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Solubility Parameter of Selected Sulfonamides

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Abstract □ This investigation was primarily concerned with the application of Hildebrand's solubility equation to the determination of the solubility parameter of selected sulfonamides. The vapor pressure of several selected solvent systems was determined by an isoteniscopic method. These data were used to calculate the solubility parameter of the mixed solvents. The heat of fusion of each sulfonamide was determined by differential thermal analysis. The solubility of the sulfonamides was measured in a series of solvent blends varying in polarity, and the solubility parameter of the sulfonamides was determined from their solubility data. An attempt was made to correlate the solubility parameter with the dielectric constant. The results were found to be linear with respect to the solvent blends of alcohol–water, alcohol–water–propylene glycol, water–glycerin, and dimethylacetamide–water–glycerin. Hildebrand's solubility concept appears to be a useful tool for predicting drug solubility where the solubility parameters of drug and solvent system are close to each other.

Keyphrases □ Sulfonamides—solubility parameter □ Solubility, solubility parameter—sulfonamides □ Isoteniscopic method—solvent vapor pressure determination □ Differential thermal analysis—heat of fusion, sulfonamides □ UV spectrophotometry—analysis

The wide application of liquid dosage forms used in pharmaceuticals is demonstrable proof of the importance of solutions in formulation. A convenient and reliable means of determining enhanced solubility of pharmaceutical substances has long been sought by formulation workers. The concept of solubility parameters has been found to be useful, particularly in guiding the selection of solvents for film formers and in the formulation of paints, varnishes, and printing inks (1). Hildebrand's solubility equation (2) was applied by Chertkoff and Martin (3) and by Restaino and Martin (4) to determine the solubility of benzoic acid

Table I—Heat of Vaporization and Solubility Parameter of Solvents Employed

Solvent	Slope	ΔH_v, kcal./mole at 25°, Determined	ΔH_v, kcal./mole at 25°, Reported Value	δ at 25°, Determined	δ at 25°, Reported Value
Water, double-distilled	−2250 ± 6	10.296	9.730[a]	23.2	23.4[c]
Absolute alcohol	−2136 ± 5	9.765	9.22[a]	12.5	—
Absolute alcohol, distilled	−2233 ± 5	10.217	10.08[b]	12.8	12.7[c] 13.0[d]
Propylene glycol	−2700 ± 7	12.357	—	12.6	—
Dimethyl-acetamide	−2297 ± 4	10.454	—	10.3	10.6[e]
2-Ethoxy-ethanol	−2516 ± 7	11.748	—	10.7	9.9[c]

[a] *Reference 13.* [b] *Reference 14.* [c] *Reference 15.* [d] *Reference 4.* [e] *Reference 16.*

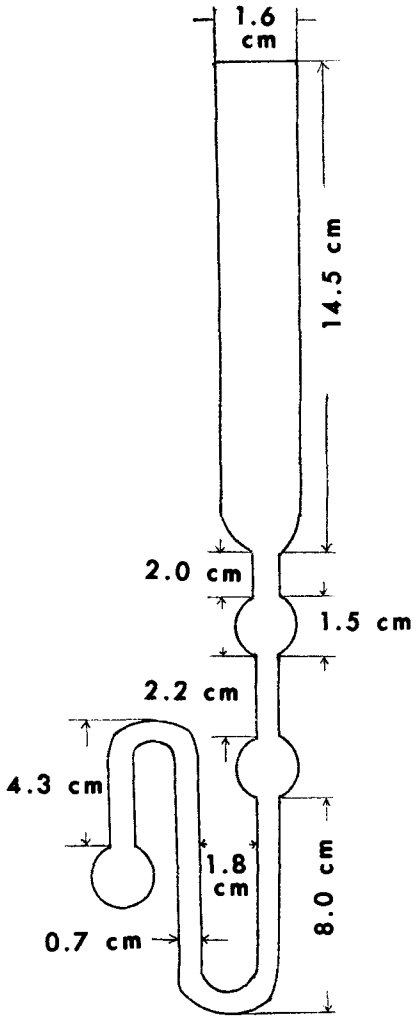

Figure 1—*Schematic diagram of the isoteniscope used for vapor pressure determination.*

