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Volumetric Studies of Drug-α-Cyclodextrin Interactions in Water at 298.15 K: Ranitidine Hydrochloride + α -Cyclodextrin + H_2O system

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Abstract

Density measurements have been carried out for ternary aqueous solutions containing a fixed concentration of α-Cyclodextrin and varying concentrations of ranitidine hydrochloride at 298.15 K. These experimental density values have been utilized to evaluate apparent molar volume of the ranitidine hydrochloride in ternary solutions at finite concentrations as well at infinitely dilute solutions. The volume changes due to complexation have been estimated by applying the method developed by Jolicoeur et al. The volume change due to transfer of drug molecule from infinite dilute solutions of aqueous solutions to a solution containing a fixed concentration of α-Cyclodextrin for ranitidine hydrochloride is also obtained. The results obtained have been interpreted in terms of host-guest interaction as well as structural specificity of guest molecules.

Keywords: Ranitidine Hydrochloride, α-*Cyclodextrin*, Density, Apparent Molar Volumes, Host-Guest Interactions.

Introduction

In recent years the study on the drug and other important biological materials has increased by many folds. To understand the drug action at the molecular level, the physicochemical properties of drugs in aqueous media yield useful information[1-7]. In biology and protein science, the studies of binding constant and binding isotherms have been proved to be of use[8]. α-cyclodextrin (α-CD) can be used as a drug carrier and treated as a model system due to its symmetric structure, water solubility and ability to form complexes with large number of guest molecules[9-11]. It is well established that α-CD acts as a host which has hydrophobic cavities that can form inclusion complexes with various kinds of guest molecules, the extent of which is controlled by the structure of guest molecule as well as the cavity diameter of host[12-14].

Despite years of investigation, the mode of interaction of drugs in body fluid systems and the mechanism involved in it are not completely understood. To probe such interactions, experimental data on thermodynamic properties of the host-guest encapsulations provide the clues regarding the mechanism of membrane (lipid)-drug molecular interactions in the form of molecular recognition. Our literature survey reveals that the study of volume changes due to complexation in case of α-CD complexes is scarce.

Recently, we reported volume changes due to complexation for some local anesthetical reagents with α-CD in which positive volume changes are observed[15]. Considering all these, we have now extended the volumetric studied to ternary aqueous solutions of fixed concentration (~0.1 mol·kg^{-1}) of α-CD and varying the drug ranitidine hydrochloride RT·HCl concentration at 298.15 K. In this present work, densities of RT·HCl in 0.1 mol·kg^{-1} aqueous solutions of α-CD have been measured and the density values was used to determine the apparent molar volume (ϕ_V) of the drug in ternary solutions at 298.15 K. The results and analysis are presented in this report.

Materials and methods

RT·HCl and α-CD (≥0.98 mass fraction purity) were purchased from Sigma-Aldrich and used as received. The molecular structures of host α-CD and guest RT·HCl are given in Figure-1. All the solutions were prepared in double distilled water on molality basis by using high precision analytical balance (Shimadzu AUW220D) with an uncertainty in weight upto ±0.01.

The experimental densities of studied ternary system were determined at 298.15 K using DMA–5000 Anton Paar digital densimeter. The densimeter was calibrated using double distilled water and the density of water was found to be 997.043 kg·m^{-3} at 298.15 K. The uncertainty in the density measurement and temperature was found to be ±1 kg·m^{-3} and ±0.01 K, respectively.

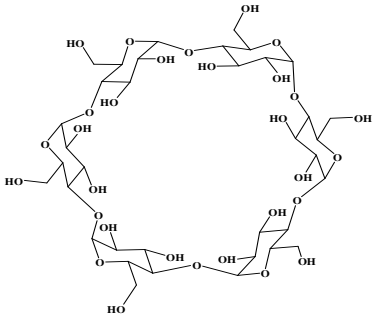
Results and discussion

Density (ρ) data of ternary system containing a fixed concentration (~0.1 mol·kg^{-1}) of α-CD and varying the RT·HCl concentration (~0.013 to ~0.20 mol·kg^{-1}) at 298.15 K is summarized in Table-1.

