Chameleonic Effect of Sulfanilamide and Sulfamethazine in Solvent Mixtures. Solubility Curves with Two Maxima

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A quantitative approach is used in this work to reproduce the solubility profile of drugs in solvent mixtures showing two solubility maxima. The solubilities of sulfanilamide and sulfamethazine were determined at 25°C in two mixtures of varying polarity (ethyl acetate–ethanol and ethanol–water). A plot of the mole fraction of the drugs *versus* the solubility parameter of the solvent mixtures shows two solubility peaks. This unusual behavior cannot be described using the Extended Hildebrand method; it is probably a result of the chameleonic effect first described by Hoy. An equation including solute-solvent interaction terms represented by the acidic and basic partial solubility parameters, together with the Hildebrand solubility parameters of the solvent mixtures, is used to reproduce the experimental solubilities. The equation yields the two solubility maxima as found experimentally.

Furthermore, the solubilities of sulfanilamide and sulfamethazine in two solvent mixtures are combined into a single equation to reproduce the two solubility maxima found for each drug. The equation is also able to predict the solubility curve of sulfamethoxypyridazine. The results show that the chameleonic effect can be described in a quantitative way in terms of Lewis acid-base interactions as represented by acidic and basic solubility parameters. Hildebrand solubility parameters, as well as the acidic and basic solubility parameters, are tabulated and they can be calculated for solvent mixtures, making easier the prediction of the best solvent mixture for a drug.

Keywords chameleonic effect; sulfonamide; solubility; predicting solubility; solvent mixture; solubility parameter

When the solubility of a drug in a polar solvent mixture is plotted against the volume fraction of the cosolvent or the solubility parameter, δ, of the solvent mixture, a smooth curve is obtained. The curve rises to a peak solubility value at a definite solvent solubility parameter, provided the solubility parameter of the drug lies in the range of the solubility parameters of the solvent mixture. The solubility parameter, δ, is defined as the square root of the cohesive energy density and is a measure of polarity.[1)]

In a similar way, when the mole fraction solubility of benzoic acid is plotted against the solubility parameter of three solvent mixtures, hexane–ethyl acetate, ethyl acetate–ethanol and ethanol–water, the solubility of the drug smoothly increases from 100% hexane and reaches a maximum at $\delta_1 = 22.50\,\mathrm{MPa}^{1/2}$ (50% (v/v) ethyl acetate in ethanol). From this point, the solubility of benzoic acid continuously decreases as the medium becomes more polar by the addition of ethanol to ethyl acetate and of water to ethanol.[2)] The solubility parameter of these mixtures is between $14.93\,\mathrm{MPa}^{1/2}$ (hexane) and $47.86\,\mathrm{MPa}^{1/2}$ (water). Solubility curves showing only a maximum are well described using the extended Hildebrand method.[3,4)] This method predicts a maximum at a certain composition of the solvent mixture, where the solubility parameter of the drug is equal to the solubility parameter of the solvent mixture, $\delta_2 = \delta_1$.

In an earlier work,[5)] the solubility behavior of sulfamethoxypyridazine was investigated in the three solvent mixtures, hexane–ethyl acetate, ethyl acetate–ethanol and ethanol–water, and surprisingly, the curve showed two maxima, one at $\delta_1 = 20.88\,\mathrm{MPa}^{1/2}$ (30% ethanol in ethyl acetate) and another at $\delta_1 = 30.87\,\mathrm{MPa}^{1/2}$ (80% ethanol in water). This unusual behavior demonstrated the chameleonic effect first described by Hoy.[6)] According to Hoy, some compounds may exhibit more than one solubility parameter in an effort to adapt to the solvent medium. The chameleonic effect was rationalized and described in a quantitative way in terms of Lewis acid-base interactions. An approach based upon the adidic and basic partial solubility parameters, δ_a and δ_b was proposed to model the two solubility peaks found for sulfamethoxypyridazine. The equation has the form[5)]:

$$\ln X_2 = c_0 + c_1\delta_1 + c_2\delta_1^2 + c_3\delta_{1a} + c_4\delta_{1b} + c_5\delta_{1a}\delta_{1b} \quad (1)$$

