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Solubility of Some Basic Drugs in Dioxane + Water Mixtures at 298.2 K

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***SUMMARY*. Solubility of four basic drugs i.e. atenolol, clonazepam, diazepam and lamotrigine in dioxane + water mixtures at 298.2 K were determined. The solubilities of atenolol, clonazepam, diazepam, and lamotrigine were increased with addition of dioxane, reached the maximum value for three drugs, and then decreased with further increase in dioxane, but the maximum solubility of diazepam was in neat dioxane. The solubility data was predicted using previously proposed model which is a combination of the Jouyban-Acree model and Abraham solvation parameters with 31.7 % prediction error.**

INTRODUCTION

Solubility is one the most important physicochemical properties in different stages of drug discovery and development. There are different methods to alter solubility of drugs in the literature and the simplest way is cosolvency. Cosolvency or mixing of solvents can be used in synthesis of drugs (as dissolution medium), drug formulation, crystallization of drugs and drug analysis [1-3]. Although dioxane is a toxic solvent and could not be used as a pharmaceutical cosolvent in the formulation of liquid dosage forms it possesses a good position in the pharmaceutical research. The solubility of drugs in dioxane + water was used as a model solvent mixture by Martin *et al.* [4] since it provides very wide polarity range. Its aqueous mixtures provides relatively wide dielectric constant (78.36 to 2.21), solubility parameter (23.5 to 10.1 H), dipole moment (1.85 to 0.00), and viscosity (0.890 to 1.168 kPa·s) ranges which could be used in many pharmaceutical applications. As examples, dioxane or dioxane + water mixtures were used in encapsulation of drugs [5], synthesis of polymers or copolymers of pharmaceutical interest [6,7] solubilization of polymers [8], separation of chiral drugs on immobilized chiral stationary phases [9], and determination of the physicochemical properties of sparingly soluble drugs/drug candidates [10].

Prediction profile of drug solubility in solvent mixtures is one the most challenging area in the pharmaceutical sciences and some efforts have been made to predict the solubility of drugs in binary solvent mixtures [11]. The Jouyban-Acree model [5] is one of the most accurate models to calculate the solubility of drugs in mixed solvents at various temperatures and was used by different researcher groups [12-15]. The general form of the model is shown in Eq. [**1**]:

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + \frac{f_1 f_2}{T} \sum_{i=0}^{2} J_i (f_1 - f_2)^i \quad [\mathbf{1}]$$

where $X_{m,T}$ is the solute solubility in the solvent mixtures, f_1 and f_2 are the fractions (volume fraction in this study) of the solvents 1 and solvent 2, $X_{1,T}$ and $X_{2,T}$ are the solubility of the solute in the neat solvents, respectively, T is temperatute (K) and J_i are the model constants. The third term of Jouyban-Acree model

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(i.e. $\frac{f_1 f_2}{T}\sum_{i=0}^{2} J_i (f_1 - f_2)^i$)

represents the solute solvent interaction and deviation of solubility from ideal mixing [16]. A number of solubility data are required to compute the numerical values of the J_i constants in binary solvent mixtures for training process and a minimum number of solubility data could provide reasonable predictions for the solubility in all composition ranges of solvent mixtures.

In this study, solubility data of four basic drugs in dioxane + water at 298.2 K were determined. Then solubility values were predicted using the Jouyban-Acree model with available numerical analyses.

MATERIALS AND METHODS

Reagents

Atenolol was purchased from Darou Pakhsh (Tehran, Iran), clonazepam and diazepam were gifted by Sobhan Pharmaceutical company (Rasht, Iran), and lamotrigine was purchased from Arastoo company (Tehran, Iran). All drugs were pharmaceutical raw materials according to USP purity criteria. The aqueous solubility of drugs from the literature and their melting points were checked to confirm their purities. Dioxane (> 99 %) from Merck (Darmstadt, Germany), double distillated water were used for preparation of the solutions and ethanol (96 % v/v) from Jahan Alcohol Teb (Arak, Iran) was used for dilution of the saturated solutions.

