

Extended Solubility Approach: Solubility Parameters for Crystalline Solid Compounds

ALFRED MARTIN *^x and JENS CARSTENSEN †

Received February 22, 1980, from the *Drug Dynamics Institute, College of Pharmacy, University of Texas, Austin, TX 78712, and the †School of Pharmacy, University of Wisconsin, Madison, WI 53706. Accepted for publication July 16, 1980.

Abstract □ A method is suggested to obtain solubility parameters for crystalline solid compounds, involving a quadratic equation based on the original Scatchard-Hildebrand solubility expression. The geometric mean, $\delta_1\delta_2$, of the Hildebrand approach is replaced by $w_{12} = K\delta_1\delta_2$, and $\log \alpha_2/(V_2\phi_1^2/2.3RT)$ is regressed against δ_1 in a second-degree power series for parabens and benzoic acid in a series of normal alcohols. The method provides reasonable solubility parameters for the solid solutes and affords a convenient calculation of the solubility of drugs in a homologous series of solvents.

Keyphrases □ Solubility parameters—calculation for crystalline solids □ Parabens—calculation of solubility parameters in normal alkanols □ Solids, crystalline—calculation of solubility parameters

Solution theory (1) begins with the well-known relation:

$$-\log X_2 = -\log X_2^i + \log \alpha_2 \quad (\text{Eq. 1})$$

where X_2 is the solute mole fraction solubility, X_2^i is the ideal solubility of the solid, and α_2 is the solute activity coefficient. According to regular solution theory as formulated by Hildebrand and Scott (1) and Scatchard (2), the logarithm of the activity coefficient is written as:

$$\log \frac{\alpha_2^s}{X_2} = \log \alpha_2 = \frac{V_2\phi_1^2}{2.303RT} (w_1 + w_2 - 2w_{12}) \quad (\text{Eq. 2})$$

where α_2^s is the activity of the solid solute referenced to the pure supercooled liquid and equals X_2^i for an ideal solution, V_2 is the molar volume of the solute (subscript 2), ϕ_1 is the volume fraction of the solvent (subscript 1), R is the molar gas constant, T is the absolute temperature at which the study is conducted, w_1 and w_2 are the cohesive energy densities of the solvent and solute, and w_{12} is the adhesion energy density of the solute-solvent pair. The square roots of the energy densities are known as solubility parameters, δ_i , and may be obtained from the energy or heat of vaporization per cubic centimeter:

$$\delta_i^2 = w_i = \frac{\Delta E^v}{V_i} = \frac{\Delta H^v - RT}{V_i} \quad (\text{Eq. 3})$$

In regular solution theory, it is assumed that the solute-solvent interaction energy, w_{12} , may be expressed as the geometric mean of the solvent, w_1 , and the solute, w_2 :

$$w_{12} = (w_1w_2)^{1/2} = \delta_1\delta_2 \quad (\text{Eq. 4})$$

Substitution of the geometric mean into Eq. 2 yields the logarithmic activity coefficient of the Hildebrand-Scatchard solubility equation:

$$\log \alpha_2 = A(\delta_1^2 + \delta_2^2 - 2\delta_1\delta_2) = A(\delta_1 - \delta_2)^2 \quad (\text{Eq. 5})$$

where A equals $V_2\phi_1^2/(2.303RT)$.

THEORETICAL

Solubility parameters of crystalline compounds usually have been obtained from solubility measurements. Equation 2 shows that when the drug is dissolved in a solvent of the same δ value, *i.e.*, when $w_1 = w_2$, the right-hand term of Eq. 2 approaches (but does not ordinarily equal) zero.

Table I—Heats of Fusion of the Parabens

Compound	Melting Point	Apparent ΔH_m (Ref. 4)	ΔH_m^f ^a
Methylparaben	399.7 °K	4352	5400
Ethylparaben	389.7 °K	4243	6100
Propylparaben	369.7 °K	4026	6250
Butylparaben	343.2 °K	3737	6410

^a Values obtained from the United States Pharmacopeial Laboratories.

