Solubility of Acetaminophen and Ibuprofen in Binary and Ternary Mixtures of Polyethylene Glycol 600, Ethanol and Water

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Experimental solubilities of acetaminophen and ibuprofen in polyethylene glycol 600–water, ethanol–polyethylene glycol 600, and polyethylene glycol 600–water–ethanol mixtures at 25 °C are reported. The solubilities of drugs in the presence of ethanol and polyethylene glycol 600 were increased. The Jouyban–Acree model was used to fit the solubility data of each drug in the binary mixtures in which the overall mean relative deviations (OMRDs) for acetaminophen and ibuprofen were 2.9% and 4.3%, respectively. The OMRDs for ternary solvent mixtures for acetaminophen and ibuprofen were 16.8% and 22.4%, respectively. Generally, the errors associated with ibuprofen are larger than that of acetaminophen in both binary and ternary solvent mixtures. The solubilities were predicted using previously trained versions of the Jouyban–Acree and log-linear models with the OMRDs of 38.8% and 52.1%, respectively. Density of the mixed solvents in the absence of the solute was measured and used to train the model and then the density of the saturated solutions was predicted using the trained model and the density of the saturated solutions in mono-solvent systems with the OMRD of 3.2%.

Key words acetaminophen; ibuprofen; mixed solvent; solubility prediction; Jouyban–Acree model

Aqueous solubility of drugs/drug candidates is one of the crucial physico-chemical properties and affects the fate of a drug candidate in which nearly 40% of the candidates fail to proceed with the trial phases, simply because of their poor solubility. Aqueous solubility enhancement[1] and its prediction methods[2] are recently reviewed. Yalkowsky and He provided an extensive database of aqueous solubility of chemicals including many pharmaceutically interested compounds.[3] Different methods could be employed to enhance the aqueous solubility of a poorly soluble drug including the addition of the cosolvents. In addition to the experimental efforts to collect solubility data of pharmaceuticals in water–cosolvent mixtures, a number of mathematical models have been developed to correlate/predict the data. These models are reviewed[4] and a comprehensive database of solubility of drugs and related compounds in binary and ternary solvent mixtures is recently published.[5]

Acetaminophen is a class III drug of biopharmaceutical classification system[6] and its oral bioavailability is limited by the barrier properties of the gastro-intestinal tract. Although its solubility is classified high in this classification system, however in the formulation of liquid dosage forms of acetaminophen, its solubility should be increased because of the volume limitations of the formulations. As an example, in order to formulate its soft gel, 500 mg of acetaminophen should be dissolved in less than 1 ml of an appropriate solvent. Ibuprofen is a class II drug of biopharmaceutical classification system and its oral bioavailability is limited by its dissolution rate.[6] Both drugs are used frequently in therapeutics as pain relief agents.

Solubility data of pharmaceuticals are required in many processes including liquid drug formulations and addition of a cosolvent to the aqueous solution is one of the most common methods to alter the solubility. Addition of the second cosolvent to the water–cosolvent mixture is necessary when the binary solvent mixture is not able to dissolve the desired amount of a drug or its concentration causes adverse effects. As a general rule, the higher the concentration of the cosolvents, the more is the increase in the solubility of the poorly soluble drug. However, because of toxicity and cost consideration, the concentration of the cosolvents should be kept as low as possible and usually less than 50 v/v % of the liquid formulations.

Aqueous polymer solutions, especially polyethylene glycols (PEGs), have an important role in the pharmaceutical industry. PEGs are neutral polyethers in linear or branched forms, according to their viscosity and density; they have different molecular weights which are determined by a number that is written after polymer name. The molecular weights of PEGs ranging from 200 to 36000, low weight polymers are in liquid form and the high weight polymers are in solid form. These polymers are freely soluble in water due to strong hydrogen-bonding with water molecules. Their low toxicity and high aqueous solubility make them as a suitable solvent for purification of the biological materials. Various applications of PEGs in the pharmaceutical, chemical, cosmetic and food industries are reviewed.[7]

In this work, PEG 600 is used for increasing the solubility of ibuprofen and acetaminophen. PEGs can be used as a solubilization agent in the formulation of liquid pharmaceutical formulations[8,9] and as dissolution rate enhancers.[10] The often used method to optimize the solvent composition of the 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 and employing cosolvency models could be an appropriate solution. Of the numerous models developed in recent years, the Jouyban–Acree model is perhaps one of the most versatile models. It provides very accurate mathematical descriptions for how the solute solubility varies with both temperature and solvent composition. The model for representing the solubility of a solute in binary solvent mixture at various temperatures is:

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

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where $C_{m,T}$ is the solute molar (M) 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, $C_{1,T}$ and $C_{2,T}$ denote the molar solubility of the solute in the neat solvents 1 and 2, respectively. The J_i terms are the constants of the model and are computed by regressing $(\log C^{\mathrm{Sat}}_{m,T} - w_1 \log C^{\mathrm{Sat}}_{1,T} - w_2 \log C^{\mathrm{Sat}}_{2,T})$ against $(w_1w_2)/T$, $[w_1w_2(w_1-w_2)]/T$, and $[w_1w_2(w_1-w_2)^2]/T$.[4] The extended models for representing the solubility data of drugs in ternary solvent mixtures are:

$$\log C_{m,T} = w_1 \log C_{1,T} + w_2 \log C_{2,T} + w_3 \log C_{3,T} + \left[\frac{w_1w_2}{T}\sum_{i=0}^{2} J_i(w_1-w_2)^i\right] + \left[\frac{w_1w_3}{T}\sum_{i=0}^{2} J'_i(w_1-w_3)^i\right] + \left[\frac{w_2w_3}{T}\sum_{i=0}^{2} J''_i(w_2-w_3)^i\right] \quad (2)$$

$$\log C_{m,T} = w_1 \log C_{1,T} + w_2 \log C_{2,T} + w_3 \log C_{3,T} + \left[\frac{w_1w_2}{T}\sum_{i=0}^{2} J_i(w_1-w_2)^i\right] + \left[\frac{w_1w_3}{T}\sum_{i=0}^{2} J'_i(w_1-w_3)^i\right] + \left[\frac{w_2w_3}{T}\sum_{i=0}^{2} J''_i(w_2-w_3)^i\right] + \left[\frac{w_1w_2w_3}{T}\sum_{i=0}^{2} J'''_i(w_1-w_2-w_3)^i\right] \quad (3)$$

where $C_{3,T}$ is the solute molar solubility in the solvent 3 at temperature T, and w_3 is the mass fraction of the solvent 3 in the absence of the solute. The J'_i and J''_i terms are computed using the same procedure of J_i terms. The J'''_i terms are the ternary solvent interaction terms and computed by regressing

$$\left\{\log C^{\mathrm{Sat}}_{m,T} - w_1 \log C^{\mathrm{Sat}}_{1,T} - w_2 \log C^{\mathrm{Sat}}_{2,T} - w_3 \log C^{\mathrm{Sat}}_{3,T} - \left[\frac{w_1w_2}{T}\sum_{i=0}^{2} J_i(w_1-w_2)^i\right] - \left[\frac{w_1w_3}{T}\sum_{i=0}^{2} J'_i(w_1-w_3)^i\right] - \left[\frac{w_2w_3}{T}\sum_{i=0}^{2} J''_i(w_2-w_3)^i\right]\right\}$$

against

$$\frac{w_1w_2w_3}{T}, \quad \frac{w_1w_2w_3(w_1-w_2-w_3)}{T}, \quad \text{and} \quad \frac{w_1w_2w_3(w_1-w_2-w_3)^2}{T}.$$

The existence of these model constants which require a number of solubility data in solvent mixtures for training process is a limitation for the model when the solubility predictions are the goal of the computations in early drug discovery studies.

Experimental solubilities of both drugs in ethanol–water mixtures were reported in the pervious works.[11,12] In this work, the experimental solubility of acetaminophen and ibuprofen in PEG 600–water, PEG 600–ethanol and PEG 600–ethanol–water mixtures at 25 °C are reported and the applicability of the Jouyban–Acree model to the measured drug solubility data is investigated. In addition, the capability of the model to represent the density of saturated solutions of drugs in mixed solvent is also shown.

Experimental

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 by determination of their melting points and comparing the measured solubilities in mono-solvents with the corresponding data from the literature.[13,14] Ethanol (99.5%) was purchased from Merck (Germany), PEG 600 was a gift from Daana pharmaceutical company (Iran) and double distilled water was used for preparation of the solutions.

Apparatus and Procedures The binary 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 solvent mixtures was determined by equilibrating an excess amount of drug at 25 °C using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature controlling system maintained constant within ±0.2 °C. Because of the high viscosity of PEG 600, after sufficient length of time (>98 h), the saturated solutions of the drugs were centrifuged in 13000 rpm for 15 min, diluted with water, and then assayed at 243 nm for acetaminophen and 222 nm for ibuprofen, using a UV–Vis spectrophotometer (Beckman DU-650, Fullerton, U.S.A.). Concentrations of the diluted solutions were determined from the calibration curves. Each experimental data point represents the average of at least three repetitive experiments with the measured M solubilities being reproducible to within ±2.7%. Densities of the saturated solutions and the solvent mixtures in the absence of the solute were measured by a 5 ml pycnometer as a single measurement.

