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Antibiotic Oxytetracycline Solvation Interctions with Ethanol-Aqueous Mixturs at Different Temperatures

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The solubility is one of the vital parameters to attain the specified concentration of the drug in circulation for the desired (anticipated) pharmacologic response. This work aimed to calculate ion-solvent interaction, the density of ethanol-water (EtOH-H2O) mixtures; the density of oxytetracycline (OTC) saturated solutions, different volumes of solvation (Van der Waals volume, molar volume and electrostriction volume and solvated radii (ro)) from solubility data. It was found that; the activity coefficient ($\gamma\_\pm$) of OTC were decreased by increasing the EtOH content in (EtOH-H2O) mixture used and also the $\log\gamma\_\pm$ decrease within the rise in temperature. The densities and also the molar volume of OTC decrease by increasing the quantitative ratio of EtOH and also was increased by rising in temperature. The electrostriction volumes and therefore the solvated radii (ro) of OTC are increased as the EtOH content increase and also are increased by the rise in temperature.

Keywords: Ion-Ion Interactions, Oxytetracycline HCl, Ethanol, Solubility, Solvation Volumes.

Introduction

Organic cosolvents, particularly ethanol, are among the foremost powerful solubilizing agents. The prediction of solubility profiles in ethanol/water mixtures is of preponderating interest and it facilitates understanding all cosolvent systems. The cosolvent solubility profile of semi-polar compounds seems to possess a maximum solubility when the polarity of the mixture is up to that of the solute. Many parabolic models are wont to address this phenomenon most of that are based on regular solution theory that does not apply to aqueous based systems. Additionally, the log-linear model was designed to determine the solubility for powerfully non-polar compounds.

Paruta et al. [1] and Martin et al. [2, 3] related the substance solubility with a parabolic performs of the dielectric constant of the solvent mixture and the solubility parameter of the solvent. Ruckenstein et al. [4] used fluctuation theory to get a new parabolic model to predict the substance solubility in the solvents. Roseman and Yalkowsky [5] projected a log-linear model that describes the aqueous solubility exponential increase for nonpolar organic compounds within the cosolvent concentration. The solubility also has a vital role for other dosage forms such as the parenteral formulations [6]. The substance solubility is one amongst the vital parameters to realize a desired concentration of the drug to attain the required pharmacological uses [7]. Poorly water soluble medicine typically needs high doses to succeed in therapeutic plasma concentrations once oral administration. Any drug should be gifting in an aqueous solution to be absorbed, so water is that the solvent of selection for pharmaceutical formulations in the liquid form. Most of the weakly acidic or basic drugs are having a low dissolution rate and poor aqueous solubility that cause insufficient bioavailability. The Biopharmaceutical Classification System (BCS) is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability provided by the U.S. Food and Drug Administration. All drugs have been divided into four classes: class-I substances are high solubility & high permeability, class-II

substances are low solubility & high permeability, class-III substances are high solubility & low permeability and class-IV substances are low solubility and low permeability [8]. Particularly for class-II substances; the solubility increasing and dissolution rate increasing of the drug within the gastrointestinal fluids causes increase in the bioavailability. For class-II drugs, the release from the dosage form and solubility in the gastric fluid are the rate limiting step, thus increasing the solubility successively will cause the increase in the drug bioavailability [9, 10]. The negative impact of substance with low solubility embodies poor absorption and bioavailability, poor solubility for IV dosing, development leading to increased development cost and time [6]. A drug is taken into   account extremely soluble once the highest dose is soluble in 250 mL of aqueous media or less according to protocols of the typical bioequivalence studies [11]. The classification of intestinal permeability is based on a comparison to the intravenous injection. All the factors are extremely vital, due to 85% of the most sold drugs are orally administered.

2. Experimental

2.1 Chemicals and Reagents

Oxytetracycline hydrochloride (OTC) and ethanol were purchased from Merck Company with a high degree of purity and used while not additional purification is required.
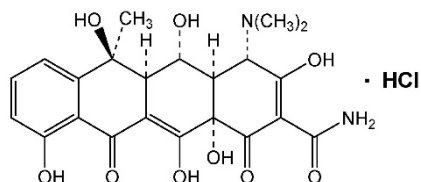

Chemical structure of OTC

2.2 Preparation of mixed solvent and saturated solutions

The saturated solutions of OTC in (EtOH-H_2O) mixed solvents were prepared by dissolving different quantity in closed check tubes containing different (EtOH-H_2O) mixtures by value percent of EtOH (0 - 100% by volume). The tubes were placed in the shaking thermostat for four days until equilibrium reached. The solubility of OTC was determined by the gravimetric method after evaporating the solvent. All the results of solubility were averaged repetition three times of the experiments.

