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Solubility prediction of drugs in water-cosolvent mixtures using Abraham solvation parameters

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ABSTRACT - PURPOSE. To provide predictive cosolvency models, the Abraham solvation parameters of solutes and the solvent coefficients were combined with the Jouyban-Acree and the log-linear models. These models require two and one solubility data points to predict the solubility of drugs in water-cosolvent mixtures. *Ab initio* prediction methods also were employed and the results were discussed. **METHOD.** The Jouyban-Acree model constants were correlated with variables derived from the Abraham solvation parameters of solutes and the solvent coefficients to present quantitative structure property relationship (QSPR) models. The calculated model constants using the QSPR models were used to predict the solubility in water-cosolvent mixtures. The mean percentage deviation (MPD), average absolute error (AAE) and root mean square error (RMSE) criteria were calculated to show the accuracy of the predictions. **RESULTS.** The overall MPD (±SD) of the proposed method employing solubility data in mono-solvents, i.e. two data points for each set, was 18.5±12.0 which indicates an acceptable prediction error from the practical point of view. The best cosolvency model employing aqueous solubility data was produced overall MPD of 75.2±72.6. The overall MPD of the proposed *ab initio* method was 74.9±19.3%. The models produced the same accuracy pattern considering MPD, AAE and RMSE criteria. **CONCLUSION.** The proposed model employing two solubility data points for each set produced acceptable prediction error (≈18 %) and could be recommended for practical applications in pharmaceutical industry. MPD, AAE and RMSE criteria produced similar results considering various models. However, MPD criterion was preferred since its numerical values could be compared with experimental relative standard deviations for repeated experiments.

INTRODUCTION

Solubility of drugs in water-cosolvent mixtures could be mathematically represented using various models. These models cover from the pioneering and the simplest cosolvency model of Yalkowsky (1) to a relatively complex fluctuation model of Ruckenstein and Shulgin (2). Available cosolvency models have been reviewed and to address the diversity of the models, all models have been converted to a unified cosolvency model in a recent work (3). From these models, the log-linear equation of Yalkowsky has often been preferred, because of its simplicity and applicability in pharmaceutical industry where researchers are more interested in models requiring simple and easy computational operations.

Solubility prediction in water-cosolvent mixtures with an acceptable error range is one of the main goals of cosolvency modeling. The produced prediction errors for such models are relatively high and thus far, an accurate predictive model has not been proposed. Recently, trained versions of the Jouyban-Acree model has been presented for solubility prediction of drugs in water-dioxane (4), water-ethanol (5), water-propylene glycol (6) and water-polyethylene glycol 400 (7) mixtures. These prediction methods should be trained for each cosolvent and also require experimental solubility data of the drug in neat water and the cosolvent as input data. An *ab initio* prediction method (without using any experimentally determined data) for solubility of drugs in water-cosolvent mixtures is of great importance in drug discovery studies specially in the first stages which scarce amount of the drug/drug candidate is available and in some cases, the aqueous solubility is low and should be

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increased using solubilization techniques including cosolvency. The main task at this stage is to find a cosolvent suitable for dissolving the desired amount of the drug. The common method to address the task is the trial and error approach which is time consuming and costly. The aims of this work are to: 1) propose a general trained version of the Jouyban-Acree model for solubility prediction of drugs in water-cosolvent mixtures using solubility of the drug in mono-solvent systems, 2) represent prediction methods employing a single solubility datum using log-linear and Abraham models, 3) provide an *ab initio* solubility prediction method in water-cosolvent mixtures by using both the log-linear model of Yalkowsky with Abraham solvation model and 4) predict the optimum solvent composition of water-cosolvent mixtures dissolving the maximum amount of a drug using the proposed method. The applicability of the methods was checked using available solubility data of drugs in water-cosolvent mixtures expressed in mole/L, with known solubility in water, neat cosolvent, Abraham solvation parameters and also Abraham solvent coefficients.

COMPUTATIONAL METHODS

Solubility prediction using two solubility data points

The Jouyban-Acree model provided accurate solubility data in water-cosolvent mixtures and its model constants were computed for four commonly studied cosolvents (4-7). The Jouyban-Acree model is:

$$\log S_m = f_c \log S_c + f_w \log S_w + f_c f_w \sum_{i=0}^{2} \frac{J_i \left(f_c - f_w\right)^i}{T} \tag{1}$$

where S_m is the solute's solubility in water-cosolvent mixtures, f_c and f_w the volume fractions of cosolvent and water in the absence of the solute, S_c and S_w the solubilities in neat cosolvent and water, respectively, T is the absolute temperature (K) and J_i are the model constants. Table 1 listed the numerical values of J_0, J_1 and J_2, the number of solubility data sets (NDS) used in the training process of the model and the references. The numerical values of J_0-J_2 represent the extent of solute-solvent interactions in the solution. In a recent work (8), the J_0-J_2 terms were correlated to Abraham solvation parameters of the solutes and the solvent coefficients of water to solvent process (9).

