Solubility of Lamotrigine, Diazepam, and Clonazepam in Ethanol + Water Mixtures at 298.15 K

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Experimental solubilities of three antiepileptic drugs, that is, lamotrigine, diazepam, and clonazepam in ethanol + water mixtures at 298.15 K were reported. The solubility of drugs was increased with the addition of ethanol, reached the maximum values, and then decreased with further increase in ethanol concentrations. The Jouyban−Acree model was fitted to the data, and the solubilities were reproduced using two previously developed relationships employing a number of the solvent's and solute's parameters and the solubility data in monosolvents in which the overall mean deviations (OMDs) of the models were 6.2 %, 22.3 %, and 23.2 %.

Introduction

The solubility of drugs is essential information in drug discovery and development investigations in the pharmaceutical industry. The solubilization of drugs is very important in the preparation of liquid drug formulation stages in the pharmaceutical industry. There are many methods for solubilization of drugs including cosolvency, surface active agents, salt formation, complexation, hydrotropism, crystal engineering, preparation of soluble prodrug, and, more recently, the addition of ionic liquids.[1−8] Among these methods, the cosolvency, or the addition of a cosolvent (permissible organic solvent) to the aqueous solution to alter the aqueous solubility, is the most common and easy-to-use method. Ethanol is a common organic solvent that was used in many commercially available oral, parenteral, and soft gelatin pharmaceutical formulations for poorly soluble drugs.[9] The concentration of the cosolvent in pharmaceutical preparations should be kept as low as possible because of the possible toxicity of the cosolvent and also because of the cost effect. The method that is often used to optimize the solvent composition of solvent mixtures for dissolving a desired amount of a drug in a given volume of the solution is the trial and error approach, which is time consuming and costly; moreover, in the early stages of drug discovery processes, the scarcity of the available amount of drug is another limiting factor. To address this issue, a number of mathematical models have been presented for predicting the solubility of drugs in water−cosolvent mixtures. These models and their advantages and limitations were recently reviewed.[10]

Of the numerous models developed in recent years, the Jouyban−Acree model is perhaps one of the more versatile models. The model provides very accurate mathematical descriptions for how the solute solubility varies with both temperature and solvent composition. The model for representing the solubility of a solute in binary mixture at various temperature is

$$\log C_{m,T}^{\mathrm{Sat}} = x_1 \log C_{1,T}^{\mathrm{Sat}} + x_2 \log C_{2,T}^{\mathrm{Sat}} + \left[\frac{x_1 x_2}{T}\sum_{i=0}^{2} J_i (x_1 - x_2)^i\right] \quad (1)$$

where $C_{m,T}^{\mathrm{Sat}}$ is the solute (mol·L^{-1}) solubility in the solvent mixtures at temperature T, x_1 and x_2 are the fractions of the solvents 1 (ethanol) and 2 (water) in the absence of the solute, $C_{1,T}^{\mathrm{Sat}}$ and $C_{2,T}^{\mathrm{Sat}}$ denote the mol·L^{-1} solubility of the solute in the neat solvents 1 and 2, respectively, and J_i are the constants of the model computed by regression analysis.[10] The existence of these model constants that require a number of solubility data in water−cosolvent mixtures for the training process is a limitation for the model when the solubility predictions are the goal of the computations in early drug discovery studies. This limitation could be resolved using a trained version of the model for a given water−cosolvent mixture[11] as well as a recently developed quantitative structure−property relationship (QSPR) model[12] to predict the numerical values of the model constants. The trained version of the Jouyban−Acree model for the prediction of drug solubility in ethanol + water mixtures at 298.15 K was[11]

$$\log C_{m,T}^{\mathrm{Sat}} = x_1 \log C_{1,T}^{\mathrm{Sat}} + x_2 \log C_{2,T}^{\mathrm{Sat}} + \frac{724.21 x_1 x_2}{298.15} + \frac{458.17 x_1 x_2 (x_1 - x_2)}{298.15} + \frac{194.21 x_1 x_2 (x_1 - x_2)^2}{298.15} \quad (2)$$

The reported QSPR models using Abraham solvation parameters were[12]

$$J_0 = 2113.119 - 1093.783(c_1 - c_2)^2 + 3380.661E(e_1 - e_2)^2 - 13.865S(s_1 - s_2)^2 - 4.921A(a_1 - a_2)^2 - 5.659B(b_1 - b_2)^2 + 15.250V(v_1 - v_2)^2 \quad (3)$$

