DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(7), 1135-1151 (1990)

RELATIONSHIP BETWEEN THE SOLUBILITY PARAMETER AND THE SURFACE FREE ENERGY OF SOME SOLIDS

Magda W. Samaha[1] and V.F. Naggar[2]

Department of Industrial Pharmacy[1]
&
Department of Pharmaceutics[2],
Faculty of Pharmacy,
University of Alexandria,
Alexandria, Egypt.

ABSTRACT

Solubility parameters for a number of drugs and related organic solids were determined from their dispersion and polar surface free energy data by means of an equation found to be valid for solvents. The relation fits quite well all solids investigated with an excellent correlation coefficient. The calculated solubility parameters, δ_o , were checked with the ones estimated from molecular groups and fragment constants according to Fedors method, δ_F . A similar δ_o of 14.6 was obtained for o-hydroxybenzoic and p-hydroxybenzoic acids. The deviations from δ_F shown in ethyl-p-aminobenzoate, benzoic acid, and aspirin were attributed to the imperfection of their vapor.

The solubility profile of hydrocortisone acetate was obtained in dioxane-water mixtures, and the solubility parameter of the drug was determined from the peak solubility in this binary solvent system. The experimental results for some drugs were compared with their solubility parameters calculated from the surface free energy data. Excellent agreement was found for hydrocortisone acetate, whereas griseofulvin and p-hydroxybenzoic agreed fairly. The " chameleonic " behavior of benzoic acid results in different experimental solubility parameter, and the percentage deviation from δ_o ranged from 3.4-20.8. A deviation of 11.8% was obtained for ethyl-p-aminobenzoate and was attributed to the influence of its crystal structure which would account for its low δ_E value measured. The relation suggested was also applied to the dicarboxylic acids. The odd-even alteration seen in their melting points is not reflected on their solubility parameters. The high δ_o calculated for these acids were related to their elongated shape.

INTRODUCTION

The solubility parameter concept is the subject of many current research works (1-6). It has proved useful in a great variety of pharmaceutical applications. However, the determination of solubility parameters of many substances from the equilibrium data is still a difficult process. This difficulty resulted from the restrictions of regular solution theory, while in real solutions forces other than dispersion forces play an important role due to the presence of polar groups and, exceptionally, $-CH_2-$ chains also. The inconstancy of the solubility parameter (δ) of small drug molecules in mixed polar solvents has been reported by Martin et al (7). In a previous study (8) on the effect of binary solvent composition on the solubility parameter determination of nalidixic and salicylic acids, the " chameleonic " effect resulted in different solubility parameters for salicylic acid ranging from 14.04 to 15.67 $cal^{1/2}cm^{-3/2}$ depending on the specific cosolvent-water system used. Hoy (9) was the first to introduce the concept of " chameleonic " materials which adopt the character of the surrounding environment. Some suggestions for dealing with the chameleon-like behavior associated with solute-solvent interaction were presented by Martin et al (10).

The important role played by the nature of solid surfaces in a variety of pharmaceutical processes has been now well documented (11-13). The contact angle is established as a true thermodynamic quantity. Accordingly, measurement of contact angles exhibited by liquids on solid surfaces has been succesfully used to estimate the surface free energy per cm^2 for a number of solids (14). It has also been applied to calculate the average surface free energy for many polymers (15,16). The contact angles for a series of pharmaceutical powders were presented by Lerk et al (17). Other methods for estimation of the surface energy of solids were reviewed by Linford (18).

A relationship between solubility parameter and surface free energy was presented earlier by Hildebrand and Scott (19) as a simple quadratic equation. In spite of the fact that a theoretical justification for the constant in the equation was not supplied, a dimensionally unbalanced equation was then set up and widely used, with misleading results. Following the Hildebrand's empirical relationship and the idealized theoretical treatment of Schonhorn (20), Beerbower (21) presented a correlation, on a three-dimensional solubility parameter basis, to compute the surface free energy for most organic liquids, molten salts, and liquid metals. Correlations of solvent solubility parameters with molar attraction constants, surface tension, dipole moment, and index of refraction have been explored, and a relation between the dispersion contribution to the surface energy of polymers and their dispersion solubility parameters has also been presented (22).

