

Ultrasonic studies of some substituted drug such as Doxycycline and Dexamethasone in dioxane-water and DMF-water mixture

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Abstract: Ultrasonic velocity of Doxycycline i.e. 4-(dimethyl amino) 1,4,4a,5,5a,6,11,12a octahydro 3,6,10,12,12a Pentahydroxyl-1,11-dioxo naphthacence-2-carboxamide and Dexamethasone i.e. 9-fluro-11 β ,17,21 trihydroxy-16a methyl pregna-1,4-diene, 3,20 dion. in dioxane-water and DMF-water mixture have been determined. From these measured values, appa,rent molal volume (ϕ_v), partial molal volume (ϕ_v^p), adiabatic compressibility $\phi_{K(s)}$, intermolecular free length (L_t) and relative association have been calculated at 305° K. The observed and calculated values have been used to explain molecular association due to strong ion-ion interactions. The above study may be helpful in understanding the dynamics between metal ions and above drug.

Key words- apparent molal volume, partial molal volume, adiabatic compressibility, intermolecular free length, relative association,

Introduction

In the recent years, ultrasonic waves have acquired the status of an important probe for the study of structure and properties of matter. In the field of technology, ultrasonic waves are being used for detection of flows, testing of materials, mechanical cleaning of surface etc. In medical sciences too, the ultrasonic waves are being used to diagnose bone fractures, cancer, tumors, foetal condition and in physiotherapy, bloodless surgery, gynecology etc. Present day applications of ultrasonic are emerging in the field of forensic science space research and in wars. Adiabatic compressibility and apparent molal compressibility have been used to study the relative association, specific constant factor and solvation number of the system. The study of molecular interactions in liquid provides valuable information regarding internal structures molecular association, complex formation internal pressure etc. Ultrasonic velocity and absorption studies in case of electrolyte solutions have led to a new insight into the process of ion association and complex formation.^{1,2} Tabhane et.al³ have investigated the cluster approach to thermodynamic behavior of ligand mixture of acrolein in methanol-cyclohexane and dioxane using Khasare's equation of state⁴. A.P. Mishra⁵ has studied the ultrasonic velocities of some bio-applicable system involving ZnCl₂, dextrose and methionine in water. The apparent and partial molal volume of electrolyte solutions has proved a very important tool in elucidating the structural interactions i.e. ion-ion, ion-solvent and solute-solvent interactions occurring in solutions. Partial molal volumes and adiabatic compressibility properties reflect the structural interactions with water molecules or organic solvent molecules and therefore some substituted drug such as Doxycycline and Dexamethasone are selected for these investigations.

Ultrasonic study of interactions in ternary solutions has been done by Pandey et.al⁶. Aswar⁷ studied the interactions between bio-molecules involving Mg ion in aqueous solutions. The compressibility and apparent molal volume of any electrolyte in mixed organic solvents are found out earlier.⁸ The compressibility and apparent molal volume of peptides in aqueous as well as water-organic solvent mixtures are studied by Khobragade et.al⁹. But compressibilities and apparent molal volumes of substituted drugs in water-organic solvent mixtures are not studied so far. Thus we herein present the ultrasonic systematic studies of substituted drugs in dioxane-water and DMF-water mixtures.

Experimental

Materials and Reagents

All analytical grade chemicals and solvents used were obtained from Merck, India. The distilled water used has a specific conductivity of about $1 \times 10^{-6} \text{ ohm}^{-1} \text{ cm}^{-1}$. Stock solutions of Doxycycline and Dexamethasone were prepared in different percentage of dioxane-water and DMF-water mixtures. Ultrasonic velocity (2 MHz) was measured by single crystal path interferometer with an accuracy of 0.03%. The density measurements were carried out at 305° K.

