PHARMACEUTICAL NANOTECHNOLOGY

Solubility Prediction of Drugs in Mixed Solvents Using Partial Solubility Parameters

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ABSTRACT: Solubility of drugs in binary and ternary solvent mixtures composed of water and pharmaceutical cosolvents at different temperatures were predicted using the Jouyban–Acree model and a combination of partial solubility parameters as interaction descriptors in the solution. The generally trained version of the model produced the overall mean percentage deviation values for the back-calculated solubility of drugs in binary solvents of 34.3% and the predicted solubilities in ternary solvent mixtures of 38.0%. In addition, the applicability of the trained model for predicting the solvent composition providing the maximum solubility of a drug was investigated. The results of collected solubility data of drugs in various mixed solvents and the newly measured solubility data of five drugs in ethanol + propylene glycol + water mixtures at 25°C showed that the model provided acceptable predictions and could be used in the pharmaceutical industry. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:4368–4382, 2011

Keywords: solubility; Jouyban-Acree model; prediction; physicochemical properties; mathematical modelling; QSPR; in silico modelling

INTRODUCTION

Solubility is one of the critical physicochemical properties in drug discovery and development. Cosolvency, or addition of a permissible organic solvent to the aqueous solution, is the most common and feasible method in the pharmaceutical industry,[1] and is used to improve solubility and stability of drugs in topical solutions and liquid dosage forms such as parenteral, ophthalmic, otic, elixir, and soft gelatin capsule formulations.[2–4] Combination of the cosolvency and change of temperature is the most common method in crystallization of drugs.[5]

Optimizing the cosolvent concentration at the lowest possible level will also reduce the price and toxicity of the pharmaceutical product. To facilitate this process, the cosolvency models were presented in 1960 to correlate/predict the solubility of drugs in solvent mixtures and interpret the cosolvency mechanisms. One of the simplest methods is the Jouyban–Acree model that promises more accuracy when compared

Additional Supporting Information may be found in the online version of this article. Supporting Information

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with other similar algorithms.[1] The general form of the model is

$$\log X_{m,T} = f_c \log X_{c,T} + f_w \log X_{w,T} + \frac{f_c f_w}{T} \sum_{i=0}^{2} J_i (f_c - f_w)^i \quad (1)$$

where $X_{m,T}$ is the solute solubility in the solvent mixtures, f_c and f_w denote the fractions of the cosolvent and water, respectively, $X_{c,T}$ and $X_{w,T}$ are the solubility of the solute in the neat cosolvent and water, respectively, T is temperatute (K), and J_i is the model constants. A number of solubility data are required to compute the numerical values of the J_i. To reduce the number of required data points, trained versions of the model were proposed for the common cosolvents [ethanol, propylene glycol (PG), and polyethylene glycol 400 (PEG 400)] in binary aqueous solvent mixtures at different temperatures that hypothesized that the solute–solvent interaction terms are independent from the solute's structure.[1] This is not the case and is just an oversimplification. In a recent work, by adding the logarithm of partition coefficient of drugs, a significant improvement has been achieved for the solubility of drugs in ethanol + water mixtures.[6]

The combination of PG and ethanol is commonly used for solubilization of drugs. There are a few reported solubility data of drugs in these solvent mixtures. In this work, solubilities of clonazepam, diazepam, lamotrigine, phenobarbital, and ibuprofen in ternary solvent mixtures of ethanol + PG + water were reported. We intended to develop liquid formulations for these five drugs, and the available experimental data reported in the literature was insufficient. Therefore, their solubilities are investigated in this work. In addition, 115 solubility data sets of binary and 13 data sets of ternary solvent mixtures were collected from the literature. The solubility data sets in binary solvents were used to train and validate a general model combined of the Jouyban–Acree model and partial solubility parameters of solvents and solutes. The trained model was used to predict the solubility of drugs in ternary solvent mixtures at various temperatures. In addition, the maximum solubility of drugs in binary solvent mixtures and the solvent composition providing the maximum solubility were calculated using the proposed model and compared with the calculated values by previous models.

MATERIALS AND METHODS

Materials

Clonazepam and diazepam were gifted by Sobhan pharmaceutical company (Rasht, Iran), ibuprofen was a gift from Daana Pharmaceutical Company (Tabriz, Iran), lamotrigine was purchased from Arastoo Company (Tehran, Iran), and phenobarbital was a gift from Pars Daru (Tehran, Iran). The melting point temperatures and the measured solubilities of drugs in monosolvents were compared with the corresponding data from the literature to check the purity of drugs. PG (99.5%) from Merck (Darmstadt, Germany), ethanol (99.9%) and methanol (99.8%) from Scharlau (Barcelona, Spain) were used. Double-distilled water was used for the preparation of the solutions.

Experimental Method

The ternary solvent mixtures were prepared by mixing the appropriate volumes of ethanol, PG, and water. The solubilities of drugs were determined by equilibrating excess amount of the drugs added to the prepared solutions.[7] These solutions were saturated in an incubator equipped with a temperature-controlling system maintained constant at 25 (±0.2)°C using a shaker (Behdad, Tehran, Iran). The solutions were saturated after 72 h that verified by studying dissolution rates of drugs. The saturated solutions were filtered using hydrophilic Durapore filters (0.45 μm; Milipore, Carrigtwohill, Ireland) and diluted by water for lamotrigine and phenobarbital, and by methanol for clonazepam, diazepam, and ibuprofen. The solutions were assayed by ultraviolet–visible spectrophotometer (Beckman DU-650, Fullerton, California), according to their calibration curves. The wavelengths used for clonazepam, diazepam, lamotrigine, ibuprofen, and phenobarbital were 309, 229, 306, 222, and 220 nm, respectively.

Computational Method

Solubility Prediction Using Partial Solubility Parameters

The Hildebrand solubility parameter (δ) is the square root of the cohesive energy density. The δ is only applicable for nonpolar systems in which the solute–solvent and solvent–solvent interactions are limited to London forces. The globally trained version of the Jouyban–Acree model was presented to predict the solubility of nonpolar solutes in nonaqueous solvent mixtures.[8] In the polar solvent systems, intermolecular forces other than London forces exist, those are mainly hydrogen bonds and dipole interactions. To provide better descriptors, the δ was extended to the partial solubility parameters and composed of the energy from dispersion bonds between molecules (δ_d), the energy from polar bonds between molecules (δ_p), and the energy from hydrogen bonds between molecules (δ_h).[9,10] The pharmaceutical applications of solubility parameters in pharmaceutical dosage form design have been reviewed by Hancock et al.[11] In addition, Navarro-Lupioón et al.[12] were correlated

partial solubility parameters to the swelling behavior of a hydrophilic polymer, and these parameters were also applied for predicting the intestinal drug absorption properties.[13]

Prediction of the solvent composition providing the maximum solubility of a drug in the mixture $(X_{m,T})_{max}$ is another data required in the pharmaceutical industry. Some efforts have been made to predict the $(X_{m,T})_{max}$ of drugs in binary solvent mixtures. The Hildebrand equation has been used for calculating the solubility of drugs in binary solvent mixtures. According to the Hildebrand equation, the maximum solubility is obtained when the solubility parameters of the solute and solvent (or mixed solvent) is equal.[14,15] The J terms of Eq. 1 represent the solute–solvent and solvent–solvent interactions in the solution.[16] These interactions could be consisted of dispersive, polar, and hydrogen bond interactions, and the terms $\delta_{ds}(\delta_{dc}-\delta_{dw})^2$, $\delta_{ps}(\delta_{pc}-\delta_{pw})^2$, and $\delta_{hs}(\delta_{hc}-\delta_{hw})^2$ could be considered as a representative of the extent of these interactions. Therefore, the Jouyban–Acree model and the partial solubility parameters could be combined for calculating the solubility of drugs in mixed solvents:

$$\begin{aligned}\log X_{m,T} &= f_c \log X_{c,T} + f_w \log X_{w,T} \\ &+ \left(\frac{f_c f_w}{T}\right)\{A_0\delta_{ds}(\delta_{dc}-\delta_{dw})^2 + A_1\delta_{ps}(\delta_{pc}-\delta_{pw})^2 \\ &+ A_2\delta_{hs}(\delta_{hc}-\delta_{hw})^2\} \\ &+ \left(\frac{f_c f_w (f_c - f_w)}{T}\right)\{A_3\delta_{ds}(\delta_{dc}-\delta_{dw})^2 \\ &+ A_4\delta_{ps}(\delta_{pc}-\delta_{pw})^2 + A_5\delta_{hs}(\delta_{hc}-\delta_{hw})^2\} \\ &+ \left(\frac{f_c f_w (f_c - f_w)^2}{T}\right)\{A_6\delta_{ds}(\delta_{dc}-\delta_{dw})^2 \\ &+ A_7\delta_{ps}(\delta_{pc}-\delta_{pw})^2 + A_8\delta_{hs}(\delta_{hc}-\delta_{hw})^2\} \qquad (2)\end{aligned}$$

in which A_0–A_8 are the model constants, δ_{ds}, δ_{ps}, and $\delta_{hs}$are the partial solubility parameters of the solutes, δ_d, δ_h, and δ_p are the partial solubility parameters of solvents and subscripts c and w denote cosolvent and water, respectively.

