

Solubility of Salicylic Acid as a Function of Dielectric Constant

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The solubility of salicylic acid was determined in various pure solvents and binary solvent mixtures having known or measured dielectric constants. When the solubility was plotted *versus* the dielectric constant, a peak solubility or "dielectric requirement" occurred at a value independent of the nature of the solvent or solvent mixture. Salicylic acid showed two rather close solubility peaks occurring at $\epsilon = 15$ and $\epsilon = 25$ which may be due to different molecular species present in solution. The magnitude of the peak solubility varied for different binary systems, but a family of curves was observed having a common shape and a common peak dielectric requirement.

IN PREDICTING solubility of solutes, Hildebrand's solubility parameter theory (1) applies quite well when both components are nonpolar. The application of this theory is most striking in "regular" or near-ideal solution (2). The theoretical solubility in these systems is maximized when the solubility parameter of both the solute and solvent mixtures are the same. Accordingly, the solubility of the solute at solubility parameter values differing from that of the solute results in diminished solubility, and a solubility distribution curve is observed.

In extending this principle to semipolar systems with its greater pharmaceutical utility, Martin and Chertkoff (3) found that the shape of the theoretical solubility curve was approximately maintained, but that the prediction of the actual solubility failed. Since this is the case, it was felt that the dielectric constant of solvents would be a more advantageous property of solutions upon which one may qualitatively predict a solubility distribution curve. This is based on the relationship of polarity to dielectric constants (4, 5).

An empirical equation linking the dielectric constant and solubility parameter which has been reported (6) is given by

$$\delta = 7.5 + 0.2\epsilon \quad (\text{Eq. 1})$$

The validity and utility of Eq. 1 depends upon observation of a solubility distribution curve as a function of the dielectric constant rather than the solubility parameter. A maximum solubility of a given solute should occur within a particular narrow dielectric constant range, regardless of whether this dielectric constant is of a pure solvent or from an appropriate mixture of two solvents.

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To test this proposition, the solubility of salicylic acid was studied in pure solvents and binary mixtures. The solvent mixtures tested were prepared so that a number of binary mixtures could be made which would cover the dielectric constant at peak solubility, and a number of binary mixtures of various chemical types could be obtained. Thus, solubility was studied as a function of the dielectric constant by "bridging" the gap between nonpolar and polar solvents through the use of semipolar solvents which were miscible with both the nonpolar and polar solvents.

EXPERIMENTAL

The solubility of salicylic acid was determined in pure solvents and solvent mixtures using 15-ml. screw-capped vials fitted with Teflon liners. The vials were attached to a rotating wheel in a water bath maintained at $30.6 \pm 0.2^\circ$. The equilibrium time of 24 hours was sufficient in all cases. The solvents were used as such or purified as previously described (7). After 24 hours, samples were withdrawn from the reaction vials using a pipet fitted with a glass wool filtering plug. The solubility of salicylic acid was determined by base titration using freshly prepared 0.1 N sodium hydroxide as titrant and phenolphthalein as the end-point indicator. The sodium hydroxide was standardized against recrystallized salicylic acid. Each solvent or solvent mixture was titrated with sodium hydroxide solution to determine the base consuming capacity of the solvent.

Although the solubility of salicylic acid was studied at $30.6 \pm 0.2^\circ$ and the dielectric constants were measured at $25 \pm 1.0^\circ$, the latter values could be used directly due to the relatively small temperature effect. Typical temperature coefficients (8) for benzene and cyclohexane are 0.002 and 0.0016, respectively. A 5° change causes an approximate change of 0.01 units in the dielectric constant for nonpolar solvents which is far below the accuracy of the experimental method.

For polar liquids such as water and methanol, a 5° change can result in a large change in the dielectric constant. For example, the dielectric constant of water is reduced to 76.3 at 30° from 78.5 at 25° . This change can result in a shift of about 0.5 dielectric constant units at peak solubility.