Computational Methods The experimental solubility data of each drug in the binary solvents was fitted to Eq. 1, the model constants were computed and the back-calculated solubilities were used to check the accuracy of the model. In the next analysis, Eq. 2 was used to predict the solubility of each drug in ternary solvents. In order to provide better predictions, the ternary interaction terms of Eq. 3 were calculated using a linear regression analysis. The model constants and the mean relative deviation (MRD) between the calculated and observed solubility values for numerical analysis methods are used to evaluate the accuracy of the model. In the other part of the analysis, we measured the density of the solvent mixtures in the absence of drugs, then by these data the Jouyban–Acree model was trained and then the density of the saturated binary mixture solutions was predicted. Then by using the sub-binary constants the ternary interaction terms of the model were calculated and using the trained version, the density of the saturated solutions of ternary solvent mixtures was predicted. The MRD was used to check the accuracy of the prediction methods for solubility and density values and is calculated using:

$$\mathrm{MRD} = 100\,\frac{\sum\left\{\dfrac{\text{calculated} - \text{observed}}{\text{observed}}\right\}}{N} \quad (4)$$

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

Results and Discussion

Tables 1 and 2 list the experimental solubilities of acetaminophen and ibuprofen in the binary and ternary solvent mixtures along with the measured density of the saturated solutions at 25 °C, respectively. The minimum solubility of acetaminophen (0.0989 M) is observed for aqueous solution and is in a good agreement with the previous data of 0.0994 M,[11] 0.0950 M,[15] 0.09133 M,[16] 0.09851 M,[14] 0.09923 M,[17] and 0.09326 M[18] and is slightly different with other reported data, *i.e.* 0.1323 M,[19] 0.0771 M,[20] 0.100 M,[21] and 0.07277 M.[22] The solubility of acetaminophen in ethanol is 1.0605 M (or 0.0659 in mole fraction) which is in agreement with other reported datum 0.0545 in mole fraction[23] and slightly is more than 0.9369 M taken from a previous work.[15] The possible reasons for such differences in solubilities arise from: 1) solute and solvents purity, 2) equilibration time, 3) temperature, 4) analysis method, 5) laboratory technique, 6) typographical error, and 7) polymorphism.[4] The maximum solubility of acetaminophen (2.0178 M) in the sol-

Table 1. Experimental Molar Solubilities ($C^{Sat}_{m,T}$) of Acetaminophen in Polyethylene Glycol 600 (1)–Ethanol (2)–Water (3) Mixtures at 25 °C and Density of the Saturated Solutions

w_1	w_2	w_3	$C^{Sat}_{m,T}$	Density
1.00	0.00	—	1.4531	1.1556
0.90	0.10	—	2.0178	1.1299
0.80	0.20	—	1.8504	1.1000
0.70	0.30	—	1.7024	1.0700
0.60	0.40	—	1.5263	1.0379
0.50	0.50	—	1.3853	1.0165
0.40	0.60	—	1.2681	0.9630
0.30	0.70	—	1.1433	0.9330
0.20	0.80	—	1.0954	0.9009
0.10	0.90	—	1.0995	0.8753
0.00	1.00	—	1.0605	0.8517
1.00	—	0.00	1.4531	1.1556
0.90	—	0.10	1.8104	1.1477
0.80	—	0.20	2.0004	1.1387
0.70	—	0.30	1.7319	1.1279
0.60	—	0.40	1.4355	1.1189
0.50	—	0.50	1.0450	1.0991
0.40	—	0.60	0.7059	1.0811
0.30	—	0.70	0.4809	1.0613
0.20	—	0.80	0.3028	1.0468
0.10	—	0.90	0.1749	1.0306
0.00	—	1.00	0.0989	1.0162
0.10	0.10	0.80	0.3782	1.0144
0.20	0.10	0.70	0.5627	1.0422
0.10	0.20	0.70	0.5209	0.9951
0.10	0.30	0.60	0.9548	0.9930
0.20	0.20	0.60	0.9886	1.0251
0.30	0.10	0.60	0.8922	1.0529
0.40	0.10	0.50	1.4980	1.0657
0.30	0.20	0.50	1.3327	1.0315
0.20	0.30	0.50	1.2762	1.0144
0.10	0.40	0.50	1.2588	0.9823
0.50	0.10	0.40	1.1594	1.0786
0.40	0.20	0.40	1.1253	1.0507
0.30	0.30	0.40	1.1984	1.0208
0.20	0.40	0.40	1.3125	0.9994
0.10	0.50	0.40	1.3487	0.9758
0.60	0.10	0.30	1.6883	1.1000
0.50	0.20	0.30	1.3807	1.0721
0.40	0.30	0.30	1.3042	1.0422
0.30	0.40	0.30	1.5686	1.0122
0.20	0.50	0.30	1.8711	0.9891
0.10	0.60	0.30	1.3926	0.9618
0.70	0.10	0.20	1.9798	1.1455
0.60	0.20	0.20	1.7943	1.1327
0.50	0.30	0.20	1.7477	1.0873
0.40	0.40	0.20	1.6498	1.0382
0.30	0.50	0.20	1.6203	1.0218
0.20	0.60	0.20	1.4478	0.9945
0.10	0.70	0.20	1.3444	0.9618
0.80	0.10	0.10	1.9684	1.1655
0.70	0.20	0.10	2.2564	1.1200
0.60	0.30	0.10	2.3094	1.0964
0.50	0.40	0.10	2.0016	1.0745
0.40	0.50	0.10	2.2757	1.0382
0.30	0.60	0.10	1.9769	0.9945
0.20	0.70	0.10	1.9602	0.9600
0.10	0.80	0.10	1.6199	0.9491

