Solubility of Acetaminophen and Ibuprofen in the Mixtures of Polyethylene Glycol 200 or 400 with Ethanol and Water and the Density of Solute-Free Mixed Solvents at 298.2 K

Abolghasem Jouyban,*,† Shahla Soltanpour,‡ and William E. Acree, Jr.§

Drug Applied Research Center and Faculty of Pharmacy, Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran, and Department of Chemistry, University of North Texas, Denton, Texas 76203-5070, United States

Experimental solubilities of acetaminophen and ibuprofen in binary and ternary mixtures of polyethylene glycols (PEGs) 200 and 400 with ethanol and water, along with the densities of the saturated and solute-free solvent mixtures at $T = 298.2$ K, are reported. The solubility data of each drug in the ternary and sub-binary solvent mixtures were correlated with the Jouyban−Acree model. The mean relative deviations of the derived correlations were 6.4 % and 14.2 % for acetaminophen and ibuprofen, respectively, and the overall value was 9.4 %. Densities of solute-free solvent mixtures are used to train the Jouyban−Acree model, and then the densities of saturated solutions are predicted using the trained versions in which the overall mean relative deviation was 1.7 %.

Introduction

Solubilization of poorly water-soluble drugs is essential for the preparation of many commercially available oral solutions, parenteral, soft gelatin, and topical pharmaceutical formulations.[1] The addition of miscible organic solvents (or cosolvents) is the most common and feasible method to increase the solubility of drugs. Usually one organic solvent is able to solve the solubility problem; however, in some cases, the addition of the second and even third cosolvent is also required to achieve the desired drug concentration in a given solution volume. In addition to enhancing the aqueous solubility of drugs, cosolvents can alter other drug properties such as chemical stability[2] and skin permeability.[3] In a detailed report, the effects of ethanol concentration on the solubility, ionization, and permeability characteristics of ibuprofen were investigated. Experimental measurements showed that the diffusion of ibuprofen from ethanol + water mixtures across human skin is increased initially by increasing the ethanol concentration, reaches a maximum value, and then decreases with the further addition of ethanol, due to the dehydration effect of ethanol on stratum corneum.[3] Ethanol is one of the most important and common cosolvents in the pharmaceutical industry and is used in many commercially available oral, parenteral, and soft gelatin formulations.[1] Polyethylene glycols (PEGs) are neutral polyethers which are freely soluble in water due to strong hydrogen-bonding with water molecules. Their low toxicity and high aqueous solubility make PEGs a suitable cosolvent for various applications in the pharmaceutical, chemical, cosmetic, and food industries.[4]

Acetaminophen is a class III drug of biopharmaceutical classification system,[5] and its solubility is classified high in this classification system; however, in the formulation of liquid dosage forms, its solubility should be increased because of the volume limitations of the formulations. Ibuprofen is a class II drug of biopharmaceutical classification system, and its oral bioavailability is limited by its dissolution rate.[5] Both drugs are used frequently in therapeutics as pain relief agents.

The solubility of drugs in solvent mixtures has received considerable attention in recent years. Numerous models have been presented for correlation or prediction of the solubility of drugs in mixed solvents. Of the recently reviewed models,[6] the Jouyban−Acree model is perhaps one of the most 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 drug in a binary solvent mixture at various temperatures is[6]

$$\log C_{m,T}^{Sat} = w_1 \log C_{1,T}^{Sat} + w_2 \log C_{2,T}^{Sat} + \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] \quad (1)$$

where $C_{m,T}^{Sat}$ is the solute solubility in the solvent mixtures at temperature T, w_1 and w_2 are the mass fractions of the solvents 1 and 2 in the absence of the solute, and $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ denote the solubility of the solute in the neat solvents 1 and 2, respectively. The J terms are computed by regressing $\log C_{m,T}^{Sat} - w_1 \log C_{1,T}^{Sat} - w_2 \log C_{2,T}^{Sat}$ against $(w_1 w_2)/T$, $(w_1 w_2 (w_1 - w_2)/T)$, and $(w_1 w_2 (w_1 - w_2)^2/T)$.[4] The model for representing the solubility of drugs in ternary solvent mixtures is

$$\log C_{m,T}^{Sat} = w_1 \log C_{1,T}^{Sat} + w_2 \log C_{2,T}^{Sat} + w_3 \log C_{3,T}^{Sat} + \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] + \left[\frac{w_1 w_3}{T}\sum_{i=0}^{2} J_i' (w_1 - w_3)^i\right] + \left[\frac{w_2 w_3}{T}\sum_{i=0}^{2} J_i'' (w_2 - w_3)^i\right] + \left[\frac{w_1 w_2 w_3}{T}\sum_{i=0}^{2} J_i''' (w_1 - w_2 - w_3)^i\right] \quad (2)$$

where $C_{3,T}^{Sat}$ is the solute solubility in the solvent 3 at temperature T and w_3 is the mass fraction of the solvent 3 in the absence of