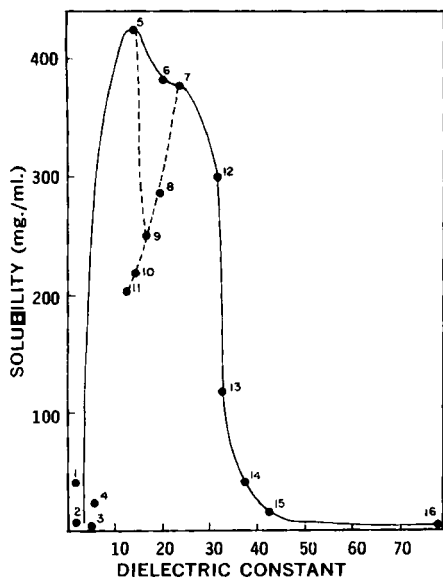


Fig. 1.—A composite plot of the solubility of salicylic acid at 30.6° vs. the dielectric constant of 16 pure solvents: Key: 1, dioxane; 2, benzene; 3, chloroform; 4, ethyl acetate; 5, ethyl cellosolve; 6, acetone; 7, ethanol; 8, propanol; 9, *n*-butanol; 10, cyclohexanol; 11, benzyl alcohol; 12, methanol; 13, propylene glycol; 14, ethylene glycol; 15, glycerin; 16, water.

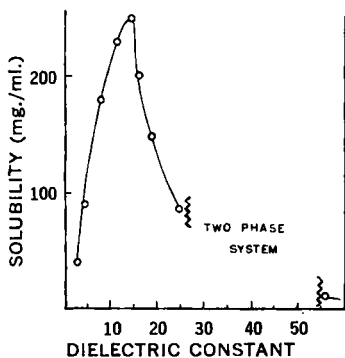


Fig. 2.—A plot of the solubility of salicylic acid at 30.6° vs. the dielectric constant in the binary mixture, dioxane-water.

However, it is felt that this shift could be neglected since the dielectric constant at peak solubility apparently varied about 3 dielectric constant units for all the binary systems studied.

The dielectric constants of all solvent systems were determined by a resonance method. The general approach was to utilize and measure the resonance peaks at 550 micromicrofarads and 200 micromicrofarads at a fixed frequency of 300 kc./second for a cell containing air. A coupled, tunable, capacitance bridge was dialed until a maximum voltage was obtained on a vacuum tube voltmeter. At the maximum voltage, the apparent capacitance was noted for a given sample.

The calibration curves were obtained by measuring the relative capacitances of a pure anhydrous

solvent at the two resonance peaks and plotting these values *versus* their known electric constants (8).

The dielectric constant was obtained by reading the dielectric constant scale at a point perpendicular to the average value of the capacitance from the calibration curves. All binary solvent mixtures were checked against both calibration curves, and average values were obtained.

RESULTS AND DISCUSSIONS

The solubility of salicylic acid was first determined in pure solvents of known dielectric constant for the purpose of scanning the dielectric constant spectrum for maximum solubility. The results are shown in Fig. 1. The dashed lines are drawn to indicate that the full line may be the sum of at least two solubility distribution curves when plotted as a function of the dielectric constant. When the peak solubility of a solute occurs at a given dielectric constant for pure solvents or solvent mix-

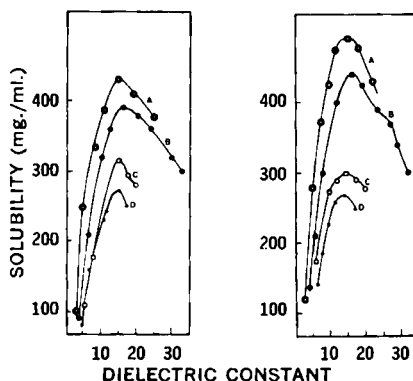


Fig. 3 (left).—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of binary mixtures of benzene and either A, ethanol; B, methanol; C, *n*-propanol; or D, *n*-butanol. Fig. 4 (right).—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of binary mixtures of dioxane and either A, ethanol; B, methanol; C, *n*-propanol; or D, *n*-butanol.

