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Effect of beta-cyclodextrin on Volumetric and Acoustic behavior of Aqueous Doxycycline Hydrochloride

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ABSTRACT: Measurements of density (ρ), and ultrasonic velocity (u) of one of the most widely prescribed antibiotic drug Doxycycline Hydrochloride (DH) have been carried for binary drug/water system and ternary drug/water/βCD system at three different temperature viz. 305.15K, 310.15K, and 315.15K. From these experimentally measured quantities, different parameters have been evaluated which throw light on the structural rearrangement of these solutions. The precise density results are used to evaluate the apparent molar volume, partial molar volume φ_v^o, partial molar expansibility ϕ_E^o, transfer partial molar volume $\Delta_{tr}\Phi_v^o$ and the Hepler's constant. The ultrasonic speed is used to measure the adiabatic compressibility of both the systems. It is inferred from these results that β-Cyclodextrin has an improving effect on the aqueous solubility of DH.

Keywords: Partial molar volume, partial molar compressibility, partial molar expansibility, Hepler's constant.

I. NTRODUCTION

Thermodynamic and transport properties of drugs in aqueous phase provide information that can be very useful in understanding of the drug action. The drug-water molecular interaction and their temperature dependence also play an important role in pharmaceutical and medicinal chemistry. Doxycycline Hydrochloride is a broad spectrum antibiotic which is used in the treatment of a number of types of infections caused by bacteria and protozoa. It can be used orally or intravenously. It is used to treat many different bacterial infections, such as acne, urinary tract infections, intestinal infections, eye infections, gonorrhea, chlamydia, periodontitis (gum disease), and others. The study of interactions of drugs with cyclodextrins (CDs) has been carried out in recent years due to its pharmaceutical interest. Cyclodextrin has been used as models for protein and enzymes, because they interact with many drugs in a similar manner. CDs are cyclic oligosaccharides of a glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to the lack of free rotation around the bonds connecting the glucopyranose units, the CDs are not perfectly cylindrical molecules but are toroidal or cone shaped. As a result of their molecular structure and shape, they possess a unique ability to act as molecular containers by entrapping guest molecules in their internal cavity [1-4]. The driving forces for the complex formation include release of enthalpy-rich water molecules from the cavity, hydrogen bonding, Vander Waals interaction, charge transfer interaction etc. The physicochemical properties of free cyclodextrin molecule differ from those in complex [5-13]. The present study was aimed to evaluate structural changes in terms of solute-solute and solute-solvent interactions of doxycycline Hydrochloride both in binary doxy/water and ternary doxy/βCD/water systems.

II. MATERIALS AND METHODS

A. Materials

Doxycycline Hydrochloride having purity > 98% was obtained from Research Aid Palampur Himachal Pradesh. *β*-Cyclodextrin (purity > 99%), was also purchased from Research Aid Palampur. The structural formulae of the drug and β-cyclodextrin are shown in figure 1 and figure 2 respectively.

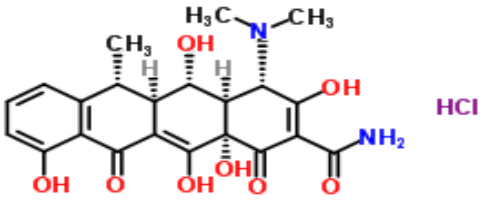

Fig. 1. Chemical structure of Doxycycline hydrochloride.

Fig. 2. Chemical structure of beta-cyclodextrin.

All the chemicals were used without further purification. Water used for the preparation of samples was de ionized and doubly distilled (conductivity lower than 5 μS).

B. Preparation of Solutions

Solutions were made on a mass basis at room temperature over a concentration range (0.001 to .01 mol kg^{-1}) using an analytical balance with a precision of ±0.001 g. The experiments were carried out at three different temperatures viz. 305.15K, 310.15K, and 315.15K. To avoid concentration gradients all solutions were stirred with the help of magnetic stirrer before the measurements.

