

Wettability of Pharmaceutical Solids: Estimates of Solid Surface Polarity

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Abstract □ Contact angle measurements of water and methylene iodide with various organic solids were used to estimate the surface free energy per square centimeter, γ_S , and the contributions of nonpolar and polar forces, γ_S^d and γ_S^p , respectively. The ratio of γ_S^p to γ_S was used as an estimate of solid surface polarity, and values ranging from 0 to 42% polarity were calculated for materials of pharmaceutical interest. Surface free energies per mole were calculated to compare the influence of different substituent groups on wettability. This approach offers a convenient means to quantitate the polarity of organic pharmaceutical solid surfaces.

Keyphrases □ Solids, pharmaceutical—wettability evaluated by measurement of surface free energy and contributions of polar and nonpolar forces, effect of substituent groups □ Wettability—pharmaceutical solids, evaluated by measurement of surface free energy and contributions of polar and nonpolar forces, effect of substituent groups □ Polarity, solid surface—quantitated by measurement of surface free energy and contributions of polar and nonpolar forces, effect of substituent groups

The nature of solid surfaces plays an important role in various pharmaceutical processes (1, 2). Such processes include crystal nucleation and growth, fracture mechanics, powder flow, powder dispersion in liquids, powder compaction, and the coating of solids. For situations where powder dispersion of drugs in water or water penetration into solid compacts is required, a lack of wetting due to unfavorable surface energetics leads to significant difficulty in disintegration and/or dissolution (3). Solid drugs exhibiting such behavior have been termed "hydrophobic," and the use of surfactants to overcome such problems is well established (3).

Some general questions one can ask at this point are:

1. How hydrophobic are the surfaces of various drugs and related solids?
2. What methodology can be used to measure hydrophobicity on a quantitative basis?
3. What factors contribute to the hydrophobic behavior?

Answers to such questions could be useful in any situation where solid surfaces are involved in interactions with other phases.

A rational approach to this problem involves determining the energy of molecules residing at the surface, as well as the contributions to surface energy from various forces, *e.g.*, dispersion forces or hydrogen bonding. For pure liquids, surface energies and entropies can be determined from surface tension measurement at various temperatures since their surface free energy per square centimeter is their surface tension (4).

Surface free energy per square centimeter can be determined for solids, but the problem is both theoretically and experimentally difficult due to the immobility of the molecules and to the heterogeneity of the surface caused by the presence of different crystal faces,

imperfections, impurities, and surface roughness (2, 5, 6). Approaches using spectroscopy, calorimetry, solubility, and vapor adsorption have been used to estimate an overall surface free energy per square centimeter or a distribution of energies. However, these techniques are generally more applicable to metals and inorganic compounds than to organic solids such as drugs (6) because of the temperatures and pressures to which solids must be subjected as well as the very high specific surface area generally required for accurate measurements.

Measurement of contact angles exhibited by liquids on solid surfaces has been used to estimate the average surface free energy per square centimeter for many polymers of relatively low surface energy, *i.e.*, polyethylene or nylon (7, 8). Despite many uncertainties when applied to more polar solids, this technique, when properly utilized and interpreted, allows some understanding of organic solid surface energetics in a relatively convenient manner. Consequently, the following report presents estimates of solid surface free energy from contact angle data for a number of drugs and related organic solids. Estimates of the contributions of polar and nonpolar forces to this term also are presented.

THEORETICAL

The basis for using contact angles to estimate surface free energies of solids rests on the relationships between solid surface free energy per square centimeter, γ_S , liquid surface free energy per square centimeter, γ_L , and their interfacial free energy per square centimeter, γ_{SL} , as developed in the Young equation (5, 7):

$$\gamma_S - \gamma_{SL} = \gamma_L \cos \theta + \pi_e \quad (\text{Eq. 1})$$

where θ is the contact angle, and π_e is the change in surface free energy per square centimeter due to any adsorption of vapor from the liquid to the solid surface:

$$\pi_e = \gamma_S - \gamma_{SV} \quad (\text{Eq. 2})$$

where γ_{SV} is the surface free energy per square centimeter of the solid after vapor adsorption.

For systems where wetting is poor and at room temperature, it is assumed the π_e is zero; for systems with a greater tendency for wetting, the possibility of vapor adsorption at room temperature is enhanced. The significance of this term recently was evaluated theoretically, and it was concluded the π_e is negligible for relatively nonpolar solids at room temperature when high boiling-point liquids are used (9). Consequently, a contribution from this term is considered to be negligible in the present case.

