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Ultrasonic Studies in the Solutions of Levofloxacin Hemihydrate, Tacrolimus Monohydrate and Lisinopril Dihydrate in Methanol

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Abstract: Ultrasonic velocity, density, and viscosity have been measured experimentally in the solutions of hydrates in non-aqueous medium i.e., methanol at two temperatures 30 and 40^{o}C. From the derived parameters like internal pressure, adiabatic compressibility, free volume etc., the solute-solvent and solute-solute interactions are estimated. Also in all the three hydrates in methanol, apparent molar volume, apparent molar compressibility are computed and the limiting / partial molar volumes and compressibilities have been obtained to reveal the nature of interactions. Jones – Dole constants also evaluated are of high value in estimating the nature of interactions. On the whole, the dominance of solute-solute interactions in the solutions of levofloxacin hemi hydrate is observed. In the solutions of tacrolimus monohydrate, mostly solute-solute interactions and strong solute-solvent interactions in the solutions of lisinopril di hydrate are found to be dominant.

Keywords: Solute-solute Interactions, Hydrates, Methanol, Apparent Molar Volume, Apparent Molar Compressibility.

1. INTRODUCTION

Studies of drugs and other compounds having medicinal value have been made by several workers [1-11]. Ultrasonic velocity, density, and viscosity measurements have been of immense use in estimating solute-solute and solute-solvent interactions. Study of various drugs in aqueous media, as well as non aqueous media, have been well carried out in understanding the molecular interactions. In the present investigation, the drugs chosen are levofloxacin hemihydrate, tacrolimus mono hydrate and lisinopril dihydrate owing to their importance in medicine, research and pharmaceutical industry. Ultrasonic velocity, density, and viscosity measurements have been carried out in the systems of methanol with the three hydrate compounds – levofloxacin hemihydrate, tacrolimus monohydrate and lisinopril dihydrate at two temperatures 30 and 40^{o}C. From the computed derived parameters like adiabatic compressibility, internal pressure etc., along with apparent molar volume (Φ_v) and compressibility (Φ_k), solute – solute and solute – solvent interactions have been estimated. Φ_v and Φ_k have been fitted to square root concentration to obtain limiting apparent molar volumes and molar compressibilities. Solvation numbers and Jones-Dole constants have also been computed to assess the nature of intermolecular interactions. Solute – solute interactions in the solutions of levofloxacin and tacrolimus with methanol while in the system lisinopril + methanol at low concentrations strong solute – solvent interactions are estimated.

2. EXPERIMENTAL

Ultrasonic velocity, density, and viscosity have been measured experimentally in the solutions of the three hydrate compounds employing the single crystal variable path ultrasonic interferometer, a double stem bicapillary type pyknometer and Ostwald viscometer with uncertainties $\pm$0.05%, 2 parts in 10^5 and $\pm$ 0.1% respectively.

The chemicals – hydrate compounds are of technical grade obtained from M/s Bioserve Clinical Research (Pvt) Ltd., Hyderabad. Methanol is of the analar grade. Standardization of the equipment has been made using triple distilled water as reference liquid.

3. THEORETICAL

From the measured velocity, density and viscosity, the following parameters can be calculated using the following expressions.

Adiabatic Compressibility $$\beta = \frac{1}{U_{exp}^{2}\,\rho_{exp}} \quad (1)$$

Internal pressure $$\pi = bRT\left|\frac{K\eta}{U}\right|^{1/2}\frac{\rho^{2/3}}{M^{7/6}} \quad (2)$$

Free volume $$V_f = \left|\frac{MU}{K\eta}\right|^{3/2} \quad (3)$$

Apparent molar volume $\varphi_v = (1000(\rho_0 - \rho)/C\rho_0) + M_{eff}/\rho_0$ (4)

Apparent molar compressibility $\varphi_k = (1000(\beta_0\rho_0 - \beta\rho)/C\rho\rho_0) + M_{eff}\beta/\rho_0$ (5)

Solvation number $$S_n = \frac{n_0}{n}\left|1 - \frac{V\beta}{n_0 V_0 \beta_0}\right| \quad (6)$$

Apparent molar volume (Φ_v) and Apparent molar compressibility (Φ_k) can be fitted to square root of molarity to obtain limiting molar volume (Φ_v^o) and limiting molar compressibility (Φ_k^o).