C. Measurements

The density and ultrasonic speed for the different solutions were measured by an automated vibrating-tube density meter (Anton Paar DMA 5000) with an uncertainty of $\pm 10^{-5}$ g cm^{-3} which was calibrated with de-ionized and triply distilled water for the temperature range investigated. The density and ultrasonic speed measurements were performed at different temperatures T = (305.15 to 315.15) ± 0.01 K.

III. RESULTS AND DISCUSSIONS

A. Volumetric Studies

The apparent molar volume of Doxycycline Hydrochloride in water and in 2mM, 4mM and 6mM (where mM stands for mili Molal) aqueous β-Cyclodextrin solutions as modified solvent at particular temperature was calculated using densities of solution (ρ) and density of solvent (ρ^o) using expression

$$\varphi_v = M_2/\rho_o + 1000(\rho_o - \rho)/m\,\rho\,\rho_o \qquad \ldots(1)$$

Where M_2 represents the molecular weight of solute, and m is the molal concentration of the aqueous solution of the drug. The standard uncertainty in molality as per stated purities is u(m)= ± 0.1 mg. Standard uncertainties in u(ρ) density measurements are $\pm 5 * 10^{-6}$ gcm^{-1}. Standard uncertainties in u(T) temperatures are $\pm 1 * 10^{-2}$. Standard uncertainties in u(P) pressures are 0.1 MPa. The values of apparent molar volume for DH in water and different concentrations of beta cyclodextrin at different temperatures are given in table (1-4).

Table 1: Partial molar volume for Doxycycline hydrochloride in water 305.15–315.15 K.

Conc. (mol Kg^{-1})	Partial molar volume (φ_v) (cm^3mol^{-1})		
	305.15K	**310.15K**	**315.15K**
0.001	367.0826	367.5395	368.9203
0.002	366.95	367.3726	368.6606
0.003	366.791	367.176	368.4664
0.004	366.6451	367.0139	368.2639
0.005	366.4727	366.8419	368.0383
0.006	366.3035	366.6895	367.8831
0.007	366.122	366.5202	367.6698
0.008	365.9575	366.3772	367.4569
0.009	365.7823	366.2189	367.2663
0.01	365.5996	366.0399	367.0517

Table: 2. Partial molar volume for Doxycycline hydrochloride in 0.002 mol Kg^{-1} aqueous beta-cyclodextrin solution at 305.15–315.15 K.

Conc. (mol Kg^{-1})	Partial molar volume (φ_v) (cm^3mol^{-1})		
	305.15K	**310.15K**	**315.15K**
0.001	370.5713	371.1024	372.529
0.002	370.4593	370.961	372.3191
0.003	370.3473	370.8129	372.0763
0.004	370.2104	370.668	371.8991
0.005	370.1032	370.5561	371.689
0.006	369.9613	370.4111	371.5445
0.007	369.8278	370.2755	371.4093
0.008	369.6995	370.1458	371.2306
0.009	369.5417	370.0089	371.1216
0.01	369.4028	369.8967	370.933

Table 3. Partial molar volume for Doxycycline hydrochloride in 0.004 mol Kg^{-1} aqueous beta-cyclodextrin solution at 305.15–315.15 K.

Conc. (mol Kg^{-1})	Partial molar volume (φ_v) (cm^{3}mol^{-1})		
	305.15K	**310.15K**	**315.15K**
0.001	371.8653	372.5037	373.97
0.002	371.8033	372.4219	373.8589
0.003	371.7412	372.3335	373.7149
0.004	371.6791	372.2384	373.5873
0.005	371.6169	372.1466	373.4267
0.006	371.5382	372.0481	373.3154
0.007	371.4642	371.96	373.1618
0.008	371.3931	371.866	373.0433
0.009	371.324	371.779	372.9484
0.01	371.2661	371.6672	372.8204

Table 4: Partial molar volume for Doxycycline hydrochloride in 0.006 mol Kg^{-1} aqueous beta-cyclodextrin solution at 305.15–315.15 K.