Table 2. Experimental Molar Solubilities ($C^{Sat}_{m,T}$) of Ibuprofen in Polyethylene Glycol 600 (1)–Ethanol (2)–Water (3) Mixtures at 25 °C and Density of the Saturated Solutions

w_1	w_2	w_3	$C^{Sat}_{m,T}$	Density
1.00	0.00	—	1.4425	1.1364
0.90	0.10	—	1.5889	1.0957
0.80	0.20	—	1.8298	1.0700
0.70	0.30	—	2.0301	1.0315
0.60	0.40	—	2.2451	0.9908
0.50	0.50	—	2.4064	0.9758
0.40	0.60	—	2.5697	0.9502
0.30	0.70	—	2.7330	0.9416
0.20	0.80	—	2.4735	0.9309
0.10	0.90	—	2.3209	0.9116
—	1.00	—	2.2882	0.8881
1.00	—	0.00	1.4425	1.1364
0.90	—	0.10	2.2635	1.1000
0.80	—	0.20	1.2379	1.0870
0.70	—	0.30	0.2866	1.0750
0.60	—	0.40	0.0501	1.0550
0.50	—	0.50	0.0195	1.0420
0.40	—	0.60	0.0072	1.0290
0.30	—	0.70	0.0036	1.0200
0.20	—	0.80	0.0028	1.0090
0.10	—	0.90	0.0020	0.9960
0.00	—	1.00	0.0004	0.9873
0.10	0.10	0.80	0.0022	1.0058
0.20	0.10	0.70	0.0059	1.0079
0.10	0.20	0.70	0.0058	0.9844
0.10	0.30	0.60	0.0354	0.9823
0.20	0.20	0.60	0.0178	1.0144
0.30	0.10	0.60	0.0149	1.0422
0.40	0.10	0.50	0.0395	1.0443
0.30	0.20	0.50	0.0699	1.0122
0.20	0.30	0.50	0.1094	0.9780
0.10	0.40	0.50	0.2006	0.9437
0.50	0.10	0.40	0.0607	1.0572
0.40	0.20	0.40	0.1306	1.0165
0.30	0.30	0.40	0.2746	0.9887
0.20	0.40	0.40	0.7166	0.9566
0.10	0.50	0.40	1.0297	0.9330
0.60	0.10	0.30	0.5803	1.0550
0.50	0.20	0.30	0.7028	1.0272
0.40	0.30	0.30	0.8164	0.9887
0.30	0.40	0.30	1.5156	0.9609
0.20	0.50	0.30	1.8407	0.9564
0.10	0.60	0.30	2.0682	0.9309
0.70	0.10	0.20	0.9826	1.0745
0.60	0.20	0.20	1.4497	1.0564
0.50	0.30	0.20	1.7217	1.0145
0.40	0.40	0.20	1.7397	0.9855
0.30	0.50	0.20	2.0192	0.9600
0.20	0.60	0.20	2.2320	0.9436
0.10	0.70	0.20	2.5951	0.9345
0.80	0.10	0.10	2.5716	1.0945
0.70	0.20	0.10	2.6806	1.0691
0.60	0.30	0.10	2.9280	1.0455
0.50	0.40	0.10	3.2792	1.0273
0.40	0.50	0.10	2.1975	0.9891
0.30	0.60	0.10	1.9701	0.9727
0.20	0.70	0.10	2.0926	0.9436
0.10	0.80	0.10	2.4165	0.9345

vent mixtures studied is observed in ethanol–PEG 600 (0.1+0.9 mass fractions) mixture.

The aqueous solubility of ibuprofen found in this work is 0.0004 M (or 0.00000672 in mole fraction) and is comparable with the corresponding values from the literature, *i.e.* 0.00038 M,[24] and is different from 0.00005478 M,[25] 0.0009430 M,[26] and 0.000043 M.[27] The solubility of ibuprofen in ethanol is 2.2882 M (or 0.2019 in mole fraction) which is in good agreement with 2.556 M,[13] and is slightly more than 0.1422 mole fraction.[28] The maximum solubility of ibuprofen (3.2792 M) in the solvent mixtures studied is observed in PEG 600–ethanol–water (0.5+0.4+0.1 mass frac-

tions) mixture.

