Solubility Prediction of Paracetamol in Water–Ethanol–Propylene Glycol Mixtures at 25 and 30 °C Using Practical Approaches

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The solubility of paracetamol in water–ethanol–propylene glycol binary and ternary mixtures at 25 and 30 °C was determined using flask shake method. The generated data extended the solubility database for further computational investigations and also was used to assess the prediction capability of the Jouyban–Acree model. A new version of the model was proposed for modeling the solubility data in water–cosolvent mixtures with the cosolvent concentration of <50% which is required in pharmaceutical formulations. The accuracy of the predicted solubilities was evaluated by the mean percentage deviation (MPD) between the predicted and experimental solubilities. The overall MPD of the Jouyban–Acree model and the log-linear model of Yalkowsky for the entire composition range of the cosolvents were 11.0±8.7 and 55.4±17.8%, respectively; the corresponding values for the predicted solubilities in mixtures having a cosolvent concentration of <50% were 12.0±9.1 and 22.0±11.0%.

Key words paracetamol; binary solvent; ternary solvent; solubility prediction

Solubility of drugs is required in many stages of drug development process and numerous solubility enhancement methods including cosolvency, complexation, addition of surface active and hydrotrop agents have been used in the pharmaceutical industry. In addition to the experimental efforts to determine the solubility of drugs in water–cosolvent mixtures, a number of cosolvency models were proposed to calculate the solubility values. The proposed models range from the simplest log-linear model of Yalkowsky[1] to the relatively complicated flucuation model of Ruckenstein and Shulgin.[2] Most of the models are correlative and also require a number of physico-chemical properties of drugs which usually are not available.

Although a comprehensive cosolvency model should cover all solvent composition ranges from 0 to 100% of a cosolvent, the models covering the cosolvent compositions up to 50% are reported in the pharmaceutical literature. This approach is more interesting from a practical point of view since most of the pharmaceutical liquid formulations contain less than 50% cosolvents. The most practical and the simplest approach for the prediction of solubility in water–cosolvent mixtures containing less than 50% cosolvent is the log-linear model of Yalkowsky.[3]

The Jouyban–Acree model was developed by our group and was used to calculate many physico-chemical properties in mixed solvent systems including the electrophoretic mobility of analytes in mixed solvent electrolyte systems,[4] the instability rate constants in binary solvent systems,[5] the acid dissociation constants in water–organic solvent mixtures at a fixed[6] and various temperatures,[7] the capacity factor of analytes in HPLC,[8] the dielectric constant,[9] surface tension,[10] viscosity,[11] density,[12] solvatochromic parameter,[13] refractive index[14] and ultrasound velocity[15] in the solvent mixtures. The model provided reasonable predictions for the solubility of drugs in the aqueous mixtures of dioxane,[16] ethanol,[17] propylene glycol[18] and polyethylene glycol 400[19] mixtures and also for the solubility of drugs in a given water–cosolvent mixtures after training by the minimum number of experimental data points.

The aims of this work are to develop and evaluate the applicability of the Jouyban–Acree model to calculate the solubility of drugs in water–cosolvent mixtures of f_1 0.50—1.00. These calculations could be used in predicting the solubility at unmeasured solvent compositions and also in screening the experimentally determined solubilities to detect possible outliers for re-determination. To show these capabilities, the solubility of paracetamol, as a model drug, was determined in binary and ternary mixtures of water–ethanol–propylene glycol mixtures at 25 and 30 °C and the accuracy of the calculations was evaluated. The accuracy of the proposed method was also compared to that of the log-linear model of Yalkowsky.

Computational Methods The Jouyban–Acree model was proposed to calculate the solubility of drugs in water-cosolvent mixtures and provided good correlation capabilities.[20] Its basic form to calculate the solubility of a solute in a binary solvent mixture at various temperatures is:

$$\ln S_{m,T} = f_1 \ln S_{1,T} + f_2 \ln S_{2,T} + \frac{f_1 f_2}{T} \sum_{i=0}^{2} A_i (f_1 - f_2)^i \quad (1)$$

where $S_{m,T}$ is the solubility of the solute in solvent mixture at temperature T (K), f_1 and f_2 the volume fractions of solvents 1 and 2 in the absence of the solute, $S_{1,T}$ and $S_{2,T}$ the solubilities at temperature T in neat solvents 1 and 2, respectively, and A_i the solvent–solvent and solute–solvent interaction terms.[21]

