The Modified Wilson Model and Predicting Drug Solubility in Water–Cosolvent Mixtures

Abolghasem JOUYBAN-GHARAMALEKI[1)]

Department of Pharmaceutical Chemistry, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran. Received November 11, 1997; accepted January 20, 1998

Applicability of the modified Wilson model for calculating drug solubility in water–cosolvent mixtures is presented. The accuracy and predictability of the model are compared with those of other models which calculate solute solubility as a function of the solvent composition. Mean of percent deviations from experimental values are 7.77, 8.70, 9.06, 10.72, 10.72 and 18.71, for the modified Wilson, double-log exponential, general single model, combined nearly ideal binary solvent/Redlich-Kister, excess free energy and mixture response surface methods, respectively.

Key words solubility; modified Wilson model; cosolvency; prediction

Solubilization of a poorly water-soluble drug has an important role in the formulation of liquid dosage forms. There are some methods which affect the solubility. One of the most effective and readily available methods is mixing a water miscible cosolvent, which this is called cosolvency. Cosolvency data modeling provides not only a means of screening experimental solubility data for possible outliers in need of redetermination, but also facilitates interpolation at other points falling between measured data. Various models have been published for mathematical representation of solubility data in binary solvents.[2–7)] In the present report, we introduce the modified Wilson model for predicting solute solubility in water–cosolvent mixtures and compare the accuracy and predictability of the model with those of other models which calculate solubility based on the solvent composition.

The models which have been published to calculate drug solubility in binary solvents as a function of solvent concentration are as follows:

The Excess Free Energy Approach[3)]

$$\ln X_m = f_c \ln X_c + f_w \ln X_w - A_{cw} f_c f_w (2f_c - 1)(V_2/V_c) + 2A_{wc} f_c^2 f_w (V_2/V_w) + C_2 f_c f_w \quad (1)$$

where X_m is mole fraction solubility of solute, f_c and f_w are volume fraction of cosolvent and water in the absence of the solute, X_c and X_w denote mole fraction solubility in the pure cosolvent and water, A_{cw}, A_{wc} and C_2 are solvent–solvent and solute–solvent interaction terms, V_2, V_c and V_w represent molar volumes of solute, colsolvent and water, respectively. Because of the constant values of A_{cw}, A_{wc}, C_2, V_2, V_c and V_w for a given system, Eq. 1 is simplified to Eq. 2 using appropriate rearrangements:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + L_1 f_c f_w + L_2 f_c^2 f_w \quad (2)$$

where L_1 and L_2 are the model constants which are calculated using least squares analysis. This approach makes to describe a) the multiple solubility peaks in solvent mixtures,[8)] b) solubility in binary solvents at various temperatures[9)] and c) solubility of structurally related drugs in binary solvents.[10)]

Mixture Response Surface Method[4)]

$$\ln X_m = S_1 f'_c + S_2 f'_w + S_3/f'_c + S_4/f'_w \quad (3)$$

where S_1—S_4 are the model constants, f'_c and f'_w are given by: $f'_c = 0.96\ f_c + 0.02$ and $f'_w = 0.96\ f_w + 0.02$.[4)]

Combined Nearly Ideal Binary Solvent/Redlich-Kister Equation[5)]

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + f_c f_w [W_0 + W_1 (f_c - f_w)] \quad (4)$$

or:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + f_c f_w \sum_{i=0}^{3} W_i (f_c - f_w)^i \quad (5)$$

where W_0, W_1 and W_i stand for the model constant calculated *via* regressing $[\ln X_m = f_c \ln X_c + f_w \ln X_w]/f_c f_w$ *versus* $(f_c - f_w)$.[5)] Equation 5 is widely used for reproducing solubility of solutes in binary solvents,[5,6)] and an improvement in predictability of the model using no intercept analysis was recently achieved.[11)] This method is also able to describe multiple solubility maxima in mixed solvents, solute solubility in solvent mixtures at various temperatures[12)] and solubility of structurally related drugs in mixed solvents.[13)]

