Solubility of Clonazepam, Diazepam, Lamotrigine, and Phenobarbital in *N*-Methyl-2-pyrrolidone + Water Mixtures at 298.2 K

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Experimental solubilities of clonazepam, diazepam, lamotrigine, and phenobarbital in binary solvent mixtures of *N*-methyl-2-pyrrolidone (NMP) + water at 298.2 K were reported. The solubility of clonazepam, diazepam, and lamotrigine was increased with the addition of NMP, and maximum values are in neat NMP. The solubility of phenobarbital was increased with addition of NMP, reached the maximum value, and then decreased with further increase in NMP concentration. The Jouyban−Acree model was fitted to the results of these measurements, and solubilities were back-calculated by employing the solubility data in monosolvents in which the overall mean deviation of the models was 10.7 %.

Introduction

Solubility is an important physicochemical parameter in pharmaceutical sciences. The aqueous solubility of drugs is one of the important key parameters to make decisions on the fate of a drug candidate. In drug development, solubility data are essential information for the preparation of drug formulations, solid phase properties, and correlation between in vitro/in vivo data. Aqueous solubility is also required to make a solution of the drug for pharmacological and toxicological tests of drug candidates. Solubility of drugs in nonaqueous solvent is important in synthesis of drugs and recrystallization for the purification process and development of pharmaceutical analysis.[1]

Solubilization of poorly soluble drugs is essential for the preparation of many commercially available oral solution, parenteral, soft gelatin, and topical pharmaceutical formulations of drugs.[2] A number of methods have been developed for solubilization of drugs including the cosolvency method. Cosolvency is mixing of a water-soluble organic solvent that is miscible with water for decreasing the polarity of dissolution medium. The main advantages of the cosolvency method are its solubilization power and ease of use.[3] The prediction of physicochemical properties in pharmaceutical sciences is very important. About cosolvency, efforts have been devoted to the presentation of mathematical models for estimation of drug solubility in water−cosolvent mixtures. These models[4−12] were recently reviewed, and their advantages and limitations were discussed.[13] One of these models developed by our group is the Jouyban−Acree model. This model was used for prediction of the solubility of many pharmaceutical and chemical compounds in binary, ternary, and quaternary solvent mixtures at different temperatures. In addition to the solubility prediction, it was used to calculate other physicochemical properties in mixed solvent systems.[13]

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Common cosolvents in pharmacy are ethanol, propylene glycol, glycerin, polyethylene glycol 400, and *N*-methyl-2-pyrrolidone (NMP).[14] NMP is a very strong solubilizing agent[2] and is an important solvent in extraction, purification, and crystallization of drugs.[15,16] Solubility data of cefotaxime,[17] dioxopromethazine hydrochloride,[18] and benzoic acid[19] in NMP at different temperatures and in NMP + water, up to 50 % of NMP for estrone and griseofulvin,[20] have been reported. Experimental solubilities of some antiepileptic drugs in ethanol + water and propylene glycol + water mixtures were reported in previous works.[21,22] However, there are no published data of the investigated drugs in the literature. Hence, in this work, the solubilities of clonazepam (CZP), diazepam (DZP), lamotrigine (LTG), and phenobarbital (PB) in NMP + water mixtures at 298.2 K were reported, and the fitness of the data to the Jouyban−Acree model was investigated.

Experimental Methods

DZP (99.7 % in mass fraction) and CZP (99.7 % in mass fraction) were gifts from Sobhan pharmaceutical (Iran). PB (99.8 % in mass fraction) was a gift from Pars Daru pharmaceutical (Iran), and LTG (99.6 % in mass fraction) was purchased from Arastoo pharmaceutical (Iran). The purity of the drugs was checked by determination of their melting temperatures and comparing the measured solubilities in solvents with the reported data from the literature. NMP (99.5 % in mass fraction) from Merck (Germany) and methanol (99.8 % in mass fraction) from Caledon (Canada) were purchased, and double distillated water (with the electrical conductivity of $< 3 \cdot 10^{-6}$ S) was used for preparation of the solutions.

Apparatus and Procedures

The binary mixtures composed of NMP + water with suitable volumes of the solvents were prepared with the uncertainty of 0.001 volume fraction. The solubility data of CZP, DZP, LTG, and PB in NMP + water were determined by the saturation shake-flask method.[23] In this method, an excess amount of the drugs was added to the prepared solutions, then these solutions were saturated in an incubator equipped with a temperature-

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Table 1. Details of Calibration Curves of Drugs

