Solubility Prediction of Paracetamol in Binary and Ternary Solvent Mixtures Using Jouyban–Acree Model

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The Jouyban–Acree model has been used to predict the solubility of paracetamol in water–ethanol–propylene glycol binary and ternary mixtures based on model constants computed using a minimum number of solubility data of the solute in water–ethanol, water–propylene glycol and ethanol–propylene glycol binary mixtures. Three data points from each binary solvent system and solubilities in neat solvents were used to calculate the binary interaction parameters of the model. Then the solubility at other binary solvent compositions as well as in a number of ternary solvents were predicted, and the mean percentage deviation (±S.D.) of predicted values from experimental solubilities was 7.4(±6.1)%.

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

Solubility data of pharmaceuticals are crucial information for the pharmaceutical/chemical industries. Increased solute solubility is required in preparation of liquid drug formulations whereas decreased solubility is essential in crystalization of chemicals. It is well known that adding a cosolvent to the aqueous solution alters the solubility. However, when a binary solvent mixture is not able to dissolve the desired amount of a drug, addition of a second cosolvent is necessary. As a general rule, the higher the concentration of the cosolvent, the more is the increase in the solubility of the poorly soluble drug. However, because of toxicity and cost considerations, the concentration of the cosolvent should be kept as low as possible, and usually at less than 50% v/v of the liquid formulations.[1] The often used method to optimise the solvent composition of binary and/or ternary solvent mixtures is the trial and error approach which is time-consuming. In addition, in many cases at the early stage of a new drug development processes, the scarcity of the available amount of the drug is another limiting factor. An attempt has been made to reduce the number of required experimental data to facilitate the solubility prediction of drugs in mixed solvent systems.[2] In the previous work, the model constants of a solution model, so called Jouyban–Acree model, were computed using solubility data of anthracene in non-aqueous sub-binary solvent mixtures. Then the model constants were employed to predict the solubility of anthracene in the corresponding non-aqueous ternary solvent mixtures using an extended form of the Jouyban–Acree model. To check the applicability of the prediction method on a semi polar solute and polar solvent system (a real pharmaceutical cosolvency system), the solubility of widely used analgesic, paracetamol in water–ethanol, water–propylene glycol, ethanol–propylene glycol and a limited number of water–ethanol–propylene glycol mixtures were determined in the present study.

Experimental

Chemicals Paracetamol was obtained from Beigang Enterprises Group Corporation (Hyzhou, China), 1,4-dioxane (99% HPLC grade) and propylene glycol (99.5%) from Sigma-Aldrich (St. Louis, MO, U.S.A.), and ethanol (absolute, 99.5%, AR grade) from Selby Biolab (Victoria, Australia). MilliQ double deionised water was used throughout the study.

Solubility Measurements Sealed flasks containing an excess of paracetamol in the pure solvent and solvent mixtures were agitated at 25±0.1 °C in a temperature controlled shaker (Shake 'n' Stack hybridization oven, Hybaid Ltd., Middlesex, 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 (Hitachi, U-2000, Tokyo, Japan). The densities of the solutions were determined at 25±0.1 °C in a 5 ml pycnometer. All the experimental results were averages of at least three replicates. The relative standard deviation (RSD=S.D./mean×100) was less than 4% among replicated samples.

Computational Methods The Jouyban–Acree model was used to correlate different physico-chemical properties in mixed solvent systems as listed in a recent paper.[3] Its basic form to calculate the solubility of a solute in a binary solvent mixture is:

$$\ln X_m = f_1 \ln X_1 + f_2 \ln X_2 + f_1 f_2 \sum_{i=0}^{2} S_i (f_1 - f_2)^i \quad (1)$$

where X_m is the mole fraction solubility of the solute in solvent mixture, f_1 and f_2 the volume fractions of solvents 1 and 2 in the absence of the solute, X_1 and X_2 the mole fraction solubilities in neat solvents 1 and 2, respectively, and S_i the solvent–solvent and solute–solvent interaction terms[4] computed using a no-intercept least square analysis[5] for each binary solvent system. The S_i coefficients in Eq. 1 do have theoretical signficance in that each coefficient is a function of two-body and three-body interaction energies that describe the attactions between the various molecules in solution.[4] In the case of a solute dissolved in a binary solvent mixture, the basic thermodynamic model from which Eq. 1 was derived included all six possible two-body (1–1, 2–2, 3–3, 1–2, 1–3, 2–3) and all ten possible three-body (1–1–1, 2–2–2, 3–3–3, 1–1–2, 1–2–2, 1–1–3, 1–3–3, 2–2–3, 2–3–3, 1–2–3) molecular interactions between similar and dissimilar mixture components. Equation 1 was derived by differentiating the integral excess Gibbs energy of mixing equation for the ternary mixture containing components 1, 2 and 3, expressed in terms of the 16 fore-mentioned two-body and three-body interaction energies, with respect to the number of moles of solute. Raoult's law was used for the entropic contribution in the integral Gibbs energy of mixing equation. The complete derivation of Eq. 1 is given elsewhere,[4] and is not repeated here.