Where X_2 is the mole fraction solubility of the drug, δ_1 is the Hildebrand solubility parameter of the solvent mixtures, and δ_{1a} and δ_{1b} are the acidic and basic partial solubility parameters, respectively. These parameters express the proton donating and proton acceptor capacity of the solvent and were proposed by Karger *et al.*[7)] In Eq. 1, δ_1 and δ_1^2 represent the contribution of the Hildebrand solubility equation, which includes the energy of cavity formation and nonspecific van der Waals interactions. The acidic and basic partial solubility parameter terms express specific Lewis acid-base interactions such as hydrogen bonding.[5)] The units on the solubility parameters are $\mathrm{cal}^{1/2}\mathrm{cm}^{-3/2}$ (also called Hildebrands) in the cgs system and $\mathrm{MPa}^{1/2}$ in the SI system. The constant terms, c_0 to c_5, are obtained from multiple regression analysis (least square method), using the statistical package NCSS (Kaysville, Utah, 1990).

In this work, this approach is extended to obtain a single equation for two sulfonamides, sulfanilamide and sulfamethazine, which both show the chameleonic effect in the solvent mixtures, ethyl acetate–ethanol and ethanol–water. Furthermore, the aim of this work is to predict the solubility curve of other structurally related drugs showing two solubility peaks.

Experimental

Materials The solutes, sulfanilamide and sulfamethazine, were purchased from Interchimia, Hamburg, Germany and were tested for purity in a differential scanning calorimeter (Mettler TA3000). The heat of fusion and temperature of fusion are 5650 ± 56 cal/mol and 437 ± 1 K for sulfanilamide and 7438 ± 170 cal/mole and 198.5 ± 0.5 K for sulfamethazine (average of three runs). The solvents used were analytical or UV-IR grade, Panreac, Monplet & Esteban, Bacelona. The solutes and solvents were used as received.

Solubility Measurements The solubilities of sulfanilamide and sulfamethazine in ethanol–water and ethyl acetate–ethanol (Table I) were determined at 25°C. Twenty-ml samples containing an excess of solute were shaken during 72 h and allowed to reach equilibrium in a constant temperature bath held at 25 ± 0.2°C. Preliminary experiments showed that 72 h was sufficient to ensure saturation at this temperature. The excess solute was eliminated by filtration through Durapore or Fluoropore filters (pore size < 1 μm), depending on the compatibility of the solvent with the filter. Four samples of each solution were diluted with methanol and assayed in a double-beam spectrophotometer (Bausch and Lomb 2000) at the maximum wavelengths, 262 nm for sulfanilamide and 269 nm for sulfamethazine. The small amount of solvent present after dilution with methanol did not affect the absorbance readings. The concentration (molarity units) of the solute in methanol was determined from a Beer's law plot. The densities of the saturated solutions, needed to express the results in mole fraction, were measured in 10-ml pycnometers at 25°C. The results are the average of at least four solubility determinations. The experimental variation in solubility was less than 3% in replicated samples.

Results and Discussion

Figures 1 and 2 show the experimental mole fraction solubility of the sulfonamides plotted against the solubility parameter of the solvent mixtures. The solubilities of the drugs smoothly increase beginning from 100% water ($\delta_1 = 47.86\ \mathrm{MPa}^{1/2}$) to reach a maximum at 20:80 (v/v) water–ethanol for sulfanilamide and sulfamethazine, corresponding to a solubility parameter of the solvent mixture, $\delta_1 = 30.87\ \mathrm{MPa}^{1/2}$ (Table I and Figs. 1 and 2). From this point the solubility decreases and shows a minimum at 100% ethanol ($\delta_1 = 26.51$). When the polarity of the solvent is decreased by the addition of ethyl acetate to ethanol, the solubility of both drugs increases to reach a second maximum at 40:60 ethanol–ethyl acetate ($\delta_1 = 21.68\ \mathrm{MPa}^{1/2}$) for sulfanilamide and 25:75 ethanol–ethyl acetate for sulfamethazine ($\delta_1 = 20.50\ \mathrm{MPa}^{1/2}$) (Figs. 1 and 2 and Table II).

