Pharmaceutical Research, Vol. 4, No. 3, 1987

Research Article

Cosolvency and Cosolvent Polarity

Joseph T. Rubino[1] and Samuel H. Yalkowsky[2]

Received July 28, 1986; accepted December 14, 1986

The solubilities of three poorly soluble drugs, phenytoin, benzocaine, and diazepam, in cosolvent–water mixtures have been previously shown to be approximated by the log-linear solubility equation; $\log (S_m/S_w) = \sigma f$, where S_m and S_w represent the solubilities of the drug in the solvent mixture and water, respectively, f is the volume fraction of cosolvent, and σ is the slope of a plot of $\log (S_m/S_w)$ vs f. In this study, the slopes, σ, of the solubility plots were related to indexes of cosolvent polarity including the dielectric constant, solubility parameter, surface tension, interfacial tension, and octanol–water partition coefficient. Those polarity indexes that reflect the cohesive properties of the solvents such as the solubility parameter and interfacial tension resulted in the highest correlations with the slope, σ. The hydrogen bonding ability of the neat cosolvent, expressed as the density of proton donating groups (HBD) or acceptor groups (HBA), was also found to be highly correlated with σ. Additional relationships derived from theories involving solubility parameters and interfacial tension provide improved correlations between the cosolvent polarity and σ. These results and analysis provide the basis for the estimation from physicochemical parameters of the appropriate type and amount of cosolvent needed to solubilize nonpolar drugs.

KEY WORDS: cosolvency; solvent polarity; solubility estimation; hydrogen bonding; log-linear solubility equation.

INTRODUCTION

Prior to the late 1950s the choice of the type and amount of cosolvent to be used in a pharmaceutical vehicle was made on a purely empirical basis (1). Solubility studies were performed on poorly soluble compounds in cosolvent–water combinations. These studies usually included propylene glycol, glycerin, or ethanol as the cosolvent component. The use of solvent polarity indexes as parameters for use in solvent blending greatly facilitated the process of selecting cosolvents to be used in pharmaceutical vehicles. The dielectric constant and solubility parameter were among the first polarity indexes to be used for solvent blending. These and some less frequently used polarity indexes such as interfacial tension, surface tension, and partition coefficient are discussed below.

DIELECTRIC CONSTANT

For molecules with both permanent and induced dipoles, the contribution of the permanent dipole moment, μ, and the polarizability, α, will affect the molar polarization. Debye considered the effect of the molecule alignment in the magnetic field as well as the opposing tendency of the thermal motion of the molecules of the dielectric material on the molar polarization, P (2):

$$P = \frac{4}{3}\pi N\alpha + \frac{4}{3}\pi\frac{N\mu^2}{3k}\frac{1}{T} = \frac{\epsilon - 1}{\epsilon - 2}\frac{M}{d} \qquad (1)$$

where T is the absolute temperature, k is the Boltzmann constant, M is the molecular weight, d is the density, ϵ is the dielectric constant, N is Avogadro's number, and μ is the dipole moment.

Equation (1) does not consider the effects of steric hindrance or intermolecular interactions on the molar polarization. Several modifications have been made to Eq. (1). These modifications are deemed necessary since the dielectric constant measurements of the dipole moments of liquids do not always agree with the dipole moment values obtained from gases of the same substances. Onsager (3) employed a slightly different derivation to produce an equation similar in form to the Debye equation. This equation was further elaborated upon by Kirkwood (4):

$$\frac{(\epsilon - 1)(2\epsilon + 1)}{7} = \frac{4\pi}{3}N\alpha + \frac{4\pi}{3}N\frac{\mu\bar{\mu}}{3kT} \qquad (2)$$

where $\bar{\mu}$ is a parameter intended to take into account the hindering effect of a molecule upon its neighbors.

Equations (1) and (2) express the effects of individual molecular properties such as the polarizability and dipole moment on the molar polarization and dielectric constant. Although these individual molecular properties, which are directional or vector-like, might be expected to relate qualitatively to phenomena such as solubility which depend on polarity, they do not reflect the "total polarity" of a substance. The concept of "total polarity" was established by Hildebrand (5) to represent the "cohesiveness" or the summation of all attractive forces which surround a molecule.

[1] School of Pharmacy, Beard Hall 200H, University of North Carolina, Chapel Hill, North Carolina 27514.

[2] College of Pharmacy, University of Arizona, Tucson, Arizona 85721.

0724-8741/87/0600-0220$05.00/0

Total polarity is represented better by measures of free energy or excess free energy.

Nonetheless, the dielectric constant has been used extensively as a measure of solvent polarity and as an important parameter used in solvent blending. Moore (6) reported a method in which the solvent dielectric constant could be used in blending solvents for liquid vehicles. The method involves the determination of the polarity of solvent needed to dissolve the required amount of drug. This can be performed in solvent mixtures such as ethanol and water. The polarity of the solvent mixture is approximated by

$$\text{ADC} = \sum_{i=1}^{n} ((\%\ \text{solvent}_i\ \epsilon_i)/100) \qquad (3)$$

The ADC is the approximate dielectric constant required to dissolve the desired amount of drug.

When the solvent components of the final formulation have been decided upon, the proper amounts of these solvents can be obtained using alternate alligation about the required ϵ value. Although this method can be valuable in determining solvent composition, it assumes that a linear relationship exists between the solubility and the dielectric constant in going from one solvent system to another. Gorman and Hall (7) found better correlations between the log solubility and the solubility parameter than between the log solubility and the dielectric constant of the pure solvent. However, these correlations were improved if homologous series of solvents were treated separately. In other words, solvents of similar bonding characteristics gave better correlations between the solubilizing ability and the dielectric constant. Linear relationships were also observed between the log solubility and the dielectric constant of mixed solvents.

The relationship between the solubility and the dielectric constant was also studied by Paruta *et al.* (8). It was concluded that there was a dielectric constant for a solvent at which the salicylic acid solubility was maximum. It was observed that this dielectric constant was independent of the solvent used and that the magnitude of solubility was independent of the dielectric constant.

The use of the dielectric constant as a polarity index for blending solvents is a great improvement over purely empirical techniques. The potential problems with its use include deviations between measured and calculated dielectric constants and the inability of this polarity index to predict solubilities in different solvent systems accurately.

SOLUBILITY PARAMETER

Hildebrand (5) considered the most important factor in determining the solubility of a solute in a solvent to be the relative internal pressures of the two components. These internal pressures are measures of the intermolecular forces of the solution components. Various methods of obtaining the relative internal pressures of solution components were also considered, the most important of which is the energy of vaporization per unit volume of substance, Ev/V (9). This quantity is also known as the "cohesive energy density." It is the total amount of energy (per unit volume) needed to break the intermolecular forces of the pure substance. It is therefore a measure of the "total polarity" of the substance. The square root of the cohesive energy density is the solubility parameter, δ. When the solubility parameters of the solute and solvent, the heat of fusion, and the melting point of the solute are known, the regular solution solubility can be calculated by Eq. (4):

$$\ln X_2 = \frac{-\Delta H_f}{RT}\left(\frac{T_m - T}{T_m}\right) - \frac{f_1^2 V_2}{RT}(\delta_1 - \delta_2)^2 \qquad (4)$$

where X_2 is the mole fractional solubility of the solute, ΔH_f is the heat of fusion of the solute, T_m is the melting point of the solute, f_1 is the volume fraction of the solvent, V_2 is the molar volume of the solute, R is the universal gas constant, and T is the absolute temperature.

