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Local composition models in pharmaceutical chemistry. III. Prediction of drug solubility in binary aqueous mixtures

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Summary

The UNIQUAC local composition model has been tested for its ability to predict the solubilizing effect of organic liquids on aqueous solutions of poorly soluble drugs. A minimum of one single experimentally measured solubility of a drug in pure water was required to predict its solubility profile in a binary mixture of water and an arbitrarily chosen organic solvent. Improved predictions were obtained when measured solubilities in pure organic co-solvent were used as input too. In principle, additional experimental information is not necessary when the number of added organic solvents is increased beyond one. The method was tested for various liquid solutes in acetic acid–water and ethanol–water, and for barbiturates in ethanol–water, xanthines in dioxane–water, hydrocortisone in propylene glycol–water, diethylstilbestrol in ethanol–water, and for a typical neuroleptic drug (pimozide) in acetic acid–water. Excellent predictions were obtained throughout. It is concluded that UNIQUAC provides a superior and generally applicable method for the computer-aided design of pharmaceutical formulations with increased solubility.

Introduction

The formulation of drugs which have to be administered parentally or as oral solutions is sometimes obstructed by insufficient aqueous solubilities. Addition of one or more non-toxic organic co-solvents such as acetic acid, propylene glycol or a polyethylene glycol of low molecular weight offers an attractive method to increase solubility in those cases. However, the determination of optimal solubilizing mixture compositions by experimental trial-and-error is tedious and costly, especially when a large number of drugs has to be formulated. A number of research groups has therefore focused on studies of drug solubility in aqueous mixtures with the ultimate goal to create predictive methods for the rational design of solubilizing blends. Yalkowsky and Rubino (1985) reported on a predictive method for water–co-solvent mixtures using an empirically established linear relationship between solubility and octanol–water partitioning (Yalkowsky et al., 1983). An extended Hildebrand solubility approach has been thoroughly tested for, among others, methylxanthines in dioxane–water (Martin et al., 1981) and for sulfonamides in various mixed solvents (Martin et al., 1985). Williams and Amidon (1984a, b and c) published an excess free

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energy approach using the series expansion technique of Wohl (1946, 1953). Studies on the Nearly Ideal Binary Solvent (NIBS) model and the UNIFAC group contribution method have been reported by Acree and Rytting in a series of papers cited by Acree (1984a). The UNIFAC method was also employed by Ochsner and Sokoloski (1985). In addition, Ochsner et al. (1985) and Belloto et al. (1985) showed that mixture response methodology can be applied to predict optimal mixture compositions for the dissolution of drugs.

It should be noticed that the majority of the above methods is based on relatively old and simplifying concept of intermolecular interactions in liquid mixtures which are known to be of limited value when strongly non-ideal mixtures are considered. For example, the original regular solution model (Hildebrand and Scott, 1949; Hildebrand et al., 1970) must be extended by means of an additional adjustable parameter (Martin et al., 1985) in order to be able to account for thermodynamic non-ideality in aqueous mixtures. In Wohl's treatment, as advocated by Williams and Amidon, the complexity of intermolecular interaction patterns in mixtures with an increasing number of components is likewise represented by an increasing number of adjustable parameters. Although more recently developed, the NIBS model is obviously not designed for aqueous mixtures which are far from being "nearly ideal". The UNIFAC group contribution scheme of Fredenslund et al. (1975) should be considered as a modern method too. However, UNIFAC predictions of liquid–liquid equilibria are known to be less accurate than those of vapour–liquid equilibria (Magnussen et al., 1981). UNIFAC is furthermore not likely to yield reliable estimates for usually very complicated molecular structures of drugs without additional corrections for proximity effects between adjacent polar groups in the drug molecule (Gmehling et al., 1982).

Historically, the limitations of the various older models have led to the development of more sophisticated models having a wider range of possible applications. Reviews of the presently available models have been published by Sørensen et al. (1979) and by Acree (1984b). Among the newer models, the class of so-called local composition models was found to be highly successful in correlating and predicting free-energy related properties of strongly non-ideal mixtures. The most important progress effectuated by several local composition models is probably that, in contrast with the older models, predictions for multicomponent systems can be made using experimental information on constituent binary systems *without* introducing additional adjustable parameters. It seemed therefore of interest to investigate whether a reliable method for the design of solubilizing aqueous mixtures can be developed on the basis of a local composition model. To this purpose, the UNIQUAC local composition model of Abrams and Prausnitz (1975) has been selected for study since this model is presently the best documented of all local composition models in the literature. The present paper reports the testing and evaluation of solubility predictions for various liquid solutes and some typical drugs in a variety of aqueous mixtures, including acetic acid–water mixtures which have never been considered before in the context of drug solubility prediction.