The apparent molal volumes (ϕ_v) and apparent molal adiabatic compressibility $\phi_{K(s)}$ of Doxycycline and Dexamethasone in solutions are determined from density (d_s) and adiabatic compressibility (β_s) of solution using following equations

$$\phi_v = \left\{ \frac{(d_0 - d_s) \times 10^3}{m d_s d_0} \right\} + \frac{M}{d_s} \quad \text{----- (1)}$$

Where M is molecular weight of the solute, m is the molality of solution, d_0 is the density of the solvent and d_s is the density of the solution.

$$\phi_{K_s} = \left\{ \frac{(\beta_s d_0 - \beta_0 d_s) \times 10^3}{m d_s d_0} \right\} + \frac{\beta_s M}{d_s} \quad \text{----- (2)}$$

Where β_s is the adiabatic compressibility of solution and β_0 is the adiabatic compressibility of solvent which can be calculated by

$$\beta_s = \frac{100}{U_s^2 \times d_s} \quad \text{----- (3) for solution and}$$

$$\beta_0 = \frac{100}{U_0^2 \times d_0} \quad \text{----- (4) for solvent}$$

Where U_s & U_0 are the ultrasonic velocities of ultrasonic waves in solution and solvent respectively.

Knowing β_s , β_0 and molecular weight of pyrazoline and isoxazolines, the values of ϕ_v and $\phi_{K(s)}$ are calculated. The values of ϕ_v and $\phi_{K(s)}$ are plotted against molality (m) of pyrazoline and isoxazolines. The curve represented the least square and ϕ_v and $\phi_{K(s)}$ can be given as

$$\phi_v = (\phi_v^0 + S_v m) \quad \text{----- (5)}$$

$$\phi_{K(s)} = (\phi_{K(s)}^0 + S_{K(s)} m) \quad \text{----- (6)}$$

Where $\phi_v^0 = v^0$ and $\phi_{K(s)}^0 = \kappa^0$ are the infinite dilution partial molal volumes and adiabatic partial molal compressibilities respectively. S_v and $S_{K(s)}$ are the experimental slopes.

The $\phi_{K(s)}$ and ϕ_v values of Doxycycline and Dexamethasone in two mixed solvents are calculated and given in Table 1 to 11.

The intermolecular free length (L_t), specific acoustic impedance (z) and relative association (R_A) are calculated by using the following relations

$$L_t = K \times (B_s)^{1/2} \quad \text{----- (7)}$$

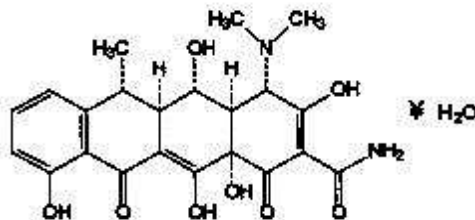
Where K is Jacobson's constant = 6.0186×10^4 and

$$Z = U_s \times d_s \quad \text{----- (8)}$$

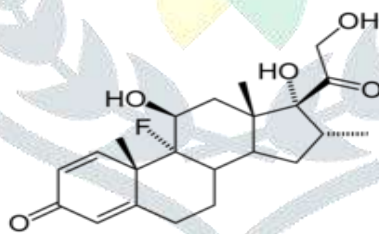
$$R_A = ds/d0 (U_0/U_s)^{1/3} \quad \text{----- (9)}$$

The ligands used in these investigations are

- 1) **Doxycycline** i.e. 4-(dimethyl amino) 1,4,4a,5,5a,6,11,12a octahydro 3,6,10,12,12a Pentahydroxyl-1,11-dioxo naphthacence-2-carboxamide



- 2) **Dexamethasone** i.e. 9-fluoro-11 β ,17,21 trihydroxy-16a methyl pregna-1,4-diene, 3,20 dion.



Results and Discussion

The experimental and calculated values of ultrasonic velocities (U_s), densities (d_s), adiabatic compressibilities (β_s), apparent adiabatic compressibility ($\beta_{K(s)}$), relative association (R_A), specific acoustic impedance (z), apparent molal volume (ϕ_v) and intermolecular free length (L_t) for Doxycycline and Dexamethasone are tabulated in Table No. 1 to 8. These values have been used to discuss the interactions of unlike molecules of solvent in presence of solute. The variation of ultrasonic velocity in solution depends on the intermolecular free length on mixing on the basis of a model for sound propagation proposed by Eyring and Kincaid¹⁰.