As pointed out earlier, benzoic acid shows a unique maximum in these same solvent mixtures[2] (Table II). The curious solubility behavior of the sulfonamides studied here shows the "chameleonic effect," and their solubility profile is similar to that found for sulfamethoxypyridazine.[5] According to the chameleonic principle, sulfanilamide and sulfamethazine exhibit two separate solubility parameters in the solvent mixtures studied here (Table II). Martin *et al.*[8] observed that the solubility parameter of theophylline and other molecules increases with the polarity of the solvent mixture. This effect is also observed here. In the more polar mixture, ethanol–water, both drugs have the same apparent solubility parameter, $\delta_2 = 30.87$, whereas in the less polar mixture, ethanol–ethyl acetate, they show lower apparent solubility parameters, $\delta_2 = 21.68$ and 20.50 for sulfanilamide and sulfamethazine, respectively (Figs. 1 and 2 and Table II). For comparison, Table II includes the maxima found for sulfamethoxypyridazine[5] and benzoic acid[2] in ethanol–water and ethanol–ethyl acetate. It is interesting to note that the solubility

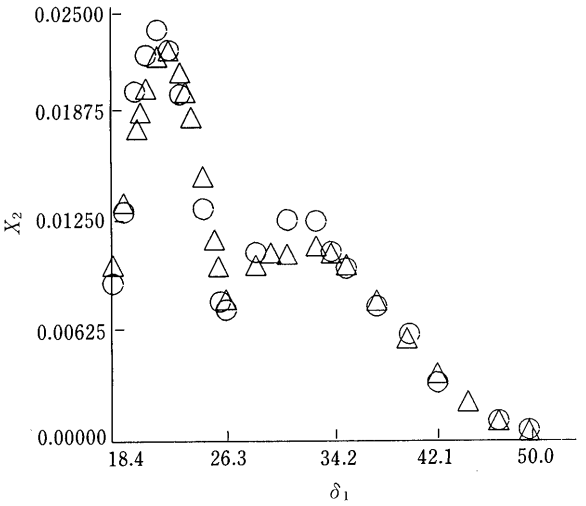


Fig. 1. Solubility of Sulfanilamide in Ethanol–Water Mixtures ($\delta_1 = 47.86$ for Water to 26.51 for Ethanol) and Ethanol–Ethyl Acetate Mixture ($\delta_1 = 26.51$ for Ethanol to 18.49 for Ethyl Acetate)

○, experimental mole fraction solubilities; △, calculated mole fraction solubilities using Eq. 2.

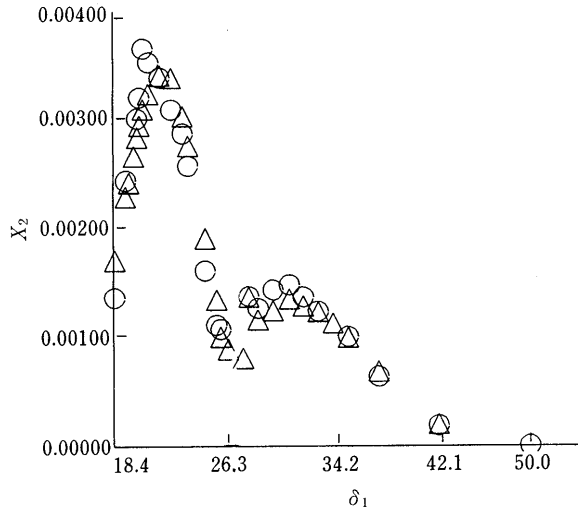


Fig. 2. Solubility of Sulfamethazine in Ethanol–Water Mixtures ($\delta_1 = 47.86$ for Water to 26.51 for Ethanol) and Ethanol–Ethyl Acetate Mixtures ($\delta_1 = 26.51$ for Ethanol to 18.49 for Ethyl Acetate)