Materials and Methods

The dissolution of a poorly soluble substance in a water–co-solvent mixture generally results in a two-phase system with an aqueous and an organic phase. For liquid solutes, both phases are ternary liquid phases containing different amounts of water, co-solvent and solute. According to classical thermodynamics, the equilibrium concentrations of each of these components follows from:

$$x_i \cdot \gamma_i = x'_i \cdot \gamma'_i \qquad (1)$$

where x_i and γ_i represent the mole fraction and Raoult's law activity coefficient, respectively, of water, co-solvent or solute. Corresponding quantities in the organic phase are indicated by primes. The UNIQUAC model provides a relationship between an activity coefficient, γ_i, and the composition of the phase considered. Mathematically, this relationship is given by:

$$\ln \gamma_i = \ln \gamma_{comb,i} + \ln \gamma_{res,i} \qquad (2a)$$

where

$$\ln \gamma_{comb,i} = \ln \frac{\Phi_i}{x_i} + \left(\frac{z}{2}\right) q_i \ln \frac{\theta_i}{\Phi_i} + l_i - \frac{\Phi_i}{x_i} \sum_j x_j \cdot l_j \quad (2b)$$

and

$$\ln \gamma_{res,i} = -q_i \cdot \ln\left(\sum_j \theta_j \cdot \tau_{ji}\right) + q_i - q_i \cdot \sum_j \frac{\theta_j \cdot \tau_{ij}}{\sum_k \theta_k \cdot \tau_{kj}} \quad (2c)$$

with

$$l_j = (z/2)(r_j - q_j) - (r_j - 1) \quad (2d)$$

$$\tau_{ij} = \exp\{-(u_{ij} - u_{jj})/RT\} \quad (2e)$$

$$A_{ij} = (u_{ij} - u_{jj})/R \quad (2f)$$

$i = 1,3 \quad j = 1,3$

θ_i and Φ_i are defined by:

$$\theta_i = \frac{q_i \cdot x_i}{\sum_j q_j \cdot x_j} \quad (2g)$$

$$\Phi_i = \frac{r_i \cdot x_i}{\sum_j r_j \cdot x_j} \quad (2h)$$

In these equations, the lattice coordination numer z was set equal to 10, as usual (Abrams and Prausnitz, 1975). The structural parameters r_i and q_i are (relative) measures of the Van der Waals volume and surface area of molecule i, respectively. These parameters have been calculated from group contribution compilations of Bondi (1964, 1967). Interaction energies between pairs of neighbouring molecules i and j are taken into account by two interaction parameters, as represented by A_{ij} and A_{ji} in Eqn. 2f.

TABLE 1

PARAMETERS OF THE UNIQUAC MODEL

Key: r_i = relative Van der Waals volume of molecule i; q_i = relative Van der Waals surface of molecule i; A_{ij}, A_{ji} = interaction parameters accounting for interactions between molecules i and j.

Type of mixture	Molecules	Structural parameters	Interaction parameters
Binary	1 and 2	r_1, r_2 q_1, q_2	A_{12}, A_{21}
Ternary	1, 2 and 3	r_1, r_2, r_3 q_1, q_2, q_3	A_{12}, A_{21} A_{13}, A_{31} A_{23}, A_{32}

Table 1 gives a summary of the various structural and interaction parameters that are required for the modelling of binary and ternary mixtures. Indicating water, co-solvent and solute by the subscripts 1, 2 and 3, respectively, it can be observed from Table 1 that binary mixtures of, for example, water and co-solvent are fully characterized by two interaction parameters (i.e. A_{12} and A_{21}) and ternary water–co-solvent–solute mixtures by three pairs: A_{12}–A_{21}, A_{13}–A_{31} and A_{23}–A_{32}. It follows that predictions of free-energy-related properties of the ternary system, such as distribution coefficients (Grünbauer and Tomlinson, 1984) and solubilities can be calculated using interaction parameter values derived from experimental information on constituent binary mixtures. The mathematical structure of UNIQUAC is such that this principle can be immediately extended to mixtures containing more than three components. Predictions for mixtures containing two or more organic co-solvents are therefore calculable from binary information too. The present study is, however, restricted to ternary mixtures containing only one co-solvent, water and a liquid solute or drug. Numerical values for interaction parameters representing the various binary interactions in such mixtures have been obtained using a number of different methods which are described below.

For many co-solvents of interest, reliable values for A_{12} and A_{21} are immediately available from literature (Sørensen and Arlt, 1980). In the ab-

sence of literature data, these parameters were arbitrarily set equal to zero which implies that the residual or energetic contribution to water–co-solvent interactions was neglected (see also de Meere, 1985; and de Meere et al., 1986). Values for A_{13} and A_{31} of *liquid* solutes have been calculated from experimentally measured mutual solubilities, as described by Grünbauer and Tomlinson (1985). For *solid* solutes, such as drugs, *mutual* solubilities are obviously not available since the organic phase itself is solid. In these cases, a liquid organic phase with a water content of 0.001 on the mole fraction scale was assumed to be in equilibrium with the aqueous drug solution considered. Numerical values of A_{13} and A_{31} were subsequently calculated using the above described procedure for liquid solutes. A detailed account of this method will be given elsewhere (Grünbauer, 1986). All liquid solutes considered are completely miscible with pure co-solvent. The corresponding solute–co-solvent parameters, A_{23} and A_{32}, were therefore set equal to zero. The same procedure was occasionally followed for solid solutes. Alternatively, A_{23} and A_{32} values for solid solutes were calculated from their solubilities in pure co-solvent using the adapted method described above for A_{13} and A_{31}.