The partial solubility parameters of the solutes and PEGs were computed by Hoy solubility parameter software[17] and those of other solvents were collected from handbook of Hansen solubility parameters.[18] The solubility and fraction of solvents were expressed in different concentration units and our numerical analyses showed that the different units do not affect the accuracy of model (details of the results are not reported in this work). Table 1 shows the details of the investigated solubility data sets in cosolvent + water mixtures. The model constants of Eq. 2 for cosolvent + water mixtures were calculated by regressing $(\log X_{m,T} - f_c \log X_{c,T} - f_w \log X_{w,T})$ against $[(\frac{f_c f_w}{T})\delta_{ds}(\delta_{dc}-\delta_{dw})^2]$, $[(\frac{f_c f_w}{T})\delta_{ps}(\delta_{pc}-\delta_{pw})^2]$, $[(\frac{f_c f_w}{T})\delta_{hs}(\delta_{hc}-\delta_{hw})^2]$, $[(\frac{f_c f_w (f_c-f_w)}{T})\delta_{ds}(\delta_{dc}-\delta_{dw})^2]$, $[(\frac{f_c f_w (f_c-f_w)}{T})\delta_{ps}(\delta_{pc}-\delta_{pw})^2]$, $[(\frac{f_c f_w (f_c-f_w)}{T})\delta_{hs}(\delta_{hc}-\delta_{hw})^2]$, $[(\frac{f_c f_w (f_c-f_w)^2}{T})\delta_{ds}(\delta_{dc}-\delta_{dw})^2]$, $[(\frac{f_c f_w (f_c-f_w)^2}{T})\delta_{ps}(\delta_{pc}-\delta_{pw})^2]$, and $[(\frac{f_c f_w (f_c-f_w)^2}{T})\delta_{hs}(\delta_{hc}-\delta_{hw})^2]$.

The validation of the model was performed by leave-many-out cross-validation method in which data sets sorted according to alphabetic order of the solutes and 10% of solubility data sets in cosolvent + water mixtures of different solvent systems or temperatures were excluded and the model was trained using the rest of solubility data sets. The trained model was used to predict the solubility of the excluded data sets. Leave-one-drug-out cross-validation was also performed by excluding solubility data of a drug and the model was trained using the rest of data set. The trained model then was used to predict the solubility of the excluded drug. Finally, the accuracy of the proposed model was confirmed by external data sets of collected and measured solubility data in ternary solvent mixtures. The accuracy of the proposed method is computed by the mean percentage deviation (MPD):

$$\mathrm{MPD} = \frac{100}{N}\sum_{1}^{N}\left[\frac{|\mathrm{Predicted}-\mathrm{Observed}|}{\mathrm{Observed}}\right] \qquad (3)$$

where N is the number of data points in each set. Also the individual percentage deviation (IPD) was computed using:

$$\mathrm{IPD} = 100\left[\frac{|\mathrm{Predicted}-\mathrm{Observed}|}{\mathrm{Observed}}\right] \qquad (4)$$

Prediction of Solvent Composition Providing the Maximum Solubility of a Drug

The numerical values of f_c (range 0.00–1.00) with 0.01 intervals and $X_{c,T}$ and $X_{w,T}$ were used to calculate $(f_c)_{max}$ of cosolvent + water mixtures providing $(X_{m,T})_{max}$values for 112 studied data sets using Hildebrand equation (method I), trained versions of the Jouyban–Acree model for aqueous mixtures of ethanol, PEG 400, and PG[1] (method II) along with the proposed model in this work (method III). According to the Hildebrand equation, the $(X_{m,T})_{max}$was observed when the solubility parameters of the solute (δ_s) and the solvent mixture (δ_m) are equal or $\delta_w < \delta_s < \delta_c$. The corresponding $(f_c)_{max}$ could be calculated by a simple manipulation:

$$\delta_m = f_c\delta_c + f_w\delta_w,\ \delta_m = \delta_s \rightarrow f_c = (f_c)_{max}$$

in which δ_c and δ_w are the Hildebrand solubility parameters of cosolvent and water.

Table 1. Details of the Solutes, Solvents, Unit of Solvent Composition and Solubility, Number of Solvent Compositions of Each Set (N) and Mean Percentage Deviation (MPD) in Cosolvent + Water Mixtures at 25°C

No.	Solute	Cosolvent	Solvent Composition	T	$\log X_{c,T}$	$\log X_{w,T}$	Solubility Unit	MPD	N	References
1	Acetaminophen	Ethanol	WF	20	−1.30	−2.82	MF	7.4	11	19
2	Acetaminophen	Ethanol	VF	20	−1.28	−2.76	MF	6.5	7	20
3	Acetaminophen	Ethanol	WF	25	−1.26	−2.73	MF	11.6	11	19
4	Acetaminophen	Ethanol	VF	25	−1.27	−2.72	MF	7.2	13	21
5	Acetaminophen	Ethanol	VF	25	−1.27	−2.72	MF	6.6	7	20
6	Acetaminophen	Ethanol	WF	30	−1.21	−2.68	MF	12.6	11	19
7	Acetaminophen	Ethanol	VF	30	2.31	1.32	W/V	19.8	11	22
8	Acetaminophen	Ethanol	VF	30	−1.21	−2.64	MF	5.9	7	20
9	Acetaminophen	Ethanol	WF	35	−1.18	−2.59	MF	11.9	11	19
10	Acetaminophen	Ethanol	VF	35	−1.18	−2.58	MF	9.8	7	20
11	Acetaminophen	Ethanol	WF	40	−1.15	−2.5	MF	11.4	11	19
12	Acetaminophen	Ethanol	VF	40	−1.15	−2.55	MF	12.3	7	20
13	Acetaminophen	NMP	WF	25	0.70	−1.00	M	15.9	11	23
14	Acetaminophen	PEG 200	VF	30	0.11	−0.84	M	14.3	11	22
15	Acetaminophen	PEG 400	VF	25	0.07	−1.04	M	9.9	11	24
16	Acetaminophen	PEG 600	WF	25	0.16	−1.00	M	10.7	11	23
17	Acetaminophen	PG	WF	20	−1.31	−2.82	MF	66.9	11	25
18	Acetaminophen	PG	WF	25	−1.29	−2.73	MF	57.3	11	25
19	Acetaminophen	PG	WF	30	−1.22	−2.68	MF	56.3	11	25
20	Acetaminophen	PG	WF	35	−1.18	−2.59	MF	60.2	11	25
21	Acetaminophen	PG	WF	40	−1.12	−2.50	MF	62.5	11	25
22	Acetanilide	Ethanol	WF	20	−0.65	−2.28	MF	4.5	8	26
23	Acetanilide	Ethanol	WF	25	−3.07	−5.14	MF	6.4	13	26
24	Acetanilide	Ethanol	VF	25	−1.09	−3.10	MF	6.9	11	27
25	Acetanilide	Ethanol	WF	30	−0.54	−2.16	MF	11.6	13	26
26	Aminopyrine	Ethanol	WF	25	2.55	1.72	W/V	21.7	11	26
27	Amobarbital	Ethanol	WF	25	2.34	−0.25	W/V	17.5	41	28
28	Antipyrine	Ethanol	WF	25	2.79	2.63	W/V	28.9	11	26
29	Barbital	Ethanol	WF	25	1.97	0.86	W/V	45.9	41	28
30	Benzocaine	Ethanol	VF	25	−0.82	−3.22	MF	46.1	11	27
31	Benzoic acid	Ethanol	WF	15	0.35	−1.70	M	50.9	11	29
32	Benzoic acid	Ethanol	WF	20	0.40	−1.62	M	22.2	11	29
33	Benzoic acid	Ethanol	WF	25	0.44	−1.55	M	14.5	11	29
34	Butabarbital	Ethanol	WF	25	1.92	−0.05	W/V	7.9	41	28
35	Caffeine	DMF	VF	25	−1.92	−2.64	MF	48.3	11	30
36	Caffeine	Ethanol	MF	5	−2.91	−2.98	MF	32.4	11	31
37	Caffeine	Ethanol	MF	15	−2.81	−2.88	MF	35.2	11	31
38	Caffeine	Ethanol	VF	25	−2.68	−2.77	MF	41.6	11	31
39	Caffeine	Ethanol	MF	35	−2.51	−2.67	M.F	50.7	11	31
40	Caffeine	Ethanol	MF	40	−2.37	−2.59	MF	49.1	11	31
41	Celecoxib	Ethanol	VF	25	1.80	−2.15	W/V	71.5	8	32
42	Chlordiazepoxide	Ethanol	VF	30	−2.47	−5.21	MF	29.0	11	33
43	Chlordiazepoxide	PEG 200	VF	30	−1.63	−5.23	MF	8.7	11	34
44	Chlordiazepoxide	PG	VF	30	−2.31	−5.20	MF	64.7	11	35
45	Clonazeopam	Ethanol	VF	25	−1.79	−4.00	M	17.7	11	36
46	Clonazeopam	PG	VF	25	−1.73	−4.00	M	136.9	11	37
47	Clonazepam	Ethanol	VF	30	−2.99	−6.05	MF	19.0	11	33
48	Clonazepam	NMP	VF	25	−0.18	−4.00	M	59.2	11	38
49	Clonazepam	PEG 200	VF	30	−1.74	−6.07	MF	39.6	11	34
50	Clonazepam	PG	VF	30	−3.01	−6.05	MF	40.0	11	35
52	Diazepam	Ethanol	VF	25	−1.04	−3.82	M	26.6	11	36
51	Diazepam	Ethanol	VF	30	−2.12	−5.48	MF	29.0	11	33
53	Diazepam	NMP	VF	25	0.09	−3.80	M	26.0	11	38
54	Diazepam	PEG 200	VF	30	−1.46	−5.46	MF	6.5	11	34
55	Diazepam	PEG 600	WF	25	−0.73	−3.72	M	110.3	11	39
56	Diazepam	PG	VF	25	−1.37	−3.82	M	41.6	11	37
57	Diazepam	PG	VF	30	−2.29	−5.46	MF	35.2	11	35
58	Iboprofen	PG	VF	20	−0.68	−4.92	MF	240.6	11	40
59	Ibuprofen	NMP	WF	25	0.74	−3.40	M	68.1	11	23