Then:

$$\log X_2 = \log \alpha_2^s = \log X_2^i \quad (\text{Eq. 6})$$

signifying that the drug is dissolved to form a nearly ideal solution, one in which maximum solubility is obtained, barring solvation effects. When a pure solvent or solvent mixture is found that yields a nearly ideal solution, characterized by a peak in the solubility profile (plot of X_2 versus δ_1), it can be assumed that the solute solubility parameter, δ_2 , is equal to the solubility parameter of the solvent system.

This peak solubility approach to finding δ_2 values for drugs and other crystalline compounds has been used in several investigations (3-5). A similar procedure, involving the observation of maximum swelling, is used in the plastics industry to obtain solubility parameters of polymers. The method has its shortcomings, particularly when a sharp, single maximum value is not observed in the solubility curve. Additional methods for obtaining δ_2 values of solids therefore would be of considerable value, not only for predicting solubilities but also in dosage form design, bioavailability studies, and studies designed to investigate pharmaceutical solutions on a theoretical basis.

Modification of the activity term of Eq. 5 provides another approach for calculating δ_2 values for crystalline compounds. In solutions ordinarily of interest to the pharmaceutical scientist, semipolar drugs are dissolved in nonpolar and polar solvents, and the geometric mean seldom can be assumed to apply. However, w_{12} and $\delta_1\delta_2$ may be related by introducing a proportionality constant, K (6):

$$w_{12} = K\delta_1\delta_2 \quad (\text{Eq. 7})$$

Equation 5 then becomes:

$$\log \alpha_2 = A(\delta_1^2 + \delta_2^2 - 2K\delta_1\delta_2) \quad (\text{Eq. 8})$$

Rearrangement of Eq. 8 yields:

$$\frac{\log \alpha_2}{A} = \delta_2^2 - (2K\delta_2)\delta_1 + \delta_1^2 \quad (\text{Eq. 9})$$

which suggests a power series of $\log \alpha_2/A$ in δ_1 (7-9)¹.

If a solid drug such as benzoic acid is dissolved in a number of solvents of a particular class, such as the normal alcohols, it should be possible to regress the experimentally obtained quantity, $\log (\alpha_2^s/X_2)/A = (\log \alpha_2)/A$, against δ_1 in a second-degree power series:

$$(\log \alpha_2)/A = B + C\delta_1 + D\delta_1^2 \quad (\text{Eq. 10})$$

By this procedure, one may obtain the solubility parameter δ_2 of crystalline compounds such as drugs, excipients, and biochemicals found in polar pharmaceutical solutions.

RESULTS AND DISCUSSION

It is assumed that $\log \alpha_2$ is known from experimental solubility mea-

¹ See G. Cavé, R. Kothari, F. Puisieux, A. Martin, and J. T. Carstensen, *Int. J. Pharm.*, 5, 267 (1980).

Table II—Coefficients of the Quadratic Equation for (Log α_2)/A Regressed on Solubility Parameters of Parabens and Benzoic Acid in *n*-Alkanols^a at 25°

Compound	Data from Ref. 4			Data from Ref. 10			Combination of Refs. 4 and 10		
	B_1	C_1	D_1	B_2	C_2	D_2	B_3	C_3	D_3
Methylparaben	186.411994	-33.477824	1.495773	70.477644	-11.539949	0.466753	63.444455	-10.524791	0.430560
Ethylparaben	143.159953	-25.763854	1.134002	75.774512	-12.834344	0.520475	70.173648	-12.018541	0.491099
Propylparaben	78.085942	-14.104458	0.618690	39.692531	-6.805210	0.276630	39.192279	-6.809410	0.279553
Butylparaben	49.701722	-8.027767	0.285181	67.542467	-10.479523	0.363866	61.081553	-9.519539	0.328528
Benzoic acid	449.521048	-79.852095	3.546044	—	—	—	—	—	—

^a The compounds were studied in methanol, ethanol, propanol, butanol, hexanol, octanol, and decanol.