$$\Phi_V = \Phi_V^0 + S_V\sqrt{C} \quad (7)$$

$$\Phi_K = \Phi_K^0 + S_K\sqrt{C} \quad (8)$$

Jones – Dole Constants A and B can also be evaluated through the relation

$$\frac{\eta_r - 1}{\sqrt{C}} = A + B\sqrt{C} \quad (9)$$

All the parameters have been explained elsewhere [12, 13]

4. RESULTS AND DISCUSSION

Ultrasonic velocity, density, and viscosity have been measured in the three systems : i) Levofloxacin hemihydrate + methanol, ii) tacrolimus monohydrate + methanol and iii) lisinopril dihydrate + methanol at low concentrations of the solute (hydrate) at 30 and 40^{o}C and are presented in Table 1. From the table, it is observed that velocity decreases with a concentration of levofloxacin, increases with a molarity of tacrolimus and decreases with molarity in the third system with lisinopril. From the measured data, thermodynamic parameters like adiabatic compressibility (β), internal pressure (π), free volume (V_f) and enthalpy (H) have been computed and presented in Table 2. In levofloxacin system, β increases with concentration and temperature while π decreases with molarity and temperature. V_f is opposite to that of π while H is similar to π. As observed from Table 2 in the solutions of tacrolimus, β, π and H decrease with a molarity of tacrolimus while V_f is opposite to π. In the third system i.e methanol + lisinopril also, β, π and H decrease with concentration, the β curve is slightly nonlinear. From these observations, weak solute-solvent interactions and dominant solute-solute interactions in lisinopril and tacrolimus systems are indicated while in the first system levofloxacin though both types of interactions are indicated, solute-solvent interactions are very weak. In all the three systems, apparent molar volumes (Φ_v) and apparent molar compressibility's (Φ_k) also have been computed and presented in Figs. 2-3. They are fitted to square root concentration through the Masson's and Gucker equations to obtain the key parameters-limiting/partial molar volume (Φ_v^o) and compressibility (Φ_k^o) (shown in Table 3), which also speak of the nature of molecular interactions. The decrease of Φ_v and Φ_k confirm weak solute – solvent and strong solute – solute interactions at both the temperatures 30 and 40^{o}C (except at 30^o from Φ_v^o positive). The decrease of solvation numbers as shown Fig.4 suggests the existence of weak solute-solvent interactions. From the Jones-Dole constants, negative A suggests solute-solute interactions while positive B indicates strong solute-solvent interactions in the levofloxacin system.

In the solutions of tacrolimus in methanol, Φ_v is positive and high and decrease with concentration as well as temperature. The decrease in temperature is also very large. Φ_k is negative and negative Φ_k decrease with both temperature and concentration. From Φ_v and Φ_k decreasing, strong solute-solute interactions are indicated. Φ_v^o and Φ_k^o are negative and positive respectively which confirms the existence of strong solute-solvent interactions except at 40^o. From S_v also strong solute-solvent interactions are noticed. Positive B also confirms strong solute-solvent interactions. Solvation numbers are positive and decrease with a concentration of the drug. From the variation of the majority of the parameters, it is suggested that there is a dominance of the solute-solute interactions even though very weak solute-solvent interactions are also observed.

In the solutions of lisinopril in methanol, Φ_v is negative at 30^{o}C and positive at 40^{o}C. Φ_v decreases at both the temperatures. Φ_k^o is negative at both the temperatures and decreases nonlinearly with molarity at 30 and 40^{o}C. Φ_v^o is positive and Φ_k^o is negative at both the temperatures. S_v and S_k are negative and positive respectively. Jones-Dole constants suggest strong solute – solvent interactions. It may be understood from the variation of the majority of parameters despite a small chance of having solute-solute interactions, mostly strong solute-solvent interactions are indicated.