The model is extended to Eq. 2 for calculating the solute solubility in ternary solvent mixtures[20] as:

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$$\ln S_{m,T} = f_1 \ln S_{1,T} + f_2 \ln S_{2,T} + f_3 \ln S_{3,T} + \frac{f_1 f_2}{T} \sum_{i=0}^{2} A_i (f_1 - f_2)^i + \frac{f_1 f_3}{T} \sum_{i=0}^{2} A_i' (f_1 - f_3)^i + \frac{f_2 f_3}{T} \sum_{i=0}^{2} A_i'' (f_2 - f_3)^i \quad (2)$$

where f_3 and $S_{3,T}$ are the volume fraction of the third solvent in the solvent mixture and the solute's solubility in the neat solvent 3, respectively, A_i' and A_i'' are the interaction parameters of the sub-binary systems. It has been shown that the addition of ternary solvent interaction terms improves the prediction capability of the Jouyban–Acree model[22] as:

$$\ln S_{m,T} = f_1 \ln S_{1,T} + f_2 \ln S_{2,T} + f_3 \ln S_{3,T} + \frac{f_1 f_2}{T} \sum_{i=0}^{2} A_i (f_1 - f_2)^i + \frac{f_1 f_3}{T} \sum_{i=0}^{2} A_i' (f_1 - f_3)^i + \frac{f_2 f_3}{T} \sum_{i=0}^{2} A_i'' (f_2 - f_3)^i + \frac{f_1 f_2 f_3}{T} \sum_{i=0}^{2} A_i''' (f_1 - f_2 - f_3)^i \quad (3)$$

The experimental solubility of paracetamol in water–ethanol, water–propylene glycol, ethanol–propylene glycol and water (1)–ethanol (2)–propylene glycol (3) mixtures at 25 °C taken from a previous work[20] was employed to compute the constants of the Jouyban–Acree model and the trained model was[20]:

$$\ln S_{m,T} = f_1 \ln S_{1,T} + f_2 \ln S_{2,T} + f_3 \ln S_{3,T} + \frac{1352.4 f_1 f_2}{T} - \frac{692.1 f_1 f_2 (f_1 - f_2)}{T} - \frac{556.5 f_1 f_2 (f_1 - f_2)^2}{T} + \frac{606.7 f_1 f_3}{T} - \frac{595.7 f_1 f_3 (f_1 - f_3)}{T} - \frac{136.8 f_1 f_3 (f_1 - f_3)^2}{T} + \frac{101.8 f_2 f_3}{T} - \frac{150.6 f_2 f_3 (f_2 - f_3)}{T} - \frac{181.3 f_2 f_3 (f_2 - f_3)^2}{T} + \frac{3398.8 f_1 f_2 f_3}{T} + \frac{2018.1 f_1 f_2 f_3 (f_1 - f_2 - f_3)}{T} \quad (4)$$

The model constants of Eq. 4 were calculated by regressing $(\log S_{m,T} - f_1 \log S_{1,T} - f_2 \log S_{2,T} - f_3 \log S_{3,T})$ against $\left(\frac{f_1 f_2}{T}\right)$, $\left(\frac{f_1 f_2 (f_1 - f_2)}{T}\right)$, $\left(\frac{f_1 f_2 (f_1 - f_2)^2}{T}\right)$, $\left(\frac{f_1 f_3}{T}\right)$, $\left(\frac{f_1 f_3 (f_1 - f_3)}{T}\right)$, $\left(\frac{f_1 f_3 (f_1 - f_3)^2}{T}\right)$, $\left(\frac{f_2 f_3}{T}\right)$, $\left(\frac{f_2 f_3 (f_2 - f_3)}{T}\right)$, $\left(\frac{f_2 f_3 (f_2 - f_3)^2}{T}\right)$, $\left(\frac{f_1 f_2 f_3}{T}\right)$ and $\left(\frac{f_1 f_2 f_3 (f_1 - f_2 - f_3)}{T}\right)$ using a no intercept least square analysis. As noticed above, the model was trained using previously reported data at 25 °C[20] and the required data for predicting the solubility of paracetamol at various temperatures are the solubility in mono-solvents.