3. RESULTS AND DISCUSSION

3.1 Ion–Ion Interaction Calculation:

For an associated ionic compound, within the formula AB, we tend to take into account the following equilibrium in its saturated solution at a given constant temperature.

$$AB(s) \leftrightarrow A^+_{(aq)} + B^-_{(aq)}, \qquad K_{sp(th)} = a_+ \cdot a_- \qquad (1)$$
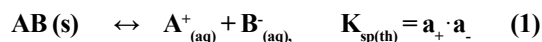
Where $K_{sp(th)}$ is the solubility product constant. a_+ and a_- are the activity of A^+ and B^- ions in the solution, respectively. For extremely low solubility, it is going to replace the activity of every ion by its concentration, so,

$$K_{sp(th)} = S_o^2 \qquad (2)$$

Where s_o represent, the concentration of AB (in molarity) within the very dilute solution. For very low concentration; the ions association phenomena may be negligible due to the electrostatic interaction are very small [12-18].

The activity coefficient (~1) can be calculated by using the Debye- Hückel limiting law at low concentration:

$$\log \tilde{a}_{\pm} = - Z_+ Z_- A\sqrt{I} \quad \text{........ applicable for } I < 10^{-2} M \qquad .... (3)$$

Z_+ and Z_- are the charges of ions in the solution, $A = 1.823 \times 10^6 (\varepsilon.T)^{-3/2}$, the ionic strength,

$$I = \frac{1}{2}\sum_i m_i z_i^2 \quad (z_i \text{ is the charge & } m_i \text{ is the molality}$$

of the ion i).

For relatively high concentration, the electrostatic interaction becomes very large [19-20] and the activity coefficient can be calculated using the extend Debye-Hückel law:

$$\log \tilde{a}_{\pm} = - \frac{Z_+ Z_- A\sqrt{I}}{I + B^{\,o}\sqrt{I}} \quad .... \text{ for } I < 10^{-1} M \qquad (4)$$

$B = 50.29 \times 10^8 (\varepsilon T)^{-1/2}$, and $r°$ is the solvated radius.

At high concentrations, the activity coefficient is determined by using the Davies equation [20] that is an associative empirical extension of Debye–Hückel theory.

$$\log \tilde{a}_{\pm} = -Z_{+}Z_{-}A\left(\frac{\sqrt{I}}{I+\sqrt{I}} - 0.3I\right) \qquad \ldots\ldots\ldots(5)$$

The term (0.3 I) goes to zero as the ionic strength (I) goes to zero, so at low concentration; the Davies equation changed to the Debye–Hückel equation. As the concentration increased, the second term becomes more necessary. Therefore the Davies equation is used for too concentrated solutions.

The results of the ionic strength (I) and (log) for OTC in (EtOH-H_2O) mixture are illustrated at different temperatures in Table (1) and is represented in Fig (1).

3.2 Dielectric Constant Calculation of Solvent mixture:

In the calculation, the dielectric constant for H_2O is obtained from [21]

D $H_2O = 87.74 - (4.0008 \times 10^{-1}t) + (9.398 \times 10^{-4}t^2) - (1.41 \times 10^{-6}t^3) \ldots$ (6)

Where; t = T − 298.15 K.

The values of dielectric constants for ethanol and water were taken from previous publications [22-23] and dielectric constants of EtOH-H_2O mixtures were calculated from the equation (7):

$$\varepsilon = X_{s(1)(H_2O)}.\varepsilon_{(H_2O)} + X_{s(2)(org.solvent)}.\varepsilon_{(org.solvent)}$$ $$\ldots\ldots\ldots (7)$$

The equation (8) used to interpolate the data with described by Akerlof [23] to calculate dielectric constant of H_2O and EtOH at different temperatures:

ln ε = ln a- bT……… (8)

The dielectric constant for H_2O and EtOH at different temperatures were used in the Jouyban-Acree model for prediction of the dielectric constant of the EtOH-H_2O mixtures [24]:

$$\ldots\ldots\ldots (9)$$

Where $\varepsilon_{M,T}$, $\varepsilon_{W,T}$, and $\varepsilon_{E,T}$ are dielectric constants of the solvent mixture, water, and ethanol at temperature T (Kelvin); f_W and f_E are the volume fractions of H_2O and ETOH, respectively.

$$\ldots\ldots\ldots (10)$$

$$\ldots\ldots\ldots (11)$$

The calculated dielectric constant (ε) for (EtOH-H_2O) mixtures are listed in Table (2).