Apparatus and Procedures

The binary solvent mixtures of dioxane and water were prepared by volume with the uncertainty of 0.01 mL. Various methods have been proposed for solubility determination of pharmaceuticals which have been reviewed in a recent publication [17]. The solubility of drugs was determined using classical saturating shake-flask method of Higuchi and Connors [18]. The excess drug powders were added to the prepared solutions and then were equilibrated on a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system having an uncertainty of 0.2 K (Nabziran, Tabriz, Iran). After equilibrium (> 3 days), the saturated solutions were centrifuged (Sanyo, Muriguchi, Japan) (10000 rpm for 10 min) and diluted by ethanol (96 % v/v). The absorptions of diluted solutions were measured using a UV-Vis spectrophotometer (Beckman DU-650, California, USA) according to their calibration curves.

Computational Method

The measured solubility data of each drug in dioxane + water mixtures was fitted to Eq. [**1**] and the model constants were computed using a no intercept least square analysis [19]. Using these constants, the solubility at other solvent compositions and various temperatures could be predicted employing the experimental solubility data in the neat water and dioxane. The solubility data of drugs in dioxane + water mixtures at various temperatures could also be predicted using a generally trained version of the Jouyban-Acree model which is reported as shown in Eq. [**2**] [20]:

$$\begin{aligned}\log X_{m,T} = {} & f_1 \log X_{1,T} + f_2 \log X_{2,T} \\ & + \left(\frac{f_1 f_2}{T}\right)\{648.01 - 404.99E + 428.69S + 340.99A - 59.03B - 56.94V\} \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)}{T}\right)\{-135.95 - 41.11E - 192.19S + 237.81A + 363.87B + 310.30V\} \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)^2}{T}\right)\{-1102.49 - 667.02E + 2070.16S + 421.15A - 924.73B - 271.54V\}\end{aligned} \quad [2]$$

in which E is the excess molar refraction, S is dipolarity/polarizability of solute, A denotes the solute's hydrogen-bond acidity, B stands for the solute's hydrogen-bond basicity and V is the McGowan volume of the solute [20]. Numerical values of these parameters for the investigated drugs computed using PharmaAlgorithms software [21] are listed in Table 1. The software calculates the parameters using previously trained equations employing the experimental S, A and B values of a large set of chemicals. These experimental values are computed by fitting the solubility data of a drug in a number of solvents with known Abraham solvent parameters [22]. The V parameter is easily calculated using atom and bond contribution of Abraham and McGowan [23] and the E descriptor is defined as indicated in Eq. [**3**]:

Drug	E	S	A	B	V
Atenolol	1.48	1.97	0.78	1.85	2.18
Clonazepam	2.36	2.25	0.47	1.09	2.11
Diazepam	2.11	1.72	0.00	1.04	2.00
Lamotrigine	2.40	2.13	0.45	0.93	1.65

Table 1. The numerical values of the Abraham solute parameters of the investigated drugs calculated using PharmaAlgorithms [21].

$$E = MRx - aV + b \qquad [3]$$

in which *MRx* is molar refraction and the units of *E* and *MRx* are ($cm^3\ mol^{-1}$)/10. *MRx* is calculated by Eq. [**4**]:

$$MRx = 10\left[\frac{\eta^2 - 1}{\eta^2 + 2}\right]V \qquad [4]$$

where η is the refractive index of the compound as a pure liquid at 20 °C [24].

The mean percentage deviation (MPD) was used to evaluate the accuracy of the computation (Eq. [**5**]):

$$MPD = \frac{100}{N}\sum_{1}^{N}\left[\frac{\left|X_{m,T}^{calculated} - X_{m,T}^{experimental}\right|}{X_{m,T}^{experimental}}\right] \qquad [5]$$

where *N* is the number of data points in each set.

RESULTS AND DISCUSSION

Table 2 shows the experimental solubilities and densities of the saturated solutions of the investigated drugs in dioxane + water at 298.2 K. Each experimental data point represents the average of at least three repetitive experiments. The solubility of drugs was increased with the addition of dioxane, and reached to the maximum values at f_1 = 0.60 (for atenolol), f_1 = 0.90 for clonazepam and f_1 = 0.80 for lamotrigine and then was decreased with further addition of dioxane. The solubility of diazepam was reached to the maximum value in neat dioxane, and in order to confirm this pattern, the solubility of diazepam was also measured in f_1 = 0.75, 0.85, and 0.95. The provided density data could be used to convert the presented mole fraction solubility data to molar solubilities which are required in some pharmaceutical applications.