The applicability of the method has been evaluated using 194 solubility data sets of five different chemicals in non-aqueous binary solvents and the predictions were in good agreement with the experimental solubilities. The basic quantitative structure property relationship (QSPR) was:

$$J_i = A_{0i} + A_{1i}(c_c - c_w)^2 + A_{2i}R_2(r_c - r_w)^2 + A_{3i}\pi_2^H(s_c - s_w)^2 + A_{4i}\sum\beta_2^H(b_c - b_w)^2 + A_{5i}V_X(v_c - v_w)^2 \tag{2}$$

The term $\sum\alpha_2^H\left(a_c - b_w\right)^2$ was omitted from the QSPR model, since $\sum\alpha_2^H$ of the studied chemicals were zero, however, the term could be added to equation 2 as:

$$J_i = A_{0i} + A_{1i}(c_c - c_w)^2 + A_{2i}R_2(r_c - r_w)^2 + A_{3i}\pi_2^H(s_c - s_w)^2 + A_{4i}\sum\alpha_2^H(a_c - a_w)^2 + A_{5i}\sum\beta_2^H(b_c - b_w)^2 + A_{6i}V_X(v_c - v_w)^2 \tag{3}$$

Table 1. Numerical values of the Jouyban-Acree model constants (J_0, J_1 and J_2) for commonly studied cosolvents, the number of data sets (NDS) employed in the training process of the model and the references.

Cosolvent	J_0	J_1	J_2	NDS	Reference
Dioxane	958.44	509.45	867.44	36	4
Ethanol	724.21	485.17	194.41	26	5
Polyethylene glycol 400	394.82	-355.28	388.89	79	7
Propylene glycol	37.03	319.49	-	27	6

where A terms were the model constants (8), c, r, s, a, b and v are the solvents coefficients, subscripts c and w denote cosolvent and water, respectively, R_2 is the excess molar refraction, π_2^H is dipolarity/polarizability of the solute, $\sum \alpha_2^H$ denotes the solute's hydrogen-bond acidity, $\sum \beta_2^H$ stands for the solute's hydrogen-bond basicity and V_X is the McGowan volume of the solute in unit of 0.01(cm^3/mole). The J_i (i.e., J_0, J_1 and J_2) terms of the studied solubility data sets were regressed against $(c_c - c_w)^2$, $R_2(r_c - r_w)^2$, $\pi_2^H(s_c - s_w)^2$, $\sum \alpha_2^H(a_c - a_w)^2$, $\sum \beta_2^H(b_c - b_w)^2$ and $V_X(v_c - v_w)^2$ values to compute $A_{j,i}$ terms, then the $A_{j,i}$ terms were replaced in equation 1 and the solubility of drugs in binary solvents were predicted employing experimental values of S_c and S_w.

Solubility prediction using aqueous solubility datum

The algebraic mixing rule (1) or log-linear model was expressed by:

$$\log S_m = f_c \log S_c + f_w \log S_w \tag{4}$$

and by replacing f_w with $(1-f_c)$, equation 4 could be re-written as:

$$\log S_m = \log S_w + f_c(\log S_c - \log S_w) \tag{5}$$

The term $(\log S_c - \log S_w)$ was called cosolvency power (σ) and was correlated to the logarithm of octanol-water partition coefficient of the solutes ($\log K_{ow}$) using:

$$\sigma = M \log K_{ow} + N \tag{6}$$

Where M and N are the model constants which are specific for the cosolvent and independent from the solute (10). The numerical values of M and N terms for the studied cosolvents are listed in Table 2. With known M and N terms along with S_w and $\log K_{ow}$ values, one can predict solubility of a drug in water-cosolvent mixtures.

The Abraham solvation parameter model provided a solubility prediction method for solutes dissolved in a wide variety of neat organic solvents (9, 11). The Abraham model employs five descriptors for each solute and six solvent coefficients that were computed for a number of common solvents (11). The basic model for processes within condensed phases is:

$$\log\left(\frac{S_c}{S_w}\right) = c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \sum \alpha_2^H + b \cdot \sum \beta_2^H + v \cdot V_X \tag{7}$$

The c, r, s, a, b and v (solvent's coefficients), which depend upon the solvent system under consideration. Numerical values of the coefficients have been reported in the literature (11) for several water-to-organic solvent systems. Equation 7 could be written as:

$$\log S_s - \log S_w = c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \sum \alpha_2^H + b \cdot \sum \beta_2^H + v \cdot V_X \tag{8}$$

Table 2. Numerical values of M, N and number of data sets (NDS) employed in the training process of the model (data taken from a reference (10)).

Cosolvent	M	N	NDS
Acetonitrile	1.16	-0.49	10
Dioxane	1.08	0.40	23
Ethanol	0.95	0.30	197
Methanol	0.89	0.36	79

Table 3. Details of experimental solubility data of solutes in water-cosolvent mixtures at various temperatures (t, °C), the logarithm of solubilities in neat cosolvent and water, the number of data points in each set (NDP), and the references