Table-1: Molality (*m*), density (*d*), apparent molar volumes (ϕ_V), fraction of complexed ions (α) and fraction of uncomplexed ions (α) data for ternary system (H_2O + ~0.1 mol·kg^{-1} α-CD + RT·HCl) at 298.15 K and at ambient pressure of 101.325 kPa.

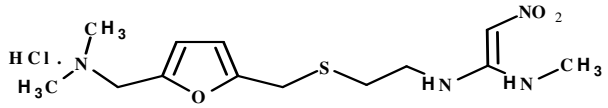
m / mol·kg^{-1}	*d* / kg·m^{-3}	$10^6 \cdot \phi_V$ / m^3·mol^{-1}	$10^6 \cdot \phi_{V\ \mathrm{Drug-Water}}{}^{*}$ / m^3·mol^{-1}	α	$\alpha' = (1-\alpha)$
0.00000	1031.667	514 .00±0.30**	-	-	-
0.01308	1030.765	411.48±0.30	265.69	1.0000	0.0000
0.02708	1032.108	323.17±0.15	266.09	1.0000	0.0000
0.05370	1033.235	309.53±0.07	266.29	1.0000	0.0000
0.08104	1035.801	286.39±0.05	265.80	0.9999	0.0001
0.10867	1036.873	289.27±0.04	264.66	0.9136	0.0864
0.13110	1039.388	277.33±0.03	263.34	0.7574	0.2426
0.17021	1041.431	278.35±0.02	260.32	0.5834	0.4166
0.20563	1045.225	268.63±0.02	256.99	0.4829	0.5171

*The $\phi_{V\ \mathrm{Drug-Water}}$ values are taken from Shaikh V. R. et al.[7]. **Extrapolated value at infinitely dilute solutions of the drug molecules in aqueous α-CD solutions at 298.15 K.



α–Cyclodextrin (α–CD)

(a)



(b)

Figure-1: (*a*) Molecular structure of α-CD and (b) Molecular structure of RT·HCl.

Further, experimental density data was used to calculate the apparent molar volume (ϕ_V) of RT·HCl in ternary solutions of finite concentrations using the equation:

$$\phi_V = \frac{(d_0 - d)}{mdd_0} + \frac{\mathrm{M}}{d} \qquad (1)$$

Where: *m* is molality of the RT·HCl in aqueous α-CD solution, *d* and *do* are the densities of ternary system and reference solvent (~ 0.1 mol·kg^{-1} aqueous α-CD solution), respectively and M is the molecular weight of RT·HCl.

Apparent molar volume at infinitely dilute solutions ϕ_V^0 of RT·HCl was obtained by using equation (2):

$$\phi_V = \phi_V^0 + \mathrm{S}_V \sqrt{m} \qquad (2)$$

Where: S_v is the experimental slope called as volumetric pair-wise interaction coefficient which includes the ion-ion and the solvent induced strength of cation-cation interactions.

The data of ϕ_V of solute is collected in Table-1. The variation of ϕ_V as a function of square root of molality of RT·HCl at 298.15 K is depicted in Figure-2 and extrapolated to limiting concentration (i.e., infinitely dilute solution), the intercept yields the apparent molar volumes at limiting concentration (ϕ_V^0) value of RT·HCl. The value of ϕ_V^0 of RT·HCl in aqueous α-CD is given in Table-2.

The value of transfer volume ($\Delta\phi_{V_{tr}}^0$) was calculated by using the values of ϕ_V^0 for RT·HCl in ternary solutions containing a fixed concentration (~ 0.1 mol·kg^{-1}) of α-CD and ϕ_V^0 of RT·HCl in binary solutions. The value of $\Delta\phi_{V_{tr}}^0$ is collected in Table-2 along with the data of ϕ_V^0 (for ternary system) and ϕ_V^0 (for binary system).

