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COMMUNICATION

Prediction of Drug Solubility in Ternary Solvent Mixture

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ABSTRACT

Applicability of the combined, nearly ideal, binary solvent/Redlich-Kister equation for calculating drug solubility in ternary mixtures is presented. The advantages of the proposed model are discussed and compared with a recently published equation that calculates the solute solubility in ternary solvent mixtures based on the mixture response methodology.
Key Words: *Drug solubility; Solubility prediction; Ternary solvent mixtures.*

The mathematical representation of the cosolvency phenomenon is of value in correlation/prediction of the solubility data in mixed solvents and is of importance in different pharmaceutical fields, including the formulation of a liquid form of a poorly water soluble drug. Numerous predictive or correlative cosolvency models have been published for calculation of the solubility in mixed solvents. Group contribution methods, such as universal functional activity coefficients (UNIFAC), have proved fairly successful in calculating solute solubility in mixed solvents. The main advantage of predictive methods like UNIFAC is that they do not employ any curve-fitting parameters; this means that one can predict the solubility without using any experimental data points. The correlative/predictive cosolvency models containing the curve-fitting parameters provide acceptable degrees of accuracy. However, they need some experimental data points to calculate the curve-fitting parameters, and from a prediction viewpoint, the best model is that which needs fewer experimental data points, and thus the time to reach solubility optimization is reduced. In this communication, an extended form of an established cosolvency equation for calculating solubility data is presented.

In a recent paper, Stephens and coworkers (1) proposed a mixture response equation for correlating/pre-

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dicting the solubility of 19-nor 1α, 25-dihydroxyvitamin D_2 in a ternary mixture of ethanol–propylene glycol–water. The proposed model is

$$\ln S_m = \beta_1 f_1 + \beta_2 f_2 + \beta_3 f_3 + \beta_4 f_1 f_2 + \beta_5 f_1 f_3 + \beta_6 f_2 f_3 + \eta \quad (1)$$

where S_m is the drug solubility in the mixed solvent; β_1–β_6 represent the curve-fitting parameters; f_1, f_2, and f_3 denote the volume fractions of ethanol, propylene glycol, and water, respectively; and η is the random error term. The authors built the following equation by employing 5 data points for predicting the drug solubility at other ternary compositions:

$$\ln S_m = 16.21 f_1 + 10.52 f_2 - 5.37 f_3 - 2.14 f_1 f_2 + 4.07 f_1 f_3 \quad (2)$$

and the solubilities of 3 other data points were predicted by Eq. 2. The percentage differences between predicted and experimental solubilities were in the range +14.9% to −16.8% (1).

The application of these equations is very appropriate for the pharmaceutical field. As an example, to prepare liquid drug formulations (i.e., oral or parenteral solutions) of poorly water soluble drugs, one may use a mixture of water and a miscible cosolvent. But, in some cases, the binary aqueous-cosolvent mixture is not able to dissolve a required amount of the drug, or there are restrictions for preparing a liquid pharmaceutical preparation containing a higher concentration of the cosolvent. In such cases, the formulator can use this second cosolvent; however, by adding this cosolvent, a large number of experiments are often required in a trial-and-error approach to find the optimum concentrations of the cosolvents. As a general rule, the higher the concentration of the cosolvent, the larger the amount dissolved of poorly water soluble drug, but because of patient toxicity considerations, the concentration of the cosolvents should be kept as low as possible, usually less than 50% v/v. In addition, by using higher concentrations of the cosolvents, it increases the cost.

By using cosolvency models, one can reduce the number of experiments by replacing the trial-and-error approach with a rational formulation procedure. In this communication, we propose an alternative model to that of Stephens and coworkers (1). Here, a comprehensive equation is presented, that is, the combined, nearly ideal, binary solvent/Redlich-Kister (CNIBS/R-K) provides more accurate results and has higher prediction capability. The CNIBS/R-K is a theoretically based solution model that has provided accurate results for the solubility of the solute in both aqueous (2) and nonaqueous (3) mixed solvents. The CNIBS/R-K model is

$$\ln S_m = f_1 \ln S_1 + f_2 \ln S_2 + f_1 f_2 [A_0 + A_1 (f_1 - f_2) + A_2 (f_1 - f_2)^2 + \ldots] \quad (3)$$

where subscripts 1 and 2 are solvents 1 and 2, and A_0–A_2 represent the curve-fitting parameters. These parameters are computed by regressing $\ln S_m - f_1 \ln S_1 - f_2 \ln S_2$ versus $f_1 f_2$, $f_1 f_2 (f_1 - f_2)$ and $f_1 f_2 (f_1 - f_2)^2$ using a no intercept, least-square analysis (4). The model produces improved accuracy of the results in comparison with other cosolvency models (2). However, the pharmaceutical formulator has to determine a minimum number of experiments to calculate the model parameters (i.e., A_0–A_2). As a solution to this problem, since these parameters are nearly constant for the structurally related drugs in a given binary solvent, the proposed model can be applied to the solubility of the structurally related compounds. After calculating A_0–A_2, one can use the model to predict the solubility of other similar drugs from the same chemical group. These types of solubility studies are regularly carried out in the pharmaceutical industry when similar drugs are synthesized from a leading compound for further biological and pharmacological tests. The accuracy of this assumption has been shown in our recent publication (5).