Modified Wilson Model[5)]

$$\ln(X_2^i/X_m) = 1 - \{f_c[1 - \ln(X_2^i/X_c)]/[f_c + f_w \Lambda_{cw}^{adj}]\} - \{f_w[1 - \ln(X_2^i/X_w)]/[f_c \Lambda_{wc}^{adj} + f_w]\} \quad (6)$$

where X_2^i denotes ideal mole fraction solubility, and Λ_{cw}^{adj} and Λ_{wc}^{adj} are adjustable parameters of the models which can be evaluated *via* least squares analysis using a computer program[14)]; this program calculates the solubility at each composition of the solvents employing pre-selected values for Λ_{cw}^{adj} and Λ_{wc}^{adj}. This model is widely used for describing the solubility in non-aqueous mixed solvents and produced comparable predictions with Eq. 5.[15)] However, the model has not been tested on polar drug molecules dissolved in water–cosolvent mixtures. To obtain a simplified version $(X_2^i = 1)$, X_2^i was eliminated from the model by Acree and coworkers[5)]:

$$-\ln(X_m) = 1 - \{f_c[1 + \ln(X_c)]/[f_c + f_w \Lambda_{cw}^{adj}]\} - \{f_w[1 + \ln(X_w)]/[f_c \Lambda_{wc}^{adj} + f_w]\} \quad (7)$$

Table 1. Details of the Solubility Data of Solutes in Water–Cosolvent Mixtures, Percent Deviation of the Models and Adjustable Parameters of the Modified Wilson Equations

No.	Cosolvent	Solute	$N^{a)}$	$X_2^{i\,b)}$	Ref.	%Dev.								Eq. 6		Eq. 7	
						Eq. 2	Eq. 3	Eq. 4[c]	Eq. 4[d]	Eq. 6	Eq. 7	Eq. 8	Eq. 9	Λ_{cw}^{adj}	Λ_{wc}^{adj}	Λ_{cw}^{adj}	Λ_{wc}^{adj}
1	Acetonitrile	Theophylline	17	0.01896	18	17.66	29.68	27.67	17.66	9.87	9.93	18.24	16.42	0.6933	2.5961	0.6533	2.4643
2	Dimethylformamide	Sulphadiazine	14	0.00300	19	8.90	8.19	12.79	8.90	7.00	11.36	8.18	8.61	0.3820	0.5868	0.8760	1.0799
3	Dioxane	Caffeine	16	0.06845	2a	7.17	16.14	11.29	7.17	31.27	3.76	4.35	7.04	2.9086	6.9019	3.4129	1.6086
4	Dioxane	*p*-Hydroxybenzoic acid	13	0.00747	2b	9.24	17.40	15.62	9.24	30.04	4.52	7.56	8.52	0.1246	7.0487	6.9028	2.4277
5	Dioxane	Paracetamol	17	0.03200	20	14.50	26.20	20.64	14.50	54.83	7.21	8.55	11.96	0.1000	9.9380	16.9279	2.5505
6	Dioxane	Phenacetin	13	0.05200[e]	21	12.07	17.78	17.73	12.07	31.55	2.78	13.74	11.83	3.0137	2.7553	10.8667	1.3629
7	Dioxane	Sulphadiazine	17	0.00300[f]	22	22.02	30.99	46.05	22.02	44.05	11.83	13.86	17.67	2.9086	4.1636	4.3991	1.0761
8	Dioxane	Sulphadimidine	19	0.00640[g]	22	18.60	28.43	74.05	18.60	45.72	9.51	11.98	12.92	29.4527	2.9086	5.1662	0.9987
9	Dioxane	Sulphamethizole	19	0.00164	17	32.61	24.71	101.58	32.61	61.92	10.42	19.68	25.10	0.1001	9.0024	8.1239	1.0238
10	Dioxane	Sulphamethoxazole	15	0.01686	22	19.07	32.84	33.24	19.07	40.72	5.79	16.72	15.93	0.2823	3.5554	10.7607	1.6458