3.3 The Density Measurements:

3.3.1-The Density of (Organic–Aqueous) Mixtures:

The density of the (organic–aqueous) mixtures (EtOH- H_2O) at different temperatures are listed in Table (3), it shows that the density of (EtOH-H_2O) decreases within the increase in the EtOH content and also decrease within increasing temperatures.

3.3.2 The Density of the saturated solutions:

Table (4) shows the density of the OTC saturated solutions in (EtOH-H_2O) mixtures, at different temperatures, it is found that the density decrease within increasing the ETOH content in mixtures and also increases by increasing in the temperature.

Table (4): Density (d) of the OTC saturated solution in (EtOH-H_2O) mixtures at different temperatures.

3.4 Calculation of the Solvation Volumes:

The molar volumes (V) [25, 26] are calculated according to equation (12).

$$V = \frac{M}{d} \qquad \ldots\ldots\ldots(12)$$

Where M is the OTC molecular weight. The molecular weights of the solvent mixtures are calculated using equation (13)

$$M = X_{S(1)(H_2O)}.M_{(H_2O)} + X_{S(2)(O.S)}.M_{(O.S)} \qquad \ldots\ldots\ldots(13)$$

$M_{(O.S)}$ $M_{(H_2O)}$ Where and are the molecular weights of H_2O and the EtOH (organic) solvent, respectively, $X_{S(1)(H_2O)}$ and $X_{S(2)(O.S)}$ are the mole fractions of H_2O and EtOH solvent used by weight which is calculated by the equation (14):

$$X_{S(1)b} \text{ wt.} = \frac{\frac{Vol.\% (1) \ X \ d(1)}{M_1}}{\frac{Vol\% (1) \ X \ d(1)}{M_1} + \frac{Vol.\% (2) \ X \ d(2)}{M_2}} \qquad \ldots\ldots\ldots(14)$$

Where $d_{(1)}$ and $d_{(2)}$ are the densities of the EtOH and water, respectively, vol. % (1) and vol. % (2) is the volume percentage of the EtOH and H_2O,

Table (1): Ionic strength (I) and Log activity coefficient (log) for OTC in (EtOH-H$_2$O) mixture at different temperatures.

EtOH vol. %	X_s	I				log			
		293.15 K	298.15 K	303.15 K	308.15 K	293.15 K	298.15 K	303.15 K	308.15 K
0	0	0.3887	0.4057	0.4352	0.4527	0.7627	0.7598	0.7571	0.7439
20	0.0788	0.1298	0.1341	0.145	0.1494	0.7528	0.7486	0.7413	0.7363
40	0.1857	0.0829	0.0852	0.0876	0.092	0.7475	0.7323	0.7273	0.7105
60	0.3391	0.0663	0.0733	0.0801	0.087	0.7293	0.7222	0.712	0.7065
80	0.577	0.0565	0.0592	0.0617	0.0691	0.6611	0.6501	0.6419	0.6262
100	1	0.0152	0.0179	0.0205	0.0232	0.508	0.4643	0.4367	0.4111

Fig (1): Relation between the activity coefficient ($\gamma_\pm$) of OTC and the EtOH mole fraction (X_s) in (EtOH–H$_2$O) mixture at different temperatures.
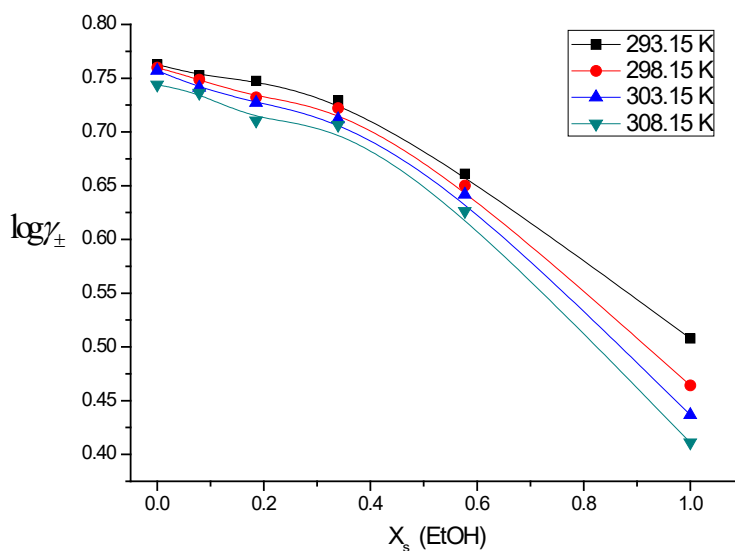
Table (2): The dielectric constant (ε) of (EtOH-H$_2$O) mixtures at different temperatures.