Another predictive model from the literature is the trained versions of the log-linear model. The model for predicting the solubility of drugs in water–ethanol–propylene glycol mixtures is:

$$\ln S_m = \ln S_1 + (2.188 \log P + 0.691) f_2 + (1.796 \log P + 0.852) f_3 \quad (5)$$

where $\log P$ is the logarithm of octanol/water partition coefficient of the solute.[3] The $\log P$ value of paracetamol used in this work was 0.51.[23] Yalkowsky and his co-workers also proposed a second version of the model for predicting the solubility at the cosolvent concentrations of <50% as:

$$\ln S_m = \ln S_1 + (1.865 \log P + 2.625) f_2 + (1.267 \log P + 2.004) f_3 \quad (6)$$

The second version of the log-linear model is more useful, since, due to both toxicological and economical considerations, for most pharmaceuticals the cosolvent concentrations should be kept as low as possible.

The mean percentage deviations (MPD) were used to check the accuracy of the predicted data and was calculated using Eq. 7.

$$\text{MPD} = \frac{100}{N} \sum \frac{|\text{calculated} - \text{observed}|}{\text{observed}} \quad (7)$$

in which N is the number of experimental solubility data. All computations were carried out using SPSS software.

Results and Discussions

Figure 1 shows the molar solubility of paracetamol in water–ethanol mixtures at 25 and 30 °C. The paracetamol solubility in water–ethanol was increased with the increasing ethanol concentration until a maximum solubility is reached at 80% ethanol by volume. There is a good agreement between the solubility data of paracetamol in water–ethanol mixtures at 25 °C from this work and those reported in a previous paper.[20] The two solubility data at 30 °C and f_2=0.7 and f_2=0.8 are likely to be erroneous since the decreasing pattern is not confirmed by the other data sets. Considering the data at 30 °C, the general pattern of the solubility data from this work and a previous paper[24] is the same, however, there are some differences between two sets. A number of possible reasons for such observations has been discussed in a pervious report.[20] Figure 1 also depicts the reproduced solubility curves of paracetamol in water-ethanol at 25 and 30 °C by using Eq. 4 employing the experimental solubilities in neat water and ethanol as input values. It should be noted that different curves could be reproduced employing various S_1 and S_2 values. This point could be considered as an advantage of the Jouyban–Acree model which can be used for pre-

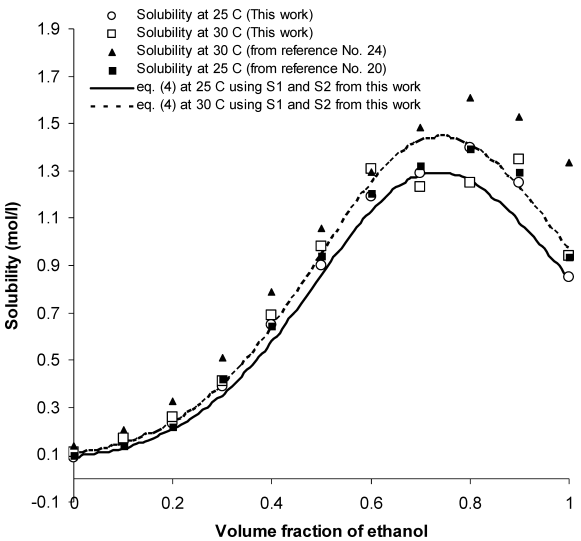

Fig. 1. The Experimental Solubility of Paracetamol in Water–Ethanol at 25 and 30 °C and the Reproduced Curves by Eq. 4 Employing the Experimental Solubilities in Water and Ethanol

dicting the solubility of different polymorphs of a drug in mixed solvents as shown in an earlier work.[25)]

Figure 2 shows the experimental solubility of paracetamol in water–propylene glycol at 25 °C from the literature[20)] and the same data at 25 and 30 °C from this work along with the reproduced curves by Eq. 4 and experimental solubilities in neat water and propylene glycol. There seem to be some deviation from the curve for the data points, the solubility in 90% and 100% of propylene glycol 30 °C. Testing the accuracy of the solubility prediction by Eq. 3 and extension of its prediction capability by addition of new solubility data and re-training enables us to provide accurate estimation tool for