The graphs are plotted between $\beta_{K(s)}$ versus mole fraction of organic solvent and are found to be linear over the entire range of mole fraction except one of the point. In each plot, one of the points is significantly away from the linearity. Therefore $\beta_{K(s)}$ measurements for these organic substances are limited for those mole fractions where linearity is being followed and this seems the range of dilute solutions.

Linear pattern of the graphs is observed in dioxane-water and DMF-water as shown in graph no. 1 to 3. The plot between ϕ_v and mole fraction of organic solvents are shown in graph no. 4 to 6 and shows that ϕ_v values varies inversely with percentage / mole fraction of organic solvent.

The plot between $\beta_{K(s)}$ and mole fraction of organic solvents indicates that $\beta_{K(s)}$ values increases with increasing percentage / mole fraction of organic solvent. Pankanti and Jahagirdar¹¹ have investigated apparent molal compressibility for amino acids in dioxane-water and acetone-water media. It is observed that $\beta_{K(s)}$ decreases upto 40% organic solvent-water mixture.

Present work reveals the increase in ($\beta_{K(s)}$) values above 70% organic solvent –water mixture (Table 1 to 8). This fact shows that $\beta_{K(s)}$ increases at higher percentage of organic solvent –water mixture. This suggests that loss of compressibility of water due to electrostatic forces in the vicinity of ions causing electro-strictive hydration of ions. The apparent molal volume (ϕ_v) has been calculated from density data of solution using equation (2). The data obtained are in well agreement with Messon equation as the plot of ϕ_v against (c)^{1/2} or mole fraction is linear. The ϕ_v

values of substituted pyrazoline and isoxazolines are found to increase with increasing percentage of organic solvent –water mixture. Das¹² studied the apparent molal volume (Δ_v) of univalent ions up to 30% dioxane-water mixture and reported that Δ_v values of these ions increases with increase in dioxane content in dioxane-water mixture. In the present investigation it is found that the values of Δ_v values are higher in dioxane-water mixture as compared to DMF-water mixture due to decreasing dielectric constant of medium¹³. It can be explained by postulating that the [polar –OH group interact with the surrounding organic solvent-water mixture through dipole-dipole interaction in such away that the surrounding water losses its own compressibility to certain extent.

The Δ_k values are found to be decrease in the following order of organic solvent-water mixture – dioxane-water < DMF-water, which suggest that Doxycycline and Dexamethasone are extensively hydrated in dioxane-water mixture than DMF-water mixture. This can be explained on the basis of higher polarity of dioxane-water mixture than DMF-water mixture. Dipole induced- dipole interactions between unlike molecules are more in dioxane-water mixture.

In the present investigation, the values of L_t , R_A and Z are also evaluated (Table 1 to 8). It could be seen from above table that intermolecular free length increase linearly with increasing concentration of Doxycycline and Dexamethasone. This indicates that there are significant interactions between ions and solvent molecules suggesting structure-promoting behaviour of added electrolyte molecule. This may also imply that decrease in number of free ions showing the occurrence of ionic association due to strong ion-ion interactions. Relative association (R_A) is influenced by two factors- 1) the breaking up of solvent molecules on addition of electrolyte to it. And 2) the solvation of ions that simultaneously present the former resulting in decrease and later increase of relative association. The increase of R_A with concentration suggest that solvation of ions predominates over the breaking up of solvent aggregates (water-water, water-dioxane and water-DMF) on addition of pyrazoline and isoxazolines. It is observed from the table that there is linear variation of R_A signifies the weaker association between solvent and solute molecules.