No.	Solute	Cosolvent	t (°C)	$\log S_c$	$\log S_w$	NDP	Reference
1	Aminopyrine	Ethanol	25	0.18	-0.64	11	15
2	Amobarbital	Ethanol	25	-0.01	-2.61	41	16
3	Antipyrine	Ethanol	25	0.52	0.35	11	15
4	Barbital	Ethanol	25	-0.30	-1.40	41	16
5	Benzocaine	Dioxane	5	-0.21	-2.70	11	17
6	Benzocaine	Dioxane	10	0.06	-2.52	11	17
7	Benzocaine	Dioxane	15	0.20	-2.40	11	17
8	Benzocaine	Dioxane	20	0.28	-2.39	11	17
9	Benzocaine	Dioxane	25	0.46	-2.25	9	17
10	Benzocaine	Dioxane	30	0.52	-2.15	8	17
11	Benzocaine	Dioxane	35	0.58	-2.01	8	17
12	Benzocaine	Dioxane	40	0.66	-2.00	7	17
13	Caffeine	Dioxane	25	-0.89	-1.00	16	18
14	Diazepam	Ethanol	30	-0.91	-3.74	11	19
15	Furosemide	Ethanol	25	-1.37	-3.89	13	20
16	Meloxicam	Ethanol	25	-0.45	-1.92	8	21
17	Metharbital	Ethanol	25	-0.67	-2.00	41	16
18	Pentobarbital	Ethanol	25	0.04	-2.66	40	16
19	Phenobarbital	Ethanol	25	-0.29	-2.29	41	16
20	Phenytoin	Ethanol	25	-1.23	-4.09	11	22
21	Phenytoin	Methanol	25	-1.03	-4.09	11	22
22	Salicylic acid	Dioxane	10	0.41	-2.10	11	17
23	Salicylic acid	Dioxane	20	0.49	-1.96	11	17
24	Salicylic acid	Dioxane	25	0.57	-1.92	8	17
25	Salicylic acid	Dioxane	30	0.60	-1.82	8	17
26	Salicylic acid	Dioxane	35	0.64	-1.77	8	17
27	Salicylic acid	Dioxane	40	0.67	-1.70	8	17
28	Salicylic acid	Ethanol	25	0.32	-1.86	11	23
29	Theophylline	Acetonitrile	25	-2.09	-1.47	17	24
30	Theophylline	Methanol	25	-1.48	-1.47	13	24

Table 4. Details of solutes Abraham solvation parameters, melting point (MP) and logarithm of partition coefficient ($\log K_{ow}$) of the solutes studied with their references

No.[a]	R_2	π_2^H	$\sum\alpha_2^H$	$\sum\beta_2^H$	Vx	Reference for solvation parameters	mp (°C)	$\log K_{ow}$	Reference for $\log K_{ow}$ values
1	1.780	1.780	0.000	1.370	1.870	25	108.0	0.90	26
2	1.030	1.110	0.470	1.230	1.797	27	157.0	2.07	26
3	1.530	1.580	0.000	1.050	1.480	25	111.5	0.23	14
4	1.030	1.140	0.470	1.180	1.374	27	189.0	0.65	26
5	1.034	1.040	0.320	0.820	1.313	27	89.0	1.97	28
6	1.034	1.040	0.320	0.820	1.313	27	89.0	1.97	28
7	1.034	1.040	0.320	0.820	1.313	27	89.0	1.97	28
8	1.034	1.040	0.320	0.820	1.313	27	89.0	1.97	28
9	1.034	1.040	0.320	0.820	1.313	27	89.0	1.97	28

Table 4 continued:

10	1.034	1.040	0.320	0.820	1.313	27	89.0	1.97	28
11	1.034	1.040	0.320	0.820	1.313	27	89.0	1.97	28
12	1.034	1.040	0.320	0.820	1.313	27	89.0	1.97	28
13	1.940	1.810	0.000	1.470	1.360	25	238.0	-0.07	28
14	2.380	2.110	0.000	1.150	2.070	25	125.5	2.99	29
15	2.050	2.550	1.360	1.470	2.100	25	206.0	1.51	29
16	2.880	3.570	0.580	1.910	2.320	25	254.0	2.80	29
17	1.092	1.160	0.210	1.190	1.515	27	150.5	1.14	26
18	1.630	1.800	0.730	1.150	1.700	27	129.5	2.07	26
19	1.030	1.110	0.470	1.230	1.797	27	174.0	1.47	26
20	1.713	2.190	0.850	1.000	1.869	25	295.0	2.47	26
21	1.713	2.190	0.850	1.000	1.869	25	295.0	2.47	26
22	1.050	0.890	0.720	0.380	0.990	25	158.0	2.24	28
23	1.050	0.890	0.720	0.380	0.990	25	158.0	2.24	28
24	1.050	0.890	0.720	0.380	0.990	25	158.0	2.24	28
25	1.050	0.890	0.720	0.380	0.990	25	158.0	2.24	28
26	1.050	0.890	0.720	0.380	0.990	25	158.0	2.24	28
27	1.050	0.890	0.720	0.380	0.990	25	158.0	2.24	28
28	1.050	0.890	0.720	0.380	0.990	25	158.0	2.24	28
29	1.930	1.840	0.420	1.380	1.220	25	272.5	-0.02	26
30	1.930	1.840	0.420	1.380	1.220	25	272.5	-0.02	26

[a] Details of data sets are the same as Table 3.

Table 5. The coefficients of equation 7 taken from a reference (11)

Solvent	c	e	s	a	b	v
Acetonitrile	0.413	0.077	0.326	-1.566	-4.391	3.364
Dioxane	0.098	0.350	-0.083	-0.556	-4.826	4.172
Ethanol	0.208	0.409	-0.959	0.186	-3.645	3.928
Methanol	0.329	0.299	-0.671	0.080	-3.389	3.512
Water	-0.994	0.577	2.549	3.813	4.841	-0.869

By replacing right hand side of equation 8 with the parenthesis term of equation 5:

$$\log S_m = \log S_w + f_c\left(c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \sum \alpha_2^H + b \cdot \sum \beta_2^H + v \cdot V_X\right) \quad (9)$$

and using equation 9, it is possible to predict solubility of solutes in water-cosolvent mixtures employing aqueous solubility of the drug.

