Review of the Cosolvency Models for Predicting Drug Solubility in Solvent Mixtures: An Update

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ABSTRACT. The cosolvency models frequently used in solubility data modeling of drugs in mixed solvents were reviewed and their accuracies for calculating the solubility of solutes were briefly discussed. The models could be used either for correlation of the generated solubility data with temperature, solvent composition etc or for prediction of unmeasured solubility data using interpolation/extrapolation technique. Concerning the correlation results employing a given number of independent variables, the accuracies of the investigated models were comparable, since they could be converted to a single mathematical form, however, the accuracies were decreased when models emplyed more independent variables. The accurate correlative models could be employed for prediction purpose and/or screening the experimental solubility data to detect possible outliers. With regard to prediction results, the best predictions were made using the cosolvency models trained by a minimum number of experimental data points and an *ab initio* accurate prediction is not possible so far and further mathematical efforts are needed to provide such a tool. To connect this gap between available accurate correlative models with the *ab initio* predictive model, the generally trained models for calculating the solubility of various drugs in different binary mixtures, various drugs in a given binary solvent and also a given drug in various binary solvents at isothermal condition and/or different temperatures were reported. Available accuracy criteria used in the recent publications were reviewed including mean percentage deviation (MPD). The MPD for correlative models is 1-10% whereas the corresponding range for predictive models is 10-80% depend on the model capability and the number of independent variables employed by the model. This is an update for a review article published in this journal in 2008.

INTRODUCTION

Solubility is an important issue in the pharmaceutical industry and still is considered as a topic under investigation (1,2), since forty percent of the marketed compounds are poorly soluble and approximately ninety percent of under development drugs can be categorized as poorly soluble (3). Solubility of a drug is the simplest phenomenon in pharmaceutical investigations and is required in many applications in the industry including; solubilization of a drug, crystallization from solutions, preparation of liquid drug formulations, preparation of nano-particles etc. Low aqueous solubility of drugs could also cause crystalluria and is a limitation in clinical application of drugs (4) or may cause beneficial effect such as prolongation of drug action in the target tissue (5). Among various solubilization methods, cosolvency is the most common and feasible method. Aqueous-organic solvent mixtures could be used in the formulation of liquid dosage forms, in solution preparation and/or crystalization processes. The solubility data in cosolvent + water mixtures could also be used in preparation of nanosuspensions of the pharmaceuticals using the bottom-up technique (6). Non-aqueous solvent mixtures are also widely used in the pharmaceutical industry in crystallization, synthesis media, nanoparticle formation or preparation of non-aqueous solutions of drugs.

The experimental determination of drug's solubility is still the most reliable method for obtaining accurate and valid data (7). Various methods were reported for drug solubility determination which were reviewed in previous works (8,9). The experimental determination is a time consuming and costly procedure and alternative methods are in demand. Smart and automated solubility determination methods (9) could be considered as an applicable alternative.

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The mathematical models were also proposed to validate the accuracy of measured solubility data or facilitate the prediction of the solubility data at other temperatures and/or solvent compositions.
From a practical application and ease of use viewpoints, the models vary from the simplest log-linear model of Yalkowsky (10) to the complex model of Ruckenstein and Shulgin (11). It is obvious that, simple models are more preferred in pharmaceutical applications of the models.

The pioneers of solubility data modeling include; Joel H. Hildebrand (1881-1983) who introduced the Hildebrand solubility approach (12) which is applicable only to the solubility of non-polar solutes in non-polar solvents. Its extended versions were reported to provide better predictions for pharmaceutical systems including methods based on solubility parameters developed by Alfred N. Martin (1919-2003) and his co-workers (13). The linear solvation energy relationship models proposed by Michael H. Abraham are the most accurate models to predict the solubility of a solute in the mono-solvent systems (14). The Abraham solvent coefficients which derived from experimental solubility data are available for a limited number of solvents, however, they are not available for some pharmaceutically relevant cosolvents like polyethylene glycols. The model provides solubility values with relatively high prediction error, however, it possesses an advantage of *in silico* prediction of aqueous solubility of drugs and no experimental data is required as input data. Another predictive model was developed by Samuel H. Yalkowsky is the general solubility equation (15) for aqueous solubilities which requires the melting point and logP of the drug as input data. The logP values could be computed using software such as ACD with reasonable accuracy.

Anthony N. Paruta and co-workers (16) correlated the solubility of drugs to the dielectric constant of the mixed solvent system. The log-linear model of Yalkowsky (10) was the next model providing a simple equation to calculate the solubility of drugs in cosolvent + water mixtures and the constants of this model were reported for most of pharmaceutically relevant cosolvents. The model requires experimental aqueous solubility data along with its logP as input data. The extended Hildebrand solubility approach of Martin et al. (13, 17-18) and further extensions of this approach made by Pilar Bustamante and her co-workers (19, 20) were the other versions of the cosolvency models. The excess free energy models of Gordon L. Amidon and his colleagues (21) was provided more accurate predictions by including experimental solubility data in the mono-solvents and also molar volumes of water, cosolvent and the drug. Kenneth A. Connors and his co-workers (22) proposed a phenomenological model derived from the free energy changes of the processes involved in the dissolution of a solute in the solvent system. The combined nearly ideal binary solvent/Redlich–Kister (CNIBS/R-K) equation was derived by William E. Acree Jr (23) and provided the most accurate solubility calculations in comparison with the above mentioned models. The general cosolvency model was reported by Mohammad Barzegar-Jalali and his co-workers (24), which is derived from above mentioned models. During last twenty years, the applications of the CNIBS/R-K equation was extended to represent solvent composition and temperature effects on solute solubility and applied to other physico-chemical properties (PCPs) of mixed solvent systems (25-37) and re-named as the Jouyban-Acree model. The model provided reasonably accurate predictions employing experimental data in mono-solvents and a number of data in mixed solvents at various temperatures. Further works on computational methods and also determination of drug solubilities in mixed solvents are ongoing in our research group.

Although considerable progresses were made in computer sciences and sophisticated software and powerful hardware are available, it must be frankly stated that we are still not able to predict the solubility of drugs as stated by Hildebrand in the last century: “There is scarcely anything more important for a chemist than a knowledge of solubilities, but unfortunately he finds it more difficult to predict how soluble a substance will be in a given solvent than it is to predict almost any other important property.”. No accurate prediction tool is available for solubility of drugs in water, organic solvents or mixed solvent systems (7, 38, 39). More experimental and computational efforts are demanded to provide such a tool. It is obvious that the quality of the experimental data is an important factor in providing accurate models (40-42). To achieve this valuable task, more comprehensive solubility database in mono- and mixed solvents should be generated by the research groups around the world and also more comprehensive and preferably theoretical predictive tools should be provided. Available solubility data of solutes in water (43) and the solubility of pharmaceuticals in

organic mono-solvents and mixed solvents (1) were compiled as separate handbooks.

A simple search using "(TITLE (solubili*) AND TITLE-ABS-KEY (model) AND TITLE (mix*))" as search words in Scopus database (44), resulted in 720 papers. Figure 1 illustrated the relative frequency of the employed solubility models in the published works in 2008-2018.