Conc. (mol Kg^{-1})	Partial molar volume (φ_v) (cm^{3}mol^{-1})		
	305.15K	**310.15K**	**315.15K**
0.001	376.1359	377.0275	378.5947
0.002	376.1146	376.9962	378.534
0.003	376.0933	376.9551	378.47
0.004	376.0719	376.9189	378.4175
0.005	376.0546	376.8827	378.3518
0.006	376.0376	376.8547	378.2877
0.007	376.0207	376.8173	378.2245
0.008	376.0003	376.7864	378.1743
0.009	375.9807	376.7598	378.1107
0.01	375.9638	376.7263	378.0575

The apparent molar volume ϕ_v of drugs was plotted against the concentration (m) in accordance with the Masson's equation,

$$\varphi_v = \varphi_v^0 + s_v m \qquad (2)$$

where φ_v^0 and S_v are calculated from intercept and slope from the extrapolation of the plot of φ_v versus m.

The values of the partial molar volume ϕ_v^o have been calculated from the intercept of the linear plots in accordance with equation (2).

The values of S_v indicating weak solute–solute interactions can be determined from the slope but are considered to be of minor significance for non-electrolytic drug solutions.

The values of ϕ_v^o and S_v are recorded in table 5.

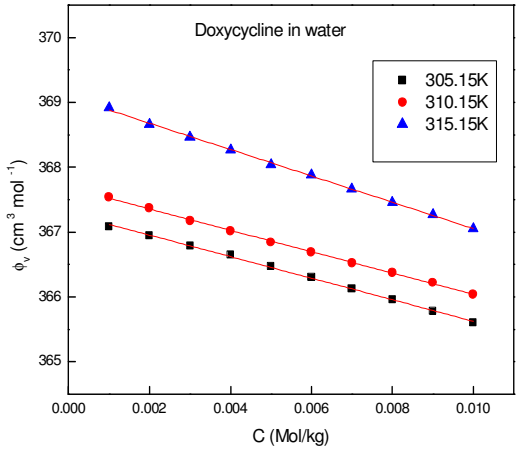

Fig. 3(a). Plot of partial molar volume Vs. drug concentration for Doxycycline Hydrochloride in water at three different temperatures.

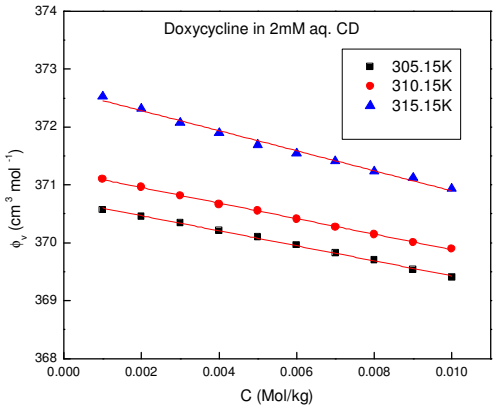

Fig. 3(b). Plot of partial molar volume Vs. drug concentration for Doxycycline Hydrochloride in 0.002 mol kg^{-1} aqueous β-Cyclodextrin solution at three different temperatures.

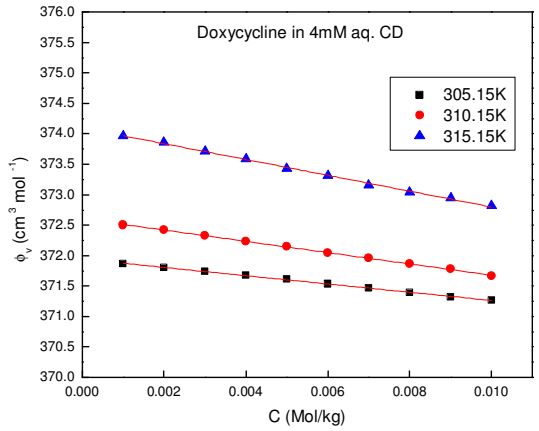

Fig. 3(c). Plot of partial molar volume Vs. drug concentration for Doxycycline Hydrochloride in 0.004 mol kg^{-1} aqueous β-Cyclodextrin solution at three different temperatures.