* Author to whom correspondence should be addressed. E-mail: ajouyban@hotmail.com, jouyban@ut.ac.ir. Fax: +98 411 3363231.
† Drug Applied Research Center and Faculty of Pharmacy.
‡ Biotechnology Research Center.
§ University of North Texas.

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Table 1. Details of Calibration Curves of the Drugs

drug	ε / L·mol^{-1}·cm^{-1}	C / mol·L^{-1}	correlation coefficient	calibration curve (A: absorbance)
acetaminophen	9163.6 to 9674.7	0.0000045 to 0.0000756	0.999	$A = 9579.9C - 0.0047$
ibuprofen	7632.4 to 9988.3	0.0000184 to 0.0001115	0.996	$A = 17340.8C + 0.0384$

the solute. The J_i''' terms are the ternary solvent interaction terms and computed by regressing

$$\left\{\log C_{m,T}^{Sat} - w_1 \log C_{1,T}^{Sat} - w_2 \log C_{2,T}^{Sat} - w_3 \log C_{3,T}^{Sat} - \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] - \left[\frac{w_1 w_3}{T}\sum_{i=0}^{2} J_i' (w_1 - w_3)^i\right] - \left[\frac{w_2 w_3}{T}\sum_{i=0}^{2} J_i'' (w_2 - w_3)^i\right]\right\}$$

against $(w_1w_2w_3/T)$, $(w_1w_2w_3(w_1 - w_2 - w_3)/T)$, and $(w_1w_2w_3(w_1 - w_2 - w_3)^2/T)$. The solvents' numbers are defined as $C_{1,T}^{Sat} > C_{2,T}^{Sat} > C_{3,T}^{Sat}$; that is, the monosolvent providing the highest solubility for a solute among other monosolvents is called solvent 1, and the monosolvent providing the lowest solubility is called solvent 3. A similar algorithm can be used to represent the density of solvent mixtures at various temperatures as shown in a previous paper.[7] The general form of the model for the density of ternary solvent mixtures at various temperatures is

$$\log \rho_{m,T} = w_1 \log \rho_{1,T} + w_2 \log \rho_{2,T} + w_3 \log \rho_{3,T} + \frac{w_1 w_2}{T}[A_0 + A_1(w_1 - w_2) + A_2(w_1 - w_2)^2] + \frac{w_1 w_3}{T}[A_0' + A_1'(w_1 - w_3) + A_2'(w_1 - w_3)^2] + \frac{w_2 w_3}{T}[A_0'' + A_1''(w_2 - w_3) + A_2''(w_2 - w_3)^2] + \frac{w_1 w_2 w_3}{T}[A_0''' + A_1'''(w_1 - w_2 - w_3) + A_2'''(w_1 - w_2 - w_3)^2] \quad (3)$$

in which $\rho_{m,T}$ is the density of the mixed solvent system in the absence of a solute, $\rho_{1,T}$, $\rho_{2,T}$, and $\rho_{3,T}$ are the density of monosolvents 1 to 3 in the absence of a solute at temperature of T, and A terms are the sub-binary and ternary interaction terms which are computed using a similar method to the J terms. The solvents' numbers are defined as $\rho_{1,T} > \rho_{2,T} > \rho_{3,T}$; that is, the monosolvent with the highest density is called solvent 1, and the monsolvent with the lowest density is called solvent 3 and the middle one solvent 2. The applicability of eq 3 for training the model using solute free densities and then predicting the density of saturated solutions employing the saturated densities of monosolvent data is shown in this work.

Experimental solubilities of both drugs in ethanol + water mixtures were reported previously.[8,9] In this work, the experimental solubility of acetaminophen and ibuprofen in PEG 200 + water, PEG 200 + ethanol, PEG 200 + ethanol + water, PEG 400 + water, PEG 400 + ethanol, and PEG 400 + ethanol + water mixtures at 298.2 K are reported, and constants of the Jouyban−Acree model for representing the generated data were calculated.