References

- [1] S.K. Kor and S. S. Bhatti, *Indian J. Pure Appl. Phys.*, 1969, **7**, 184.
- [2] V.S. Soitkar and S.N. Jajoo, *Acoustic Lett.*, 1984, **7**, 191.
- [3] V.A. Tabhane, V.T. Bhandarkar and S.B. Khasare, *Indian J. Pure Appl. Phys.*, 1995, **33**, 248.
- [4] S.B. Khasare, *Indian J. Pure Appl. Phys.*, 1993, **31**, 224.
- [5] A.P. Mishra, *Indian J. Chem.*, 2004, **43A**, 730.
- [6] V. Wadhvani, Y. Akhtar and J.D. Pandey, *Proc. Indian Acad. Sci.*, 1997, **109**, 353.
- [7] A.S. Aswar, *J. Pure Appl. Ultrason.*, 1998, **20**, 82
- [8] S.D. Hammn and S.C. Limb, *Aus. J. Chem.*, 1954, **7**, 329
- [9] B.G. Khobragade and M.L. Narwade, Ph.D. thesis in Chemistry, Amravati University, Amravati, 1999.
- [10] H. Erying and J.F. Kincaid, *J. Chem. Phys.*, 1938, **6**, 620
- [11] S.U. Pankanti and D.V. Jahagirdar, Ph.D. thesis in Chemistry, Marathwada University, Aurangabad, 1986.
- [12] P.B. Das, *J. Indian Chem. Soc.*, 1989, **66**, 380
- [13] P.B. Das, *Electromechim. Acta*, 1981, **26**, 1099.

Table No. 1

Ultrasonic velocities (U_s), densities (ds), adiabatic compressibilities (Δ_s) and intermolecular free length (L_t) at different concentrations of ligand in different percentage of dioxane-water mixture at 303 K. System L_1 . Doxycycline i.e. 4-(dimethyl amino) 1,4,4a,5,5a,6,11,12a octahydro 3,6,10,12,12a Pentahydroxyl-1,11-dioxo naphthacence-2-carboxamide

Ultrasonic frequency: 2MHz Temperature: 303 K Medium: Dioxane-water

% Dioxane	Conc. in mol dm ⁻³	Ultrasonic velocities	Densities (ds) in g cm ⁻³	Adiabatic compressibilities (Δ_s)	Inter molecular free length (L_t)
95	9.5 X 10 ⁻³	1411.2	1.0538	4.76 X 10 ⁻⁵	4.15 X 10 ²
90	9.0 X 10 ⁻³	1427.2	1.0633	4.61 X 10 ⁻⁵	4.08 X 10 ²
85	8.5 X 10 ⁻³	1457.6	1.0604	4.43 X 10 ⁻⁵	4.00 X 10 ²
80	8.0 X 10 ⁻³	1469.0	1.0549	4.23 X 10 ⁻⁵	3.91 X 10 ²
75	7.5 X 10 ⁻³	1507.2	1.0588	4.17 X 10 ⁻⁵	3.88 X 10 ²
70	7.0 X 10 ⁻³	1535.0	1.0593	4.00 X 10 ⁻⁵	3.80 X 10 ²

Table No. 2

Apparent molal volume (Δ_v), apparent adiabatic compressibility (Δ_k), specific acoustic impedance (z) and relative association (R_A) at different concentrations of ligand in different percentage of dioxane-water mixture at 303 K.

System L_1 -**Doxycycline** i.e. 4-(dimethyl amino) 1,4,4a,5,5a,6,11,12a octahydro 3,6,10,12,12a Pentahydroxyl-1,11-dioxo naphthacence-2-carboxamide Ultrasonic frequency: 2MHz Temperature: 303 K Medium: Dioxane-water

Conc. in mol dm ⁻³	Apparent molal volume (Δ_v)	Apparent adiabatic compressibility (Δ_k)	Relative association (R_A)	Specific acoustic impedance (z)
9.5 X 10 ⁻³	-692.0	-1.99 X 10 ⁻⁴	1.0063	1.487 X 10 ³
9.0 X 10 ⁻³	-1695.6	-4.34 X 10 ⁻⁴	1.0116	1.517 X 10 ³

8.5×10^{-3}	-1515.5	-6.45×10^{-4}	1.0017	1.545×10^3
8.0×10^{-3}	-1011.7	-9.01×10^{-4}	0.9879	1.578×10^3
7.5×10^{-3}	-1181.9	-10.58×10^{-4}	0.9892	1.595×10^3
7.0×10^{-3}	-1788.2	-13.663×10^{-4}	0.9838	1.620×10^3

Table No. 3

Ultrasonic velocities (U_s), densities (ds), adiabatic compressibilities (\square_s) and intermolecular free length (L_t) at different concentrations of ligand in different percentage of dioxane-water mixture at 303 K.