Ab initio solubility prediction

Variuos equations were reported to predict aqueous solubility of drugs including the general solubility equation (GSE) of Yalkowsky and Valvani (12) and the amended solvation energy relationship (ASER) of Abraham and Le (13). The GSE and ASER are:

$$\log S_w = 0.5 - 0.01(mp - 25) - \log K_{ow} \quad (10)$$

$$\log S_w = 0.518 - 1.004 R_2 + 0.771 \pi_2^H + 2.168 \sum \alpha_2^H + 4.238 \sum \beta_2^H - 3.362 \sum \alpha_2^H \sum \beta_2^H - 3.987 V_X \quad (11)$$

where mp is the melting point of the solute (°C). An updated version of ASER (UASER) was presented by Stovall et al. (11) as:

$$\log S_w = 0.395 - 0.955 R_2 + 0.320 \pi_2^H + 1.155 \sum \alpha_2^H + 3.255 \sum \beta_2^H - 0.785 \sum \alpha_2^H \sum \beta_2^H - 3.330 V_X \quad (12).$$

The log S_w term of equations 5 and 9 could be predicted using equations 7, 11 and/or 12, and it is possible to employ the models as an *ab initio* method. In addition, mean predicted solubility (MPS) of drugs in water is also checked for providing better predictions.

Accuracy criteria

The accuracies of the GSE and ASER have been compared (14) using the average absolute error (AAE) and the root mean square error (RMSE) criteria defined as:

$$AAE = \frac{\sum \left| \log S_{Calculated} - \log S_{Observed} \right|}{NDP}$$

$$RMSE = \sqrt{\frac{\sum \left(\log S_{Calculated} - \log S_{Observed} \right)^2}{NDP}}$$

in which NDP is the number of solubility data points. Yang et al. (14) compared the GSE and ASER models employing aqueous solubility of 664 organic compounds and found that both models produced comparable accuracies. The AAE and RMSE of GSE were 0.45 and 0.62, respectively, and those of the UASER were 0.43 and 0.62. It has also been concluded that the mean predicted $\log S_w$ provided better predictions as the AAE and RMSE of the mean predicted $\log S_w$ were 0.38 and 0.53 (14).

The mean percentage deviation (MPD) is also used to check the accuracy of the prediction methods in this work and is calculated using:

$$MPD = \frac{100}{NDP} \sum \left(\frac{| S_{Calculated} - S_{Observed} |}{S_{Observed}} \right)$$

MPD values are comparable with experimental relative standard deviation (RSD) values for repeated experiments, therefore, we prefer to use MPD criterion. However, to compare the accuracy of the proposed method with the accuracies of GSE and ASER methods, AAE and RMSE criteria were also computed for predicted solubilities in this work.

Results

Solubility prediction using two solubility data points

The 30 available data sets (15-24) of drug solubilities in mole/L unit (for details and the required parameters (11, 25-29) see Tables 3-5), were fitted to equation 1 for computing the numerical values of J_0-J_2 and then these constants were used to calculate the model constants of the proposed QSPR model (i.e. equation 3). The resulted QSPR models for predicting J_0-J_2 are as:

$$J_0 = 2113.119 - 1093.783(c_c - c_w)^2 + 3380.661 R_2 (r_c - r_w)^2 - 13.865 \pi_2^H (s_c - s_w)^2 - 4.921 \sum \alpha_2^H (a_c - a_w)^2 - 5.659 \sum \beta_2^H (b_c - b_w)^2 + 15.250 V_X (v_c - v_w)^2$$

(13)

$$J_1 = -2001.561 + 1142.780(c_c - c_w)^2 - 2735.160 R_2 (r_c - r_w)^2 - 38.541 \pi_2^H (s_c - s_w)^2 + 13.176 \sum \alpha_2^H (a_c - a_w)^2 + 0.811 \sum \beta_2^H (b_c - b_w)^2 + 38.508 V_X (v_c - v_w)^2$$

(14)

$$J_2 = 1474.963 - 1507.479(c_c - c_w)^2 + 4421.302 R_2 (r_c - r_w)^2 + 17.981 \pi_2^H (s_c - s_w)^2 - 21.196 \sum \alpha_2^H (a_c - a_w)^2 + 6.595 \sum \beta_2^H (b_c - b_w)^2 - 13.386 V_X (v_c - v_w)^2$$

(15).

Using equations 13-15, J_0-J_2 could be easily predicted employing solute's Abraham parameters and solvent coefficients. To check the accuracy of the proposed QSPRs for computing solubility data of drugs, the calculated J_0-J_2 constants for each data set along with the experimental solubility data of the drug in water and neat cosolvent were used to calculate the solubility in water-cosolvent mixtures and the results of MPDs were listed in Table 6. The best results (2.6 %) was found for metharbital in water-ethanol mixtures, the wrost one (66.2 %) was for antipyrine in water-ethanol mixtures and the overall MPD (±SD) was 18.5 (±12.0). The overall MPD (±SD) was reduced to 16.8 (±8.1) after excluding MPD of antipyrine (see column 2 of Table 6). Figure 1 showed the relative frequency of residuals for the models studied and the Jouyban-Acree model provided the best residual distribution as all residuals were in the range of -0.5 to 0.25.

