

attributed to the existence of different chemical races of the species; however, this possibility now appears remote. A more likely conclusion is that that report, like numerous others attributing hallucinogenic properties to *Panaeolus* species, was based on a misidentification of the specimens examined.

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## Dielectric Constants and Solubility

Sir:

A recent publication of Sorby, Bitter, and Webb (1) reporting the dielectric constants of the water-ethanol-glycerin and water-ethanol-propylene glycol systems has prompted this communication. Since we are also presently engaged in studies of this nature, we wish to indicate briefly some additional observations concerning the possible relation between dielectric constant and the solubility of nonelectrolytes. These observations will be the subject of detailed reports at a later date.

Our studies have led us to believe that the dielectric constant principle of solvent blending outlined by Moore (2) is fortuitous. Implicit in Moore's suggestion is the presumption that solvent systems of approximately the same dielectric constant will show the same solvent properties for given drugs. Goyan (3) has recently pointed out the limitations of this assumption. Sorby, *et al.* (1), have suggested that Moore's method may fail in practice because of the approximations made in computing rather than directly measuring dielectric constants of complex mixtures. In a previous communication (4) we had pointed out that Moore had not considered cosolvency phenomena in his treatment.

A detailed examination of one of Moore's examples, the solubility of phenobarbital as a function of dielectric constant, proves illustrative. Figure 1 shows the solubility data of phenobarbital in several binary systems which were originally reported by Krause and Cross (5) and Peterson and Hopponen (6). The peak solubilities in different blends are seen to fall within a

narrow range of dielectric constant (27-30). This observation led to our suggestion (4) that a dielectric requirement (DR) for solubility exists, *i.e.*, the dielectric constant at which peak solubility is observed in a solvent blend. At constant temperature, this requirement should be independent of the actual nature of the solvents in the blend and dependent only upon the nature of the drug. The existence of such a requirement has been confirmed in the cases of salicylic acid (DR:  $\sim 15$ ) and theobromine (DR:  $\sim 20$  and  $\sim 42$ ) in binary systems of widely differing composition (7).

If Moore's technique is valid, then its application should not critically depend upon the selection of the solvent which determines the value of the approximate dielectric constant (A.D.C.)

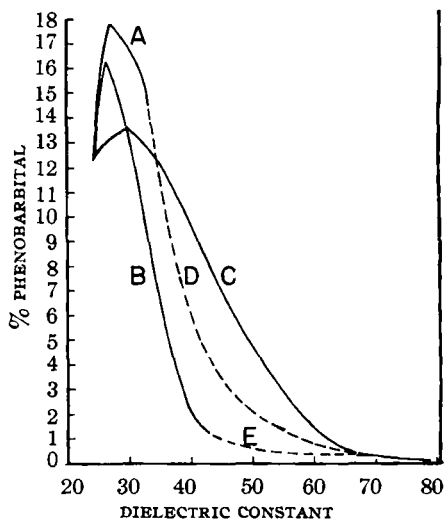


Fig. 1.—Solubility (w/v %) of phenobarbital in various binary systems at 25° plotted as a function of dielectric constant. Key: A, propylene glycol-ethanol; B, glycerin-ethanol; C, water-ethanol; D, propylene glycol-water; E, glycerin-water.

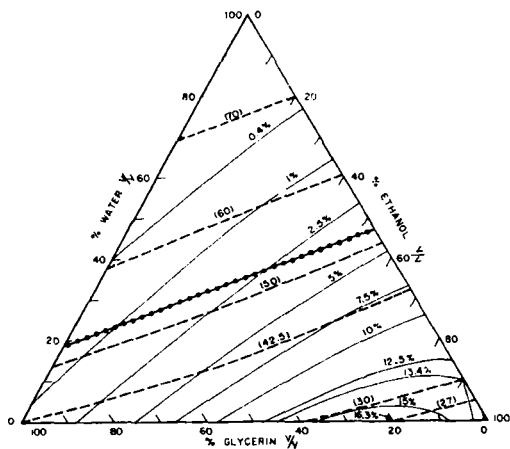


Fig. 2.—Phenobarbital solubility and dielectric constant-volume percentage relationships for the water-ethanol-glycerin system. Key: —, tie lines representing constant solubilities (w/v %) of phenobarbital at 25°; ----, tie lines representing isodielectric mixtures where figures in ( ) are dielectric constants; —●—●—, tie line representing dielectric constant of 50 reported by Sorby, *et al.* (1).

at which a certain solubility is to be maintained. It is evident from Fig. 1 that no apparent correlation can be made between dielectric constant and actual solubility. Solubilities differ significantly in blends of the same dielectric constant (isodielectric blends). If we desired to prepare a 2% solution of phenobarbital, our choice of A.D.C. would depend on whether we happened to use a glycerin-alcohol, propylene glycol-water, alcohol-water, or some other solvent for its measurement.

Correlation of solubility and dielectric constant in tertiary solvent blends is more complex. Figure 2 shows the solubility of phenobarbital in the water-ethanol-glycerin system. This is represented on the ternary diagram as tie lines of constant solubility which were interpolated from the data of Krause and Cross (5). The isodielectric lines shown on the chart were computed from our own measurements of dielectric constant. They were made using a technique similar to that described by Sorby, *et al.* (1), except that dioxane-water (8) instead of acetone-water mixtures were used to standardize the oscillometer. However, our values for systems with dielectric constants less than 60 (*e.g.*, compare the isodielectric 50 lines in Fig. 2) are significantly greater than those reported by Sorby (1). The dielectric constant

values of the water-acetone system which they used (9) are lower in this region than those reported by Albright (10).

In any case, it is again evident that considerably different solubilities will be observed in isodielectric mixtures. Optimum solvent power, however, will be observed in blends with an apparent DR of 27–30. If the solubility of phenobarbital in the system water-ethanol-propylene glycol (6) was analyzed in the same fashion, similar conclusions could be drawn.

We suggest that the maximum utility of the dielectric constant as an aid to formulation of solvent blends for nonelectrolytes is gained from knowledge of the dielectric requirement. One may readily measure this for any drug by determining its solubility in dioxane-water mixtures of known dielectric constant and noting the dielectric constant(s) at which peak solubility is observed. Furthermore, studies directed toward the interpretation of solubility behavior of drugs in terms of the dielectric character of solvent systems will prove most fruitful if solubilities are compared at the dielectric requirement where solute-solvent interaction is a maximum. Our interest in this area of research lies in establishing the validity of these statements.

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