Experimental Method

Materials. Acetaminophen was purchased from Arastoo Pharmaceutical Company (Iran), and ibuprofen was purchased from Sobhan Pharmaceutical Company (Iran). The purity of the drugs was checked through melting point determinations and

Table 2. Experimental Solubilities $C_{m,T}^{Sat}$ of Acetaminophen in the Mixtures of PEG 200 or 400 (1), Ethanol (2), and Water (3) at a Temperature of 298.2 K and Density ρ of the Saturated Solutions

mass fractions w_1	w_2	w_3	$C_{m,T}^{Sat}$ ($N = 3$) / mol·L^{-1}	ρ ($N = 1$) / g·cm^{-3}
PEG 200	Ethanol	Water		
		1.000	0.0989	1.0162
0.200		0.800	0.2078	1.0362
0.400		0.600	0.4414	1.0691
0.600		0.400	0.9384	1.1062
0.800		0.200	1.5092	1.1248
1.000			1.3282	1.1454
	1.000		1.0605	0.8512
0.200	0.800		0.9679	0.8858
0.400	0.600		1.0848	0.9352
0.600	0.400		1.3143	1.0156
0.800	0.200		1.4674	1.0836
0.900	0.100		1.6066	1.1124
1.000			1.3282	1.1454
0.100	0.100	0.800	0.2761	1.0079
0.100	0.200	0.700	0.3221	0.9908
0.100	0.500	0.400	0.8936	0.9758
0.100	0.600	0.300	1.2938	0.9564
0.200	0.200	0.600	0.6016	1.0208
0.200	0.300	0.500	0.9705	1.0079
0.200	0.600	0.200	0.8727	0.9891
0.200	0.700	0.100	0.9661	0.9545
0.300	0.400	0.300	1.0745	1.0058
0.400	0.100	0.500	0.8887	1.0614
0.400	0.400	0.200	1.3529	1.0364
0.400	0.500	0.100	1.1748	1.0327
0.500	0.100	0.400	0.7878	1.0764
0.500	0.200	0.300	0.7231	1.0700
0.600	0.200	0.200	1.2903	1.1273
0.600	0.300	0.100	1.3140	1.0909
0.800	0.100	0.100	1.0356	1.1600
PEG 400	Ethanol	Water		
		1.000	0.0989	1.0162
0.200		0.800	0.2583	1.0382
0.400		0.600	0.5597	1.0712
0.600		0.400	1.0915	1.1062
0.800		0.200	1.6484	1.1289
0.900		0.100	1.5370	1.1351
1.000			1.3978	1.1474
	1.000		1.0605	0.8512
0.200	0.800		1.0219	0.8899
0.300	0.700		1.0776	0.9126
0.400	0.600		1.2307	0.9394
0.600	0.400		1.3978	1.0176
0.800	0.200		1.8015	1.0856
0.900	0.100		1.9825	1.1186
1.000			1.3978	1.1474
0.100	0.100	0.800	0.3443	1.0101
0.100	0.200	0.700	0.3958	0.9930
0.100	0.500	0.400	1.2068	0.9758
0.100	0.600	0.300	1.3459	0.9600
0.200	0.200	0.600	0.8122	1.0229
0.200	0.300	0.500	1.2575	1.0101
0.200	0.600	0.200	1.2207	0.9909
0.200	0.700	0.100	1.4114	0.9582
0.300	0.300	0.400	1.1914	1.0186
0.300	0.400	0.300	1.4155	1.0079
0.400	0.100	0.500	1.0766	1.0614
0.400	0.400	0.200	1.5895	1.0364
0.400	0.500	0.100	1.6480	1.0345
0.500	0.100	0.400	0.9966	1.0764
0.500	0.200	0.300	1.1650	1.0700
0.600	0.200	0.200	1.5408	1.1309
0.600	0.300	0.100	1.9125	1.0927
0.800	0.100	0.100	1.2305	1.1618