Continued

Table 1. Continued

No.	Solute	Cosolvent	Solvent Composition	T	$\log X_{c,T}$	$\log X_{w,T}$	Solubility Unit	MPD	N	References
60	Ibuprofen	PEG 600	WF	25	0.16	−3.40	M	62.1	11	41
61	Ketoprofen	PG	VF	25	0.24	−3.37	M	29.6	11	42
62	Ketoprofen	PG	VF	37	0.31	−3.29	M	23.2	11	42
63	Lamotrigine	Ethanol	VF	25	−1.85	−3.14	M	33.1	11	36
64	Lamotrigine	NMP	VF	25	−1.25	−3.15	M	20.8	11	38
65	Lamotrigine	PEG 600	WF	25	−0.22	−3.14	M	67.6	11	39
66	Lamotrigine	PG	VF	25	−0.69	−3.14	M	72.2	11	37
67	Lorazepam	Ethanol	VF	30	−2.71	−5.46	MF	22.5	11	33
68	Lorazepam	PEG 200	VF	30	−1.02	−5.46	MF	21.6	11	34
69	Lorazepam	PG	VF	30	−2.32	−5.46	MF	67.6	11	35
70	Meloxicam	Ethanol	VF	25	−0.45	−1.92	W/V	93.2	8	32
71	Metharbital	Ethanol	WF	25	1.62	0.30	W/V	6.5	41	28
72	Nalidixic acid	Ethanol	VF	25	−3.69	−5.62	MF	7.4	13	43
73	Naproxen	Ethanol	WF	20	−1.91	−5.37	MF	28.8	11	44
74	Naproxen	Ethanol	WF	25	−1.83	−5.29	MF	23.4	11	44
75	Naproxen	Ethanol	WF	30	−1.7	−5.23	MF	20.5	11	44
76	Naproxen	Ethanol	WF	35	−1.63	−5.18	MF	20.3	11	44
77	Naproxen	Ethanol	WF	40	−1.55	−5.11	MF	20.3	11	44
78	Nimesulide	Ethanol	VF	25	0.52	−1.85	W/V	66.0	8	32
79	Oxolinic acid	Ethanol	VF	20	−5.17	−6.06	MF	27.7	11	45
80	Oxolinic acid	Ethanol	VF	25	−5.08	−5.97	MF	25.9	11	45
81	Oxolinic acid	Ethanol	VF	30	−4.98	−5.87	MF	23.1	11	45
82	Oxolinic acid	Ethanol	VF	35	−4.89	−5.79	MF	23.1	11	45
83	Oxolinic acid	Ethanol	VF	40	−4.79	−5.69	MF	20.5	11	45
84	Pentobarbital	Ethanol	WF	25	2.4	−0.30	W/V	24.3	40	28
85	Phenacetin	Ethanol	VF	25	−1.84	−4.00	MF	20.8	11	27
86	Phenobarbital	Ethanol	WF	25	2.07	0.08	W/V	16.6	41	28
87	Phenobarbital	NMP	VF	25	0.37	−2.28	M	54.3	11	38
88	Phenobarbital	PG	VF	25	−0.19	−2.28	M	87.5	11	37
89	Phenytoin	Ethanol	VF	25	4.17	1.31	mW/V	19.1	11	46
90	Phenytoin	PEG 400	VF	25	−3.55	−7.00	M	16.6	11	46
91	Phenytoin	PG	VF	25	−1.16	−4.09	M	81.4	11	46
92	Rofecoxib	Ethanol	VF	25	−0.17	−2.05	W/V	15.4	8	32
93	Rofecoxib	Ethanol	VF	25	2.59	0.91	mW/V	27.2	6	47
94	Rofecoxib	Ethanol	VF	30	2.7	0.97	mW/V	34.5	6	47
95	Rofecoxib	Ethanol	VF	35	2.79	1.05	mW/V	37.2	6	47
96	Rofecoxib	PG	WF	25	−3.26	−4.58	M	9.1	6	48
97	Rofecoxib	PG	WF	30	−3.22	−4.52	M	13.2	6	48
98	Rofecoxib	PG	WF	35	−3.14	−4.45	M	11.5	6	48
99	Salicylic acid	Ethanol	VF	25	−0.89	−3.62	MF	22.9	11	49
100	Salicylic acid	Ethanol	VF	25	−0.85	−3.70	MF	27.7	11	27
101	Salicylic acid	PG	VF	25	0.26	−1.86	M	121.9	11	49
102	Sulfadiazine	DMF	WF	20	−1.22	−5.48	MF	17.7	14	50
103	Sulfadiazine	DMF	WF	30	−1.20	−5.26	MF	16.3	14	50
104	Sulfadiazine	DMF	WF	40	−1.18	−5.03	MF	10.4	14	50
105	Sulfanilamide	Ethanol	VF	25	−2.12	−3.19	MF	43.8	12	51
106	Theophylline	PG	VF	30	−1.16	−1.32	M	34.9	8	52
107	Thiamylal	Ethanol	WF	25	2.21	−1.3	W/V	18.3	40	28
108	Valdecoxib	Ethanol	VF	25	3.98	1.01	mW/V	42.3	6	53
109	Valdecoxib	Ethanol	VF	30	4.13	1.02	mW/V	45.8	6	53
110	Valdecoxib	Ethanol	VF	35	4.19	1.05	mW/V	49.0	6	53
111	Valdecoxib	Ethanol	WF	37	4.15	1.05	mW/V	46.6	7	54
112	Valdecoxib	PG	WF	25	−2.34	−4.49	M	7.0	6	55
113	Valdecoxib	PG	WF	30	−2.21	−4.48	M	20.9	6	55
114	Valdecoxib	PG	WF	35	−2.03	−4.45	M	24.2	6	55
115	Vinbarbital	Ethanol	WF	25	1.79	−0.15	W/V	8.6	41	28
							Overall MPD%	34.3 ± 31.9%		

M, mol/L; MF, mole fraction; mW/V, μg/mL; W/V, g/L or mg/mL; VF, volume fraction; WF, mass fraction; DMF, dimethylformamide; NMP, N-methyl-2-pyrrolidone; PG, propylene glycol; PEG, polyethylene glycol.