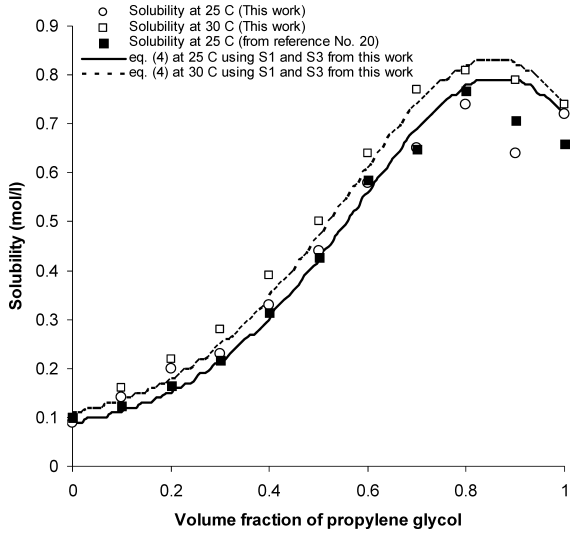

Fig. 2. The Experimental Solubility of Paracetamol in Water–Propylene Glycol at 25 and 30 °C and the Reproduced Curves by Eq. 4 Employing the Experimental Solubilities in Water and Propylene Glycol

solubility of the solutes at temperature of interest by determination of two data, *i.e.* S_1 and S_2. Using S_1 and S_2 values at two temperatures, it is possible to predict the solubility at other temperatures by an interpolation technique as shown in a previous paper.[26)]

The MPD of the generated and a number of collected data sets from the literature for the predicted solubilities using Eqs. 4 and 5 along with the temperature, the solubilities in neat solvents and number of data points in each set are summarized in Table 1. Equation 4 also produced accurate predictions at 20—40 °C. The minimum MPD for Eq. 4 was observed for the solubility of paracetamol in water–ethanol mixtures at 20 °C reported by Jimenez and Martinez[27)] and the maximum MPD was observed for water–propylene glycol mixtures at 25 °C and the overall MPD±S.D. was 10.9± 10.6% (N=125). The solubility of paracetamol was also predicted by Eq. 5 in the entire composition range where the overall MPD±S.D. was 64.1±29.7%. These results indicated that with using trained version of the Jouyban–Acree model, more accurate predictions could be achieved when the predictions were compared with those of Yalkowsky's model. However, one should keep in mind that the log-linear model of Yalkowsky requires one experimental data point (S_1) for prediction process, while the Jouyban–Acree model requires two data point, *i.e.* S_1 and S_2. We believe that the time that it takes for this one additional solubility determination is more than offset by the increased predictive accuracy. The accuracy of predictions was improved by more than 6 times.

As noticed earlier, for most pharmaceuitcal applications, the cosolvent concentration is <50% and Eq. 6 was proposed by Yalkowsky's group to provide such solubility predictions. To compare the accuracy of the models, the solubility at these solvent compositions was predicted using Eqs. 4 and 6 and the MPDs are also listed in Table 1. The overall

Table 1. The Mean Percentage Deviation (MPD) of the Predicted Solubilities of Paracetamol in Water–Cosolvent Mixtures for the Entire Composition Ranges and for Cosolvent Concentrations <50%; the Logarithms of Solubilities of Paracetamol in Water ($\ln S_1$), Ethanol ($\ln S_2$) and Propylene Glycol ($\ln S_3$), Expressed as Different Concentration Units at Temperature (t) and the References of Data

Solvent system	t (°C)	S (unit[a)])	$\ln S_1$	$\ln S_2$	$\ln S_3$	$N^{b)}$	MPD of Eq. 4	MPD of Eq. 5	$N^{b)}$	MPD of Eq. 4	MPD of Eq. 6	Reference
						The entire composition range			The cosolvent concentration <50%			
Water–ethanol	25	1	−2.41	−0.16	−0.33	11	7.8	55.5	6	9.4	26.2	This work
Water–propylene glycol	25	1	−2.41	−0.16	−0.33	11	9.0	36.5	6	9.9	15.9	This work
Water–ethanol–propylene glycol	25	1	−2.41	−0.16	−0.33	36	15.0	63.9	10	13.2	25.4	This work
Water–ethanol	30	1	−2.21	−0.06	−0.30	11	5.4	50.0	6	2.9	18.2	This work
Water–propylene glycol	30	1	−2.21	−0.06	−0.30	11	7.6	33.3	6	11.6	13.4	This work
Water–ethanol–propylene glycol	30	1	−2.21	−0.06	−0.30	36	11.4	61.5	10	8.0	27.1	This work
Water–ethanol	30	2	3.04	5.31	—	11	13.1	48.2	6	7.8	13.9	24
Water–ethanol	30	3	−6.17	−2.78	—	11	9.1	70.0	6	14.5	43.2	27
Water–ethanol	35	3	−5.97	−2.71	—	11	8.6	68.4	6	13.7	40.8	27
Water–ethanol	40	3	−5.76	−2.65	—	11	11.3	67.7	6	16.5	40.1	27
Water–propylene glycol	25	3	−6.35	—	−3.03	11	22.0	62.8	6	20.6	25.7	20
Water–ethanol	20	3	−6.35	−2.95	—	7	8.3	57.5	3	6.8	10.6	28
Water–ethanol	25	3	−6.27	−2.92	—	13	9.6	71.1	5	7.4	31.0	29
Water–ethanol	25	3	−6.26	−2.92	—	7	9.6	59.1	3	8.2	12.9	28
Water–ethanol	30	3	−6.07	−2.79	—	7	9.7	58.1	3	8.2	12.9	28
Water–ethanol	35	3	−5.94	−2.72	—	7	13.3	59.8	3	9.8	16.8	28
Water–ethanol	40	3	−5.87	−2.65	—	7	15.2	61.4	3	12.3	21.3	28
Water–ethanol	20	3	−6.49	−2.99	—	11	4.9	69.3	6	6.8	39.7	27
Water–ethanol	25	3	−6.29	−2.91	—	11	8.2	69.9	6	13.2	42.7	27