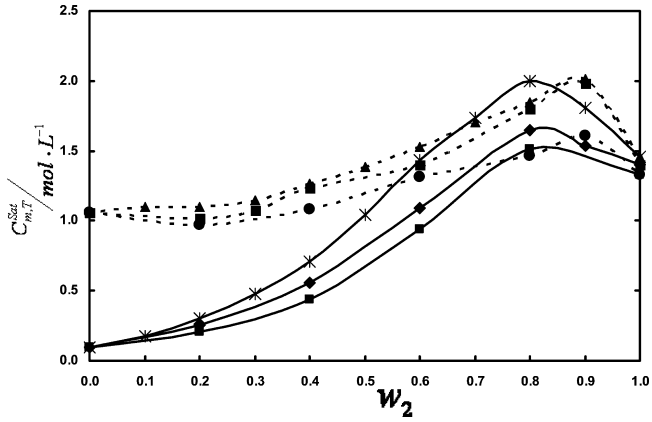

Figure 1. Solubility of acetaminophen ($C^{Sat}_{m,T}$) in water and ethanol binary mixtures of polyethylene glycols (PEGs) at various mass fractions of PEGs (w_2); —■—, PEG 200 + water; —●—, PEG 400 + water; —∗—, PEG 600 + water taken from ref 10; - -●- -, PEG 200 + ethanol; - -■- -, PEG 400 + ethanol; - -▲- -, PEG 600 + ethanol taken from ref 10.

comparing the measured solubilities in monosolvents with the corresponding data from the literature which are summarized in a previous paper.[10] Ethanol (mass fraction purity of 0.995) and PEG 200 (mass fraction purity of 0.995) were purchased from Merck (Germany); PEG 400 was a gift from Daana Pharmaceutical Company (Iran), and double-distilled water was used for preparation of the solutions.

Apparatus and Procedures. The solvent mixtures were prepared by mixing the appropriate grams of the solvents with the uncertainty of 0.1 g. The solubility of acetaminophen and ibuprofen in the presence of these two cosolvents was determined by equilibrating an excess amount of drug at $T = 298.2$ K using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system maintained constant within ± 0.2 K. After a sufficient length of time (> 98 h), the saturated solutions of the drugs were centrifuged in 13 000 rpm for 0.25 h, diluted with water and methanol for acetaminophen and ibuprofen, respectively, and then assayed at 243 nm for acetaminophen and 222 nm for ibuprofen, using a UV−vis spectrophotometer (Beckman DU-650, Fullerton, USA). Concentrations of the diluted solutions were determined from the calibration graphs. Details of calibration graphs are given in Table 1. Each experimental data point represents the average of at least three repetitive experiments with the measured mol·L^{-1} solubilities with $\sigma_{n-1} = 0.00004$ to $\sigma_{n-1} = 0.10897$ mol·L^{-1} being reproducible to within ± 3.4 %. Densities of the saturated solutions are measured using a 5 mL pycnometer as a single determination.

Computational Methods. Equation 1 is fitted to the experimental solubility data of each drug in solvent mixtures, and the back-calculated solubilities are used to calculate the accuracy of the fit. In the next analysis, eq 2 is fitted to the solubility of drugs in ternary mixtures. Similar numerical methods were applied to the density data. The mean relative deviation (MRD) is used to check the uncertainty of the prediction methods and is calculated using

$$\mathrm{MRD} = \frac{\sum\left\{\dfrac{|\mathrm{Calculated} - \mathrm{Observed}|}{\mathrm{Observed}}\right\}}{N} \qquad (4)$$

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

Table 3. Experimental Solubilities $C^{Sat}_{m,T}$ of Ibuprofen in the Mixtures of Ethanol (1), PEG 200 or 400 (2), and Water (3) at a Temperature of 298.2 K and Density ρ of the Saturated Solutions