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	45217 to 77215	$3.48 \cdot 10^{-6}$ to $2.79 \cdot 10^{-5}$
CZP	11297 to 12050	$1.66 \cdot 10^{-5}$ to $1.33 \cdot 10^{-4}$
PB	3753 to 3073	$8.53 \cdot 10^{-5}$ to $4.26 \cdot 10^{-4}$

controlling system maintained constant at 298.2 (± 0.2) K and using a shaker (Behdad, Tehran, Iran). Also for PB powders in a binary solvent mixture before incubation at 298.2 K, solutions were sonicated for 20 min. After a sufficient length of time (> 5 days for PB and > 3 days for other drugs), the saturated solutions of the drugs were filtered using hydrophilic Durapore filters (0.45 μm, Milipore, Ireland) diluted with water for LTG and with methanol for CZP, DZP, and PB. Diluted samples were then assayed at (306, 229, 309, and 230) nm, respectively, using a UV−vis spectrophotometer (Beckman DU-650, Fullerton, USA). Preliminary investigations showed that the filter did not absorb the solutes through the filtration process. The concentrations of solutions were determined according to the calibration curves. Details of calibration curves were shown in Table 1. Each experimental data point represents the average of at least three repeated measurements with the measured mole per liter solubilities being reproducible to within ± 4.1 %. Calculated standard deviations ranged from ($\sigma_{n-1} = 0.0000029$ to $\sigma_{n-1} = 0.1455292$) $mol \cdot L^{-1}$. Densities of the saturated solutions were determined using a 5 mL pycnometer with the uncertainty of 0.0001 $g \cdot cm^{-3}$.

Computational Methods

The general form of the Jouyban−Acree model for calculation of solubility in binary solvent mixtures at different temperatures is[13]

$$\log C_{m,T}^{Sat} = \varphi_1 \log C_{1,T}^{Sat} + \varphi_2 \log C_{2,T}^{Sat} + \left[\frac{\varphi_1 \varphi_2}{T} \sum_{i=0}^{2} J_i (x_1 - x_2)^i\right] \quad (1)$$

where $C_{m,T}^{Sat}$ is the solute ($mol \cdot L^{-1}$) solubility in the solvent mixtures at temperature T; φ_1 and φ_2 are volume fractions of solvents 1 (NMP) and 2 (water) in the absence of solute; $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ denote the $mol \cdot L^{-1}$ solubility of the solute in solvents 1 and 2, respectively; and J_i are constants of the model computed by a regression analysis. These constants represent differences in various solute−solvent and solvent−solvent interactions in the mixture.

Equation 1 was fitted to the experimental solubility data of each drug, and the back-calculated solubilities were used to calculate the accuracy of the fitness. The mean deviation (MD) was used to check the accuracy and was calculated using

$$MD = \frac{\sum \left\{ \frac{|(C_m^{Sat})_{pred} - (C_m^{Sat})|}{(C_m^{Sat})} \right\}}{N} \quad (2)$$

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

Result and Discussion

Table 2 lists the experimental solubilities of CZP, DZP, LTG, and PB in NMP + water mixtures at 298.2 K. There were good agreements between the reported solubility of LTG in water[24] (0.000664 $mol \cdot L^{-1}$ at 298.15 K) and DZP in water[25] (0.00014817 at 295.15 K to 297.15 K) from the literature and the measured solubilities of LTG in water (0.000729 $mol \cdot L^{-1}$ at 298.2 K) and DZP in water (0.0001517 at 298.2 K) in this work. The computed solubilities of these drugs were compared via the fitness of eq 1 to experimental data and also the density of the saturated solutions. The solubilities of CZP, DZP, and LTG increased with the addition of NMP, and the maximum values are in neat NMP. The solubility of PB increased with the addition of NMP, reached the maximum value, and then decreased with a further increase in NMP concentration. Figures 1 and 2 illustrate the solubility profile of drugs in various volume fractions of NMP in the binary mixtures and the back-calculated solubilities by eq 1. The calculated solubilities were compared with the corresponding experimental data, and MD values were computed and listed in Table 3 along with the model constants. The results show that the Jouyban−Acree model calculates the solubility of drugs in

Table 2. Experimental Solubilities of CZP, DZP, LTG, and PB in NMP (1) + Water (2) Mixtures at 298.2 K, Density ρ of the Saturated Solutions, and the Back-Calculated Solubilities Using Equation 1