The purpose of this work is to investigate the possibility of using surface free energy data, which takes into consideration the contributions of polar and non polar forces, to estimate the solubility parameter of some drugs and related organic solids from relation found to be valid for solvents.

EXPERIMENTAL

MATERIALS

Hydrocortisone acetate was obtained from (Upjohn Co., Kalamazoo, Michigan, USA). Dioxane was obtained from (El-Nasr Pharmaceuticals Chemicals Co., Cairo, Egypt).

METHODS

Solubility Determination

The solubility of hydrocortisone acetate was determined in mixed solvents consisting of dioxane ($\delta_{1d} = 10.01$) and water ($\delta_{1w} = 23.45$). Different concentrations ranging from 0-100% (V/V) of dioxane in distilled water were prepared. Excess solute was introduced into screw-capped vials containing 10ml of the dioxane-water mixture. The vials were agitated for 72 h in a shaker bath maintained at $30^o \pm 0.1$. After equilibrium was attained, the samples were filtered and aliquots were diluted appropriately with distilled water depending upon the quantity of solute in solutions. The solutions were analyzed spectrophotometrically at 245 nm (no interference from dioxane occurred after dilution). All experiments were run in triplicate and average values were calculated. Reference absorptivity constants were determined in a solution containing 10% ethanol and 90% water (V/V).

Solubility Parameter of Binary Solvents

The solubility parameter, δ_1, for a mixture of dioxane, d, and water, w, is calculated using the expression (2):

$$\delta_1 = \frac{\phi_d \ \delta_w \ + \ \phi_w \ \delta_d}{\phi_d \ + \ \phi_w} \qquad \text{Eq. 1}$$

Where δ_1 is the solubility parameter of the binary solvent mixtures, and is averaged in terms of volume fractions of dioxane, ϕ_d, and water, ϕ_w.

Solubility Parameter and Molar Volume of Solids

Since the energy of vaporization and the molar volume are additive on functional group bases, the molar volume, V_m, and the

solubility parameter, δ_F, for solids were computed using Fedors method (23). The solubility parameters of solids, δ_o, were also calculated from the surface free energy data.
For hydrocortisone acetate, the solubility parameter was obtained experimentally at the peak solubility where the δ_1 value of the binary solvent used should equal δ_E as required by the Hildebrand-Scatchard equation (2).

Surface Free Energy Data

The experimental surface free energies for the compounds under investigation were taken from Zografi and Tam (14), who used the contact angle measurements to estimate the solid surface free energy (γ_o) based on the assumption that no highly specific interaction and orientation of molecules occur at the solid-liquid interfaces.

THEORETICAL CONSIDERATIONS

The energy of vaporization, ΔE_v, per unit volume was defined by Hildebrand and Scott (19) as the cohesive energy density, C.E.D., and its square root as the solubility parameter, δ.

$$\delta = (\text{C.E.D.})^{1/2} = \left(\frac{\Delta E_v}{V_m}\right)^{1/2} = \left(\frac{\Delta H_v - RT}{V_m}\right)^{1/2} \qquad \text{Eq. 2}$$

Where V_m is the molar volume, and ΔH_v is the heat of vaporization. The surface free energy, γ, was then related to the energy of vaporization by :

$$\gamma = k\,(\Delta H_v - RT)^{2/3}\; N^{1/3} \qquad \text{Eq. 3}$$

Where N is Avogadro's number, and k is a constant. However, the numerical evaluation produced an arbitrary value of k, and an exponent of γ equaling 0.86, which breakdown the dimensional balance.