Equation (4) is known as the Scatchard–Hildebrand equation (10). This equation has been found to be very useful in a number of industrial applications in nonaqueous solvents. However, it is not useful for predicting solubilities in aqueous solvents.

Martin *et al.* (11,12) modified the Scatchard–Hildebrand equation to justify its use in predicting solute solubilities in polar solvents. The extended Hildebrand equation is written as

$$-\log X_2 = \frac{\Delta H_f}{2.303RT}\left(\frac{1}{T} - \frac{1}{T_m}\right) + \frac{f_1^2 V_2}{2.303RT}(\delta_1 + \delta_2 - 2W) \qquad (5)$$

Equation (5) has been used as the basis for a semiempirical approach to predict drug solubilities in pure and mixed solvents. Values of W were obtained by defining a polynomial which described W in terms of δ_1, the solubility parameter of the pure or mixed solvent for a particular solute. Thus W was calculated using the polynomial relationship with δ_1, and this as well as the other constants could be used to calculate log X_2. The extended Hildebrand solubility approach has been demonstrated for several solutes in mixed solvent systems including caffeine, theobromine, theophylline, tolbutamide, acetohexamide, and sulfisomidine (11–14).

Although the extended Hildebrand approach has been shown to describe successfully the solubility data over a wide range of drug and solvent polarities, it suffers from the fact that it is largely an empirical approach. Calculation of W, the term accounting for solute–solvent interactions, requires nonlinear regression of solubility data of the drug in the solvent system of interest. The parameter W has not been related to any physical characteristics of the solvent or solute and is therefore useful only for drug–solvent systems in which the relationship between W and δ_1 has been previously defined.

INTERFACIAL TENSION

Amidon *et al.* (15) developed an approach that uses the molecular surface area of the solute and the interfacial tension between the solute and the solvent to predict solubilities. The approach is based on the "cavity model," which is analogous to the derivation of the Scatchard–Hildebrand equation described by Martin *et al.* (16). The following expression can be derived based on this approach:

$$\log X = \frac{-\Delta H_f}{2.303RT}\left(\frac{T_m - T}{T_m}\right) - \frac{\gamma_{12} A_2}{2.303RT} \qquad (6)$$

where γ_{12} is the interfacial tension between the solute and the solvent and A_2 is the molar surface area of the solute. Equation (6) can be used to predict the solubility of a crystalline solute if the enthalpy of fusion, solute–solvent interfacial tension, and solute molar surface area are known.

The use of interfacial tension to predict the solubility of nonpolar solutes in mixed solvents was studied further (17). It was suggested that the solubility of a compound in a water–cosolvent mixture could be expressed by Eq. (7):

$$\log S_m = \log S_w + \frac{\Delta\gamma_h A_h + \Delta\gamma_p A_p}{2.303RT} f \qquad (7)$$

where $\Delta\gamma_h = \gamma_{wh} - \gamma_{ch}$, $\Delta\gamma_p = \gamma_{wp} - \gamma_{cp}$, and S_m is the solubility in the cosolvent–water mixture. The subscripts w and c represent water and cosolvent, respectively; h and p represent the hydrophobic and polar portions of solute molecules, respectively. Equation (7) predicts a logarithmic increase in solubility with increasing volume fraction of cosolvent. The slope of a log S_m vs f plot can be given the symbol σ:

$$\log S_m = \log S_w + f\sigma \qquad (8)$$

The slope, σ, can be expressed in terms of the solute–solvent interfacial tensions:

$$\sigma = \frac{\Delta\gamma_h A_h + \Delta\gamma_p A_p}{2.303RT} \qquad (9)$$

It was shown that $\Delta\gamma_p$ was small in comparison to $\Delta\gamma_h$. Equation (9) can be simplified to give

$$\sigma = \frac{C\Delta\gamma_h A_h}{2.303RT} = \frac{C(\gamma_{wh} - \gamma_{ch})A_h}{2.303RT} \qquad (10)$$

The constant term C is added to Eq. (10) to account for the curvature at the solute molecule–solvent interface. Zografi and Yalkowsky (18) have shown that the interfacial tensions between various polar liquids and several nonpolar liquids are essentially constant. That is, the interfacial tension between water and hexane is very similar to the interfacial tension between water and tetradecane or paraffin. Similarly, the interfacial tensions between various cosolvents were similar when measured against various nonpolar phases. Therefore, the interfacial tension between a cosolvent and some nonpolar liquid would be expected to correspond to the interfacial tension between the cosolvent and the hydrophobic portion of the solute molecule and could be used as a measure of σ. This constancy makes interfacial tension a useful parameter for studying the solubility of hydrophobic solutes.

The advantage of using interfacial tension as a measure of solute–solvent interactions is that it can be measured for substances whose intermolecular forces are quite different from each other. This can be contrasted with δ_{12}, the solubility parameter related to the intermolecular attraction between the solute and the solvent. δ_{12} can be estimated using the geometric mean rule when London dispersion forces are involved between solute and solvent. In these solutions, the intermolecular forces between solute and solvent could be quite similar and interfacial tensions would not be measurable due to miscibility of the solute and solvent phases. A parameter such as interfacial tension is useful when intermolecular forces between solute and solvent are very different, as may be the case for lipophilic compounds and aqueous solutions.

PARTITION COEFFICIENT

It can be shown that the octanol–water partition coefficients of a number of organic compounds qualitatively agree with other polarity indexes such as the solubility parameter and dielectric constant (19). Of particular importance to the study of aqueous solutions is the fact that octanol–water partition coefficients have been used to estimate the aqueous solubility of organic compounds.

Valvani *et al.* (20) showed that the following relationship exists between log S_w and log $PC_{o/w}$ for a number of liquid solutes:

$$\log S_w = -0.95 \log PC_{o/w} + 2.40 \qquad (11)$$

where S_w is expressed as grams per liter. The coefficient of log $PC_{o/w}$ is close to -1.0. Therefore, log S_w is approximately inversely proportional to log $PC_{o/w}$.

The slope, σ, of the solubilization curves has been shown to be related to the octanol–water partition coefficient of the solute for a given cosolvent–water system by the following expression (21):

$$\sigma = A \log PC_{o/w} + B \qquad (12)$$

The validity of Eq. (12) has been tested for a number of solutes in propylene glycol–water mixtures (22). In most cases the use of Eq. (12) in conjunction with Eq. (8) estimated the solubilities of the compounds to within a factor of two or less of the measured solubility. The experimental variation in measuring PC and the mutual saturation effects of octanol and water in altering solvent polarities may account for sources of error in these systems. The use of partition coefficients as an index of solvent polarity for blending solvents has not been investigated previously. Therefore it was decided to examine the ability of this index to predict the slopes of the solubilization curves in a system consisting of a single solute in various cosolvent–water mixtures and to compare it with the more conventional solvent polarity indexes.