○, experimental mole fraction solubilities; △, calculated mole fraction solubilities using Eq. 3.

peaks found for the three sulfonamides in the more polar mixture, ethanol–water, occurs at the same solubility parameter value, $\delta_1 = 30.87$ (Table II). The δ_1 value at the maximum in the less polar mixture, ethanol–ethyl acetate, decreases from the more polar drug (sulfanilamide) to the less polar drug (sulfamethazine). The solubility of these drugs in ethanol and in water also decreases in the same order (Table II).

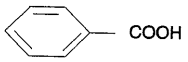
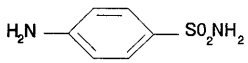
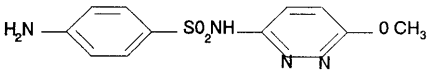
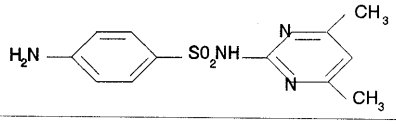
The chameleonic effect is quantitatively treated here in terms of the different ability of the functional groups of the sulfonamides to interact through hydrogen bonding and other Lewis acid-base effects with solvent mixtures having different donor-acceptor capacity. Sulfonamides have both proton-donor and proton-acceptor ability; the solubility curves show a difference in behavior toward those solvent mixtures largely self-associated and with a

TABLE I. Solubilities of Sulfanilamide and Sulfamethazine at 25 °C

Ethanol (v/v)	δ_1 [a]	δ_{1a} [a]	δ_{1b} [a]	Sulfanilamide		Sulfamethazine	
				$\ln X_2$	$\ln X_2$ [b]	$\ln X_2$	$\ln X_2$ [c]
Water–ethanol							
0	47.86	13.70	65.45	−7.347	−7.484	−12.708	−12.136 [d]
10	45.73	14.03	60.04	−6.758	−6.749	—	—
20	43.59	14.36	54.61	−6.209	−6.093	—	—
30	41.44	14.69	49.19	−5.694	−5.547	−8.572	−8.636
40	39.31	15.01	43.77	−5.103	−5.130	—	—
50	37.19	15.34	38.35	−4.861	−4.817	−7.355	−7.258
60	35.04	15.67	32.93	−4.614	−4.594	−6.904	−6.853
65	33.98	15.82	30.23	−4.522	−4.529	—	—
70	32.91	16.00	27.51	−4.371	−4.493	−6.694	−6.634
75	31.85	16.16	24.81	—	—	−6.592	−6.597
80	30.86	16.32	22.09	−4.366	−4.534	−6.512	−6.562
85	29.70	16.49	19.39	—	—	−6.544	−6.671
90	28.64	16.65	16.67	−4.525	−4.672	−6.672	−6.770
95	27.98	16.81	13.95	—	—	−6.588	−6.627
100	26.51	16.98	11.25	−4.885	−4.810	−7.197	−7.115
Ethanol–ethyl acetate							
95	25.98	16.67	10.88	—	—	−6.839	−6.986
90	25.69	16.36	10.51	—	—	−6.802	−6.674
80	24.89	15.75	9.78	−4.315	−4.185	−6.428	−6.301
70	25.00	15.14	9.04	−4.075	−3.983	—	—
65	23.69	14.83	8.67	—	—	−5.963	−5.910
60	23.30	14.52	8.30	−3.915	−3.853	−5.854	−5.808
50	22.50	13.91	7.57	−3.794	−3.795	−5.780	−5.688
40	21.68	13.30	6.83	−3.744	−3.810	−5.689	−5.677
30	20.88	12.68	6.10	−3.807	−3.898	−5.648	−5.727
25	20.50	12.38	5.73	—	—	−5.612	−5.770
22	20.25	12.19	5.51	—	—	−5.744	−5.822
20	20.09	12.07	5.36	−3.906	−4.058	−5.807	−5.861
10	19.29	11.45	4.62	−4.328	−4.290	−6.016	−6.080
0	18.49	10.84	3.89	−4.704	−4.594	−6.597	−6.383

