite dilution Λ_m^o. The limiting molar conductance is evaluated by using Kraus-Bray conductivity equation[55,56]. The structural effects of ions on the solvents in aqueous solutions are derived by comparison of their Walden product at different temperatures[57,58]. Greater the Walden product of the electrolyte in a given solvent, greater is its solute-solvent interactions. Structure maker/breaker behaviour of an electrolyte is determined by plotting Walden product versus temperature. Negative temperature coefficient suggests that electrolyte behaves as a structure breaker and the positive coefficient accounts for the structure making behaviour of the electrolyte[59]. The viscosity of a solute is usually studied to obtain information on ion-solvent interactions[60,61].

The values of specific conductance (κ) for metformin hydrochloride in water and water-sorbitol system increases with increase in concentrations. The values of specific conductance increases with rise in the temperature in water and water-sorbitol system which may be due to increase in ionic conductance of the solute with rise in temperature.

The plots of variation of specific conductance with concentration and with temperature for metformin hydrochloride in water and water-sorbitol system are given in Fig. 6.

The molar conductance for metformin hydrochloride in water and water-sorbitol system is calculated by the below given equation:

$$\Lambda_m = \frac{\kappa \times 1000}{c} \qquad (11)$$

Here κ is specific conductance and *C* is molar concentration. The molar conductance for metformin hydrochloride in water and in sorbitol at 305.15 K, 310.15 K and 315.15 K temperatures have been recorded in Table 5.

The value of molar conductance of MH decreases with increase in concentration of sorbitol (Fig. 7(a-d)) which may be due to decrease in dissociation of MH. The plots (a-d) i.e.

