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Prediction of drug solubility in ethanol-ethyl acetate mixtures at various temperatures using the Jouyban-Acree model

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The profile of twenty-six solubility data sets in ethanol-ethyl acetate mixtures at various temperatures were reproduced using a trained version of the Jouyban-Acree model. The mean percentage deviation between predicted and observed solubilities was 13.1%. The maximum solubility ($logX_{m,max}$) in the mixed solvent system and the corresponding solvent composition ($f_{1,max}$) were also predicted by the model. The overall average error of $log_{Xm,max}$ was 0.07 ± 0.04 in logarithmic scale and for $f_{1,max}$ was 0.07 ± 0.07, which is equal to 7% when solvent composition is expressed as volume percentage of the cosolvent.

Key words: Solubility prediction – Maximum solubility – Optimized solvent composition – Jouyban-Acree model – Ethanol-ethyl acetate.

Solubilization of a low soluble drug/drug candidate using a miscible cosolvent is the most common technique to increase solubility and is still a challenging subject in pharmaceutical area. In addition to experimental efforts, a number of computational methods have been presented to calculate the solubility in mixed solvents. Most of these models have been reviewed in a recent paper and consider a single phenomenon, i.e. solubility of a solute in mixed solvents, the question raised was; why are there numerous models to represent a phenomenon? To address this point, a number of approaches are discussed and a unified cosolvency model has been derived using algebraic manipulations [1]. Previous results showed that the Jouyban-Acree model (formerly known as the combined NIBS/Redlich-Kister model) was the most accurate model among similar algorithms [2]. The model was able to represent the solubility of structurally related drugs [3], the chameleonic effect [4], solubility of drugs at various temperatures [4], solubility of polymorphs [5] and solubility of ionizable compounds such as amino acids [6] and electrolytes [7] in mixed solvents. The model is also able to predict the solubility of drugs in ternary solvents based on the model constants computed from binary solvent data [8]. The main drawback of the model is its constant terms that require a number of experimental data points to compute the numerical values of these constants. To address this limitation, a trained version of the Jouyban-Acree model was presented to predict the solubility of drugs in water-dioxane mixtures at various temperatures. Using the trained version, only two solubility data points in neat water and dioxane are required to predict the solubility of a drug in the mixtures and the percentage deviation (%D) of the predicted data sets was 27% [9]:

$$\%D = \frac{100}{N}\sum \frac{\left|X_m^{Predicted} - X_m^{Observed}\right|}{X_m^{Observed}}$$

In this communication, a general trained model is presented to predict the solubility of drugs in non-aqueous mixture and its capability of predicting the maximum solubility in the binary mixture ($log_{Xm,max}$) and the corresponding solvent composition ($f_{1,max}$) is checked. The latter two figures are highly demanded in drug discovery studies where a suitable solubilization medium is investigated usually by trial and error. In order to provide better solubilization solvent to prepare liquid formulations and/or desolubilization solvent system for crystallization of drugs, mixed solvent systems are often used. It is obvious that any computational method for predicting solubility in mixed solvents is a great tool for replacing experimental trial and errors or even reducing the number of required experiments. Although ethanol-ethyl acetate mixtures are not used in drug formulations, the mixtures are employed in many cosolvency studies as a model solvent system.

The Jouyban-Acree model [8, 10] is:

$$\ln X_m = f_1 \ln X_1 + f_2 \ln X_2 + f_1 f_2 \sum_{i=0}^{2} A_i (f_1 - f_2)^i \qquad \textbf{Eq. 1}$$

where X_m is the mole fraction solubility of the solute in solvent mixture, f_1 and f_2 are the fractions of solvents 1 and 2 in the absence of the solute, X_1 and X_2 denote the mole fraction solubilities in solvents 1 and 2, respectively, and A_i are the model coefficients. Subscript 1 of f and X terms represent the fraction of solvent and solute solubility in solvent with higher solubility and for all solvent systems $X_1 > X_2$. As examples, for the solubility of caffeine in ethanol-ethyl acetate, ethyl acetate is the solvent 1 and ethanol is solvent 2, whereas for the solubility of paracetamol in ethanol-ethyl acetate, ethanol is the solvent 1 and ethyl acetate is the solvent 2. As indicated above, the applicability of the model was also extended to calculate the solubility of drugs in binary solvents at various temperatures [4] as:

$$\ln X_{m,T} = f_1 \ln X_{1,T} + f_2 \ln X_{2,T} + \left(\frac{f_1 f_2}{T}\right)\sum_{i=0}^{2} J_i (f_1 - f_2)^i \qquad \textbf{Eq. 2}$$

where $X_{m,T}$, $X_{1,T}$ and $X_{2,T}$ are the solubility of the solute in solvent mixture, solvents 1 and 2 at temperature (T, K) and J_i are the model constants.

The available solubility data of drugs in ethanol-ethyl acetate mixtures at various temperatures (26 sets) taken from the literature [11-17] were fitted to *Equation 2* and the trained model is:

$$\ln X_{m,T} = f_1 \ln X_{1,T} + f_2 \ln X_{2,T} + \left(\frac{f_1 f_2}{T}\right)\left[382.987 + 125.663(f_1 - f_2) + 214.579(f_1 - f_2)^2\right] \qquad \textbf{Eq. 3}$$

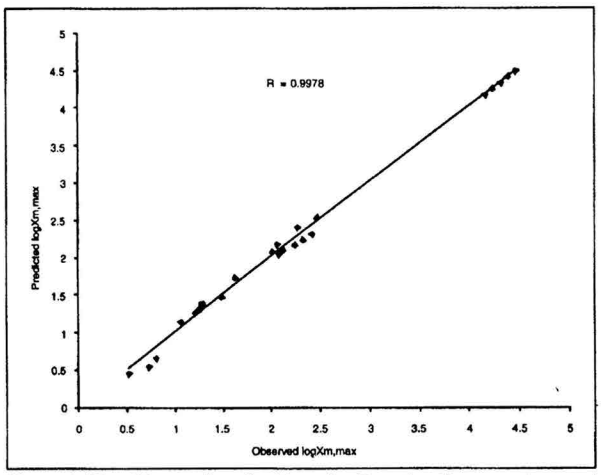

Figure 1 - Plot of the predicted $logX_{m,max}$ (by *Equation 3*) versus observed $logX_{m,max}$ of drugs studied (n = 26) and the correlation coefficient.

Then the solubility of drugs was predicted using *Equation 3* and %D was computed. The minimum (3.0) and maximum (32.9) %Ds were observed for caffeine in ethyl acetate-ethanol mixtures at 35°C and salicylic acid in ethanol-ethyl acetate at 25°C, respectively, and the overall %D (± SD) was 13.1 ± 8.1.

The minimum (0.01) and maximum (0.17) absolute error (AE = |Predicted-Observed|) for $logX_{m,max}$ were observed for phenacetin data in ethyl acetate-ethanol mixtures at 25°C and salicylic acid in ethanol-ethyl acetate mixtures at 25°C, respectively, and the overall AE (± SD) was 0.07 ± 0.04. *Figure 1* showed the predicted $logX_{m,max}$ versus observed values for the twenty-six data sets studied. A high correlation coefficient (R = 0.9978) revealed that the model provides accurate predictions. The minimum, maximum and overall AE (± SD) values for AE of $f_{1,max}$ were 0.01 (for niflumic acid in ethyl acetate-ethanol mixtures at 25°C), 0.26 (salicylic acid in ethanol-ethyl acetate mixtures at 25°C) and 0.07 ± 0.07, respectively.

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In conclusion, the proposed model was capable of providing accurate predictions for the solubility of drugs in ethanol-ethyl acetate mixtures at various temperatures and the required information is the solubility of drugs in neat solvents which is usually available from the early stage of drug discovery studies.

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