RATIONALE

The solubility of nonpolar solutes in water–cosolvent mixtures can be approximated by Eq. (8) (23–25). This equation could be used alone to estimate the proper quantities of water and cosolvent needed to solubilize a particular quantity of drug by determining the solubility of drug in pure water and pure cosolvent, plotting these points on semilog paper at $f = 0$ and $f = 1.0$, respectively, and connecting these two points by a straight line. The proper amount of cosolvent to be used can be estimated from a knowledge of the desired concentration of drug and the corresponding fraction of cosolvent along the straight line.

Alternatively, the slope, σ, of the solubilization curves could be defined in terms of a polarity index or a combination of indexes using least-squares regression techniques. This treatment was performed on the solubility data which were collected for phenytoin, diazepam, and benzocaine in order to determine which polarity indexes of the solvent

best describe the slope of the solubilization plots and to present the parameters for the regression equation which can be used to estimate these slopes for the solutes studied here. This approach could be applied toward determining the type and amount of cosolvent needed to solubilize a drug with a minimum of experimental data.

EXPERIMENTAL

Solubility Determinations

The solubilities of phenytoin, benzocaine, and diazepam in the cosolvent–water mixtures were determined as discussed previously (23–25). The cosolvents included 70% (w/w) sorbitol (SORB), glycerin (GLYC), propylene glycol (PG), 1,3-butanediol (BUTDIOL), polyethylene glycol 200 and 400 (PEG), methanol (MEOH), ethanol (ETOH), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), dimethylformamide (DMF), dimethylisosorbide (DMI), dioxane, and triglyme (TRIG).

Dielectric Constants

Dielectric constant values were taken from various literature souces (see Table I for references). All values used were for 25°C unless otherwise specified.

Solubility Parameters

Solubility parameters were obtained from the literature or determined experimentally from the heat of vaporization using the formula

$$\delta_c = \frac{(\Delta H_v - RT)^{1/2}}{v}$$

where ΔH_v is the molar heat of vaporization and V is the molar volume of the cosolvent and δ_c is the solubility parameter of the cosolvent. The molar volume was estimated from the solvent density and molecular weight. ΔH_v was determined using a differential scanning calorimeter (DSC) (DuPont Co., Analytical Instrument Division, Wilmington, Del. 19898). The sample was placed in aluminum sample pans and hermetically sealed to prevent gradual evaporation of the solvent before the boiling point.

In the case of the polyethylene glycols, degradation occurred before a ΔH_v value could be obtained. The solubility parameter was estimated using the group contribution method of Fedors (26). The solubility parameter for 70% (w/w) sorbitol was obtained from the linear combination of the value for sorbitol and water:

$$\delta_c = 0.70\ (\delta_{sorbitol}) + 0.30\ (\delta_{water})$$

Volume fractions were estimated from the following formula:

$$f = \frac{X_1 V_1}{X_1 V_1 + X_2 V_2}$$

where X is the mole fraction, V is the molar volume, and the subscripts 1 and 2 represent solvent and drug, respectively. The V's were estimated as being equal to the molecular weight divided by the density. The density of the solute was assumed to be unity. X was estimated from the solubility of drug in the solvent and the density of the solvent.

Table I. Polarity Indexes of Solvents

Solvent	Dielectric constant	Solubility parameter	Interfacial tension (dynes/cm)	Surface tension (dynes/cm)	log *PC*	HBD	HBA
Water	78.5[a]	23.4[b]	45.6[c]	72.7[d]	−4.00	111.0	111.0
SORB	62.0[e]	23.4[c]	42.2[c]	73.3[c]	−3.37[e,f]	72.5	102.0
GLYC	42.5[a]	17.7[b]	32.7[c]	60.6[c]	−2.00[c]	41.1	82.2
PG	32.0[a,g]	12.6[b]	12.4[c]	37.1[c]	−1.00[c]	27.4	54.8
BUTDIOL		11.6[b]	11.8[c]	37.9[c]	−0.82[c]	22.4	44.8
PEG 200		12.9[c]	13.2[c]	46.0[c]	−1.38[c,h]	11.3	56.4
PEG 400	13.6[i]	11.3[c]	11.7[c]	46.0[c]		5.6	50.8
MEOH	32.6[a]	14.5[b]	0.7[c]	22.5[c]	−0.73[e]	24.6	49.2
ETOH	24.3[a]	12.7[b]	0.5[c]	21.9[c]	−0.32[e]	17.0	34.0
DMSO	46.7[a]	12.0[b]	0.9[c]	44.0[c]	−1.40[j]	0.0	28.2
DMA	37.8[a]	10.8[b]	4.6[c]	35.7[c]	−0.66[c]	0.0	32.3
DMF	36.7[a]	12.1[b]	6.9[c]	36.8[c]	−0.85[c]	0.0	38.7
DMI		8.63[c]	4.2[c]	36.9[c]	−0.52[c]	0.0	53.2
Dioxane	2.21[a]	9.90[b]	0.0[c]	33.6[c]	−0.42[e]	0.0	46.8
TRIG		8.37[c]	1.6[c]	32.8[c]	−0.60[c]	0.0	44.4

[a] Source: Ref. 34.
[b] Source: Ref. 35.
[c] Source: this work.
[d] Source: Ref. 21.
[e] Source: Ref. 27.
[f] The value for mannitol was used. log PC = 0.70 (log PC mannitol) + 0.30 (log PC water).
[g] Measured at 20°C.
[h] The value for tetraethylene glycol was used.
[i] Source: Ref. 36.
[j] Source: Ref. 37.

Surface and Interfacial Tensions

Surface and interfacial tensions were determined at room temperature (Model 70535 Tensiometer, Central Scientific Co., Chicago, Ill. 60623) (24 ± 0.5°C). Interfacial tensions of the cosolvents were measured against light liquid petrolatum (Fisher Scientific Co., Fair Lawn, N.J. 07410).

The surface areas of drug and solvent were estimated by assuming spherical molecules. The molar surface areas, A, were estimated from the molar volumes by

$$A = 3(4\pi/3)^{1/3}V^{2/3}$$

The surface area fractions, f_a, were calculated by

$$f_a = \frac{X_1A_1}{X_1A_1 + X_2A_2}$$

Octanol–Water Partition Coefficients

Octanol–water partition coefficients of the cosolvents were taken from the compilations of Leo *et al.* (27) or determined experimentally.

Hydrogen Bond Donor Densities

Hydrogen bond donor densities (HBD) were determined for the neat cosolvents from the density of the cosolvent and the number of proton donor groups on the molecule:

$$\frac{\text{(No. of proton donor groups)} \times \text{(density of cosolvent)} \times 1000}{\text{molecular weight of cosolvent}}$$

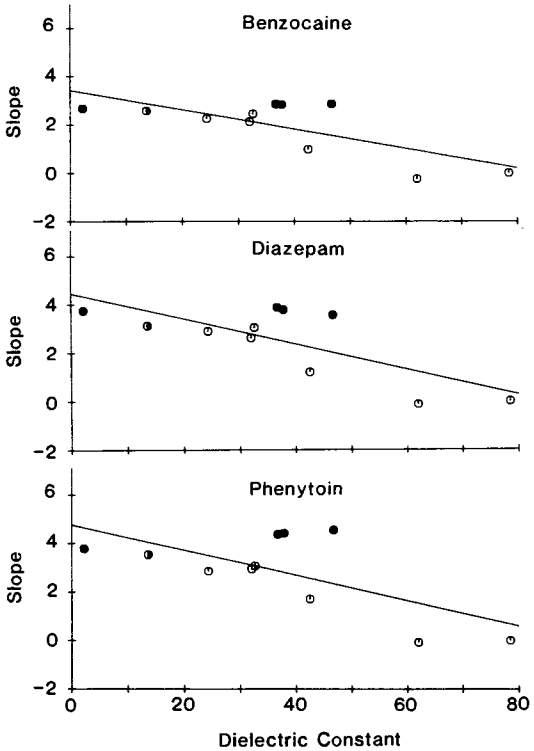

Fig. 1. Slope (σ) vs dielectric constant.