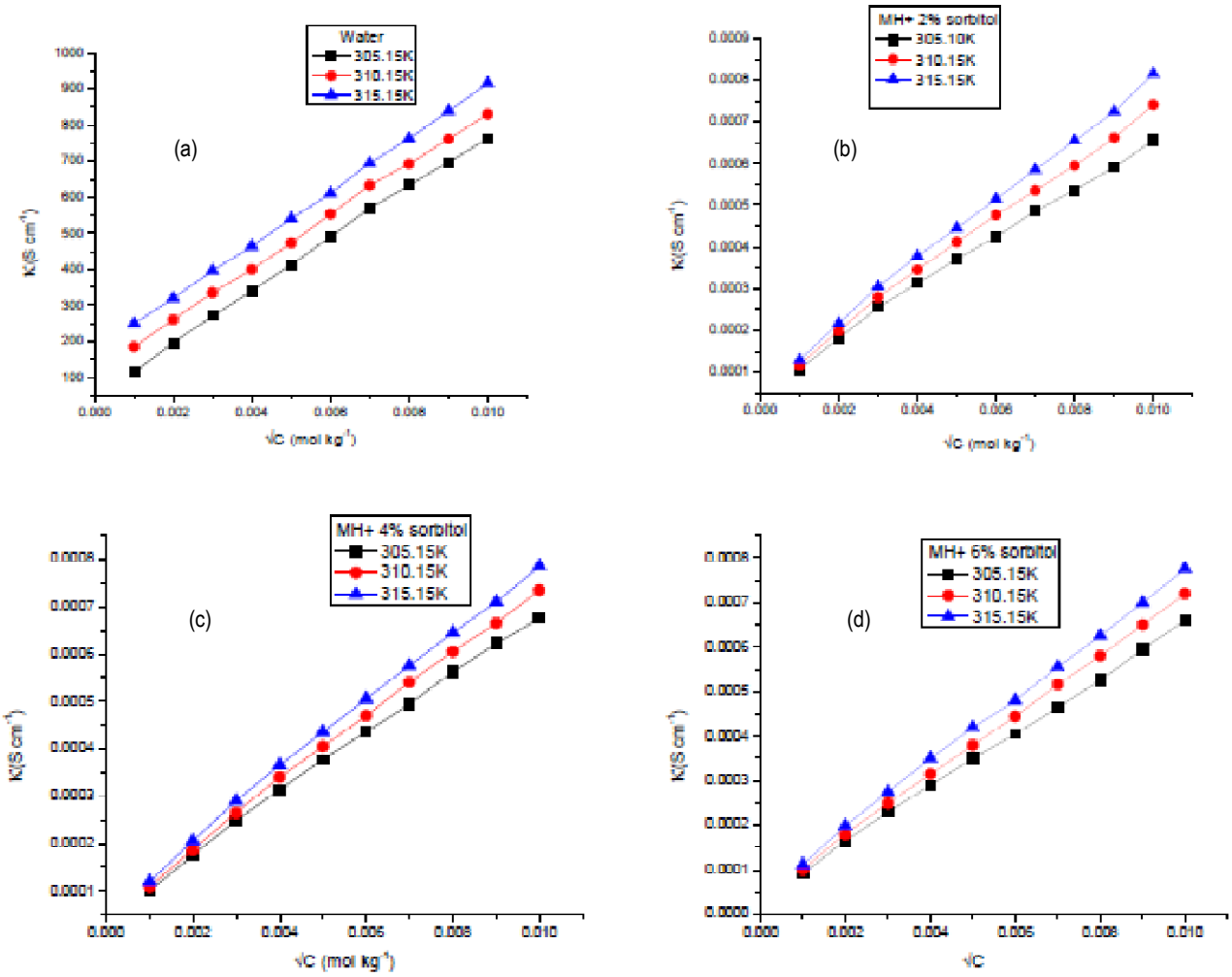


Fig. 6. Plots for variation of specific conductance with concentration for metformin hydrochloride in water and water-sorbitol system at different temperatures.

molar conductance versus *c* for MH in water and water-sorbitol system are curved which shows great association between MH and aqueous sorbitol. The value of molar conductance for MH in water and water-sorbitol system increases with rise in temperature which is as a result of increase in dissociation of MH in water and water-sorbitol system (Fig. 7(a-d)).

The limiting molar conductance has been obtained from the intercept by applying the least squares fit to the experimental values of $1/\lambda_m$ vs $\lambda_m C$ by using Kraus-Bray conductivity equation which is another form of Ostwald's dilution law[62]:

$$1/\lambda_m = 1/\lambda_m^{o} + \lambda_m C/K_c\lambda_m^{o\,2} \qquad (12)$$

Here λ_m^{o} is the limiting molar conductance, K_c is dissociation constant and C is molar concentration. The limiting molar conductance (Λ_m^0), signifies solute-solvent interactions[63]. In the present study, linear plots of $1/\lambda_m$ versus $\lambda_m C$ have been obtained for metformin hydrochloride (0.001–0.01 m) in water and in aqueous solution of sorbitol at 305.15, 310.15, and 315.15 K temperatures. The values of limiting molar conductance for MH in water and water-sorbitol system increases with rise in temperature which may be due to increase in the mobility of ions. The sample plot for the variation of $1/\lambda_m$ vs $\lambda_m C$ for MH in 2% sorbitol is shown in Fig. 8.