Table 2. Molar Solubility of Clonazepam, Diazepam, Ibuprofen, Lamotrigine, and Phenobarital in Ethanol ($f_{ethanol}$) + PG (f_{PG}) + water (f_w) at 25°C and Their Relative Standard Deviation (RSD)

			Clonazepam		Diazepam		Ibuprofen		Lamotrigine		Phenobarbital	
$f_{ethanol}$	f_{PG}	f_w	$X_{m,T}$	RSD	$X_{m,T}$	RSD	$X_{m,T}$	RSD	$X_{m,T}$	RSD	$X_{m,T}$	RSD
0.33	0.34	0.33	0.0068	5.5	0.0458	0.6	0.5309	0.0	0.0263	1.7	0.3403	2.6
0.20	0.40	0.40	0.0040	3.2	0.0210	1.5	0.0561	0.6	0.0390	3.8	0.1592	0.7
0.40	0.20	0.40	0.0064	3.2	0.0339	1.3	0.2146	1.8	0.0417	1.3	0.1515	2.5
0.10	0.50	0.40	0.0029	2.7	0.0195	0.7	0.0349	0.5	0.0321	3.2	0.1094	1.2
0.50	0.10	0.40	0.0078	1.4	0.0335	0.6	0.2389	1.5	0.0418	3.4	0.3575	1.6
0.40	0.40	0.20	0.0135	3.1	0.0642	1.9	0.5516	0.4	0.1063	4.6	0.3161	2.1
0.40	0.50	0.10	0.0205	2.6	0.0576	1.4	1.1786	0.9	0.1272	4.5	0.3224	2.1
0.40	0.10	0.50	0.0037	1.8	0.0227	1.5	0.0594	1.4	0.0208	2.0	0.0625	4.6
0.10	0.40	0.50	0.0014	3.5	0.0081	1.5	0.0203	1.6	0.0271	2.7	0.0650	2.4
0.50	0.40	0.10	0.0213	2.0	0.1061	1.5	1.7149	2.6	0.0966	1.5	0.3289	3.2
0.30	0.30	0.40	0.0050	2.6	0.0266	1.1	0.1077	0.3	0.0377	5.0	0.1640	3.0
0.40	0.30	0.30	0.0100	6.1	0.0549	1.4	0.5276	0.3	0.0697	4.0	0.3709	1.0
0.30	0.40	0.30	0.0081	4.7	0.0521	1.0	0.3489	0.2	0.0667	1.3	0.3139	2.2
0.10	0.10	0.80	0.0005	4.7	0.0012	1.6	0.0016	0.9	0.0024	2.5	0.0865	1.7
0.80	0.10	0.10	0.0219	1.5	0.1131	0.8	1.1984	1.7	0.0405	1.3	0.5340	2.7
0.10	0.80	0.10	0.0153	4.6	0.0585	0.8	3.1484	0.3	0.1889	3.7	0.2903	5.3

The $(f_c)_{max}$ and $(X_{m,T})_{max}$of previously trained versions of the model and the proposed model could be computed using an iteration method. The accuracies of these equations for predicting the $(f_c)_{max}$ and $(X_{m,T})_{max}$ values of drugs in solvent mixtures were compared with each other.

RESULTS AND DISCUSSION

Experimental Solubility of Clonazepam, Diazepam, Lamotrigine, Ibuprofen, and Phenobarbital in Ethanol + PG + Water Mixtures at 25°C

Table 2 lists the experimental solubilities of clonazepam, diazepam, lamotrigine, ibuprofen, and phenobarbital in ternary mixtures of ethanol + PG + water at 25°C. The solubility of drugs increased with the addition of the cosolvents. The maximum solubilities are achieved for 0.80 volume fractions of ethanol and 0.10 of PG for clonazepam, diazepam, and phenobarbital, and 0.10 volume fractions of ethanol and 0.80 of PG for lamotrigine and ibuprofen. Solubilities of these drugs in ethanol + water and PG + water binary mixtures were reported in the literature.[28,36,37,41,56] Table 3 gives the maximum solubility values in solvent mixtures. Comparison of the measured solubility in ternary solvent mixtures in this study with reported solubility data in binary solvent mixtures reveal that addition of the second cosolvent is useful for further solubilization of ibuprofen.

Solubility Predication Using Eq. 2 in Cosolvent + Water Mixtures

Training of Eq. 2 for Cosolvent + Water Mixtures

The 115 solubility data sets listed in Table 1 were fitted to Eq. 2, employing partial solubility parameters of the solutes and solvents and the trained model after excluding nonsignificant model constant was:

$$\begin{aligned}\log X_{m,T} &= f_c \log X_{c,T} + f_w \log X_{w,T} \\ &+ \left(\frac{f_c f_w}{T}\right)\{0.606\delta_{ps}(\delta_{pc}-\delta_{pw})^2 \\ &+ 0.013\delta_{hs}(\delta_{hc}-\delta_{hw})^2\} \\ &+ \left(\frac{f_c f_w (f_c - f_w)}{T}\right)\{-8.696\delta_{ds}(\delta_{dc}-\delta_{dw})^2 \\ &+ 0.376\delta_{ps}(\delta_{pc}-\delta_{pw})^2 + 0.013\delta_{hs}(\delta_{hc}-\delta_{hv})^2\} \\ &+ \left(\frac{f_c f_w (f_c - f_w)^2}{T}\right)\{9.277\delta_{ds}(\delta_{dc}-\delta_{dw})^2 \\ &- 0.461\delta_{ps}(\delta_{pc}-\delta_{pw})^2 + 0.017\delta_{hs}(\delta_{hc}-\delta_{hw})^2\} \quad (5)\end{aligned}$$

Table 3. The Maximum Solubility and Corresponding Fraction of Cosolvents (in parentheses) of Drugs in Binary and Ternary Solvent Mixtures

	Clonazepam	Diazepam	Ibuprofen	Lamotrigine	Phenobarbital
Ethanol + water	0.1957 (0.9)	0.1347 (0.9)	2.5590 (1.0)	0.4386 (0.8)	0.5697 (0.9)
PG + water	0.0185 (1.0)	0.0428 (1.0)	0.9376 (1.0)	0.2042 (1.0)	0.6423 (1.0)
Ethanol + PG + water	0.0219 (0.8, 0.1)	0.1131 (0.8, 0.1)	3.1484 (0.1, 0.8)	0.1889 (0.1, 0.8)	0.5340 (0.8, 0.1)

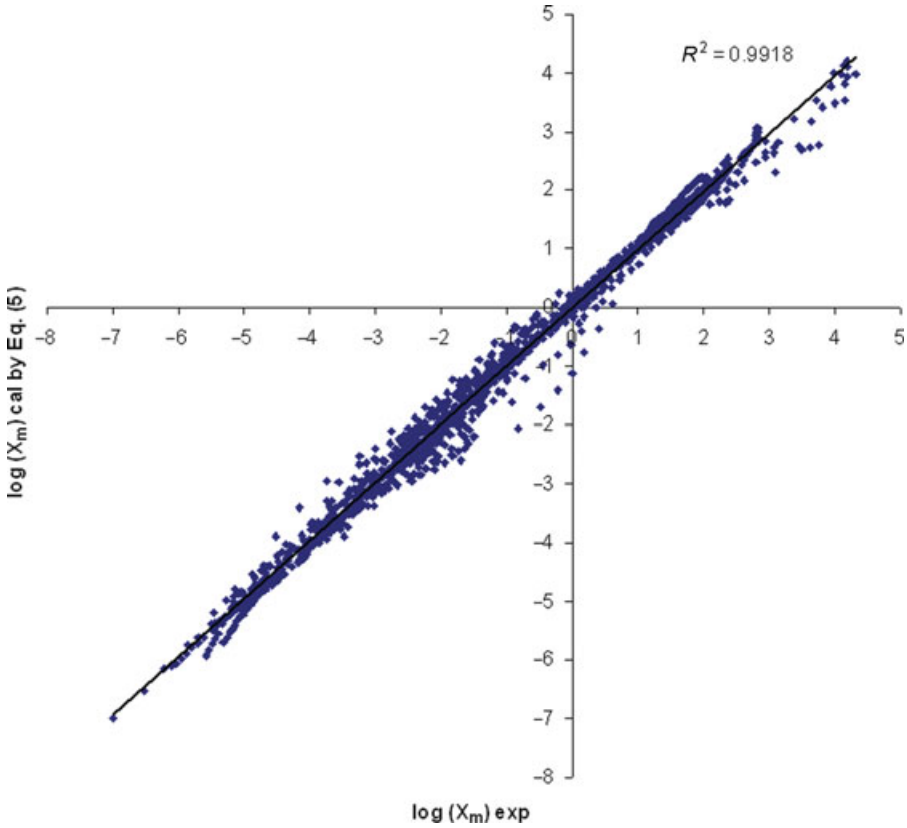

Figure 1. Calculated solubilities ($N = 1419$) against the corresponding experimental values (cosolvent + water).

The correlation was statistically significant ($p < 0.05$) with the F value of 394. The minimum and maximum MPD for the predicted solubilities in cosolvent + water mixtures were 4.5% for solubility of acetanilide in ethanol + water at 20°C and 240.6% for solubility data of ibuprofen in PG + water at 20°C, respectively. The overall MPD of 115 data sets (including 1419 data points) was 34.3%. Correlation between calculated solubilities and the corresponding experimental values is shown in Figure 1. This is a good mathematical correlation with a squared correlation coefficient of $R^2 = 0.992$ for the calculated experimental values. The MPD values for ibuprofen, salicylic acid, and clonazepam in PG + water and diazepam in PEG 600 + water were higher than 100%. The solubility profiles of these sets were almost linear against cosolvent concentrations. On the basis of the preliminary analysis, niflumic acid solubility data sets in ethanol + water mixtures[31] at various temperatures behave as outliers. To confirm this, the solubilities data of niflumic acid in water (0.0000012 expressed as mole fraction solubility)[57] and ethanol (0.0145)[58] at 25°C were collected and the values were used to predict the solubility of niflumic acid in ethanol + water mixtures at 25°C. The obtained MPD was 76.7%, whereas the MPD using originally reported values in ethanol and water was 215%. The findings are also confirmed by other numerical analyses from our previous report,[59] therefore these data sets were excluded from training procedure of Eq. 2.