Using a Lennard-Jones potential for the molecular interactions, the following derivation was deduced (22):

$$\gamma = \left(1 - \frac{n_s}{n}\right) \frac{\epsilon}{A} \qquad \text{Eq. 4}$$

Where γ is the surface tension, n_s and n are the coordination numbers in the surface layer and in the bulk phase, respectively. A is the cross-sectional area per molecule, and ϵ is the minimum potential in L-J potential curve. Based on the assumption that the molecules are spherical, i.e., $A = V_m^{2/3}$, and ΔE_v is proportional to ϵ, Equation 4 may thus be written as :

$$\text{C.E.D.} = \delta^2 = K \left(\frac{1}{V_m}\right)^{1/3} \gamma \qquad \text{Eq. 5}$$

In which K is a constant. Eq. 5 has been derived using other approaches than the spherical symmetric type of potential around a molecule (19,21). Beerbower (21) was able to relate the surface free energies of most organic liquids, fused salts, and liquid metals to their energies of vaporization, using the Hansen parameters for London force (δ_D), polar (δ_p), and hydrogen bonding (δ_H) energies

$$\gamma = 0.0715 \; V_m^{1/3} \left(\delta_D^2 + 0.632 \left(\delta_p^2 + \delta_H^2\right)\right) \qquad \text{Eq. 6}$$

From the least-squares analysis of solvent data, the following relation was also found (22) :

$$\delta_D^2 + \delta_p^2 = 13.8 \left(\frac{1}{V_m}\right)^{1/3} \gamma \qquad \text{Eq. 7}$$

The reason for the absence of δ_H in Eq. 7 is due to the fact that the interactions responsible for liquid-vapor interfacial energy do not involve the breaking of hydrogen bonds (22).

The simplest of all equations used (21,24) to relate the surface free energy of most substances to the energy of vaporization is :

$$\gamma_o = 0.0715 \; V_m^{1/3} \; \delta_o^2 \qquad \text{Eq. 8}$$

and

$$\delta_o = (\gamma_o / 0.0715 \, V_m^{1/3})^{1/2} \qquad \text{Eq. 9}$$

Where the value of 0.0715 is a constant derived from the number of nearest neighbors lost in surface formation, assuming that the molecules tend to occupy, on the average, the corners of regular octahedra (21).

RESULTS AND DISCUSSION

In this study, equation 9 was adopted for estimating the solubility parameters, δ_o, of the solids listed in Table 1, from dispersion and polar surface free energies measurements. The relation fits quite well all substances with a correlation coefficient of 0.9997 (Fig. 1).
The per cent deviations of δ_o, from the predicted values, δ_F, calculated from molecular groups and fragment constants using Fedors approach are illustrated in the last column of Table 1. The greater deviation occurred with ethyl-p-aminobenzoate (20.9%), where a δ_o value of 13.47 was obtained in correspondence to a δ_F value of 11.14, followed by benzoic acid (14.7%), then aspirin (11.6%). This anomaly is probably associated with their energy of vaporization, ΔE_v. Because of the imperfection of the vapor of these substances, a lower ΔE_v than is needed to account for the high surface free energy resulted (21).

The solubility parameters, δ_o, obtained from the surface free energy data for p-hydroxybenzoic and o-hydroxybenzoic acids were identical and in good agreement with their computed δ_F values (Table 1). The OH in the position para to the carboxylic group is able to donate electrons through the nucleus to the acid function creating a definite dipolar molecule. The o-hydroxybenzoic acid should produce a dipole moment as strong, if there are only resonant and inductive forces determining the electron shifts in the molecule (25). The structure of the ortho compound is such that the hydroxyl and the carbonyl oxygen of the acid group can interact

