AAPS PharmSciTech, Vol. 15, No. 1, February 2014 (© 2013)
DOI: 10.1208/s12249-013-0037-z

Brief/Technical Note

Comments on "Prediction of Drug Solubility in Lipid Mixtures from the Individual Ingredients"

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Received 25 July 2013; accepted 19 September 2013; published online 22 October 2013

KEY WORDS: genistein; indomethacin; nifedipine; probucol; solubility; solvent mixtures.

Experimental solubilities of genistein, probucol, nifedipine, and indomethacin in a number of lipids and some lipid mixtures at 40°C have been reported by Sanchetti and Nejati (1) in this journal. The authors correlated the experimental milligrams per gram solubilities using models derived from the mixture response methodology:

$$S_m = \sum_{i=1}^{4} a_i m_i + \sum_{j=i+1}^{4} b_{ij} m_i m_j. \quad (1)$$

In addition, the weighted average solubilities were calculated using:

$$S_m = \sum_{i=1}^{4} m_i S_i \quad (2)$$

along with its logarithmic transformations:

$$\log S_m = \sum_{i=1}^{4} m_i \log S_i. \quad (3)$$

The aim of this communication is to point out several capabilities of an established cosolvency model, i.e., the Jouyban–Acree model for representing the solubility of pharmaceuticals in mixed solvent systems. The basic model does contain provisions for representing both the effects of solvent composition and temperature on the solubility of solutes (2):

$$\log S_{m,T} = m_1.\log S_{1,T} + m_2.\log S_{2,T} + \frac{m_1.m_2}{T}.\sum_{i=0}^{2} J_i.(m_1 - m_2)^i \quad (4)$$

where $S_{m,T}$ is the solute solubility in the mixed solvent at temperature T, m_1, and m_2 are the mass fractions of solvents 1 and 2 in the absence of the solute; $S_{1,T}$ and $S_{2,T}$ denote the solubility of the solute in the mono-solvents 1 and 2; and the J_i terms are the constants of the model computed by regression analysis (3). The Jouyban–Acree model provided accurate predictions for the solubility of drugs in mixed solvents (binary and ternary solvent mixtures) at various temperatures (4–7). It is possible to extend its applicability to quaternary solvents at various temperatures as:

$$\begin{aligned} \log S_{m,T} = {} & m_1.\log S_{1,T} + m_2.\log S_{2,T} + m_3.\log S_{3,T} + m_4.\log S_{4,T} \\ & + \frac{m_1.m_2}{T}.\sum_{i=0}^{2} J_i.(m_1 - m_2)^i + \frac{m_1.m_3}{T}.\sum_{i=0}^{2} J'_i.(m_1 - m_3)^i \\ & + \frac{m_1.m_4}{T}.\sum_{i=0}^{2} J''_i.(m_1 - m_4)^i + \frac{m_2.m_3}{T}.\sum_{i=0}^{2} J'''_i.(m_2 - m_3)^i \\ & + \frac{m_2.m_4}{T}.\sum_{i=0}^{2} J''''_i.(m_2 - m_4)^i + \frac{m_3.m_4}{T}.\sum_{i=0}^{2} J'''''_i.(m_3 - m_4)^i \end{aligned} \quad (5)$$

where $S_{3,T}$ and $S_{4,T}$ are the solubility of the solute in the mono-solvents 3 and 4, J terms are the model constants. Using Eq. (5), it is possible to train the model using solubility data of a solute in the sub-binary solvent systems, then predict the solubility of the solute in ternary or quaternary (or higher order) solvent mixtures (7). Addition of ternary or quaternary solvent interaction terms provided more accurate calculations (5–7), however, it requires more experimental data points in the training process which is a limiting factor in the solubility

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Table I. The Mean Relative Deviation (MRD) for Various Equations Investigated in this Communication for Back-Calculated Solubilities

	Genistein	Probucol	Nifedipine	Indomethacin	Overall
Equation 1	2.9±3.5	16.8±19.8	2.4±1.4	2.3±2.5	6.1±11.8*
Equation 2	10.6±13.7	9.6±6.6	4.4±3.4	3.9±4.0	7.1±8.5**
Equation 3	14.4±11.5	12.9±8.1	7.6±6.2	8.6±7.1	10.9±8.8**
The proposed model	1.7±1.4	5.4±5.8	1.9±1.7	1.6±1.7	2.7±3.5*,**

*Mean difference is statistically significant (paired t test, $p<0.002$)
**Mean differences are statistically significant (paired t test, $p<0.0005$)

prediction studies at early stages of drug development because of the scarcity of the new drug.

