Solubility of Several Solutes as a Function of the Dielectric Constant of Sugar Solutions

By ANTHONY N. PARUTA*

The solubility of several pharmaceutical solutes has been determined in sucrose solutions of varying concentration. These syrup vehicles possess dielectric constant values lower than pure water, their respective dielectric constants decreasing with increasing concentration. The effect of both the concentration and the dielectric constant of sucrose in syrup vehicles upon the solubility of several solutes has been determined. The solubility of the solutes studied are seen to increase directly with increasing sucrose concentration and inversely with dielectric constant for the range and systems studied.

The common use of syrup vehicles in liquid pharmaceutical preparations indicates a need for determining certain properties of these dissolution media. It has often been assumed that a given solute will be about equally soluble in water and in syrup. To test this assumption, the solubility of various solutes was determined in sucrose solutions of varying concentration.

The useful concept of the "polarity" of dissolution media may be advantageously applicable to sugar solutions *via* a parameter which in some fashion quantitates "polarity." The parameter chosen was the dielectric constant as a function of sucrose concentration.

The dielectric constant of sucrose solutions has been determined by Maryott and Malmberg (1) and Akerlof (2). These workers found that the dielectric constant of these solutions decreased with increasing concentrations of sugar. Simple syrup has a dielectric constant of about 60, placing it about halfway between water, $\epsilon = 78$, and glycerin, $\epsilon = 42$, on the dielectric constant scale.

As the polarity of the dissolution media decreases, *i.e.*, hydroalcoholic mixtures, the solubility of semipolar solutes increases, due to a medium of more favorable polarity. Increased solubility of semipolar solutes in mixtures of pharmaceutical solvents of decreasing polarity has been reported previously (3-5).

This study was undertaken to determine the solvency characteristics of syrup vehicles and to illustrate the polarity-dielectric constant relationship of dissolution media (6, 7).

EXPERIMENTAL

Materials.—The solutes used in this study were recrystallized from water-ethanol mixtures and dried to constant weight at 40° in a convection oven. The solutes studied were quinine alkaloid, phenobarbital, PABA, and sulfanilamide. Sugar solutions were prepared from commercial sucrose in distilled water. Solvents used to establish a calibration dielectric constant curve were from fresh unopened bottles assuming labeled water contents were true values. Calibration values were subsequently corrected for water content.

Equipment.—Sargent chemical oscillometer model V, Sargent thermomonitor water bath equipment, and Beckman DK-2 ratio recording spectrophotometer were used.

Dielectric Constant Determinations.—The dielectric constant of sucrose solutions, from 10 to 80% w/v in 10% steps was determined by the use of a Sargent chemical oscillometer. A calibration curve was prepared by measuring the apparent capacitances of anhydrous liquids of known dielectric constants (8). The prepared sucrose solutions were measured in a 10-ml. cell in the order of increasing viscosity. Each solution was determined at least three times with about 1 minute between each reading. Each successive solution was measured in the above fashion after rinsing the cell twice with the solution to be measured. Since day-to-day variations were found in the calibration curve, water and other solvents were also tested on a given day for adjustment of the calibration curve. It is interesting to note that these variations led to a family of calibration curves which were continuously parallel over the dielectric constant range studied. The dielectric constant of the sugar solutions was determined from the prepared calibration curve. The relative error associated with these determinations and graphical interpretation is felt to be about $\pm 0.5\%$ or about ± 0.4 dielectric constant units.

Solubility Determination.—The solubility of the solutes studied was determined in 15-ml. vials attached to a submerged rotating plastic disk. The plastic disk unit was attached to a dispersator motor fitted with an aluminum shaft and submerged with attached samples in an 8-gal. water bath. The temperature of the bath was maintained at 24.6 ± 0.2° by a Sargent thermomonitor unit. Solubility equilibration was about 72 hours; this rather long period was needed because of the relatively high viscosity of the syrup vehicles.