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

$$\ln X_m = f_1 \ln X_1 + f_2 \ln X_2 + f_3 \ln X_3 + f_1 f_2 \sum_{i=0}^{2} S_i (f_1 - f_2)^i + f_1 f_3 \sum_{i=0}^{2} S_i' (f_1 - f_3)^i + f_2 f_3 \sum_{i=0}^{2} S_i'' (f_2 - f_3)^i \quad (2)$$

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where f_3 and X_3 are the volume fraction of the third solvent in the solvent mixture and the solute's mole fraction solubility in the neat solvent 3, respectively, and S_i' and S_i'' are the interaction parameters of the next sub-binary systems. After calculating the sub-binary interaction terms using a minimum number of solubility data in binary solvents, the solubility in binary and ternary solvent mixtures was predicted. The mean percentage deviations (MPD) were used to check the accuracy of the prediction method and was calculated using Eq. 3.

$$\mathrm{MPD} = \frac{100}{N} \sum \frac{|\,\mathrm{calculated} - \mathrm{observed}\,|}{\mathrm{observed}} \tag{3}$$

in which N is the number of experimental solubility data. All computations were carried out using SPSS software.[6)]

Results and Discussion

Figure 1 shows the mole fraction solubility of paracetamol in binary solvent mixtures at 25 °C. The paracetamol solubility in water–propylene glycol and water–ethanol was increased with the amount of cosolvent until a maximum solubility is reached, whereas for ethanol–propylene glycol mixtures presence of the cosolvent produces only slight variations in the solubility. The solubility results of paracetamol in water–ethanol mixtures are similar to those published previously[7,8)] (see Fig. 2). The published aqueous solubility data (in mole fraction) of paracetamol were (0.001,[9)] 0.001915[7)]) as compared with the present result (0.001752). The possible reasons for the sligth difference in solubilities could be generally due to: a) solute and solvent purity, b) equilibration time, c) temperature variations during solubility study, d) analysis method, e) enantiomeric forms for chiral compounds,[10)] f) polymorphism[11)] and g) laboratory technique used. As additional evidence for the variability of solubility data, Kishi and Hashimoto[12)] summarized the solubility data of anthracene and fluoranthene from 17 different laboratories using a standard method from the environmental agency of Japan, and their results showed that even when all variables were kept constant, inter-laboratory differences were significant. The mean solubilities of anthracene and fluoranthene span 0.17 and 0.36 log unit with the MPD value being 51%.[12)] It is obvious that the ranges of individual solubilities are even greater where the range of logarithm of mol/l solubility for anthracene is −7.08 to −5.23. Further, the RSD values for the repeated experiments from the same laboratory were also high, *e.g.* 9.2%,[13)] 4.4%[14)] and 10%.[15)] To overcome these limitations, solubility prediction using a minimum number of experimental data could be a reasonable procedure. Experimental solubility (in gram per liter) of paracetamol in mixed solvent systems along with density values of saturated solutions were determined and listed in Tables 1—4. The data were converted to mol/l and mole fraction solubilities using conventional methods. Solubility of paracetamol in water is the lowest while the solubility in water–

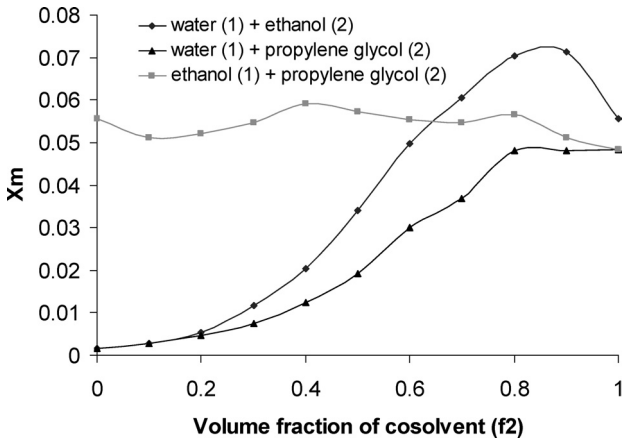

Fig. 1. The Mole Fraction Solubility (X_m) of Paracetamol in Binary Solvent Mixtures