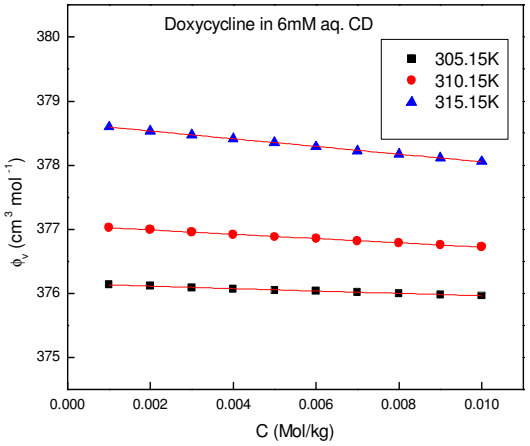

Fig. 3(d). Plot of partial molar volume Vs. drug concentration for Doxycycline Hydrochloride in 0.006 mol kg^{-1} aqueous β-Cyclodextrin solution at three different temperatures.

The limiting apparent molar volume ϕ_v^o is a measure of solute-solvent interactions[14-18]. It is evident from Table5 that the values of ϕ_v^o for Doxycycline in water and different compositions (2, 4 and 6mM) of aqueous β-Cyclodextrin solution are positive and high. This suggests that the solute-solvent interactions for Doxycycline in water and different composition (2, 4 and 6mM) of aqueous β-Cyclodextrin solution are high.

The order of solute-solvent interactions for Doxycycline in water and different composition (2, 4 and 6mM) of aqueous β-Cyclodextrin solution is given below:

Water < 2mM aqueous β-Cyclodextrin < 4mM aqueous β-Cyclodextrin < 6mM aqueous β-Cyclodextrin.

ϕ_v^o increases with temperature as well as with increase in the concentration of β-cyclodextrin in the system this implies solute-solvent interactions increases with temperature as well as with increase in the concentration of β-cyclodextrin in the system.

S_v decreases with temperature this implies solute-solute interactions decreases with temperature

The temperature dependence of ϕ_v^ocan be expressed by the following equation.

$$\phi_v^0 = a_0 + a_1 T + a_2 T^2 \qquad (3)$$

Separate relations were formed for each temperature in different solvents and were solved for the values of a_o, a_1 and a_2 by the method of elimination. The limiting apparent molar volume expansibility defined as $\phi_E^o = \left[\partial \phi_v^o / \partial T\right]p$ was also calculated using equation 4

$$\phi_E^o = a_1 + 2a_2 T \qquad (4)$$

The structure making/ breaking capacity of doxycycline Hydrochloride was interpreted with the help of Hepler's reasoning [19-20] using sign of $\left[\partial^2 \phi_v^o / \partial T^2\right]p$. The structure-making solutes have positive values of $\left[\partial^2 \phi_v^o / \partial T^2\right]p$, whereas structure-breaking solutes should show negative values of $\left[\partial^2 \phi_v^o / \partial T^2\right]p$.

Partial volume of transfer have been calculated using following relation

$\Delta_{tr}\Phi_v^o$ = Φ_v^o (solution) – Φ_v^o (water)

The values of $\Delta_{tr}\Phi_v^o$ are by definition free from solute-solute interactions and therefore provide information regarding solute-solvent interactions. The sign of the $\Delta_{tr}\Phi_v^o$ is often interpreted in terms of the strength of the solute- co solute interactions.

It is evident from table 5 that ϕ_E^o increases with increase in temperature for Doxycycline in water and different composition (2, 4 and 6mM) of aqueous β-Cyclodextrin solution, indicating thereby the presence of "caging effect". Although we see that as we increase the concentration of β-Cyclodextrin this increase in the value of ϕ_E^o with increase in temperature shifts to a lower value suggesting that this "caging effect" is reduced as we replaced water with aqueous β-Cyclodextrin solution, and the caging is further decrease as we go on increasing the concentration of β-Cyclodextrin in our solution.