MODELS REPRESENTING SOLUBILITY DATA IN A GIVEN SOLVENT AT VARIOUS TEMPERATURES

The van't Hoff equation is extensively used to correlate the logarithm of solute's mole fraction solubility ($\ln x_T$) to the reciprocal of absolute temperature ($\frac{1}{T}$) (45). The van't Hoff equation is:

$$\ln x_T = A + \frac{B}{T} = \frac{\Delta S_d^o}{R} - \frac{\Delta H_d^o}{RT} \quad (1)$$

where x_T is the solubility at a given solvent composition at various temperatures, A and B are the constants computed from correlation of the experimental solubility data. ΔH_d^o is the molar enthalpy of dissolution, ΔS_d^o refers to molar entropy of dissolution and R is the gas constant. These coefficients reflect the variations in activity coefficients and indicate the effect of solution non-ideality on the solubility.

Hildebrand equation presents $\ln x_T$ as a linear function of $\ln T$ as:

$$\ln x_T = A' + B' \ln T \quad (2)$$

in which A' and B' are the model constants (46). Grant et al. (47) represented a three parameter equation to provide better correlations. The equation is:

$$\ln x_T = A'' + \frac{B''}{T} + C'' \ln T \quad (3)$$

in which A'', B'' and C'' are the model constants. The model was derived from van't Hoff relation by employing apparent partial molar enthalpy of solution (ΔH^*) instead of the partial molar enthalpy of solution (ΔH) and ΔH^* was assumed as a linear function of temperature as:

$$\Delta H^* = \alpha + \beta T \quad (4)$$

in which α could be considered as the hypothetical value of ΔH^* at T=0 K and β as the change in the apparent partial molar heat capacity of the solute at a constant pressure (ΔC_p). Equation 3 was represented by Apelblat and Manzurola in 1999 (48) and is commonly used in the recent literature as Apelblat equation (49-53). Both Hildebrand and van't Hoff equations provide accurate calculations especially at a narrow temperature range which is commonly used in the pharmaceutical applications. However, Grant et al. (47) recommended when more than five data points covering a relatively wide temperature range are available, it is better to use Eq. 3. The main advantage of the Hildebrand and van't Hoff equations over Apelblat equation is their linear patterns which make them more reliable for prediction of the solubility at various temperatures using interpolation and/or extrapolation techniques.

The Buchowski model (54) with two adjustable parameters (λ and h) correlates the mole fraction solubility of the solute (x_T) and temperature T. It is expressed as:

$$\ln[1 + \frac{\lambda(1 - x_T)}{x_T}] = \lambda h(\frac{1}{T} - \frac{1}{T_{fus}}) \quad (5)$$

where T_{fus} refers to the fusion temperature of the solute.

The main limitation of the models correlating the solubility of a drug in a given mono-solvent (or mixed solvent) as a function of temperature is that their trained versions are valid only for the solvent and there is no way to extend the prediction capability to other mono-solvents or solvent compositions. It is obvious that this sort of predictions are required in the pharmaceutical applications when recrystalization processes are designed based on anti-solvent addition and decreasing the temperature of the solution.

COSOLVENCY MODELS AT ISOTHERMAL CONDITIONS

Semi-theoretical models

The logarithm of the mole fraction solubility of a drug in the solvent mixtures ($\ln x_m$) at a constant temperature T and different solvent mass fractions

can be calculated using the algebraic mixing rule (10):

$$\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 \quad (6)$$

where w_1 and w_2 represent the fraction of mono-solvents 1 and 2 in binary solvent mixtures in the absence of the drug, x_1 and x_2 are the drug solubility in the mono-solvents 1 and 2. The model could be converted to the log-linear model of Yalkowsky (10) simply by repalcing w_2 with (1-w_1) and subsequent re-arrangements as:

$$\begin{aligned}\ln x_m &= w_1 \ln x_1 + (1-w_1)\ln x_2 \\ &= w_1 \ln x_1 + \ln x_2 - w_1 \ln x_2\end{aligned} \quad (7)$$

$$\begin{aligned}\ln x_m &= \ln x_2 + w_1 \ln x_1 - w_1 \ln x_2 \\ &= \ln x_2 + w_1(\ln x_1 - \ln x_2)\end{aligned} \quad (8)$$

since $\ln x_2$ and $(\ln x_1 - \ln x_2)$ are constant values at a given temperature, one may write the equation as:

$$\ln x_m = Intercept + Slope \cdot w_1 \quad (9).$$

The log-linear model could also be derived from Hildebrand solubility approach as has been shown in an earlier report (55).

The excess free energy models of Williams-Amidon (21) are expressed by:

$$\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 + A_{1-2} w_1 w_2 \left(\frac{V_s}{V_1}\right) \quad (10)$$

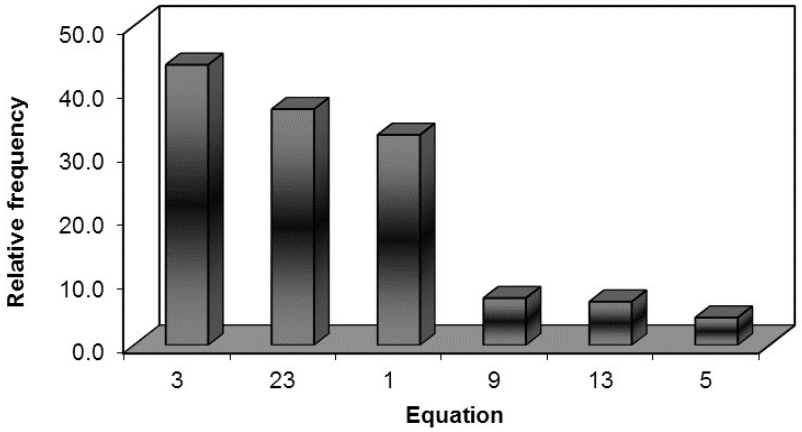

Figure 1. Relative frequency of solubility models employed in recent studies

$$\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 - A_{1-2} w_1 w_2 (2w_1 - 1)\left(\frac{V_s}{V_1}\right) + 2A_{2-1} w_1^2 f_2 \left(\frac{V_s}{V_2}\right) + C_s w_1 w_2 \quad (11)$$

$$\begin{aligned}\ln x_m = {} & w_1 \ln x_1 + w_2 \ln x_2 - A_{1-2} w_1 w_2 (2w_1 - 1)\left(\frac{V_s}{V_1}\right) + 2A_{2-1} w_1^2 w_2 \left(\frac{V_s}{V_2}\right) + 3D_{12} w_1^2 w_2^2 \left(\frac{V_s}{V_2}\right) \\ & + C_2 w_1 w_2^2 \left(\frac{V_s}{V_2}\right) + C_1 w_1^2 w_2\end{aligned} \quad (12)$$

where A_{1-2}, A_{2-1}, C_s, D_{12}, C_2 and C_1 are solvent-solvent or solute-solvent interaction terms, V_1 and V_2 represent the molar volumes of solvents 1 and 2, respectively (21).