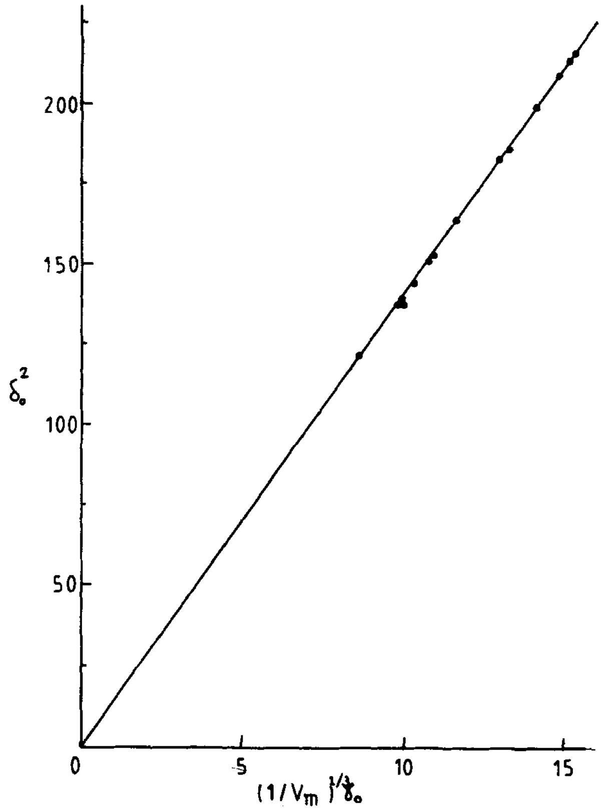

Figure 1. Relation between surface free energy and solubility parameter for solids.

through intramolecular hydrogen bonding. Whereas, the para isomer of hydroxybenzoic acid favors intermolecular hydrogen bond giving rise to a high degree of association. The polar contribution to the surface free energy, γ_p, for the ortho compound is equal to 26.2 in relation to a value of 27.7 obtained for para substituent (Table 1). However, the contribution of permanent dipoles to the cohesive energy density was represented empirically by the linear relationship (22) :

$$\delta_p = 9.5 \frac{\mu}{V_m^{1/2}} \qquad \text{Eq. 10}$$

Where δ_p is the solubility parameter due to dipole forces, and μ is the dipole moment.

TABLE 1

Computed Molar Volumes, Surface free Energy Terms in ergs cm^{-2}, and Solubility Parameters in $cal^{1/2}cm^{-3/2}$, for Various Solids at 25°

Solid	V_m^a	γ_d^b	γ_p^b	γ_o^b	δ_o^c	δ_F^d	% deviation
Hydrocortisone	258.9	45.1	23.6	68.7	12.30	12.38	0.65
Hydrocortisone acetate	266.3	46.9	16.5	63.4	11.75	11.63	1.02
Griseofulvin	374.0	45.5	16.7	62.2	10.99	10.41	5.57
Indomethacin	238.8	47.3	14.5	61.8	11.81	12.33	4.22
Aspirin	132.4	39.4	28.1	67.5	13.62	12.20	11.64
Ethinamate	104.1	43.3	27.6	70.0	14.44	13.79	4.71
Phenacetin	148.8	45.8	12.5	58.3	12.34	11.55	6.84
Benzoic acid	99.9	39.0	22.7	61.7	13.65	11.90	14.71
P-OH-benzoic acid	90.9	40.6	27.7	68.3	14.59	15.40	5.36
O-OH-benzoic acid	90.9	42.3	26.2	68.5	14.61	15.40	5.14
P-F-benzoic acid	98.9	36.0	19.1	54.1	12.80	12.41	3.14
P-Cl-benzoic acid	104.9	43.3	5.7	49.0	12.06	12.73	5.37
P-Br-benzoic acid	110.9	46.5	3.4	49.9	12.06	12.72	5.19
P-NH_2-benzoic acid	100.1	40.6	25.3	65.9	14.10	13.12	7.47
Ethyl-p-aminobenzoate	139.2	48.1	19.0	67.1	13.47	11.14	20.92

a) V_m, the molar volumes were calculated from the group contribution method of Fedors (23).

b) γ_d, γ_p, and γ_o ($\gamma_d + \gamma_p$) were taken from Zografi and Tam (14).

c) Solubility parameters, δ_o calculated according to Eq. 9.

d) Solubility parameters, δ_F calculated using Fedors method (23).

e) Per cent deviations were calculated from ($\delta_F - \delta_o / \delta_F$) x 100.