11	Dioxane	Sulphapyridine	17	0.00587[e]	23	19.36	15.82	41.72	19.36	3.51	6.04	10.00	12.89	7.8658	0.8233	4.5587	0.5509
12	Dioxane	Sulphamethoxypyridazine	19	0.01130[g]	22	16.14	33.63	46.28	16.14	70.77	5.82	12.38	11.47	0.1424	7.0406	12.9842	1.7607
13	Dioxane	Sulphanilamide	16	0.00480	24	14.93	28.51	45.89	14.93	45.94	7.54	10.83	10.42	0.2078	4.8144	26.3866	2.4129
14	Dioxane	Sulphasomidine	21	0.00046	25	21.29	28.96	60.39	21.29	60.68	11.09	10.89	14.85	0.0742	19.6474	5.2334	1.3847
15	Dioxane	Theobromine	11	0.00291	26	2.15	23.95	2.22	2.15	16.09	1.90	1.97	2.33	2.9086	4.2746	1.4470	1.5101
16	Dioxane	Theophylline	21	0.01896	27	12.31	18.84	18.59	12.31	45.51	4.75	6.49	10.80	2.9086	8.5277	4.5327	1.3052
17	Ethanol	Paracetamol	13	0.03200	20	6.62	19.52	8.01	6.62	31.58	5.86	6.13	6.68	0.3154	3.1681	6.0180	1.2989
18	Ethanol	Sulphamethazine	11	0.00640[g]	28	10.55	17.17	19.23	10.55	25.86	7.52	6.82	9.49	2.9086	5.5970	2.2741	1.6258
19	Ethanol	Sulphanilamide	12	0.00480	28	3.14	19.66	3.02	3.14	28.48	2.67	3.58	3.24	0.2098	4.7710	2.8153	1.2091
20	Ethylene glycol	Naphthalene	18	0.11617[e]	18	2.29	11.24	3.31	2.29	2.01	1.96	2.53	1.93	0.2006	3.1935	0.2114	3.2889
21	Ethylene glycol	Theophylline	17	0.01896[h]	18	3.01	5.47	3.06	3.01	2.88	2.89	3.11	3.02	1.0848	1.0771	1.0353	1.0893
22	Methanol	Theophylline	13	0.01896[h]	18	5.86	25.29	7.25	5.86	5.84	5.81	5.05	5.16	0.9917	1.2846	0.9593	1.2656
23	Propylene glycol	Butyl *p*-aminbenzoate	11	0.44083[i]	29	4.42	10.49	6.87	4.42	13.32	9.75	5.90	4.78	0.0628	0.9442	0.1072	1.0734
24	Propylene glycol	Butyl *p*-hydroxybenzoate	11	0.43730[j]	29	14.13	22.71	18.45	14.13	41.33	29.38	27.34	14.29	1.4319	0.8626	0.0656	0.8676
25	Propylene glycol	Ethyl *p*-aminobenzoate	11	0.20107[i]	29	3.56	7.08	4.12	3.56	12.32	5.36	3.29	3.62	29.3332	0.9018	0.1565	1.3471
26	Propylene glycol	Ethyl *p*-hydroxybenzoate	11	0.18606[j]	29	4.98	9.60	4.82	4.98	22.27	11.31	4.82	5.16	0.6792	0.9162	0.1468	1.2450
27	Propylene glycol	Methyl *p*-aminobenzoate	11	0.12845[i]	29	2.78	4.92	2.99	2.78	6.43	3.29	2.73	2.82	0.0671	1.0802	0.2143	1.4642
28	Propylene glycol	Methyl *p*-hydroxybenzoate	11	0.15482[j]	29	3.17	9.19	3.77	3.17	21.83	11.84	3.33	3.41	0.9995	1.0000	0.0751	1.3946
29	Propylene glycol	Proply *p*-aminobenzoate	11	0.31141[i]	29	3.81	7.15	4.14	3.81	10.94	5.98	3.96	3.92	0.0628	0.9142	0.1533	1.0909
30	Propylene glycol	Proply *p*-hydroxybenzoate	11	0.26865[j]	29	5.21	9.90	6.25	5.21	27.76	15.13	6.97	5.52	29.4527	0.8794	0.0628	1.2229
					Average:	10.72	18.71	22.37	10.72	28.41	7.77	8.70	9.06				