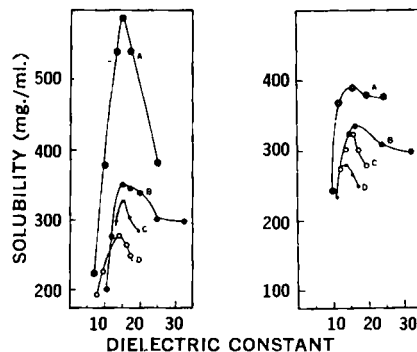


Fig. 5 (left).—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of binary mixtures of chloroform and either A, ethanol; B, methanol; C, *n*-propanol; or D, *n*-butanol. Fig. 6 (right).—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of binary mixtures of ethyl acetate and either A, ethanol; B, methanol; C, *n*-propanol; or D, *n*-butanol.

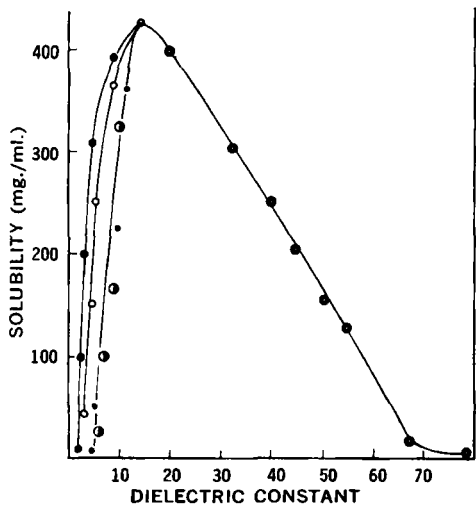


Fig. 7.—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of binary mixtures of ethyl cellosolve and either benzene (●), dioxane (○), chloroform (◐), ethyl acetate (◑), or water (⊙). The peak occurs in pure ethyl cellosolve.

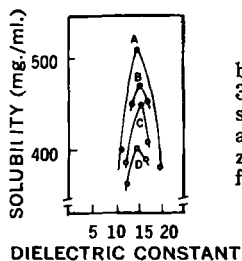


Fig. 8.—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of binary mixtures of acetone and either A, benzene; B, dioxane; C, chloroform; or D, ethyl acetate.

tures, this dielectric constant value is defined as the "dielectric requirement" of the solute. It would appear that the dielectric requirement for salicylic acid may be species dependent. Under these conditions, the first peak at a value of about 15 may be due in part to a certain degree of solute association. The prediction of the species present is complex in view of another possible peak at a value of 25. Whether the first peak is due to some association and the possible second peak due entirely to the monomeric species is difficult to interpret, since these values are rather close to each other. It is further possible that if a solvent of the correct chemical nature and dielectric constant were tested, these two solubility curves may be superseded by a major peak, the dielectric requirement being a value intermediate between these two solubility curves.

Since dioxane-water mixtures can be made to cover the dielectric constant range from 2 to about 80, it was deemed advisable to scan the solubility curve in these mixtures. In Fig. 2, the solubility of salicylic acid is plotted versus the dielectric constant for the binary mixtures of dioxane and water. It is evident that only one peak is present at a value of about 15. A mixture of dioxane and water with a dielectric constant value of above 25 formed a two-phase immiscible system in the presence of salicylic acid; therefore, if a second peak did exist, it could not be determined for these binary mixtures.

In Figs. 3-6, the solubility of salicylic acid is

plotted versus the dielectric constant of the binary mixtures noted. Since the binary mixtures described below contained the same four alcohols, it was thought necessary to vary the nonpolar component with respect to chemical type and to provide a narrow range of dielectric constants. The four nonpolar components chosen as one component of the binary mixtures were benzene, dioxane, chloroform, and ethyl acetate, which have dielectric constant values of 2.2, 2.2, 4.8, and 6.0, respectively. The purpose of using these four solvents was to test the assumption of a fairly constant dielectric requirement, irrespective of the nature of the solvents used to prepare the binary mixtures.