As noted in Introduction, prediction of the solvent composition ($f_{c,max}$) providing the maximum solubility ($S_{m, max}$) is crucial for preformulation studies. The proposed method is able to predict the volume fraction of the cosolvent to achieve the maximum solubility in a water-cosolvent mixture. Table 7 listed the experimentally observed and predicted $f_{c, max}$ using the Jouyban-Acree model.

Solubility prediction using aqueous solubility datum

In searching the pharmaceutical literature, different aqueous solubility and logP values were found for some solutes. The possible reasons for different aqueous solubilities could be: 1) solute purity; 2) insufficient equilibration time; 3) uncontrolled temperatures during solubility measurement; 4) analysis method employed; 5) laboratory techniques used; 6) typographical errors in reporting data; 7) polymorphism (30) and 8) enantiomeric forms of a solute (31). The impact of different S_w and logP values of the solutes on the solubility prediction in water-cosolvent mixtures is also studied by computing MPDs.

The commonly used single point solubility prediction method in water-cosolvent mixtures is the log-linear model of Yalkowsky (equation 5) in combination with the cosolvency power approach (equation 6). The minimum MPD (33.7 %) was observed for metharbital in water-ethanol mixtures and the maximum MPD (804.3 %) was for meloxicam in water-ethanol mixtures. The overall MPD of this numerical analysis after excluding MPD of meloxicam was 51.6 (± 8.6) % (see column 3 of Table 6).

Equation 9 produced the lowest MPD of 28.2 % for phenobarbital in water-ethanol mixtures, and the highest MPD of 451.2 % for antipyrine in water-ethanol mixtures. This data set produced reasonable results for other numerical methods including *ab initio* method and this observation means that there is an error in $\log S_w$ of antipyrine. To confirm this assumption, various available $\log S_w$ were used to predict the solubilities in water-ethanol mixtures; with $\log S_w=0.7$ (14) MPD was 1104.7, $\log S_w=-0.6$ (32) MPD was 69.2, $\log S_w=-0.56$ (25) MPD was 69.2 and $\log S_w=0.48$ (33) MPD was 627.4 %. To avoid any bias, the MPD of antipyrine (451.2 %) was excluded from computing overall MPD and the obtained MPD (±SD) was 62.2 (±15.2) % (see column 4 of Table 6).

Ab initio solubility prediction

Predicted aqueous solubility of drugs using GSE, ASER, UASER and their mean predicted solubilities (MPS) were used to compute the MPD values and listed in Table 8. Although GSE, ASER, UASER and MPS were developed to calculate aqueous solubility at 25 °C, there were no significant differences between the MPDs for all temperatures studied and those at 25 °C as shown in the last rows of Table 8. A possible reason for such an observation should be underestimated aqueous solubilities using the mentioned models.

The predicted aqueous solubilities using GSE, ASER, UASER and MPS were employed to predict the solubility of drugs in water-cosolvent mixtures using equation 9. As noted above, using this method, no experimental solubility data is required to predict the solubility in water-cosolvent mixtures and the knowledge of melting point, logP and Abraham solvation parameters are required. The minimum and maximum MPD of predicted solubilities using equation 9 and GSE were 38.9 and 660.6 % respectively for metharbital and furosemide in water-ethanol mixtures (see column 5 of table 6). Different $\log K_{ow}$ values of furosemide were found in the literature and as it is expected, these values affected the predicted solubilities using GSE. Using $\log K_{ow}=2.6$ (34) produced MPD was 53.3 % for furosemide. The overall MPD after excluding furosemide data was 81.5 (±15.4).

Predicted aqueous solubilities of drugs using ASER were used to predict the solubility of drugs in water-cosolvent mixtures and the MPD range was 47.9-964.2 %. More details of this analysis were not reported in this work. The UASER and equation 9 was used to predict solubility in water-cosolvent mixtures and the minimum (35.7) and maximum (459.4) MPDs were observed for phenobarbital and meloxicam in water-ethanol mixtures. The overall MPD (±SD) after excluding the meloxicam MPD was 111.1 (± 92.0) % (see column 6 of Table 6).

Table 6. The number of required experimental data for various models, the mean precentage deviations (MPDs), overall MPD, standard deviations (SD) for all data sets and after exclusion of a data set producing the maximum MPD for each model