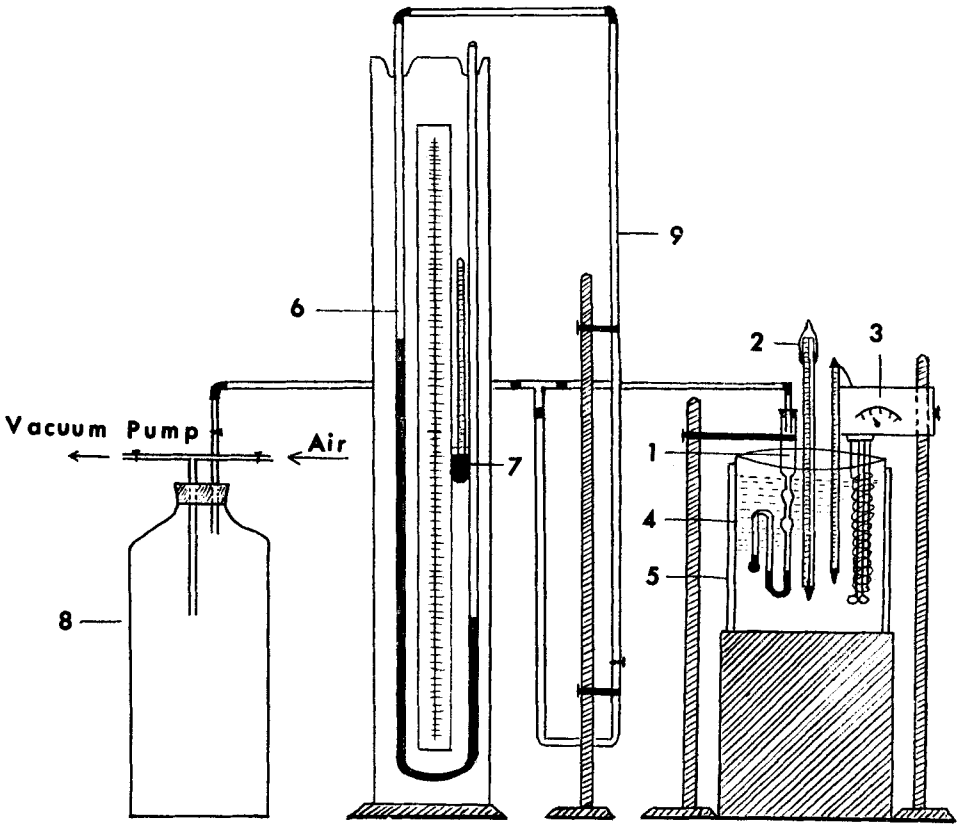

Figure 2—*Schematic diagram of the apparatus used for vapor pressure determination. Key: 1, isoteniscope; 2, differential thermometer; 3, constant-temperature circulator; 4, crystallization jar; 5, metal bath jacket; 6, open-tube manometer; 7, differential thermometer; 8, ballast bottle; and 9, glass tubing.*

and the esters of *p*-hydroxybenzoic acid in a series of *n*-alkanols. Gorman and Hall (5) studied the relationship of the dielectric constant with solubility, solubility parameters, and the application of an approximate dielectric constant to cosolvent systems (6).

This study was also concerned with the applicability of Hildebrand's solubility parameter concept. The solubilities of several sulfonamides in polar solvent blends were determined.

To apply the equation, the heat of vaporization of the solvents, the heat of fusion, the molar volumes of the sulfonamide, and the solubility of each solid were also determined.

EXPERIMENTAL

Solvents—The following were used: water, double-distilled; alcohol USP;[1] absolute alcohol USP[1] (distilled and treated with calcium oxide); propylene glycol USP;[2] dimethylacetamide[3] (DMAC, technical grade); 2-ethoxyethanol[4] (industrial grade); and glycerin USP.[5]

Sulfonamides—Sulfonamides used were recrystallized from supersaturated solution: sulfathiazole[6] form I (7, 8) from distilled water; sulfathiazole[6] form II (7, 8) and sulfadiazine USP[6] from warm acetone; and sulfamerazine USP,[6] sulfamethazine USP,[6] sulfisomidine,[7] sulfameter[8] (8), sulfamethoxazole,[9] and sulfisoxazole[9] from warm alcohol.

[1] U. S. Industrial Chemical Co., New York, N. Y.
[2] Ruger Chemical Co., Irvington, N. Y.
[3] E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.
[4] Cellosolve solvent, Union Carbide Corp., New York, N. Y.
[5] Fisher Scientific Co., Fair Lawn, N. J.
[6] American Cyanamid Co., Pearl River, N. Y.
[7] Ciba Pharmaceutical Co., Summit, N. J.
[8] A. H. Robins Co., Richmond, Va.
[9] Hoffmann-La Roche, Inc., Nutley, N. J.

Procedure—*Determination*[10] *of Heat of Vaporization of Solvents from Vapor Pressures*—The modified static isoteniscope (Fig. 1) (9) was used to determine vapor pressures of all solvents except glycerin. The liquid to be determined was placed in the isoteniscope shown in Fig. 2 so that the bulb was almost full. The U-tube was filled with about 3 cm. of liquid. The two bulbs above the U-tube prevent the ascent of the confining liquid by suction in the U-tube. The isoteniscope was connected to the ballast bottle which regulates the pressure.

The manometer was then filled with mercury. For all connections, glass tubing and high pressure rubber were used. They were tightened with the aid of copper wire. To determine the vapor pressure, the isoteniscope was immersed in the heating bath filled with water (10) for solvents boiling below 100°. For solvents boiling above 100°, light mineral oil was used as the bath liquid. A differential thermometer was placed in the mercury tube and suspended along the gauge of the barometer and between the arms of the manometer tube to read the nearest temperature of the mercury in the manometer indirectly.

A very thin wire was attached to the outside of the glass thermostat vessel to eliminate any error due to parallax in reading. Air was removed from the bulb by lowering the pressure in the ballast bottle until the liquid in the bulb boiled at a reasonable rate. After approximately 3 min., the pressure was raised until the boiling stopped and the liquid levels in both arms of the U-tube were equal. Then the temperature of the system and the ascending and descending pressures from the zero point were recorded. The barometric pressure was recorded at the same time. This procedure was repeated to ensure complete removal of air in the system. By heating the thermostat bath, new pressures and temperatures were recorded at approximately 5° intervals. The liquid levels in the U-tube were kept approximately equal by manipulating two stopcocks on the ballast bottle. All manometer and barometer readings were corrected to 0° by multiplying the factor $(1 - 1.8 \times 10^{-4})$ (11), where it is the centigrade temperature of the manometer and barometer.

[10] All experimental values reported in this work represent the mean of three determinations.