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$$J_1 = -2001.561 + 1142.780(c_1 - c_2)^2 - 2735.160E(e_1 - e_2)^2 - 38.541S(s_1 - s_2)^2 + 13.176A(a_1 - a_2)^2 + 0.811B(b_1 - b_2)^2 + 38.508V(v_1 - v_2)^2 \quad (4)$$

$$J_2 = 1474.963 - 1507.479(c_1 - c_2)^2 + 4421.302E(e_1 - e_2)^2 + 17.981S(s_1 - s_2)^2 - 21.196A(a_1 - a_2)^2 + 6.595B(b_1 - b_2)^2 - 13.386V(v_1 - v_2)^2 \quad (5)$$

where c, e, s, a, b, and v are the solvent coefficients, subscripts 1 and 2 denote the cosolvent and water, respectively, E is the excess molar refraction, S is the dipolarity/polarizability of the 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 in units of 0.01 ($cm^3 \cdot mol^{-1}$). The numerical values of Abraham solute parameters of the drugs and the Abraham solvent coefficients employed in this work are listed in Tables 1 and 2, respectively.

In this work, the experimental solubility of lamotrigine (LTG), diazepam (DZP), and clonazepam (CZP) in ethanol + water mixtures at 298.15 K was reported. In addition, the fitness of the data to the Jouyban−Acree model and the prediction capability of the above-mentioned models for predicting the solubility of drugs in ethanol + water mixtures were investigated.

Experimental Methods

LTG was purchased from Arastoo pharmaceutical (Iran) and DZP and CZP were gifts from Sobhan pharmaceutical (Iran). The purity of the drugs was checked by determining their melting points and comparing the measured solubilities in monosolvents with the corresponding data from the literature. Ethanol (99.9 %) was purchased from Merck (Germany), methanol (99.8 %) was obtained from Calendon (Canada), and double-distilled water was used for the preparation of the solutions.

Apparatus and Procedures. We prepared the binary solvent mixtures by mixing the appropriate volumes of the solvents with the accuracy of 0.10 volume fraction. The solubility of LTG, DZP, and CZP in ethanol + water mixtures was determined by equilibrating an excess amount of the solid at 298.15 K using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system with ± 0.2 K. After a sufficient length of time (> 48 h), the saturated solutions were filtered using hydrophilic Durapore filters (0.45 μm, Millipore, Ireland) and were then diluted by water for LTG and by methanol for DZP and CZP and assayed at 309, 229, and 309 nm, respectively, using a UV−vis spectrophotometer (Beckman DU-650, Fullerton). The preliminary investigations showed that the filter did not absorb the solutes through the filtration process. Concentrations of the diluted solutions were determined from the calibration curves. Details of calibration curves are shown in Table 3. Each experimental data point was an average of at least three repeated experiments with the measured $mol \cdot L^{-1}$ solubilities being reproducible within ± 3.5 %. The calculated standard deviation ranged from $\sigma_{n-1} = 0.0000013$ to 0.0046685. The densities of the saturated solutions were determined using a 5 mL pycnometer.

Computational Methods. In the numerical analysis of method I, eq 1 was fitted to the experimental solubility data of drugs,

Table 1. Abraham Solute Parameters of the Drugs Taken from the Literature[17,18]

drug	E	S	A	B	V
LTG[a]	2.79	2.81	0.50	1.09	1.65
DZP[a]	2.38	2.11	0.00	1.15	2.07
CZP[b]	2.46	1.75	0.33	1.50	3.02

[a] From ref 17. [b] From ref 18.

Table 2. Abraham Solvent Coefficients Employed in This Work[16]

solvent	c	e	s	a	b	v
ethanol	0.208	0.409	− 0.959	0.186	− 3.645	3.928
water	− 0.994	0.577	2.549	3.813	4.841	− 0.869

Table 3. Details of Calibration Curves

drug	ε / $L \cdot mol^{-1} \cdot cm^{-1}$	C / $mol \cdot L^{-1}$
LTG	6681 to 6904	$3.59 \cdot 10^{-5}$ to $1.80 \cdot 10^{-4}$
DZP	45 217 to 77 215	$3.48 \cdot 10^{-6}$ to $2.79 \cdot 10^{-5}$
CZP	11 297 to 12 050	$1.66 \cdot 10^{-5}$ to $1.33 \cdot 10^{-4}$