For liquid solutes, a different type of calculation has been performed as well. In these calculations, interaction parameter values were determined by non-linear curve-fitting using all N available experimental solubilities in a particular water–co-solvent mixture. This procedure is similar to that reported by Grünbauer and Tomlinson (1985), except for its use of solubility data referring to the solute alone. The number of data points in the curve-fit is thereby decreased from 3N to N. In the remaining text, this procedure will be indicated as "correlation", in order to make a clear distinction with truly predictive computations.

The calculation of solubilities in ternary systems is straightforward once the necessary structural and interaction parameter values have been collected. Substitution of all relevant parameter values in three equations of the type of Eqn. 2a and application of the thermodynamic iso-activity criterion, as visualized by Eqn. 1, yields a set of non-linear equations from which the composition of the system has been calculated numerically using the minimization algorithm of Marquardt (1963). The reliability of predictions was characterized by absolute and relative mean deviations which were calculated from Eqns. 3a and 3b, respectively.

$$MD = (1/N)\Sigma|x_3 - x_3^*| \tag{3a}$$

$$MD(\%) = (100/N)\Sigma|\{x_3 - x_3^*\}/x_3^*| \tag{3b}$$

In these equations, experimental and calculated mole fraction solubilities have been indicated by x_3^* and x_3, respectively. N represents the number of experimental data points employed to check the accuracy of a predicted solubility profile.

In summary, the following minimum amount of information is required to predict the solubility profile of a drug in an aqueous mixture: (1) the Van der Waals volume and surface area of all molecules involved (to be calculated from tabulated group contributions); and (2) the experimental solubility of the drug in water. This type of prediction has been indicated as "one-data point" predictions since only one experimental data point is involved in their calculation. If desired, improved predictions can be obtained by using the experimental solubility of the drug in pure co-solvent as an additional piece of information. The resulting predictions are referred to as "two-data point" predictions.

Results and Discussion

Results of one-data point predictions and correlations for a number of liquid solutes in acetic acid–water have been summarized in Table 2. For all solutes considered, complete miscibility occurs when the acetic acid concentration is increased beyond a certain limit which is called the plait point. The plait point in acetic acid–water solutions of esters, ketones and alcohols is usually found at lower acetic acid concentrations than those of aliphatic and aromatic hydrocarbons. The acetic acid concentration range for which solubilities can be measured is therefore variable and

TABLE 2

ONE-DATA POINT PREDICTIONS AND CORRELATIONS OF SOLUBILITIES OF VARIOUS LIQUID SOLUTES IN ACETIC ACID–WATER MIXTURES

Key: X_s = mole fraction solubility in pure water; n = number of experimental data points involved in correlations and in the calculation of mean deviations; MD = absolute mean deviation in mole fraction units; MD(%) = relative mean deviation, expressed as a percentage.