The CNIBS/R-K was derived from a thermodynamic mixing model and expressed as:

$$\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 + w_1 w_2 \sum_{i=0}^{2} S_i (w_1 - w_2)^i \quad (13)$$

where S_i stand for the model constants. The S_i terms are computed using either a classical least square analysis (56) or a no intercept least squares analysis (57). The latter numerical method produces more accurate computations for drug's solubility in aqueous binary solvents (57) and is recommended for future applications. The application of Eq. 13 could be extended to calculate the solute solubility in ternary solvent mixtures based on the model parameters obtained from solubility data in the sub-binary solvent systems as (58, 59):

$$\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 + w_3 \ln x_3 + w_1 w_2 \sum_{i=0}^{2} S_i (w_1 - w_2)^i + w_1 w_3 \sum_{i=0}^{2} S_i^{'} (w_1 - w_3)^i + w_2 w_3 \sum_{i=0}^{2} S_i^{''} (w_2 - w_3)^i \quad (14)$$

in which $S_i^{'}$ and $S_i^{''}$ are the model constants calculated using solubility data in sub-binary solvent mixtures. One may add ternary solvent interaction terms to provide more accurate calculations (60) as:

$$\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 + w_3 \ln x_3 + w_1 w_2 \sum_{i=0}^{2} S_i (w_1 - w_2)^i + w_1 w_3 \sum_{i=0}^{2} S_i^{'} (w_1 - w_3)^i + w_2 w_3 \sum_{i=0}^{2} S_i^{''} (w_2 - w_3)^i + w_1 w_2 w_3 \sum_{i=0}^{2} S_i^{'''} (w_1 - w_2 - w_3)^i \quad (15)$$

in which $S_i^{'''}$ are the model constants calculated using solubility data in ternary solvent mixtures.

The modified Wilson model represents a drug solubility in binary solvents at a given temperature as (61):

$$-\ln x_{\mathrm{m}} = 1 - \frac{w_1 (1 + \ln x_1)}{w_1 + w_2 \lambda_{12}} - \frac{w_2 (1 + \ln x_2)}{w_1 \lambda_{21} + w_2} \quad (16)$$

in which λ_{12} and λ_{21} are the model parameters computed using a non-linear least square analysis.

Most of these models could be converted to a general single model (GSM) or unified cosolvency model (UCM) as has been shown in previous papers (24, 62). The GSM was derived from the excess free energy and the CNIBS/R-K models (24) and was already used as an empirical equation to correlate solute solubility in the pharmaceutical literature (17, 63, 64). GSM is expressed as (24):

$$\ln x_m = K_0 + K_1 f_1 + K_2 f_1^2 + K_3 f_1^3 + \Lambda \quad (17)$$

where $K_0 - K_3$ denote the model constants calculated using least squares analysis.

Using similar algebraic manipulations and some simplifications, UCM could be derived from non-linear cosolvency models (61) as:

$$\ln x_m = \frac{K_0^{'} + K_1^{'} w_1 + K_2^{'} w_1^2 + K_3^{'} w_1^3 + \Lambda}{K_0^{''} + K_1^{''} w_1 + K_2^{''} w_1^2 + K_3^{''} w_1^3 + \Lambda} \quad (18)$$

where $K_i^{'}$ and $K_i^{''}$ terms denote the model constants.

The cosolvency models usually overestimate or underestimate the solubility data and to provide better calculations, mean predicted solubility (MPS) approach was proposed and it was shown that, MPS approach provides more accurate correlations and/or predictions. In this approach, the solubility data calculated using various cosolvency models were averaged (65).

Empirical models

The mixture response surface method for correlation of solubility values is written as:

$$\ln x_m = \beta_1 w_1^{'} + \beta_2 w_2^{'} + \beta_3 \left(\frac{1}{w_1^{'}} \right) + \beta_4 \left(\frac{1}{w_2^{'}} \right) + \beta_5 w_1^{'} w_2^{'} \quad (19)$$

here, $\beta_1 - \beta_5$ are model's constants and $w_1^{'}$ and $w_2^{'}$ are given by $w_1^{'} = 0.96\ w_1 + 0.02$ and $w_2^{'} = 0.96\ w_2 + 0.02$ (66).

The double log-log model for linearizing the solubility data can be presented as (67):

$$\ln\left(\ln \frac{x_m}{x_2} \right) = \ln\left(\ln \frac{x_{m_{0.5}}}{x_2} \right) + D \ln\left(\frac{w_1}{w_2} \right)$$

for $0 < w_1 \leq 0.5$ (20)

$$\ln\left(\ln \frac{x_1}{x_m} \right) = \ln\left(\ln \frac{x_1}{x_{m_{0.5}}} \right) + d \ln\left(\frac{w_2}{0.5} \right)$$

for $0 < w_2 \leq 0.5$ (21)

in which $x_{m_{0.5}}$ is drug solubility in the fraction of 0.5 of the cosolvent, *D* and *d* are the model's constants. The double log-log model considers whole composition range of a binary solvent mixture as solvent 1 rich area and solvent 2 rich area and believed that should provide more accurate calculations. A number of other empirical models were reported which did not attract more attention from the research groups (68).

The main disadvantage of these models (Eqs. 6-21) is that they could be used at isothermal condition and should be trained for each temperature of interest.

COSOLVENCY MODELS AT VARIOUS TEMPERATURES

Semi-theoretical models

The logarithm of the mole fraction solubility of a solute at temperature *T* and different solvent compositions ($\ln x_{\mathrm{m,T}}$) is calculated using an extended version of the algebraic mixing rule as (69, 70):

$$\ln x_{\mathrm{m,T}} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) \qquad (22)$$

which is just a simple replacement of $\ln x_{1,\mathrm{T}}$ and $\ln x_{2,\mathrm{T}}$ with their values from van't Hoff equation. It is obvious that Eq. 22 represents the ideal mixing behaviour of the solution and is not the case for most of pharmaceutical solutions. In the Jouyban-Acree model, additional solute-solvent and solvent-solvent interaction terms could cover non-ideal mixing behaviour of the solutions. It correlates the solubility data in terms of temperature and solvent composition and represented as (71, 72):

$$\ln x_{\mathrm{m,T}} = w_1 \ln x_{1,\mathrm{T}} + w_2 \ln x_{2,\mathrm{T}} + \frac{w_1 w_2}{T}\sum_{i=0}^{2} J_{\mathrm{i}}(w_1 - w_2)^{\mathrm{i}} \qquad (23)$$

where $x_{1,\mathrm{T}}$ and $x_{2,\mathrm{T}}$ are the solubility in the mono-solvents 1 and 2 at various temperatures T and J_i are the model constants computed using regression of $\left(\ln x_{\mathrm{m,T}} - w_1 \ln x_{1,\mathrm{T}} - w_2 \ln x_{2,\mathrm{T}}\right)$ against $\frac{w_1 w_2}{T}$, $\frac{w_1 w_2 (w_1 - w_2)}{T}$ and $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$ (57, 72). Equation 23 requires two experimental solubility data points at each temperature and this restricts its practical applications. On the other hand, since the effect of drug solid state charactristics is an important parameter in its solubility, *e.g.* different polymorphs of a drug, and its effects could be reflected in $x_{1,\mathrm{T}}$ and $x_{2,\mathrm{T}}$ values. Employing these experimental data points in such cases is preferred and provided a useful tool for predictive purposes. As an example, the solubility of two polymorphs of a drug could be represented using the model parameters of one polymorph and the solubility data of other polymorph in the mono-solvents (73).