The results of previous workers are cited here for comparison to substantiate our results and interpretations:

From the density, ultrasonic velocity and viscosity measurements of four pharmacologically sufficient drugs in methanol at 25^{0}C, Φ_v, Φ_k etc., are computed. Φ_v^0 and B show different solute-solvent interactions while Φ_k^0 show that drugs suppress the solvent to the same extent. The same is supported by solvation numbers [1]. Acoustical properties of four drugs in methanol at 25^{0}C and some sympathomimetic drugs in their aqueous solutions [2] at four temperatures are studied. Meshran and Narwada [3] have studied ultrasonically some substituted pyrazolines (drugs) in acetone – water mixture and observed specific molecular interactions. Paradkar et al. [4] have also contributed to the study of drugs. Baluja and Oza [5] have studied the ultrasonic behavior (also thermodynamic) of some organic compounds in both aqueous and non-aqueous media. From a theoretical calculation of sound velocities in the binary solutions of tartaric acid in water, methanol, and ethanol [6], the theories NR, IDR and JUNJIE appear to suit well. Sharma et al. have made viscosity and velocity studies of drugs tramacip and parvodex in binary mixtures of alcohol + water [7]. From computed parameters β, L_f, Φ_v, Φ_k, Z, R_A, S_n, Jones - Dole constants A and B, molecular interactions are estimated in the solutions of Digoxin and Thiabenzadole (two drugs) in 1, 4 dioxanes at 303.15K. Weak solute-solvent interactions in digoxin-1, 4 dioxane and strong solute-solvent interactions in the thiabenzadole system are indicated [8]. Aswale et al. [9] have studied molecular interactions in coumaran-3- Ones in polar and non-polar solvents from ultrasonic velocity measurements. Solute-solvent interactions have been indicated in the solutions of coumaran-3-Ones in acetone and dioxane from β, Φ_v, Φ_k, L_f, Z etc. Roumana et al [10] from their investigation of Doxycycline hyclate with Ricinoleic acid, have indicated that the doxycycline hyclate exhibits liphophilic interaction effectively and turns to be a monomeric form at a physiological temperature from its dimer form. The inactivation of doxycycline molecules will result due to the molecular interactions with ricinoleic acid. The behaviour of L-Arginine with urea (Aq) solvent has been studied from β, Φ_v and Φ_k by Rita Mehra and Shilpi Vats [11]. Solute – solvent interactions are observed to be dominant and the amino acid L-Arginine behaves as a structure maker in the system.

On comparison of the three drugs (hydrates) in methanol, it is observed that from the variation of the majority of parameters, dominant solute – solute interactions and very weak solute - solvent interactions are suggested in the solutions of levofloxacin hemihydrate at low concentrations. In the solutions of tacrolimus monohydrate in methanol, solute-solute interactions are suggested predominantly while weak solute-solvent interactions are also observed at some concentrations. But in the third system, i.e. methanol + lisinopril dihydrate at low concentrations, unlike in the other two systems, mostly strong solute – solvent interactions are indicated.

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Table 1(i). Velocity, Density and Viscosity Data for the Mixture: Levofloxacin + Methanol

Molarity of Levofloxacin	Velocity (ms^{-1})	Density ($kg\ m^{-3}$)	Viscosity (milli Pa.s)
30^0C			
0.000162	1117.4	0782.73	0.46915
0.000432	1114.6	0784.31	0.45968
0.000621	1111.3	0782.97	0.46721
0.000877	1109.0	0782.34	0.46763
0.001080	1107.0	0782.06	0.46831
0.001350	1101.0	0781.75	0.46883
0.001660	1097.0	0781.39	0.46878
40^0C			
0.000162	1086.2	0778.28	0.43348
0.000432	1084.2	0778.64	0.42014
0.000621	1083.0	0775.74	0.42459
0.000877	1082.0	0775.63	0.42685
0.001080	1081.0	0775.42	0.42809
0.001350	1080.0	0774.63	0.42860
0.001660	1079.0	0773.16	0.42920

Table 2(i). Thermodynamic Parameters for the Mixture: Levofloxacin + Methanol

Molarity of Levofloxavin	Adiabatic compressibility ($10^{-10}\ N^{-1}\ m^2$)	Internal Pressure (atms)	Free Volume (m^3)	Enthalpy ($KJ\ mole^{-1}$)
30^0C				
0.000162	1.022	1014476	0.00017	711
0.000432	1.024	828266	0.00022	685
0.000621	1.032	741150	0.00025	681
0.000877	1.037	642006	0.00030	668
0.001080	1.041	580006	0.00034	659
0.001350	1.053	513712	0.00040	650
0.001660	1.062	452451	0.00047	639
40^0C				
0.000162	1.087	996526	0.00018	696
0.000432	1.091	806629	0.00024	667
0.000621	1.097	717479	0.00028	660
0.000877	1.099	622006	0.00033	648
0.001080	1.102	561829	0.00038	640
0.001350	1.105	495957	0.00044	630
0.001660	1.109	435887	0.00052	619