Solute	X_s	n	Prediction		Correlation	
			MD	MD (%)	MD	MD (%)
Acetaldehyde, diacetate	6.45×10^{-3}	7	2.42×10^{-3}	10	1.86×10^{-4}	1
Cyclohexyl acetate	3.68×10^{-4}	5	6.44×10^{-4}	8	6.66×10^{-5}	1
Ethenyl acetate	2.41×10^{-3}	8	6.03×10^{-3}	23	1.45×10^{-3}	2
Ethyl acetate	1.60×10^{-2}	9	2.53×10^{-3}	7	2.64×10^{-4}	1
iso-Butyl acetate	1.33×10^{-3}	15	8.06×10^{-4}	32	1.20×10^{-4}	3
iso-Propyl acetate	3.95×10^{-3}	6	3.17×10^{-3}	14	3.11×10^{-4}	1
Methyl propionate	1.31×10^{-2}	4	2.41×10^{-3}	8	5.19×10^{-4}	2
Ethyl propionate	3.51×10^{-3}	6	2.96×10^{-3}	14	1.28×10^{-4}	1
Propyl propionate	9.19×10^{-4}	4	1.45×10^{-3}	18	3.31×10^{-4}	3
Ethyl pentanoate	3.47×10^{-4}	4	1.14×10^{-4}	5	7.29×10^{-5}	1
2-Butanone	7.63×10^{-2}	13	5.89×10^{-3}	5	2.01×10^{-4}	1
3-Pentanone	1.20×10^{-2}	7	2.02×10^{-3}	13	1.92×10^{-5}	1
Furfural	1.63×10^{-2}	23	6.86×10^{-3}	18	1.17×10^{-3}	3
4-Methyl-2-pentanone	3.19×10^{-3}	69	1.38×10^{-3}	9	8.57×10^{-4}	7
2,6-Dimethyl-4-heptanone	1.14×10^{-4}	14	4.77×10^{-3}	56	1.52×10^{-3}	14
Hexanoic acid	1.66×10^{-3}	8	3.34×10^{-3}	103	9.90×10^{-5}	3
1-Butanol	1.92×10^{-2}	16	1.56×10^{-3}	8	1.54×10^{-3}	7
3-Methyl-1-butanol	5.40×10^{-3}	10	2.10×10^{-3}	14	8.59×10^{-5}	1
4-Methyl-2-pentanol	2.86×10^{-3}	5	1.18×10^{-3}	33	7.69×10^{-5}	2
Cyclohexanol	7.08×10^{-3}	6	2.81×10^{-3}	11	6.69×10^{-4}	3
Diethyl ether	5.18×10^{-2}	6	1.52×10^{-3}	5	1.82×10^{-4}	1
Diisopropyl ether	2.00×10^{-3}	10	2.37×10^{-3}	30	3.89×10^{-4}	6
Hexane	2.78×10^{-6}	10	2.50×10^{-1}	659	1.73×10^{-3}	4
Cyclohexane	1.20×10^{-5}	11	2.42×10^{-1}	475	1.24×10^{-3}	5
Benzene	4.05×10^{-4}	47	1.34×10^{-2}	60	2.22×10^{-3}	11
Toluene	1.06×10^{-4}	13	5.90×10^{-3}	70	7.84×10^{-5}	3
Chlorobenzene	6.25×10^{-5}	8	2.74×10^{-3}	41	7.19×10^{-5}	5
Dichloromethane	4.17×10^{-3}	8	5.54×10^{-3}	33	5.39×10^{-4}	2
Trichloromethane	1.19×10^{-3}	14	9.12×10^{-4}	14	9.61×10^{-4}	10
Tetrachloromethane	9.20×10^{-5}	19	4.93×10^{-2}	127	1.36×10^{-3}	6
1,2-Dichloroethane	1.59×10^{-3}	15	6.89×10^{-3}	29	5.14×10^{-4}	3
Nitromethane	3.04×10^{-2}	6	6.02×10^{-3}	9	1.70×10^{-3}	3

depends to some extent on the type of solute considered. In all instances, the plait point is, however, far above pharmaceutically interesting acetic acid concentrations which justifies the inclusion of these solutes in the present study.

According to Raoult's law, ideal mixtures are characterized by *identical* interaction energies between pairs of like and unlike molecules. The interaction parameters of the UNIQUAC model are accounting for deviations from ideality (i.e. for *different* interaction energies between pairs of like and unlike molecules). Mutual similarities in the molecular structures of interacting molecules are therefore likely to decrease the magnitude of corresponding interaction parameters. As a consequence, the implicit neglect of solute–acetic acid parameters in one-data point predictions is expected to yield better results as the similarity between the molecular structures of solute and acetic acid increases. The data in Table 2 tend to

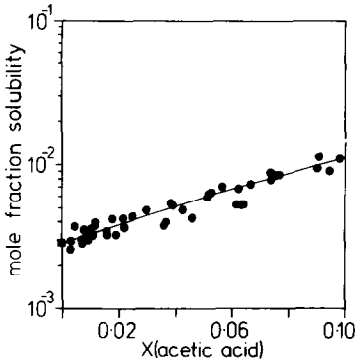

Fig. 1. Experimental (●) and calculated solubility profiles of 4-methyl-2-pentanone in acetic acid–water. The curve represents a one-data point prediction whereby the experimental solubility in pure water (■) is used as input.

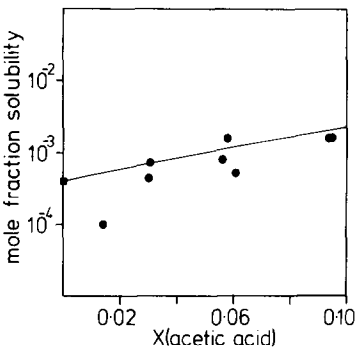

Fig. 2. Experimental (●) and calculated solubility profiles of benzene in acetic acid–water. The curve represents a one-data point prediction whereby the solubility in pure water (■) is used as input.