In Fig. 3, the solubility of salicylic acid is plotted versus the dielectric constant of the binary mixtures composed of benzene and *n*-alkyl alcohols ranging from methanol to butanol. The apparent dielectric requirement for salicylic acid in these binary mixtures is about 15. It is observed further that solubility distribution curves exist when the solubility of salicylic acid for these binary mixtures is plotted on common axes. The difference in solubility at the peak observed for the different binary mixtures is probably related to the magnitude of the particular solute-solvent interaction.

Figure 4 shows a plot of the solubility of salicylic acid versus the dielectric constant of the binary mixtures composed of dioxane and *n*-alkyl alcohols

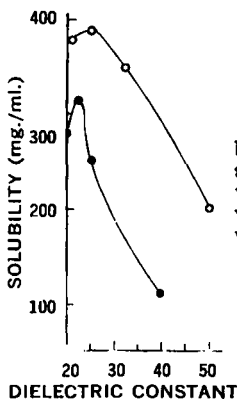


Fig. 9.—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of the binary mixtures acetone-water (○), and *n*-propanol-water (●).

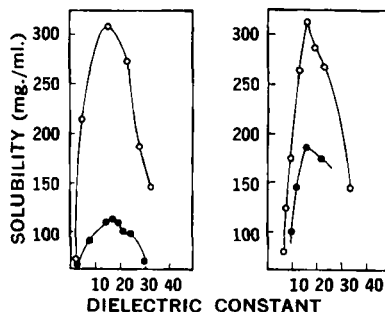


Fig. 10 (left).—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of the binary mixtures propylene glycol-dioxane (○) and ethylene glycol-dioxane (●). Fig. 11 (right).—Plots of the solubility of salicylic acid at 30.6° vs. the dielectric constant of the binary mixtures propylene glycol-chloroform (○) and ethyl acetate-propylene glycol (●).

ranging from methanol to butanol. The same remarks apply here as discussed under Fig. 1. It is interesting to note a shoulder in the methanol-dioxane binary mixture at a value of about 25. This experimental point and points close to it were determined several times.

Again, in each solubility distribution curve, the peak solubility for salicylic acid occurred at a dielectric constant of about 15. A shoulder occurred at a value of 25 when methanol and dioxane mixtures were used, but could not be duplicated in mixtures of benzene and other alcohols since this dielectric constant value cannot be attained in these mixtures. The decreasing magnitude of the solubility at the peak values is in the order: ethanol, methanol, propanol, and butanol.

In Fig. 5, the solubility of salicylic acid is plotted *versus* the dielectric constant for the binary mixtures composed of chloroform and *n*-alkyl alcohols ranging from methanol to butanol. As with the previous mixtures with these alcohols, these binary mixtures show the same solubility behavior, having a peak at about 15. Chloroform-methanol mixtures also show a shoulder at a value of about 25.

The results for the binary mixtures formed between ethyl acetate and *n*-alkyl alcohols are shown in Fig. 6.

Figure 7 gives the solubility curve for salicylic acid as a function of the dielectric constants obtained from binary mixtures using ethyl cellosolve as a common solvent. Since the dielectric constant of this solvent is approximately 15, which is also the dielectric requirement for salicylic acid, greater solubility should be expected in this solvent alone. Adding solvents with a greater or lesser dielectric constant than 15 should result in a binary solvent with decreased solvent power for salicylic acid. This was true when the solubility of salicylic acid was determined in ethyl cellosolve-water mixtures or mixtures with either benzene, dioxane, chloroform, or ethyl acetate. Figure 7 illustrates these distribution curves which all show a peak occurring at the value for pure ethyl cellosolve.

In Fig. 8, the solubility of salicylic acid is plotted for the binary mixtures of acetone with either benzene, dioxane, chloroform, or ethyl acetate. Again, the dielectric requirement for salicylic acid in these binary mixtures have a common value of about 15. When acetone is the common solvent, the magnitudes of the solubility in these binary mixtures are in the decreasing order benzene, dioxane, chloroform, and ethyl acetate. It is interesting to note

that this is also in the order of increasing dielectric constant of the pure solvent.

