Faculty of Pharmacy and Drug Applied Research Center[1], Tabriz University of Medical Sciences, Tabriz, Iran, Faculty of Pharmacy[2], The University of Sydney, Sydney, Australia, Kimia Research Institute[3], Tabriz, Iran, Department of Chemistry[4], University of North Texas, Denton, USA

Solubility prediction of salicylic acid in water-ethanol-propylene glycol mixtures using the Jouyban-Acree model

A. Jouyban[1], N. Y. K. Chew[2], H. K. Chan[2], M. Khoubnasabjafari[3], W. E. Acree Jr[4]

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Dr. A. Jouyban, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran
ajouyban@hotmail.com

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To show the applicability of a solution model, i.e. the Jouyban-Acree model, for predicting the solubility of a solute in ternary solvent systems based on model constants computed using solubility data of the solute in binary solvent systems, the solubility of salicylic acid in water-ethanol, water-propylene glycol, ethanol-propylene glycol mixtures was determined. A minimum number of three data points from each binary system was used to calculate the binary interaction parameters of the model. Then the solubility in other binary solvent compositions and also in a number of ternary solvents was predicted, and the mean percentage deviation (MPD) was calculated as an accuracy criterion. The overall MPD ($\pm$SD) was 7.3 ($\pm$7.3)% and those of a similar predictive model was 15.7 ($\pm$11.5)%. The mean difference between the proposed and a previous model was statistically significant (paired t-test, $p < 0.004$).

1. Introduction

Solubility data of pharmaceuticals are required in many industrial processes including liquid drug formulations and adding a cosolvent to the aqueous solution is one of the most common methods to alter the solubility. 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 considerations and also the cost of the process, the concentration of the cosolvent should be kept as low as possible and usually less than 50% v/v of the liquid formulations (Rubino 1990). A method often used 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 first stages 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 experimental data required to facilitate the solubility prediction of drugs in mixed solvent systems (Jouyban et al. 2002). In the previous work, the model constants of a solution model, so called Jouyban-Acree model, were calculated using solubility data of anthracene in sub-binary solvent mixtures, and then the model constants were used to predict the solubility of anthracene in the corresponding ternary solvent mixtures using an extended form of the Jouyban-Acree model. Anthracene is a polycyclic aromatic hydrocarbon and relatively non-polar solute compared to drug molecules and the solvent systems employed were alkane and alkanol mixtures. The produced prediction percentage errors were 1.5 and 3.7%. The previous results on the accuracy of the Jouyban-Acree model on polar and semi-polar/non-polar systems showed that the higher the polarity of the system is, the higher is the error associated with the model (Barzegar-Jalali and Jouyban-Gh. 1996). Therefore, it is expected that the solubility prediction of a semi-polar drug molecule in a ternary aqueous solvent mixture based on model constants calculated using sub-binary solubility data produces a higher prediction error compared to the result of a similar work on anthracene solubility data. The solubilty of salicylic acid in binary solvent mixtures has been reported at 30.6 °C by Paruta et al. (1964), however, the data was for binary aqueous mixtures and no data has been reported for ethanol-propylene glycol mixtures so far. To check the applicability of the prediction method, the solubility of salicyclic acid in water-ethanol, water-propylene glycol, ethanol-propylene glycol and a limited number of water-ethanol-propylene glycol mixtures was determined as a model system. The accuracy of the proposed method was also compared with that of a previously published method by Williams and Amidon (1984).

2. Investigations, results and discussion

2.1. Computational methods

A solution model (i.e. the Jouyban-Acree model) was used to correlate different physico-chemical properties in mixed solvent systems which is briefly reviewed in a recent paper (Jouyban et al. 2005). Its basic form to calculate a solute solubility 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 (Acree 1992) computed using a no-intercept least square analysis (Jouyban-Gh. and Hanaee 1997) for each binary solvent system. The model is extended to Eq. (2) for calculating a solute solubility in ternary solvent mixtures (Jouyban et al. 2002) as:

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

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 binary experimental data, the solubility in mixed solvent systems were predicted using Eq. (2). The mean percentage deviations (MPD) were used to check the accuracy of the prediction method and is calculated using Eq. (3).

$$\text{MPD} = \frac{100}{N} \sum \frac{|\text{Calculated} - \text{Observed}|}{\text{Observed}} \quad (3)$$

in which N is the number of experimental solubility data.

2.2. Results and discussion

Experimentally determined solubility values of salicylic acid in mixed solvent systems along with density values of saturated solutions are listed in Tables 1–3. The data were converted to mol/L and mole fraction solubilities using conventional methods. Solubility of salicylic acid in neat water is the lowest and the solubility in water-ethanol (10 : 90% v/v) is the highest among the studied solvent systems. The maximum relative standard deviations for repeated solubility experiments at each solvent composition were ~3%.

