Solubility of Lamotrigine, Diazepam, Clonazepam, and Phenobarbital in Propylene Glycol + Water Mixtures at 298.15 K

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Experimental solubilities of four antiepileptic drugs, that is, lamotrigine, diazepam, clonazepam, and phenobarbital in propylene glycol + water mixtures at 298.15 K were reported. The solubility of drugs was increased with the addition of propylene glycol, and the maximum values are observed in neat propylene glycol. The Jouyban–Acree model was used to fit the experimental data, and the solubilities were reproduced using a previously trained version of the Jouyban–Acree model and the solubility data in monosolvents in which the overall mean deviations (OMDs) of the models were 6.0 % and 14.3 %, respectively. Solubilities were also predicted by a previously established log-linear model of Yalkowsky with an OMD of 37.7 %. More accurate predictions were provided using the Jouyban–Acree model in comparison with the log-linear model of Yalkowsky.

Introduction

The solubility of drugs is essential information in drug discovery and development investigations in the pharmaceutical industry, and the solubilization of a low-soluble drug is required in various applications including the preparation of liquid drug formulations. 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. Propylene glycol is a stable and low-toxic pharmaceutical cosolvent that is used in many commercially available oral and parenteral pharmaceutical formulations of poorly soluble drugs.^{1,2} Table 1 lists commercially available parenteral formulations solubilized by propylene glycol along with their propylene glycol percentage, and Table 2 lists the oral pharmaceutical formulations containing propylene glycol as a cosolvent.

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 the additional cost incurred with using cosolvents. 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 expensive. Moreover, in the early stages of drug discovery processes, the scarcity of the available amount of drug/drug candidate 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.³

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

Table 1. List of Commercially Available Injection Pharmaceutical Formulations Solubilized by Propylene Glycol and the Percentage of Cosolvent Used in the Formulation¹

drug	percentage of propylene glycol in formulation
diazepam	40
digoxin	40
fenoldopam mesylate	50
melphalan HCl	60
oxytetracycline	67 to 75
paricalcitol	30
pentobarbital sodium	40
phenytoin sodium	40
chlordiazepoxide HCl	20
lorazepam	≤ 80
phenobarbital	≤ 68

Table 2. List of Oral Pharmaceutical Formulations Prepared by Using Propylene Glycol as a Cosolvent¹

drug	formulation
amprenavir	oral solution
amprenavir	soft gelatin capsule
clofazimine	soft gelatin capsule
cyclosporin A	oral solution
cyclosporin A	soft gelatin capsule
digoxin	soft gelatin capsule
lopinavir	oral solution
lopinavir	soft gelatin capsule
ritonavir	oral solution
sirolimus	oral solution
loratadin	syrup
itraconazole	oral solution

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 temperatures is

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

where $C_{m,T}^{\text{Sat}}$ is the solute ($\text{mol} \cdot \text{L}^{-1}$) solubility in the solvent mixtures at temperature T/K , x_1 and x_2 are the volume fractions

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Figure 1. Solubility of lamotrigine ($C_{m,T}^{\text{Sat}}/\text{mol}\cdot\text{L}^{-1}$) at various volume fractions of propylene glycol (x_1) in binary solvent mixtures; ●, experimental; and the computed solubilities using: ---, method I; —, method II; — · —, method III.

Figure 2. Solubility of diazepam ($C_{m,T}^{\text{Sat}}/\text{mol}\cdot\text{L}^{-1}$) at various volume fractions of propylene glycol (x_1) in binary solvent mixtures; ●, experimental; and the computed solubilities using: ---, method I; —, method II; — · —, method III.