Table-2: Limiting apparent molar volumes of the drug molecules (ϕ_V^0), partial molar volumes of transfer of drug molecules at infinite dilution ($\Delta\phi_{V_{tr}}^0$), volume change due to complexation at infinite dilution ($\Delta\phi_c^0$) data for H_2O + ~0.1 mol·kg^{-1} α-CD + RT·HCl ternary system at 298.15 K and at ambient pressure of 101.325 kPa.

$10^6 \cdot \phi_V^0$ (ternary system) / m^3·mol^{-1}	$10^6 \cdot \phi_V^{0\,*}$ (binary system) / m^3·mol^{-1}	$10^6 \cdot \Delta\phi_{V_{tr}}^0$ / m^3· mol^{-1}	$10^6 \cdot \Delta\phi_c^0$ / m^3· mol^{-1}
514	265.11	248.89	200

*The ϕ_V^0 (binary system) value is taken from Shaikh V.R. et al.[7].

By adopting the methods developed by Jolicoeur[16] and ourselves[17], we treat the apparent molar volumes of RT·HCl in a dilute solution of α–CD as:

$$\phi_{V\,\text{solution}} = \phi_{V\,\text{Drug}-H_2O} + \alpha\,\Delta\phi_c + B'm \qquad (3)$$

Where: $\phi_{V\,\text{Drug}-H_2O}$ is apparent molar volumes of RT·HCl in water at same molar concentration, α is the fraction of complexed ions, $B'm$ term is the contributions from solute–solute interactions (where: m is the molal concentration of the studied drug).

The complexation reaction between the host (H) and guest (drug) cation (D^+) is given as:

$$H + D^+ = HD^+ \qquad (4)$$

$$\text{with equation } K_{eq} = \frac{[HD^+]}{[H][D^+]} \text{ and } \alpha = \frac{[HD^+]}{[D^+]_0} \qquad (5)$$

Where: $[D^+]_0$ is the total concentration of D^+ in the solution. For simplification, we assume $[HD^+] = x$, $[D^+]_0 = a$ and $[H] = b$, hence we can write expression as:

$$K_{eq} = \frac{x}{(a-x)(b-x)} \text{ and } \alpha = \frac{x}{a} \qquad (6)$$

Where

$$x = \frac{1}{2}\{(a+b+K_{eq}^{-1}) - [(a+b+K_{eq}^{-1})^2 - 4ab]^{1/2}\} \qquad (7)$$