All determined solubility data were fitted using Eq. (2) and the back-calculated solubilities were used to calculate MPD values. The correlation coefficient (R), F, p and MPD values of the correlation were 0.989, 139, < 0.0005 and 4.5%, respectively, revealing that the model is able to accurately correlate the data and could be used to simulate solubility in binary/ternary solvent mixtures. This analysis could be used to check the accuracy of a mathematical model for representation of experimental data and also to screen the collected experimental data for detecting possible outliers. Usually an outlier point produces very large percentage deviation from the overall mean value (i.e. MPD) and should be re-determined experimentally. The highest deviation among our collected data was 24% for solubility of salicylic acid in water-ethanol-propylene glycol (0.45 : 0.45 : 0.10), however, since the acceptable error range in solubility correlation is ~30% (Beerbower et al. 1984; Dickhut et al. 1991; Reillo et al. 1995), we considered the result to be acceptable.

To test the applicability of the proposed model to predict the solubility data of salicylic acid in mixed solvents, 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 and 0.7) were fitted to Eq. (2) and the model constants were calculated. The obtained model is:

$$\begin{aligned} \ln X_m = &- 8.339 f_1 - 2.045 f_2 - 1.991 f_3 + 4.386 f_1 f_2 \\ &- 5.041 f_1 f_2 (f_1 - f_2) - 5.439 f_1 f_2 (f_1 - f_2)^2 \\ &+ 0.533 f_1 f_3 - 3.808 f_1 f_3 (f_1 - f_3) \\ &- 0.667 f_1 f_3 (f_1 - f_3)^2 + 0.348 f_2 f_3 \\ &- 0.106 f_2 f_3 (f_2 - f_3) + 0.348 f_2 f_3 (f_2 - f_3)^2 \end{aligned} \quad (4)$$

Table 1: Experimental solubility (S_m in g/L) of salicylic acid in water (1)-ethanol (2), the relative standard deviation (RSD) of three repeated solubility measurements and the density (ρ in g/cm³) of the saturated solution

f_1	Sm	RSD	ρ
1.0	1.89	0.7	1.0337
0.9	2.39	0.3	1.0193
0.8	4.47	1.0	1.0060
0.7	11.17	1.1	0.9953
0.6	29.00	1.2	0.9890
0.5	66.48	2.1	0.9760
0.4	132.82	2.7	0.9730
0.3	191.28	2.2	0.9713
0.2	254.35	1.9	0.9630
0.1	305.32	0.9	0.9610
0.0	291.30	2.6	0.9443

Table 2: Experimental solubility (S_m in g/L) of salicylic acid in water (1)-propylene glycol (3), the relative standard deviation (RSD) of three repeated solubility measurements and the density (ρ in g/cm³) of the saturated solution

f_1	Sm	RSD	ρ
1.0	1.89	0.7	1.0337
0.9	2.40	1.7	1.0460
0.8	3.24	1.2	1.0510
0.7	5.24	2.1	1.0577
0.6	9.29	2.5	1.0680
0.5	20.36	2.7	1.0756
0.4	40.39	2.7	1.0850
0.3	75.52	3.0	1.0910
0.2	126.55	1.0	1.0990
0.1	187.63	1.2	1.1073
0.0	248.63	1.8	1.1150

Table 3: Experimental solubility (S_m in g/L) of salicylic acid in ethanol (2)-propylene glycol (3), the relative standard deviation (RSD) of three repeated solubility measurements and the density (ρ in g/cm³) of the saturated solution

f_2	Sm	RSD	ρ
1.0	291.30	2.6	0.9443
0.9	325.73	2.7	0.9647
0.8	314.35	3.1	0.9823
0.7	300.27	0.9	1.0037
0.6	298.28	2.9	1.0187
0.5	289.47	1.8	1.0370
0.4	306.26	1.8	1.0547
0.3	278.21	1.7	1.0690
0.2	261.25	0.8	1.0887
0.1	243.82	2.8	1.1010
0.0	248.63	1.8	1.1150

Equation (4) is able to predict the solubility of salicylic acid in other solvent compositions of binary solvents as well as the ternary solvent systems. To check the practical applicability of the trained model, the solubility of salicylic acid with $f = 0.1$, 0.2, 0.4, 0.6, 0.8 and 0.9 in these binary and ternary solvent systems were predicted and compared with the corresponding experimental solubilities using MPD value. The MPDs of predicted solubilities in water-ethanol, water-propylene glycol, ethanol-propylene glycol and water-ethanol-propylene glycol mixtures were 5.6 ($\pm$5.6, $N = 6$)%, 5.3 ($\pm$5.0, $N = 6$)%, 6.6 ($\pm$3.0, $N = 6$)% and 16.1 ($\pm$15.0, $N = 3$)%, respectively. The overall MPD for solubility of salicylic acid in binary/ternary solvent mixtures was 7.3 ($\pm$7.3)%.