Figure 9 shows a plot of the solubility of salicylic acid in the usual manner for the binary mixtures composed of acetone and water and *n*-propanol and water. In both of these binary mixtures, a solubility distribution curve is observed, but in these cases the dielectric requirement for salicylic acid is about 25. This is a confirmation that a second peak for this solute exists, although only a shoulder is found in the pure solvent scan.

To test the existence of this second peak in other binary mixtures, the solubility of salicylic acid was determined in propylene glycol-dioxane and ethylene glycol-dioxane mixtures. The glycol solvents were chosen to broaden the dielectric constant range so that the second peak at a value of 25 would be a value intermediate between the extremes of the pure solvents (Fig. 10). Both of these solvent systems give a dielectric requirement for salicylic acid at a value of 15. Enough experimental points were obtained only for the dioxane-ethylene glycol mixtures; the resultant solubility curve showed a shoulder at a value of 25.

Since propylene glycol was miscible with both chloroform and ethyl acetate, it was deemed advisable that data with a glycol as one component in binary mixtures should provide a further basis for the dielectric requirement being essentially independent of the nature of the components (Fig. 11).

In a previous communication (6), a correlation between solubility parameters and dielectric constants was presented. This study illustrates the utility of studying solubility phenomena in terms of dielectric constants.

The data obtained for the dielectric requirement for the binary mixtures tested have been summarized in Table I.

The binary mixtures studied are listed in Table II and give the peak solubility for the first peak of salicylic acid. Also given in this table are the maximum solubilities of salicylic acid for the first peak along with a solubility ratio. In this case, the solubility ratio is defined as the experimentally determined solubility compared to an arbitrary standard solubility of 500 mg./ml. The purpose of this table is to illustrate further the relatively constant dielectric requirement for the first salicylic acid peak, but the magnitude of the solubility at this dielectric requirement varies widely. From these results, it can be stated qualitatively that the magnitude of the peak solubility depends mainly

TABLE I.—SUMMARY OF THE EXPERIMENTALLY DETERMINED DIELECTRIC REQUIREMENT OF SALICYLIC ACID IN BINARY MIXTURES

Solvent	Benzene ε _{req.}	Dioxane ε _{req.}	Chloroform ε _{req.}	Ethyl Acetate ε _{req.}	Water ε _{req.}
Ethyl cellosolve	14.5 ^a	14.5 ^a	14.5 ^a	14.5 ^a	14.5 ^a
Acetone	15.6	15.5	16.1	15.0	25.0 ^b
<i>n</i> -Butanol	15.4	14.5	14.0	15.0	...
<i>n</i> -Propanol	15.3	14.8	15.3	15.3	22.3 ^b
Ethanol	15.8	15.0	15.7	16.0	...
Methanol	16.0	16.3 ^c	16.0	16.0	...
Ethylene glycol	...	17.5 ^c
Propylene glycol	...	15.1	16.2	16.3	...
Water	...	14.5

^a Dielectric requirement of salicylic acid and dielectric constant of ethyl cellosolve have about equal values; thus "peak" exists at the dielectric constant. ^b Dielectric requirement for the second peak. ^c Shouldering in these systems exists at about 25.

TABLE II.—SUMMARY OF THE SOLUBILITY OF SALICYLIC ACID AND SOLUBILITY RATIO AT THE PEAK VALUES FOR THE BINARY MIXTURES INDICATED

Solvent Mixture	Solubility	
	mg./ml.	Ratio ^a
Ethanol-chloroform	595	1.19
Benzene-acetone	510	1.02
Dioxane-ethanol	495	0.99
Dioxane-acetone	475	0.95
Chloroform-acetone	445	0.89
Dioxane-methanol	440	0.88
Benzene-ethanol	430	0.86
Benzene-ethyl cellosolve ^b	425	0.85
Dioxane-ethyl cellosolve ^b	425	0.85
Chloroform-ethyl cellosolve ^b	425	0.85
Ethyl acetate-ethyl cellosolve ^b	425	0.85
Ethyl acetate-acetone	415	0.83
Ethyl acetate-ethanol	390	0.78
Benzene-methanol	390	0.78
Ethyl acetate- <i>n</i> -propanol	355	0.71
Chloroform-methanol	348	0.70
Ethyl acetate-methanol	335	0.67
Ethyl acetate- <i>n</i> -butanol	330	0.66
Chloroform- <i>n</i> -propanol	315	0.63
Benzene- <i>n</i> -propanol	315	0.63
Dioxane- <i>n</i> -propanol	305	0.61
Chloroform-propylene glycol	292	0.58
Dioxane-propylene glycol	290	0.58
Chloroform- <i>n</i> -butanol	282	0.56
Dioxane- <i>n</i> -butanol	268	0.54
Dioxane-water	250	0.50
Ethyl acetate-propylene glycol	160	0.32
Dioxane-ethylene glycol	89	0.18