In addition to the predictive purposes, cosolvency models could be used to explain the interactions in solutions. From this point of view, theoretical or semitheoretical models with less curve-fitting parameters provide better physicochemical explanations. Regarding the proposed models by our group, Eq. 1 provided the most accurate correlations for describing the solubility of a drug in a given cosolvent + water mixtures at various temperatures. The first two terms (i.e., $f_c \log X_{c,T}$ and $f_w \log X_{w,T}$) of the model provide the ideal mixing behavior of the solution, $X_{c,T}$ and $X_{w,T}$ represent the effects of drug properties and also the enthalpic and entropic changes during dissolution of the drug in monosolvent systems. The J terms represent the two-body and three-body interactions in txd he solution containing the cosolvent and water.[16] These terms are specific values for a drug dissolved in a given binary solvent system. By including the physicochemical properties of drugs, and solvents 1 and 2, it is possible to provide a generally trained model to predict the solubility of various drugs in different binary mixtures. In Eq. 2, this hypothesis was

examined and the results indicated acceptable predictions. Any difference in the solubility parameters of the solvents should be reflected in the extent of the solvent–solvent and also solute–solvent interactions in the solution. To include the effects of drug structure, its solubility parameters are incorporated in the proposed terms, that is, $\delta_{js}(\delta_{jc} - \delta_{jw})^2$, in which j is the dispersion, polarity, or hydrogen bonding partial solubility parameters. The numerical values of A_0–A_8 of Eq. 2 represent the extent of these interactions and also the effects of solvent compositions included in $f_c f_w (f_c - f_w)^j$ terms concerning the Redlich–Kister extension.[16] It is obvious that the physical interpretations of the numerical values of A_0–A_8 are sometimes misleading because of relatively large number of curve-fitting parameters of the model, and from this point of view, Eq. 5 should be considered as an empirical equation.

Internal Validation of the Proposed Model

The results of the 10-fold cross-validation show that there is no significant difference between calculated MPD using Eq. 5, that is, 32.2%, and calculated MPD after 10-fold cross-validation, that is, 33.0% ($p > 0.05$), revealing that Eq. 5 is a robust equation. Another cross-validation was carried out by excluding solubility data sets of a drug. The results of leave-one-drug-out cross-validation revealed that the overall MPD was increased from 35.5% to 36.7%, indicating that there are acceptable changes in MPD of cross-validation in comparing with MPD of Eq. 5. Details of the internal validation of the proposed method can be found in Tables S1 and S2 of the supporting informtion.

Prediction of Solubility Data in Cosolvent 1 + Cosolvent 2 + Water Mixtures

Equation 5 could be extended to Eq. 6 for predicting the solubility of drugs in ternary solvents as:

$$\begin{aligned}
\log X_{m,T} &= f_{c_1} \log X_{c_1,T} + f_{c_2} \log X_{c,T} + f_w \log X_{w,T} \\
&+ \left(\frac{f_{c_1} f_w}{T}\right) \{0.606\delta_{ps}(\delta_{pc1} - \delta_{pw})^2 \\
&+ 0.013\delta_{hs}(\delta_{hc_1} - \delta_{hw})^2\} \\
&+ \left(\frac{f_{c_1} f_w (f_{c_1} - f_w)}{T}\right) \{-8.696\delta_{ds}(\delta_{dc_1} - \delta_{dw})^2 \\
&+ 0.376\delta_{ps}(\delta_{pc_1} - \delta_{pw})^2 + 0.013\delta_{hs}(\delta_{hc_1} - \delta_{hv})^2\} \\
&+ \left(\frac{f_{c_1} f_w (f_{c_1} - f_w)^2}{T}\right) \{9.277\delta_{ds}(\delta_{dc_1} - \delta_{dw})^2 \\
&- 0.461\delta_{ps}(\delta_{pc_1} - \delta_{pw})^2 + 0.017\delta_{hs}(\delta_{hc_1} - \delta_{hw})^2\} \\
&+ \left(\frac{f_{c_2} f_w}{T}\right) \{0.606\delta_{ps}(\delta_{pc_2} - \delta_{pw})^2 \\
&+ 0.013\delta_{hs}(\delta_{hc_2} - \delta_{hw})^2\} \\
&+ \left(\frac{f_{c_2} f_w (f_{c_2} - f_w)}{T}\right) \{-8.696\delta_{ds}(\delta_{dc_2} - \delta_{dw})^2 \\
&+ 0.376\delta_{ps}(\delta_{pc_2} - \delta_{pw})^2 + 0.013\delta_{hs}(\delta_{hc_2} - \delta_{hv})^2\} \\
&+ \left(\frac{f_{c_1} f_w (f_{c_2} - f_w)^2}{T}\right) \{9.277\delta_{ds}(\delta_{dc_2} - \delta_{dw})^2 \\
&- 0.461\delta_{ps}(\delta_{pc_2} - \delta_{pw})^2 + 0.017\delta_{hs}(\delta_{hc_2} - \delta_{hw})^2\} \\
&+ \left(\frac{f_{c_1} f_{c_2}}{T}\right) \{0606\delta_{ps}(\delta_{pc_1} - \delta_{pc_2})^2 \\
&+ 0.013\delta_{hs}(\delta_{hc_1} - \delta_{hc_2})^2\} \\
&+ \left(\frac{f_{c_1} f_{c_2} (f_{c_1} - f_{c_2})}{T}\right) \{-8.696\delta_{ds}(\delta_{dc_1} - \delta_{dc_2})^2 \\
&+ 0.376\delta_{ps}(\delta_{pc_1} - \delta_{pc_2})^2 + 0.013\delta_{hs}(\delta_{hc_1} - \delta_{hc_2})^2\} \\
&+ \left(\frac{f_{c_1} f_{c_2} (f_{c_1} - f_{c_2})^2}{T}\right) \{9.277\delta_{ds}(\delta_{dc_1} - \delta_{dc_2})^2 \\
&- 0.461\delta_{ps}(\delta_{pc_1} - \delta_{pc_2})^2 + 0.017\delta_{hs}(\delta_{hc_1} - \delta_{hc_2})^2\}
\end{aligned} \tag{6}$$

in which subscripts c_1 and c_2 are the parameters of cosolvents 1 and 2, respectively.

Table 4 shows the results of predicted solubility of drugs in ternary solvents mixtures at different temperatures. Unfortunately, only 13 data sets were reported in the literature. The solubilities of the five drugs in ternary mixtures of ethanol + PG + water are determined in this study and increased the number of data sets to 18. These 18 data sets (including 470 data points) were selected as an external set and the solubility in cosolvent 1 + cosolvent 2 + water mixtures at different temperatures was predicted using Eq. 6. The minimum and maximum MPDs for the predicted solubilities in ternary solvent mixtures were 11.0% for solubility of acetaminophen in ethanol + PG + water at 25°C and 104.7% for solubility of ibuprofen in PEG 600 + PG + water mixtures, respectively, and the overall MPD was 38.0%. Correlation between calculated solubilities in ternary solvent mixtures and the corresponding experimental values is shown in Figure 2. Correlation coefficients of the calculated experimental values are in acceptable value.

The results showed that the proposed general model (Eq. 5) for cosolvent 1 + water mixtures using combination of the Jouyban–Acree model and partial solubility parameters could be extend to Equation (6) for predicting the solubility of drugs in cosolvent 1 + cosolvent 2 + water mixtures for the majority of applied solvents in the pharmaceutical processes. The partial solubility parameters (dispersion, polar, or hydrogen bonding forces) of solute and solvents indicate

Table 4. Details of the Solutes, Solvents, Number of Solvent Compositions of Each Set (N) and Mean Percentage Deviation (MPD) of Various Numerical Analyses on Solubility of Solutes in Ternary Solvent Mixtures (Cosolvent 1 + Cosolvent 2 + Water) at Different Temperatures