Williams and Amidon (1984) proposed a method based on an excess free energy approach of Wohl to predict the mole fraction solubility of a solute in mixed solvent systems. Their model possesses a number of solvent-solvent interaction parameters calculated from vapor pressure data of solvent mixtures in the absence of the solute, and a number of solute-solvent interaction terms which should be determined using experimental solubility data of the solute in binary and also ternary solvent mixtures. In addition, the model requires the knowledge of molar volumes of the solvents and also the solute. The model is trained using the above mentioned training data points and one value (i.e. solubility of salicylic acid in solvent composition of $f_1 = 0.45$, $f_2 = 0.10$ and $f_3 = 0.45$) from the ternary mixture, the solvent-solvent interaction terms reported by Williams and Amidon (1984) and the molar volume data of the solvents and solute taken from the literature (Gadalla et al. 1987). The obtained equation is:

$$\begin{aligned}\ln X_m = &- 8.339f_1 - 2.045f_2 - 1.991f_3 \\ &- 1.138\left[f_1f_2(2f_1 + 2f_3 - 1)\left(\frac{V_s}{V_1}\right)\right] \\ &+ 0.9047\left[2f_1f_2(f_1 + f_3)\left(\frac{V_s}{V_2}\right)\right] \\ &- 0.1633\left[f_1f_3(2f_1 - 1)\left(\frac{V_s}{V_1}\right)\right] \\ &+ 0.5688\left[2f_1^2f_2\left(\frac{V_s}{V_3}\right)\right] \\ &+ 0.0828\left[f_2f_3(2f_3 - 1)\left(\frac{V_s}{V_3}\right)\right] \\ &- 0.0308\left[2f_2f_3^2\left(\frac{V_s}{V_2}\right)\right] + 0.1068[V_sf_1f_2f_3] \\ &+ 0.027[V_sf_1f_2] - 0.003[V_sf_1f_3] \\ &+ 0.006[V_sf_2f_3] - 0.038[V_sf_1f_2f_3] \qquad (5)\end{aligned}$$

where V is the molar volume, and subscripts 1–3 and s are solvents 1–3 and the solute, respectively. The model constants of the last line of Eq. (5) were calculated using training data points and others were taken from the reference by Williams and Amidon (1984). The solubility of salicylic acid in the studied binary/ternary solvents was predicted using Eq. (5) and the obtained overall MPD ($\pm$SD) was 15.7 ($\pm$11.5)%. The result of the paired t-test showed that the proposed method provided more accurate predictions than Eq. (5) at a significance level of less than 0.004. In addition to the less accuracy of Eq. (5), it requires a minimum number of experimental data points in ternary solvent systems, whereas the proposed method uses only solubility data in binary solvents.

Determination of density of the saturated solution needs further experimental efforts. 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 resulting equation was:

$$\begin{aligned}\ln S_m = &- 4.290f_1 + 0.746f_2 + 0.588f_3 + 4.163f_1f_2 \\ &- 4.916f_1f_2(f_1 - f_2) - 5.859f_1f_2(f_1 - f_2)^2 \\ &- 0.253f_1f_3 - 4.267f_1f_3(f_1 - f_3) \\ &- 0.993f_1f_3(f_1 - f_3)^2 + 0.292f_2f_3 \\ &+ 0.077f_2f_3(f_2 - f_3) + 0.301f_2f_3(f_2 - f_3)^2 \qquad (6)\end{aligned}$$

where S_m is the solubility of the solute in mol/L in the mixed solvent system. The produced overall MPD ($\pm$SD) for predicting solubility of salicylic acid in mixed solvents in mol/L concentration unit was 6.8 ($\pm$7.2)% and there was a significant difference between the overall MPDs obtained from mole fraction and mol/L concentration units, i.e. 7.3 and 6.8%, (paired t-test, $p < 0.007$). Therefore, since the latter prediction method produces more accurate predictions and 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 and the expected prediction error is $\sim$7% which is acceptable for pharmaceutical applications.

3. Experimental

3.1. Chemicals

Salicylic acid (Unilab, 99.5%) was obtained from Ajax (Sydney, Australia), 1,4-dioxane (99% HPLC grade) and propylene glycol (99.5%) from Sigma-Aldrich (St. Louis, MO), and ethanol (absolute, 99.5%, AR grade) from Selby Biolab (Victoria, Australia). MilliQ double deionised water was used throughout the study.

3.2. Solubility measurements

Sealed flasks containing an excess of drug powder in the pure solvent and solvent mixtures were shaken at 25$\pm$ 0.1 °C in a temperature controlled shaker (Shake 'n' Stack hybridization oven, Hybaid Ltd, Middlesex, UK). The dissolution profile of drugs was monitored with time. When a saturated solution was attained, the solid phase was removed first by centrifugation and subsequently by filtration (Durapore® membrane filters, type HV, 0.45 µm, Millipore, MA). No significant adsorption of the drug to the filtration membranes was found. The clear solutions were diluted with ethanol and assayed in a double beam spectrophotometer (Hitachi, U-2000, Tokyo, Japan). The densities of the solutions were determined at 25 $\pm$ 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 $\times$ 100) was within 2–3% among replicated samples.

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