confirm this reasoning. Absolute and relative mean deviations of predictions are given in the fourth and fifth column of this table. It is seen that predicted solubilities of esters, alcohols and ketones are generally more reliable than those of aromatic and aliphatic hydrocarbons. An example of a highly satisfactory result is given by Fig. 1 where the predicted solubility profile of 4-methyl-2-pentanone, as calculated from its solubility in pure water, is found to be in excellent agreement with 69 experimental data points from 9 different literature sources (see Sørensen and Arlt (1980) for appropriate references). Solubilities in pure water are always reproduced exactly by the predicted curves since solute–water interaction parameters derived from aqueous solubilities are involved in the calculations. Therefore, deviations between experiment and prediction tend to increase with increasing co-solvent concentration. It is not surprising that, for many poorly soluble compounds, accurate predictions have been obtained at relatively low acetic acid concentrations although larger deviations from experiment are observed at higher concentrations. An example is given by Fig. 2 where the solubility profile of benzene at acetic acid concentrations up to $x_2 = 0.1$ (which corresponds to about 5 mol/l) is found to be predicted in a very satisfactory way.

Correlations using all available acetic acid–water solubility data are characterized by their mean deviations as given by the sixth and seventh column of Table 2. The difference between a correlation procedure and predictive calculations is that interaction parameters are now derived from the ternary information itself. In other words, resulting mean deviations provide a test of the performance of UNIQUAC as a smoothing function for the reproduction of solubility data in water–acetic acid mixtures. It is readily observed from Table 2 and in accordance with literature evidence (Sørensen and Arlt, 1980) that UNIQUAC is highly suited to this purpose. Solubility curves originating from a single set of measurements are usually reproduced within experimental error. Mean deviations referring to data from more than one laboratory generally reflect discrepancies between different data sets too. This is particularly evident for 4-methyl-2-pentanone, benzene and furfural where the correlation had to deal with 9, 6 and 4 different data sets, respectively. In this light, the calculated relative mean deviations for these compounds of 11% or less are very satisfactory.

Results of one-data point predictions and correlations for a variety of liquid solutes in ethanol–water have been collected in Table 3. As before, absolute and relative mean deviations of predicted solubility profiles are given in the fourth and fifth column. Generally, the reliability of predictions is comparable to those obtained for the acetic acid–water system. Except for 1-pentanol, all solubility profiles of hydroxy- or ester-group

TABLE 3
ONE-DATA POINT PREDICTIONS AND CORRELATIONS OF SOLUBILITIES OF VARIOUS LIQUID SOLUTES IN ETHANOL–WATER MIXTURES
Key: see Table 2

Solute	X_s	n	Prediction		Correlation	
			MD	MD (%)	MD	MD (%)
Ethyl acetate	1.60×10^{-2}	4	4.96×10^{-3}	11	2.67×10^{-4}	1
Ethyl propionate	3.51×10^{-3}	6	7.63×10^{-3}	23	2.34×10^{-3}	8
Ethyl propenoate	3.70×10^{-3}	4	7.16×10^{-4}	10	2.09×10^{-4}	3
1-Butanol	1.92×10^{-2}	10	1.06×10^{-3}	3	4.27×10^{-4}	1
2-Methyl-1-propanol	2.10×10^{-2}	4	5.10×10^{-3}	11	8.95×10^{-5}	1
1-Pentanol	3.75×10^{-3}	4	2.44×10^{-3}	130	1.47×10^{-8}	1
3-Methyl-1-butanol	5.40×10^{-3}	3	4.79×10^{-3}	18	1.77×10^{-3}	5
4-Metyl-2-pentanol	2.86×10^{-3}	22	2.91×10^{-3}	37	2.23×10^{-3}	15
Diethyl ether	5.18×10^{-2}	19	3.81×10^{-3}	8	6.76×10^{-4}	7
Hexane	2.78×10^{-6}	16	1.04×10^{-1}	93	6.77×10^{-3}	8
Heptane	5.00×10^{-7}	10	1.76×10^{-1}	122	8.04×10^{-3}	6
Octane	1.10×10^{-7}	5	3.03×10^{-1}	231	5.94×10^{-4}	1
2,2,4-Trimethylpentane	3.50×10^{-7}	10	6.51×10^{-2}	133	2.21×10^{-3}	13
Cyclohexane	1.20×10^{-5}	3	3.71×10^{-2}	56	3.67×10^{-5}	1
Cyclohexene	4.67×10^{-5}	4	5.94×10^{-3}	46	3.67×10^{-3}	9
Benzene	4.05×10^{-4}	65	1.18×10^{-2}	38	5.63×10^{-3}	16
Toluene	1.06×10^{-4}	9	3.41×10^{-4}	40	5.11×10^{-4}	5
1,2-Dimethylbenzene	3.25×10^{-5}	9	3.56×10^{-3}	38	2.94×10^{-4}	3
1,3-Dimethylbenzene	2.95×10^{-5}	10	2.77×10^{-3}	37	2.03×10^{-4}	4
1,4-Dimethylbenzene	3.42×10^{-5}	9	2.89×10^{-3}	32	7.80×10^{-4}	8
Nitrobenzene	2.83×10^{-4}	3	3.40×10^{-2}	19	1.09×10^{-2}	5
Trichloromethane	1.19×10^{-3}	9	2.65×10^{-3}	153	8.88×10^{-4}	23
Tetrachloromethane	9.20×10^{-5}	4	2.02×10^{-3}	2	9.87×10^{-4}	1
1,1-Dichloroethane	9.19×10^{-4}	4	2.24×10^{-2}	35	4.08×10^{-3}	5