Considering this capability, we have fitted the model to the solubility of four investigated drugs in the mixtures of lipids at 40°C and calculated the model constants along with the mean relative deviation (MRD) values defined by:

$$MRD = \frac{100}{N}\sum\left|\frac{S_m^{Calculated} - S_m^{Experimental}}{S_m^{Experimental}}\right| \quad (6)$$

in which N is the number of data point in each set.

Table VI of Sancchetti and Nejati (1) reported the computed model constants of Eq. 1, their p values for the constants and the coefficient of determination (R^2) of the correlations. They reported the constants with the p values of <0.0005 for m_1m_2 and m_2m_4 terms of genistein up to 0.907 for m_2m_3 term of probucol. As a general rule, the model constants with the p value of more than 0.10 do not significantly contribute to the prediction capability of the model. As an example, the mean relative distribution (MRD) of the probucol data set using all constants, i.e.:

$$S_m = 158.20m_1 + 184.96m_2 + 98.15m_3 + 7.15m_4 + 14.58m_1m_2 + 52.47m_1m_3 + 127.83m_1m_4 + 69.56m_2m_3 - 5.48m_2m_4 + 52.20m_3m_4 \quad (7)$$

is 16.8%. When the model constants with p values of 0.907 (i.e., m_2m_4) and 0.755 (i.e., m_1m_2) are excluded from the model (Eq. 8):

$$S_m = 158.20m_1 + 184.96m_2 + 98.15m_3 + 7.15m_4 + 52.47m_1m_3 + 127.83m_1m_4 + 69.56m_2m_3 + 52.20m_3m_4 \quad (8)$$

the obtained MRD is again 16.8%. To avoid any confusion for the readers, we have included all reported model constants (both significant and non-significant) by Sancchetti and Nejati in our comparisons. The calculated MRDs for the four investigated drugs using Eqs. 1–3 are listed in Table I. In addition, the solubility data were regressed according to Eq. 5 and the significant model constants ($p<0.10$) are listed in Table II along with the R^2, F and p values of the correlations. The reported J_0 terms in Table II provide acceptable prediction accuracy and we included only J_0 terms in the computations inclusion of J_1 and J_2 terms provide more accurate calculations, however require more experimental solubility data points. The J (J_0, J_1, and J_2) terms represent various two-body and three-body interactions between binary solvents and the solute and further details of these constants have been provided in the literature (8). Among the investigated drugs, the best results for all models are obtained for indomethacin. The weighted average solubilities provided the best results among three models presented by Sancchetti and Nejati and the mean difference between MRDs of Eqs. 1 and 2 was not statistically significant (paired t test, $p>0.415$). Equation 2 requires only experimental solubility data in the mono-solvents and more preferred when one wishes to estimate the solubility using minimum experimental efforts. Equation 5 provided the most accurate results and the mean differences were statistically significant with Eq. 1 ($p<0.002$) and Eqs. 2 and 3 ($p<0.0005$). This finding is in agreement with the previous findings (7,9,10). Considering the number of minimum solubility data required in the training process of Eqs. 1 and 5, both models need 10 data points.

The main advantages of the Jouyban–Acree model over Eqs. 1–3 for representing the solubility of solutes in the mixtures are as follows: (1) A uniform mathematical representation of solubility and other physico-chemical properties, (2) the calculated equation coefficients for binary solvent mixtures can be combined to estimate solute solubility in ternary and higher order multi-component systems (7), and (3) the model contains provisions for correlating experimental solubility as a function of both temperature and solvent composition, (4) it was successfully used to calculate the solubility of a large number of pharmaceuticals in aqueous and non-aqueous solvent mixtures at various temperatures (11), (5) it could be trained using a minimum number of experimental data points and then predict the solubility at other temperatures and solvent compositions (12), (6) globally trained versions of the model are available to predict the solubility of pharmaceuticals (13,14), and (7) it possesses a theoretical background (8). Concerning these findings, it is recommended to use the Jouyban–Acree model in pharmaceutical applications.

Table II. Statistical Details of the Proposed Model

	Genistein	Probucol	Nifedipine	Indomethacin
J_0	0.836	NS	0.446	0.467
J_0'	0.095	NS	0.125	0.115
J_0''	0.073	0.522	0.134	0.054
J_0'''	0.386	0.287	0.092	0.181
J_0''''	0.439	0.173	0.090	0.233
J_0'''''	NS	0.334	NS	NS
R	0.995	0.890	0.971	0.982
F	414	22	71	120
p value	<0.0005	<0.0005	<0.0005	<0.0005

NS not statistically significant ($p>0.10$)

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