mass fractions			$C^{Sat}_{m,T}$ ($N = 3$)	ρ ($N = 1$)
w_1	w_2	w_3	mol·L^{-1}	g·cm^{-3}
Ethanol	PEG 200	Water		
		1.000	0.0004	1.0013
	0.200	0.800	0.0013	1.0090
	0.400	0.600	0.0060	1.0180
	0.600	0.400	0.0314	1.0420
	0.800	0.200	0.8709	1.0710
	0.900	0.100	1.1787	1.0960
	1.000		0.9467	1.1310
0.100	0.900		1.2256	1.0710
0.200	0.800		1.4618	1.0490
0.400	0.600		1.6979	0.9810
0.600	0.400		2.1338	0.9460
0.700	0.300		2.4607	0.9310
0.800	0.200		2.4062	0.9170
1.000			2.2882	0.8760
0.100	0.100	0.800	0.0018	1.0015
0.100	0.400	0.500	0.0267	1.0400
0.100	0.500	0.400	0.0450	1.0529
0.100	0.800	0.100	1.6790	1.0927
0.200	0.100	0.700	0.0040	0.9801
0.200	0.200	0.600	0.0145	1.0079
0.200	0.500	0.300	0.3215	1.0229
0.200	0.600	0.200	1.0842	1.0509
0.300	0.200	0.500	0.0694	0.9716
0.300	0.300	0.400	0.1667	0.9844
0.300	0.600	0.100	2.2057	1.0400
0.400	0.300	0.300	1.0434	0.9544
0.400	0.400	0.200	1.2295	0.9818
0.500	0.100	0.400	0.6438	0.9266
0.500	0.400	0.100	1.8152	0.9836
0.600	0.100	0.300	1.3203	0.9273
0.600	0.200	0.200	1.7290	0.9400
0.700	0.200	0.100	1.8016	0.9400
Ethanol	PEG 400	Water		
		1.000	0.0004	1.0013
	0.200	0.800	0.0016	1.0030
	0.400	0.600	0.0070	1.0200
	0.600	0.400	0.0367	1.0440
	0.800	0.200	1.0344	1.0730
	0.900	0.100	1.4294	1.0980
	1.000		1.2055	1.1330
0.100	0.900		1.4618	1.0730
0.200	0.800		1.5889	1.0510
0.400	0.600		1.8250	0.9830
0.600	0.400		2.1883	0.9480
0.700	0.300		2.5697	0.9330
0.800	0.200		2.4062	0.9190
1.000			2.2882	0.8760
0.100	0.100	0.800	0.0020	1.0037
0.100	0.400	0.500	0.0301	1.0400
0.100	0.500	0.400	0.0487	1.0550
0.100	0.800	0.100	1.9905	1.0927
0.200	0.100	0.700	0.0046	0.9823
0.200	0.200	0.600	0.0147	1.0101
0.200	0.500	0.300	0.4713	1.0251
0.200	0.600	0.200	1.2477	1.0527
0.300	0.200	0.500	0.0860	0.9737
0.300	0.300	0.400	0.2049	0.9865
0.300	0.600	0.100	2.3174	1.0418
0.400	0.300	0.300	1.2931	0.9566
0.400	0.400	0.200	1.3221	0.9836
0.500	0.100	0.400	0.8254	0.9288
0.500	0.400	0.100	1.9178	0.9855
0.600	0.100	0.300	1.5038	0.9273
0.600	0.200	0.200	1.8851	0.9418
0.700	0.200	0.100	1.9542	0.9418

Results and Discussion

Table 2 lists the experimental solubility of acetaminophen in different mass fractions of PEG 200 (1) + ethanol (2) + water (3) and PEG 400 (1) + ethanol (2) + water (3) mixtures at 298.2 K along with the densities of the saturated solutions. There are good agreements between generated data in this work with those summarized in a previous paper.[10] Similar solubility

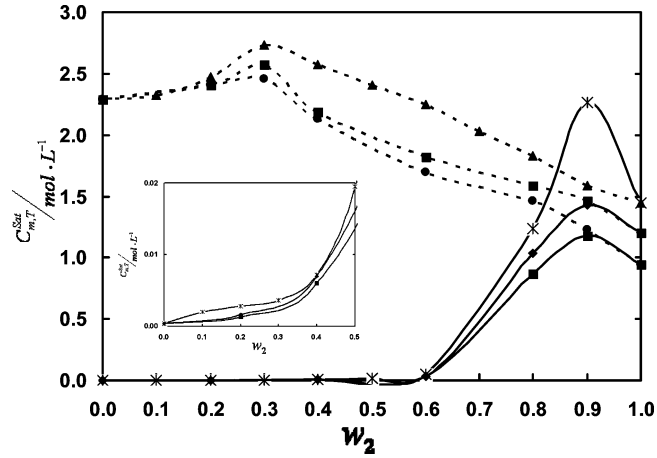

Figure 2. Solubility of ibuprofen ($C^{Sat}_{m,T}$) in water and ethanol binary mixtures of PEGs at various mass fractions of PEGs (w_2); −■−, PEG 200 + water; −◆−, PEG 400 + water; −∗−, PEG 600 + water taken from ref 10; - -●- -, PEG 200 + ethanol; - -■- -, PEG 400 + ethanol; - -▲- -, PEG 600 + ethanol taken from ref 10.