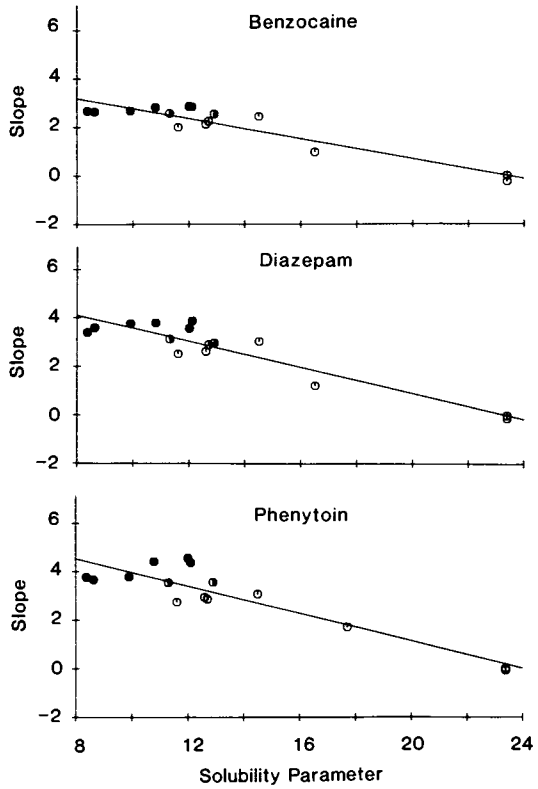

Fig. 2. Slope (σ) vs solubility parameter.

Hydrogen bond acceptor densities (HBA) were calculated in a similar manner:

$$\frac{\text{(No. of nonbonding electron pairs)} \times \text{(density of cosolvent)} \times 1000}{\text{molecular weight of cosolvent}}$$

Regression Analysis

Simple linear and multiple linear regressions were performed using Subprogram Regression from the Statistical Package for the Social Sciences (28). The slopes, σ, used as the dependent variable in the regression analyses were the ideal, end-to-end slopes which were described previously (23–25).

RESULTS

The application of Eq. (8) in describing the solubilities of the three drugs has been discussed elsewhere (23,24). In most cases, the solubilities were estimated to be within a factor of two or less of the actual solubilities. Larger deviations can occur in aprotic cosolvents. The potential source of these deviations is discussed in the following paper (25).

The various polarity indexes for the cosolvents used are listed in Table I. Figures 1–7 are the plots of the slope, σ, vs polarity indexes for the three drugs studied. The symbols are shaded differently to represent different classes of cosolvents. The open circles represent amphiprotic cosolvents, i.e., alcohols and polyhydroxy compounds. The filled circles represent aprotic cosolvents such as dioxane, DMF, DMA,

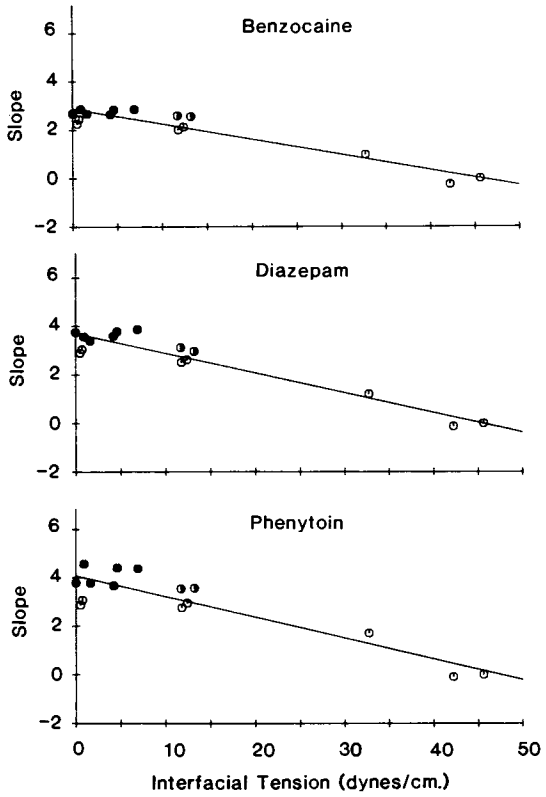

Fig. 3. Slope (σ) vs interfacial tension.

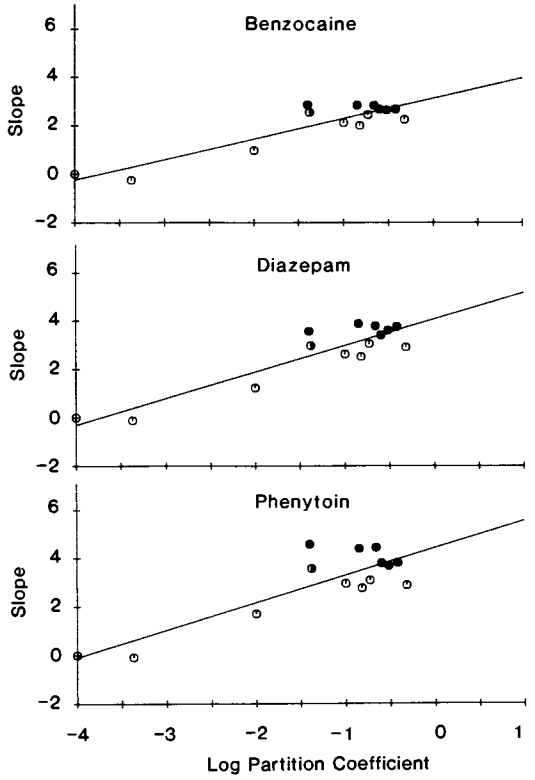

Fig. 5. Slope (σ) vs octanol–water partition coefficient.

DMI, DMSO, and triglyme, and the half-filled circles represent the polyethylene glycols.