a) Solubility parameters and partial solubility parameters are calculated for each solvent mixture from the expression: $\delta(\text{mix}) = \sum \delta_i \phi_i$, where δ_i is the value for the pure solvent and ϕ_i the volume fraction of the solvent in the solvent mixture. The units are $\text{MPa}^{1/2}$. *b*) Calculated with Eq. 2. *c*) Calculated with Eq. 3. *d*) This value is the prediction corresponding to the experimental value, $\ln X_2 = -12.708$ that was not used to obtain Eq. 3.

TABLE II. Solubility Peaks of Several Drugs in Solvent Mixtures of Polarity Ranging between $\delta_1 = 18.49\ \text{MPa}^{1/2}$ to $\delta_1 = 47.86\ \text{MPa}^{1/2}$

		Ethanol–water		Ethanol–ethyl acetate		X_2 (water)	X_2 (ethanol)
		δ_1	% ethanol	δ_1	% ethanol	25 °C	
Benzoic acid [a]		No peak		22.50	50	5×10^{-4}	0.1789
Sulfanilamide		30.87	80	21.68	40	6.45×10^{-4}	7.57×10^{-3}
Sulfamethoxypyridazine [b]		30.87	80	20.88	30	3.72×10^{-5}	1.45×10^{-3}
Sulfamethazine		30.87	80	20.50	25	3.03×10^{-6}	7.49×10^{-4}

a) From reference 2. *b*) From reference 5.

high degree of structure, and less structured solvent mixtures with a proton acceptor solvent, ethyl acetate.

Equation 1 is applied to fit the experimental solubilities ($\ln X_2$) of each drug, sulfanilamide and sulfamethazine, in the two solvent mixtures. The experimental $\ln X_2$ values, the acidic and basic partial solubility parameters, δ_{1a} and δ_{1b}, and the Hildebrand solubility parameter δ_1 of the solvent mixtures are given in Table I. The equation obtained for sulfanilamide in the two-solvent mixtures, ethanol–ethyl acetate and ethanol–water, is:

$$\ln X_2 = -19.4096 + 1.2356\delta_1 - 0.0276\delta_1^2 + 0.8068\delta_{1b} - 0.0410\delta_{1a}\delta_{1b}$$
$$r^2 = 0.990,\quad \text{s.d.} = 0.108,\quad n = 21 \qquad (2)$$

The equation obtained for sulfamethazine in the same solvent mixtures is:

$$\ln X_2 = -33.5941 + 2.7578\delta_1 - 0.0369\delta_1^2 - 1.0062\delta_{1a} + 0.3797\delta_{1b} - 0.0414\delta_{1a}\delta_{1b} \quad (3)$$
$$r^2 = 0.980, \quad \text{s.d.} = 0.112, \quad n = 24$$

It should be noted that δ_{1a} is not statistically significant and was dropped from Eq. 2. This same variable, δ_{1a}, is statistically significant in the case of sulfamethazine (Eq. 3), although the negative sign obtained on this variable means that higher δ_{1a} values of the solvent mixtures disfavor solubility. On the other hand, higher δ_{1b} values increase solubility as shown by the positive sign on this variable in Eqs. 2 and 3.

Table I lists the experimental and calculated $\ln X_2$ values for sulfanilamide and sulfamethazine using Eq. 2 and 3, respectively. Water was not used in Eq. 3 because its Cook distance[9] is larger than unity, meaning that this case is very influential in the overall regression. Cook's distance measures the consistency of a single case with the overall regression model: a value larger than unity suggests that the corresponding case may be incompatible with the overall regression model. Calculation of the Cook distance is a standard option in most statistical packages such as NCSS, used here.