Table 4. Numerical Values of Solubilization Power (ω) for PEGs to Solubilize the Drugs in Cosolvent + Water Mixtures

drug	PEG 200	PEG 400	PEG 600
acetaminophen	1.48	1.53	1.63
ibuprofen	3.85	3.95	4.17

patterns were obtained for the solubility of acetaminophen in PEGs + water, and the maximum values were achieved in mass fractions of 0.800 of PEGs 200 and 400; it was also the same for PEG 600 + water mixtures from a previous work.[10] In the case of PEGs + ethanol mixtures, the maximum values were obtained at mass fraction of 0.900 of PEGs. Considering a given solvent composition, there is a relationship between molar masses of PEGs and the solubility of acetaminophen in PEGs + water and PEGs + ethanol mixtures as shown in Figure 1, in which the more the molar mass of PEG, the higher the solubility is observed.

Table 3 lists the measured solubility of ibuprofen in ethanol (1) + PEG 200 (2) + water (3) and ethanol (1) + PEG 400 (2) + water (3) at 298.2 K. For ibuprofen, ethanol dissolves more solute when compared with PEGs; therefore, ethanol is defined as solvent 1. The maximum solubility of ibuprofen (2.5697 mol·L^{-1}) is observed in ethanol + PEG 400 of 0.700:0.300 mass fractions. Figure 2 shows the solubility profiles of ibuprofen in six binary solvents investigated in this work. The solubility maxima for PEGs + water and ethanol + PEGs mixtures were obtained at PEG mass fractions of 0.900 and 0.300, respectively.

The solubilization power of the cosolvents to increase the solubility of a solute in a binary mixture could be defined as solubilization power, ω,

Table 6. Densities of Solute-Free Binary and Ternary Mixtures of Different Solvent Compositions of PEGs 200 or 400 (1) + Water (2) + Ethanol (3) at 298.2 K

			PEG 200	PEG 400
w_1	w_2	w_3	ρ/g·cm^{-3} (N = 1)	
	1.00		0.997	0.997
0.20	0.80		1.015	1.017
0.40	0.60		1.033	1.035
0.60	0.40		1.065	1.067
0.80	0.20		1.086	1.098
0.90	0.10		1.098	1.114
1.00			1.112	1.124
	0.92	0.08	0.975	0.975
	0.83	0.17	0.967	0.967
	0.75	0.25	0.954	0.954
	0.65	0.35	0.930	0.930
	0.56	0.44	0.912	0.912
	0.46	0.54	0.884	0.884
	0.35	0.65	0.865	0.865
	0.24	0.76	0.830	0.830
	0.12	0.88	0.811	0.811
		1.00	0.783	0.783
0.20		0.80	0.801	0.803
0.30		0.70	0.830	0.832
0.40		0.60	0.876	0.878
0.60		0.40	0.966	0.968
0.80		0.20	1.045	1.043
0.90		0.10	1.080	1.082
0.10	0.30	0.60	0.899	0.901
0.10	0.40	0.50	0.929	0.931
0.10	0.70	0.20	0.976	0.978
0.10	0.80	0.10	1.000	1.002
0.20	0.10	0.70	0.886	0.888
0.20	0.20	0.60	0.903	0.905
0.20	0.50	0.30	0.966	0.968
0.20	0.60	0.20	0.998	1.002
0.30	0.30	0.40	0.956	0.958
0.30	0.40	0.30	0.976	0.978
0.40	0.10	0.50	0.951	0.955
0.40	0.20	0.40	0.970	0.972
0.40	0.50	0.10	1.039	1.041
0.50	0.30	0.20	1.019	1.023
0.50	0.40	0.10	1.049	1.053
0.60	0.10	0.30	1.018	1.019
0.60	0.20	0.20	1.039	1.043
0.80	0.10	0.10	1.075	1.079