Code	Drug	Cosolvent 1	Cosolvent 2	Solvent Composition	$\log X_{c1,T}$	$\log X_{c2,T}$	$\log X_{w,T}$	Solubility Unit	T	N	MPD	Reference
1	Acetaminophen	Ethanol	PG	VF	−0.07	−0.14	−1.05	M	25	36	14.1	60
2	Acetaminophen	Ethanol	PG	VF	−0.03	−0.13	−0.96	M	30	36	11.0	60
3	Acetaminophen	PEG 600	Ethanol	MF	0.16	0.03	−1.00	M	25	36	19.5	41
4	Acetaminophen	PEG 600	PG	VF	0.16	0.02	−1.00	M	25	36	34.9	61
5	Biphenyl dimethyl dicarboxylate	DMA	Ethanol	VF	1.96	−0.09	−2.70	W/V	25	49	21.9	62
6	Clonazepam	PEG 600	Ethanol	MF	−0.74	−1.79	−3.99	M	25	36	46.2	39
7	Clonazepam	PG	Ethanol	VF	−1.73	−1.79	−4.00	M	25	16	33.2	This work
8	Diazepam	Ethanol	PG	VF	1.44	0.87	−1.32	W/V	20	5	51.6	46
9	Diazepam	PEG 600	Ethanol	MF	−0.73	−1.08	−3.72	M	25	36	30.9	39
10	Diazepam	Ethanol	PG	VF	−1.04	−1.37	−3.82	M	25	16	45.5	This work
11	Ibuprofen	Ethanol	PEG 600	VF	0.36	0.16	−3.40	M	25	36	53.8	41
12	Ibuprofen	PEG 600	PG	MF	0.16	−0.03	−3.40	M	25	36	104.7	61
13	Ibuprofen	Ethanol	PG	VF	0.36	−0.03	−3.40	M	25	16	48.9	This work
14	Lamotrigine	PEG 600	Ethanol	MF	−0.22	−1.85	−3.14	M	25	36	28.0	39
15	Lamotrigine	PG	Ethanol	VF	−0.69	−1.85	−3.14	M	25	16	35.3	This work
16	Phenobarbital	PG	Ethanol	VF	−0.19	−1.85	−2.27	M	25	16	62.2	This work
17	Phenytoin	PG	Ethanol	VF	4.25	4.17	1.31	mW/V	25	6	22.9	46
18	Phenytoin	PEG 400	PG	VF	4.86	4.25	1.31	mW/V	25	6	22.1	46
											38.0	

M, mol/L; MF, mole fraction; mW/V, μg/mL; W/V, g/L or mg/mL; VF, volume fraction; WF, mass fraction; DMA, dimethyl acetamide; PG, propylene glycol; PEG, polyethylene glycol.

the extent of solute–solvent interactions in the solution. The expected prediction errors are quite acceptable and only the experimental solubility data in the three monosolvents is required.

Prediction of the Solvent Composition Providing Maximum Solubility

The $(f_c)_{max}$ providing the $(X_{m,T})_{max}$ of 112 solubility data of drugs in cosolvent + water mixtures at different temperatures were predicted using the Hildebrand equation (method I), trained versions of the Jouyban–Acree model for aqueous mixtures of ethanol, PEG 400, and PG (method II) and Eq. 5 (method III). The results of predictions including list of drugs and cosolvents, experimental $(f_c)_{max}$ and $(X_{m,T})_{max}$, and their predicted and IPD values are summarized in Table 5. Solubility data of rofecoxib in PG + water at different temperatures were excluded from this analysis because solubility data were reported up to 50% of PG. The results showed that the overall IPD values for predicting $(f_c)_{max}$ using methods I, II, and III were 18.2, 11.6 (average of three cosolvents), and 10.2 and those of $(X_{m,T})_{max}$ values for methods II and III were 11.2 and 8.0, respectively. The number of data points for methods I and III were 112 and for method II was 103 because there is no trained model for predicting the solubility of drugs in N-methyl-2-pyrrolodone (NMP) and dimethylformamide (DMF). The differences between the overall IPDs of methods I, II, and III were statistically significant ($p < 0.001$). There is also significant difference between overall IPDs of methods II and III ($p < 0.05$). In addition to providing the more accurate predictions, method III against of method II that were proposed for a given cosolvent, method III could be extended to other solubility data sets in different cosolvent mixtures. The results show good accuracy for proposed model in this study to predict fraction of optimized solvent composition in solvent mixtures.

CONCLUSIONS

A prediction method for solubility of drugs in cosolvent + water and cosolvent 1 + cosolvent 2 + water mixtures at different temperatures using a combination of the Jouyban–Acree model and partial solubility parameters was proposed. The model only needs experimental solubility data points of drugs in monosolvents. This method provided good accuracy and could be used for predicting the optimized solvent composition of cosolvent + water mixtures providing the maximum solubility of a drug with more accuracy in comparison with previously published models.

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Table 5. The Observed and Calculated Values of $(f_c)_{max}$ Providing the $(X_{m,T})_{max}$ Using Different Methods Along with Their Individual Percentage Deviations (IPD)

No.	Drug	Cosolvent	T	$(f_c)_{max}$	log $(X_m)_{max}$	$(f_c)_{max}$ Calculated Using Method I	IPD	$(f_c)_{max}$ Calculated Using Method II	IPD	$(f_c)_{max}$ Calculated Using Method III	IPD	log X_m Calculated Using Method II	IPD	log X_m Calculated Using Method III	IPD
1	Acetaminophen	Ethanol	20	0.90	−1.20	0.92	2.1	0.81	10.0	0.81	10.0	−1.02	15.3	−1.17	2.9
2	Acetaminophen	Ethanol	20	0.85	−1.14	0.92	8.1	0.80	5.9	0.81	4.7	−0.99	13.2	−1.14	0.0
3	Acetaminophen	Ethanol	25	0.90	−1.18	0.92	2.1	0.81	10.0	0.81	10.0	−0.98	16.9	−1.12	5.3
4	Acetaminophen	Ethanol	25	0.85	−1.10	0.92	8.1	0.80	5.9	0.81	4.7	−0.99	9.8	−1.13	2.9
5	Acetaminophen	Ethanol	25	0.85	−1.10	0.92	8.1	0.80	5.9	0.81	4.7	−0.99	9.8	−1.13	2.9
6	Acetaminophen	Ethanol	30	0.90	−1.13	0.92	2.1	0.81	10.0	0.81	10.0	−0.94	16.8	−1.08	4.6
7	Acetaminophen	Ethanol	30	0.80	2.39	0.92	14.8	0.76	5.0	0.75	6.3	2.68	12.3	2.54	6.1
8	Acetaminophen	Ethanol	30	0.85	−1.06	0.92	8.1	0.80	5.9	0.81	4.7	−0.93	12.2	−1.08	1.9
9	Acetaminophen	Ethanol	35	0.90	−1.09	0.92	2.1	0.80	11.1	0.81	10.0	−0.91	16.7	−1.05	4.0
10	Acetaminophen	Ethanol	35	0.85	−1.01	0.92	8.1	0.80	5.9	0.81	4.7	−0.90	10.7	−1.04	3.1
11	Acetaminophen	Ethanol	40	0.90	−1.04	0.92	2.1	0.80	11.1	0.8	11.1	−0.87	16.3	−1.01	2.9
12	Acetaminophen	Ethanol	40	0.85	−0.97	0.92	8.1	0.81	4.7	0.81	4.7	−0.88	9.7	−1.02	4.5
13	Acetaminophen	NMP	25	1.00	0.70	0.79	21.3			0.91	9.0			0.80	12.1
14	Acetaminophen	PEG 400	25	0.80	0.29	0.75	5.7	0.93	16.3	0.83	3.7	0.13	55.5	0.27	8.1
15	Acetaminophen	PEG 400	30	1.00	0.24	0.75	24.5	0.96	4.0	0.82	18.0	0.08	66.7	0.33	27.2
16	Acetaminophen	PEG 600	25	0.80	0.30	0.73	9.0	0.96	20.0	0.82	2.5	0.16	46.9	0.41	26.6
17	Acetaminophen	PG	20	1.00	−1.31	1.00	0.0	1.00	0.0	0.89	11.0	−1.31	0.3	−1.27	3.4
18	Acetaminophen	PG	25	0.60	−1.07	1.00	66.7	1.00	66.7	0.88	46.7	−1.29	21.1	−1.24	14.1
19	Acetaminophen	PG	30	1.00	−1.22	1.00	0.0	1.00	0.0	0.89	11.0	−1.22	0.0	−1.18	3.4
20	Acetaminophen	PG	35	1.00	−1.18	1.00	0.0	1.00	0.0	0.88	12.0	−1.18	0.2	−1.14	3.3
21	Acetaminophen	PG	40	1.00	−1.12	1.00	0.0	1.00	0.0	0.88	12.0	−1.12	0.3	−1.08	4.1
22	Acetanilide	Ethanol	20	0.84	−0.60	1.00	18.8	0.82	2.6	0.89	5.7	−0.39	35.5	−0.62	2.5
23	Acetanilide	Ethanol	25	0.90	−3.05	1.00	11.1	0.85	5.6	1.00	11.1	−2.89	5.3	−3.07	0.6
24	Acetanilide	Ethanol	25	1.00	−1.09	1.00	0.0	0.85	15.0	0.99	1.0	−0.90	17.2	−1.09	0.3
25	Acetanilide	Ethanol	30	0.85	−0.50	1.00	17.7	0.82	3.5	0.9	5.9	−0.30	39.9	−0.52	4.0
26	Aminopyrine	Ethanol	25	0.70	2.64	1.00	42.9	0.75	7.1	0.81	15.7	2.97	12.6	2.60	1.5
27	Amobarbital	Ethanol	25	1.00	2.34	1.00	0.0	0.89	11.0	1.00	0.0	2.45	4.6	2.34	0.1
28	Antipyrine	Ethanol	25	0.60	2.83	1.00	66.7	0.67	11.7	0.63	5.0	3.41	20.6	3.05	7.3
29	Barbital	Ethanol	25	0.85	2.08	0.86	1.5	0.77	9.4	0.76	10.6	2.33	11.9	2.21	5.8
30	Benzocaine	Ethanol	25	1.00	−0.82	1.00	0.0	0.87	13.0	1.00	0.0	−0.69	15.4	−0.82	0.6
31	Benzoic acid	Ethanol	15	1.00	0.35	0.88	12.4	0.84	16.0	0.91	9.0	0.55	56.7	0.38	7.6
32	Benzoic acid	Ethanol	20	1.00	0.40	0.88	12.4	0.85	15.0	0.91	9.0	0.59	48.0	0.43	7.3
33	Benzoic acid	Ethanol	25	1.00	0.44	0.88	12.4	0.85	15.0	0.91	9.0	0.63	43.5	0.47	6.6
34	Butabarbital	Ethanol	25	0.88	1.96	1.00	14.3	0.84	4.0	0.89	1.7	2.11	7.8	1.96	0.1
35	Caffeine	DMF	25	0.80	−1.85	1.00	25.0			0.92	15.0			−1.88	1.4
36	Caffeine	Ethanol	5	0.30	−2.24	1.00	233.3	0.66	120.0	0.62	106.7	−2.22	0.7	−2.47	9.5
37	Caffeine	Ethanol	15	0.30	−2.06	1.00	233.3	0.66	120.0	0.62	106.7	−2.14	3.8	−2.39	13.8
38	Caffeine	Ethanol	25	0.40	−1.83	1.00	150.0	0.66	65.0	0.62	55.0	−2.04	11.3	−2.28	19.6
39	Caffeine	Ethanol	35	0.40	−1.60	1.00	150.0	0.67	67.5	0.63	57.5	−1.92	19.7	−2.15	25.4
40	Caffeine	Ethanol	40	0.40	−1.50	1.00	150.0	0.68	70.0	0.65	62.5	−1.81	20.8	−2.04	26.5
41	Celecoxib	Ethanol	25	1.00	1.80	1.00	0.0	0.97	3.0	1.00	0.0	1.81	0.5	1.80	0.1