Table 3. Details of Calibration Curves of Drugs

drug	molar absorptivity (ϵ)	C	correlation coefficient	calibration curve (A: absorbance)
	$\text{L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$	$\text{mol}\cdot\text{L}^{-1}$		
LTG	6681 to 6904	$3.59\cdot 10^{-5}$ to $1.80\cdot 10^{-4}$	0.9995	$C = 6931.4A - 0.0010$
DZP	45217 to 77215	$3.48\cdot 10^{-6}$ to $2.79\cdot 10^{-5}$	0.9995	$C = 40228A + 0.1327$
CZP	11297 to 12050	$1.66\cdot 10^{-5}$ to $1.33\cdot 10^{-4}$	0.9995	$C = 11062A + 0.0244$
PB	7658 to 7454	$1.96\cdot 10^{-5}$ to $1.96\cdot 10^{-4}$	0.9995	$C = 7434.2A + 0.0122$

of the solvents 1 (propylene glycol) and 2 (water), respectively, in the absence of the solute, $C_{1,T}^{\text{Sat}}$ and $C_{2,T}^{\text{Sat}}$ denote the $\text{mol}\cdot\text{L}^{-1}$ 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.³ 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. The trained version of the Jouyban–Acree model for the prediction of drug solubility in propylene glycol + water mixtures at 298.15 K is⁴

$$\log C_{m,T}^{\text{Sat}} = x_1 \log C_{1,T}^{\text{Sat}} + x_2 \log C_{2,T}^{\text{Sat}} + \left[\frac{37.030x_1x_2}{T} + \frac{319.490x_1x_2(x_1 - x_2)}{T} \right] \quad (2)$$

The alternative prediction method is the trained version of the log-linear model of Yalkowsky,⁵ which is expressed by

$$\log C_{m,T}^{\text{Sat}} = \log C_{2,T}^{\text{Sat}} + (0.37 + 0.78 \log P)x_1 \quad (3)$$

where $\log P$ is the logarithm of the drug's partition coefficient.⁶ The experimentally obtained values of $\log P$ for lamotrigine (LTG), diazepam (DZP), clonazepam (CZP), and phenobarbital (PB) employed in this work were 1.19,⁷ 2.99,⁸ 2.41,⁹ and 1.47,⁸ respectively.

Table 4. Experimental Solubilities $C_{m,T}^{\text{Sat}}$ (Standard Deviation) of Lamotrigine, Diazepam, Clonazepam, and Phenobarbital in Propylene Glycol (x_1) + Water Mixtures at 298.15 K and Density (ρ) of the Saturated Solutions (Result of a Single Measurement)

x_1	ρ $\text{g}\cdot\text{cm}^{-3}$	$C_{m,T}^{\text{Sat}}$ $\text{mol}\cdot\text{L}^{-1}$
lamotrigine		
0.000	1.000	0.00073 (0.0000227)
0.100	1.012	0.00125 (0.0000666)
0.200	1.021	0.00201 (0.0000928)
0.300	1.025	0.00311 (0.0001443)
0.400	1.033	0.00732 (0.0003003)
0.500	1.040	0.01267 (0.0000878)
0.600	1.044	0.03533 (0.0015892)
0.700	1.054	0.05994 (0.0014427)
0.800	1.050	0.11219 (0.0036307)
0.900	1.050	0.17438 (0.0092753)
1.000	1.046	0.20419 (0.0060065)
diazepam		
0.000	1.002	0.00015 (0.0000029)
0.100	1.010	0.00044 (0.0000054)
0.200	1.019	0.00052 (0.0000048)
0.300	1.027	0.00094 (0.0000138)
0.400	1.033	0.00171 (0.0000276)
0.500	1.038	0.00285 (0.0000276)
0.600	1.046	0.00552 (0.0001229)
0.700	1.054	0.01168 (0.0000950)
0.800	1.048	0.02164 (0.0004175)
0.900	1.044	0.03494 (0.0001044)
1.000	1.042	0.04282 (0.0006263)
clonazepam		
0.000	1.004	0.00010 (0.0000013)
0.100	1.038	0.00011 (0.0000206)
0.200	1.017	0.00018 (0.0000149)
0.300	1.027	0.00028 (0.0000407)
0.400	1.035	0.00058 (0.0000569)
0.500	1.040	0.00098 (0.0000745)
0.600	1.048	0.00274 (0.0002150)
0.700	1.054	0.00469 (0.0005689)
0.800	1.054	0.00890 (0.0008600)
0.900	1.044	0.01173 (0.0008211)
1.000	1.042	0.01854 (0.0022379)
phenobarbital		
0.000	1.004	0.00533 (0.0002133)
0.100	1.008	0.00912 (0.0004651)
0.200	1.015	0.01127 (0.0004651)
0.300	1.027	0.01895 (0.0008232)
0.400	1.035	0.03291 (0.0017178)
0.500	1.042	0.05680 (0.0015504)
0.600	1.046	0.08903 (0.0038761)
0.700	1.050	0.16642 (0.0025268)
0.800	1.056	0.25161 (0.0134064)
0.900	1.065	0.51125 (0.0221813)
1.000	1.075	0.64226 (0.0171641)