a) 1: mol/l; 2: mg/ml; 3: mole fraction. *b*) N is the number of data points in each set.

MPD±S.D. values for Eqs. 4 and 6 were 9.8±9.5 and 21.2±20.9%, respectively. Again an improvement was obtained using the Jouyban–Acree model by the expense of one additional experimental data point. Figure 3 shows the experimental solubility of paracetamol in water–ethanol mixtures at 25 °C and the curves reproduced by Eqs. 4, 5 and 6. Although Eq. 6 provides better predictions when compared with Eq. 5, its prediction capability is less accurate than the proposed Eq. 4.

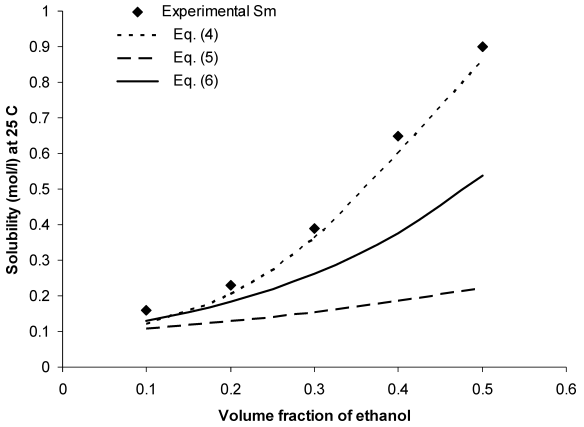

Fig. 3. Differences between Experimental Solubilities of Paracetamol in Water–Ethanol Mixtures at 25 °C (from This Work) and the Reproduced Curves by Eqs. 4, 5 and 6

Table 2 lists the experimental and predicted solubility values of paracetamol in ternary mixtures of water–ethanol–propylene glycol mixtures at 25 and 30 °C. The minimum percentage deviation (0.6%) between experimental and predicted values by Eq. 4 was observed for solvent composition of (f_1=0.1 : f_2=0.3 : f_3=0.6) at 25 °C and the maximum deviation was observed for (f_1=0.4 : f_2=0.3 : f_3=0.3) at 25 °C and the overall MPD±S.D. was 13.2±9.1% (N=72). The corresponding overall MPD±S.D. for Eq. 5 was 62.5±9.5%. The oveall MPD±S.D. for solvent compostions with cosolvents <50% for Eqs. 4 and 6 were 12.7±9.8 and 26.3±8.6%, respectively. Careful examination of the results reveal that the Jouyban–Acree model provides more accurate predictions in comparison with the log-linear model of Yalkowsky. Experimental paracetamol solubilities in the systems studied cover up to a 33-fold range when expressed as mole fractions.

In conclusion, it has been shown that a trained version of the Jouyban–Acree model is able to predict the solubility of paracetamol (as a model drug) in binary and ternary solvents at various temperatures and the prediction error is within an

