Correlation Between Solubility Parameters and Dielectric Constants

Sir:

There is general agreement that one of the fundamental problems in pharmaceutical research involves the description of solubility phenomena. In attempting to explain these phenomena we usually resort to either qualitative description in terms of relative "polarity" or more quantitatively with the aid of the thermodynamic approach embodied in Hildebrand's solubility parameter concept (1). It is the purpose of this communication to present some of our observations relevant to these two approaches.

Some earlier solubility studies of pharmaceutical importance (2–4) have illustrated the existence of a peak solubility of solutes when the components of cosolvent mixtures were varied in concentration. In these cases, the treatment of solubility offers no quantitative explanation for this behavior.

Moore (5), however, suggested a semiempirical use of dielectric constants to solvent mixtures to predict the acceptability of cosolvent blends to maintain solubility. Although the peak solubility or dielectric requirement had not been determined, this work illustrates the usefulness of employing an appropriate dielectric constant in the choice of a solvent or solvent mixture for the maintenance of solubility for a given solute. A more comprehensive study reported by Semenchenko (6) shows that the solubility of some 41 solutes have been measured as a function of the dielectric constant of the solvent system and claims that ". . . an ascending branch and descending branch are observed, including a peak value for the solubility . . . ." In this case, a distribution curve is described wherein the peak value is dependent on the characteristics of both the solute and solvent system and can be considered the dielectric requirement of the solute.

On the other hand, Chertkoff and Martin (7) recently applied the solubility parameter concept (1) in their studies of the solubility of benzoic acid in mixed solvent systems. This was an attempt to extend Hildebrand's theory of solubility to "semipolar" solutes. They, too, find a peak solubility as a function of solubility parameters of the solvent system in accord with the

theoretical curve predicted by Hildebrand's equation.

In treating solubility data, whether in terms of dielectric constants or solubility parameters, the end results are similar. This immediately suggests that at least an empirical relationship exists between the two concepts. The following paragraphs present further observations to substantiate this contention and show the utility of such a relationship.

The first example is illustrated in Fig. 1 which shows a plot of both solubility parameters and dielectric constants *vs.* the number of carbon atoms for a homologous series of *n*-alkyl alcohols (8). When the solubility parameter and dielectric constant of one member is matched
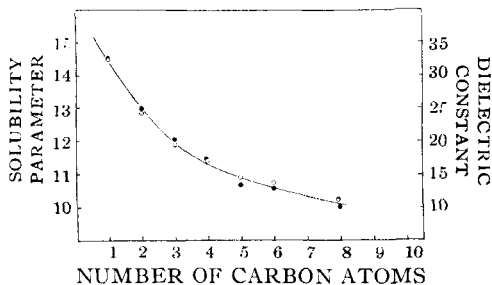

Fig. 1.—An illustration of the superimposition of curves when either the solubility parameter, O, or dielectric constant, ●, of a series of *n*-alkyl alcohols is plotted *vs.* the number of carbon atoms.
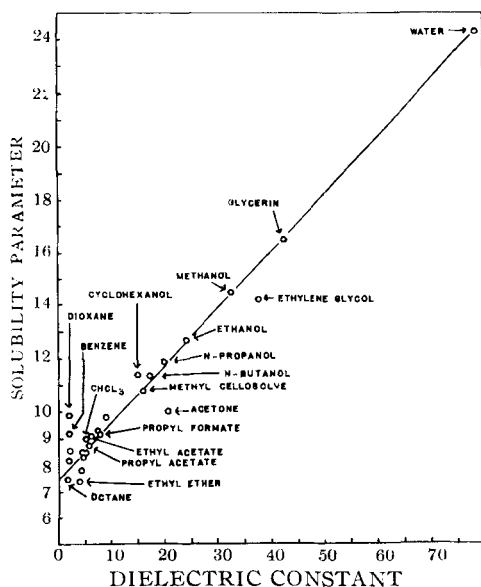

Fig. 2.—A plot of solubility parameters of common solvents *vs.* their respective dielectric constants to show the linear trend.

on a sliding ordinate, the two curves become superimposable. Obviously, a plot of solubility parameters *vs.* dielectric constants for these alcohols would result in a straight line.

Furthermore, by extending representative solvents beyond mere alcohols to include various classes of solvents, a similar straight line plot of solubility parameter *vs.* dielectric constant should also result. This was essentially found to be the case with 25 solvents and is illustrated in Fig. 2. The equation for this straight line can be written

$$\delta = 0.22 \, \epsilon + 7.5 \qquad \text{(Eq. 1)}$$

where δ is the solubility parameter and ϵ is the dielectric constant. The intercept value is obtained in the extrapolation to $\epsilon = 1$.

To show the utility of this equation, we have analyzed the data on the solubility of phenobarbital from several sources. The results are summarized in Table I. It can be seen that irrespective of the composition of solvent mixtures showing peak solubility for phenobarbital, there are striking similarities when their dielectric constants are compared.

Similarly, using data reported by Chertkoff and Martin [7] one can calculate the dielectric requirement of benzoic acid. Equation 1 predicts a value of 18.2 from the reported solubility parameter of 11.5 for benzoic acid. Analysis of solubility data given by Seidell [9] predicts a dielectric requirement of about 20 for benzoic acid. These examples are given to illustrate how completely independent sources of data aid to confirm the validity of Eq. 1.

There are some obvious advantages to the correlation of solubility parameters with dielectric constants. For example, the range of solubility parameters is quite small with values falling between 7.5 for "nonpolar" compounds, and about 24.3 for water. The dielectric constant spectrum, on the other hand, varies from about 2 to 80, giving over a fivefold expansion of a reference scale from that of solubility parameters and would follow a regular order with respect to "polarity."

Secondly, dielectric constants of solvents are more easily determined experimentally than solubility parameters. Furthermore, the solubility parameters of solids can ordinarily be obtained only after elaborate approximations of physical data are made. Thus, it appears that measurement of dielectric constants provides convenient means for determining apparent solubility parameters through Eq. 1, with all the incumbent advantages for applications of such knowledge.

It is obvious from Fig. 2 that, in general, the solvents which associate primarily through hydrogen bonding give the best correlation between reported solubility parameters and their respective dielectric constants. Fortuitously, these are the solvents of pharmaceutical importance.

Greatest deviation from the linear trend in Fig. 2 occurs with the nonpolar solvents which are of less pharmaceutical significance. The values for these solvents all fall in clusters in a small segment in the lower portion of the spectrum of dielectric constants. This scatter may be due, in part, to the diversity of chemical types and the slight variations in the reported values of solubility parameters, especially when different methods were employed for their determination.

It would be of interest to determine under what circumstances the solubility parameter concept might be extended into the semipolar and polar solvents and to determine if the empirical Eq. 1 has any physical significance. Each is currently being investigated in these laboratories and our findings shall be reported.

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TABLE I.—SUMMARY OF PROPERTIES OF SOLVENTS SHOWING PEAK SOLUBILITY FOR PHENOBARBITAL

Composition, v/v	Dielectric Constant[a]	Solubility Parameter[b]	Ref.
Ethanol-water (9:1)	26.6	13.23	2
Ethanol-glycerin (8:2)	25.7	13.15	· 2
Ethanol-propylene glycol (1:1)	26.5	13.23	3

[a] Experimentally measured by the resonance method. [b] Determined from Eq. 1.