The values of limiting molar conductance for metformin hydrochloride in water, 2, 4 and 6 wt.% aqueous sorbitol at

Table 5. Molar conductance (Λ_m) of metformin hydrochloride in water and aqueous sorbitol at different temperatures

Concentration (mol/L) $C^{1/2}$	Λ_m (Ω^{-1} cm^2 mol^{-1})		
	305.15 K	310.15 K	315.15 K
	Water		
0.031623	119.01	175.00	210.01
0.044721	105.00	132.51	160.00
0.054772	95.04	111.66	135.12
0.063246	87.50	98.75	121.25
0.070711	81.02	91.00	112.21
0.077460	75.81	84.16	104.16
0.083666	77.10	86.42	99.28
0.089443	73.75	86.50	95.25
0.094868	74.66	84.55	93.11
0.100000	72.01	83.10	91.50
	2% Aqueous sorbitol		
0.031623	112.00	127.12	135.11
0.044721	96.00	107.00	114.12
0.054772	86.00	94.66	101.33
0.063246	78.75	85.75	93.25
0.070711	74.00	81.56	86.02
0.077460	71.33	79.80	82.83
0.083666	69.71	77.50	80.00
0.089443	68.00	75.71	78.62
0.094868	66.44	75.00	77.77
0.100000	65.00	74.12	77.66
	4% Aqueous sorbitol		
0.031623	105.01	120.00	127.24
0.044721	92.00	103.00	108.25
0.054772	83.33	91.66	97.66
0.063246	78.25	84.00	89.14
0.070711	72.80	77.01	82.17
0.077460	69.33	75.83	80.51
0.083666	68.57	73.14	77.14
0.089443	66.87	72.62	75.62
0.094868	65.55	71.84	73.88
0.100000	64.50	71.53	72.51
	6% Aqueous sorbitol		
0.031623	90.22	100.27	108.01
0.044721	78.00	83.24	87.53
0.054772	69.33	72.33	76.67
0.063246	63.75	64.75	69.25
0.070711	59.00	59.36	63.35
0.077460	55.33	57.89	62.76
0.083666	54.28	55.57	60.28
0.089443	53.12	55.35	59.12
0.094868	52.12	54.22	58.77
0.100000	51.52	53.15	57.52