^a Solubility ratio based on 500 mg./ml. = 1. ^b In these mixtures curves continuously rise to a maximum solubility corresponding to the solubility in ethyl cellosolve alone.

upon the degree of the solute-solvent mixture interactions. However, the prediction of the degree of these interactions cannot be deduced from the nature of the binary mixtures tested. Furthermore, there appears to be no apparent order in the magnitude of solubility for solvent mixtures containing a common liquid or functional group.

The only important qualitative observation made is that the maximum solubility is a function of the difference of the dielectric constant of the individual solvents with respect to the value of the dielectric requirement.

The data concerning the only two binary mixtures which exhibited the second peak are given in Table III. Both the solubility and solubility ratio are also given. Systems showing shouldering at the dielectric requirement of 25 are not included.

All the pure solvents used in this study with their respective dielectric constants are given in Table IV. Also listed are the respective salicylic acid solubilities in these pure solvents and the solubility ratio as defined above. Table IV is presented to illustrate the cosolvent effect by comparison with solubility ratio values in Table III. For example, the solubility ratios for salicylic acid in pure ethanol and pure chloroform are 0.74 and approximately 0.004, respectively. Yet an appropriate mixture of ethanol and chloroform gives a solubility ratio of 1.2 at peak solubility. Thus, salicylic acid shows a greater solubility in mixtures of solvents than in

TABLE III.—SUMMARY OF THE EXPERIMENTALLY DETERMINED DIELECTRIC REQUIREMENT OF SALICYLIC ACID FOR THE SECOND PEAK AND SOLUBILITY RATIO

Solvent Mixture	Exptl. req.	mg./ml.	Ratio ^a
Acetone-water	25.0	387	0.77
Water- <i>n</i> -propanol	22.3	320	0.64

^a Ratio based on 500 mg./ml. = 1.

TABLE IV.—SUMMARY OF THE SOLUBILITY AND SOLUBILITY RATIO FOR SALICYLIC ACID IN PURE SOLVENTS

Solvent	ϵ^a	mg./ml.	Ratio ^b
Benzene	2.2	7	0.014
Dioxane	2.2	40	0.080
Chloroform	4.8	2	0.004
Ethyl acetate	6.0	23	0.040
Benzyl alcohol	13.00	203	0.406
Ethyl cellosolve	14.5	425	0.850
Cyclohexanol	15.0	217	0.430
<i>n</i> -Butanol	17.1	251	0.500
<i>n</i> -Propanol	20.1	287	0.560
Acetone	20.7	381	0.760
Ethanol	24.3	377	0.740
Methanol	32.6	299	0.600
Propylene glycol	33.0	118	0.230
Ethylene glycol	37.7	42	0.084
Glycerin	42.5	15	0.030
Water	78.5	3	0.006

^a Dielectric constant of pure solvent. ^b Solubility ratio based on 500 mg./ml. = 1.

either one alone. By comparing the solubility ratio of any pure solvent to the solubility ratio of any binary mixture formed from that solvent, the binary mixture always shows greater solvent power.

That a reproducible peak solubility occurs within a narrow range of dielectric constant of the solvent and apparently independently of its chemical nature, strongly indicates a close tie to Hildebrand's solubility parameter theory. Possibly the more rigorous link to the dielectric constant and solubility parameter lies in a closer examination of the "cohesive energy density" concept. This, of course, requires a more exact knowledge of the liquid state which is yet unresolved.

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