containing molecules are accurately predicted whereas larger deviations are observed for hydrocarbons and tetrachloromethane at very high concentrations of ethanol. Accuracies of correlations are very similar to those referring to acetic acid–water mixtures too. Benzene is now the most frequently studied compound as it is represented by experimental solubilities from 7 different laboratories.

The ability of UNIQUAC to predict solubility profiles of a class of drugs has been tested in some detail using barbiturates as a typical example. The solubility behaviour of barbiturates in ethanol–water mixtures has been well characterized in a paper by Breon and Paruta (1970) reporting solubility profiles of 9 different compounds of this class. Their solubility data in pure water and in pure ethanol have been transformed into the mole fraction solubilities shown in Table 4. The names of the barbiturates concerned are given in the first column of this table. The remaining columns represent relative Van der Waals volumes and surfaces, and interaction parameters calculated from solubilities in water or in ethanol. These parameters have been used for predictive calculations which are summarized by Table 5. The second and third column of Table 5 are devoted to one-data point predictions using A_{13} and A_{31} values from experimental solubilities in water, together with literature values (Sørensen and Arlt, 1980) for A_{12} and A_{21} whilst assuming $A_{23} = A_{32} = 0$. It is immediately clear that, for ethanol volume fraction up to 10%, all solubility profiles have been predicted within less than 25%. Similar results are found for predictions up to 20% (v/v) ethanol which can be regarded as the upper limit to practical biopharmaceutical applications. Here, a maximum deviation of only 44% is observed

TABLE 4

EXPERIMENTAL SOLUBILITIES AND UNIQUAC PARAMETERS OF BARBITURATES

Key: X_w = mole fraction solubility in water; X_e = mole fraction solubility in ethanol; r = relative Van der Waals volume; q = relative Van der Waals surface; A_{13}, A_{31} = interaction parameters for barbiturate–water interactions; A_{23}, A_{32} = interaction parameters for barbiturate–ethanol interactions.

Barbiturate	X_w	X_e	r	q	A_{13}	A_{31}	A_{23}	A_{32}
Barbital	7.16×10^{-4}	2.86×10^{-2}	6.750	5.488	−29.60	1527	−46.28	1158
Metharbital	1.82×10^{-4}	1.23×10^{-2}	7.403	6.032	13.03	1498	−20.06	1140
Vinbarbital	5.67×10^{-5}	1.61×10^{-2}	7.012	8.539	24.86	1517	−53.72	1195
Thiopental	5.99×10^{-6}	1.35×10^{-2}	9.195	7.240	66.83	1462	−55.38	1197
Thiamylal	3.55×10^{-6}	3.58×10^{-2}	9.639	7.568	67.10	1469	−98.51	1256
Butabarbital	7.70×10^{-5}	2.28×10^{-2}	8.098	6.564	20.99	1502	−60.86	1195
Phenobarbital	9.34×10^{-5}	2.91×10^{-2}	8.196	6.232	−36.66	1520	−74.28	1198
Amobarbital	4.47×10^{-5}	5.39×10^{-2}	8.772	7.104	17.62	1519	−106.4	1261
Pentobarbital	4.01×10^{-5}	6.12×10^{-2}	8.772	7.104	22.20	1515	−112.1	1269

whereas the average mean deviation amounts to 33%.

Two-data point predictions have been calculated using solubilities in pure water and pure ethanol for the derivation of A_{13}–A_{31} and A_{23}–A_{32}, respectively. Values for A_{12} and A_{21} were taken from the literature, as before. The reliabilities of calculated predictions have been collected in the fourth to sixth column of Table 5. As expected, the quality of these predictions is significantly improved as compared to their one-data point analogues. Experimental solubilities up to 10% (v/v) or 20% (v/v) ethanol are now predicted with an average mean deviation of 13% and 22%, respectively. Accuracies of predictions of total solubility profiles, as represented by the sixth column of Table 5, are observed to amount to 28% on the average. Some representative plots are given in Fig. 3 where the very large solubilizing effect of ethanol on the aqueous solubilities of barbital and metharbital is seen to be predicted with very high accuracy.

The results obtained for barbiturates are typical for other classes of drugs and co-solvents too. An example is given by Fig. 4 where two-data point predictions for caffeine and theobromine in dioxane–water are compared to experimental data of Adjei et al. (1980) and of Martin (1981). The

TABLE 5

ACCURACIES IN % OF ONE- AND TWO-DATA POINT PREDICTIONS OF SOLUBILITIES OF BARBITURATES IN ETHANOL–WATER MIXTURES

Key: Φ_e = volume fraction of ethanol.