Table 5: limiting apparent molar volume ϕ_v^o, S_v, apparent molar expensibility ϕ_E^o, transfer apparent molar volume Δ_{tr} ϕ_v^o and Hepler's constant for Doxycycline Hydrochloride in water and different compositions (2, 4 and 6mM) of aqueous β-Cyclodextrin solution at different temperatures (i.e. 305.15K, 310.15K, 315.15K).

Temp. (K)	$\phi^o_v = V^O_2$ ($cm^3 mol^{-1}$)	S^*_v ($cm^3 L^{1/2} mol^{3/2}$)	Φ_E^o ($cm^3 mol^{-1} K^{-1}$)	$\Delta_{tr}\Phi_v^o$	Hepler'sconstant $\left[\partial^2\phi_v^o/\partial T\right.$
Doxycycline Hydrochloride/water					
305.15	367.28	-164.85	- 0.02	--	0.04
310.15	367.68	-166.21	0.18	--	
315.15	369.08	-203.40	0.38	--	
Doxycycline Hydrochloride/ 2mM aq. βCD					
305.15	370.72	-130.10	0.01	3.44	0.036
310.15	371.22	-134.39	0.19	3.54	
315.15	372.62	-173.26	0.37	3.54	
Doxycycline Hydrochloride/ 4mM aq. βCD					
305.15	371.9	-67.94	0.06	4.62	0.032
310.15	372.60	-92.72	0.22	4.92	
315.15	374.1	-130.00	0.38	5.02	
Doxycycline Hydrochloride/ 6mM aq. βCD					
305.15	376.15	-18.92	0.11	8.37	0.028
310.15	377.05	-33.59	0.25	9.37	
315.15	377.65	-60.11	0.39	9.57	

Also we notice that the value of ϕ_E^o is slightly negative for doxycycline in water at 305.15K indicating that doxycycline has a poor solubility in water which increase with increase in temperature and also with increase in the concentration of β-Cyclodextrin in our system. So this clearly shows that β-Cyclodextrin has an improving effect on the aqueous solubility of doxycycline.

Further qualitative information on hydration of solutes can be obtained from the criteria proposed by Hepler (1969), called hydrophobicity criteria, It is suggested that the structure breaking solutes are accompanied by the negative $\left[\partial^2\phi_v^o/\partial T^2\right]p$ values. Correspondingly, the positive values of $\left[\partial^2\phi_v^o/\partial T^2\right]p$ are associated with the structure-making solutes. Strongly hydrated solutes are known as kosmotropes (structure makers), while weakly hydrated ones are chaotropes (structure breakers) [21]. A drug interacts with water to yield the intermolecular H-bonding between them. It is well known that the formation of H-bond results in a decrease in the partial molar volume due to shortening of the inter-atomic distance.

Inspection of table5 shows that in the present investigation Hepler's constant have very small positive values, the positive values suggest that doxycycline is a kosmotrope, i.e. structure makers in water. But as we replace our solvent with aqueous β-Cyclodextrin solution the structures making effect of doxycycline is reduced and go on decreasing with increase in the concentration of β-Cyclodextrin in the system.

These results were also supported by transfer volume and adiabatic compressibility trends.

Here high positive values of $\Delta_{tr}\Phi_v^o$ indicates strong solute- co solute interactions present in our system which increases with increased concentration of β-Cyclodextrin as well as with increase in temperature.

B. Ultrasonoic studies

Ultrasonic velocities (u), combined with corresponding densities are then used to obtain adiabatic compressibility [22-24].