Table 3(i). Partial/apparent molar volumes, molar compressibilities and Jones- Dole constants for the mixture: Levofloxacin + methanol

Temperature	Φ_V^0	Φ_K^0	S_v	S_k	Jones- Dole Constants
30^0C	1093.98	-4.88E-5	-9409.18	0.00133	A= -11.00 B= 219.04
40^0C	-34074.53	-6.18E-5	984806.02	0.00165	A= -8.610 B= 164.82

Table 1 (ii). Velocity, Density and Viscosity Tacrolimus + Methanol

Molarity of Tacrolimus	Velocity (ms^{-1})	Density ($kg\ m^{-3}$)	Viscosity (milli Pa.s)
30^0C			
0.00015	1101.2	0.78148	0.4709
0.00032	1108.0	0.78112	0.46925
0.00052	1118.0	0.78054	0.46358
0.00076	1130.0	0.78039	0.46129
0.00083	1144.0	0.77981	0.45668
0.00095	1160.0	0.77929	0.45129
0.00109	1188.0	0.77879	0.44746
40^0C			
0.00015	1067.0	0.77461	0.42954
0.00032	1074.0	0.77421	0.42605
0.00052	1092.5	0.77416	0.41925
0.00076	1112.6	0.77387	0.41738
0.00083	1125.0	0.77352	0.41563
0.00095	1150.0	0.77337	0.41029
0.00109	1164.0	0.77348	0.40839

Table 2(ii). Thermodynamic parameters for the mixture: Tacrolimus + Methanol

Molarity of Tacrolimus	Adiabatic compressibility ($10^{-10}\ N^{-1}\ m^2$)	Internal Pressure (atms)	Free Volume (m^3)	Enthalpy ($KJ\ mole^{-1}$)
30^0C				
0.00015	1.055	906610	0.00019	706
0.00032	1.043	702997	0.00027	678
0.00052	1.025	551903	0.00037	649
0.00076	1.004	437424	0.00051	624
0.00083	0.98	408707	0.00057	613
0.00095	0.95	366464	0.00067	597
0.00109	0.91	324362	0.00080	578
40^0C				
0.00015	1.13	883407	0.00021	688
0.00032	1.12	681921	0.00029	659
0.00052	1.08	531604	0.00041	627
0.00076	1.04	419302	0.00057	601
0.00083	1.02	393136	0.00063	591
0.00095	0.98	350859	0.00075	573
0.00109	0.95	313018	0.00088	560

Table2 (iii). Partial/apparent molar volumes, molar compressibilities and Jones- Dole constants for the Mixture: Tacrolimus + Methanol

Temperature	Φ_V^0	Φ_K^0	S_v	S_k	Jones- Dole Constants
30^0C	17531.14	-1.047E-5	-424025	-1.42E-4	A= -10.71 B= 201.70
40^0C	1002.38	-5.62E-6	21874	-5.029E-4	A= -9.060 B= 160.83

Table 3(i). Velocity, Density and Viscosity Lisinopril + Methanol

Molarity of Lisinopril	Velocity (ms^{-1})	Density ($kg\ m^{-3}$)	Viscosity (milli Pa.s)
30^0C			
0.00028	1125.4	0783.09	0.45855
0.00050	1122.8	0783.19	0.45993
0.00077	1117.0	0783.33	0.46229
0.00113	1107.4	0783.53	0.46440
0.00143	1100.2	0783.84	0.46607
0.00195	1096.0	0784.18	0.46971
0.00226	1090.0	0784.37	0.47146
40^0C			
0.00028	1128.0	0772.82	0.39520
0.00050	1125.8	0773.14	0.39836
0.00077	1123.0	0773.38	0.40357
0.00113	1118.5	0773.49	0.40933
0.00143	1113.1	0773.59	0.41205
0.00195	1106.1	0773.70	0.41386
0.00226	1100.2	0773.78	0.41523