To provide a more practical version of the model to calculate drug solubility in solvent mixtures, the Jouyban-Acree model could be combined with van't Hoff equation as (69, 74, 75):

$$\ln x_{\mathrm{m,T}} = w_1(A_1 + \frac{B_1}{T}) + w_2(A_2 + \frac{B_2}{T}) + \frac{w_1 w_2}{T}\sum_{i=0}^{2} J_{\mathrm{i}}(w_1 - w_2)^{\mathrm{i}} \qquad (24)$$

where A_{i}, B_{i} and J_{i} parameters have the same meanings in Eqs. 1 and 23. The constants of Eq. 24 could be computed using either:

1) regression of $\ln x_{1,\mathrm{T}}$ against $\frac{1}{T}$, $\ln x_{2,\mathrm{T}}$ against $\frac{1}{T}$ (to obtain A and B terms of van't Hoff equation), then regression of $\left(\ln x_{\mathrm{m,T}} - w_1(A_1 + \frac{B_1}{T}) - w_2(A_2 + \frac{B_2}{T})\right)$ against $\frac{w_1 w_2}{T}$, $\frac{w_1 w_2 (w_1 - w_2)}{T}$ and $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$; which is a recommended procedure, or:

2) regression of $\ln x_{m,\mathrm{T}}$ against w_1 , $\frac{w_1}{T}$, w_2 , $\frac{w_2}{T}$, $\frac{w_1 w_2}{T}$, $\frac{w_1 w_2 (w_1 - w_2)}{T}$ and $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$ using a no intercept least square analysis; which is a recommended

procedure for data sets in which the solubility in neat mono-solvents are not available.

The numerical values of *J* terms computed from two numerical methods are slightly different from each other, but the overall fitness of the models is the same.

The model was also combined with Apelblat model as (76):

$$\ln x_{m,T} = w_1\left(A_1^{"} + \frac{B_1^{"}}{T} + C_1^{"}\ln T\right) + w_2\left(A_2^{"} + \frac{B_2^{"}}{T} + C_2^{"}\ln T\right) + \frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i \quad (25)$$

in which $A_1^{"}$, $B_1^{"}$, $C_1^{"}$, $A_2^{"}$, $B_2^{"}$, and $C_2^{"}$ are the model constants.

Empirical models

Equation 22 could be re-arranged as:

$$\ln x_{m,T} = w_1\left(A_1 + \frac{B_1}{T}\right) + (1 - w_1)\left(A_2 + \frac{B_2}{T}\right) \quad (26)$$

$$\ln x_{m,T} = A_1 w_1 + \frac{B_1 w_1}{T} + A_2 + \frac{B_2}{T} - A_2 w_1 - \frac{B_2 w_1}{T} \quad (27)$$

$$\ln x_{m,T} = A_2 + \frac{B_2}{T} + (A_1 - A_2)w_1 + \frac{(B_1 - B_2)w_1}{T} \quad (28)$$

$$\ln x_{m,T} = E_0 + \frac{E_1}{T} + E_2 w_1 + \frac{E_3 w_1}{T} \quad (29)$$

in which E_0-E_3 are the model constants.

Yang et al. (77) and Sun et al. (78) manipulated Eq. 23 and reported a modified version of the model as:

$$T\ln x_m = G_0 + G_1 T + G_2 T x_2 + G_3 T x_2 + G_4 x_2^2 + G_5 x_2^3 + G_6 x_2^4 \quad (30)$$

in which *G* terms are the model constants. There is no way to derive Eq. 30 from their manipulations and the correct derivation could be obtained from a similar manipulations on Eq. 24 as has been shown in previous papers (79, 80). The correct derivation is:

The replacement of w_2 with $(1 - w_1)$ in Eq. 24 and series of algebraic manipulations:

$$T\ln x_{m,T} = (B_2 - B_2 w_1 + B_1 w_1)T + (A_1 w_1 + A_2 - A_2 w_1) + \left[J_0 w_1 - J_0 w_1^2\right] + \left[(J_1 w_1 - J_1 w_1^2)(2w_1 - 1)\right] + \left[(J_2 w_1 - J_2 w_1^2)(4w_1^2 - 4w_1 + 1)\right] \quad (34)$$

$$T\ln x_{m,T} = B_2 T - B_2 w_1 T + B_1 w_1 T + A_1 w_1 + A_2 - A_2 w_1 + \left[J_0 w_1 - J_0 w_1^2\right] + \left[2J_1 w_1^2 - J_1 w_1 - 2J_1 w_1^3 + J_1 w_1^2\right] + \left[4J_2 w_1^3 - 4J_2 w_1^2 + J_2 w_1 - 4J_2 w_1^4 + 4J_2 w_1^3 - J_2 w_1^2\right] \quad (35)$$

and like terms are combined:

$$T\ln x_{m,T} = A_2 + (A_1 - A_2 + J_0 - J_1 + J_2)w_1 + B_2 T + (B_1 - B_2)w_1 T + (-J_0 + 3J_1 - 5J_2)w_1^2 + (-2J_1 + 8J_2)w_1^3 + (-4J_2)w_1^4 \quad (36)$$

Since all of the A, B and J terms in Eq. 36 are constant values, one may re-write it in a simplified version of Eq. 30.

Equation 24 could be re-arranged as:

$$\ln x_{m,T} = G_1 + \frac{G_2}{T} + G_3 w_1 + \frac{G_4 w_1}{T} + \frac{G_5 w_1^2}{T} + \frac{G_6 w_1^3}{T} + \frac{G_7 w_1^4}{T} \quad (37)$$

by replacing w_2 with (1-w_1) and further algebraic manipulations (81, 82). *G* terms are the model constants and computed using a classical least square analysis.

The correlation abilities of Eqs. 24, 30 and 37 were compared employing 56 solubility data sets of drugs in aqueous and non-aqueous binary solvent mixtures at various temperatures (83). The obtained mean percentage deviations (MPD) were 9.9 ± 11.8, 14.1 ± 21.4% and 14.1 ± 21.4 %, respectively for Eqs. 24, 30 and 37. There were five data sets producing relatively large MPD values for all models, and by excluding these five data sets, the MPDs were reduced to 6.6 ± 4.5, 8.6 ± 6.6% and 8.7 ± 6.6 %, respectively for the mentioned equations (83).