The experimental solubility of several antiepileptic drugs in ethanol + water mixtures was reported in a previous work.¹⁰ In this work, the experimental solubility of LTG, DZP, CZP, and PB in propylene glycol + water mixtures at 298.15 K were reported. There were no published data on the solubility of these drugs in propylene glycol + water mixtures at 298.15 K. In addition, we illustrate the applicability of the Jouyban–Acree model to the measured drug solubility data and assess the prediction capability of the above-mentioned trained model for predicting the solubility of drugs in propylene glycol + water mixtures. The accuracy of the developed method is also compared with that of the log-linear model of Yalkowsky.

Experimental Method

Materials. LTG was purchased from Arastoo pharmaceutical company (Iran), DZP and CZP were gifts from Sobhan

pharmaceutical company (Iran), and PB was a gift from Amin pharmaceutical company (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.^{9,11–14} Propylene glycol (99.5 %) was purchased from Merck (Germany), methanol (99.8 %) was obtained from Caledon (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 0.001 volume fraction. The solubility of LTG, DZP, CZP, and PB in propylene glycol + 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 maintained constant to within ± 0.2 K. Prior to incubation at 298.15 K, PB powder suspended in the solvent mixture was sonicated for 20 min. After a sufficient length of time (> 72 h), the saturated solutions of the drugs were filtered using hydrophilic Durapore filters ($0.45 \mu\text{m}$, Milipore, Ireland) and were then diluted by water for LTG and PB and by methanol for DZP and CZP. The diluted samples were then assayed at (306, 220, 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 represents the average of at least three repetitive experiments with the measured $\text{mol}\cdot\text{L}^{-1}$ solubilities being reproducible to within ± 3.7 %. Calculated standard deviations of $\text{mol}\cdot\text{L}^{-1}$ solubilities ranged from $\sigma_{n-1} = 0.0000013$ to 0.0221823. 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 each drug, and the back-calculated solubilities were used to calculate the accuracy of the fit. In method II, the solubilities of four drugs were predicted using eq 2 by employing the experimental solubility of drugs in neat propylene glycol and water. In method III, the solubilities of these drugs were predicted using eq 3 with the experimental log P data and their solubilities in neat water. The mean deviation (MD) was used to check the accuracy of the prediction methods and is calculated using

$$\text{MD} = \frac{\sum \left\{ \frac{|(C_m^{\text{Sat}})_{\text{pred}} - (C_m^{\text{Sat}})|}{(C_m^{\text{Sat}})} \right\}}{N} \quad (4)$$

where N is the number of data points in each set. Goodness of fit to each method was also shown by plotting the predicted and experimental solubilities of the drugs against the volume fraction of propylene glycol.