Table 2. The Logarithms of Experimental Solubility of Paracetamol (mol/l) in Water (f_1)–Ethanol (f_2)–Propylene Glycol (f_3) Mixtures at 25 and 30 °C and the Predicted Solubilities Using Eqs. 4 and 5

f_1	f_2	f_3	$\ln S_{m,298.15\,K}$			$\ln S_{m,303.15\,K}$		
			Experimental	Eq. 4	Eq. 5	Experimental	Eq. 4	Eq. 5
0.8	0.1	0.1	−1.75	0.19	−2.05	−1.44	0.22	−1.87
0.7	0.2	0.1	−1.05	0.33	−1.87	−0.92	0.39	−1.69
0.6	0.3	0.1	−0.61	0.56	−1.69	−0.49	0.64	−1.51
0.5	0.4	0.1	−0.30	0.86	−1.51	−0.03	0.96	−1.33
0.4	0.5	0.1	0.07	1.14	−1.33	0.15	1.27	−1.15
0.3	0.6	0.1	0.22	1.30	−1.15	0.25	1.43	−0.96
0.2	0.7	0.1	0.42	1.26	−0.97	0.47	1.39	−0.78
0.1	0.8	0.1	0.45	1.06	−0.79	0.56	1.17	−0.60
0.7	0.1	0.2	−1.42	0.28	−1.87	−1.01	0.32	−1.69
0.6	0.2	0.2	−0.84	0.50	−1.69	−0.69	0.57	−1.51
0.5	0.3	0.2	−0.46	0.80	−1.51	−0.23	0.89	−1.33
0.4	0.4	0.2	−0.01	1.10	−1.33	0.02	1.22	−1.15
0.3	0.5	0.2	0.11	1.29	−1.15	0.23	1.41	−0.97
0.2	0.6	0.2	0.38	1.27	−0.97	0.43	1.39	−0.79
0.1	0.7	0.2	0.43	1.07	−0.79	0.52	1.17	−0.61
0.6	0.1	0.3	−0.98	0.41	−1.70	−0.83	0.46	−1.51
0.5	0.2	0.3	−0.54	0.70	−1.52	−0.46	0.77	−1.33
0.4	0.3	0.3	−0.34	1.02	−1.34	−0.01	1.12	−1.15
0.3	0.4	0.3	0.08	1.24	−1.15	0.15	1.35	−0.97
0.2	0.5	0.3	0.28	1.26	−0.97	0.42	1.37	−0.79
0.1	0.6	0.3	0.37	1.08	−0.79	0.40	1.17	−0.61
0.5	0.1	0.4	−0.66	0.56	−1.52	−0.49	0.62	−1.34
0.4	0.2	0.4	−0.41	0.88	−1.34	−0.12	0.96	−1.16
0.3	0.3	0.4	−0.06	1.14	−1.16	0.07	1.24	−0.98
0.2	0.4	0.4	0.19	1.22	−0.98	0.48	1.31	−0.80
0.1	0.5	0.4	0.25	1.09	−0.80	0.39	1.17	−0.62
0.4	0.1	0.5	−0.50	0.72	−1.34	−0.27	0.78	−1.16
0.3	0.2	0.5	−0.13	1.00	−1.16	0.02	1.08	−0.98
0.2	0.3	0.5	0.06	1.14	−0.98	0.10	1.22	−0.80
0.1	0.4	0.5	0.39	1.07	−0.80	0.28	1.14	−0.62
0.3	0.1	0.6	−0.20	0.85	−1.17	−0.18	0.91	−0.98
0.2	0.2	0.6	0.05	1.03	−0.99	0.06	1.10	−0.80
0.1	0.3	0.6	0.11	1.02	−0.81	0.07	1.08	−0.62
0.2	0.1	0.7	0.01	0.90	−0.99	−0.04	0.96	−0.81
0.1	0.2	0.7	0.05	0.95	−0.81	0.06	1.00	−0.63
0.1	0.1	0.8	0.02	0.87	−0.81	0.05	0.91	−0.63

acceptable range and these trained models could be recommended to the pharmaceutical industry for practical applications.

Experimental

Chemicals Paracetamol was a gift from Zahravi Pharmaceutical Company (Tabriz, Iran), propylene glycol and ethanol were purchased from Merck (Germany). Double distilled water was used throughout this study.

Solubility Measurements Sealed flasks containing an excess of paracetamol in the pure solvent and solvent mixtures were agitated at 25 ± 0.1 and 30 ± 0.1 °C in a temperature controlled shaker bath (Clifton, U.K.). The dissolution profile of the drug was monitored with time. When saturated solution was attained, the solid phase was removed by centrifugation followed by filtration (Durapore® membrane filters, type HV, 0.45 μm, Millipore, MA, U.S.A.). No significant adsorption of the drug was found on the filtration membranes. The clear solutions were diluted with ethanol and assayed by a double beam spectrophotometer (Shimadzo, Japan) at 245 nm. All the experimental results were averages of at least three replicates.

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