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Short Communication

Estimation of organic solute solubilities using liquid chromatography parameters

T.L. HAFKENSCHEID and E. TOMLINSON *

Subfaculty of Pharmacy, University of Amsterdam, Plantage Muidergracht 24, 1018 TV Amsterdam (The Netherlands)

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Solubility is a key factor in pharmaceutical science and in chemistry, being relevant in (amongst others), drug delivery, transport and distribution, and in both analytical and environmental sciences. Practical problems arise for direct determinations of solubilities below levels of approximately 0.3% (w/v). For example, the aqueous solubility of DDT is found (Tulp and Hutzinger, 1978) to be reported as being between 0.2 and 1 000 ppb. Additionally, it may arise that insufficient compound is available, or that the compound is too unstable, for direct measurement. Clearly there exists a need to be able to either predict solubilities in simple and mixed systems a priori, or to make reliable estimates using readily obtainable parameters. Several schemes have been proposed for solid drug substances, including 3 methods due to Higuchi and co-workers (1979). These are: a facilitated dissolution approach; a predictive method based on functional group contributions; and an approach using a large excess of solid together with a highly specific analytical determination of the main component. These authors conclude that in the special (sic) case of extremely low aqueous solubility that combining an estimate of liquid/liquid distribution, K_d, from group values (assuming additivity; Davis et al., 1974) with the known solubility in an organic liquid may be the only feasible method of obtaining an accurate estimate of solubility. Other approaches appear to refute this, particularly that due to Yalkowsky and Valvani (1980), with which reasonable estimates of aqueous solubility for liquid or crystalline organic non-electrolytes can be obtained using a semi-empirical approach based on knowledge of the K_d, melting point, and entropy of fusion of the solute. Thus, for a solid, taking as a good approximation that the latent heat of fusion, ΔH_f, is independent of temperature, and that the difference in heat capacities of the crystalline form and molten forms of the solid is small, then it can be shown (Hildebrand and Scott, 1962; and e.g., Moore, 1972) that the temperature variation of the mole fraction ideal solubility of a pure solid A$_s$, (X^i_{As}), is:

$$\ln X^i_{As} = \frac{\Delta H_f}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \qquad (1)$$

* To whom correspondence should be addressed.

where T_m and T are the melting point and temperature at which pure solid is in equilibrium with the solution of mole fraction X.

For a liquid solute we can recall the Gibbs free energy excess function, (G^E_{Al}), as:

$$G^E_{Al} = RT \ln \gamma_{Al} = (G_{Al} - G^i_{Al}) \tag{2}$$

where γ is the activity coefficient. It follows that:

$$\log X_{Al} = \log X^i_{Al} - \log \gamma_{Al} \tag{3}$$

and since, using a mole fraction scale, the ideal solubility is equal to one, it follows that:

$$\log X_{Al} = -\log \gamma_{Al} \tag{4}$$

As, at T_m, $\Delta G_f = 0$, then from the Gibbs equation:

$$\frac{\Delta H_f}{T_m} = \Delta S_f \tag{5}$$

Thus the actual solubility of a solid can be given (Yalkowsky and Valvani, 1980) by:

$$-\log X_{As} = \frac{\Delta S_f}{2.3R}\left(\frac{T_m - T}{T}\right) - \log \gamma_A \tag{6}$$

The first term in Eqn. 6 can be readily obtained from ΔS_f and T_m values, (although since ΔS_f is fairly constant for molecules of similar geometry, Yalkowsky and Valvani (1980) have shown that excellent approximations are given by:

$$\log X^i_{As} = 0.01\,(T_m - 25) \tag{7}$$

(for rigid non-spherical molecules), and by:

$$-\log X^i_{As} = (0.01 + 0.0018\,(n - 5))(T_m - 25) \tag{8}$$

(for partially flexible molecules, where n is the number of carbon and/or heteroatoms in a solute sidechain), and where measurements are at 25°C.