Table II—Heat of Fusion of Selected Sulfonamides Employed

Sulfonamide	Molecular Weight	Fusion Temperature	Heat of Fusion, ΔH_f, cal./mole
Sulfathiazole			
Form I	255.33	164°[a]	(1420 ± 40)[c]
		(161°)[b]	1552 ± 25[d]
Form II	255.33	201.5°	6247 ± 220
		(200°)[b]	(5970 ± 230)[b]
Sulfamerazine	264.31	242.0°	7541 ± 70
Sulfamethazine	278.33	198.5°	7438 ± 170
Sulfisomidine	278.34	250.4°	10,194 ± 170
Sulfadiazine	250.28	265.6°	7464 ± 180
Sulfameter	280.32	213.5°	8255 ± 14
Sulfamethoxazole	253.31	166.3°	6852 ± 110
Sulfisoxazole	267.30	195.0°	6990 ± 13

[a] Temperature of transition. [b] Reported value (19). [c] Heat of transition reported (19). [d] Heat of transition.

By employing the Clausius-Clapeyron equation, the slopes were calculated by the linear least-squares treatment of these data using a library program, STAT 9A, available on the Control Data Multi-Access Computer (System 420). From these slopes the heat of vaporization for each solvent was calculated. The compressibility factor was taken as unity for these calculations. Solubility parameters for the solvents (Table I) were calculated, using the following equation (12):

$$\delta = \frac{H_v - RT^{1/2}}{V^1} \qquad \text{(Eq. 1)}$$

where δ = solubility parameter, H_v = molar heat of vaporization, R = gas constant, T = absolute temperature, and V^1 = molar volume.

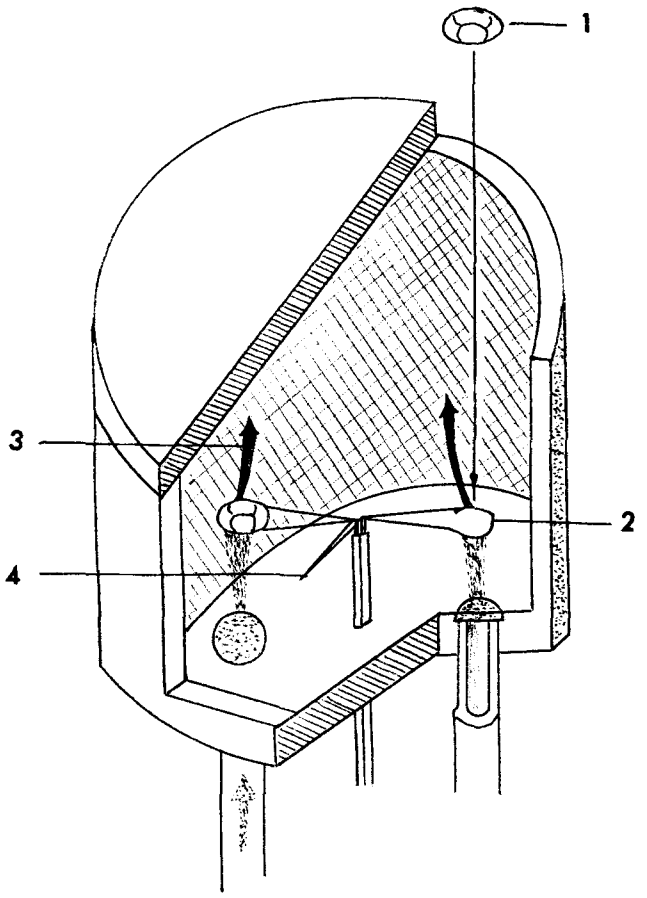

Figure 3—*Schematic diagram of the sample holder of differential thermal analyzer. Key: 1, sample dish; 2, differential thermocouple, bead; 3, flooding gas; and 4, reference thermocouple, bead.*

Table III—Apparent Molar Volumes at 25°

Sulfonamide	V_2, ml./mole
Sulfathiazole, form II	162
Sulfamerazine	186
Sulfamethazine	197
Sulfisomidine	195
Sulfadiazine	156
Sulfameter	183
Sulfamethoxazole	176
Sulfisoxazole	188

The solubility parameter value (δ = 16.5) for glycerin was taken from Burrell (15). Equation 2 (15) was employed to calculate the solubility parameter for mixed solvents:

$$\delta_{mix} = (x_1V_1\,\delta_1 + x_2V_2\delta_2)/(x_1V_1 + x_2V_2) \qquad \text{(Eq. 2)}$$

where x = mole fraction and V = molar volume.

Determination of Heat of Fusion—The determinations of the heat of fusion of the sulfonamides were made using a differential thermal analyzer.[11]

The sample holder assembly consists of two separate platinel differential thermocouples and a platinel furnace couple which is utilized for programming the furnace (Fig. 3). The instrument was calibrated by the method reported by David (17) utilizing a linear programming rate of 10°/min.; the K values, where K is the heat transfer coefficient of the system in cal./mm.^{2}, were determined using the heat of fusion of tin, 14.0 cal./g. (18).

K was determined employing the following equations:

$$\frac{\text{area}}{\text{g.}} = \frac{\text{area of sample transition} \times \text{range setting of interest } (\mu\text{v.})}{\text{sample wt. (g.)}} \qquad \text{(Eq. 3)}$$

$$\frac{H_f \text{ of standard (cal./g.)}}{\text{area/g.}} = \frac{\text{cal.}}{\text{area}} = \frac{\text{cal.}}{\text{mm.}^2} = K \qquad \text{(Eq. 4)}$$

The K for flattened tin was found to be 6.1×10^{-7} cal./mm.^{2}. Samples of each sulfonamide were weighed on a Cahn Electrobalance[12] and ranged from approximately 1.6 to 3.0 ± 0.002 mg.