EtOH vol. %	ε (EtOH-H$_2$O) mixtures			
	293.15 K	298.15 K	303.15 K	308.15 K
0	80.10	78.30	76.31	74.30
10	79.13	77.35	75.38	72.59
20	77.97	76.20	74.26	70.60
30	76.54	74.80	72.90	68.26
40	74.75	73.05	71.18	65.48
50	72.45	70.79	68.98	62.11
60	69.37	67.77	66.03	57.94
70	65.04	63.52	61.88	52.66
80	58.51	57.11	55.61	45.74
90	47.51	46.31	45.07	36.30
100	25.09	24.30	23.57	22.63

Table (3): Density (d$_o$) of (EtOH-H$_2$O) mixtures at different temperatures.

EtOH	X$_s$	Density (d$_o$)			
vol. %		293.15K	298.15K	303.15K	308.15K
0	0	1.0004	0.997	0.9942	0.9912
20	0.0788	0.9853	0.982	0.9789	0.9758
40	0.1857	0.9643	0.9612	0.9577	0.9544
60	0.3391	0.9335	0.9306	0.9264	0.9229
80	0.577	0.8836	0.8811	0.8756	0.8717
100	1	0.7889	0.7873	0.7789	0.7738

Table (4): Density (d) of the OTC saturated solution in (EtOH-H2O) mixtures at different temperatures.

EtOH	X$_s$	(d)			
vol. %		293.15 K	298.15 K	303.15 K	308.15 K
0	0	1.115	1.13	1.143	1.159
20	0.0788	0.967	0.982	0.991	1.016
40	0.1857	0.931	0.94	0.948	0.971
60	0.3391	0.89	0.914	0.935	0.955
80	0.577	0.84	0.857	0.882	0.897
100	1	0.776	0.78	0.785	0.789

respectively.
The packing density of relatively large molecules (more than 40) is found to be constant. Therefore, we can use equation (15) to calculate the Van der Waals volumes (V$_w$).

Packing density (P) = $\dfrac{V_w}{V}$ **= 0.661 ± 0.017 ……… (15)**

(V and V$_w$ are the partial molar volumes and Van der Waals, respectively).
The electrostriction volume (V$_e$) [25-26] is calculated by using equation (**16**).

$$V_e = V_w - V \qquad ……… (16)$$

The values of **V, V$_w$** and **V$_e$** of OTC in (EtOH-H$_2$O) mixtures are listed in Tables (5-6), it is was observed that the molar volume of EtOH mixtures with H$_2$O are increased by increasing the EtOH

content due to the increase in the EtOH volume compared to water.
All the calculated electrostriction volumes for

OTC in (EtOH- H$_2$O) mixtures having negative values and increase in negativity within increasing the percentage of the EtOH solvent, indicating the more work on the solvation sheaths of OTC molecules.

.3.5 Calculation of the Solvated Radii:

The solvated radii of the organic-aqueous mixtures; (EtOH-H$_2$O) at different temperatures were calculated by using equation (17) by considering the spherical form of the solvated molecules [27].

$$V = \frac{1}{6}\pi N\sigma^3 \qquad ………(17)$$

σ is the solvated diameter that calculated by adding the crystal radius of OTC to the radii of solvent mixtures are listed in Table (5)

The solvated radii of OTC in (EtOH- H$_2$O) mixtures found to increased as the EtOH content increased and also increased as the temperature increased as a result of the excess solvation processes, and the higher solvated radii of the EtOH solvent used than that of water and also due to the increasing in the electronic clouds around the solvated OTC because of the increasing in their rotation and vibration motions within increasing the temperature.

The solubility of a solid in a liquid is strongly dependent upon the strengths of the intermolecular forces among the dissolved solute and the surrounding solvent molecules. A common saying among chemists comes from the Latin phrase similis similibus solvuntur (like dissolves like). In the absence of interactions, intermolecular forces between chemically similar species lead to a smaller endothermic the enthalpy of the solution than those between dissimilar species. Dissolution must be accompanied by a decrease in the Gibbs energy. For this reason, a low endothermic enthalpy is preferable to a large one. In addition to the intermolecular forces between solute and solvent, several other factors play a role in determining the solubility of a solid in a liquid.