According to Jacobson's Model, when the ultrasonic pressure waves are incident on liquid molecules, they get perturbed. Since the medium has some elasticity the perturbed molecules regain their equilibrium positions. Writing E for the bulk modulus of elasticity, the velocity of sound in the medium can be given by relation:

$$u = \sqrt{E/\rho} \qquad \text{or} \qquad E = u^2\rho$$

Table 6: Adiabatic compressibility Doxycycline hydrochloride in water at 305.15–315.15 K.

Conc. (mol Kg^{-1})	Adiabatic Compressibility (β) ($10^{-10}Pa^{-1}$)		
	305.15K	**310.15K**	**315.15K**
0.001	4.391508	4.331498	4.290865
0.002	4.389998	4.329936	4.28968
0.003	4.388486	4.3286	4.288158
0.004	4.387089	4.327037	4.287025
0.005	4.385577	4.325869	4.285558
0.006	4.384297	4.324363	4.284034
0.007	4.382785	4.322799	4.282734
0.008	4.381446	4.321463	4.280988
0.009	4.380224	4.320011	4.279299
0.01	4.378944	4.31873	4.277327

Table 7: Adiabatic compressibility Doxycycline hydrochloride in 0.002 mol Kg^{-1} aqueous beta-cyclodextrin solution at 305.15–315.15 K.

Conc. (mol Kg^{-1})	Adiabatic Compressibility (β) ($10^{-10}Pa^{-1}$)		
	305.15K	**310.15K**	**315.15K**
0.001	4.385233	4.329055	4.286052
0.002	4.383801	4.327493	4.284887
0.003	4.382253	4.325988	4.283664
0.004	4.380763	4.324483	4.282273
0.005	4.379331	4.322976	4.281105
0.006	4.377898	4.321472	4.279657
0.007	4.376641	4.320022	4.278208
0.008	4.37515	4.318517	4.276705
0.009	4.373777	4.317237	4.275147
0.01	4.372172	4.3159	4.273422

Writing the reciprocal of elasticity as β, the compressibility of liquid, we obtain

$$u^2\rho = 1/\beta \quad \text{or} \quad \beta = 1/u^2\rho$$

Table 8: Adiabatic compressibility Doxycycline hydrochloride in 0.004 mol Kg^{-1} aqueous beta-cyclodextrin solution at 305.15–315.15 K.

Conc. (mol Kg^{-1})	Adiabatic Compressibility (β) ($10^{-10}Pa^{-1}$)		
	305.15K	**310.15K**	**315.15K**
0.001	4.379466	4.322893	4.280058
0.002	4.378451	4.321571	4.278905
0.003	4.377204	4.320135	4.277696
0.004	4.375841	4.318868	4.276375
0.005	4.374479	4.317489	4.275277
0.006	4.373349	4.315997	4.274122
0.007	4.37193	4.314674	4.272579
0.008	4.370455	4.313239	4.271203
0.009	4.368922	4.311862	4.269439
0.01	4.367102	4.310202	4.267675

Table 9: Adiabatic compressibility Doxycycline hydrochloride in 0.006 mol Kg^{-1} aqueous beta-cyclodextrin solution at 305.15–315.15 K.

Conc. (mol Kg^{-1})	Adiabatic Compressibility (β) ($10^{-10}Pa^{-1}$)		
	305.15K	**310.15K**	**315.15K**
0.001	4.374182	4.317631	4.274461
0.002	4.373074	4.316277	4.273277
0.003	4.371736	4.315148	4.272092
0.004	4.370455	4.313851	4.270741
0.005	4.369117	4.312554	4.269278
0.006	4.367665	4.311145	4.268039
0.007	4.366156	4.309679	4.266411
0.008	4.364821	4.308327	4.265062
0.009	4.363313	4.306806	4.263657
0.01	4.361922	4.305173	4.26242

Fig. 4(a-d) shows a gradual and almost linear decrease in adiabatic compressibility was observed as concentration of β-cyclodextrin is increased in the solution. Due to breaking of hydrogen bonds, the solvent molecules within the primary solvation shell of drug solution are rendered incompressible moreover increasing concentration of solution results in more solvent molecules to engage in incompressible solvation spheres thereby decreasing the adiabatic compressibility.