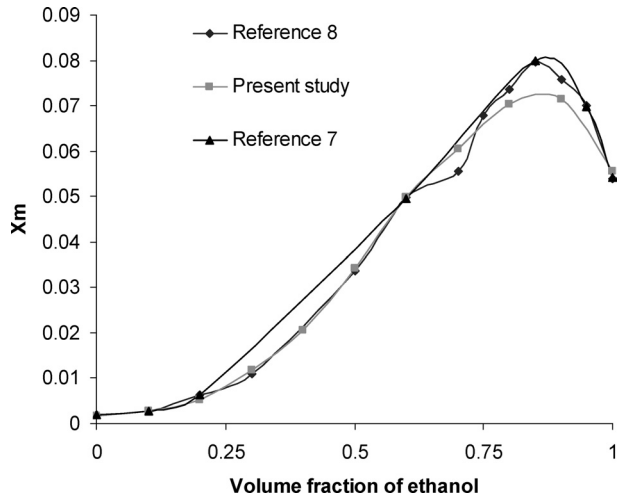

Fig. 2. Comparison of the Generated Data of Paracetamol in Water–Ethanol with the Published Data[7,8)]

Table 1. Experimental Solubility (S_m in g/l) of Paracetamol in Water (1)–Ethanol (2), the Relative Standard Deviation (RSD) of Three Repeated Solubility Measurements, the Density (ρ in g/cm^3) of the Saturated Solutions and Their Standard Deviations

f_1	S_m	RSD	ρ	S.D. of ρ
1.0	15.03	1.4	1.0350	0.0004
0.9	20.64	2.9	1.0230	0.0010
0.8	33.34	0.9	1.0127	0.0005
0.7	63.74	2.6	1.0067	0.0004
0.6	97.27	0.3	0.9990	0.0009
0.5	141.85	2.9	0.9920	0.0007
0.4	182.22	2.2	0.9827	0.0004
0.3	199.67	2.7	0.9710	0.0009
0.2	210.36	1.7	0.9523	0.0014
0.1	195.56	2.4	0.9233	0.0002
0.0	141.62	2.8	0.8750	0.0004

Table 2. Experimental Solubility (S_m in g/l) of Paracetamol in Water (1)–Propylene Glycol (3), the Relative Standard Deviation (RSD) of Three Repeated Solubility Measurements, the Density (ρ in g/cm^3) of the Saturated Solutions and Their Standard Deviations

f_1	S_m	RSD	ρ	S.D. of ρ
1.0	15.03	1.4	1.0350	0.0004
0.9	18.58	3.1	1.0443	0.0003
0.8	24.80	0.3	1.0543	0.0002
0.7	32.86	3.2	1.0633	0.0004
0.6	47.57	2.0	1.0733	0.0001
0.5	64.45	2.9	1.0817	0.0004
0.4	88.44	2.0	1.0897	0.0005
0.3	97.95	1.6	1.0933	0.0001
0.2	116.01	2.8	1.0950	0.0001
0.1	106.90	2.9	1.0927	0.0002
0.0	99.82	1.4	1.0883	0.0004

Table 3. Experimental Solubility (S_m in g/l) of Paracetamol in Ethanol (2)–Propylene Glycol (3), the Relative Standard Deviation (RSD) of Three Repeated Solubility Measurements, the Density (ρ in g/cm^3) of the Saturated Solutions and Their Standard Deviations

f_2	S_m	RSD	ρ	S.D. of ρ
1.0	141.62	2.8	0.8750	0.0002
0.9	127.88	1.7	0.8960	0.0003
0.8	126.42	2.0	0.9197	0.0006
0.7	129.36	0.5	0.9430	0.0001
0.6	135.51	2.3	0.9650	0.0001
0.5	129.22	1.2	0.9880	0.0002
0.4	122.29	2.0	1.0083	0.0002
0.3	118.63	1.5	1.0270	0.0011
0.2	120.04	2.1	1.0490	0.0002
0.1	107.32	3.3	1.0687	0.0003
0.0	99.82	1.4	1.0883	0.0002

Table 4. Experimental Solubility (S_m in g/l) of Paracetamol in Water (1)–Ethanol (2)–Propylene Glycol (3), the Relative Standard Deviation (RSD) of Three Repeated Solubility Measurements, the Density (ρ in g/cm^3) of the Saturated Solutions and Their Standard Deviations

f_1	f_2	f_3	S_m	RSD	ρ	S.D. of ρ
0.10	0.45	0.45	166.08	1.0	1.0090	0.0001
0.45	0.10	0.45	93.80	1.6	1.0683	0.0010
0.45	0.45	0.10	173.70	2.1	0.9977	0.0005

ethanol (10 : 90% v/v) is the highest value among the studied solvent systems.