Zhou et al. (84) introduced a modified version of Eq. 25 by replacing w_2 with (1-w_1). The modified Jouyban-Acree-Apelblat model (85) is:

$$\ln x_{m,T} = F_1 + \frac{F_2}{T} + F_3 \ln T + F_4 w_1 + \frac{F_5 w_1}{T} + \frac{F_6 w_1^2}{T} + \frac{F_7 w_1^3}{T} + \frac{F_8 w_1^4}{T} + F_9 w_1 \ln T \quad (38).$$

in which F terms are the model constants.

Although both modified versions and the classical version of the Jouyban-Acree model produce the same accuracies for correlation of the solubility data of a given drug in a certain cosolvent + water mixtures, the classical version of the Jouyban-Acree model is preferred for future works. The main reasons for this preference are:

1. Theoretical basis of the model (71, 72)
2. Capability of providing the most accurate correlation/prediction for solubility of drugs in various cosolvent + water mixtures (63, 83, 86)
3. Possibility of extension of the model's applicability to calculate the solubility in ternary or higher order solvent mixtures (87-89)
4. Providing generally trained models to predict the solubility of drugs in a given cosolvent + water mixtures (90-96)
5. Providing generally trained model for a given drug in different solvent mixtures (97, 98)
6. Accurate representation of some commonly observed phenomena in the solutions such as chameleonic effect (99) and solubility of various polymorphs of a drug in cosolvent + water mixtures (73)
7. Providing globally trained versions of the model using Abraham parameters (100) and/or Hansen solubility parameters (101)
8. The model could be used for representing both solvent composition effects and salt formation (102, 103), surfactants (104, 105), complexing agents (106-108), combined effects of surfactants and complexing agents (109), polymers (110, 111), and ionic strength (112).
9. Possibility of representing drug's pKa in solvent mixtures at various temperatures (27)
10. Representing thermodynamic parameters of the solutions in mixed solvents (113)
11. Possibility of representing the solvent mixtures properties such as viscosity (31), density (32) *etc* at various temperatures. The general form of the Jouyban-Acree model is:

$$\ln PCP_{m,T} = w_1 \ln PCP_{1,T} + w_2 \ln PCP_{2,T} + w_1 w_2 \sum_{i=0}^{2} \frac{J_i (w_1 - w_2)^i}{T} \quad (40)$$

where $PCP_{m,T}$, $PCP_{1,T}$ and $PCP_{2,T}$ are the numerical values of the physico-chemical property of the mixture and solvents *1* and *2* at temperature T, respectively, w_1 and w_2 are the volume (weight or mole) fractions of solvents *1* and *2* in the mixture and J_i represent the model constants.

12. The applicability of the model to extend for representation of the solubility and *PCPs* in ternary solvents as:

$$\begin{aligned} \ln PCP_{m,T} = {} & w_1 \ln PCP_{1,T} + w_2 \ln PCP_{2,T} + w_3 \ln PCP_{3,T} \\ & + w_1 w_2 \sum_{i=0}^{2} \frac{J_i (w_1 - w_2)^i}{T} + w_1 w_3 \sum_{i=0}^{2} \frac{J_i' (w_1 - w_3)^i}{T} \\ & + w_2 w_3 \sum_{i=0}^{2} \frac{J_i'' (w_2 - w_3)^i}{T} + w_1 w_2 w_3 \sum_{i=0}^{2} \frac{J_i'' (w_1 - w_2 - w_3)^i}{T} \end{aligned} \quad (41)$$

where subscript *3* is the solvent *3* characteristics, J_i', J_i'' and J_i''' are the sub-binary model constants (114).

ACCURACY OF COSOLVENCY MODELS

MPD is one of the most commonly used scale-independent accuracy criteria in cosolvency computations. The possible determination errors in solubility experiments may result in an outlier point which will produce large MPD value in the computations. The MPD value could be directly compared with the relative standard deviation which is a measure of accuracy and precision of experimental determination procedure. It could be extremely large when the target experimental

solubility datum is very close to zero (83). MPD will be ~100 when the calculated solubility datum is very close to zero. On the other hand, scale-dependent accuracy measures such as average absolute error (AAE) and root mean square error (RMSE) are vastly affected from the high solubility data and neglects the lower ones. The solubility in mole fraction unit is ranged from ~0 to ~1. This is the reason why MPD was the most widely used criteria despite its mentioned limitation.

The other generally used accuracy criterion includes the *RMSE* defined as (115-116):

$$RMSE = \sqrt{\frac{\sum \left(Observed - \Pr edicted\right)^2}{N}} \quad (47)$$

where *N* is the number of predicted solubility data points. The next criterion is the AAE which is defined as (115, 117):

$$AAE = \frac{\sum \left|Observed - \Pr edicted\right|}{N} \quad (48)$$

The RMSE and AAE values could be defined in logarithmic ($\log x_m$ or $\ln x_m$) or arithmatic (x_m) scales and to compare its reported values in different papers, the scale should be kept in mind. The percentage deviation (%Dev.) (118-122) is:

$$\%Dev. = \left(\frac{100}{N}\right)\sum \left|\ln\left(\frac{\Pr edicted}{Observed}\right)\right| \quad (49).$$

The mean squared deviation (MSD) was also used in the literature:

$$MSD = \sqrt{\frac{\left(x_m^{Calculated} - x_m^{Observed}\right)^2}{N - 1 - p}} \quad (50)$$

where *p* is the number of the parameters of the model (123).

The MPD was used by our group (61, 83, 91-95) and is defined as:

$$MPD = \frac{100}{N}\sum_{1}^{N}\left(\frac{\left|x_m^{Calculated} - x_m^{Observed}\right|}{x_m^{Observed}}\right) \quad (51).$$

The same definition was also used in some reports using various terminologies, such as percent mean error (124), average percentage deviation (125) and percent deviation (63).

The squares of the percent difference between calculated and experimental solubilities ($\sum \left(\%D\right)^2$) is defined as (126):

$$\sum \left(\%D\right)^2 = \sum_{i=1}^{N}\left\{100\left[\frac{x_m^{Calculated} - x_m^{Observed}}{x_m^{Observed}}\right]\right\}^2 \quad (52).$$

Accuracy of correlative models

The ideal value for the accuracy criterion for a correlative model is ~0 which means data excellently fit to the model. However, due to the experimental and other erros associated with the experimental data, the value is usually more than zero (63, 71, 83, 86). One may consider the accuracy criterion around the uncertainity values for repeated experiments (which is usually 1-10%) as an ideal value for the accuracy of the correlative models. As discussed in this work, MPD is a very similar term to the relative standard deviation (RSD) for repeated experiments and the expected MPD for correlative models could be considered in the range of 1 to 10 % as an acceptable range.

Barzegar-Jalali et al. (126) compared the accuracy of 3 cosolvency models for correlating the solubility data sets of 11 drugs in pharmaceutical cosolvents + water at 25 °C using $\sum \left(\%D\right)^2$ as an accuracy criterion and found that the CNIBS/R-K model provided the most accurate correlations.