Table 3(ii). Thermodynamic parameters for the mixture: lisinopril + Methanol

Molarity of Lisinopril	Adiabatic compressibility ($10^{-10}\ N^{-1}\ m^2$)	Internal Pressure (atms)	Free Volume (m^3)	Enthalpy ($KJ\ mole^{-1}$)
30^0C				
0.00028	1.006	877381	0.00021	688
0.00050	1.013	744161	0.00026	674
0.00077	1.023	623325	0.00032	660
0.00113	1.039	510536	0.00041	644
0.00143	1.054	444582	0.00048	635
0.00195	1.062	359646	0.00063	619
0.00226	1.071	321893	0.00072	611
40^0C				
0.00028	1.017	814977	0.00026	642
0.00050	1.021	691711	0.00032	629
0.00077	1.025	580212	0.00039	618
0.00113	1.033	476018	0.00050	605
0.00143	1.043	414242	0.00059	596
0.00195	1.056	334568	0.00077	581
0.00226	1.068	299345	0.00088	574

Table 3(iii). Partial/apparent molar volumes, molar compressibilities and Jones- Dole constants for the mixture: Tacrolimus + Methanol

Temperature	Φ_V^0	Φ_K^0	S_v	S_k	Jones- Dole Constants
30^0C	675	-3.81E-5	-31043	8.88E-4	A= -10.02 B= 173.50
40^0C	10011	-7.33E-5	-224122	0.00159	A= 12.38 B= 223.01

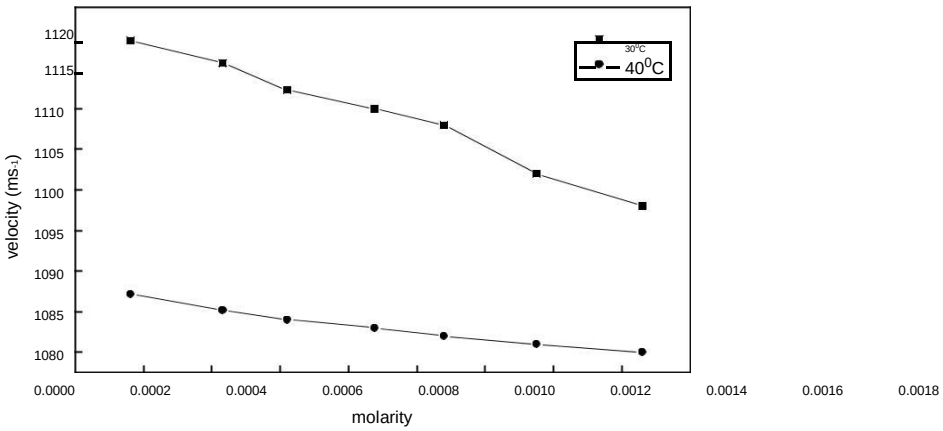

Fig.1(i). Variation of velocity with molarity of levofloxacin in the mixture: Levofloxacin + methanol

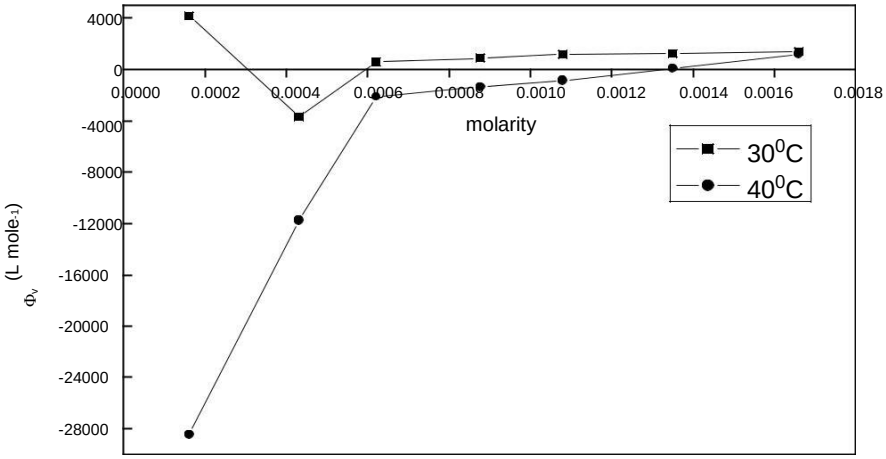

Fig. 2(i). Variation of apparent molar volume with molarity of levofloxacin in the mixture: Levofloxacin + methanol