Solubility Analysis.—After equilibration, samples of appropriate volume were withdrawn through a fine glass-wool plug fitted to a pipet with a short rubber tube. The pipet was overdrawn, the plug removed, and the pipet wiped clean with a towel. The sample was placed in a volumetric flask and diluted to the appropriate volume for subsequent analysis. The concentration of solute in solution was determined by a Beckman DK-2 spectrophotometer from sample absorbance and previously established Beer-Lambert law plots for each solute. The absorption maxima for the solutes were as follows: PABA, 270 mμ; sulfanilamide, 259 mμ; quinine alkaloid, 327 mμ; and phenobarbital, 269 mμ (sh). These absorption maxima were from 2 to 4 mμ greater than the values reported in the literature.

RESULTS AND DISCUSSION

The experimentally determined dielectric constants of sucrose solutions of varying concentration

Received January 9, 1964, from the School of Pharmacy, University of Pittsburgh, Pittsburgh, Pa.
Accepted for publication February 25, 1964.
* Present address: Pharmaceutical Technology, Warner-Lambert Research Institute, Morris Plains, N. J.

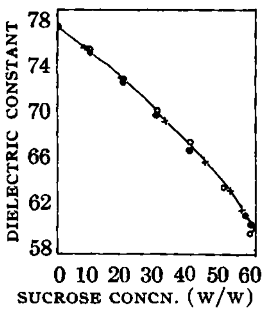

Fig. 1.—A plot of the dielectric constant variation of sucrose solutions reported by Maryott (●), Akerlof (○), and the author (×).

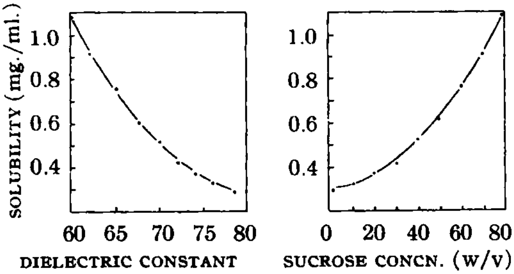

Fig. 2.—A plot of the solubility of quinine alkaloid in mg./ml. at 25°C. as a function of dielectric constant and sucrose concentration.

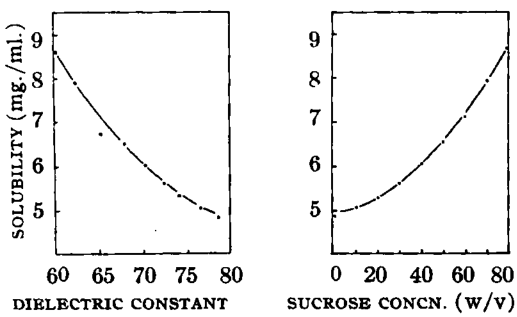

Fig. 3.—A plot of the solubility of *p*-aminobenzoic acid in mg./ml. at 25°C. as a function of dielectric constant and sucrose concentration.

are shown in Fig. 1. The values obtained have been converted to the w/w notation from density measurements. This was done to show the comparison to data previously reported (1, 2). The values compare favorably with other workers, although the data reported by Akerlof are slightly lower at higher concentrations.

The solubility of the solutes used in this study are shown in Figs. 2–5. In each case, the solubility has been plotted as a function of the dielectric constant and sucrose concentration. Each point is the average solubility of three runs, the sucrose concentration varying from 10 to 80% in 10% increments. The solubility of each of these solutes increases with increasing sucrose concentration or decreasing dielectric constant. The use of hydroalcoholic mixtures in increasing or maintaining solubility of semipolar solutes in solution is well known. In this study, the solubility is increased by a series of successive dissolution media of more favorable polarity. Thus, the observed increase may be explained on the basis of decreasing polarity of syrup vehicles as reflected by their respective dielectric constants.

Quinine alkaloid and *p*-aminobenzoic acid gave smooth nonlinear curves when solubility was plotted *versus* either the dielectric constant or concentration of these syrup vehicles. These curves did not give a first-order or linear relationship when the log solubility was plotted *versus* the dielectric constant. The solubility of the solutes in distilled water compared favorably with the values reported in the official compendia.