There is no published experimental data of drugs in the investigated solvent mixtures. In two papers, the solubilities of acetaminophen in PEG 400–water at 23 °C,[24] and also in PEG 400–water and PEG 4000–water at 30 °C[29] have been reported. Figure 1 illustrates these solubility profiles. According to these papers, the solubility of acetaminophen was measured after 24 h equilibration time, however, because of high viscosity of PEG solutions, we believe that 24 h is not enough for equilibration. To confirm this hypothesis, the dissolution rate of acetaminophen in neat PEGs was investigated and shown in Fig. 2. The measured solubilities of acetaminophen in neat PEG 200 and PEG 400 at 25 °C after 72 h shaking in incubator were 1.30 M and 1.40 M for PEG 200 and PEG 400, respectively.

The Jouyban–Acree model fits very well to the experimental solubility data of drugs in binary solvent mixtures at all composition ranges of ethanol and PEG 600. The MRDs for back-calculated solubilities of acetaminophen in PEG 600–ethanol, ethanol–water and PEG 600–water are 2.4, 5.0 and 1.3%, with the overall MRD (OMRD) of 2.9%. The corresponding values for ibuprofen data are 1.5, 9.3 and 2.0%, respectively, with the OMRD of 4.3%. Also the model fits well to the experimental solubility of drugs in ternary solvents with given fractions of the cosolvents where the MRDs for acetaminophen and ibuprofen data are 16.8 and 22.4%, respectively. These findings are also supported by small MRD values of the back-calculated and experimental solubility data as shown in Table 3, in which the computed constants of the model were also listed. Although the produced MRDs are very low, especially for sub-binary solvents, it should be kept in mind that, the constants are computed using the solubility of acetaminophen and/or ibuprofen which need experimental efforts.

In a previous work, Eq. 1 was trained using experimental solubility of drugs in PEG 400–water mixtures and the obtained model was[30]:

$$\log C_{m,T} = w_1 \log C_{1,T} + w_2 \log C_{2,T} + \frac{w_1 w_2}{T}[394.82 - 355.28(w_1 - w_2) + 388.89(w_1 - w_2)^2] \quad (5)$$

In deriving Eq. 5, we assumed that the extents of solute–solvent interactions are the same for all solutes in PEG 400–water mixtures. Since ethylene glycols have similar structural features with PEG 400, therefore, it is expected that Eq. 5 is able to predict the solubility of drugs in aqueous mixtures of ethylene glycols and this hypothesis was examined in a previous work[31] and showed that the accurate predictions could be made using Eq. 5 for various aqueous mixtures of ethylene glycol and also polyethylene glycols in which the produced mean prediction error was <24%. Therefore, Eq. 5 should provide good predictions for the solubility of acetaminophen and ibuprofen in PEG 600–water mixtures. The produced MRDs were 12.0% and 65.5%, respectively for acetaminophen and ibuprofen.

As an alternative predictive method, the log-linear model of Yalkowsky[32] is a simple and well established cosolvency model providing reasonable predictions. The model required aqueous solubility of the drug ($\log C_{3,T}$) and its logarithm of partition coefficient ($\log P$) as input data. To our knowledge, there is no trained version of the log-linear model for PEG 600–water mixtures, however, the trained version of the model[33] for PEG 400–water data is available as:

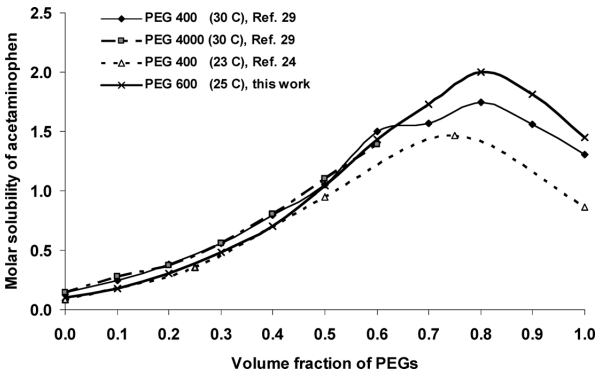

Fig. 1. Comparison of the Experimental Data Sets for the Solubility of Acetaminophen in PEGs–Water Mixtures

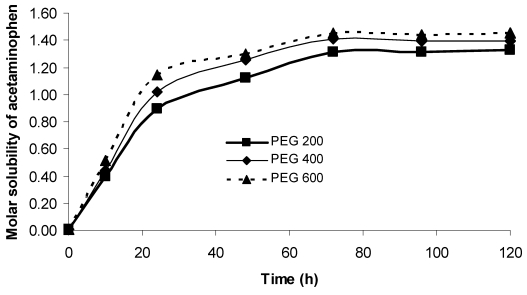

Fig. 2. Dissolution Rate of Acetaminophen in Neat PEG 200, PEG 400 and PEG 600

Table 3. The Constants of the Jouyban–Acree Model and the Mean Relative Deviations (MRD) for Solubility of Acetaminophen and Ibuprofen in Binary and Ternary Solvents