No.[a]	Jouyban-Acree $+S_c+S_w$	Cosolvency power + S_w	Equation 9+ S_w	Equation 9 + GSE	Equation 9 + UASER	Equation 9 + MPS
1	21.8	40.0	93.8	64.5	97.7	87.0
2	12.4	57.1	58.1	76.4	80.3	58.1
3	66.2	60.6	451.2	69.2	98.0	88.1
4	6.7	42.9	51.8	80.0	78.4	45.2
5	23.2	64.0	78.7	82.3	144.5	114.5
6	17.5	60.3	76.6	80.2	113.6	100.7
7	13.2	59.2	76.6	74.0	92.0	85.2
8	12.1	64.3	79.3	77.6	86.8	83.1
9	5.1	58.3	74.5	73.2	81.1	77.9
10	7.8	52.7	71.1	70.1	72.1	70.1
11	15.5	44.8	67.3	67.2	66.8	65.8
12	9.5	48.1	68.8	68.5	67.2	67.3
13	19.3	54.2	82.1	95.1	74.7	69.3
14	23.4	47.2	47.1	72.8	83.4	52.3
15	31.7	53.9	53.8	660.6	459.4	68.5
16	14.7	804.3	73.6	99.9	97.4	99.4
17	2.6	33.7	44.1	38.9	120.1	95.0
18	28.4	68.5	77.2	76.4	72.4	76.2
19	15.0	51.9	28.2	46.5	35.7	36.6
20	20.6	52.8	52.1	87.3	279.5	51.8
21	35.3	43.8	41.3	84.3	367.2	44.6
22	25.3	50.7	62.4	97.2	52.3	68.7
23	17.8	52.6	61.6	97.4	51.8	74.9
24	13.9	48.2	57.2	97.0	49.5	73.4
25	14.4	49.0	54.0	97.1	51.0	76.2
26	15.2	51.2	54.4	97.1	54.2	78.4
27	16.3	54.9	54.1	97.2	60.7	80.8
28	25.9	35.7	35.8	94.4	43.4	51.3
29	3.8	57.3	70.0	90.2	270.4	99.0
30	19.8	37.9	58.9	86.6	380.8	106.6
Overall MPD	18.5	76.7	75.2	100.0	122.8	74.9
SD	12.0	137.7	72.6	106.9	110.5	19.3

Table 6 continued:

Overall MPD after excluding a data set	16.8	51.6	62.2	80.6	111.1	73.5
SD	8.1	8.6	15.2	15.3	92.0	18.1

[a] Details of data sets are the same as Table 3.

As MPD values reported in Table 8 showed, the GSE, ASER and UASER models produced underestimated and/or overestimated aqueous solubilities, however, their mean values should be the closest solubilities to the experimental values and this fact was confirmed in our computations. Therefore, using MPS approach better predictions should be provided. The MPD range using MPS was 44.6 – 114.5 and the overall MPD (±SD) after excluding a data set with the highest MPD was 73.5 (±18.1) % (see the last column of Table 6).

Comparison of the models concerning various accuracy criteria

As noted under “Computational Methods”, MPD, AAE and RMSE criretia were used to express the accuracy of cosolvency models (4, 14). Figures 2-4 showed the overall MPD, AAE and RMSE and their standard deviations for various models. The accuracy order of the models considering MPD criterion was:

Jouyban-Acree model + S_c + S_w > Equation 9 + S_w ≈ Cosolvency power + S_w ≈ Equation 9 +MPS > Equation 9 + GSE > Equations 9 + UASER

After excluding a data set with the highest MPD, the accuracy order was the same. As a general rule, the more experimental data points employed by the model, the more accurate predictions provided.

Considering AAE criterion, the minimum and maximum AAEs, for Jouyban – Acree model were the same as those for MPDs, i.e. set numbers 17 and 3, respectively. As Figure 5 showed, there is high correlations between MPD, AAE and RMSE criteria. However, MPD criterion was preferred as it is comparable with RSD values for repeated experiments. The accuracy order considering overall AAE after excluding a data set for each model was:

Jouyban-Acree model + S_c + S_w > Cosolvency power + S_w > Equation 9 + S_w ≈ Equations 9 + UASER ≈ Equation 9 +MPS > Equation 9 + GSE.

A similar pattern was the case considering RMSE criterion. Figure 1 showed the relative frequency of residuals where the Jouyban-Acree model produced the best residual distribution and the most of other models produced underestimations.

Table 7. The experimental $f_{c,\ max}$, the corresponding predicted values by the Jouyban-Acree model and differences between experimental and predicted values

No.[a]	Experimental	Predicted	Difference
1	0.70	0.80	-0.10
2	1.00	1.00	0.00
3	0.40	0.60	-0.20
4	0.85	0.85	0.00
5	0.90	0.80	0.10
6	0.90	0.90	0.00
7	0.90	0.90	0.00
8	0.90	0.90	0.00
9	0.90	0.90	0.00
10	0.90	0.90	0.00
11	0.90	0.90	0.00
12	0.90	0.90	0.00
13	0.40	0.65	-0.25
14	0.90	0.90	0.00
15	1.00	1.00	0.00
16	1.00	1.00	0.00
17	0.85	0.85	0.00
18	0.98	1.00	-0.03
19	0.90	0.85	0.05
20	0.90	1.00	-0.10
21	1.00	1.00	0.00
22	0.90	0.80	0.10
23	0.90	0.80	0.10
24	0.90	0.80	0.10
25	0.90	0.90	0.00
26	0.90	0.90	0.00
27	0.90	0.80	0.10
28	0.90	1.00	-0.10
29	0.23	0.23	0.00
30	0.46	0.46	0.00

[a] Details of data sets are the same as Table 3.