Barbiturate	One-data point predictions		Two-data point predictions		
	$\Phi_e \leq 0.1$	$\Phi_e \leq 0.2$	$\Phi_e \leq 0.1$	$\Phi_e \leq 0.2$	$0 \leq \Phi_e \leq 1$
Barbital	21	34	15	20	13
Metharbital	15	34	8	16	19
Vinbarbital	23	43	16	26	24
Thiopental	16	33	10	19	44
Thiamylal	24	44	22	39	34
Butabarbital	15	30	9	17	28
Phenobarbital	13	24	8	12	21
Amobarbital	19	37	17	31	35
Pentobarbital	12	15	11	16	36
Mean	18	33	13	22	28

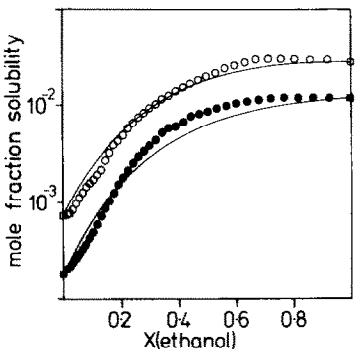

Fig. 3. Experimental (○ and ●) and calculated solubility profiles in ethanol–water of barbital and metharbital, respectively. The curves represent two-data point predictions whereby the solubilities in pure water and in pure ethanol (□ and ■) are used as input.

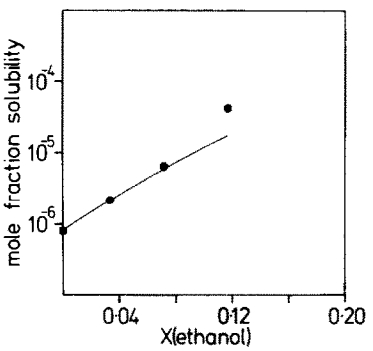

Fig. 5. Experimental (●) and calculated solubility profiles of diethylstilbestrol in ethanol–water. The curve represents a one-data point prediction whereby the solubility in pure water (■) is used as input. Experimental data points in the mixed solvent region correspond to 10, 20 and 30% (v/v) ethanol.

solubilities of these compounds increase more than 10-fold upon addition of relatively small amounts of dioxane. Fig. 4 shows that the total solubility profiles are accurately reproduced by two-data point predictions. The mean deviations of both curves amount to 19% and 29% for caffeine and theobromine, respectively.

Diethylstilbestrol is a very good example of a biologically active compound which is almost insoluble in water. A one-data point prediction for ethanol–water mixtures is shown in Fig. 5, together with experimental data from Gabaldon et al. (1968). Up to 20% (v/v) ethanol, excellent agreement between experiment and prediction is observed. Hydrocortisone is another example of a poorly soluble compound of pharmaceutical interest. Solubilities of hydrocortisone in propylene glycol–water mixtures have been reported by Hagen and Flynn (1983). Fig. 6 reveals a less satisfactory agreement between their experimental results and one- or two-data point predictions. There are two plausible reasons for this effect. First, UNIQUAC calculations for the propylene–water system are hampered by a lack of propylene glycol–water interaction parameters

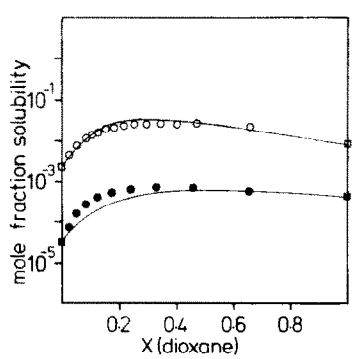

Fig. 4. Experimental (○ and ●) and calculated solubility profiles in dioxane–water of caffeine and theobromine, respectively. The curves represent two-data point predictions whereby the solubilities in pure water and in pure ethanol (□ and ■) are used as input.

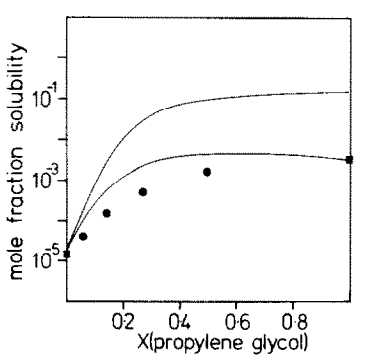

Fig. 6. Experimental (●) and calculated solubility profiles of hydrocortisone in propylene glycol–water. The curves represent one- and two-data point predictions whereby either the solubility in pure water (upper curve) or the solubilities in pure water and in pure propylene glycol (lower curve) are used as input. Experimental data points in the mixed solvent region correspond to 20, 40, 60 and 80% (v/v) propylene glycol.

in the compilation of Sørensen and Arlt (1980). The present calculations have been performed whilst neglecting these parameters which obviously yields less reliable results. The second reason might be found in a general failure of (crystallographic) Van der Waals data to represent true molecular surfaces and volumes in solution. This problem has been studied before (Allinger, 1976; Grünbauer and Tomlinson, 1985) and it might be at the origin of the present discrepancies too. Hagen and Flynn (1983) reported a molecular volume of 293 ml/mol for hydrocortisone whereas the Van der Waals volume amounts to 207 ml/mol. However, in spite of observed shortcomings, both one- and two-data point predictions are not without practical value since a semi-quantitative estimate, at least, has been obtained of the solubilizing effect of propylene glycol.