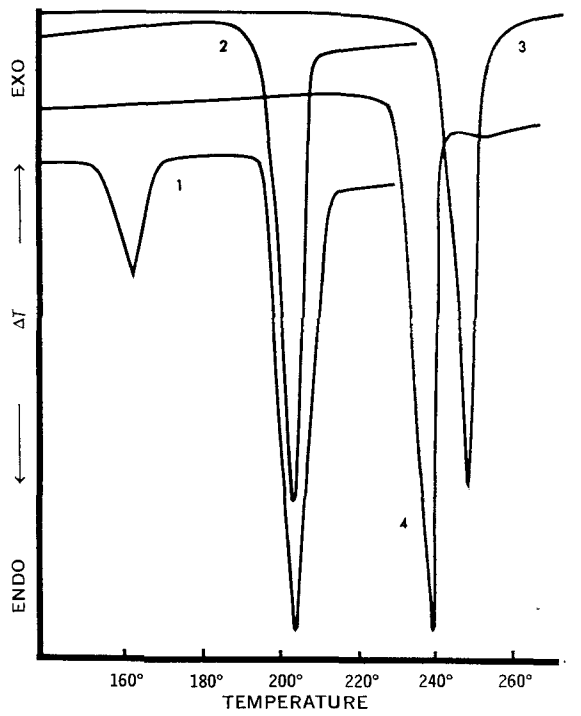

Figure 4—*Thermograms of sulfathiazole form I (1) and form II (2), sulfisomidine (3), and sulfamerazine (4).*

[11] Model KA-2H, Robert L. Stone Co., Austin, Tex.
[12] Model M-10, Cahn Instrument Co., Paramount, Calif.

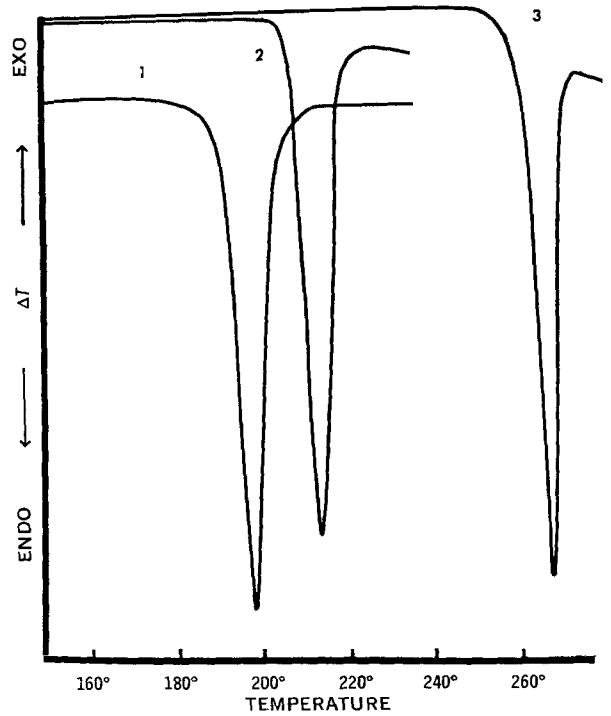

Figure 5—*Thermograms of sulfamethazine (1), sulfameter (2), and sulfadiazine (3).*

The areas encompassed by endothermic peaks were determined utilizing a Keuffel and Esser compensating polar planimeter. The heat of fusion was calculated from the following equation:

$$H_f \text{ or } H_v = \frac{K \times \text{area in mm.}^2 \times \text{range setting of interest } (\mu\text{v.})}{\text{g.}} \qquad \text{(Eq. 5)}$$

Thermograms and heats of fusion for the selected sulfonamides are presented in Figs. 4–6 and Table II, respectively.

Solubility Studies—The solubility was determined by the method reported by Restaino and Martin (4). Saturated solutions of sulfonamides at 25 ± 1.0° were prepared in 20 different cosolvent systems varying in polarity. Spectrophotometric assays were carried out with the supernatant liquid on a Coleman-Hitachi 124 double-beam spectrophotometer at predetermined wavelengths [sulfathiazole,