Accuracy of predictive models trained using a minimum number of experimental data points

Solubility prediction by employing the trained models using a minimum number of experimental data points (65, 69, 126-132) is perhaps the most accurate and feasible prediction method so far. It has been shown that the trained models using sufficient number of training data points provide acceptable predictions and could be used in the pharmaceutical industry. One could predict the solubility of a drug at a narrow temperature range after training the van't Hoff equation using just two experimental data points, since the van't Hoff equation is a linear model (69). For solubility prediction of a drug in a binary solvent mixture, one datum (10, 14, 90), two data points (10, 129), three data points (128), four data ponits (128), five data points (65, 126) and seven data points (107, 131) have been examined. The overall MPD

for predictive models is 10-80% for various models used in recent publications. As a general rule, the more data points in the training set, resulted in more accurate solubility predictions. On the other hand, more independent variables included, the more comprehensive solubility predictions were provided, however less accurate predictions were made. As an example, the van't Hoff model with only one independent variable, *i.e.* temperature, produced the most accurate predictions, while the Jouyban-Acree-Abraham model (100) with four independent variables, *i.e.* solvent composition, temperature, nature of solvents and nature of solutes, produced less accurate predictions. This point should be considered when accuracy comparison of the solubility models are investigated.

Models for a given drug in various solvent mixtures

Trained versions of the Jouyban-Acree model were reported for prediction of paracetamol (87) and salicylic acid (132) in water + ethanol + propylene glycol ternary and sub-binary solvent mixtures. A trained version of the Jouyban-Acree-Abraham model was proposed to calculate the solubility of hesperidin in a number of cosolvents + water mixtures at various temperatures as (133):

$$\begin{aligned}\ln x_{m,T} &= w_1 \ln x_{1,T} + w_2 \ln x_{2,T} \\ &+ \left(\frac{w_1 w_2}{T}\right)\left\{-38893.1c_1^2 + 9164.4e_1^2 - 5860.6a_1^2 + 158.0b_1^2\right\} \\ &+ \left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right)\left\{111935.7c_1^2 - 14412.0e_1^2 + 14625.7a_1^2 - 267.1b_1^2\right\} \\ &+ \left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right)\left\{-92240.1c_1^2 - 7131.4e_1^2 - 8364.4a_1^2 + 210.1b_1^2\right\}\end{aligned} \quad (53)$$

which is a simplified version of Eq. 54. Abraham solvent coefficients; e is the excess molar refraction, s is the dipolarity/polarizability of the solvent, a denotes the hydrogen-bond acidity of solvent, b stands for hydrogen-bond basicity of solvent, and v is the McGowan volume of the solvent. Another trained version was reported for calculating the solubility of lamotrigine in non-aqueous binary solvent mixtures as (134):

$$\begin{aligned}\ln x_{m,T} &= w_1 \ln x_{1,T} + w_2 \ln x_{2,T} \\ &+ \left(\frac{w_1 w_2}{T}\right)\left\{\begin{array}{l}238.81 + 5221.44\left[(c_1 - c_2)^2\right] - 10525.96(e_1 - e_2)^2 \\ +141.65(s_1 - s_2)^2 + 368.67(a_1 - a_2)^2 - 86.57(b_1 - b_2)^2 \\ +251.30(v_1 - v_2)^2\end{array}\right\} \\ &+ \left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right)\left\{\begin{array}{l}-191.11 + 30503.53\left[(c_1 - c_2)^2\right] + 94447.51(e_1 - e_2)^2 \\ -1446.39(s_1 - s_2)^2 - 954.07(a_1 - a_2)^2 + 465.31(b_1 - b_2)^2\end{array}\right\} \\ &+ \left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right)\left\{\begin{array}{l}303.74 - 197.26(s_1 - s_2)^2 \\ +111.22(b_1 - b_2)^2 - 1831.16(v_1 - v_2)^2\end{array}\right\}\end{aligned} \quad (54)$$

Models for various drugs in a given solvent mixture

The predictive version of the log-linear model of Yalkowsky (135) was applied to predict the solubility of drugs in various cosolvent + water mixtures at room temperature using:

$$\ln x_m = \ln x_2 + w_1(M \log_{10} P + N) \quad (55)$$

where $\log_{10} P$ is the logarithm of drug's partition coefficient. Table 1 summerized the M and N values for a number of cosolvent systems.

Table 1. Numerical values of M and N values of common cosolvents for calculating the slope (σ) of the log-linear model (133)

	M	N
Acetone	1.14	-0.10
Acetonitrile	1.16	-0.49
Butylamine	0.64	1.86
Dimethyl acetamide	0.96	0.75
Dimethyl formamide	0.83	0.92
Dimethyl sulphoxide	0.79	0.95
Dioxane	1.08	0.40
Ethanol	0.95	0.30
Ethylene glycol	0.68	0.37
Glycerol	0.35	0.28
Methanol	0.89	0.36
Polyethylene glycol 400	0.88	0.68
1-Propanol	1.09	0.01
2-Propanol	1.11	-0.50
Propylene glycol	0.78	0.37
Carbitol	1.60[a]	5.43[a]

[a] Taken from a reference (94).

Attempts were made to calculate the solubility of structurally related drugs in a given cosolvent + water mixtures to provide prediction tools for practical applications in the pharmaceutical industry. Bustamante et al. (19) proposed a modified version of the extended Hildebrand solubility approach as:

$$\ln x_{\mathrm{m}} = B_0 + B_1 \ln x_1 + B_2 \ln x_2 + B_3 \delta_m \delta_{Drug} + B_4 \delta_m^2 + B_5 \delta_m^3 + B_6 \delta_{mb} \quad (56)$$

in which δ_m is the solubility parameter of the solvent mixture calculated using $\left(w_1\delta_1 + w_2\delta_2\right)$, and δ_{mb} is the basic solubility parameter of the solvent mixture. The accuracy of Eq. 56 was compared with that of the CNIBS/R-K model using 8 solubility data sets of sulfonamides in dioxane + water and 8 alkylbenzoates in propylene glycol + water mixtures, where the CNIBS/R-K model provided more accurate correlations (125).

Abraham and Acree (14) proposed the Abraham solvent coefficients for ethanol + water mixtures with 0.1 fraction intervals and predicted the solubility of various drugs in ethanol + water mixtures employing their Abraham solute parameters (14). The accuracy of this method was not compared using accuracy criterions and the authors just compared using graphical comparisons of a sample data sets (see Figures 1-4 of the original paper (14) for details). The graphical comparisons reveal that the accuracy of the proposed method (14) was comparable with that of the Jouyban-Acree-Abraham model (Eq. 65) for calculating the solubility of drugs in ethanol + water mixtures. A disadvantage of the method is that it cannot be used for interpolation of the solubility data in the fractions other than 0.1 intervals.