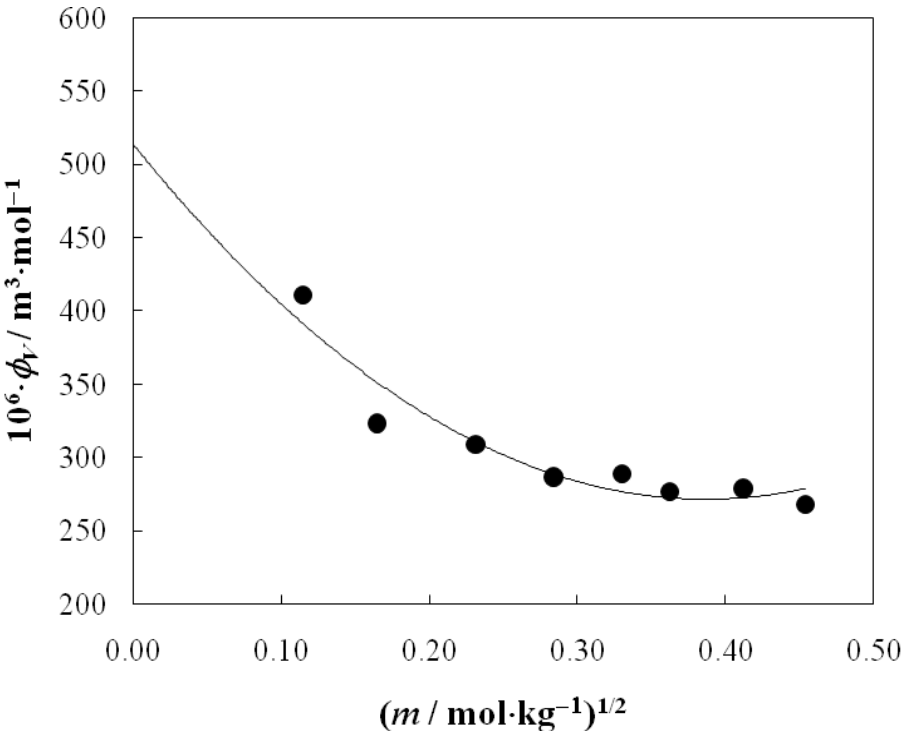


Figure-2: Variation of apparent molar volumes (ϕ_V) of the drug molecule in ternary aqueous solutions as a function of square root of molality of drug RT·HCl at 298.15 K

Using Osmometry technique, for RT·HCl in aqueous α-CD solutions the equilibrium constant value was found to be $7.94 \cdot 10^5$ at 298.15 K[11].

In Table-2, $\phi_{V\ \text{solution}}$ and α data at 298.15 K for ternary system (H_2O + ~ 0.1 mol·kg^{-1} α-CD + RT·HCl) is summarized. When we plot a graph of $\frac{(\phi_{V\ \text{solution}} - \phi_{V\ \text{Drug}-H_2O})}{\alpha}$ parameter as a function of molality (*m*/mol·kg^{-1}) and extrapolated to infinitely dilute solution, the intercept gives the value of volume change due to complexation ($\Delta\phi_c^0$), which is reported in Table-2.

Discussion: The variation of ϕ_V of the studied drug molecule in ternary aqueous solutions as a function of square root of molality of drug at 298.15 K is shown in Figure-2. Examination of Figure-2 reveals that, the variation of ϕ_V for the RT·HCl in aqueous α-CD solutions decreases with increase in concentration of drug molecule. Initially there is a rapid decrease in ϕ_V values which can be interpreted in terms of hydrophobic hydration of the α-CD-drug complexed molecules, while after stoichiometric concentration; the ϕ_V values remain more or less constant. The value of ϕ_V^0 of the RT·HCl in ternary solution is obtained by extrapolation at limiting concentration as shown in Figure-2 and the value is found to be $514 \cdot 10^{-6}$ m^3·mol^{-1} at 298.15 K.

The value of partial molar volume of transfer of drug molecules at infinitely dilute solutions ($\Delta\phi_{V_{tr}}^0$) from aqueous solution to ternary solution containing a fixed concentration (~0.1 mol·kg^{-1}) of α-CD for RT·HCl is found to be $248.89 \cdot 10^{-6}$ m^3·mol^{-1} at 298.15 K. The positive value of partial molar volume of transfer of drug molecules at infinitely dilute solutions indicated that complexed species get solubilized with cavity effect, van der Waals and dipole-dipole interactions and almost the whole RT·HCl molecules get entrapped in α-CD cavity.

The variation of $\frac{(\phi_{V\ \text{solution}} - \phi_{V\ \text{Drug}-H_2O})}{\alpha}$ parameter as a function of molality of RT·HCl has been depicted in Figure-3 and the volume change due to complexation ($\Delta\phi_c^0$) for RT·HCl drug in aqueous solutions containing a fixed concentration of α-CD is found to be $200 \cdot 10^{-6}$ m^3·mol^{-1} at 298.15 K. The examination of Figure-3 indicates that, the quantity initially decreases and further remains almost constant with increase in drug concentration.