The results of the single-parameter and multiple-parameter regressions are presented in Tables II through IV. From the r^2 values and the plots in Figs. 1–5 it can be seen that the dielectric constant showed the poorest correlation with the slope, σ, of the solubilization plots. The best single-parameter correlations were obtained with the interfacial tension

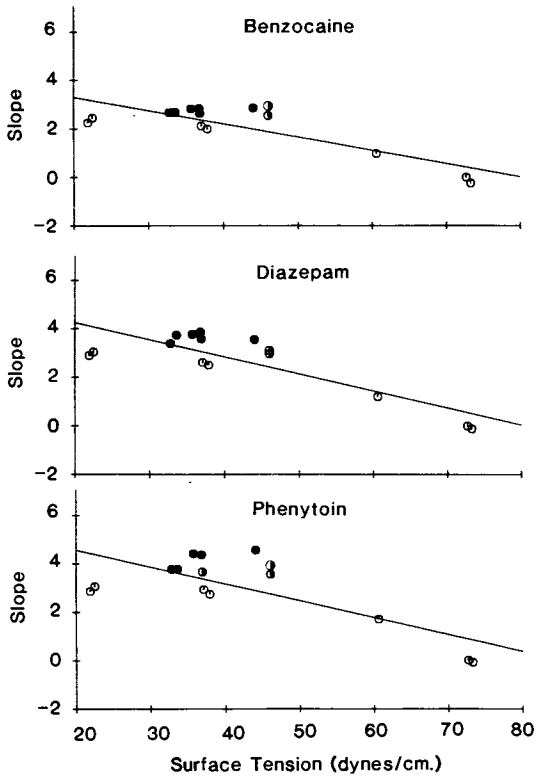

Fig. 4. Slope (σ) vs surface tension.

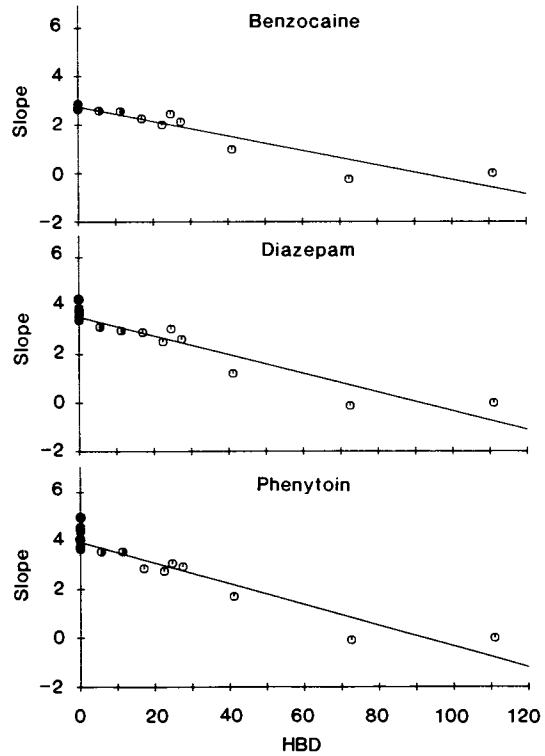

Fig. 6. Slope (σ) vs HBD.

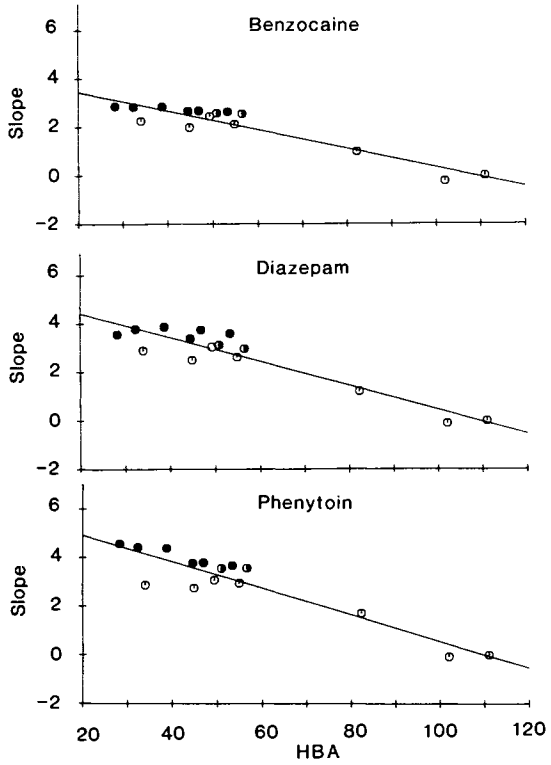

Fig. 7. Slope (σ) vs HBA.

and solubility parameter. Good correlations were also obtained for HBD and HBA. The partition coefficient and surface tension showed somewhat poorer correlations.

The results of the multiple-parameter regressions invariably show an improved correlation between the slope and the polarity index. The significance of these results is discussed below.

DISCUSSION

Single-Parameter Regressions

It was shown previously (21) that the slope, σ, of the log (S_m/S_w) vs f plots could be defined as

$$\sigma = \log ac_w - \log ac_c \qquad (13)$$

In cosolvent–water systems where the drug remains the same and the cosolvent is varied, ac_w will remain constant. According to Eq. (13) those polarity indexes that best represent the solvent activity coefficient should give the best correlation with slope. Further, as the intermolecular interactions between the cosolvent molecules become more similar to those between the drug molecules, log ac_c should approach zero and the slope will be a maximum since log ac_w is a positive number for the drugs studied.

The dielectric constant gave the poorest correlation with the slope. This supports the observations of Paruta *et al.* (8) that the magnitude of salicylic acid solubility in various cosolvents was independent of the dielectric constant of the medium. Since the quantity $(\epsilon - 1)/(\epsilon + 2)$ relates to molecular properties such as polarizability and dipole moment, this quantity was also regressed with the slope, σ. This modification resulted in an even poorer correlation with the slope.

The poor correlation between dielectric constant and slope may be due to the fact that the dielectric constant is a measure of the individual molecular properties, polarizability and dipole moment. Hildebrand (5) has stated that solubility is a phenomenon that depends upon the "total polarity" of the solvent. Although the total polarity probably has contributions from the individual molecular properties, it is the total energy that surrounds the molecule which determines its ability to solubilize a given solute.

The total polarity is better measured by indexes that reflect the cohesiveness of the solvent. Therefore, solubility parameter and interfacial tension might be expected to give better correlations with the slope since they are parameters which measure cohesive properties of the solvent. This is confirmed by the improved correlation between σ and the solubility parameter in Tables II through IV.

Yalkowsky *et al.* (17) have shown that the slope of the solubilization curves should be related to the interfacial tension by Eq. (10). According to this equation, a negative correlation should exist between σ and $\Delta\gamma_{ch}$ since $\Delta\gamma_{wh}$ and A_h remain constant for a given solute. This is supported by the results of the regression analysis presented in Tables II through IV. The correlation between slope and interfacial tension is better for benzocaine and diazepam than for phenytoin, possibly because of its high solubility in solvents such as DMSO, DMA, and DMF. This high solubility may be indicative of some specific interaction between these solvents and phenytoin such as a shift in the keto-enol tautomerism of phenytoin toward the enol form (25). The high solubility of phenytoin in these solvents is also responsible for the poor correlations between slope and the other single-parameter polarity indexes.

Surface and interfacial tension should also correlate with slope. However, surface tension gave much poorer correlations with slope than interfacial tension (Fig. 4, Table II). An examination of Fig. 4 shows that the slopes are higher than expected for the aprotic cosolvents based on their surface tensions. The prediction for the solubilization slopes in these solvents was better when interfacial tensions were used as seen in Fig. 3. Partial miscibility may occur between these cosolvents and paraffin, thus resulting in a lower tension at the interface. The partial miscibility of paraffin in these cosolvents may be a reflection of the lower cohesive energy density of these solvents, particularly since hydrogen bonding does not occur in the pure cosolvents. Thus the cosolvent–paraffin interface parallels the cosolvent–drug interface more closely than the cosolvent–air interface.