The trained versions of Eq. 23 were reported for solubility prediction of drugs in the aqueous mixtures of ethanol and several cosolvents at various temperatures (90-96). In these models, the *J* terms of Eq. 23 were assumed as independent parameters from drugs interactions which is not the case for most of the pharmaceutical systems. Attempts were made to cover this point by including HyperChem® solute parameters or Abraham solvent and solute parameters in the computations. The calculated structural parameters of drugs using HyperChem 7.0 (136) were employed to consider the effects of drugs' stuructures on their solubilities, and the obtained models for dioxane + water and ethyl acetate + ethanol solvent mixtures were:

$$\ln x_{m,T} = \left[w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + w_1 w_2 \left(\frac{2206.9}{T} + \frac{1173.1(w_1 - w_2)}{T} + \frac{1997.4(w_1 - w_2)^2}{T} \right) \right] + 3.113HE' - 5.124HOMO' - 9.697TE' + 11.782Vol' + 0.238 \log P' \quad (57)$$

$$\ln x_{m,T} = \left[w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + w_1 w_2 \left(\frac{881.9}{T} + \frac{289.4(w_1 - w_2)}{T} + \frac{494.1(w_1 - w_2)^2}{T} \right) \right] + 1.020HE' - 2.818HOMO' - 1.143TE' + 3.068Vol' - 0.072 \log P' \quad (58)$$

where *HE* is hydration energy, *HOMO* is energy of the highest occupied molecular orbital, *TE* is total energy, *Vol* is molar volume, and *logP* is the logarithm of partition coefficient, all computed by HyperChem as described in the published work (136). Their normalized values were used in the computations and calculated using:

$$HC' = \frac{w_1 w_2 HC}{\overline{HC}} \quad (59)$$

where $\overline{HC}$ is the mean of HC value for the investigated drugs. Eqs. 57 and 58 were correlated the data with the overall MPDs of 17.9 % and 9.6 %, respectively for dioxane + water and ethyl acetate + ethanol solvent mixtures which were significantly less than their simplified models without structural parameters (136). More variables from HyperChem computations were included to the model and the results were tested using solubility data sets in aquoeus binary mixtures of propylene glycol, ethanol and PEG 400. The combined model was:

$$\ln x_{m,T} = \left[w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + w_1 w_2 \left(\frac{J_0}{T} + \frac{J_1(w_1 - w_2)}{T} + \frac{J_2(w_1 - w_2)^2}{T} \right) \right] + J_3 SAA' + J_4 HE' + J_5 \log P' + J_6 MR' + J_7 MW' + J_8 TE' + J_9 DM' + J_{10} HOMO' + J_{11} LUMO' + J_{12} Vol' \quad (60)$$

The Abraham solute parameters, *i.e. E*, *S*, A, *B* and *V* represent the interactions of solute with solvent system. The combined version of Eq. 23 with Abraham parameters was (100):

$$\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \frac{w_1 w_2}{T} \{ (\kappa_0 + \kappa_1 E + \kappa_2 S + \kappa_3 A + \kappa_4 B + \kappa_5 V \} + \frac{w_1 w_2 (w_1 - w_2)}{T} \{ (\kappa_0' + \kappa_1' E + \kappa_2' S + \kappa_3' A + \kappa_4' B + \kappa_5' V \} + \frac{w_1 w_2 (w_1 - w_2)^2}{T} \{ (\kappa_0'' + \kappa_1'' E + \kappa_2'' S + \kappa_3'' A + \kappa_4'' B + \kappa_5'' V \} \quad (61)$$

in which κ terms are the model constants. Trained versions of Eq. 61 were provided for dioxane + water (100), ethanol + water (100), ethanol + ethyl acetate (138), ethanol + propylene glycol (139) and some other binary solvent mixtures.

Models for calculating the solubility of various drugs in different binary solvent mixtures:
An attempt was also made to provide a general version of the Jouyban-Acree-Abraham model to correlate the solubility of anthracene in non-aqueous binary solvents as:

$$\begin{aligned}
&\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 \\
&+ w_1 w_2 \left[0.128 - 4.772(c_1 - c_2)^2 - 1.123(e_1 - e_2)^2 + 0.546(s_1 - s_2)^2 + 0.670(b_1 - b_2)^2 + 1.262(v_1 - v_2)\right] \\
&+ w_1 w_2 (w_1 - w_2)\left[0.194 - 10.404(c_1 - c_2)^2 - 1.746(e_1 - e_2)^2 + 0.133(s_1 - s_2)^2 + 0.372(b_1 - b_2)^2 - 1.402(v_1 - v_2)\right] \\
&+ w_1 w_2 (w_1 - w_2)^2\left[-0.047 - 1.340(c_1 - c_2)^2 - 0.934(e_1 - e_2)^2 + 0.140(s_1 - s_2)^2 + 0.178(b_1 - b_2)^2 + 0.876(v_1 - v_2)\right]
\end{aligned} \quad (62)$$

where the overall MPD of 5.5 % was obtained by employing the experimental solubility data of anthracene in the mono-solvents as input data. When the solubilities of anthracene in the mono-solvents predicted by the Abraham model were replaced in the above equation, the overall MPD of 37.9 % was obtained (140). The applicability of Eq. 62 to predict the solubility of anthracene in 49 binary solvents and 32 ternary solvent systems have been shown where the overall MPD of 7.9 % and 10.7 % were obtained. By replacing the Abraham equation predicted solubilities in the mono-solvents, the overall MPDs of 47.9 % and 23.9 %, were observed respectively for binary and ternary prediction data sets (141).

To provide more generally trained models, both solutes and solvents parameters were included in the computations. The solubility of five polycyclic aromatic hydrocarbons in non-aqueous binary solvent was correlated using:

$$\begin{aligned}
&\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 \\
&+ w_1 w_2 \left[0.028 + 2.123(c_1 - c_2)^2 - 0.160E(e_1 - e_2)^2 + 0.282S(s_1 - s_2)^2 + 1.713B(b_1 - b_2)^2 + 2.006V(v_1 - v_2)\right] \\
&+ w_1 w_2 (w_1 - w_2)\left[0.033 + 0.670(c_1 - c_2)^2 - 0.477E(e_1 - e_2)^2 + 0.051S(s_1 - s_2)^2 + 0.476B(b_1 - b_2)^2 - 0.234V(v_1 - v_2)\right] \\
&+ w_1 w_2 (w_1 - w_2)^2\left[0.022 + 2.024(c_1 - c_2)^2 - 0.204E(e_1 - e_2)^2 + 0.034S(s_1 - s_2)^2 + 0.243B(b_1 - b_2)^2 + 0.848V(v_1 - v_2)\right]
\end{aligned} \quad (63)$$

which calculates the solute's solubility with the overall MPD of 4.7%. This MPD value is quite reasonable, when it was compared with the relative standard deviation of the repeated experiments which is between 5 to 10%. To provide an *in silico* version of the model, the solute's solubilty in the mono-solvents were calculated using the Abraham model and included in Eq. 63 instead of x_1 and x_2 values, where the overall MPD value of 33.4% was obtained (142). Further predictions for 80 data sets of anthracene and pyrene in non-aqueous ternary solvent mixtures confirmed the good prediction capacity of Eq. 63 (143). The solute-solvent interactions of polycyclic aromatic hydrocarbons and non-aqueous solvents are not too complex, so the obtained models are accurate for these sorts of solutions. A similar version of the model for calculating the molar solubility of drugs in binary solvent mixtures was proposed as (90):

