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Letter to the Editor

Comments concerning: solubility prediction of caffeine in aqueous *N*,*N*-dimethylformamide mixtures using the extended Hildebrand solubility approach

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In a recent paper published in this journal, Herrador and Gonzalez (1997) reported the experimental and predicted solubilities of caffeine in varying proportions of water–*N*,*N*-dimethylformamide (DMF) using:

$$-\log x_2 = -\log x_2^{id} + \phi_1^2 V_2(\delta_1^2 + \delta_2^2 - 2W)/(2.303RT) \quad (1)$$

the extended Hildebrand solubility approach. A power series of δ_1 was employed to calculate the values of W:

$$W = 48.051 + 8.258\delta_1 + 0.0094\delta_1^3 \quad (2)$$

The various terms in Eqs. (1) and (2) are defined in the original paper.

The purpose of this communication is not to criticize the work of the authors, but rather to present an alternative solution model which provides a more accurate mathematical representation of drug solubility in water–cosolvent mixtures. The theoretically based model, the combined nearly ideal binary solvent/Redlich–Kister (CNIBS/R–K), was originally developed for predicting solute solubility in binary solvents (Acree 1992, 1996)

$$\log x_2 = \phi_{DMF}\log(x_2)_{DMF} + \phi_w\log(x_2)_W + \phi_{DMF}\phi_W[A_0 + A_1(\phi_{DMF} - \phi_W) + A_2(\phi_{DMF} - \phi_W)^2] \quad (3)$$

where ϕ_{DMF} and ϕ_W are the initial volume fraction of DMF and water in the binary solvent system calculated as if the solute were not present, $(x_2)_{DMF}$ and $(x_2)_W$ denote the solute solubility in pure DMF and water, respectively, and $A_0 - A_2$ stand for the curve-fit coefficients. Regressional analysis of the experimental caffeine solubility data in accordance with Eq. (3) yielded numerical values of the three curve-fit coefficients of $A_0 = 0.084$, $A_1 = 1.210$ and $A_2 = 1.657$. The curve-fit coefficients back-calculate the eleven experimental mol fraction solubilities to an average absolute percent deviation (i.e. $\%Dev = (100/11)\,\Sigma\,|(x_2^{calc} - x_2^{exp})/x_2^{exp}|$) of 3.95%. Eq. (1), on the other hand,

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has a significantly larger average absolute percent deviation of 10.67%.

From a purely practical point-of-view, the CNIBS/R–K model requires fewer input parameters than does the extended Hildebrand solubility approach. One does not require a prior knowledge of x_2^{id} (calculated from the solute's molar enthalpy of fusion and melting point temperature), the solute solubility parameter (δ_2) and solute molar volume (V_2) in order to use Eq. (3). For drug molecules that decompose upon melting or near the melting point temperature, it is not always possible to measure accurately the solute molar enthalpy of fusion. Solubility parameters of crystalline drug molecules are often deduced from group contribution methods, measured solute solubilities in several solvents, or from plots of mole fraction solubility versus the solubility parameter of the binary solvent mixtures. Rarely do the methods give the same numerical value. In the case of caffeine, Herrador and Gonzalez (1997) calculated a value of $\delta_2 = 13.8$ using the van Krevelen (1990) group contribution method and a value of $\delta_2 = 13.5$ based upon the maximum observed in the mole fraction solubility versus solvent solubility parameter for the DMF–water system. Naturally, whenever two (or more) δ_2 values are calculated there is always some question regarding which of the values should be used in the mathematical representation/prediction. The CNIBS/R–K model eliminates this problem.

In closing we note that the CNIBS/R–K model has been used successfully to describe the solubility behavior of structurally related drugs and solute solubility as a function of temperature (Jouyban-Gharamaleki et al., 1998a), and to describe multiple solubility peaks (Jouyban-Gharamaleki and Acree, 1998) in mixed solvents. Our computations (Acree, 1996; Jouyban-Gharamaleki et al., 1998b) have further documented that the CNIBS/R–K model often provides a more accurate mathematical representation of experimental solubility behavior in mixed solvents than equations derived from other cosolvency models.

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