The octanol–water partition coefficient of the cosolvents was somewhat better than surface tension in its ability to predict the slope (Fig. 5). However, it is a poor parameter for predicting compared to the solubility parameter or interfacial tension. The poor correlation may be the result of the experimental variability in the measurement of the partition coefficient. The cosolvents used are all hydrophilic and only small amounts partition into the octanol phase. Further variation may be introduced by the varying degrees of mutual saturation of each phase.

The aprotic cosolvents consistently gave a higher degree of solubilization than predicted. Paruta *et al.* (29) also noticed that non-hydrogen bonding solvents showed unusual

Table II. Summary of Regression Analyses, Slope vs Polarity Index for Phenytoin

(A) Single-parameter equations

Index	n	m	(SE)	b	F	(Sig.)	r^2
Dielectric constant	11	−0.0521	(0.0195)	4.7721	7.12	(0.026)	0.4418
Solubility parameter	15	−0.2860	(0.0370)	6.8239	59.9	(0.000)	0.8216
Surface tension	15	−0.0698	(0.0169)	5.9662	17.1	(0.001)	0.5686
Interfacial tension	15	−0.0854	(0.0112)	4.0731	58.4	(0.000)	0.8180
log *PC*	14	1.1280	(0.2034)	4.4131	30.7	(0.000)	0.7193
HBD	15	−0.0428	(0.0040)	3.9466	115.	(0.000)	0.8981
HBA	15	−0.0547	(0.0060)	6.0171	82.4	(0.000)	0.8637

(B) Multiple-parameter equations

Index	n	m	(SE)	F	(Sig.)	r^2
HBD	15	−0.0268	(0.0087)	115.	(0.000)	0.9240
HBA	15	−0.0229	(0.0113)	73.	(0.000)	
Constant		4.8557	(0.4697)			
$\delta^2 f^2$	15	−0.0093	(0.0039)	141.	(0.000)	0.9750
δf^2	15	0.0571	(0.1312)			
f^2	15	−1.1037	(1.0537)			
Constant		4.7899	(0.1830)			
$\gamma_{ch} f^2_{ca}$	15	−0.0855	(0.0095)	81.4	(0.000)	0.8623
Constant		3.9970	(0.1809)			

behavior in that their dielectric constants did not correlate as well with the solubility parameter as hydrogen bonding solvents. Gorman and Hall (7) found that correlations between polarity indexes and drug solubilities were improved if structurally similar solvents were considered as separate groups.

One approach toward obtaining better predictability between solubility and solvent polarity would be to consider amphiprotic and aprotic cosolvents separately. Another approach would be to use a parameter that reflects the ability of the solvent or cosolvent to donate or accept a proton in a hydrogen bond. The simple index HBD was applied as the

Table III. Summary of Regression Analyses, Slope vs Polarity Index for Diazepam

(A) Single-parameter equations

Index	n	m	(±SE)	b	F	(Sig.)	r^2
Dielectric constant	11	−0.0522	(0.0156)	4.4628	11.1	(0.009)	0.5528
Solubility parameter	15	−0.2658	(0.0286)	6.2382	86.6	(0.000)	0.8695
Surface tension	15	−0.0702	(0.0126)	5.6650	30.8	(0.000)	0.7033
Interfacial tension	15	−0.0811	(0.0073)	3.7044	123.	(0.000)	0.9045
log *PC*	14	1.0935	(0.1448)	4.0621	57.1	(0.000)	0.8262
HBD	15	−0.0387	(0.0036)	3.5401	115.	(0.000)	0.8983
HBA	15	−0.0495	(0.0053)	5.4196	86.8	(0.000)	0.8698

(B) Multiple-parameter equations

Index	n	m	(±SE)	F	(Sig.)	r^2
HBD	15	−0.0235	(0.0077)	115.	(0.000)	0.9267
HBA	15	−0.0217	(0.0100)	75.9	(0.000)	
Constant		4.4006	(0.4166)			
$\delta^2 f^2$	15	−0.0091	(0.0048)	87.1	(0.000)	0.9596
δf^2	15	0.0792	(0.1659)			
f^2	15	−2.0323	(1.5620)			
Constant		5.0647	(0.4283)			
$\gamma_{ch} f^2_{ca}$	15	−0.0809	(0.0063)	165.	(0.000)	0.9270
Constant		3.6540	(0.1206)			

Table IV. Summary of Regression Analyses, Slope vs Polarity Index for Benzocaine

(A) Single-parameter equations

Index	n	m	(SE)	b	F	(Sig.)	r^2
Dielectric constant	11	−0.0403	(0.0123)	3.4397	10.7	(0.010)	0.5436
Solubility parameter	15	−0.2068	(0.0226)	4.8478	83.8	(0.000)	0.8657
Surface tension	15	−0.0546	(0.0099)	4.4015	30.3	(0.000)	0.6999
Interfacial tension	15	−0.0630	(0.0059)	2.8750	113.	(0.000)	0.8967
log *PC*	14	0.8430	(0.1155)	3.1338	53.3	(0.000)	0.8161
HBA	15	−0.0388	(0.0040)	4.2247	92.8	(0.000)	0.8771
HBD	15	−0.0300	(0.0029)	2.7468	104.	(0.000)	0.8888

(B) Multiple-parameter equations

Index	n	m	(SE)	F	(Sig.)	r^2
HBD	15	−0.0168	(0.0061)	104.	(0.000)	0.9246
HBA		−0.0189	(0.0079)	73.6	(0.000)	
Constant		3.4992	(0.3294)			
$\delta^2 f^2$	15	−0.0037	(0.0034)	318.	(0.000)	0.9886
δf^2	15	−0.0377	(0.1213)			
f^2	15	0.1723	(1.0486)			
Constant		2.9591	(0.0691)			
$\gamma_{ch} f^2_{ca}$	15	−0.0620	(0.0035)	313.	(0.000)	0.9601
Constant		2.7118	(0.0649)			

independent variable in the data regressions to reflect this property of the cosolvents, and the correlation between σ and HBD is fairly good (Fig. 6).

There is one cosolvent at HBD = 72.5 that is an outlier for all three drugs. This solvent is 70% sorbitol. The low solubilizing potential of sorbitol may be due to two phenomena. Sorbitol, like other sugars and sugar alcohols, may interact strongly with water through its six hydroxyl groups. Perhaps equally important is the fact that sorbitol may become integrated into water structure better than other cosolvents, which tend to perturb water structure to some extent (30,38).

The correlations between HBA and slope (Fig. 7) were not as good as HBD but this parameter provides a better prediction of the slope than the dielectric constant, surface tension, or partition coefficient. One advantage to the use of HBA vs HBD as a polarity index is that it was able to differentiate among the slopes for the aprotic cosolvent–water systems more efficiently.