Drug	Solvent system	J_0	J_1	J_2	MRD %
Acetaminophen	PEG 600 (1)–Ethanol (2)	45.251	235.724	249.015	2.4
Acetaminophen	Ethanol (2)–water (3)	640.732	77.698	−324.630	5.0
Acetaminophen[a]	PEG 600 (1)–water (3)	525.292	178.743	110.225	1.3
Acetaminophen	PEG 600 (1)–Ethanol (2)–water (3)	317.46	[c]	[c]	16.8
Ibuprofen	PEG 600 (1)–Ethanol (2)	157.482	−39.780	−85.785	1.5
Ibuprofen[b]	PEG 600 (1)–water (3)	−174.520	652.899	2596.431	9.3
Ibuprofen	Ethanol (2)–water (3)	978.397	1119.209	−1152.574	2.0
Ibuprofen	PEG 600 (1)–Ethanol (2)–water (3)	3392.634	[c]	[c]	22.4

a) Solubility data taken from a previous work[11] and the reported volume fractions of the solvents were converted to mass fractions. *b*) Solubility data taken from a previous work.[12] *c*) Not significant.

$$\log C_{m,T}=\log C_{3,T}+(0.88+0.68\log P)w_1 \quad (6)$$

for ethylene glycol–water data as:

$$\log C_{m,T}=\log C_{3,T}+(0.68+3.37\log P)w_1 \quad (7)$$

and for ethanol–water data as:

$$\log C_{m,T}=\log C_{3,T}+(0.31+0.94\log P)w_1 \quad (8)$$

where in Eqs. 6—8, the term w_1 is the cosolvent mass fraction in the solvent mixture and $C_{3,T}$ is the aqueous solubility of the solute. For ternary solvent mixtures, Eq. 9 could be combined from Eqs. 6 and 8[33,34]

$$\log C_{m,T}=\log C_{3,T}+(0.88+0.68\log P)w_1+(0.31+0.94\log P)w_2 \quad (9)$$

The accuracy of Eq. 5 was also compared with those of Eqs. 6 and 7, and the results are given in Table 4. We can compare the results of the Eqs. 9 and 3 (with separate set of constants for each drug), where both of them are used for solubility prediction in ternary solvent mixtures and the OMRDs for them are 27.9% and 70.4%, respectively.

The trained version of Eq. 1[35]:

$$\log C_{m,T} = w_1 \log C_{1,T} + w_2 \log C_{2,T} + \frac{w_1 w_2}{T}[724.21 - 485.17(w_1 - w_2) + 194.21(w_1 - w_2)^2] \quad (10)$$

was used to predict the solubility of acetaminophen and ibuprofen in ethanol–water mixtures, in which the MRDs are 26.5% and 42.7%, respectively. The corresponding values for Eq. 7 were 58.3% and 73.3%.

Density of the saturated solutions is required in converting the molar solubilities to mole fraction solubilities. Any attempt to predict the density of the saturated solutions can save time and cost of the experimental efforts. In a previous paper,[36] the applicability of the Jouyban–Acree model for prediction of the density of liquid mixtures at various temperatures was investigated. The investigated liquid mixtures were solute free, so for showing the model applicability in predicting the density of the saturated solutions composed of liquid mixtures, first, the model was fitted to the density of saturated solutions (listed in Tables 1 and 2) of binary mixtures and the sub-binary constants were calculated for each system separately. Then by using these constants, the ternary model constants for ternary mixtures were obtained. With putting each constant in the Jouyban–Acree model, the den-

Table 4. Comparing the Mean Relative Deviations (MRD) of Jouyban–Acree Model and the Yalkowsky's Log-Linear Model for Solubility

Drug	MRD %		
		PEG 600–water	
	Eq. 5	Eq. 6	Eq. 7
Acetaminophen	12.0	42.2	58.3
Ibuprofen	65.5	41.2	75.2
		Ethanol–water	
	Eq. 8	Eq. 10	
Acetaminophen	55.4	44.3	
Ibuprofen	49.7	57.9	
		PEG 600–ethanol–water	
	Eq. 3	Eq. 9	
Acetaminophen	16.8	67.4	
Ibuprofen	22.4	75.5	