Three, and sometimes, four other factors contribute to determining whether or not a solid will dissolve:

(a) breaking of the (solute-solute) interactions in the crystalline lattice;

Table (5): Molar volume (V), Van der Waals volume (V_w), electrostriction volume (V_e) and Solvated radii (r_o) of OTC in different (EtOH-H_2O) mixed solvents. ($Cm^3.mol^{-1}$).

EtOH vol. %	X_s	V	V_w	V_e	r_o	V	V_w	V_e	r_o
			293.15K				298.15K		
0	0	445.42	294.42	-150.99	4.7385	439.48	290.49	-148.98	4.7175
20	0.0788	513.98	339.73	-174.23	4.9689	506.00	334.46	-171.53	4.9435
40	0.1857	533.99	352.96	-181.02	5.0322	528.73	349.48	-179.23	5.0160
60	0.3391	558.73	369.32	-189.40	5.1083	543.57	359.30	-184.27	5.0632
80	0.577	591.95	391.27	-200.66	5.2077	579.71	383.18	-196.52	5.1730
100	1	642.39	424.62	-217.77	5.3471	637.77	421.56	-216.20	5.3379

EtOH vol. %	X_s	V	V_w	V_e	r_o	V	V_w	V_e	r_o
			303.15K				308.15K		
0	0	434.47	287.18	-147.28	4.6995	428.44	283.20	-145.24	4.6778
20	0.0788	501.31	331.36	-169.94	4.9285	488.80	323.09	-165.70	4.8877
40	0.1857	524.12	346.44	-177.67	5.0019	511.42	338.04	-173.37	4.9621
60	0.3391	531.04	351.01	-180.02	5.0250	519.65	343.49	-176.16	4.9896
80	0.577	562.67	371.92	-190.74	5.1237	553.01	365.53	-187.46	5.0949
100	1	633.08	418.46	-214.61	5.3266	629.32	415.97	-213.33	5.3175

(b) the breaking of (solvent-solvent) interactions often referred to as cavity formation;

(c) the formation of (solute-solvent) interactions

(d) the perturbation of (solvent-solvent) interactions in the immediate vicinity of the solute, as in the solvent structuring.

Each of these four contributions may be divided further into specific chemical (complexation) and nonspecific (simple dispersion) interactions. Specific interactions arise from charge transfer species, hydrogen bond formation, and strong dipole-dipole interactions. Specific interactions occur only in complexing systems, whereas nonspecific interactions occur in both complexing and noncomplexing systems. Systems containing specific interactions and nonspecific interactions deviate from ideality. The activity coefficient, γ, reflects the solute & the solvent intermolecular forces. More negative ($\gamma < 1$) or more positive ($\gamma > 1$) deviations usually accompany specific interactions. However, systems containing only nonspecific interactions usually are characterized by small to moderate positive deviations from ideality. For this reason, solubility tends to be enhanced for negative deviations and decreased for positive deviations.

For the solubility of a crystalline solute in a liquid solvent, as these conclusions rigorously apply to ideal solutions ($\gamma_i = 1$), they only can be applied to real solutions that do not deviate excessively from ideal behavior. However, they do serve as useful guides regarding the solubility of solids in liquids.

For a given solid-solvent system, the solubility increased as the temperature increased. The rate of increase is proportional to the enthalpy of fusion and, to a first approximation, does not depend on the melting point (triple point) temperature, i. e., $\partial \ln(\gamma_A \chi_A)/\partial T \approx \Delta H_{fus}/RT^2$.

4. Conclusion

From the solubility and density experiments of OTC saturated solutions in (EtOH-H$_2$O) mixtures solvents, we calculated ion-ion interaction, dielectric constant, solvation volumes, and solvated radii. The activity coefficient (log) of OTC in (EtOH-H$_2$O) mixture was decreased by increasing in the EtOH content used and the values of the (log) found to decrease with the increase in temperature. The density of the OTC saturated solutions decreased by increasing the EtOH content and also increases by increasing the temperature. The molar volume of EtOH mixtures with water is increased

by increasing the EtOH content in the solvent mixtures due to the increase in the volume of EtOH as compared to H$_2$O. All the electrostriction volumes calculated for OTC having negative values and increase in negativity within increasing the percentage of the EtOH. The solvated radii of OTC are increased as the EtOH content increased and also increased as the temperature increased.

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