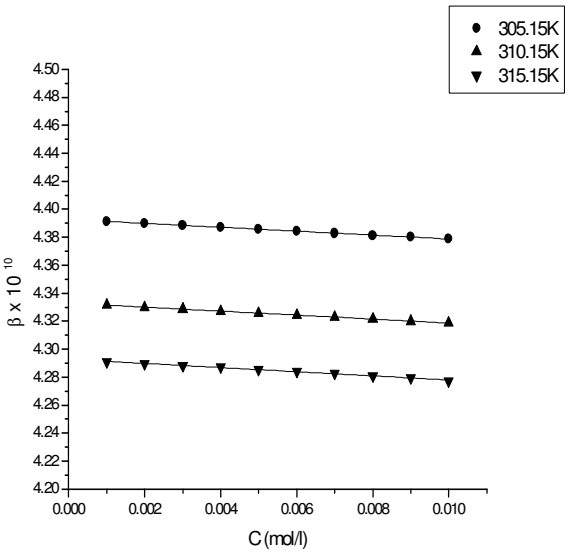

Fig. 4(a). Plot of adiabatic compressibility Vs. drug concentration for Doxycycline Hydrochloride in water at three different temperatures.

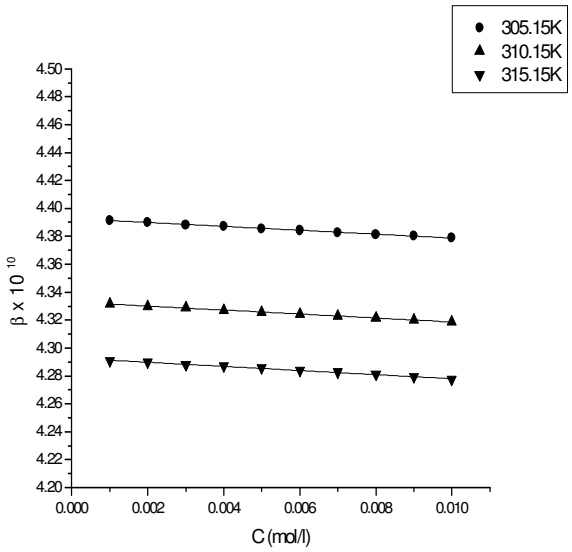

Fig. 4(b). Plot of adiabatic compressibility Vs. drug concentration for Doxycycline Hydrochloride in 0.002 mol kg^{-1} aqueous β-Cyclodextrin solution at three different temperatures.

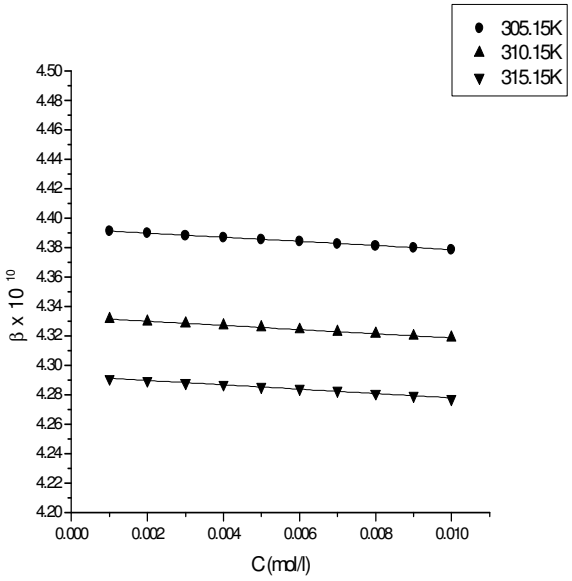

Fig. 4(c). Plot of adiabatic compressibility Vs. drug concentration for Doxycycline Hydrochloride in 0.004 mol kg^{-1} aqueous β-Cyclodextrin solution at three different temperatures.