Table 8. The mean percentage deviation (MPD)[a] for predicted aqueous solubilities using various models

No.	Solute	t	GSE	ASER	UASER	MPS
1	Aminopyrine	25	74.1	87.5	98.6	92.4
2	Amobarbital	25	47.9	-17.8	-204.1	-23.1
3	Antipyrine	25	88.8	97.5	99.6	97.8
4	Barbital	25	59.1	-176.9	-256.0	-59.2
5	Benzocaine	5	-288.1	-974.7	-692.0	-591.3
6	Benzocaine	10	-158.8	-616.5	-428.0	-360.9
7	Benzocaine	15	-94.1	-437.3	-296.0	-245.6
8	Benzocaine	20	-89.3	-424.2	-286.3	-237.2
9	Benzocaine	25	-38.6	-283.8	-182.9	-146.9
10	Benzocaine	30	-10.9	-207.1	-126.3	-97.5
11	Benzocaine	35	20.0	-121.6	-63.3	-42.5
12	Benzocaine	40	22.4	-114.9	-58.4	-38.3
13	Caffeine	25	72.6	-5796.0	-137.0	-236.9
14	Diazepam	30	-74.8	-29.9	75.7	18.0
15	Furosemide	25	-1085.6	97.5	-771.9	-37.9
16	Meloxicam	25	99.8	95.2	90.0	97.8
17	Metharbital	25	-26.2	-753.0	-293.6	-248.6
18	Pentobarbital	25	-9.8	39.6	-117.1	-13.0
19	Phenobarbital	25	32.9	43.6	-45.7	18.0
20	Phenytoin	25	73.4	-124.5	-692.6	-67.8
21	Phenytoin	25	73.4	-124.5	-692.6	-67.8
22	Salicylic acid	10	89.4	-255.9	-114.3	6.7
23	Salicylic acid	20	92.3	-158.8	-55.8	32.2
24	Salicylic acid	25	92.9	-137.3	-42.9	37.8
25	Salicylic acid	30	94.3	-89.8	-14.3	50.3
26	Salicylic acid	35	95.0	-67.5	-0.8	56.1
27	Salicylic acid	40	95.7	-42.4	14.3	62.7
28	Salicylic acid	25	93.8	-107.8	-25.1	45.5
29	Theophylline	25	67.4	-2492.3	-1071.1	-362.7
30	Theophylline	25	67.4	-2492.3	-1071.1	-362.7
	MPD	All data sets	111.0	550.0	270.6	128.5
	SD		191.1	1168.0	312.0	140.7
	MPD	=25	123.8	762.8	346.6	118.6
	SD	=25	249.2	1518.8	362.2	114.5

[a] Sign (-) means the aqueous solubility is underestimated.

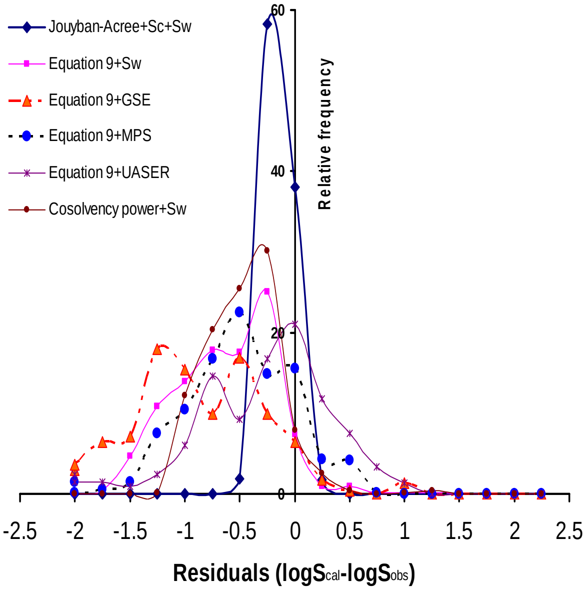

Figure 1. Relative frequency of residuals for models studied.

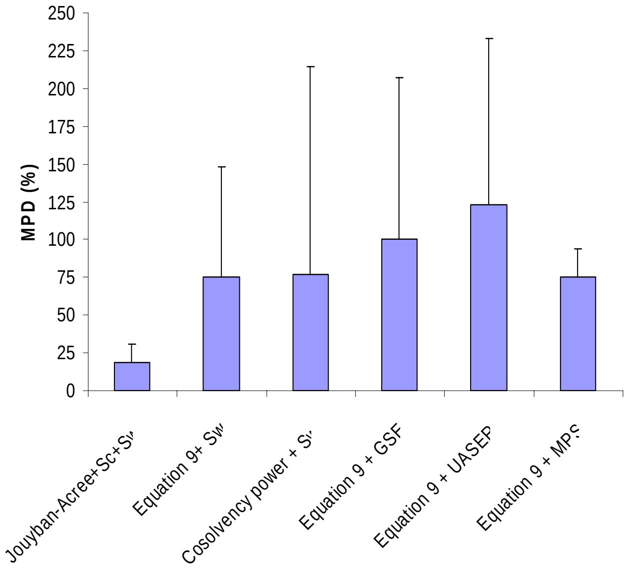

Figure 2. Overall mean percentage deviation (MPD (±SD)) for various numerical methods.

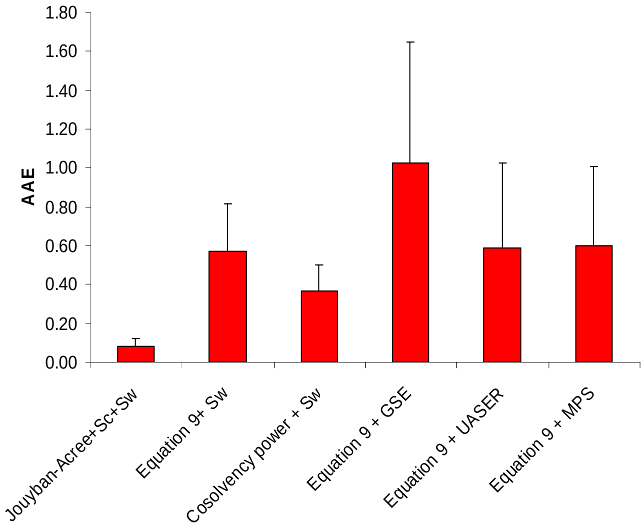

Figure 3. Overall average absolute error (AAE (±SD)) for various numerical methods