The available data for halides fit quite well into Eq. 9 with a 3-5% deviation from the Fedors solubility parameters, δ_F .

The experimentally determined solubilities of hydrocortisone acetate at 30° in pure water ($\delta_w = 23.45$), pure dioxane ($\delta_d = 10.01$), and in the binary solutions composed of these solvents are found in Table 2. The water solubility of the steroid was 0.0125 mg/ml at 30°, which is in a good agreement with the previously determined value of 0.01 mg/ml at 25° (26).
The solubility curve for hydrocortisone acetate in dioxane-water system is illustrated in Fig. 2. The curve has been normalized by subtracting the log aqueous solubility, log S_w , from the log composite-solvent solubility, log S_f . This normalization does not in any way alter the shape of the curve (8). A maximum solubility was obtained at a δ_1 value of 11.6 corresponding to 88% dioxane in water mixture. Since the solubility measurements are not spaced closely enough in the solvent composition, more precise result may be obtained by drawing two intersecting straight lines tangent to the curved line passing through the points (Fig. 2). This gives a δ_E value of 11.7 $cal^{1/2}cm^{-3/2}$ for hydrocortisone acetate.

A comparison between the experimentally determined solubility parameters, δ_E , and the ones calculated using surface free energy data, δ_o , for some pharmaceutical solids is presented in Table 3. For hydrocortisone acetate, the experimental solubility parameter determined in this study matched perfectely with δ_o , calculated from the dispersion and polar surface free energies according to Eq. 9. The estimated solubility parameter for p-hydroxybenzoic, δ_o , was in reasonably good agreement with the experimentally reported value (27), and deviates from it by 4.6%.
For griseofulvin, benzoic acid, and ethyl-p-aminobenzoate, the calculated solubility parameters, δ_o , were generally higher than the experimental ones. This can be attributed to the methylene iodide and water contact angle data used to determine the surface free energy γ_o . It has been noted that (14) the total surface free energy values obtained with methylene iodide and water are higher than those obtained with the various semi polar liquids.
The δ_E values of benzoic acid range from 13.2 in the highly polar

TABLE 2

Solubility of Hydrocortisone Acetate in Dioxane-Water Mixtures at 30°

Dioxane %	δ_1	Solubility (mg/ml)	S_f/S_w [a]
0	23.45	12.5×10^{-3}	-
20	20.76	10.8×10^{-2}	8.64×10^{0}
40	18.07	59.3×10^{-2}	4.74×10^{1}
60	15.39	36.0×10^{-1}	2.88×10^{2}
80	12.70	16.5×10^{0}	1.32×10^{3}
85	12.03	23.0×10^{0}	1.84×10^{3}
88	11.62	34.4×10^{0}	2.75×10^{3}
90	11.35	25.8×10^{0}	2.06×10^{3}
95	10.68	26.8×10^{0}	2.14×10^{3}
100	10.01	22.1×10^{0}	1.77×10^{3}

a) S_f is the composite-solvent solubility, and S_w is the aqueous solubility.