φ_1	ρ/g·cm^{-3}	C_m^{Sat}/mol·L^{-1} experimental	C_m^{Sat}/mol·L^{-1} calculated
		CZP	
0.00	1.004	0.00010	0.00010
0.10	1.012	0.00035	0.00028
0.20	1.015	0.00075	0.00077
0.30	1.025	0.00173	0.00202
0.40	1.033	0.00448	0.00514
0.50	1.040	0.01354	0.01261
0.60	1.052	0.02813	0.02990
0.70	1.060	0.07433	0.06846
0.80	1.067	0.16433	0.15138
0.90	1.087	0.38975	0.32326
1.00	1.100	0.66671	0.66671
		DZP	
0.00	1.002	0.00015	0.00015
0.10	1.010	0.00366	0.00219
0.20	1.015	0.00737	0.00856
0.30	1.025	0.01259	0.01598
0.40	1.033	0.01938	0.02213
0.50	1.044	0.03349	0.03112
0.60	1.054	0.06420	0.05329
0.70	1.060	0.13502	0.11709
0.80	1.065	0.28493	0.30516
0.90	1.087	0.59634	0.76559
1.00	1.117	1.31710	1.31710
		LTG	
0.00	1.000	0.00073	0.00073
0.10	1.010	0.00321	0.00288
0.20	1.017	0.00732	0.00742
0.30	1.027	0.01243	0.01387
0.40	1.038	0.02013	0.02057
0.50	1.044	0.02946	0.02619
0.60	1.050	0.03061	0.03058
0.70	1.056	0.03283	0.03455
0.80	1.052	0.04023	0.03939
0.90	1.048	0.04576	0.04669
1.00	1.040	0.05853	0.05853
		PB	
0.00	1.004	0.00533	0.00533
0.10	1.008	0.11851	0.07184
0.20	1.019	0.20182	0.26435
0.30	1.033	0.38069	0.46778
0.40	1.046	0.58587	0.60939
0.50	1.069	0.94975	0.77761
0.60	1.112	1.31473	1.12400
0.70	1.137	1.64962	1.84987
0.80	1.144	2.73952	3.02833
0.90	1.175	3.88533	3.74434
1.00	1.169	2.30766	2.30766

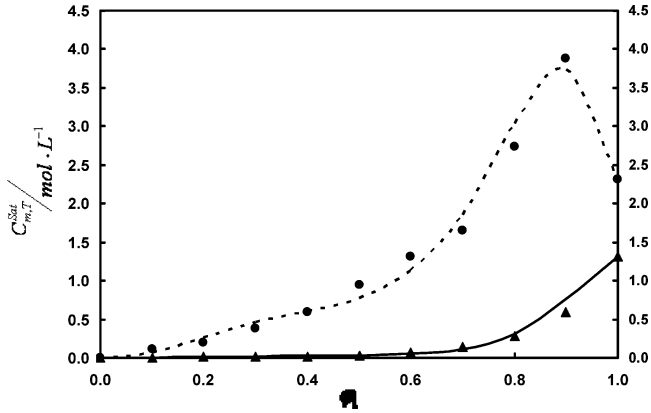

Figure 1. Experimental solubilities of diazepam and phenobarbital ($C^{Sat}_{m,T}$/ mol·L^{-1}) at various volume fractions of *N*-methyl-2-pyrrolidone (φ_1) in binary solvent mixtures: ●, phenobarbital; ▲, diazepam and the back-calculated solubilities using eq 1: - - -, phenobarbital; —, diazepam.

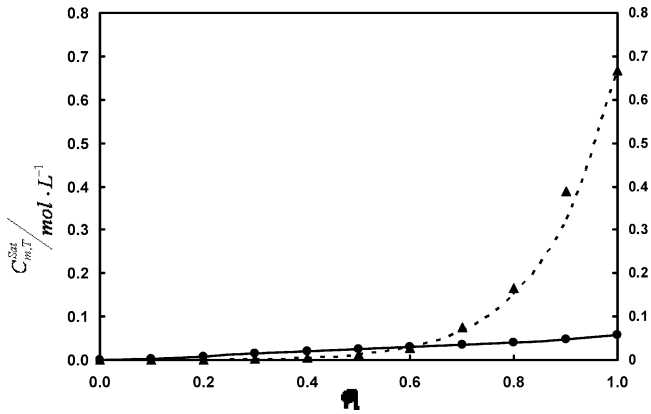

Figure 2. Experimental solubilities of clonazepam and lamotrigine ($C^{Sat}_{m,T}$/ mol·L^{-1}) at various volume fractions of *N*-methyl-2-pyrrolidone (φ_1) in binary solvent mixtures: ●, lamotrigine; ▲, clonazepam and the back-calculated solubilities using eq 1: —, lamotrigine; - - -, clonazepam.

Table 3. Numerical Values of the Model Constants and the Mean Deviation (MD) for the Back-Calculated Solubilities of CZP, DZP, LTG, and PB in NMP + Water Mixtures at 298.2 K Using Equation 1

drug	J_0	J_1	J_2	100·MD
CZP	225.298	−	−	9.0
DZP	411.662	−1264.200	1758.640	15.5
LTG	718.924	−648.150	164.157	4.2
PB	1008.716	−811.896	1891.487	14.2
	Overall 100·MD			10.7

NMP + water to within 10.7 % error. More experimental solubility data sets are needed to present a generally trained version of the model for predicting the solubility of other drugs in NMP + water mixtures.

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