Table III—Solute Solubility Parameter and *K* Value Obtained from Quadratic Equation of Table II and Eqs. 13 and 14

Compound	Data from Ref. 4		Data from Ref. 10		Combined Results from Refs. 4 and 10	
	δ_2	<i>K</i>	δ_2	<i>K</i>	δ_2	<i>K</i>
Methylparaben	11.16	1.00244	12.29	1.00602	12.14	1.00686
Ethylparaben	11.24	1.01103	12.07	1.02184	11.95	1.02365
Propylparaben	11.23	1.01462	11.98	1.02685	11.84	1.02860
Butylparaben	13.20	1.06615	13.62	1.05694	13.64	1.06254
Benzoic acid	11.26	1.00002	—	—	—	—

surements, together with an estimate of X_2^i , which usually is obtained by measuring the heat of fusion and the melting point of the compound by differential scanning calorimetry (8, 10) or differential thermal analysis (11). The values of *A*, V_1 , V_2 , and δ_1 also are assumed to be known. Restaino and Martin (4) determined the heats of fusion for the *p*-hydroxybenzoic acid esters relative to the heat of fusion of benzoic acid, and Alexander *et al.* (10) used these results in a later study. However, basing the heats of fusion on the literature value of benzoic acid was incorrect².

The laboratories of the United States Pharmacopeial Convention supply reference standards for the parabens and have performed differential scanning calorimetry tests on these esters. The heats of fusion and melting points for the parabens are found in Table I³. These values were used in the present study to calculate ideal solubility for methyl-, ethyl-, propyl-, and butylparabens by employing the following equations (8):

$$\Delta H_m^f/T_m = \Delta S_m^f \quad (\text{Eq. 11})$$

$$\log X_2^i = \frac{\Delta S_m^f}{R} \log \frac{T}{T_m} \quad (\text{Eq. 12})$$

where ΔH_m^f and ΔS_m^f are the heat and entropy of fusion at the melting point, respectively; *R* is the ideal gas constant; and *T* and T_m are the temperature of the experiment and the melting temperature of the compound in degrees Kelvin, respectively.

In two studies (4, 10), the mole fraction solubility of a series of parabens was determined in normal alcohols at 25 °C. Restaino and Martin (4) began the solvent series with propanol, while Alexander *et al.* (10) started with methanol and ethanol. These investigators omitted pentanol and added decanol. Because of the different choice of solvents in the two studies, different regression equations would be expected. The two sets of data yielded quadratic equations, the coefficients of which are shown in Table II for methyl-, ethyl-, propyl-, and butylparabens. The solute solubility parameter, δ_2 , and the proportionality constant, *K*, are calculated as follows. The coefficients of the quadratic expressions of Table II correspond to the terms *B*, *C*, and *D* in Eq. 10. Referring to Eq. 9, it is observed that *B/D* corresponds to δ_2^2 and that *C/D* corresponds to $-2K\delta_2$. Therefore:

$$B/D = \delta_2^2 \quad (\text{Eq. 13})$$

$$-\frac{C/D}{2\delta_2} = K \quad (\text{Eq. 14})$$

The solute solubility parameter is calculated using Eq. 13 with the values of *B* and *D* found in Table II. The δ_2 value then is combined with the coefficients *C* and *D* of Eq. 14 to obtain *K*. The values of δ_2 (Table III) correspond well (except in the case of butylparaben) with those obtained

by the maximum solubility method (4). In the peak solubility method, methylparaben, ethylparaben, propylparaben, and benzoic acid had solubility parameters of 11–11.5; butylparaben exhibited a more diffuse maximum solubility, with a δ_2 of ~11–12.