System L₂ - Dexamethasone i.e. 9-fluro-11 β ,17,21 trihydroxy-16a methyl pregna-1,4-diene, 3,20 dion.

Ultrasonic frequency: 2MHz Temperature: 303 K Medium: Dioxane-water

% Dioxane	Conc. in mol dm ⁻³	Ultrasonic velocities	Densities (ds) in g cm ⁻³	Adiabatic compressibilities (\square_s)	Inter molecular free length (L_t)
95	9.5×10^{-3}	1374.4	1.0679	4.957×10^{-5}	4.237×10^2
90	9.0×10^{-3}	1409.6	1.0546	4.772×10^{-5}	4.157×10^2
85	8.5×10^{-3}	1476.8	1.0423	4.399×10^{-5}	3.991×10^2
80	8.0×10^{-3}	1539.2	1.0529	4.008×10^{-5}	3.810×10^2
75	7.5×10^{-3}	1569.6	1.0562	3.843×10^{-5}	3.731×10^2
70	7.0×10^{-3}	1596.8	1.0740	3.651×10^{-5}	3.636×10^2

Table No. 4

Apparent molal volume (\square_v), apparent adiabatic compressibility (\square_{k_s}), specific acoustic impedance (z) and relative association (R_A) at different concentrations of ligand in different percentage of dioxane-water mixture at 303 K.

System L₂ - Dexamethasone i.e. 9-fluro-11 β ,17,21 trihydroxy-16a methyl pregna-1,4-diene, 3,20 dion.

Ultrasonic frequency: 2MHz Temperature: 303 K Medium: Dioxane-water

Conc. in mol dm ⁻³	Apparent molal volume (\square_v)	Apparent adiabatic compressibility (\square_{k_s})	Relative association (R_A)	Specific acoustic impedance (z)
9.5×10^{-3}	-1127.2	-1.994×10^{-4}	1.0119	1467.72
9.0×10^{-3}	120.87	-3.400×10^{-4}	0.9909	1486.56
8.5×10^{-3}	1431.21	-7.194×10^{-4}	0.9643	1539.26
8.0×10^{-3}	290.25	-12.840×10^{-4}	0.9607	1620.02
7.5×10^{-3}	-107.50	-15.960×10^{-4}	0.9576	1657.81
7.0×10^{-3}	-2429.31	-20.537×10^{-4}	0.9576	1714.96

Table No. 5

Ultrasonic velocities (U_s), densities (ds), adiabatic compressibilities (\square_s) and intermolecular free length (L_t) at different concentrations of ligand in different percentage of DMF-water mixture at 303 K.

System L₁ - Doxycycline i.e. 4-(dimethyl amino) 1,4,4a,5,5a,6,11,12a octahydro 3,6,10,12,12a Pentahydroxyl-1,11-dioxo naphthacence-2-carboxamide

Ultrasonic frequency: 2MHz Temperature: 303 K Medium: DMF-water

% Dioxane	Conc. in mol dm ⁻³	Ultrasonic velocities	Densities (ds) in g cm ⁻³	Adiabatic compressibilities (\square_s)	Inter molecular free length (L_t)
95	9.5×10^{-3}	1520.8	0.9867	4.381×10^{-5}	398.36
90	9.0×10^{-3}	1542.4	0.9912	4.240×10^{-5}	391.90
85	8.5×10^{-3}	1611.2	0.9726	3.960×10^{-5}	378.74
80	8.0×10^{-3}	1611.2	0.9950	3.871×10^{-5}	374.46
75	7.5×10^{-3}	1628.8	0.9825	3.836×10^{-5}	372.76
70	7.0×10^{-3}	1651.2	1.032	3.554×10^{-5}	358.80

Table No. 6

Apparent molal volume (\square_v), apparent adiabatic compressibility (\square_{k_s}), specific acoustic impedance (z) and relative association (R_A) at different concentrations of ligand in different percentage of DMF-water mixture at 303 K.

