Chameleonic Effect and Some Models for Predicting Drug Solubility in Solvent Mixtures

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A new model derived from an excess free energy approach which expresses drug solubility in solvent mixtures showing multiple solubility peaks, the chameleonic effect, with respect to the concentrations of solvents in a mixture is proposed. Accuracy and predictability of the model are compared with those of a previous model which expresses drug solubility based on Hildebrand, acidic and basic solubility parameters. The results indicate that the new model is more accurate than the previous model and average percent mean errors are 5.32 and 13.66, respectively.

Key words solubility; chameleonic effect; two solubility maxima; predicting model; excess free energy

The chameleonic effect, existence of multiple peaks in the plot of solubility *versus* solubility parameter of solvent (δ_1), was described first by Hoy in 1970.[1] Other investigators reported this phenomenon for some drugs in certain mixed solvents.[2-5]

In the present report a new equation derived from an excess free energy approach[6] for predicting drug solubility in the presence of the chameleonic effect has been proposed and some statistical parameters of the model are compared with those of a previous model presented by Escalera *et al.*[3]

The previously published model which describes the chameleonic effect in a quantitative way in terms of Lewis acid–base interactions is as follows:

$$\ln(X_m)=C_0+C_1\delta_1+C_2\delta_1^2+C_3\delta_{1a}+C_4\delta_{1b}+C_5\delta_{1a}\delta_{1b} \quad (1)$$

where X_m represents the mole fraction solubility of a drug in mixed solvent, C_0—C_5 are the model constants and δ_1, δ_{1a} and δ_{1b} are Hildebrand, acidic and basic solubility parameters for mixed solvents, respectively.[3] The values of δ_1, δ_{1a} and δ_{1b} are calculated by Eqs. 2—4:

$$\delta_1=f_a\delta_{1(a)}+f_b\delta_{1(b)}+f_c\delta_{1(c)} \quad (2)$$

$$\delta_{1a}=f_a\delta_{1a(a)}+f_b\delta_{1a(b)}+f_c\delta_{1a(c)} \quad (3)$$

$$\delta_{1b}=f_a\delta_{1b(a)}+f_b\delta_{1b(b)}+f_c\delta_{1b(c)} \quad (4)$$

in which f_a, f_b and f_c are the volume fractions of solvents a, b and c in the solvent mixture and $\delta_{1(a)}$, $\delta_{1(b)}$, $\delta_{1(c)}$, $\delta_{1a(a)}$, $\delta_{1a(b)}$, $\delta_{1a(c)}$, $\delta_{1b(a)}$, $\delta_{1b(b)}$ and $\delta_{1b(c)}$ represent Hildebrand, acidic and basic solubility parameters of solvents a, b and c, respectively.

Williams and Amidon[6] proposed an excess free energy approach for calculating solubility in ternary solvent systems. This equation is represented as:

$$\begin{aligned}\ln(X_m)=&f_a\ln(X_a)+f_b\ln(X_b)+f_c\ln(X_c)-A_{a-b}f_af_b(2f_a+2f_c-1)(q_2/q_a)\\&+2A_{b-a}f_af_b(f_a+f_c)(q_2/q_b)-A_{a-c}f_af_c(2f_a-1)(q_2/q_a)\\&+2A_{c-a}f_a^2f_c(q_2/q_c)-A_{c-b}f_bf_c(2f_c-1)(q_2/q_c)\\&+2A_{b-c}f_bf_c^2(q_2/q_b)+G_{a2b}q_2f_af_b+G_{a2c}q_2f_af_c+G_{2bc}q_2f_bf_c\\&-G_{abc}q_2f_af_bf_c-Kq_2f_af_bf_c\end{aligned} \quad (5)$$

where X_a, X_b and X_c denote drug solubility in the neat solvents a, b and c, respectively, q_2, q_a, q_b and q_c are the molar volumes of solute and solvents a, b and c. A_{a-b}, A_{b-a}, A_{a-c}, A_{c-a}, A_{c-b}, A_{b-c}, G_{a2b}, G_{a2c}, G_{2bc}, G_{abc} and K represent the interaction terms which have constant values for a certain system.