Table 4. Experimental Solubilities of LTG, DZP, CZP in Ethanol + Water Mixtures at 298.15 K, Density (ρ) of the Saturated Solutions, and the Computed Solubilities Using Equation *1* and Various Numerical Analyses

x_1	ρ	C ($mol \cdot L^{-1}$)			
volume fraction of ethanol	$g \cdot cm^{-3}$	experimental	method I	method II	method III
		LTG			
0.00	1.000	0.00073	0.00073	0.00073	0.00073
0.10	0.988	0.00187	0.00140	0.00135	0.00164
0.20	0.977	0.00231	0.00266	0.00245	0.00291
0.30	0.965	0.00439	0.00509	0.00439	0.00437
0.40	0.948	0.00969	0.00980	0.00770	0.00583
0.50	0.931	0.02032	0.01833	0.01292	0.00721
0.60	0.910	0.03562	0.03140	0.01993	0.00852
0.70	0.885	0.04242	0.04528	0.02687	0.00983
0.80	0.862	0.04386	0.04919	0.02959	0.01121
0.90	0.831	0.03762	0.03510	0.02457	0.01264
1.00	0.790	0.01398	0.01398	0.01398	0.01398
		DZP			
0.00	1.002	0.00015	0.00015	0.00015	0.00015
0.10	0.990	0.00039	0.00033	0.00040	0.00037
0.20	0.981	0.00074	0.00082	0.00102	0.00093
0.30	0.963	0.00199	0.00222	0.00257	0.00235
0.40	0.950	0.00666	0.00615	0.00637	0.00579
0.50	0.931	0.01673	0.01623	0.01509	0.01327
0.60	0.915	0.03925	0.03811	0.03287	0.02734
0.70	0.887	0.07486	0.07443	0.06255	0.04904
0.80	0.867	0.10071	0.11281	0.09729	0.07424
0.90	0.840	0.13473	0.12377	0.11404	0.09222
1.00	0.808	0.09158	0.09158	0.09158	0.09158
		CZP			
0.00	1.004	0.00010	0.00010	0.00010	0.00010
0.10	0.988	0.00013	0.00013	0.00022	0.00016
0.20	0.977	0.00025	0.00026	0.00049	0.00033
0.30	0.965	0.00063	0.00066	0.00110	0.00074
0.40	0.948	0.00190	0.00176	0.00241	0.00170
0.50	0.937	0.00452	0.00430	0.00502	0.00377
0.60	0.910	0.00836	0.00877	0.00964	0.00763
0.70	0.883	0.01336	0.01415	0.01617	0.01325
0.80	0.862	0.01788	0.01787	0.02216	0.01868
0.90	0.825	0.01957	0.01824	0.02288	0.02031
1.00	0.794	0.01619	0.01619	0.01619	0.01619

Table 5. Numerical Values of the Mean Deviation (MD) for the Predicted Solubilities of LTG, DZP, CZP in Ethanol + Water Mixtures Using Various Numerical Analyses and Their Overall Values

drug	method I	method II	method III
LTG	8.4	21.7	39.7
DZP	6.6	12.2	18.8
CZP	3.6	32.9	11.2
overall MD %	6.2	22.3	23.2

and the back-calculated solubilities were used to calculate the accuracy of the fitness. In method II, the solubilities of three drugs were predicted using eq 2 by employing the experimental solubility of drugs in neat ethanol and water. In method III, the model constants of the Jouyban−Acree model were predicted using eqs 3, 4, and 5, and the predicted J_0 to J_2 values were used in eq 1 to predict the solubility of drugs. The mean deviation (MD) was used to check the accuracy of the prediction methods and is calculated using

$$\mathrm{MD} = \frac{\sum \left\{ \frac{\left| \left(C_m^{\mathrm{Sat}}\right)_{\mathrm{pred}} - \left(C_m^{\mathrm{Sat}}\right) \right|}{\left(C_m^{\mathrm{Sat}}\right)} \right\}}{N} \qquad (6)$$

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

Results and Discussion

Table 4 lists the experimental solubilities of LTG, DZP, CZP in ethanol + water mixtures at 298.15 K, the computed solubilities of these drugs employing eq 1 using methods I, II, and III, and the density of the saturated solutions. There were good agreements between the reported solubilities of LTG in water[13] (0.00066 mol·L^{-1} at 298.15 K), DZP in water[14] (0.00015 mol·L^{-1} at (295.15 to 297.15) K), and CZP in ethanol[15] (0.0165 mol·L^{-1} at 298.15 K) from the literature and the measured solubilities of LTG in water (0.00073 mol·L^{-1} at 298.15 K), DZP in water (0.00015 mol·L^{-1} at 298.15 K), and CZP in ethanol (0.016192 mol·L^{-1} at 298.15 K) in this work. The solubilities of these drugs increased with the addition of ethanol, reached the maximum values, and then decreased with the further increase of ethanol concentrations. The solubilities of these drugs were predicted using numerical methods I, II, and III. The predicted solubilities were compared with the corresponding experimental data, and the MD values were computed and are listed in Table 5. In general, the overall MDs observed in these predictions show that the developed models are robust and could be used for prediction purposes with the prediction error of less than 24 %.

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