There are good agreements between aqueous solubility data for clonazepam, diazepam and lamotirigne with their published aqueous solubility data [25]. Aqueous solubility data of atenolol (0.00141 mole fraction) agrees with the corresponding data (0.00137 mole fraction in pH = 7.4) from the literature [26].

The model constants and the calculated MPD values for the investigated data sets are listed in Table 3. The MPDs vary between 6.0 to 11.8 % with the overall value of 9.0 %. These calculations could be used to detect possible outliers in order to repeat the experimental measurements. In addition, as it has been shown in earlier works [27,28], using the trained model at 298.2 K, the solubility of the drug at other temperatures could be predicted employing the experimental solubility data in the mono-solvents at the temperature of interest.

The solubility data of the investigated drugs in water and dioxane along with their Abraham solute parameters were employed to predict the solubility in dioxane + water mixtures using Eq. [**2**]. The produced MPD for atenolol (number of predicted data points; N = 9), clonazepam (N = 9), diazepam (N = 12), and lamotrigine (N = 9) are 39.4, 21.4, 13.9, and 52.0 %, respectively. The overall MPD is 31.7 % which could be considered as an acceptable error in the pharmaceutical area [29,30].

Figure 1 shows the experimental, back-calculated solubilities using Eq. [**1**] and the model constants reported in Table 3 and the predicted solubility data by Eq. [**2**]. As shown in the Figure 1, Eq. [**1**] fits the data very well and only a number of data points behave like outliers. Eq. [**2**] underestimated the solubility of atenolol and lamotrigine, predicted the solubility of clonazepam with good accuracy and overestimated the solubility of diazepam. These observations are in agreement with the MPD values of Eq. [**2**] for these drugs.

CONCLUSION

Experimental mole fraction solubility of atenolol, clonazepam, diazepam, and lamotrigine in aqueous binary mixtures of dioxane at 298.2 K were reported. The solubilities of drugs were increased with the addition of dioxane. In order to provide a computational method to calculate the solubilities, the Jouyban-Acree model was fitted to the results of these measurements, and solubilities were back-calculated with employing the solubility data in mono-solvents in which the overall mean deviation of the models was 9.0 %. A generally trained version of the Jouyban-Acree model was used to predict the solubility of drugs in dioxane + water mixtures employing the experimental solubility data in mono-solvents in which the overall prediction error was 31.7 %.

Drug	Volume fraction of dioxane	X (mole fraction)	RSD	Density of solution (g/cm³)
Atenolol	0.00	0.001409	0.14	1.01
	0.10	0.003486	0.34	1.02
	0.20	0.006408	0.62	1.03
	0.30	0.011598	1.12	1.04
	0.40	0.022517	2.15	1.05
	0.50	0.034146	3.23	1.06
	0.60	0.046749	4.41	1.06
	0.70	0.044695	4.22	1.06
	0.80	0.044576	4.23	1.05
	0.90	0.032689	3.13	1.05
	1.00	0.002985	0.29	1.02
Clonazepam	0.00	0.000002	2.65	1.00
	0.10	0.000007	1.29	1.01
	0.20	0.000026	3.32	1.02
	0.30	0.000086	1.57	1.03
	0.40	0.000273	3.20	1.03
	0.50	0.000716	3.72	1.04
	0.60	0.002105	3.83	1.04
	0.70	0.004973	4.17	1.05
	0.80	0.011292	3.48	1.05
	0.90	0.016915	3.14	1.05
	1.00	0.008651	2.39	1.04
Diazepam	0.00	0.000003	4.67	1.00
	0.10	0.000019	1.95	1.00
	0.20	0.000075	0.99	1.01
	0.30	0.000277	1.74	1.02
	0.40	0.000890	4.78	1.03
	0.50	0.002841	2.27	1.04
	0.60	0.009682	2.37	1.05
	0.70	0.025404	3.93	1.06
	0.75	0.036265	0.81	1.07
	0.80	0.056031	1.23	1.07
	0.85	0.063551	1.45	1.07
	0.90	0.073016	4.98	1.08
	0.95	0.081473	1.58	1.08
	1.00	0.095044	0.89	1.08
Lamotrigine	0.00	0.000014	0.54	1.00
	0.10	0.000060	1.31	1.01
	0.20	0.000205	1.59	1.02
	0.30	0.000719	2.71	1.03
	0.40	0.002224	3.48	1.03
	0.50	0.005773	0.89	1.04
	0.60	0.011443	1.34	1.05
	0.70	0.017718	0.70	1.06
	0.80	0.036397	1.94	1.07
	0.90	0.032102	1.47	1.06
	1.00	0.007121	1.32	1.03