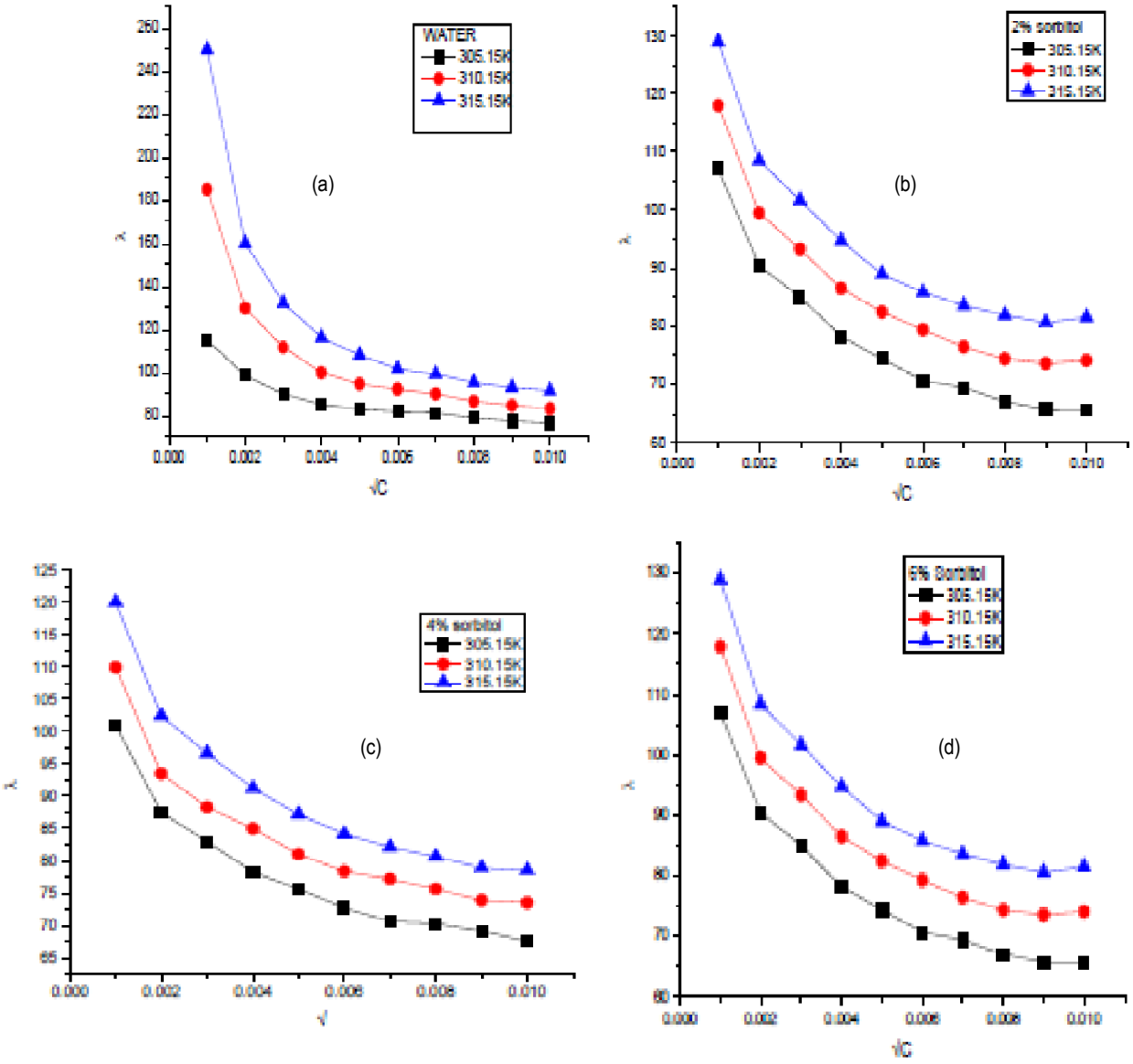


Fig. 7. Plots for the variation of molar conductance with water and different concentration of sorbitol.

different temperatures (305.15 K, 310.15 K, 315.15 K) have been recorded in Table 6.

Walden product is the product of limiting molar conductance and the viscosity of the solvent system. Larger the viscosity of the medium, the lesser is the mobility and hence lesser is the conductance of the ion. The values of viscosity and hence the values of Walden product increases with increase in the concentration of sorbitol. Greater values of Walden product at higher concentrations signifies greater solute-solvent interactions. Structure maker/breaker behaviour[64] of metformin hydrochloride in sorbitol is determined by plotting Walden product with temperature. The positive temperature coefficient suggests that metformin hydrochloride behaves as a structure maker in water-sorbitol system.

The values of Walden product, viscosity and limiting molar conductance for metformin hydrochloride in water and water-sorbitol system at 305.15 K, 310.15 K and 315.15 K temperatures have been recorded in Table 7.

The Walden product data for metformin hydrochloride in

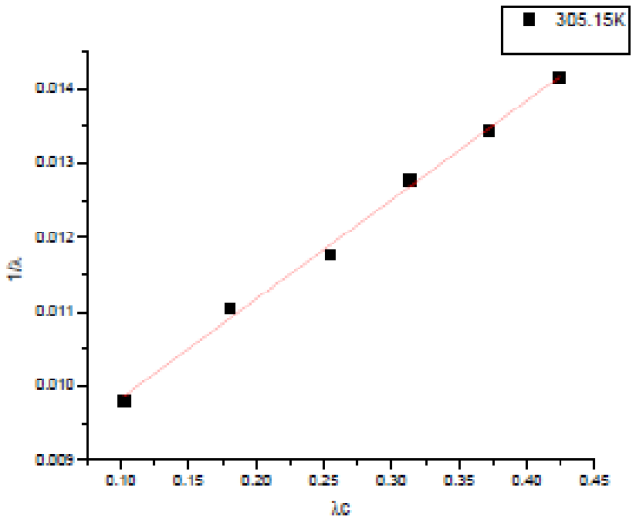


Fig. 8. The sample plot of $1/\lambda_m$ vs $\lambda_m C$ for metformin hydrochloride in 2% aqueous sorbitol solution at 305.15 K.

Table 6. Limiting molar conductance at different temperature for MH in water and 2, 4, and 6 wt.% aqueous sorbitol

Solvent	Λ_m^o (Ω^{-1} cm^2 mol^{-1})		
	305.15 K	310.15 K	315.15 K
Water	151.74	218.34	456.62
2% Sorbitol	142.80	175.43	181.81
4% Sorbitol	125.20	163.93	169.49
6% Sorbitol	114.90	158.73	166.65

Table 7. Viscosity and Walden product for water and 2, 4 and 6 wt.% aqueous solutions of sorbitol