It has been the suggestion of Yalkowsky and Valvani (1980) that the activity coefficient of a solute in water can be approximated by the l-octanol/water K_d value, (see also Hansch et al., 1968), by assuming that the activity coefficient of drugs in this oil are equal to one. Problems arise with the use of this K_d scale; practically, it is difficult to determine log K_d values greater that 4; solutes need to be pure and stable, and there is a high solute consumption. If one resorts to calculation of K_d via a group or fragmental constant approach (e.g. Rekker, 1977), problems arise with neighbourhood effects, and the data banks available are unable to predict K_d in mixed solvents (as would be the intention for estimating solute solubilities in a co-solvent). We have demonstrated that the use of reversed phase high-performance liquid/solid chromatography (RP-HPLSC) reten-

tion parameters is suitable for estimating solute chemical potentials in polar solvents, (Tomlinson et al., 1981), and it appeared to us useful to attempt to use HPLC parameters within the Yalkowsky model for estimating organic solute solubility.

From the Sovophobic Theory of retention in reversed phase chromatography (Horváth et al., 1976) it can be shown that the solute's capacity ratio (k′; which is dimensionless), is related to mobile phase solvation effects by:

$$\ln k' = C - \left(\frac{\Delta G_{solv,A}}{RT}\right) = \ln\left(\frac{t_{R_A} - t_{R_0}}{t_{R_0}}\right) \tag{9}$$

where C, ΔG_{solv} and t_R are a constant, the free energy of solvation of solute in the chromatographic system, and retention time, respectively, and where subscripts A and o refer to solute and a compound which is non-retained by the chromatographic process.

Since at the low concentrations found in liquid chromatography solute activity coefficients are concentration-independent, we may write (Novák, 1975):

$$\Delta G_{solv,A} = G^E_{Am} = RT \ln \gamma_{Am} \tag{10}$$

where subscript m refers to mobile phase, and for which it is assumed (Horváth et al., 1976), that stationary phase activity is constant. Thus it follows that the chromatographic capacity ratio is a measure of mobile phase solute activity.

To study this approach we have determined the retention behaviour of benzene and 13 mono- and di-substituted liquid and solid benzenes in an octadecyl (Hypersil ODS 5 μm) RP-HPLSC system using aqueous methanol mobile phases at 20°C, and with t_{Ro} times being determined by injecting a slightly different composition of mobile phase. Methanol is used to improve retention times and peak shape, and to modify the water's properties. It also enables us to measure the retention of extremely hydrophobic solutes (e.g. anthracene). To obtain a measure of k′ at a theoretical 100% water mobile phase composition (k'_o), we have determined k′ values over a methanol concentration range of $0.320 < (X\gamma) < 0.675$, (where γ was obtained from literature isothermal P-X tables, (Timmermans, 1960), and then used the following relationship to calculate k'_o:

$$\log k' = \log k'_o + B(X\gamma)_{methanol} \tag{11}$$

For all solutes examined the correlation coefficients, (r), for this relationship were greater than 0.996.

Solubility data were taken from the literature (Yalkowsky and Morozowich, 1980), or determined using a 72-h equilibration time method. Entropies of fusion and solute melting points were taken from the literature (Weast, 1979). Hence, mole fraction solubility data has been regressed against extrapolated k'_o, ΔS_f and T_m values according to a modified form of Eqn. 6, and using standard multiple regression analysis. Thus:

$$-\log X = -0.525 + 1.42 \log k'_o + 0.000177\, \Delta S_f\, (T_m - 20) \qquad n = 12;\ R = 0.969 \tag{12}$$

where n and R are the number of data points and the multiple regression coefficient respectively, and where n is restricted by the ΔS_f values reported in the literature. Using

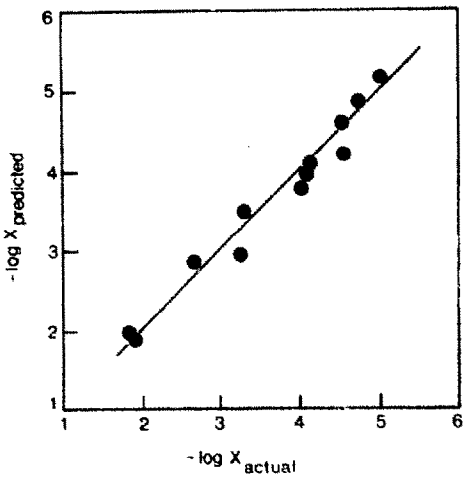

Fig. 1. Relation between actual mole fraction aqueous solubility of liquid and solid mono- and di-substituted benzenes and the predicted mole fraction solubility found using Eqn. 12. The drawn line is the multiple regression analysis line according to Eqn. 12.

the approximation that ΔS_f is constant (Eqn. 7), then we obtain for the same data set

$$-\log X = -0.591 + 1.44 \log k'_o + 0.0110 (T_m - 20) \quad n = 12; R = 0.931 \tag{13}$$

It is seen from these two regressions that the approach of using liquid chromatographic parameters within the framework of the Yalkowsky-Valvani equation does have merit, and that better correlations are obtained using ΔS_f data than when using the approximation that it is constant. (It is also interesting to note that with the same compounds and using K_d as the approximation of γ, that a R value of only 0.857 is obtained.) The excellent relationship found between solubility, entropies of fusion, melting points, and liquid chromatographic parameters is given in Fig. 1.