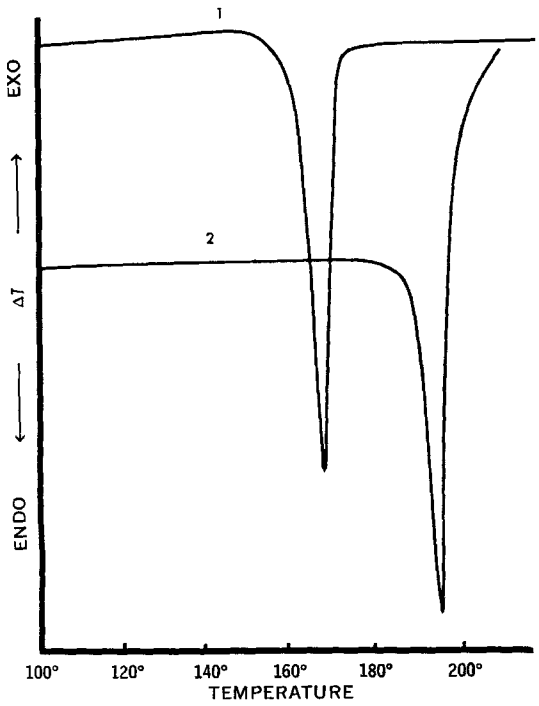

Figure 6—*Thermograms of sulfamethoxazole (1) and sulfisoxazole (2).*

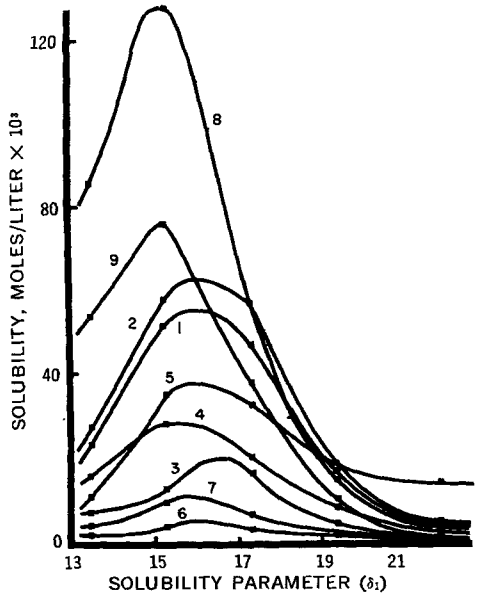

Figure 7—*Solubility in alcohol–water system. Key: 1, sulfathiazole form I; 2, sulfathiazole form II; 3, sulfamerazine; 4, sulfamethazine; 5, sulfisomidine; 6, sulfadiazine; 7, sulfameter; 8, sulfamethoxazole; and 9, sulfisoxazole.*

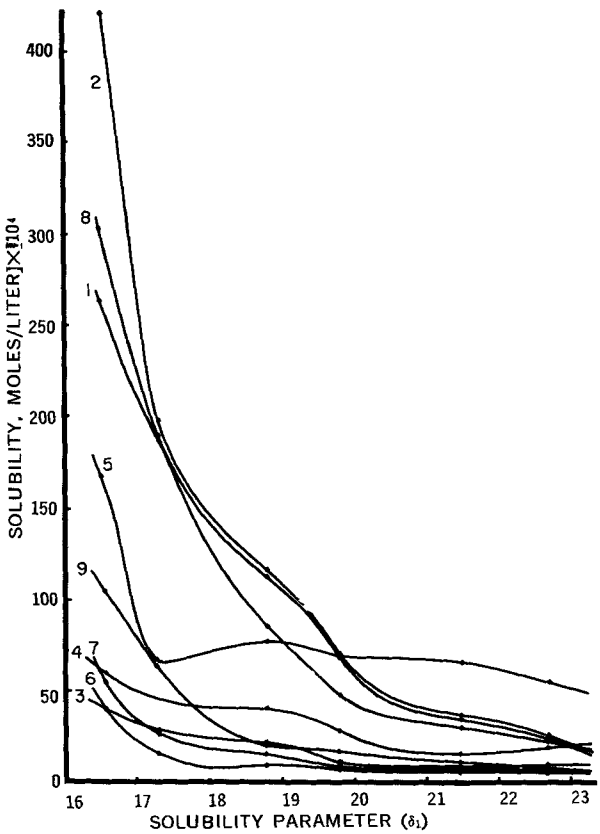

Figure 8—*Solubility in water–glycerin system. Key: 1, sulfathiazole form I; 2, sulfathiazole form II; 3, sulfamerazine; 4, sulfamethazine; 5, sulfisomidine; 6, sulfadiazine; 7, sulfameter; 8, sulfamethoxazole; and 9, sulfisoxazole.*

Table IV—Density of Selected Sulfonamides

Sulfonamide	Density at 25 ± 0.02°
Sulfathiazole	1.5375
Sulfamerazine	1.3390
Sulfamethazine	1.4038
Sulfisomidine	1.4005
Sulfadiazine	1.4703[a]
Sulfameter	1.4819
Sulfamethoxazole	1.4777
Sulfisoxazole	1.4136

[a] Reported value 1.50 (23).

280 nm. (20); sulfameter, 271 nm.; sulfamerazine, sulfamethazine, sulfadiazine, and sulfisoxazole, 270 nm.; and sulfamethoxazole, 271 nm.], diluting with 95% alcohol or water.

Determination of Solubility Parameter of Sulfonamides—The modified Hildebrand's equation (2) was used to determine the solubility parameter of each sulfonamide:

$$\log x_2 = \frac{-\Delta H_m^f (Tm - T)}{4.575(TmT)} - \frac{V_2}{4.575T}(\delta_1 - \delta_2)^2\phi_1^2 \quad \text{(Eq. 6)}$$

where x_2 = mole fraction solubility of solute, ΔH_m^f = heat of fusion of solute at melting point, Tm = absolute melting temperature of solute, T = experimental absolute temperature, V_2 = molar volume of supercooled solute, δ_1 and δ_2 = solubility parameter of solvent and solute, and ϕ_1 = volume fraction of solvent.

The apparent molar volume of each sulfonamide was calculated from the solubility data of several solvent systems employing the equation (22) to approximate the molar volume of the supercooled solute which is not ordinarily available (Table III). To substantiate the experimental result of the apparent molar volume, the density of the sulfonamide was determined by a pycnometric method, using the crystalline form of the compounds (Table IV). The volume fraction was calculated utilizing the following equation:

$$\phi_1 = \frac{n_1 v_1}{n_1 v_1 + n_2 v_2} \quad \text{(Eq. 7)}$$

where ϕ_1 = volume fraction of Component 1, n_1 and n_2 = number of moles of Components 1 and 2, and v_1 and v_2 = molar volume of Components 1 and 2.