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Table 5. Continued

No.	Drug	Cosolvent	T	$(f_c)_{max}$	log $(X_m)_{max}$	$(f_c)_{max}$ Calculated Using Method I	IPD	$(f_c)_{max}$ Calculated Using Method II	IPD	$(f_c)_{max}$ Calculated Using Method III	IPD	log X_m Calculated Using Method II	IPD	log X_m Calculated Using Method III	IPD
42	Chlordiazepoxide	Ethanol	30	0.90	−2.30	0.97	7.3	0.90	0.0	1.00	11.1	−2.38	3.4	−2.47	6.8
43	Chlordiazepoxide	PEG 200	30	1.00	−1.63	0.88	11.5	1.00	0.0	1.00	0.0	−1.63	0.3	−1.63	0.3
44	Chlordiazepoxide	PG	30	1.00	−2.31	1.00	0.0	1.00	0.0	1.00	0.0	−2.31	0.1	−2.31	0.1
45	Clonazeopam	Ethanol	25	0.90	−1.71	0.94	4.2	0.86	4.4	0.85	5.6	−1.63	4.6	−1.69	1.1
46	Clonazeopam	PG	25	1.00	−1.73	1.00	0.0	1.00	0.0	1.00	0.0	−1.73	0.1	−1.73	0.1
47	Clonazepam	Ethanol	30	0.90	−2.98	1.00	11.1	0.92	2.2	1.00	11.1	−2.93	1.6	−2.99	0.4
48	Clonazepam	NMP	25	1.00	−0.18	0.80	19.6			1.00	0.0			−0.18	0.5
49	Clonazepam	PEG 200	30	1.00	−1.74	0.86	14.0	1.00	0.0	1.00	0.0	−1.74	0.2	−1.74	0.2
50	Clonazepam	PG	30	1.00	−3.01	1.00	0.0	1.00	0.0	1.00	0.0	−3.01	0.1	−3.01	0.1
51	Diazepam	Ethanol	25	0.9	−0.87	1.00	11.1	0.90	0.0	0.96	6.7	−0.95	9.1	−1.03	15.5
52	Diazepam	Ethanol	30	0.90	−2.07	1.00	11.1	0.94	4.4	1.00	11.1	−2.08	0.7	−2.12	2.5
53	Diazepam	NMP	25	1.00	0.09	0.94	6.5		100.0	1.00	0.0			0.09	1.6
54	Diazepam	PEG 200	30	1.00	−1.46	1.00	0.0	1.00	0.0	1.00	0.0	−1.46	0.3	−1.46	0.3
55	Diazepam	PEG 600	25	1.00	−0.73	0.87	13.5	1.00	0.0	1.00	0.0	−0.73	0.7	−0.73	0.7
56	Diazepam	PG	25	1.00	−1.37	1.00	0.0	1.00	0.0	1.00	0.0	−1.37	0.1	−1.37	0.1
57	Diazepam	PG	30	1.00	−2.29	1.00	0.0	1.00	0.0	1.00	0.0	−2.29	0.1	−2.29	0.1
58	Iboprofen	PG	20	1.00	−0.68	1.00	0.0	1.00	0.0	1.00	0.0	−0.68	0.3	−0.68	0.3
59	Ibuprofen	NMP	25	0.90	0.74	1.00	11.1			1.00	11.1			0.74	0.2
60	Ibuprofen	PEG 600	25	1.00	0.35	1.00	0.0	1.00	0.0	1.00	0.0	0.16	54.9	0.16	121.7
61	Ketoprofen	PG	25	1.00	0.24	1.00	0.0	1.00	0.0	1.00	0.0	0.24	1.8	0.24	1.8
62	Ketoprofen	PG	37	1.00	0.31	1.00	0.0	1.00	0.0	1.00	0.0	0.31	1.1	0.31	1.1
63	Lamotrigine	Ethanol	25	0.80	−1.36	0.93	16.4	0.79	1.3	0.76	5.0	−1.53	12.7	−1.56	13.0
64	Lamotrigine	NMP	25	1.00	−1.25	0.80	20.2			0.95	5.0			−1.23	2.0
65	Lamotrigine	PEG 600	25	1.00	−0.22	0.74	26.2	1.00	0.0	0.98	2.0	−0.22	1.6	−0.22	1.6
66	Lamotrigine	PG	25	1.00	−0.69	1.00	0.0	1.00	0.0	1.00	0.0	−0.69	0.0	−0.69	0.0
67	Lorazepam	Ethanol	30	0.90	−2.57	0.72	20.4	0.90	0.0	0.94	4.4	−2.62	1.9	−2.69	4.5
68	Lorazepam	PEG 200	30	1.00	−1.02	0.66	34.4	1.00	0.0	1.00	0.0	−1.02	0.1	−1.02	0.1
69	Lorazepam	PG	30	1.00	−2.32	0.87	13.3	1.00	0.0	1.00	0.0	−2.32	0.0	−2.32	0.0
70	Meloxicam	Ethanol	25	1.00	−0.45	0.75	24.8	0.81	19.0	0.76	24.0	−0.17	62.3	−0.19	137.4
71	Metharbital	Ethanol	25	0.85	1.71	1.00	17.7	0.79	7.1	0.83	2.4	1.93	12.9	1.70	0.5
72	Nalidixic acid	Ethanol	25	0.85	−3.56	0.95	11.3	0.84	1.2	0.91	7.1	−3.49	2.0	−3.66	2.7
73	Naproxen	Ethanol	20	1.00	−1.91	1.00	0.0	0.94	6.0	1.00	0.0	−1.87	1.9	−1.91	0.2
74	Naproxen	Ethanol	25	1.00	−1.83	1.00	0.0	0.94	6.0	1.00	0.0	−1.8	1.4	−1.83	0.2
75	Naproxen	Ethanol	30	1.00	−1.70	1.00	0.0	0.95	5.0	1.00	0.0	−1.67	2.0	−1.70	0.2
76	Naproxen	Ethanol	35	1.00	−1.63	1.00	0.0	0.95	5.0	1.00	0.0	−1.61	1.5	−1.63	0.3
77	Naproxen	Ethanol	40	1.00	−1.55	1.00	0.0	0.95	5.0	1.00	0.0	−1.53	1.1	−1.55	0.2
78	Nimesulide	Ethanol	25	0.90	0.55	0.96	6.5	0.87	3.3	0.89	1.1	0.66	19.7	0.54	2.1
79	Oxolinic acid	Ethanol	20	0.80	−4.76	0.80	0.1	0.75	6.3	0.73	8.8	−4.75	0.2	−4.86	2.1
80	Oxolinic acid	Ethanol	25	0.80	−4.68	0.80	0.1	0.75	6.3	0.73	8.8	−4.68	0.0	−4.79	2.3