a) N is number of data in each set. *b*) X_2^i Denotes the ideal mole fraction solubility of the solute. *c*) %Dev. obtained *via* regressing $(\ln X_m - f_c \ln X_c - f_w \ln X_w)/(f_c f_w)$ *versus* $(f_c - f_w)$.[5] *d*) %Dev. obtained *via* regressing $(\ln X_m - f_c \ln X_c - f_w \ln X_w)$ *versus* $f_c f_w$ and $f_c f_w (f_c - f_w)$ using no intercept analysis.[11] *e*) Calculated using Eqs.10 and 11. *f*) Taken from reference.[19] *g*) ΔH_f^{app} taken from reference[16] and X_2^i calculated by Eq. 10. *h*) Taken from Martin *et al.*[27] *i*) ΔH_f taken from Neau *et al.*[30] and X_2^i calculated by Eq. 10. *j*) ΔH_f taken from reference[31] and X_2^i calculated by Eq. 10.

Double-log Exponential Model[6]

$$\ln(-\ln X_m) = J_{-1}10^{-f_c} + J_0 + J_1 10^{f_c} + J_3 10^{3f_c} \quad (8)$$

where J_{-1}, J_0, J_1 and J_3 are the model constants. Although the model is empirical in nature, it produces good predictions.

General Single Model[7]

$$\ln X_m = A_0 + A_1 f_c + A_2 f_c^2 + A_3 f_c^3 \quad (9)$$

where A_0—A_3 denote the model constants which are calculated using least squares analysis. Previously used as an empirical equation,[2b] a theoretical justification for the model was provided using theoretically based cosolvency models, *i.e.* Eqs. 2 and 5.[7]

The available drug solubility data in water–cosolvent mixtures were collected from the pharmaceutical literature and details of data are shown in Table 1. The value of X_2^i is taken from the papers, but for some solutes the value of X_2^i was not shown in the references, so we calculated it from the experimental value of ΔH_f, or the estimated value of ΔH_f (ΔH_f^{app}),[16] and T_m employing Eqs. 10 and 11:

$$\ln X_2^i = -\Delta H_f(T_m - T)/(R \cdot T \cdot T_m) \quad (10)$$

$$\Delta H_f^{app} = [0.01(T_m - T)\ R \cdot T_m]/\log(T_m/T) \quad (11)$$

where ΔH_f denotes the fusion heat of the solute, T_m and T are the fusion temperature of the solute and the absolute temperature, respectively, R is the molar gas constant and ΔH_f^{app} stands for apparent ΔH_f.[16]

The solubility data were fitted to the various models to assess the accuracy and predictability of the models and percent deviation, %Dev., was calculated as the comparison criterion using Eq. 12:

$$\%\text{Dev.} = 100/N \sum |(X_m^{Calculated} - X_m)/X_m| \quad (12)$$

where N is the number of data in each set.

All the models compared contain four constant terms, *i.e.* the known values of X_c and X_w as well as 2 model constants for Eqs. 2, 4, 6 and 7, or four model constants in the case of Eqs. 3, 8 and 9. Table 1 shows %Dev. of the models and adjustable parameters of the modified Wilson equations.

Careful examination of Table 1 showed that Eq. 7 provides accurate mathematical representation. All of %Dev. for Eq. 7 are less than 30% which is an acceptable error range from a pharmaceutical point of view.[17] Despite the non-aqueous solubility data which Eq. 6 was predicted better than Eq. 7, in the case of water–cosolvent mixtures it is apparent that Eq. 7 is better than Eq. 6. The results of analysis of variance indicated that some models produced accurate predictions. Figure 1 shows the order of accuracy as well as the results of Duncan's multiple range test. Differences between Eqs. 2, 4 (using no intercept analysis) and 7—9 are not significant, and the least %Dev. was obtained for Eq. 7.

Equations 2 and 4 are mathematically identical,[7] and so they produce the same predictions. The accuracy of original forms of the modified Wilson model and combined nearly ideal binary solvent/Redlich–Kister equation,[5] *i.e.* 28.41 and 22.37, are in parallel with the other findings which employed solute solubility data in non-aqueous solvent mixtures.[15] In the case of Eqs. 3, 4, 8 and 9, the 5-constant forms can also be considered. The obtained means of %Dev. are 6.33, 5.92, 4.51 and 8.53, respectively. It is obvious that more curve-fit parameters will produce more accurate predictions, however, more experimental determinations are needed. In the pharmaceutical industry, because of practical and economical considerations, a minimum number of solubility determinations are required to suggest the optimum concentration of the cosolvent for preparing a liquid dosage form of a drug, especially in the preformulation studies of a new drug of which only small quantities are available.

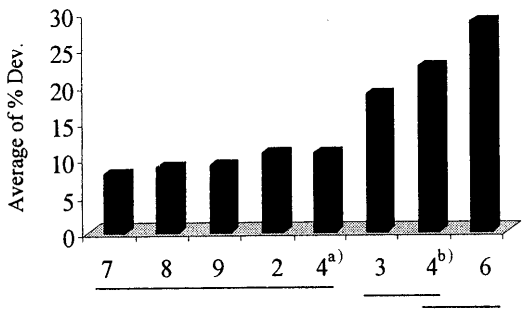

Fig. 1. Average of %Dev. for Various Cosolvency Models as Well as Results of Duncan's Multiple Range Test

Differences between equations underlined are not significant. *a*) %Dev. obtained with no intercept analysis.[11] *b*) %Dev. obtained with intercept analysis.[5]

References and Notes

1) Present address: *Department of Pharmaceutical Chemistry, School of Pharmacy, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK.*
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