The largest residual ($\ln X_2 - \ln X_{2(\text{calculated})}$) for sulfanilamide (Eq. 2) is -0.168 for $\delta_1 = 30.87$; most of the remaining residuals are smaller than 0.10 ln units. For sulfamethazine (Eq. 3), the largest residual (0.572) is found for the predicted $\ln X_2$ in water ($\delta_1 = 47.86$); most of the residuals were smaller than 0.10 ln units. As observed in Figs. 1 and 2, the curves for the mole fraction solubility, $X_2 = \exp(\ln X_2)$, as calculated from Eqs. 2 and 3, reproduce the two maxima, and the calculated values are close to the experimental mole fraction solubilities throughout the range of the curves.

Equations 2 and 3 are empirical models that apply to the particular drug used in the regression analysis. In order to obtain a more general model which serves to reproduce the solubility curves of structurally related solutes in solvent mixtures showing two solubility maxima, Eq. 1 is rewritten as follows:

$$\ln X_2 = b_0 + b_1 \ln X_{2\text{EtOH}} + b_2\delta_1 + b_3\delta_1^2 + b_4\delta_{1a} + b_5\delta_{1b} + b_6\delta_{1a}\delta_{1b} \quad (4)$$

Equation 4 includes the same solute–solvent interaction terms represented by the acidic and basic solubility parameters as found in Eq. 1 so that the equation is able to reproduce the two solubility peaks due to the chameleonic effect of drugs showing similar solute–solvent interactions, for example, other sulfonamides. To account for different classes of solutes, Eq. 4 also includes the logarithm of the mole fraction solubility of each drug in one of the pure solvents, ethanol, $X_{2\text{EtOH}}$. The solubility of a solid drug in ethanol (or in any other solvent) includes the step of the solid solute going from the solid to the liquid state, *i.e.*, the ideal solubility of the drug, and solute-solvent interactions in that solvent. This term is a constant for a given drug and it is not needed as a variable in Eq. 1, where only one drug is considered. However, when several drugs are to be included in a common equation, the properties of each drug in the solid state will influence the solubility and need to be considered as variables in the equation. Previous trials showed that the use of the actual solubility of each drug in one of the pure solvents in Eq. 4 gives better results than the use of the ideal solubilities of the drugs (calculated from the heat of fusion and temperature of fusion). The solubilities of the drugs in ethyl acetate and in water are highly correlated with the solubility in ethanol. Therefore, only the solubility in one pure solvent, say ethanol, is needed in the solubility equation. The solubility in ethanol seems to be a better choice than the solubility in water. The solubility parameter of ethanol, $\delta_1 = 26.51$, lies between the solubility parameters of ethyl acetate ($\delta_1 = 18.49$) and water ($\delta_1 = 47.86$). On the other hand, water was not compatible with the remaining solvent mixtures in Eq. 3. The solubility of a drug in water has particular characteristics due to the possible structuring of water around the nonpolar parts of the drug (hydrophobic hydration).[10] This effect is characteristic only of aqueous solutions or mixtures with a high water content; as the cosolvent is added to water, the solvent mixture becomes less ordered and the hydrophobic effect disappears.

Equation 4 is tested using the experimental solubilities of both sulfanilamide and sulfamethazine (Table I) in the two mixed solvents. The common equation obtained for the two drugs is:

$$\ln X_2 = -25.7676 + 0.9062 \ln X_{2\text{EtOH}} + 2.5611\delta_1 - 0.0339\delta_1^2 - 0.9031\delta_{1a} + 0.4088\delta_{1b} - 0.0423\delta_{1a}\delta_{1b} \quad (5)$$
$$r^2 = 0.980, \quad \text{s.d.} = 0.182, \quad n = 44$$