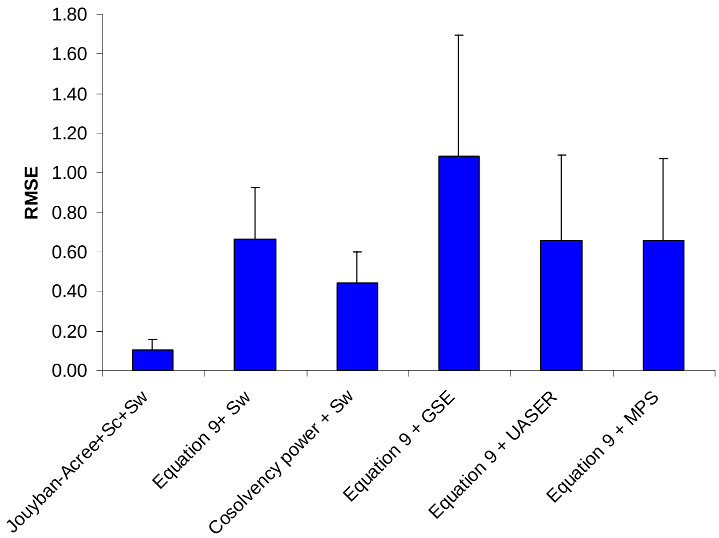

Figure 4. Overall root mean square error (RMSE (±SD)) for various numerical methods.

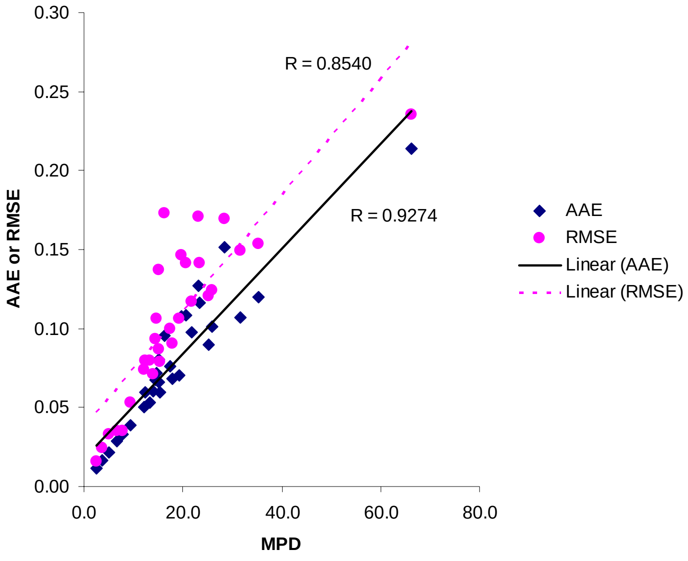

Figure 5. Correlations between AAE and RMSE with MPD accuracy criteria for solubilities predicted by the Jouyban-Acree model.

DISCUSSION

Abraham solvation parameters were developed to calculate the properties of solutes including their solubility at 25 °C (9, 11). However, our observations reveal that using the combined Jouyban-Acree and Abraham models, it is possible to use the Abraham solvation parameters for calculating solubility at temperatures higher/lower than 25 °C. The main reason for such applicability is the employment of experimental S_w and S_c at the corresponding temperatures in the computations.

The proposed model provided reasonable $f_{c,\ max}$ predictions in comparison with the other numerical methods as in 57 % of the cases, the predicted $f_{c,\ max}$ was equal to the experimental value whereas the relative frequency for other models was 20 %. For some cases, there is no definite $S_{m,\ max}$ value since the solubility profile in binary mixtures showed a plateau. As an example, there are no significant differences in $\log S_{m,\ max}$ at f_c=0.85 to 0.95, however, we have considered $\log S_{m,\ max}$= -0.24 and the corresponding f_c (i.e. 0.90) as $f_{c,\ max}$, where the predicted $f_{c,\ max}$ by the Jouyban-Acree model was 0.85, therefore, this case was not considered as a successful $f_{c,\ max}$ prediction in computations.

The Jouyban-Acree, equation 9 and cosolvency power approach of Yalkowsky (equations 5+6) provided more accurate predictions concerning the accuracy criteria. The main limitation of these models are their required experimental solubility data which are two data points for the Jouyban-Acree model and a single data point for the other models. The limitation could be overcomed by improvements in solubility prediction methods in mono-solvent systems.

CONCLUSION

A solubility estimation method for calculating drug solubility in water-cosolvent mixtures using *ab initio* method was provided by a combination of two well-established models. The expected prediction error is ~ 75% using MPS approach which is relatively high error when acceptable error range is considered. To provide better predictions, it was expected that including one experimental data point, i.e. S_w, reduces the prediction error. However, with slight reduction in the prediction errors, it is still relatively high and the expected error is ~ 60%. Employing two experimental data points improve the accuracy of the predictions within an acceptable error range and the expected error for this model (the Jouyban-Acree model) is ~ 18%. Therefore, collecting two data points and prediction of the solubility of drugs in water-cosolvent mixtures at temperatures of interest using the Jouyban-Acree model is recommended for industrial applications.

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