The mole fraction solubility data of the solute in neat solvents 1—3 and three solubility data from each sub-binary solvent system with equal volume fraction intervals (*i.e.* f=0.3, 0.5, 0.7) were fitted to Eq. 2 and the model constants were computed. The obtained model is:

$$\begin{aligned}\ln X_m = &-6.347f_1 - 2.891f_2 - 3.029f_3 \\ &+4.965f_1f_2 - 1.568f_1f_2(f_1-f_2) - 1.532f_1f_2(f_1-f_2)^2 \\ &+2.969f_1f_3 - 1.631f_1f_3(f_1-f_3) - 1.156f_1f_3(f_1-f_3)^2 \\ &+0.402f_2f_3 - 0.334f_2f_3(f_2-f_3) - 0.874f_2f_3(f_2-f_3)^2 \end{aligned} \quad (4)$$

Equation 4 is able to predict the solubility of paracetamol in other solvent compositions of binary mixtures as well as ternary solvent systems. To check the practical applicability of the trained model, the solubility of paracetamol with f=0.1, 0.2, 0.4, 0.6, 0.8 and 0.9 in the binary and ternary solvent systems was predicted and compared with the corresponding experimental solubilities using MPD value. The MPDs for predicted solubilities of paracetamol in binary and ternary solvents were 5.8(±4.1)% (N=18) and 18.5(±7.4)% (N=3), respectively. Figure 3 shows the plot of predicted solubilities of paracetamol in ternary solvents *versus* experimentally obtained values and there was good agreement between predicted and experimental solubilities. The MPD for ternary solvents was relatively higher than binary data, however, one should keep in mind that the model is trained using binary data and no experimental data from ternary solvent mixtures have been used as training data. In other words, the model is completely predictive for solubility data of paracetamol in the ternary solvent mixture. The MPD of predicted solubilities in binary/ternary solvent mixtures was 7.4(±6.1)% (N=21) which is an acceptable error range in pharmaceutical applications.[16—18] One of the main disadvantages of least square methods is that the model constants is varied using different training data sets used, specially when the number of training points are limited. Beside this disadvantage, the prediction capability of the proposed model was not significantly changed when three other solubility data from each sub-binary solvent system (*i.e.* f=0.4, 0.6, 0.8) were used to train Eq. 2. The MPD of predicted solubilities in binary/ternary solvent mixtures was 9.2(±7.5)% (N=21) which was not significant difference between 7.4 and 9.2% obtained from two different training sets (paired t-test, $p>0.05$).

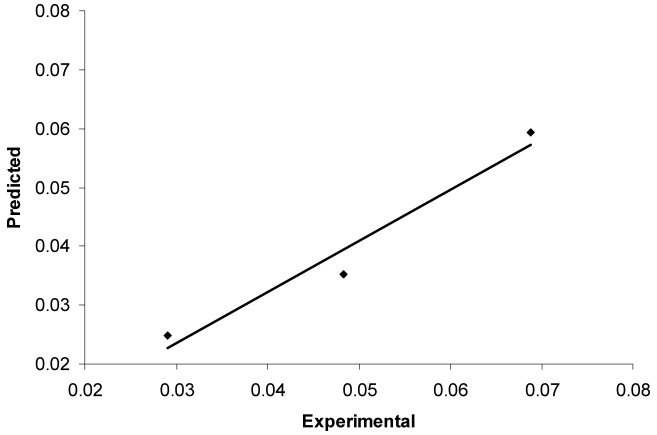

Fig. 3. Plot of the Experimental Solubility Data of Paracetamol in Water–Ethanol–Propylene Glycol *versus* Predicted Data Using Eq. 4

In order to show the applicability of the model in mol/l solubilities, the data were fitted to the model and the produced accuracy was not statistically different from that of fitting in the mole fraction solubilities. This is expected since the model contains a number of curve-fitting parameters that could be adjusted by any variations in the numerical values of the dependent and independent variables. Therefore, the aforementioned solubility data in mol/l were used to train the model and the resulted equation was:

$$\begin{aligned}\ln S_m = &-2.308f_1 - 0.065f_3 - 0.415f_3 \\ &+4.493f_1f_2 - 1.456f_1f_2(f_1-f_2) - 1.468f_1f_2(f_1-f_2)^2 \\ &+2.037f_1f_3 - 1.994f_1f_3(f_1-f_3) - 1.372f_1f_3(f_1-f_3)^2 \\ &+0.333f_2f_3 - 0.318f_2f_3(f_2-f_3) - 0.859f_2f_3(f_2-f_3)^2 \end{aligned} \quad (5)$$

where S_m is the solubility of the solute in mole per liter unit in the mixed solvent system. The produced MPD(±S.D.) for predicting solubility of paracetamol in mixed solvents in mol/l concentration unit was 7.7(±6.4)% (N=21) and since this prediction method does not require the density values, it is recommended for practical applications.

In conclusion, it has been shown that one could determine a minimum number of experimental solubility data in binary solvents, then predict the solubility in all solvent compositions of binary and also ternary solvents. The expected prediction error is found to be within an acceptable error range in pharmaceutical applications.

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