The solubility of phenobarbital and sulfanilamide showed an approximately linear relationship with dielectric constants and sucrose concentration. The results are shown in Figs. 4 and 5. The rates of change of solubility per dielectric constant unit for phenobarbital and sulfanilamide were 0.06 and 0.2 mg., respectively. The solubility of the above solutes also compared favorably with values reported in the literature.

The ratio of the solubility of these solutes in 80% w/v syrup vehicle relative to distilled water is presented in Table I. The ratios vary from a low value 1.5 for sulfanilamide to a striking 3.7 for quinine alkaloid.

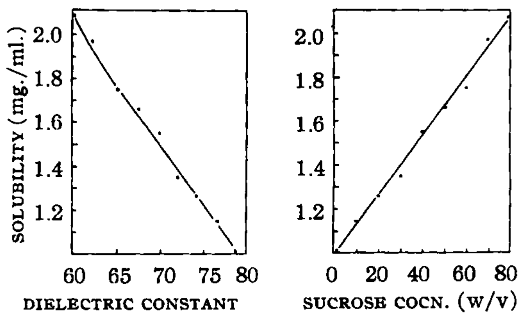

Fig. 4.—A plot of the solubility of phenobarbital in mg./ml. at 25°C. as a function of dielectric constant and sucrose concentration.

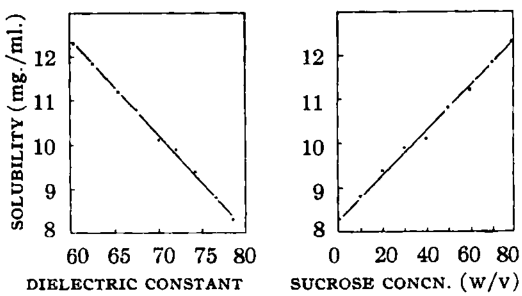

Fig. 5.—A plot of the solubility of sulfanilamide in mg./ml. at 25°C. as a function of dielectric constant and sucrose concentration.

TABLE I.—SUMMARY OF THE SOLUBILITY RATIO FOR THE SOLUTES STUDIED

Solute	—Solubility, mg./ml.— A, Water	B, 80% w/v Sucrose	Ratio B/A
Quinine alkaloid	0.3	1.1	3.7
Phenobarbital	1.0	2.1	2.1
PABA	4.8	8.6	1.8
Sulfanilamide	8.3	12.3	1.5

This simple study leads to manifold consequences which may be advantageously utilized by the formulator and researcher. Control of solubility as a function of dielectric constant variation might have many applications such as increasing the solubility of drugs by using additives such as sucrose or other sugars. On the other hand, decreased solubility may also be useful in a kinetic sense. Since a drug, such as aspirin suspension, will only degrade depending upon the amount of drug in solution, decreased solubility could lead to increased stability to some degree. This approach could be quite useful for aspirin, sulfonamides, antibiotics, and other common pharmaceutical suspensions.

Preliminary work indicates that methocel and other viscosity-inducing agents in solution have dielectric constants higher than that of pure water. These vehicles also possess the proper consistency for physical suspension, stability, and palatability. Increased chemical stability *via* decreased solubility or increased polarity (dielectric constant) is a definite possibility. Studies along these lines are being conducted in these laboratories and results will be reported in future communications.

REFERENCES

(1) Maryott, A. A., and Malmberg, C. G., *J. Res. Natl. Bur. Std.*, **45**, 299(1950).
(2) Akerlof, G., *J. Am. Chem. Soc.*, **54**, 4125(1932).
(3) Krause, G. M., and Cross, J. M., THIS JOURNAL, **40**, 137(1951).
(4) Peterson, C. F., and Hoppenen, R. E., *ibid.*, **42**, 540 (1953).
(5) Chertkoff, M. J., and Martin, A. N., *ibid.*, **49**, 444 (1960).
(6) Moore, W. E., *ibid.*, **47**, 855(1958).
(7) Paruta, A. N., Sciarrone, B. J., and Lordi, N. G., *ibid.*, **51**, 704(1962).
(8) Maryott A A., and Smith, E. R., *Natl. Bur. Std. (U. S.) Circ.* 514(1951.)