The CNIBS/R-K model for ternary solvent mixture is

$$\begin{aligned} \ln S_m = {} & f_1 \ln S_1 + f_2 \ln S_2 + f_3 \ln S_3 \\ & + f_1 f_2 [A_0 + A_1 (f_1 - f_2) + A_2 (f_1 - f_2)^2 + \ldots] \\ & + f_1 f_3 [B_0 + B_1 (f_1 - f_3) + B_2 (f_1 - f_3)^2 + \ldots] \\ & + f_2 f_3 [C_0 + C_1 (f_2 - f_3) + C_2 (f_2 - f_3)^2 + \ldots] \end{aligned} \quad (4)$$

where B_0–B_2 and C_0–C_2 are the additional curve-fitting parameters representing the solvent-solvent and solute-solvent interactions. These parameters, shown as the *A*, *B*, and *C* terms in Eq. 4, can be computed from experimental solubility data in binary mixtures by employing statistically significant curve-fitting parameters, as has been shown in a recent paper (6). From this information, it is possible to predict the drug solubility in a ternary solvent mixture by using the sub-binary solubility data. In practice, the ternary solvents are employed when the binary mixtures are not able to dissolve the appropriate

amount of the drug. Therefore, the produced binary data can be used for further solubility predictions in ternary mixtures.

It is obvious that both Eqs. 1 and 4 are the same from a mathematical point of view; therefore, by replacing ln S_1, ln S_2, and ln S_3 with β_1–β_3 and using a simplified form of Eq. 4, one can convert Eq. 4 into Eq. 1 or vice versa.

$$\ln S_m = f_1 \ln S_1 + f_2 \ln S_2 + f_3 \ln S_3 + A_0 f_1 f_2 + B_0 f_1 f_3 + C_0 f_2 f_3 \quad (5)$$

The main advantages of the proposed equation in comparison with Eq. 1 are

1. The values of S_1, S_2, and S_3 are known for most of the drugs or drug candidates in the common solvents like water or ethanol. Therefore, there is no need to carry out more experiments.
2. The solvent-solvent and solute-solvent interaction terms (i.e., *A*, *B*, and *C* in Eq. 5) can be estimated from solubility data in binary solvents (6).
3. The prediction capability of the CNIBS/R-K model is higher than the mixture response method when a minimum number of data points is employed for estimation of the curve-fitting parameters. It has been shown (7) that, using a set of five data points for 8 alkyl benzoate esters in water–propylene glycol and phenytoin solubility data in propylene glycol–water, 1,3-butanediol–water, and polyethylene glycol 200–water mixtures employed as a training set, the solubility at other solvent compositions could be predicted.
4. The proposed model has a theoretical background. The basic model includes contributions from two-body and three-body interactions. A further explanation of the theoretical background of the CNIBS/R-K model has been discussed elsewhere (8). This is not the case for Eq. 1; however, a possible theoretical justification for Eq. 1 can be provided by the proposed equation.
5. One can employ more curve-fitting parameters in our proposed model to provide more accurate results.
6. The model can be employed for predicting the solubility of the drug in the whole composition range of the solvents. This is not the case for the mixture response model of Stephens and coworkers (1), for which the model allows the prediction with a composition defined in the experimental space of the design.
7. The CNIBS/R-K model is also applicable to correlate/predict the solubility of the drug at different temperatures (5).
8. The model is applicable to predict the solubility of the structurally related drugs in mixed solvents (5).

Up to the present, numerous cosolvency models have been presented to calculate the solubility data of a solute in mixed solvents. Some of these models have been briefly reviewed and their accuracy compared (2). It has been shown that most of the solution models that employ the curve-fitting parameters have reproduced the experimental solubility data. As a rule, the higher the number of curve-fitting parameters, the more accurate the results (2). However, a model containing a large number of curve-fitting parameters is not particularly useful in the pharmaceutical industry. This is because they need more experimental data points to compute the model constants, and this is not often possible due to the scarcity of the drug/new drug candidate. Therefore, in the preformulation stage of a potential new drug, the pharmaceutical formulator often wishes to find the right solvent composition to dissolve the poorly water soluble drug by the fastest route possible, generally with a minimum number of experiments.

In considering the above advantages for the CNIBS/R-K model and its high correlation/prediction capabilities, it can be suggested that this model is one of the best cosolvency models for pharmaceutical applications.

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