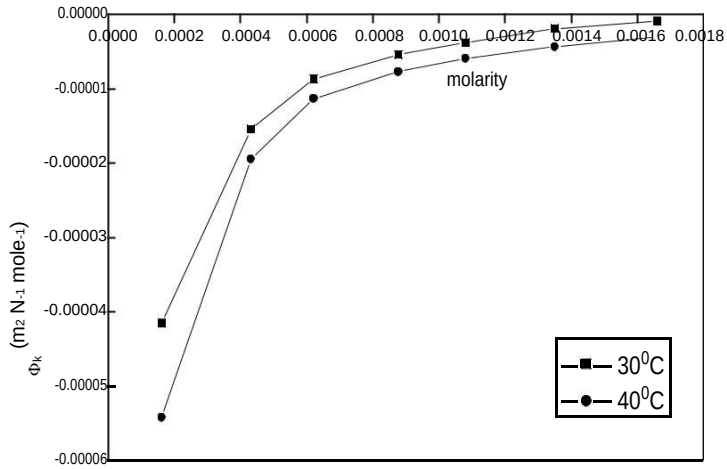

Fig. 3(i). Variation of apparent molar compressibility with molarity of levofloxacin in the mixture: Levofloxacin + methanol

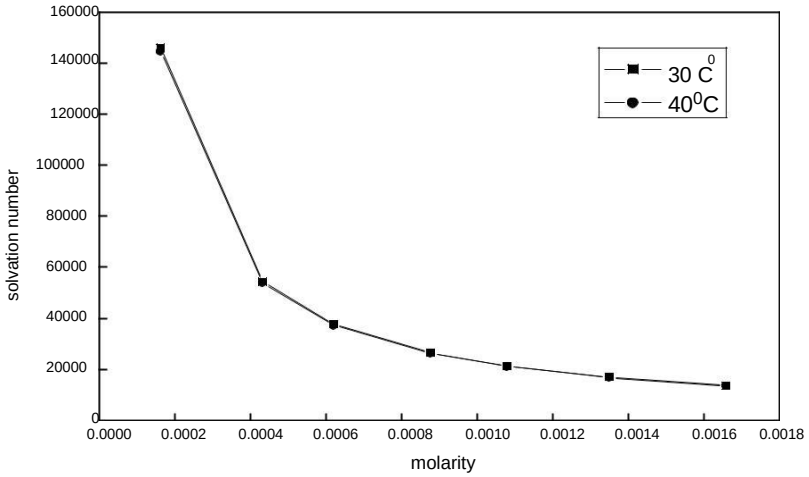

Fig. 4(i). Variation of solvation number with molarity of levofloxacin in the mixture: Levofloxacin + methanol

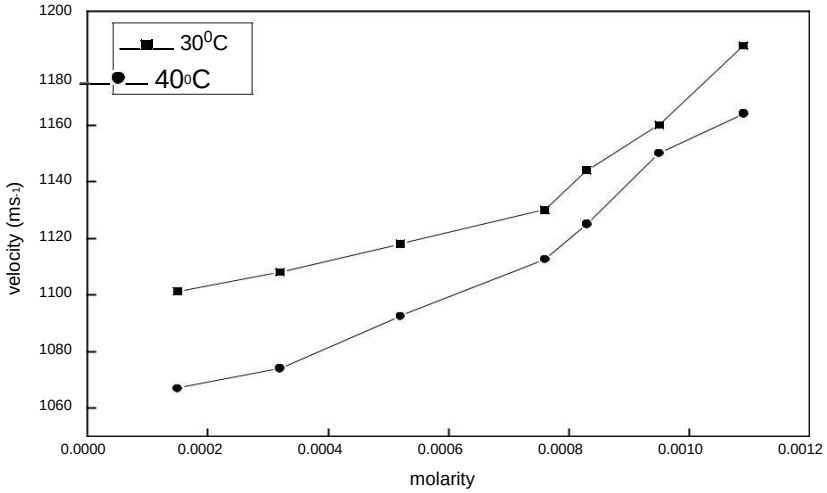

Fig. 1(ii). Variation of velocity with molarity of tacrolimus in the mixture: Tacrolimus + methanol