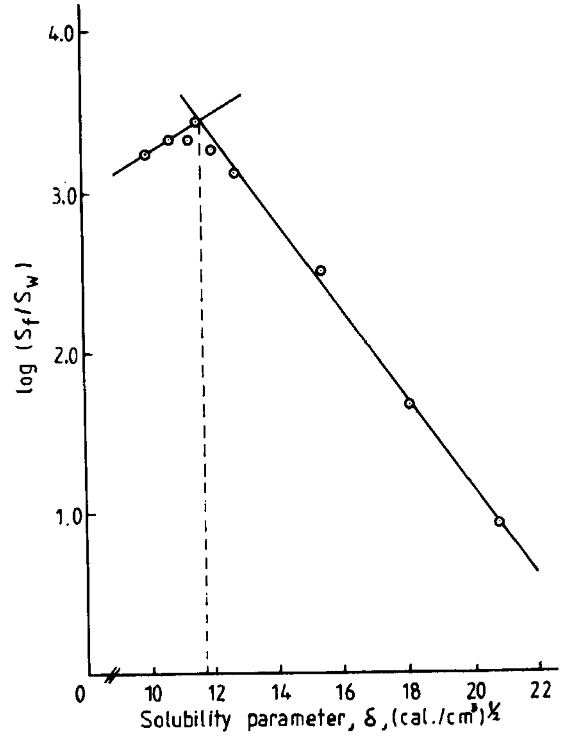

Figure 2. Solubility of hydrocortisone acetate in dioxane-water mixtures at 30°.

solvent mixtures to 11.3 in the less polar systems (10). Accordingly, the percentage deviation from δ_o was 3.4 to 20.8. The variability in benzoic acid δ_E , resulting from its " chameleonic " behavior was explained as a reflection of a deviation from the geometric mean assumption of regular solution theory (10). Suggestions for dealing with the chameleonic effect associated with benzoic acid-solvent interaction were also presented (10).

The " loading group " present in ethyl-p-aminobenzoate, viz., the aromatic ring and the polar moiety is a property determining for its crystal structure (28). X-ray diffraction patterns obtained for alkyl-p-aminobenzoates revealed the influences of the crystal structure. The angle of least diffraction was related to the longest d spacing of the crystal, this latter is defined as the distance between adjacent molecular planes of the unit cell. Ethyl-p-

TABLE 3

Comparison of the Experimental and Calculated Values for the Solubility Parameter, δ_E , and δ_o , of some Solids.

Solid	δ_E	δ_o	% deviation
Hydrocortisone acetate	11.70[a]	11.75	0.43
Griseofulvin	10.24[b]	10.99	7.32
benzoic acid	13.2-11.3[c]	13.65	3.4-20.8
P-OH-benzoic acid	15.30[d]	14.59	4.64
Ethyl-p-aminobenzoate	12.05[e]	13.47	11.76

a) This work.

b) Taken from reference 4.

c) Taken from reference 10.

d) Taken from reference 27.

e) Taken from reference 28.

TABLE 4

Computed Molar Volumes, Total Surface Free Energies in ergs cm^{-2}, and Solubility Parameters in $cal^{1/2}cm^{-3/2}$, for Some Dicarboxylic Acids at 25^{o}

Acids[a]	V_m	γ_o^b	δ_o^c	δ_F^d	% deviation
Pimelic (C_7)	137.5	75.0	14.27	11.79	21.03
Suberic (C_8)	153.6	78.1	14.29	11.49	24.36
Sebacic (C_{10})	185.8	58.4	11.97	11.04	8.40
Dodecanedioic (C_{12})	218.0	63.5	12.16	10.70	13.64
Thopsic (C_{16})	282.4	60.0	11.32	10.26	10.33

a) Acids structures are : $HOOC(CH_2)_nCOOH$, with n ranging from 5-14.

b) Total surface free energies, γ_o, taken from Zografi and Tam (14).

c) Solubility parameters, δ_o, calculated according to Eq. 9.

d) Solubility parameters, δ_F, calculated using Fedors method (23),

$$\delta_F = \left(\frac{\Sigma \Delta E_v}{\Sigma V_m}\right)^{1/2} .$$

aminobenzoate has a length that may not allow the ethyl group to be any farther from the amine group than the ester oxygen, such as in case of methyl-p-aminobenzoate (28). This structure would permit aromatic orbitals overlapping, and maximum dipole-dipole interactions between adjacent molecules, which would account for its low δ_E value determined (Table 3).