For liquids we have found that

$$-\log X = 1.01 + 0.984 \log k'_o \quad n = 5; R = 0.997 \tag{14}$$

which indicates that our use of Eqn. 11 and the assumptions made in obtaining Eqn. 10 are valid. The success of using liquid chromatographic parameters in the Yalkowsky-Valvani equation, and the improved correlations and ease of parameter determination has encouraged us to further develop this approach, and we are currently challenging the viability of the method by examining environmental effects, (such as temperature, pH, ionic strength, etc), as well as the effects of co-solvents and co-solutes on the predicted solubility of drug molecules. Additionally, the behaviour of non-benzenoids, aliphatics, polar compounds and extremely hydrophobic solutes will be examined. Our initial findings with the latter suggest that solubilities (log mole fraction units) of at least −10 can be conveniently determined using this approach.

Finally we make the remark that although the use of chromatography for studying organic solute solubility has been reported (e.g. May et al., 1978), such studies only use chromatography as a separation and analysis tool, and do not utilize the retention parameters as indicators of physicochemical character (as is done in this present study).

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REFERENCES

Davis, S.S., Higuchi, T. and Rytting, J.H., Determination of thermodynamics of functional groups in solutions of drug molecules. Adv. Pharm. Sci., 4 (1974) 73–261.

Hansch, C. and Helmer, F., Extrathermodynamic approach to the study of the adsorption of organic compounds by macromolecules. J. Polymer Sci., 6 (1968) 3295–3302.

Higuchi, T., Shih, F-M.L., Kimura, T. and Rytting, J.H. Solubility determination of barely soluble organic solids, J. Pharm. Sci., 68 (1979) 1267–1272

Hildebrand, J.H. and Scott, R.L., Regular Solutions, Prentice Hall, Englewood, N.J., 1962.

Horváth, Cs., Melander, W. and Molnár, I., Solvophobic interactions in liquid chromatography with nonpolar stationary phases. J. Chromatogr., 125 (1976) 129–156.

May, W.E., Wasik, S.P. and Freeman, D.H., Determination of the aqueous solubility of polynuclear aromatic hydrocarbons by a coupled column liquid chromatographic technique. Anal. Chem., 50 (1978) 175–179

Moore, W.J., Physical Chemistry, 5th edn., Longman, London, 1972, p. 249.

Novák, J., Physico-chemical basis of chromatographic retention in liquid–liquid and liquid–solid systems. J. Chromatogr. Library, 3 (1975) 45–56.

Rekker, R.F., The Hydrophobic Fragmental Constant, Elsevier/North-Holland, Amsterdam, 1977.

Timmermans, J., Physicochemical Constants of Binary Systems in Concentrated Solution, Vol. IV, Interscience, 1960, pp. 151–170.

Tomlinson, E., Poppe, H. and Kraak, J.C., Thermodynamics of functional groups in reversed-phase high performance liquid–solid chromatography. Int. J. Pharm., 7 (1981) 225–243.

Tulp, M.Th.M. and Hutzinger, O., Some thoughts on aqueous solubilities and partition coefficients of PCB, and the mathematical correlation between bioaccumulation and physico-chemical properties, Chemosphere, No. 10 (1978) 849–860.

Weast, W.C. Editor: "CRC Handbook of Chemistry and Physics" 60th edn., CRC Press, Fla, U.S.A., 1979/1980.

Yalkowsky, S.H. and Morozowich, W., A Physicochemical basis for the design of orally active prodrugs. In E.J. Ariens, (Ed.), Drug Design, Vol. IX, 1980, pp. 122–183.

Yalkowsky, S.H. and Valvani, S.C. Solubility and partitioning. I: Solubility of nonelectrolytes in water. J. Pharm. Sci., 69 (1980) 912–922.