All the regression coefficients of Eq. 5 are statistically significant at the 0.01 level. The solvent mixtures containing more than 90% water in ethanol are not compatible with the overall equation (the Cook distance is larger than unity) and they were removed from the regression analysis. However, Eq. 5 can be used to predict the solubility of the drugs in these solvent mixtures, using $\ln X_{2(\text{EtOH})}$ and δ's of these solvent mixtures found in Table I. The largest residuals (0.8 to 1.05 ln units) are found for the solvent mixtures of $\delta_1 > 45.73$, *i.e.*, 90% to 100% water in ethanol, most of the remaining residuals being with in 0.2 ln units. Although a higher level of accuracy would be desirable, at the current stage of solubility predictions, the accuracy for the interactive solvents in most cases is within a factor of 0.5 log units (1.1 ln units), that is, three times the experimental mole fraction solubilities.[11] The experimental $X_2 = \exp(\ln X_2)$ and calculated $X_{2\text{calc}} = \exp(\ln X_{2\text{calc}})$ mole fraction solubilities for sulfanilamide and sulfamethazine are shown in Fig. 3 (upper and lower curves, respectively).

Furthermore, Eq. 5 is used to predict the solubility curve of another sulfonamide, sulfamethoxypyridazine, a data set that was not used to obtain Eq. 5. Unlike regression, prediction does not involve any fitting of data and is a better evaluation of the model (Eq. 5). The prediction coefficient, p^2, is strictly analogous to r^2, and is given by[12]:

$$p^2 = 1 - \frac{\sum(S_{\text{obs}} - S_{\text{pred}})^2}{\sum(S_{\text{obs}} - S_{\text{mean}})^2} \quad (6)$$

where S_{pred} is the $\ln X_{2\text{calc}}$ predicted by the model (Eq. 5)

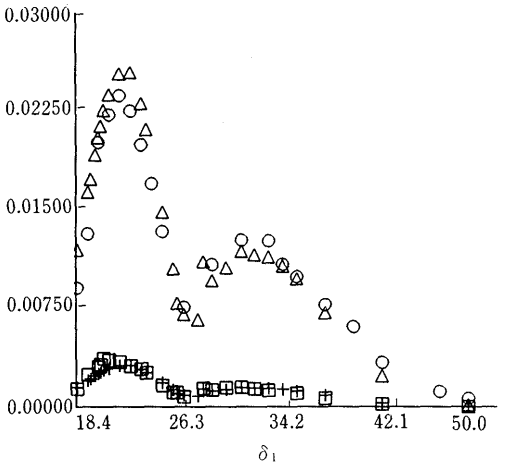


Fig. 3. Solubility Curves for Sulfanilamide and Sulfamethazine in Ethanol–Water ($\delta_1 = 47.86$ for Water to 26.51 for Ethanol) and Ethanol–Ethyl Acetate ($\delta_1 = 26.51$ for Ethanol to 18.49 for Ethyl Acetate) Mixtures

Experimental (○) and calculated (△) mole fraction solubilities of sulfanilamide (upper curve). Experimental (□) and calculated (+) mole fraction solubilities for sulfamethazine (lower curve). The calculated values of both sulfonamides are obtained using Eq. 5.

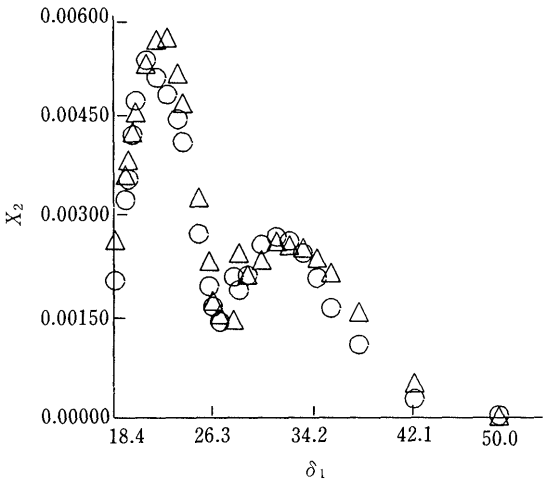


Fig. 4. Experimental (○) (Reference 5) and Predicted (△) Mole Fraction Solubilities for Sulfamethoxypyridazine in Ethanol–Water and Ethanol–Ethyl Acetate Mixtures, a Data Set That was Not Used to Obtain Eq. 5