The method suggested in this study to determine the solubility parameter was then checked for a particular class of drugs, which is found difficult to handle, viz., the dicarboxylic acids. As can be seen in Table 4, the predicted δ_F decreases as the chain length increases; whereas the δ_o determined from surface free energy data exhibited a different trend. In general, higher δ_o values were obtained for these acids than their δ_F calculated ones, with a deviation ranging from 8.4% for sebacic acid (C_{10}) to 24.4% for suberic acid (C_8). The odd-even alteration seen in their melting points, which is characteristic of long-chain compounds, is not reflected on their solubility parameters. For instance, the melting point of pimelic acid (C_7) is 105.8°, and that of suberic acid (C_8) is 142.0°, whereas a similar δ_o value of 14.3 was obtained for both acids (Table 4). The high δ_o results obtained for the dicarboxylic acids investigated may be attributed to the increasing deviation from the octahedral geometry, applied in Equation 9, due to their elongated shape (21).

This approach is appealing to make use of the results of surface chemistry to calculate the solubility parameter for drugs and related solids.

REFERENCES

1. K.C. James, C.T. Ng, and P.R. Noyce, J. Pharm. Sci., 65, 657 (1976).

2. A. Martin, J. Newburger, and A. Adjei, J. Pharm. Sci., 69, 487 (1980).

3. A. Martin and J. Carstensen, J. Pharm. Sci., 70, 170 (1981).

4. D.J.W. Grant and I.K.A. Abougela, Int. J. Pharm., 17, 77 (1983).

5. H. Schott, J. Pharm. Sci., 73, 790 (1984).

6. P.L.Gould, M. Goodman, and P.A. Hanson, Int. J. Pharm., 19, 149 (1984).

7. A. Martin, A.N. Paruta, and A. Adjei, J. Pharm. Sci., 70, 1115 (1981).

8. M.A.F. Gadalla, G.M. Ghaly, and M.W. Samaha, under publication.

9. K. Hoy, J. Paint Technol., 42, 76 (1970).

10. A. Martin, P.L. Wu, Z. Liron, and S. Cohen, J. Pharm. Sci., 74, 638 (1985).

11. N.A. El-Gindy and M.W. Samaha, Int. J. Pharm., 13, 35 (1983).

12. E.N. Hiestand, J. Pharm. Sci., 55, 1325 (1966).

13. G. Zografi, Compilation of Symposium Papers, 5th National Meeting, APhA Academy of Pharmaceutical Sciences, 1968, p. 190.

14. G. Zografi and S.S. Tam, J. Pharm. Sci., 65, 1145 (1976).

15. W.A. Zisman, " Contact Angle, Wettability, and Adhesion ", Advances in Chemistry Series 43, American Chemical Society, 1964, p.1.

16. F.M. Fowkes, Ind. Eng. Chem., 56, 40 (1964).

17. C.F. Lerk, M. Lagas, J.P. Boelstra, and P. Broersma, J. Pharm. Sci., 66, 1480 (1977).

18. R.G. Linford, Chem. Soc. Rev., 1, 445 (1972).

19. J. Hildebrand and R. Scott, " Solubility of Non-Electrolytes ", 3rd ed., Reinhold Publishing Corp., New York, 1949.

20. H. Schonhorn, J. Chem. Phys., 43, 2041 (1965).

21. A. Beerbower, J. Coll. Interf. Sci., 35, 126 (1971).

22. D.M. Koenhen and C.A. Smolders, J. Appl. Polym. Sci., 19, 1163 (1975).

23. R.F. Fedors, Polym. Eng. Sci., 14, 147 (1974).

24. J. Panzer, J. Colloid Interfac. Sci., 44, 142 (1973).

25. S.M. Blaug and G.R. Arthur, J. Pharm. Sci., 54, 30 (1965).

26. P. Kabasakalian, E. Britt, and M.D. Yudis, J. Pharm. Sci., 55, 642 (1966).

27. P.L. Wu and A. Martin, J. Pharm. Sci., 72, 499 (1983).

28. S.H. Yalkowsky, G.L. Flynn, and T.G. Slunick, J. Pharm. Sci., 61, 852 (1972).