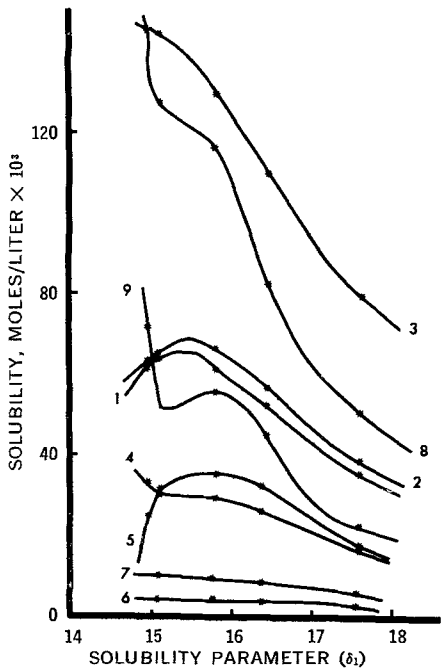

Figure 9—*Solubility in alcohol–water–propylene glycol system. Key: 1, sulfathiazole form I; 2, sulfathiazole form II; 3, sulfamerazine; 4, sulfamethazine; 5, sulfisomidine; 6, sulfadiazine; 7, sulfameter; 8, sulfamethoxazole; and 9, sulfisoxazole.*

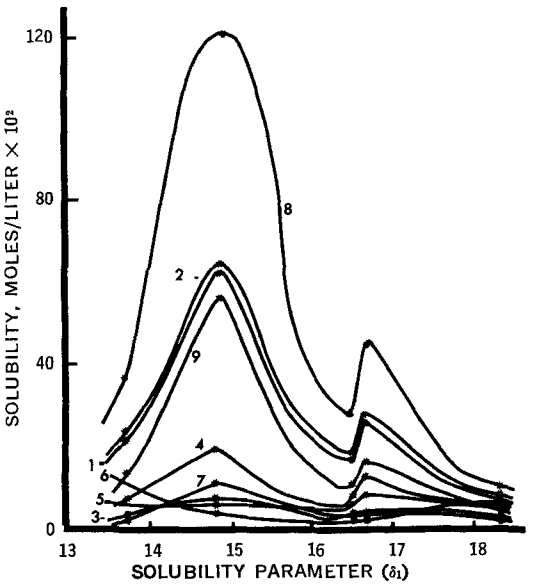

Figure 10—*Solubility in DMAC–water–glycerin system. Key: 1, sulfathiazole form I; 2, sulfathiazole form II; 3, sulfamerazine; 4, sulfamethazine; 5, sulfisomidine; 6, sulfadiazine; 7, sulfameter; 8, sulfamethoxazole; and 9, sulfisoxazole.*

Mole fraction solubilities of all sulfonamides, except sulfadiazine, were determined in 2-ethoxyethanol. For sulfadiazine, the solubility data in DMAC was used (Table V). From knowledge of the reported values experimentally determined, the solubility parameter of each sulfonamide was calculated (Table V). Plots of solubility in moles per liter *versus* δ of each solvent blend are given in Figs. 7–10.

The approximate dielectric constant (A.D.C.) in percent volume-to-volume for each solvent blend was calculated by the method reported by Moore (6):

$$\text{A.D.C.} = \sum (\%\ \text{solvent}_1 \times \text{D.C. solvent}_1) + (\%\ \text{solvent}_2 \times \text{D.C. solvent}_2) \cdots + (\%\ \text{solvent}_n \times \text{D.C. solvent}_n) \div 100 \quad \text{(Eq. 8)}$$

The dielectric constants at 25° for solvents used are: alcohol, 24.3 (24); glycerin, 42.5 (24); water, 78.54 (24); DMAC, 37.78 (25); and propylene glycol, 32.0 (26). A plot was constructed to show the relationship between the solubility parameter and A.D.C. of solvent blends by the linear least-squares method reported previously (Fig. 11).

DISCUSSION

The results in Table I show good agreement between the solubility parameter calculated from the vapor pressure of pure solvent by the isoteniscopic method and the reported value. It is obvious from these results that the purified solvents exhibited closer correlation with reported values. The effect of water content was quite

Table V—Mole Fraction Solubility and Solubility Parameter of Selected Sulfonamides at 25°

Sulfonamide	Mole Fraction Solubility, X_2	δ
Sulfathiazole, form II	0.0224	11.1
Sulfamerazine	0.0109	13.4
Sulfamethazine	0.0184	12.6
Sulfisomidine	0.0111	19.7
Sulfadiazine	0.0239[a]	26.9
Sulfameter	0.0119	13.9
Sulfamethoxazole	0.0911	16.4
Sulfisoxazole	0.0495	15.1

[a] X_2 was obtained from DMAC. All other mole fraction solubilities were obtained from 2-ethoxycthanol.