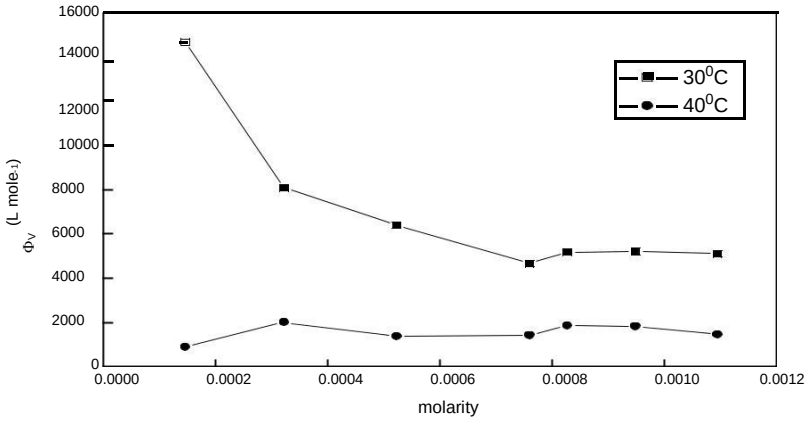

Fig. 2(ii). Variation of apparent molar volume with molarity of tacrolimus for the mixture: Tacrolimus + methanol

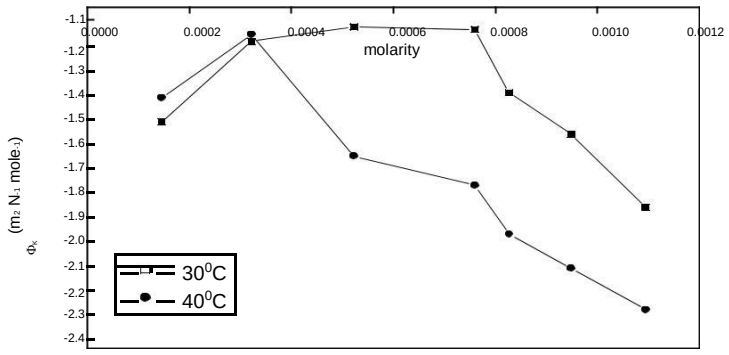

Fig. 3(ii). Variation of apparent molar compressibility with molarity of tacrolimus for the mixture: Tacrolimus + methanol

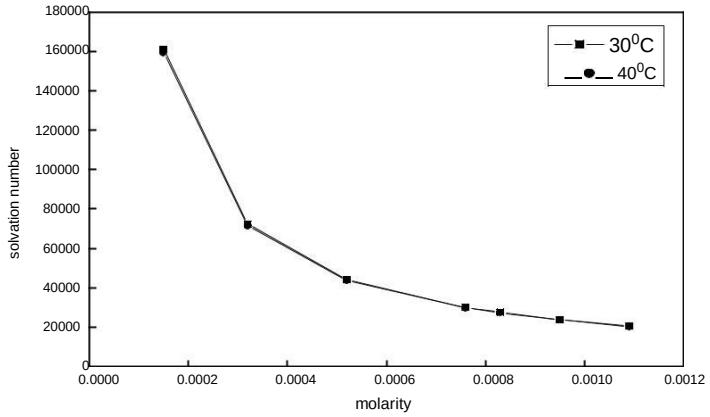

Fig. 4(ii). Variation of solvation number with molarity of tacrolimus in the mixture: Tacrolimus + methanol