Table 5. Experimental Density Values for Solute Free Solvent Mixtures of Polyethylene Glycol 600 (1), Ethanol (2) and Water (3) at 25 °C

w_1	w_2	w_3	Density
1.00	0.00	—	1.1291
0.90	0.10	—	1.0939
0.80	0.20	—	1.0506
0.70	0.30	—	1.0073
0.60	0.40	—	0.9723
0.50	0.50	—	0.9332
0.40	0.60	—	0.9023
0.30	0.70	—	0.8755
0.20	0.80	—	0.8425
0.10	0.90	—	0.8137
0.00	1.00	—	0.7849
1.00	—	0.00	1.1291
0.90	—	0.10	1.1248
0.80	—	0.20	1.1186
0.70	—	0.30	1.1124
0.60	—	0.40	1.1042
0.50	—	0.50	1.0897
0.40	—	0.60	1.0691
0.30	—	0.70	1.0527
0.20	—	0.80	1.0321
0.10	—	0.90	1.0197
0.00	—	1.00	0.9837
—	0.00	1.00	0.9837
—	0.08	0.92	0.9750
—	0.17	0.83	0.9670
—	0.25	0.75	0.9540
—	0.35	0.65	0.9300
—	0.44	0.56	0.9120
—	0.54	0.46	0.8840
—	0.65	0.35	0.8650
—	0.76	0.24	0.8303
—	0.88	0.12	0.8110
—	1.00	0.00	0.7849
0.10	0.10	0.80	1.0038
0.20	0.10	0.70	1.0059
0.10	0.20	0.70	0.9824
0.10	0.30	0.60	0.9803
0.20	0.20	0.60	1.0123
0.30	0.10	0.60	1.0401
0.40	0.10	0.50	1.0422
0.30	0.20	0.50	1.0102
0.20	0.30	0.50	0.9760
0.10	0.40	0.50	0.9419
0.50	0.10	0.40	1.0550
0.40	0.20	0.40	1.0145
0.30	0.30	0.40	0.9867
0.20	0.40	0.40	0.9547
0.10	0.50	0.40	0.9312
0.60	0.10	0.30	1.0529
0.50	0.20	0.30	1.0251
0.40	0.30	0.30	0.9867
0.30	0.40	0.30	0.9589
0.20	0.50	0.30	0.9545
0.10	0.60	0.30	0.9290
0.70	0.10	0.20	1.0638
0.60	0.20	0.20	1.0458
0.50	0.30	0.20	1.0044
0.40	0.40	0.20	0.9756
0.30	0.50	0.20	0.9504
0.20	0.60	0.20	0.9342
0.10	0.70	0.20	0.9252
0.80	0.10	0.10	1.0836
0.70	0.20	0.10	1.0584
0.60	0.30	0.10	1.0350
0.50	0.40	0.10	1.0170
0.40	0.50	0.10	0.9792
0.30	0.60	0.10	0.9630
0.20	0.70	0.10	0.9342
0.10	0.80	0.10	0.9252

sity of the mixtures in both binary and ternary mixtures was back-calculated. The MRDs for binary and ternary mixtures were 0.5% and 2.9%, respectively, and the overall MRD was 1.7%.

The trained model using the density of drug free solutions (details of data listed in Table 5) for predicting the saturated density of solutions for acetaminophen and ibuprofen is:

$$\log \rho_{m,T} = w_1 \log \rho_{1,T} + w_2 \log \rho_{2,T} + w_3 \log \rho_{3,T} - 0.176 \frac{w_1 w_2}{T} + 1.409 \frac{w_1 w_3}{T} + \frac{w_2 w_3}{T}[0.899 - 0.931(w_2 - w_3)] + \frac{7.001 w_1 w_2 w_3}{T} \quad (11)$$

The predicted densities using Eq. 11 and experimental $\rho_{1,T}$, $\rho_{2,T}$ and $\rho_{3,T}$ of the saturated solutions were compared with the corresponding experimental values and the MRDs for densities of acetaminophen and ibuprofen were 3.5% and 3.2%, respectively. We used the predicted densities of the saturated solutions and the experimental densities for converting the molar solubility to the mole fraction solubility separately, and the results show that the OMRD between the mole fraction solubilities for this analysis was 2.2%, which is the acceptable MRD for using the predicted densities instance of the measured densities.

Conclusion

This work presented the experimental solubility data of acetaminophen and ibuprofen in binary mixtures of PEG 600, ethanol and water and their ternary mixtures at 25 °C. The data extended the present database of drugs solubility in water-cosolvent mixtures[5] and could also be used in solubilization investigations of drugs as liquid or soft gelatin capsule formulations.

The constants of the Jouyban–Acree model for binary and ternary solvent mixtures provided. These constants could be used to predict the solubility of drugs at different solvent compositions and also at various temperatures by employing the solubility data in mono-solvents. Generally the OMRDs observed in these predictions show that the Jouyban–Acree model provided more accurate predictions in the presence of the cosolvent in aqueous solution or combining two cosolvents. For the densities, according to the results, it's not necessary to measure the density of the all saturated solutions, and by measuring the density of the solute free solvent mixtures and with trained version of the Jouyban–Acree model, the density of the saturated solutions can be predicted within an acceptable MRD. The predicted densities can be used for converting the molar solubility to the mole fraction and the produced error is very small.