Table 5. Model Constants and the Mean Relative Deviations (MRDs) for Solubilities of Acetaminophen and Ibuprofen

drug	solvent system	J_0/K^{-1}	J_1/K^{-1}	J_2/K^{-1}	100 MRD
acetaminophen	PEG 200 (1) + ethanol (2)	3.302	191.258	*a*	0.1
	PEG 200 (1) + water (3)	304.442	292.332	132.145	0.5
	ethanol (2) + water (3)[b]	640.732	77.698	−324.630	5.0
	PEG 200 (1) + ethanol (2) + water (3)	−778.973	*a*	*a*	18.2 (22.9)[c]
	PEG 400 (1) + ethanol (2)	68.602	296.006	*a*	4.6
	PEG 400 (1) + water (3)	415.805	170.298	*a*	2.5
	PEG 400 (1) + ethanol (2) + water (3)	−534.457	−1361.868	*a*	14.1 (14.7)[c]
ibuprofen	ethanol (1) + PEG 200 (2)	170.106	*a*	*a*	3.7
	PEG 200 (2) + water (3)	−220.937	910.545	1814.360	16.6
	ethanol (1) + water (3)[b]	978.397[b]	1119.209[b]	−1152.574[b]	2.0[b]
	ethanol (1) + PEG 200 (2)+ water (3)	2350.057	*a*	*a*	20.9 (32.7)[c]
	ethanol (1) + PEG 400 (2)	128.761	*a*	*a*	3.4
	PEG 400 (2) + water (3)	−206.519	816.881	1863.842	16.3
	ethanol (1) + PEG 400 (2)+ water (3)	2804.285	*a*	*a*	24.0 (35.9)[c]
					9.4

[a] Not statistically significant, coefficient was set equal to zero. [b] Experimental data are taken from a previous paper,[8] and the solvent compositions are converted to mass fraction. [c] MRDs are computed employing only sub-binary constants and without using ternary interaction terms.

Table 7. Model Constants and the MRDs for Solute-Free Densities of PEGs, Ethanol, and Water Mixtures

solvent system	A_0/K^{-1}	A_1/K^{-1}	A_2/K^{-1}	100 MRD
PEG 200 (1) + water (2)	−2.150	*a*	*a*	0.2
PEG 200 (1) + ethanol (3)	−7.778	40.021	−26.347	0.1
water (2) + ethanol (3)[b]	6.421	4.826	*a*	0.3
PEG 200 (1) + water (2) + ethanol (3)	138.876	*a*	*a*	1.2 (2.6)[c]
PEG 400 (1) + water (2)	−2.737	*a*	*a*	0.2
PEG 400 (1) + ethanol (3)	−9.238	33.851	−33.710	0.2
PEG 400 (1) + water (2) + ethanol (3)	144.623	*a*	*a*	1.2 (2.7)[c]
overall				0.5

[a] Not statistically significant with zero. [b] Experimental data are taken from a previous paper,[8] and the solvent compositions are converted to mass fraction. [c] MRDs are computed employing only sub-binary constants and without using ternary interaction terms.

Table 8. MRDs for Densities of Saturated Solutions of Drugs in PEGs, Ethanol, and Water Mixtures

drug	solvent system	100 MRD
acetaminophen	PEG 200 (1) + ethanol (2)	0.7
	PEG 200 (1) + water (3)	0.6
	ethanol (2) + water (3)[a]	1.5
	PEG 200 (1) + ethanol (2) + water (3)	3.6
	PEG 400 (1) + ethanol (2)	1.1
	PEG 400 (1) + water (3)	0.6
	PEG 400 (1) + ethanol (2) + water (3)	2.5
ibuprofen	ethanol (1) + PEG 200 (2)	2.3
	PEG 200 (2) + water (3)	1.1
	ethanol (1) + water (3)[a]	1.4
	ethanol (1) + PEG 200 (2) + water (3)	2.2
	ethanol (1) + PEG 400 (2)	2.3
	PEG 400 (2) + water (3)	1.1
	ethanol (1) + PEG 400 (2) + water (3)	2.2
overall		1.7

[a] Experimental data are taken from a previous paper,[8] and the solvent compositions are converted to mass fraction.

$$\omega = \frac{\log\left(\frac{C^{Sat}_{m,max}}{C^{Sat}_{2,T}}\right)}{w_{1,max}} \quad (5)$$

where $C^{Sat}_{m,max}$ is the maximum observed solubility and $w_{1,max}$ denotes the fraction of the solvent 1 producing the maximum solubility. Considering the numerical values of ω for the PEGs (as listed in Table 4), the solubilization power of the cosolvents is PEG 600, followed by PEG 400 and PEG 200, for both drugs investigated. It is obvious that the solubility increase for ibuprofen was more than acetaminophen using the same mass fraction of PEGs.