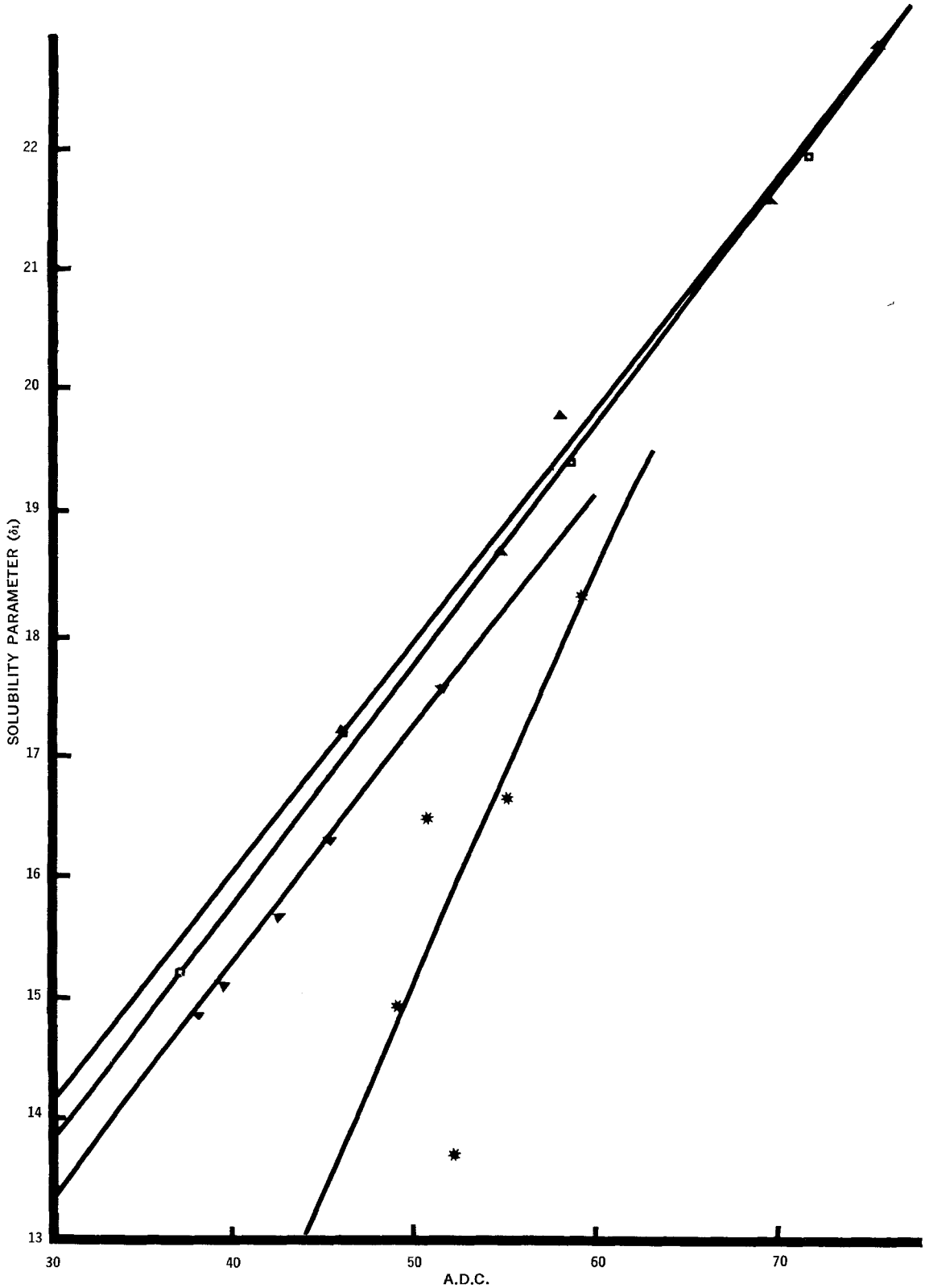

Figure 11—*Plot of solubility parameters of solvent blends used* versus *their respective A.D.C.'s. Key:* □, *alcohol–water;* ▲, *water–glycerin;* ▼, *alcohol–water–propylene glycol; and* *, *DMAC–water–glycerin.*

apparent in the case of absolute alcohol, resulting in a decrease in its heat of vaporization. Because of this effect, it is important to purify each solvent before determining vapor pressure values to calculate the solubility parameter of the solvent indirectly. It is also important to introduce an extremely high vacuum in the system; otherwise there is a considerable decrease in the vapor pressure. All data determined experimentally with a vacuum pump having a capacity of less than 30 psig. gave results much below the reported values. The reproducibility of each determination of solvent vapor pressure was excellent. The sulfonamides were recrystallized to obtain a pure crystal form, employing the same procedures recommended by Mesley and Houghton (7). The existence of polymorphism could only be detected for sulfathiazole by changing the rate of heating employed with the differential thermal analyzer. Sulfathiazole form I could only be produced by recrystallizing from water. The melting point of the polymorphic mixture obtained

from alcohol varied with the ratio of form II to form I, as reported by Miyazaki (8). The presence of a larger ratio of form II gave a form II melting point, while rapid melting between 170 and 175° gave a melting point corresponding to form I. The thermogram produced with a linear programming rate of 10°/min. showed the presence of two polymorphs of sulfathiazole with different melting points at 171–175° and 200–205°. It is conceivable that the polymorphs reported for other sulfonamides can be detected by utilizing a slower rate of heating.

The heat of fusion values obtained by differential thermal analysis proved to be reproducible with the particle-size range and amount of sample used in this study. An average of three determinations showed a deviation of less than 3%. It has been reported that a number of factors affecting differential thermal analysis results are dependent on the particle size and amount of sample used (27). Areas were constructed by drawing a straight line to close the open end of the differential thermal analysis peak. The base line for sulfisoxazole is shifted appreciably. It is believed that another reaction is involved after fusion occurs.

The solubility of the sulfonamides was determined by spectrophotometric assays in 20 different solvent blends of different polarity.

To utilize Hildebrand's solubility equation for the calculation of the solubility parameter of a solid, the molar volume of the supercooled solid must be known. As Hildebrand pointed out, it is ordinarily not available (15). Therefore, the apparent molar volume derived from solubility data in several solvent blends used for solubility determinations was used instead. It is extremely difficult to apply the equation used for molar volume determination to a solid having very limited solubility in the solvent system, yielding an insignificant density differential between solvent and solution.

As can be seen in Fig. 7, when the solubility parameter value of each sulfonamide approaches the δ value of the solvent blend, sulfamethoxazole and sulfisoxazole show peak solubility. However, the remaining sulfonamides do not show this peak solubility in the alcohol–water system.