$$\begin{aligned}
&\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} \\
&+ 2.303\left(\frac{w_1 w_2}{T}\right)\begin{Bmatrix}(2113.119 - 1093.783[(c_1 - c_2)^2] + 3380.661[(E(e_1 - e_2)^2] - 13.865[(S(s_1 - s_2)^2] \\ - 4.921[(A(a_1 - a_2)^2] - 5.659[(B(b_1 - b_2)^2] + 15.250[(V(v_1 - v_2)^2]\end{Bmatrix} \\
&+ 2.303\left(\frac{w_1 w_2}{T}\right)(w_1 - w_2)\begin{Bmatrix}-2001.561 + 1142.780[(c_1 - c_2)^2] - 2735.160[(E(e_1 - e_2)^2] - 38.541[(S(s_1 - s_2)^2] \\ + 13.176[(A(a_1 - a_2)^2] + 0.811[(B(b_1 - b_2)^2] + 38.508[(V(v_1 - v_2)^2]\end{Bmatrix} \\
&+ 2.303\left(\frac{w_1 w_2}{T}\right)(w_1 - w_2)^2\begin{Bmatrix}1474.963 - 1507.479[(c_1 - c_2)^2] + 4421.302[E(e_1 - e_2)^2] + 17.981[S(s_1 - s_2)^2] \\ - 21.196[A(a_1 - a_2)^2] + 6.595[B(b_1 - b_2)^2] - 13.386[V(v_1 - v_2)^2]\end{Bmatrix}
\end{aligned} \quad (64)$$

in which e_1, b_1, s_1, a_1, b_1, v_1 and e_2, b_2, s_2, a_2, b_2, v_2 are the Abraham solvation parameters of solvents 1 and 2 and w_1 and w_2 are the mass fractions of solvents 1 and 2 in binary mixtures, respectively.

The model correlates the solubility of drugs in four aqueous-cosolvent mixtures with the overal MPD of 18.5%. Theoretically the model should be able to predict the solubility of solutes employing the solubilities in the mono-solvents. An updated version of the model for drugs solubility prediction in the binary solvents at various temperatures was proposed as (100):

$$\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T}$$
$$+ 2.303(\frac{w_1 w_2}{T})\begin{Bmatrix}(1639.07 - 561.01[(c_1 - c_2)^2] - 1344.81[(E(e_1 - e_2)^2] - 18.22[(S(s_1 - s_2)^2]\\ -3.65[(A(a_1 - a_2)^2] + 0.86[(B(b_1 - b_2)^2] + 4.40[(V(v_1 - v_2)^2]\end{Bmatrix}$$
$$+ 2.303(\frac{w_1 w_2}{T})(w_1 - w_2)\begin{Bmatrix}-1054.03 + 10.43.54[(c_1 - c_2)^2] + 359.47[(E(e_1 - e_2)^2] - 1.20[(S(s_1 - s_2)^2]\\ +30.26[(A(a_1 - a_2)^2] - 2.66[(B(b_1 - b_2)^2] - 0.16[(V(v_1 - v_2)^2]\end{Bmatrix}$$
$$+ 2.303(\frac{w_1 w_2}{T})(w_1 - w_2)^2\begin{Bmatrix}2895.07 - 1913.07[(c_1 - c_2)^2] - 901.29[E(e_1 - e_2)^2] - 10.87[S(s_1 - s_2)^2]\\ +24.62[A(a_1 - a_2)^2] + 9.79[B(b_1 - b_2)^2] - 24.38[V(v_1 - v_2)^2]\end{Bmatrix} \quad (65)$$

employing solubility of 48 drugs in 8 aqueous binary cosolvent mixtures at various temperatures which correlates the data with the overall MPD of 42.4% (100).

The main limitation of the Jouyban-Acree-Abraham models (Eqs. 62-65) is that the Abraham solvent coefficients are not available for a number of pharmaceutically relevant cosolvents. To cover this point, another generally trained model based on Eq. 23 using Hansen solubility parameters was proposed as (101):

$$\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln w_{2,T} + 2.303(\frac{w_1 w_2}{T})\{(0.606\delta_{p1}(\delta_{p2} - \delta_{p3})^2 + 0.013\delta_{h1}(\delta_{h2} - \delta_{h3})^2\}$$
$$+ 2.303(\frac{w_1 w_2}{T})(w_1 - w_2)\{-8.696\delta_{h1}(\delta_{h2} - \delta_{h3})^2 + 0.376\delta_{p1}(\delta_{p2} - \delta_{p3})^2 + 0.013\delta_{h1}(\delta_{h2} - \delta_{h3})^2 \quad (66)$$
$$+ 2.303(\frac{w_1 w_2}{T})(w_1 - w_2)^2\{9.277\delta_{d1}(\delta_{d2} - \delta_{d3})^2 - 0.461\delta_{p1}(\delta_{p2} - \delta_{p3})^2 + 0.017\delta_{h1}(\delta_{h2} - \delta_{h3})^2$$

where δ_{h1}, δ_{p1}, δ_{d1}, δ_{h2}, δ_{p2}, δ_{d2}, δ_{h3}, δ_{p3} and δ_{d3} are the partial solubility parameters of the solutes, solvents *1* and *2*. δ_d is the energy from dispersion bonds between molecules, δ_p is the energy from polar bonds between molecules, and δ_h is the energy from hydrogen bonds between molecules.

***In silico* models**

Solubility of anthrecene and pyrene in a number of non-aqueous ternary solvent mixtures was predicted using an *in silico* model reported in earlier papers (140-143). The Abraham model (14) was used to predict the solubility in the mono-solvents and the mixed solvent interaction terms of Eq. 62 was used to predict the solubility in solvent mixtures in which the obtained prediction errors were acceptable (143). Several attempts to provide an *in silico* model to predict drug solubility in binary solvents were not successful so far and more efforts should be made to achieve this valuable goal.

CONCLUSION

The accuracies of a number of cosolvency models were compared using 30 data sets of the solubility of drugs in aqueous binary solvent mixtures at a given temperature concerning the number of curve-fitting parameters and input data. The results showed that %Dev for correlated solubility data varied from 22.3% (for CNIBS/R-K model with three constant terms) to 3.1% (for the same model with 7 constant terms) as was expected. Concerning a given number of constant terms for various models, the observed %Dev were relatively the same for multi-linear models (63). This observation could be theoretically justified since all these models could be converted to GSM

as discussed earlier (24). As a general conclusion, there is no full predictive model for solubility of drugs in mixed solvent systems. To provide such models, more comprehensive solubility database is required and researches are ongoing to provide such a big database. However, employing a minimum number of experimental data points for a given drug in a certain mixed solvent system, one may provide prediction tools with acceptable accuracy to save the time and cost of the experimental works in the pharmaceutical industry.

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