The solubilities given by Restaino and Martin (4) differ by ~10% from those of Alexander *et al.* (10), and such differences must be accepted in solubility work when results are obtained in different laboratories. To investigate a larger series of solvents, the separate results of the two studies were combined and a single regression equation was obtained for each solute of the paraben series. Using the regression coefficients of Table II, the δ_2 and *K* values from Refs. 4 and 10 and the combined calculations are recorded in Table III. The δ_2 values from the combined calculations are reasonable when compared with those obtained by using the solubility data of Ref. 4 or 10 independently and when checked against δ_2 values obtained by other methods. The values for butylparaben were somewhat larger than expected.

Figure 1 shows the solubility of methyl- and propylparabens in the *n*-alkanols. For methylparaben, the solubility of which is plotted against δ_2 for the eight normal alcohols, the resulting δ_2 values from Refs. 4 and 10 are not in complete agreement. The peak solubilities from Ref. 4 result in a solubility parameter for methylparaben of 11.16, which falls between

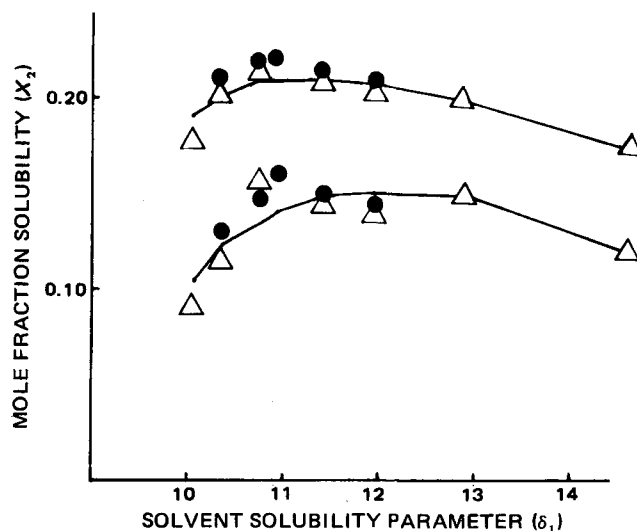


Figure 1—Mole fraction solubility of methylparaben (lower curve) and propylparaben (upper curve) in *n*-alkanols ranging from decanol ($\delta_2 = 10$) to methanol ($\delta_2 = 14.5$). Key: ●, solubility data from Ref. 4; Δ, solubility data from Ref. 10; and —, calculated solubility line using the appropriate combined quadratic equation (Table II) and Eq. 16. The lines were obtained by connecting points of back-calculated solubilities at each solvent δ value.

² A. Beerbower, Industrial Consultant, San Diego, Calif., Mar. 1980, personal communication.

³ Provided by L. T. Grady and S. Sun, United States Pharmacopeial Convention, Rockville, Md.

that of pentanol (10.9) and butanol (11.4), where maximum solubility is observed. Alexander *et al.* (10) omitted pentanol and included ethanol and methanol. Figure 1 shows that this choice of solvents shifted the peak of the combined back-calculation curve of Refs. 4 and 10 to the right, yielding a maximum solubility at a δ_1 value of ~ 12 . Accordingly, a regression of $\log \alpha_2/A$ versus δ_1 employing the data of Ref. 10 yields a δ_2 value of 12.29 from methylparaben, and the combined regression equation gives $\delta_2 = 12.14$.

The combined results of Tables II and III appear to follow the values of Alexander *et al.* (10) for δ_2 for the various parabens and correspond to the K values relative to the data of Alexander *et al.* (10) more closely than the results of Restaino and Martin (4). For the present, one would choose the combined regression equation to obtain reasonable solubilities of the parabens in normal alcohols. However, the most satisfactory approach would be repetition of the study, including all of the solvents of Restaino and Martin (4) and Alexander *et al.* (10) so that the solubilities determined by the two groups of investigators, employing different solvent series, would not bias the results. Figure 1 also shows the solubilities of propylparaben in the series of n -alkanols together with the back-calculated curve. In this case, similar δ_2 values (Table III) were obtained from Restaino and Martin (4), Alexander *et al.* (10), and the combined results of the two groups.