The experimental solubility data of acetaminophen and ibuprofen in binary and ternary solvent mixtures were fitted to the Jouyban−Acree model as explained in the Introduction; the numerical values of the model constants were computed and listed in Table 5. The solubilities were back-calculated using trained models, and the MRDs for each set were computed and reported in Table 5, where the overall MRD for the investigated data sets was 9.4 %. For solubility data of solutes in ternary solvent mixtures, the solubilities were predicted using the experimental data of sub-binary solvents and without employing any experimental solubility data in ternary solvent mixtures, and the obtained MRDs for the predicted data points were 22.9 %, 14.7 %, 32.7 %, and 35.9 %, respectively, for acetaminophen and ibuprofen in PEG 200 and PEG 400 mixtures. The overall MRD for this predicted data points was 26.6 %. Although the MRD is relatively high, it does not require any experimental data to predict the solubility in ternary solvent mixtures.

As noted in the Introduction, the Jouyban−Acree model is capable of representing the density of mixed solvents at various temperatures. The sub-binary and ternary interaction terms of eq 3 for representing the density of solute free solvent mixtures (for details see Table 6) are listed in Table 7 along with the MRD values. The trained versions of the models could be used for predicting the density of the saturated solutions of a drug. The models for predicting the density of saturated solution of acetaminophen in PEG 200 (1) + ethanol (2) + water (3) mixtures and PEG 400 (1) + ethanol (2) + water (3) after excluding nonsignificant constants are

$$\log \rho^{Sat}_{m,T} = w_1 \log \rho^{Sat}_{1,T} + w_2 \log \rho^{Sat}_{2,T} + w_3 \log \rho^{Sat}_{3,T} + \frac{w_1 w_2}{T}[-7.778 + 40.021(w_1 - w_2) - 26.347(w_1 - w_2)^2] + \frac{w_1 w_3}{T}[-2.150] + \frac{w_2 w_3}{T}[6.421 - 4.826(w_2 - w_3)] + \frac{138.876 w_1 w_2 w_3}{T} \quad (6)$$

and

$$\log \rho^{Sat}_{m,T} = w_1 \log \rho^{Sat}_{1,T} + w_2 \log \rho^{Sat}_{2,T} + w_3 \log \rho^{Sat}_{3,T} + \frac{w_1 w_2}{T}[-9.238 + 33.851(w_1 - w_2) - 33.710(w_1 - w_2)^2] + \frac{w_1 w_3}{T}[-2.737] + \frac{w_2 w_3}{T}[6.421 - 4.826(w_2 - w_3)] + \frac{144.623 w_1 w_2 w_3}{T} \quad (7)$$

in these equations, $\rho^{Sat}_{m,T}$ is the density of the drug-saturated solution of the mixed solvent system, $\rho^{Sat}_{1,T}$, $\rho^{Sat}_{2,T}$, and $\rho^{Sat}_{3,T}$ are the density of drug-saturated solutions of monosolvents 1 to 3 at the temperature T. It should be noticed that the algebraic signs of A_1 terms depend on the definition of the solvents. As an example, in the training process of the model for solute-free densities, the solvents' numbers were PEGs (1) + water (2) + ethanol (3). In the solubility data sets of acetaminophen, concerning the solubility values in monosolvents, the numbers were defined as PEGs (1) + ethanol (2) + water (3); therefore, the corresponding A terms were included in the equations, and in the case of water + ethanol systems, since their numbers are changed, the sign of 4.826 was changed as well. Employing $\rho^{Sat}_{1,T}$, $\rho^{Sat}_{2,T}$, and $\rho^{Sat}_{3,T}$ experimental data, the density of saturated solutions of acetaminophen could be predicted. The MRDs for the predicted densities for sub-binary and ternary solvent mixtures are summarized in Table 8.

Conclusion

The Jouyban−Acree model was fitted to the binary and ternary solvent data as described above, and the model constants for acetaminophen and ibuprofen solubilities are reported in

Table 5. The Jouyban−Acree model provides a reasonably accurate mathematical description of the observed solubility data of the investigated drugs in the three sub-binary solvent systems at all cosolvent compositions. This finding is also supported by small MRD values for the back-calculated solubility data.

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