Multiple-Parameter Regressions

According to Eq. (13), the slope, σ, is the difference between the log activity coefficient of the solute in pure water and that in pure cosolvent. The following equation can be written based on solubility parameter theory:

$$\sigma = \frac{V_s f_w^2 (\delta_w - \delta_s)^2}{2.303RT} - \frac{V_s f_c^2 (\delta_c - \delta_s)^2}{2.303RT} \qquad (14)$$

where V_s is the molar volume of solute, f_w and f_c are the volume fractions of water and cosolvent, and δ_w and δ_c are the solubility parameters of water and cosolvent, respectively. In a system where the drug solubility is measured in various cosolvent–water systems, f_w, V_s, δ_w, and δ_s will remain essentially constant. Therefore Eq. (14) can be rewritten:

$$\sigma = B - C(f_c^2\delta_c^2 - Df_c^2\delta_c - Ef\delta_c^2) \qquad (15)$$

σ was thus regressed against $f_c^2\delta_c$, $f_c^2\delta_c$, and f_c^2. The results are reported in Tables II to IV. The observed vs predicted values are plotted in Fig. 8 for all three solutes. A significantly better correlation is obtained using Eq. (15) rather than the single solubility parameter of the solvent. However, the values for the regression constants are not equal to the constants calculated from Eqs. (14) and (15) for any one cosolvent–water system. This emphasizes the inadequacy of solubility parameter theory in predicting solubilities in hydrogen-bonded solvent systems. Barton (31) has viewed solubility parameter theory as being more useful as a method for fitting data than as a method for predicting solubilities from known physical constants. The use of solubility parameter in the form of Eq. (15) is consistent with this view.

The improved correlations observed with the use of Eq. (15) is due partly to the increased number of parameters used in the regression analysis. However, according to theory, Eq. (15) is more appropriate than a single-parameter equation.

Equation (10) can be modified to include the surface area fraction of the solvent (32):

$$\sigma = \frac{2Cf_{wa}^2 A_h \gamma_{wh}}{2.303RT} - \frac{2Cf_{ca}^2 A_h \gamma_{ch}}{2.303RT} \qquad (16)$$

where f_{wa} is the surface area fraction of water, A_h is the hydrophobic surface area of the drug, γ_{wh} is the interfacial ten-

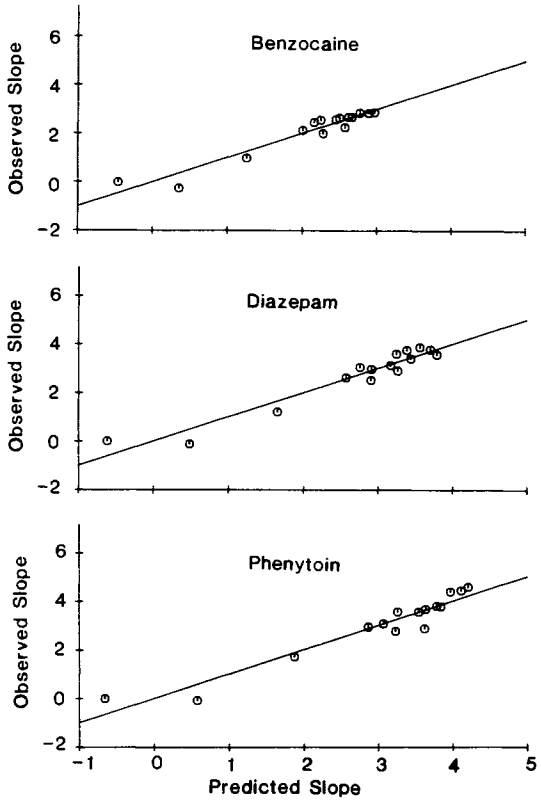

Fig. 8. Observed vs predicted slope for solubility parameter multiple regression.

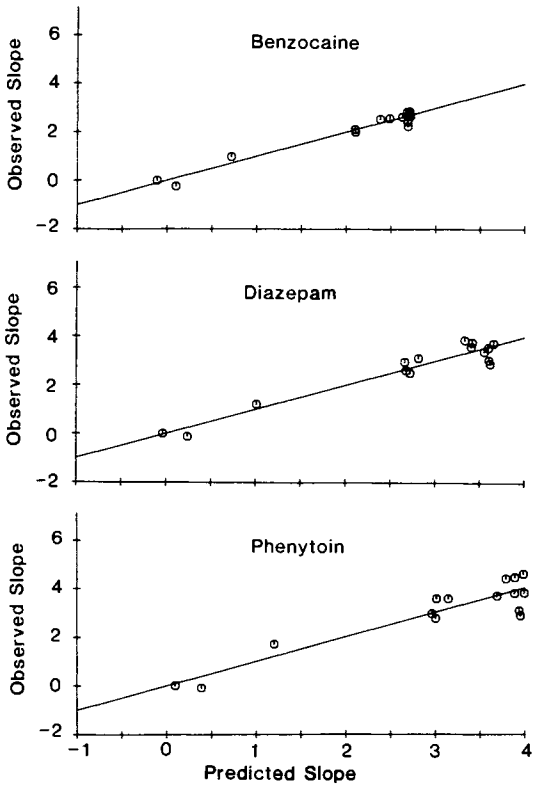

Fig. 9. Observed vs predicted slope for interfacial tension multiple regression.

sion between the drug and water, f_{ca} is the surface area fraction of the cosolvent, and γ_{ch} is the interfacial tension between drug and cosolvent. In a system where the drug remains the same and the cosolvent is varied, the first term on the right-hand side of Eq. (16) will remain constant as well as A_h. Therefore Eq. (16) reduces to

$$\sigma = A' - B' f_{ca}^2 \gamma_{ch} \quad (17)$$

Tables II to IV report the results of the regression analysis of σ vs f_{ca}^2, γ_{ch} for the three drugs in the cosolvent–water mixtures studied. The observed vs predicted slopes are seen in Fig. 9 for the three solutes. In all three cases the ability of interfacial tension to predict σ is improved by the addition of the surface area fraction term. The results are most dramatic for phenytoin and benzocaine. These solutes had the greatest solubility in DMSO, DMA, and DMF and were most affected by the inclusion of the surface area fraction term. The curvature correction constant, C, gives similar values when calculated from constant A' or B'. This agrees with the results of a previous publication which reported that C remains relatively constant for a given solute in various solvents (33).

The combination of HBD and HBA resulted in improved correlations with the slope over the use of either single parameter. The greater significance of HBD over HBA is evident from a comparison of the entering F values reported for the stepwise regression. The advantage of these two parameters as polarity indexes is that the HBD and HBA values can easily be calculated from a knowledge of the cosolvent molecular structure and the density of the neat cosolvent without any physical measurements. The disadvantage of these indexes is the lack of physical significance of the regression coefficients. The observed vs predicted slopes are plotted for each solute in Fig. 10.

In conclusion, the slopes of the solubilization curves can be successfully correlated with various index of polarity. Those polarity indexes that are reflections of solvent cohesiveness such as the solubility parameter and interfacial tension provide the best correlations with the slope of the solubilization curves. It was found that the aprotic cosolvents gave a much higher degree of solubility than the amphiprotic cosolvents. Therefore, the ability of a cosolvent to donate a proton in forming a hydrogen bond can be an important factor in determining the solubilizing potential of a cosolvent. This ability can be expressed as HBD or HBA, and these indexes were shown to correlate well with the slope.