Results and Discussion

Table 4 lists the experimental solubilities of LTG, DZP, CZP, and PB in propylene glycol + water mixtures at 298.15 K, and the density of the saturated solutions. There were good agreements between the previously published solubility data of LTG in water⁹ ($0.000664 \text{ mol}\cdot\text{L}^{-1}$ at 298.15 K), DZP in water¹¹ ($0.00014817 \text{ mol}\cdot\text{L}^{-1}$ at (295.15 to 297.15) K), CZP in propylene glycol¹² ($0.016471 \text{ mol}\cdot\text{L}^{-1}$ at 298.15 K), and PB in water ($(0.005168^{13}$ and $0.005090^{14}) \text{ mol}\cdot\text{L}^{-1}$ at 298.15 K) from the literature and the solubilities of LTG in water (0.000729

Figure 3. Solubility of clonazepam ($C_{m,T}^{Sat}/\text{mol}\cdot\text{L}^{-1}$) at various volume fractions of propylene glycol (x_1) in binary solvent mixtures; •, experimental; and the computed solubilities using: ---, method I; —, method II; - - -, method III.

Figure 4. Solubility of phenobarbital ($C_{m,T}^{Sat}/\text{mol}\cdot\text{L}^{-1}$) at various volume fractions of propylene glycol (x_1) in binary solvent mixtures; •, experimental; and the computed solubilities using: ---, method I; —, method II; - - -, method III.

Table 5. Numerical Values of the Adjusted Parameters of Equation 1 and the Mean Deviation (MD) for the Predicted Solubilities of Lamotrigine, Diazepam, Clonazepam, and Phenobarbital in Propylene Glycol + Water Mixtures Using Various Numerical Analyses and Their Overall Values

drug	J_0	J_1	J_2	method I	method II	method III
lamotrigine	76.860	471.556	252.450	5.9	11.6	63.4
diazepam	61.681	133.889	684.395	5.9	15.9	16.3
clonazepam	-73.201	532.023	-81.136	6.5	18.8	29.9
phenobarbital	-49.420	161.543	172.109	5.8	11.0	41.0
overall MD %				6.0	14.3	37.7

$\text{mol}\cdot\text{L}^{-1}$ at 298.15 K), DZP in water ($0.00015 \text{ mol}\cdot\text{L}^{-1}$ at 298.15 K), CZP in propylene glycol ($0.01854 \text{ mol}\cdot\text{L}^{-1}$ at 298.15 K), and PB in water ($0.00533 \text{ mol}\cdot\text{L}^{-1}$ at 298.15 K) determined in this work. The solubilities of these drugs increased with the addition of propylene glycol, and the maximum values were observed in neat propylene glycol. The solubilities of the four drugs were predicted using numerical methods I, II, and III. The experimental and predicted solubilities of the drugs versus the volume fraction of propylene glycol in the binary mixtures were plotted in Figures 1, 2, 3, and 4. As shown in the Figures, the Jouyban–Acree model fits the experimental solubility data of drugs at all composition ranges of propylene glycol very well. This finding is also supported by the small MD values of the

back-calculated and experimental solubility data. The main limitation of eq 1 is that it should be trained for each drug employing a minimum number of experimental data in binary solvents. The predictive version of the model, that is, eq 2, predicts the solubility values with reasonable MD values. The log-linear model, that is, eq 3, predicts the solubility of CZP and DZP with reasonable MD values; however, the model underestimates the solubility of LTG and PB, especially at propylene glycol rich regions. The predicted solubilities were compared with the corresponding experimental data, and MD values were computed and are listed in Table 5. In general, the overall MDs observed in these predictions show that the Jouyban–Acree model is robust and could be used for prediction

purposes with an error of less than 15 %. This error level is in agreement with a previous finding in which the overall MD of the predicted solubility of 27 data sets was 24.1 %.⁴ In conclusion, the Jouyban–Acree model provided more accurate predictions in comparison with a previously established log-linear model. However, the log-linear model requires only a single solubility datum in neat water and the log *P* value that could be computed using commercial software packages.

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