Table 2. Mole fraction solubility of atenolol, clonazepam, diazepam, lamotrigine, naproxen in dioxane + water at 298.2 K and their relative standard deviation (RSD) and density of saturated solutions.

Drug	J_0	J_1	J_2	MPD	N
Atenolol	1401.744	1026.831	1099.193	11.6	11
Clonazepam	934.895	638.000	784.656	6.0	11
Diazepam	892.074	229.666	337.668	6.7	14
Lamotrigine	1443.260	842.107	880.305	11.8	11

Table 3. The numerical values of the constants of the Jouyban-Acree model, the mean percentage deviations (MPDs) for the fitted model and the number of data points in each set.

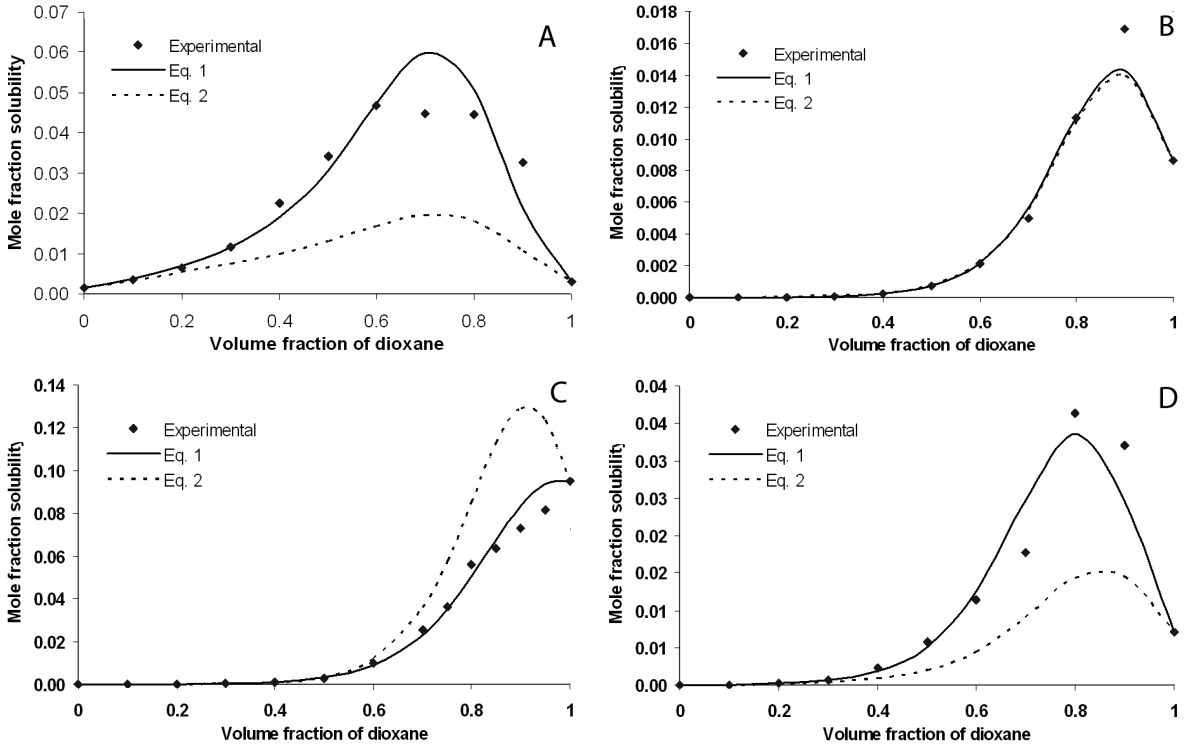

Figure 1. Mole fraction solubilities of drugs in dioxane + water mixtures. **A**: atenolol, **B**: clonazepam, **C**: diazepam, **D**: lamotrigine.

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