In all solvent mixtures which showed two solubility maxima[3-5] the value of f_a or f_c is zero, thus all terms containing f_af_c are omitted from the equation. So one can assume the other constant terms as the new coefficients and appropriate rearrangements:

$$\begin{aligned}\ln(X_m)=&f_a\ln(X_a)+f_b\ln(X_b)+f_c\ln(X_c)+B_1f_a^2f_b+B_2f_af_b\\&+B_3f_c^2f_b+B_4f_cf_b\end{aligned} \quad (6)$$

where $B_1=-2A_{a-b}(q_2/q_a)+2A_{b-a}(q_2/q_b)$, $B_2=A_{a-b}(q_2/q_a)+G_{a2b}q_2$, $B_3=-2A_{c-b}(q_2/q_c)+2A_{b-c}(q_2/q_b)$ and $B_4=A_{c-b}(q_2/q_c)+G_{2bc}q_2$. These coefficients represent solvent–solvent and solute–solvent interactions at the molecular level.

The available solubility data with two solubility maxima are fitted to Eq. 6 and the obtained results are compared with those of Eq. 1 presented in the original papers.[3-5] Table 1 shows the characteristics of data and values of

Table 1. Data Fitted to Equation 6 as well as PME, and Coefficient of Determination, r^2, for Eqs. 1 and 6

Solute[a]	N[b]	Eq. 1		Eq. 6		Reference
		r^2	PME[c]	r^2[d]	PME[c]	
Sulfanilamide	21	0.990	8.33	0.9981	2.65	4
Sulfamethazine	24	0.980	11.29	0.9933	7.30	4
Sulphamethoxypyridazine	26[e]	0.990	18.19	0.9989	2.42	3
Paracetamol	25	0.970	16.84	0.9808	8.92	5

a) Solvent systems are water–ethanol and ethanol–ethyl acetate mixtures. *b*) N: number of experimental data in each set. *c*) PME: percent mean error is calculated by:

$$\mathrm{PME}=(100/N)\sum|(X_m^{\mathrm{Calculated}}-X_m^{\mathrm{Experimental}})/X_m^{\mathrm{Experimental}}|$$

d) r^2: Correlated the experimental values of $\ln(X_m)-f_a\ln(X_a)-f_b\ln(X_b)-f_c\ln(X_c)$ *versus* $f_a^2f_b$, f_af_b, $f_c^2f_b$ and f_cf_b. *e*) Experimental data of ethyl acetate–hexane mixtures has been excluded from calculations.

percent mean error, (PME), as well as coefficient of determination, r^2, for Eqs. 1 and 6. The accuracy and predictability of Eq. 6 is a factor of 2.6 better than that of Eq. 1.

Equation 1 can be converted to a multivariate equation with substitution of values of δ_1, δ_{1a} and δ_{1b} from Eqs. 2—4 and replacing of f_c with $(1-f_a-f_b)$ and simplification of the resultant equation. The obtained Eq. is:

$$\ln(X_m) = M_0 + M_1 f_a + M_2 f_b + M_3 f_a^2 + M_4 f_b^2 + M_5 f_a f_b \quad (7)$$

where M_0—M_5 are model constants which are calculated by commercial software. Fitting data sets cited in Table 1 to Eq. 7 resulted in 10.19 for average percent mean error, (APME), while APME for Eqs. 1 and 6 are 13.66, and 5.32, respectively.

It is obvious that a definite experimental phenomenon must have a single mathematical representation and for presentation of a solute solubility in solvent mixtures, cosolvency, numerous models had been published.[3-10] However, in a recent report, we have shown that some of the models that predicted solubility in binary solvents were, in fact, mathematically identical.[7] In conclusion, the excess free energy model can predict the solute solubility in a binary or two binary solvent systems with a common solvent without solubility peak and with single or multiple peaks in solubility profiles.

Acknowledgment The author would like to thank Professor M. Barzegar-Jalali, Department of Pharmaceutics, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran for his helpful comments.

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