Effects of Various Growth Regulators on *Datura meteloides*

By JAMES H. BENNETT and LEO A. SCIUCHETTI

Datura meteloides D.C. was treated during a 4-week period with Amo-1618, CCC, AMAB, Phosphon, B995, and CO-11. Growth was not significantly affected by the treatments. The concentration of alkaloids was increased 26 per cent in the roots of the Amo-1618 group and 17 per cent in the roots of the Phosphon group. The total alkaloid content was increased 25 per cent in the leaf-tops of the CO-11 group, 32 per cent in the roots of the Amo-1618 group, and 19 per cent in the roots of the B995 group. Increases of about 18 per cent in chlorophyll concentration were found in the Phosphon, B995, and CO-11 groups. The results of a selective solvent extraction of the leaf-tops are reported.

NUMEROUS CHEMICAL COMPOUNDS have been recently reported to cause a marked decrease in stem and petiole elongation (1–9). These compounds can be conveniently classified into three chemical groups, *viz.*, the quaternary ammonium compounds, the quaternary phosphonium compounds, and a few selected organic acids. Members of the first group include 4-hydroxy-5-isopropyl-2-methylphenyl trimethylammonium chloride, 1-piperidine carboxylate (Amo-1618), (2-chloroethyl) trimethylammonium chloride (CCC), and allyltrimethylammonium bromide (AMAB). Reduction of internode length resulting in shorter plants has been reported in various plants by treatment with Amo-1618 (1–6), CCC (4, 6, 7), and AMAB (6, 7). CCC and AMAB have been shown to increase the alkaloid content of *Nicotiana tabacum* L. and decrease that of *N. rustica* L. (6).

A phosphonium compound which has been reported to inhibit plant growth is 2,4-dichlorobenzyltributylphosphonium chloride (Phosphon) (2, 3, 6, 8, 9). This compound and the three aforementioned ones are considered to be antigibberellins (1, 3, 6, 9–11). Lockhart (12) concludes that Phosphon and CCC retard stem elongation by partially blocking the system which provides gibberellin to the growth mechanism. Among the organic acids reported to retard plant growth are *N*-dimethylaminomaleamic acid (CO-11) and *N*-dimethylaminosuccinamic acid (B995) (13). These two compounds are closely related to maleic hydrazide (MH), which is considered by some to be an inhibitor of auxin (14, 15).

Since these compounds with reported growth-retarding activity had not been tested on *Datura* spp., it was decided to determine their effects on the growth and synthesis of certain chemical constituents of *Datura meteloides*. In addition, since some of these compounds appear to be antigibberellins and since gibberellin treatment generally reduces the concentration of alkaloids in many medicinal plants (16, 17), it was of interest to note whether a "growth retardant" would cause an increase in the concentration of alkaloids of the plants.

EXPERIMENTAL

Procedure.—Seventy uniform plants were grown under greenhouse conditions in a soil mixture composed of 1 part sand, 2 parts sandy loam, and 10 Gm. of organic fertilizer[1] per gallon can. On July 12, 1962, *Daturas* which were about 34 days old were labeled according to the following plan for treatment: Amo-1618-treated plants, CCC-treated plants, AMAB-treated plants, CO-11-treated plants, B995-treated plants, Phosphon-treated plants, and control (untreated) plants. Each of the above groups consisted of 10 plants. On that date the plants were randomly arranged on a greenhouse bench, and treatment was instituted. Treatments

Received November 4, 1963, from the School of Pharmacy, Oregon State University, Corvallis.
Accepted for publication February 3, 1964.
Abstracted in part from a thesis submitted by James H. Bennett to the Graduate School, Oregon State University in partial fulfillment of Master of Science degree requirements.
Research paper No. 464, School of Pharmacy, Department of Pharmacognosy, Oregon State University.

[1] Organic Morcrop, Chas. Lilly Co., Seattle, Wash. *Anal.* —5% total nitrogen, 3% available phosphate, 2% available potash.