System L₁ - Doxycycline i.e. 4-(dimethyl amino) 1,4,4a,5,5a,6,11,12a octahydro 3,6,10,12,12a Pentahydroxyl-1,11-dioxo naphthacence-2-carboxamide

Ultrasonic frequency: 2MHz Temperature: 303 K Medium: DMF-water

Conc. in mol dm ⁻³	Apparent molal volume (\square_v)	Apparent adiabatic compressibility (\square_{k_s})	Relative association (R_A)	Specific acoustic impedance (z)

9.5×10^{-3}	149.02	-3.570×10^{-4}	0.9907	1500.47
9.0×10^{-3}	-381.1	-5.578×10^{-4}	0.9906	1528.82
8.5×10^{-3}	1850.4	-8.354×10^{-4}	0.9580	1567.05
8.0×10^{-3}	-3200.00	-11.160×10^{-4}	0.9800	1603.24
7.5×10^{-3}	-305.82	-11.730×10^{-4}	0.9642	1600.29
7.0×10^{-3}	-6338.08	-19.178×10^{-4}	1.0906	1704.03

Table No. 7

Ultrasonic velocities (U_s), densities (d_s), adiabatic compressibilities (β_s) and intermolecular free length (L_t) at different concentrations of ligand in different percentage of DMF-water mixture at 303 K.

System L_2 - Dexamethasone i.e. 9-fluoro-11 β ,17,21 trihydroxy-16a methyl pregna-1,4-diene, 3,20 dion.

Ultrasonic frequency: 2MHz Temperature: 303 K Medium: DMF-water

% Dioxane	Conc. in mol dm ⁻³	Ultrasonic velocities	Densities (d_s) in g cm ⁻³	Adiabatic compressibilities (β_s)	Inter molecular free length (L_t)
95	9.5×10^{-3}	1523.20	1.06790.9715	4.436×10^{-5}	4.008×10^{-2}
90	9.0×10^{-3}	1560.00	1.0039	4.093×10^{-5}	3.850×10^{-2}
85	8.5×10^{-3}	1625.60	1.0129	3.735×10^{-5}	3.678×10^{-2}
80	8.0×10^{-3}	1678.40	1.0232	3.461×10^{-5}	3.545×10^{-2}
75	7.5×10^{-3}	1694.40	1.0253	3.397×10^{-5}	3.507×10^{-2}
70	7.0×10^{-3}	1699.20	1.0261	3.375×10^{-5}	3.416×10^{-2}

Table No. 8

Apparent molal volume (\bar{v}_v), apparent adiabatic compressibility (β_{k_s}), specific acoustic impedance (z) and relative association (R_A) at different concentrations of ligand in different percentage of DMF-water mixture at 303 K.

System L_2 - Dexamethasone i.e. 9-fluoro-11 β ,17,21 trihydroxy-16a methyl pregna-1,4-diene, 3,20 dion.

Ultrasonic frequency: 2MHz Temperature: 303 K Medium: DMF-water

Conc. in mol dm ⁻³	Apparent molal volume (\bar{v}_v)	Apparent adiabatic compressibility (β_{k_s})	Relative association (R_A)	Specific acoustic impedance (z)
9.5×10^{-3}	-1591.46	-0.4979	1.0065	1479.78
9.0×10^{-3}	-5402.90	-1.0717	1.0316	1566.08
8.5×10^{-3}	-6787.60	-1.5973	1.0268	1646.57
8.0×10^{-3}	-8564.20	-2.0686	1.0372	1663.31
7.5×10^{-3}	-9322.40	-3.3110	1.0283	1720.86
7.0×10^{-3}	-10128.53	-2.5122	1.0258	1738.62

Table No. 9

Limiting apparent molal volume (\bar{v}_v^∞) and limiting molal compressibility ($\beta_{k_s}^\infty$) of different ligands in Dioxane-water and DMF-water mixture at 303 K.

Sr.No.	System	$\beta_{k_s}^\infty$	\bar{v}_v^∞
1	L_1 (Dioxane-water)	-16.00	-2200.00
2	L_2 (Dioxane-water)	-22.50	-----
3	L_1 (DMF-water)	-----	-7600.00
4	L_2 (DMF-water)	-3.70	-12000.00