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References

1) Moore M. D., Wildfong P. L. D., *J. Pharm. Innov.*, **4**, 36—49 (2009).
2) Jouyban A., Fakhree M. A. A., Shayanfar A., *Recent Pat. Chem. Eng.*, **1**, 220—231 (2008).
3) Yalkowsky S. H., He Y., "Handbook of Aqueous Solubility Data," CRC Press, Boca Raton, 2003.
4) Jouyban A., *J. Pharm. Pharm. Sci.*, **11**, 32—58 (2008).
5) Jouyban A., "Handbook of Solubility Data For Pharmaceuticals," CRC Press, Boca Raton, 2009.
6) Lindenberg M., Kopp S., Dressman J. B., *Eur. J. Pharm. Biopharm.*, **58**, 265—278 (2004).
7) Harris J. M., "Poly(ethylene glycol) Chemistry, Biotechnical and Biomedical Applications," Plenum Press, New York, 1992.
8) Strickley R. G., *Pharm. Res.*, **21**, 201—230 (2004).
9) Rubino J. T., "Encyclopedia of Pharmaceutical Technology," ed. by Swarbrick J., Boylan J. C., Marcel Dekker, New York, 1990.
10) Nair R., Gonen S., Hoag S. W., *Int. J. Pharm.*, **240**, 11—22 (2002).
11) Jouyban A., Chan H. K., Chew N. Y. K., Khoubnasabjafari M., Acree W. E. Jr., *Chem. Pharm. Bull.*, **54**, 428—431 (2006).
12) Manrique J., Martínez F., *Lat. Am. J. Pharm.*, **26**, 344—354 (2007).
13) Pacheo D. P., Manrique Y. J., Martinez F., *Fluid Phase Equilib.*, **262**, 23—31 (2007).
14) Manzo R. H., Ahumada A. A., *J. Pharm. Sci.*, **79**, 1109—1115 (1990).
15) Chow Y. P., Repta A. J., *J. Pharm. Sci.*, **61**, 1454—1458 (1972).
16) Dearden J. C., Patel N. C., *Drug Dev. Ind. Pharm.*, **4**, 529—535 (1978).
17) Paruta A. N., Irani S. A., *J. Pharm. Sci.*, **54**, 1334—1338 (1965).
18) Walters V., *J. Pharm. Pharmacol.*, **20**, 228—231 (1968).
19) Bauguess C. T., Sadlik F., Fincher J. H., Hartman C. W., *J. Pharm. Sci.*, **64**, 117—120 (1975).
20) Dearden J. C., Collett J. H., Tomlinson E., *Experientia*, **23**, 37—40 (1976).
21) Kovach I. M., Pitman I. H., Higuchi T., *J. Pharm. Sci.*, **64**, 1070—1071 (1975).
22) Pitah J., Milecki J., Fales H., Uekama K., *Int. J. Pharm.*, **29**, 73—82 (1986).
23) Martinez F., *Acta Farm. Bonaerense*, **24**, 215—224 (2005).
24) Rytting E., Lentz K. A., Chen X. Q., Qian F., Venkatesh S., *AAPS J.*, **7**, E78—E105 (2005).
25) Chiarini A., Tartarini A., *Arch. Pharmazie*, **317**, 268—273 (1984).
26) Dwivedi S. K., Sattari S., Jamali F., Mitchell A. G., *Int. J. Pharm.*, **87**, 95—104 (1992).
27) Fini A., Laus M., Orienti I., Zecchi V., *J. Pharm. Sci.*, **75**, 23—25 (1986).
28) Bustamante P., Pena M. A., Barra J., *Int. J. Pharm.*, **194**, 117—124 (2000).
29) Prakongpan S., Nagai T., *Chem. Pharm. Bull.*, **32**, 340—343 (1984).
30) Jouyban A., *Chem. Pharm. Bull.*, **54**, 1561—1566 (2006).
31) Jouyban A., Soltanpour Sh., Tamizi E., *Pharmazie*, **63**, 548—550 (2008).
32) Yalkowsky S. H., Roseman T., "Solubilization of Drugs by Cosolvents," Marcel Dekker, New York, 1981.
33) Li A., Yalkowsky S. H., *Ind. Eng. Chem. Res.*, **37**, 4470—4475 (1998).
34) Wells J. I., "Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances," Halsted Press, New York, 1988.
35) Shayanfar A., Fakhree M. A. A., Acree Jr. W. E., Jouyban A., *J. Chem. Eng. Data*, **54**, 1107—1109 (2009).
36) Jouyban A., Fathi-Azarbayjani A., Khoubnasabjafari M., Acree Jr. W. E., *Ind. J. Chem. A*, **44**, 1553—1560 (2005).