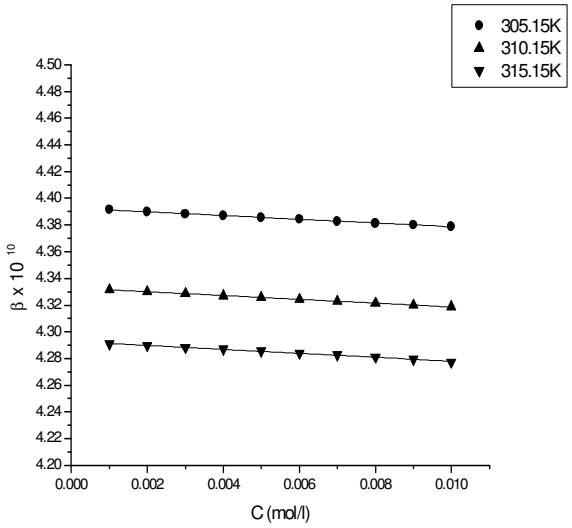

Fig. 4(d). Plot of adiabatic compressibility Vs. drug concentration for Doxycycline Hydrochloride in 0.006 mol kg^{-1} aqueous β-Cyclodextrin solution at three different temperatures.

Further with increase in temperature attractive forces among solvent-solvent molecules decreases and thus there are more free solvent molecules available for solvation of drug which is confirmed by decreasing values of β with increase in temperature.

This decrease in adiabatic compressibility with increasing concentration of β-cyclodextrin as well as with temperature shows presence of prominent solute solvent interactions in the system.

IV. CONCLUSION

The main objective of the present work is to do the rudimental investigation of the molecular interactions prevailing in Doxycycline Hydrochloride in aqueous medium and to see how these interactions are affected by using different compositions of aqueous β-Cyclodextrin solution as a modified solvent. The structural changes were evaluated in terms of the solute-solute and solute-solvent interactions of doxycycline both in binary doxy/water and ternary doxy/water/βCD systems. Extensive study of the thermo-physical properties of Doxycycline Hydrochloride in water and aq. βCD solution over a concentration range of drug from 0.001 to 0.01M was done at three different temperatures for three different compositions of aq. βCD. The study reveals that in both our systems solute-solvent interactions predominate over the solute-solute interactions. The values of partial molar volume are high and positive which decreases with the extent of H-bonding for doxycycline Hydrochloride in water. The structural effects of β-CD give a favorable support in the molecular interactions. We notice that the value of ϕ_E^o (partial molar expansibility) is slightly negative for doxycycline in water at 305.15K indicating that doxycycline has a poor solubility in water which increases with increase in temperature and also with increase in the concentration of β-Cyclodextrin in our system. So this clearly shows that β-Cyclodextrin has an improving effect on the aqueous solubility of doxycycline. Also we see that Hepler's constant $\left[\partial^2\phi_v^o / \partial T^2\right]p$ have very small positive values which go on decreasing with increase in the concentration of β-Cyclodextrin. So according to Heplers criteria Doxycycline behaves as a structure maker solute in water. But as we replace our solvent with aqueous β-Cyclodextrin solution the structures making effect of doxycycline is reduced and go on decreasing with increase in the concentration of β-Cyclodextrin in the system. The ultrasonic velocity, (U), for Doxycycline in water and different composition (2, 4 and 6mM) of aqueous β-Cyclodextrin solution were measured at temperatures 305.15K, 310.15K, and 315.15K. A gradual and almost linear decrease in adiabatic compressibility was observed as concentration of β-cyclodextrin is increased in the solution.

Due to breaking of hydrogen bonds, the solvent molecules within the primary solvation shell of drug solution are rendered incompressible moreover increasing concentration of solution results in more solvent molecules to engage in incompressible solvation spheres thereby decreasing the adiabatic compressibility. All these parameters give insight regarding various interactions present in the solution system. The results, data and parameters would be useful in determining physicochemical changes occurred in the presence of β-CD. This gives us strong evidences about the Doxycycline/CD complex formation.

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