In the water–glycerin mixture, it can be predicted from Fig. 7 that, except for sulfadiazine, the solubility of the sulfonamides whose δ is much greater than 16.5 will increase (Fig. 8).

In the alcohol–water–propylene glycol system, sulfamerazine, sulfamethoxazole, sulfisoxazole, sulfameter, and sulfamethazine show a tendency for solubility increase as their solubility parameter values approach the solubility parameter value of the solvent blend.

In the DMAC–water–glycerin system (Fig. 10), all the sulfonamides, except sulfadiazine, show peak solubility at the solubility parameter values of 15 and 16.5, regardless of their δ values. Only sulfamethoxazole and sulfisoxazole show the predicted peak point as their δ values approach the δ value of the solvent blend.

An attempt was made to correlate the solubility parameter with A.D.C. (Fig. 11). Excellent linear relationships exist between the solubility parameter and A.D.C. in the solvent systems of the alcohol group and in the DMAC–water–glycerin system. This correlation agrees with that reported by Paruta *et al.* (28).

SUMMARY AND CONCLUSIONS

The static isoteniscopic method was utilized to determine the solubility parameter of several solvents from vapor pressure data. The heat of fusion of several sulfonamides was determined utilizing differential thermal analysis; this technique showed good reproducibility. The solubility of the sulfonamides was determined using a spectrophotometric method in solvent mixtures of varying polarity.

Sulfamethoxazole had the highest solubility and sulfadiazine the lowest solubility in most solvent blends used. The solubility parameter of the sulfonamides was experimentally determined from thermodynamic and solubility data.

Hildebrand's solubility concept appears to be a useful tool for predicting drug solubility where the solubility parameters of drug and solvent system are close to each other.

Finally, an attempt was made to correlate the solubility parameter with the dielectric constant. The results were found to be linear with respect to all solvent blends employed.

REFERENCES

(1) K. C. Kwan, "Solubility Considerations in Dosage Form Design," presented to the APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, November 1968.

(2) J. H. Hildebrand and R. L. Scott, "The Solubility of Nonelectrolytes," 3rd ed., Dover Publications, New York, N. Y., 1964, p. 150.

(3) M. J. Chertkoff and A. N. Martin, *J. Amer. Pharm. Ass., Sci. Ed.*, **49,** 444(1960).

(4) F. A. Restaino and A. N. Martin, *J. Pharm. Sci.*, **53,** 636(1964).

(5) W. G. Gorman and G. D. Hall, *ibid.*, **53,** 1017(1964).

(6) W. E. Moore, *J. Amer. Pharm. Ass., Sci. Ed.*, **47,** 855(1958).

(7) R. J. Mesley and E. E. Houghton, *J. Pharm. Pharmacol.*, **19,** 300(1967).

(8) H. Miyazaki, *Japan J. Pharm. Chem.*, **19,** 133(1947); through *Chem. Abstr.*, **45,** 355h(1951).

(9) A. Smith and A. W. C. Menzies, *J. Amer. Chem. Soc.*, **32,** 1415(1910).

(10) *Ibid.*, **32,** 899(1910).

(11) D. P. Shoemaker and C. W. Garland, "Experiments in Physical Chemistry," 2nd ed., McGraw-Hill, New York, N. Y., 1967, p. 165.

(12) J. H. Hildebrand and R. L. Schott, "The Solubility of Nonelectrolytes," 3rd ed., Dover Publications, New York, N. Y., 1964, p. 425.

(13) F. Daniels and R. A. Alberty, "Physical Chemistry," 3rd ed., Wiley, New York, N. Y., 1967, p. 129.

(14) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., p. 408.

(15) H. Burrell, "Solubility Parameter," *Interchem. Rev.*, **14,** 13 (Spring 1955).

(16) D. O. Kirkland, "Parameter of Solubility," Humble Oil and Refining Co. Bulletin, 1968, p. 15.

(17) D. J. David, *J. Anal. Chem.*, **36,** 2164(1964).

(18) C. D. Hodgman, "Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland, Ohio, 1955.

(19) J. K. Guillory, *J. Pharm. Sci.*, **56,** 72(1967).

(20) A. E. O. Marzys, *Analyst*, **86,** 460(1961).

(21) "The Merck Index," 8th ed., G. P. Specher, M. Windholz, D. S. Leahy, D. M. Bolton, and L. G. Eaton, Eds., Merck & Co., Inc., Rahway, N. J., 1968, p. 996.

(22) I. M. Klotz, "Chemical Thermodynamics," W. A. Benjamin, New York, N. Y., 1964, p. 268.

(23) A. N. Martin, J. Swarbrick, and A. Cammarata, "Physical Pharmacy," 2nd ed., Lea & Febiger, Philadelphia, Pa., 1969, p. 487.

(24) R. C. Weast, "Handbook of Chemistry and Physics," 48th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1967–1968, p. E-57.

(25) G. R. Leader and J. F. Gormley, *J. Amer. Chem. Soc.*, **73,** 5731(1951).

(26) L. Meites, "Handbook of Analytical Chemistry," 1st ed., McGraw-Hill, New York, N. Y., 1963, pp. 1–48.

(27) W. J. Smothers and Y. Chiang, "Handbook of Differential Thermal Analysis," Chemical Publishing Co., New York, N. Y., 1966, p. 124.

(28) A. N. Paruta, B. J. Sciarrone, and N. G. Lordi, *J. Pharm. Sci.*, **51,** 704(1962).

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