Solvent	λ_m^o (Ω^{-1} cm^2 mol^{-1})	η_o (*cP*)	$\lambda_m^o \eta_o$ (Ω^{-1} cm^2 mol^{-1} P)
Water			
305.15 K	151.74	0.7679	1.16
310.15 K	218.34	0.7089	1.54
315.15 K	456.62	0.6272	2.86
2% Sorbitol			
305.15 K	142.80	0.8153	1.16
310.15 K	175.43	0.7635	1.33
315.15 K	181.82	0.7493	1.36
4% Sorbitol			
305.15 K	128.21	0.8423	1.07
310.15 K	163.93	0.7805	1.27
315.15 K	169.49	0.7680	1.30
6% Sorbitol			
305.15 K	114.64	0.8620	1.01
310.15 K	158.73	0.8001	1.26
315.15 K	166.66	0.7800	1.29

water and in aqueous solutions of 2, 4 and 6 wt.% sorbitol at different temperatures (305.15 K, 310.15 K, 315.15 K) is recorded in Table 7. The temperature coefficient of Walden product i.e. $\left(\frac{d(\Lambda_m^0 \eta_0)}{dT}\right)$ is positive for metformin hydrochloride in 2, 4 and 6 wt.% aqueous sorbitol suggests that MH behave as structure maker[65,66] in aqueous sorbitol system. The sample plots showing variation of $\Lambda_m^0 \eta_0$ versus temperature for metformin hydrochloride (0.001–0.01m) in water and in aqueous solutions of sorbitol at different temperatures (305.15 K, 310.15 K, 315.15 K) are shown in Fig. 9.

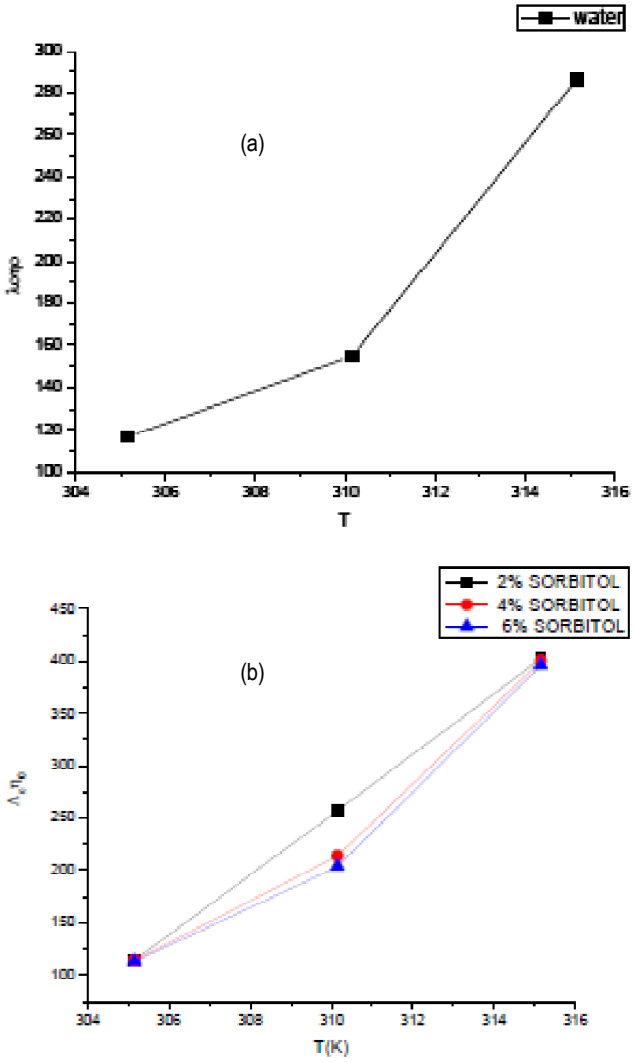


Fig. 9. Plots of $\Lambda_m^0 \eta_0$ vs temperature for metformin hydrochloride in water and aqueous sorbitol at different temperatures.

Conclusion

The partial molar volume, partial molar expansibility, adiabatic compressibility, intermolecular free length and specific acoustic impedance values for MH in water and water-sorbitol system indicate the presence of strong solute-solute and solute-solvent interactions and the interactions are strengthened with increase in concentration of sorbitol. The increase in the value of Φ_E^0 with temperature and positive value of Hepler's constant for MH in water and water-sorbitol system indicates that MH behaves as a structure maker in water and aqueous sorbitol system. The conclusion drawn from conductance studies also shows that metformin hydrochloride behave as structure maker in 2, 4 and 6 wt.% aqueous sorbitol at 305.15 K, 310.15 K, and 315.15 K. Since MH behaves as structure maker hence it is safer for the patient suffering from hypertension also.

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