Multiple-parameter equations including solubility parameters and interfacial tension combined with volume fraction and surface area fraction terms, respectively, provided an improved correlation of the polarity index with the slope. The combination of HBD and HBA also provides a better correlation with the slope than either index alone.

Since the slopes of the solubilization curves could be related to several polarity indexes by a linear relationship, it is possible to predict the slope in any cosolvent with a knowledge of four parameters: the solubility of the compound in water, the solubility of the compound in two cosolvents, and a polarity index of the cosolvents. Hence, if the octanol–water partition coefficient of the drug is known, it is theoretically possible to estimate the solubility in any co-

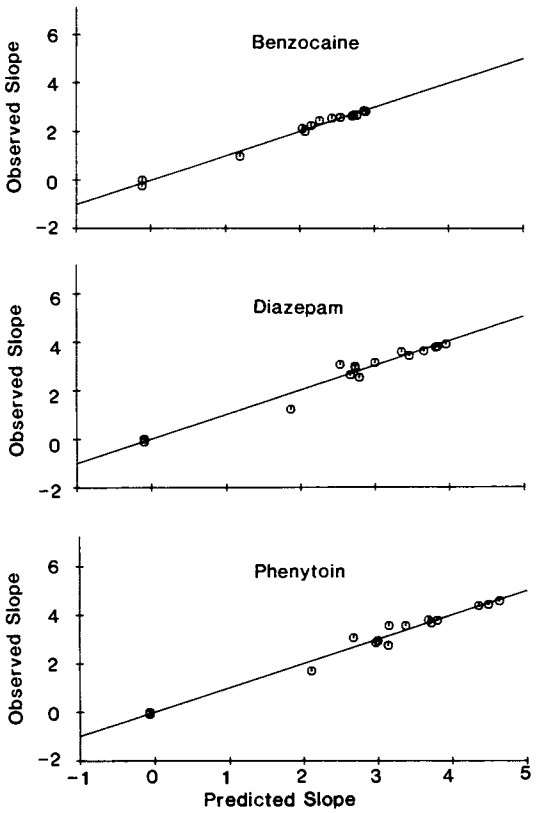

Fig. 10. Observed vs predicted slope for HBD, HBA multiple regression.

solvent–water mixture from a knowledge of the polarity of the cosolvent.

REFERENCES

1. M. Barr and L. Tice. *Am. J. Pharm* 129:332–342 (1957).
2. G. M. Barrow. *Physical Chemistry*, 4th ed., McGraw–Hill, New York, 1979.
3. L. Onsager. *J. Am. Chem. Soc.* 58:1486–1493 (1936).
4. J. G. Kirkwood. *J. Chem. Phys.* 7:911–919 (1939).
5. J. H. Hildebrand. *J. Am. Chem. Soc.* 38:1452–1473 (1916).
6. W. E. Moore. *J. Am. Pharm. Assoc. Sci. Ed.* 47:855–857 (1958).
7. W. G. Gorman and G. D. Hall. *J. Pharm. Sci.* 53:1017–1020 (1964).
8. A. N. Paruta, B. J. Sciarrone, and N. G. Lordi. *J. Pharm. Sci.* 53:1349–1353 (1964).
9. J. H. Hildebrand. *J. Am. Chem. Soc.* 41:1067–1080 (1919).
10. J. H. Hildebrand and R. L. Scott. *Solubility of Nonelectrolytes*, Reinhold, New York, 1950, Chap. 7.
11. A. Martin, J. Newberger, and A. Adjei. *J. Pharm. Sci.* 68:IV (1979).
12. A. Martin, J. Newberger, and A. Adjei. *J. Pharm. Sci.* 69:487–491 (1980).
13. A. Martin, A. N. Paruta, and A. Adjei. *J. Pharm. Sci.* 70:115–1120 (1981).
14. A. Martin and M. J. Miralles. *J. Pharm. Sci.* 71:439–442 (1982).
15. G. L. Amidon, S. H. Yalkowsky, and S. Leung. *J. Pharm. Sci.* 63:1858–1866 (1974).
16. A. Martin, J. Swarbrick, and A. Cammarata. *Physical Pharmacy*, Lea & Febiger, Philadelphia, 1969.
17. S. H. Yalkowsky, S. C. Valvani, and G. L. Amidon. *J. Pharm. Sci.* 65:1488–1494 (1976).
18. G. Zografi and S. H. Yalkowsky. *J. Pharm. Sci.* 63:1533–1536 (1974).
19. S. H. Yalkowsky. *Techniques of Solubilization of Drugs*, Marcel Dekker, New York, 1981, Chaps. 1 and 3.
20. S. C. Valvani, S. H. Yalkowsky, and T. J. Roseman. *J. Pharm. Sci.* 70:502–507.
21. S. H. Yalkowsky and T. J. Roseman. *Techniques of Solubilization of Drugs*, Marcel Dekker, New York, 1981, Chap. 3.
22. S. H. Yalkowsky and J. T. Rubino. *J. Pharm. Sci.* 74:416–421 (1985).
23. J. T. Rubino, J. Blanchard, and S. H. Yalkowsky. *J. Parent. Sci. Technol.* 38:215–221 (1984).
24. J. T. Rubino and S. H. Yalkowsky. *J. Parent. Sci. Technol.* 39:106–111 (1985).
25. J. T. Rubino and S. H. Yalkowsky. *Pharm. Res.* 4:231 (1987).
26. R. F. Fedors. *Polymer Eng. Sci.* 14:147–154 (1974).
27. A. Leo, C. Hansch, and D. Elkins. *Chem. Rev.* 71:525–616 (1971).
28. N. H. Nie, C. H. Hull, J. G. Jenkins, K. Steinbrenner, and D. H. Bent. *Statistical Package for the Social Sciences*, McGraw–Hill, New York, 1975.
29. A. N. Paruta, B. J. Sciarrone, and N. G. Lordi. *J. Pharm. Sci.* 51:704–705 (1962).
30. F. Franks. In F. Franks (ed.), *Physico-chemical Processes in Mixed Aqueous Solvents*, American Elsevier, New York, 1967.
31. A. F. M. Barton. In A. F. M. Barton, (ed.), *Handbook of Solubility Parameters and Other Cohesion Parameters*, CRC Press, Boca Raton, Fla., 1983, Vol. 85, p. 153.
32. J. T. Rubino. *Solubilization of Some Poorly Soluble Drugs by Cosolvents*, Ph.D. dissertation, University of Arizona, Tucson, 1984.
33. S. H. Yalkowsky, G. L. Amidon, G. Zografi, and G. L. Flynn. *J. Pharm. Sci.* 64:48–52 (1975).
34. Anonymous. *Physical Properties of Some Organic Solvents*, Eastman Kodak, Rochester, N.Y., 1975.
35. A. F. M. Barton. *Chem. Rev.* 75:731–753 (1975).
36. S. N. Pagay, R. I. Poust, and J. L. Colaizzi. *J. Pharm. Sci.* 63:44–47 (1974).
37. J. Pitha, L. Szenta, and J. Greenberg. *J. Pharm. Sci.* 72:665–668 (1983).
38. R. Hüttenrauch and S. Fricke. *Pharmazie* 37:147–148 (1982).