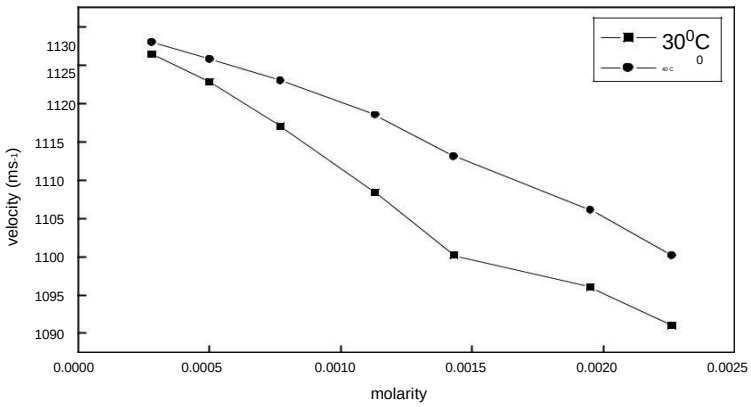

Fig. 1(iii). Variation of velocity with molarity of lisinopril for the mixture: Lisinopril + methanol

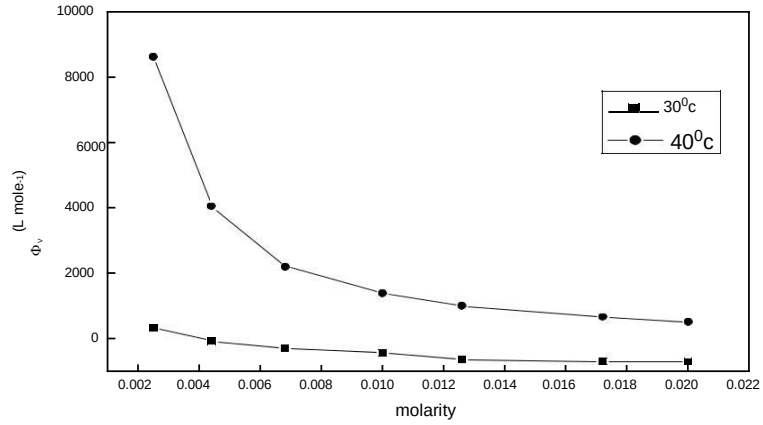

Fig. 2(iii). Variation of apparent molar volume with molarity of lisinopril in the mixture: Lisinopril + methanol

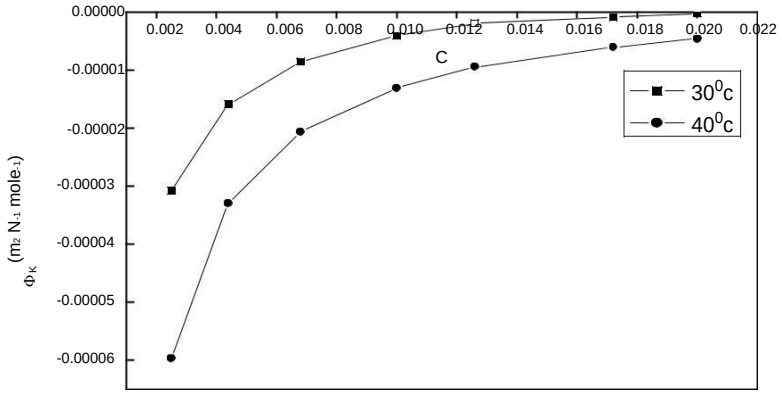

Fig. 3(iii). Variation of apparent molar compressibility with molarity of lisinopril in the mixture: Lisinopril + methanol

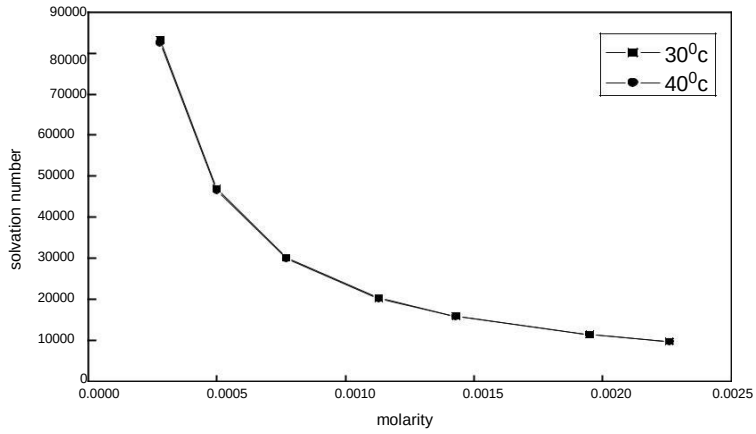

Fig. 4(iii). Variation of solvation number with molarity of lisinopril in the mixture: Lisinopril + methanol