Variation of pH is a current practical approach to the solubilization of ionizable drugs. In this context, a very interesting problem is formed by pimozide or 1-{1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]}-1,3-dihydro-2H-benzimidazol-2-one (Janssen, 1974). This compound is a weak organic base with tranquilizing properties. Its structural formula is given by Fig. 7. On a mole fraction scale, the solubility of the neutral form of pimozide is near 10^{-7}. In a 0.01 N solution of hydrochloric acid with pH = 4 the solubility is increased to 10^{-5} due to protonation of the neutral molecule. However, further addition of hydrochloric acid has a *decreasing* effect on the solubility. A strikingly different behaviour is observed when hydrochloric acid is replaced by acetic acid since, in this case, the solubility of pimozide remains on the same level up to acetic acid concentrations of 1 mol/l. A two-data point prediction using the aqueous solubility of the neutral form is represented by the dashed line in Fig. 8. As expected, the calculated solubility profile deviates significantly from experimental solubilities at 0.01, 0.1

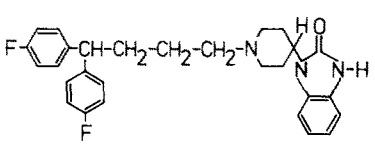

Fig. 7. Chemical structure of pimozide.

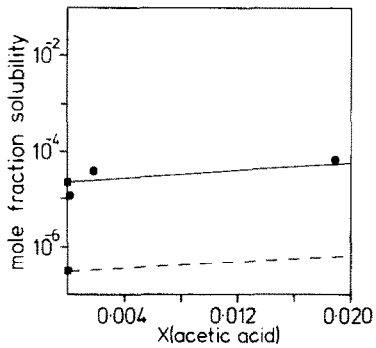

Fig. 8. Experimental (●) and calculated solubilities of pimozide in acetic acid–water. The solid curve represents a two-data point prediction whereby the solubility in a 0.01 N HCl solution in water (pH = 4) is used as input, together with the solubility in glacial acetic acid (not shown). The dashed curve results from similar calculations whereby the solubility of pimozide in pure water is used as input. Experimental data points in the mixed solvent region correspond to 0.01, 0.1 and 1 m solutions of acetic acid in water.

and 1 molar acetic acid. A correct solubility profile is, however, predicted when the experimental solubility in 0.01 N hydrochloric acid is used as input. This result strongly suggests that the solubilizing capacity of acetic acid is composed of a contribution arising from protonation of pimozide and an additional, smaller effect of favourable intermolecular interactions between protonated pimozide and acetic acid moieties. Finally, it is evident that UNIQUAC might be successfully employed for the design of formulations of weakly basic or acidic drugs provided that proper experimental solubilities are chosen as input.

In the present study, attention has been paid to solubilization by single co-solvents alone. The UNIQUAC model is, however, not restricted to this type of formulation. One-data point predictions for co-solutes, such as sugars, are expected to be as reliable as their co-solvent analogues. Accurate predictions for added polymers can probably be calculated as well since the UNIQUAC model is based on the Staverman entropy concept which is highly successful with polymers. Extension of the present results to mixtures of more than one solubilizing compound is also feasible. Due to the mathematical structure of UNIQUAC, predictions for aqueous mixtures containing a number of added compounds can be calculated without intro-

ducing additional experimental information as input. These applications of UNIQUAC are presently investigated in this laboratory.

Conclusions

It can be concluded that UNIQUAC provides a very useful method for the computer-aided design of formulations with significantly increased solubility. This method is superior to existing approaches for both its generality and the smaller number of experimental data required. In practice, the most efficient way of application probably consists of performing at first one single solubility measurement in pure water, followed by the calculation of one-data point predictions in various co-solvent–water mixtures of interest. Subsequently, the best co-solvent can be selected and, eventually, the solubility in pure co-solvent can be measured too in order to improve the quality of the prediction. In principle, the whole procedure is readily extended to aqueous mixtures containing more than one added compound without additional experimental information being required. It can be expected that this design method is capable of at least semi-quantitative predictions of solubilizing effects exhibited by a wide variety of organic compounds, including solids, polymers and weak electrolytes.

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