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Table 5. Continued

No.	Drug	Cosolvent	T	$(f_c)_{max}$	log $(X_m)_{max}$	$(f_c)_{max}$ Calculated Using Method I	IPD	$(f_c)_{max}$ Calculated Using Method II	IPD	$(f_c)_{max}$ Calculated Using Method III	IPD	log X_m Calculated Using Method II	IPD	log X_m Calculated Using Method III	IPD
81	Oxolinic acid	Ethanol	30	0.80	−4.59	0.80	0.1	0.75	6.3	0.74	7.5	−4.58	0.2	−4.69	2.2
82	Oxolinic acid	Ethanol	35	0.80	−4.48	0.80	0.1	0.76	5.0	0.74	7.5	−4.51	0.6	−4.61	2.7
83	Oxolinic acid	Ethanol	40	0.80	−4.39	0.80	0.1	0.76	5.0	0.74	7.5	−4.41	0.5	−4.52	2.9
84	Pentobarbital	Ethanol	25	0.98	2.40	1.00	2.6	0.89	8.7	1.00	2.6	2.50	4.2	2.40	0.1
85	Phenacetin	Ethanol	25	0.90	−1.76	1.00	11.1	0.86	4.4	1.00	11.1	−1.68	4.8	−1.84	4.1
86	Phenobarbital	Ethanol	25	0.90	2.12	1.00	11.1	0.85	5.6	0.9	0.0	2.26	6.5	2.10	1.0
87	Phenobarbital	NMP	25	0.90	0.60	0.89	1.3			0.97	7.8			0.38	58.5
88	Phenobarbital	PG	25	1.00	−0.19	1.00	0.0	1.00	0.0	1.00	0.0	−0.19	1.2	−0.19	1.2
89	Phenytoin	Ethanol	25	0.90	4.19	1.00	11.1	0.90	0.0	1.00	11.1	4.25	1.4	4.17	0.5
90	Phenytoin	PEG 400	25	1.00	−3.55	0.88	11.6	1.00	0.0	1.00	0.0	−3.55	0.1	−3.55	0.1
91	Phenytoin	PG	25	1.00	−1.16	1.00	0.0	1.00	0.0	1.00	0.0	−1.16	0.3	−1.16	0.3
92	Rofecoxib	Ethanol	25	0.90	0.02	1.00	11.1	0.84	6.7	0.87	3.3	0.04	129.2	−0.15	111.6
93	Rofecoxib	Ethanol	25	0.80	2.94	1.00	25.0	0.82	2.5	0.83	3.7	2.83	3.9	2.64	11.5
94	Rofecoxib	Ethanol	30	0.80	3.07	1.00	25.0	0.83	3.7	0.84	5.0	2.92	5.0	2.73	12.6
95	Rofecoxib	Ethanol	35	0.80	3.14	1.00	25.0	0.83	3.7	0.85	6.2	3.00	4.5	2.82	11.4
96	Salicylic acid	Ethanol	25	1.00	−0.89	1.00	0.0	1.00	0.0	0.93	7.0	−0.89	0.0	−0.86	3.5
97	Salicylic acid	Ethanol	25	1.00	−0.85	1.00	0.0	1.00	0.0	0.94	6.0	−0.85	0.6	−0.83	3.0
98	Salicylic acid	PG	25	1.00	0.26	1.00	0.0	1.00	0.0	0.94	6.0	0.26	1.8	0.28	8.8
99	Sulfadiazine	DMF	20	1.00	−1.22	0.72	27.9			1.00	0.0			−1.22	0.0
100	Sulfadiazine	DMF	30	1.00	−1.20	0.72	27.9			1.00	0.0			−1.20	0.1
101	Sulfadiazine	DMF	40	1.00	−1.18	0.87	12.7			1.00	0.0			−1.18	0.2
102	Sulfanilamide	Ethanol	25	1.00	−1.90	0.82	17.6	0.77	23.0	0.71	29.0	−1.75	7.8	−1.63	16.4
103	Theophylline	PG	30	1.00	−0.84	0.82	17.6	0.81	19.0	0.62	38.0	−1.07	27.6	−0.68	23.3
104	Thiamylal	Ethanol	25	1.00	2.21	0.82	17.6	0.94	6.0	1.00	0.0	2.25	2.0	2.21	0.2
105	Valdecoxib	Ethanol	25	0.70	4.16	0.52	26.0	0.91	30.0	1.00	42.9	4.06	2.3	3.98	4.4
106	Valdecoxib	Ethanol	30	0.70	4.21	0.80	14.4	0.92	31.4	1.00	42.9	4.19	0.4	4.13	1.9
107	Valdecoxib	Ethanol	35	1.00	4.32	1.00	0.0	0.92	8.0	1.00	0.0	4.24	1.9	4.19	3.1
108	Valdecoxib	Ethanol	25	0.80	4.15	0.98	22.2	0.92	15.0	1.00	25.0	4.20	1.1	4.15	0.1
109	Valdecoxib	PG	25	0.80	−2.34	0.98	22.2	1.00	25.0	1.00	25.0	−2.34	0.0	−2.34	0.0
110	Valdecoxib	PG	30	0.80	−2.21	0.98	22.2	1.00	25.0	1.00	25.0	−2.21	0.1	−2.21	0.1
111	Valdecoxib	PG	35	1.00	−2.03	0.98	2.3	1.00	0.0	1.00	0.0	−2.03	0.0	−2.03	0.0
112	Vinbarbital	Ethanol	25	0.93	1.80	1.00	8.1	0.84	9.7	0.93	0.0	2.00	11.0	1.80	0.1
							18.2		11.6		10.2		11.2		8.0

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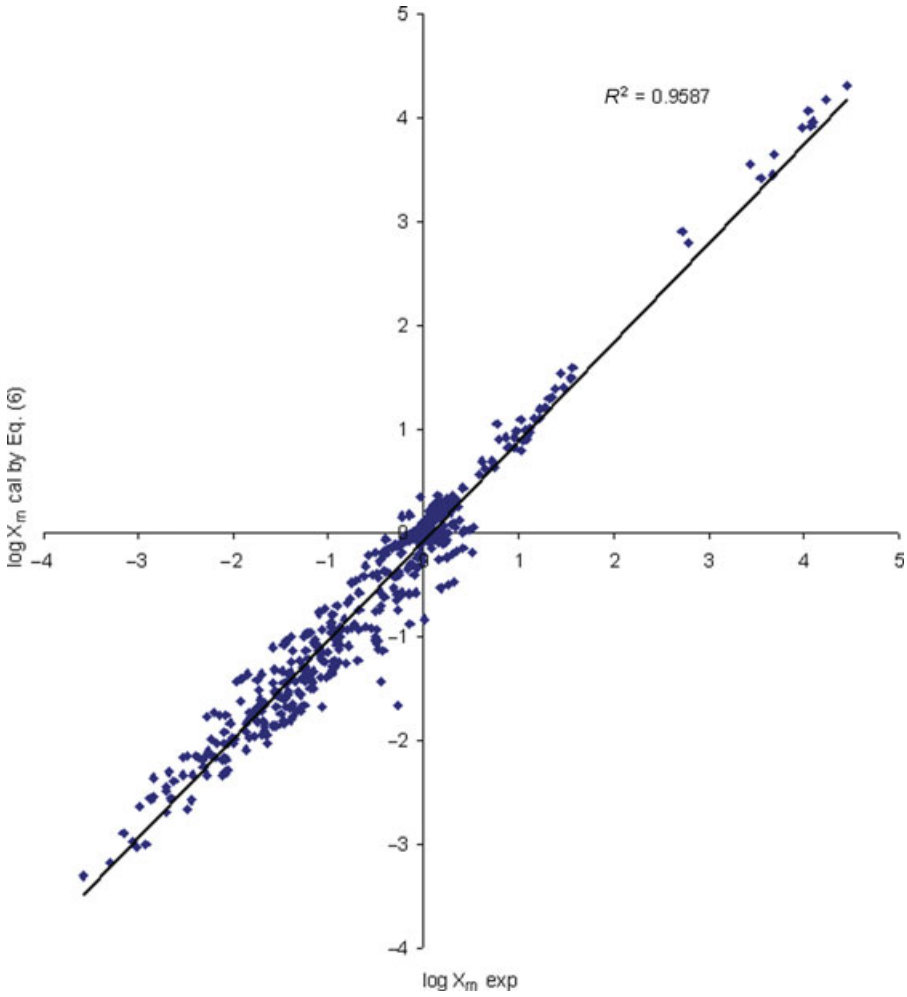

Figure 2. Calculated solubilities ($N = 470$) against the corresponding experimental values (cosolvent 1 + coslvent 2 + water).

SUPPORTING INFORMATION

The developed model in this work is included in an Excel file to predict the solubility of drugs in cosolvent + water and cosolvent 1 + cosolvent 2 + water mixtures at different temperatures using Eqs. 5 and 6. The required data are solubilities in the neat cosolvents and water at the temperatures of interest and the partial solubility parameters of solutes, cosolvents, and water. Tables S1 and S2 provide the detailed results of internal validation of the proposed model.

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