As shown in Table III, the K value for benzoic acid in the series of normal alcohols is unity. This finding indicates that $w_{12} = \delta_1\delta_2$; therefore, use of the Hildebrand-Scatchard equation, involving a geometric mean, should provide reasonable solubility values for benzoic acid in the n -alkanols.

The present method alters the activity coefficient term of the solubility equation (Eq. 2) in the following ways. In modifying the regression equation to make it correspond to the quadratic form of Eq. 9, the terms involving solubility parameters were divided by D , the coefficient associated with δ_1^2 . This process may be considered as a normalization procedure, utilized to provide coefficients of unity for δ_1^2 and δ_2^2 . Since the right side of Eq. 10 is divided by D , the left side must be treated in the same way:

$$\frac{(\log \alpha_2)/A}{D} = \frac{B}{D} + \frac{C}{D} \delta_1 + \frac{D}{D} \delta_1^2 \quad (\text{Eq. 15})$$

The complete solubility equation (Eqs. 1 and 2) then becomes:

$$-\log X_2 = -\log X_2^i + DA(\delta_1^2 + \delta_2^2 - 2K\delta_1\delta_2) \quad (\text{Eq. 16})$$

Multiplication of A by D in Eq. 16 may be considered to yield an empirical coefficient, A' , associated with the solubility parameter term of Eq. 16. The case of ethylparaben dissolved in n -propanol (4, 10) is taken to illustrate the calculations involved. Employing the combined quadratic expression of Table II:

$$\delta_2^2 = \frac{B}{D} = 142.891 \quad (\text{Eq. 17})$$

$$\delta_2 = 11.95 \quad (\text{Eq. 18})$$

$$K = -\frac{C/D}{2\delta_2} = 1.02365 \quad (\text{Eq. 19})$$

These values of δ_2 and K are found in Table III. With $-\log X_2^i = 0.91589$, $\delta_1 = 11.9$ from Ref. 4, D from Table II = 0.491099, $A = V_2\phi_1^2/2.303RT = 0.053570$, and $A' = (0.491099)(0.053570) = 0.026308$, one writes:

$$-\log X_2 = 0.91589 + 0.026308[(11.95)^2 + (11.9)^2 - 2(1.02365)(11.95)(11.9)] \quad (\text{Eq. 20})$$

$$-\log X_2 = 0.73902 \quad (\text{Eq. 21})$$

with $X_2(\text{calc}) = 0.182$ and $X_2(\text{obs}) = 0.171$ (4) and 0.176 (10).

The calculated values for the solubility using δ_2 , K , and A' are within 5–25% of the observed solubility. The method was tested with polar drugs, such as the methyl xanthenes, in different mixtures of polar solvents, and the results were less satisfactory; δ_2 values sometimes are obtained that do not correspond well with values obtained from the peak solubility method⁴.

In an earlier study¹, a somewhat different regression method was employed using the results of Restaino and Martin (4) to obtain estimates of δ_2 and the molar volume of the solute, V_2 . Satisfactory δ_2 values were calculated, but the method failed to produce reasonable V_2 values. This result may have been due to the creation, through regression methodology, of an empirical A' term, as noted, which involves the molar volume of the solute.

CONCLUSION

The present approach provides a convenient means of obtaining solubility parameters and K values from solubility data for parabens in normal alkanols. It yields a normalization parameter, D , which provides unit coefficients for δ_1^2 and δ_2^2 , and D is multiplied by the A term of the solubility equation ($AD = A'$) to yield the correct value of $\log \alpha_2$. The $\log \alpha_2$ calculated in this way, together with the ideal solubility of a drug, provides good estimates of the solubility of paraben derivatives in a series of normal alcohols. In studies to be reported later, the method gave satisfactory results for drugs in hydrocarbons and less acceptable values in binary mixtures of polar solvents.

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⁴ A. Martin, unpublished results.