and S_{obs} and S_{mean} are the observed ln X_2 and mean ln X_2, respectively. The predicted values for sulfamethoxypyridazine are obtained by substituting in Eq. 5 the mole fraction solubility of the drug in ethanol, $\ln X_{2EtOH} = -6.5390$ and the solubility parameters and partial solubility parameters of the solvent mixtures.[5] The p^2 obtained is:

$$p^2 = 1 - \frac{1.091459}{26.1978} = 0.9583 \quad (7)$$

The p^2 value obtained is satisfactory, close to unity. The largest residual (experimental ln X_2 − predicted ln X_2) is 0.6 for $\delta_1 = 41.44$, *i.e.*, 30% ethanol in water, the remaining residuals being within 0.3 ln units. The experimental[5] and predicted X_2 values are plotted in Fig. 4. Sulfamethoxypyrizane also shows the chameleonic effect, as manifested in the two solubility peaks.

The results obtained with the equations for each individual sulfonamide (Eqs. 2 and 3) demonstrate in a quatitative way that the two maxima found, and hence the chameleonic effect, may be described in terms of the proton donating and/or proton accepting capacities of the solvent mixtures represented by the acidic and basic partial solubility parameters. The model is empirical, but the variables used are related to the different solute–solute, solvent–solvent and solute–solvent interactions that may occur in solution. The model has been expanded to include two drugs, sulfanilamide and sulfamethazine, and Eq. 5 is able not only to back-calculate the solubility profile of these two drugs, but also to predict the solubility behavior of another sulfonamide not included in the equation. The individual Eqs. 2 and 3, for each drug only apply to a particular drug, whereas Eq. 5 has more predictive capacity. This equation could be used for other drugs showing the chameleonic effect, provided they exhibit similar solute–solvent interactions. To obtain the solubility curve of another related drug, only one experimental determination is needed, the solubility of the drug in ethanol. The Hildebrand solubility parameters, as well as the acidic and basic partial solubility parameters of the solvent mixtures, can be calculated from the values of the pure solvents and the volume fraction of the solvent mixture (see footnote of Table I). This approach provides a quantitative explanation of the chameleonic effect; and it may help the pharmacist to find the best combination of solvents for drugs showing complex solubility behavior, such as sulfonamides and other drugs having both proton donor and proton acceptor capacities. Of course, all solvents must be checked for nontoxicity before being combined into a pharmaceutical system for human or animal use.

References

1) J. H. Hildebrand, J. M. Prausnitz, R. L. Scott, "Regular and Related Solutions," Van Nostrand Reinhold, New York, 1970, pp. 26—27.
2) M. J. Chertkoff, A. Martin, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 444 (1960).
3) A. Martin, J. Newburger, A. Adjei, *J. Pharm. Sci.*, **68**, IV (1979).
4) P. L. Wu, A. Martin, *J. Pharm. Sci.*, **72**, 587 (1983).
5) J. B. Escalera, P. Bustamante, A. Martin, *J. Pharm. Pharmacol.*, **46**, 172 (1994).
6) K. Hoy, *J. Paint Tech.*, **42**, 76 (1970).
7) B. L. Karger, L. R. Snyder, C. Eon, *J. Chromatogr.*, **125**, 71, (1976).
8) A. Martin, P. L. Wu, Z. Liron, S. Cohen, *J. Pharm. Sci.*, **74**, 638 (1985).
9) J. Neter, W. Wasserman, M. K. Kutner, "Applied Linear Regression Models," Irwing, Ilinois, 1983, pp. 407—409.
10) R. B. Hermann, *J. Phys. Chem.*, **75**, 363 (1971).
11) D. J. W. Grant, T. H. Higuchi, "Solubility Behavior of Organic Compounds," in Techniques of Chemistry, Vol. 21, Wiley, New York, 1990, p. 61.
12) S. H. Yalkowsky, S. Banerjee, "Aqueous Solubility. Methods of Estimation for Organic Compounds," Dekker, New York, 1992, p. 131.