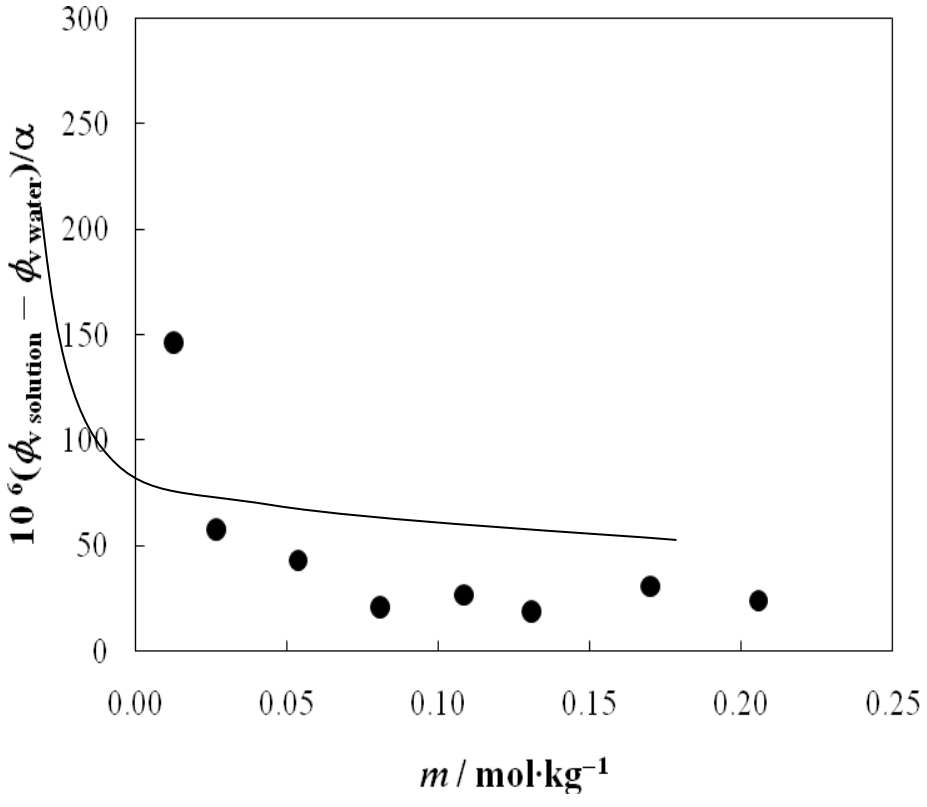


Figure-3: Variation of parameter $\frac{(\phi_{V\ \text{solution}} - \phi_{V\ \text{Drug}-H_2O})}{\alpha}$ as a function of molality (*m*/mol·kg^{-1}) for drug RT·HCl at 298.15 K.

Conclusion

In biological processes, the drug-macromolecular interactions are very important phenomenon which helps in formulating the drug-action in membranes, blood and bio-fluids. In this work, we reported the measurements of densities for ternary system containing host α-CD fixed concentration and varying the concentrations of a guest RT·HCl drug at studied temperature. The limiting apparent molar volumes ϕ_V^0 of RT·HCl in ternary solution is estimated and found to be $514 \cdot 10^{-6}$ $m^3 \cdot mol^{-1}$. The volume change due to transfer of RT·HCl drug molecule from infinitely dilute aqueous solutions to a ternary solution of RT·HCl containing a fixed concentration of α-CD is also obtained and found to be $248.89 \cdot 10^{-6}$ $m^3 \cdot mol^{-1}$. The RT·HCl drug molecule form very stable inclusion complex in solution phase having α-CD as the host species and the volume change due to complexation was found to $200 \cdot 10^{-6}$ $m^3 \cdot mol^{-1}$ at 298.15 K. It is felt that for drug-design and drug-transport, better strategies as well experimentation is required involving CD's and different types of drug molecule capable of inclusion phenomena.

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