To obtain γ_S from Eq. 1, γ_L and θ can be measured, but no direct estimate of γ_{SL} can be made experimentally. The interfacial free energy between any two phases, γ_{12} , can be estimated by knowing the individual surface free energies, γ_1 and γ_2 , and the energies associated with the interactions taking place across the interface (8, 10). This relationship can be written in the general form (11):

$$\gamma_{12} = \gamma_1 + \gamma_2 - 2\phi^d - 2\phi^p \quad (\text{Eq. 3})$$

where ϕ^d and ϕ^p are terms reflecting nonpolar and polar interactions, respectively. The further assumption (8) that the surface free energy

Table I—Contact Angles and Surface Free Energy Terms for Various Liquids Using Paraffin at 25°

Liquid	γ_L , ergs/cm ²	Contact Angle	γ_L^d	γ_L^p
Water	72.0	109°	23.2	48.8
Glycerin	63.7	96°	32.0	31.7
Formamide	58.3	91°	32.3	26.0
Ethylene glycol	48.9	79°	33.4	15.5
1,3-Butanediol	39.1	62°	32.5	6.6
Methylene iodide	50.4	65°	50.4	0

of a solid or liquid contains contributions from polar and nonpolar forces gives:

$$\gamma_i = \gamma_i^d + \gamma_i^p \quad (\text{Eq. 4})$$

Although a number of forces can contribute to γ_i^d and γ_i^p , the methods used to determine these values give γ_i^d primarily due to London dispersion forces and γ_i^p due to all other forces, with hydrogen bonding predominating. To estimate ϕ^d and ϕ^p , Fowkes (8) suggested taking the geometric mean of the surface free energy components for each phase such that:

$$\phi^d = (\gamma_1^d \gamma_2^d)^{1/2} \quad (\text{Eq. 5})$$

$$\phi^p = (\gamma_1^p \gamma_2^p)^{1/2} \quad (\text{Eq. 6})$$

Wu (11) suggested using a reciprocal mean such that:

$$\phi^d = \frac{2\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} \quad (\text{Eq. 7})$$

and:

$$\phi^p = \frac{2\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} \quad (\text{Eq. 8})$$

Either pair of terms can then be used in Eq. 3 to give the expressions:

$$\gamma_{12} = \gamma_1 + \gamma_2 - 2(\gamma_1^d \gamma_2^d)^{1/2} - 2(\gamma_1^p \gamma_2^p)^{1/2} \quad (\text{Eq. 9})$$

$$\gamma_{12} = \gamma_1 + \gamma_2 - \frac{4\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} - \frac{4\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} \quad (\text{Eq. 10})$$

Calculations (11) of interfacial tension for a series of immiscible liquid polymers, using either Eq. 9 or 10, reveal good agreement with experimental values in both cases if one or both of the polymers are relatively nonpolar. However, Eq. 10 gives better agreement for systems containing two relatively polar polymers (11).

To measure γ_S^d and γ_S^p , Eqs. 1 and 9 were combined to give Eq. 11 (12), and Eqs. 1 and 10 were combined to give Eq. 12 (11). These equations are:

$$\gamma_L(1 + \cos \theta) = 2[(\gamma_L^d \gamma_S^d)^{1/2} + (\gamma_L^p \gamma_S^p)^{1/2}] \quad (\text{Eq. 11})$$

and:

$$(b + c - a)\gamma_S^d \gamma_S^p + c(b - a)\gamma_S^d + b(c - a)\gamma_S^p - abc = 0 \quad (\text{Eq. 12})$$

where a is $(\gamma_L/4)(1 + \cos \theta)$, b is γ_L^d , and c is γ_L^p .

In Eqs. 11 and 12 there are two unknowns, γ_S^d and γ_S^p , so it is necessary to obtain contact angles on a particular solid with two liquids of known γ_L^d and γ_L^p . Then the best fit of γ_S^d and γ_S^p for both sets of contact angle data can be determined by computer analysis.

Table II—Contact Angles for Various Liquids on Nylon 11 and β -Sitosterol at 25°

Liquid	Contact Angle	
	Nylon	β -Sitosterol
Water	76°	94°
Glycerin	65°	83°
Formamide	61°	69°
Ethylene glycol	51°	54°
1,3-Butanediol	36°	48°
Methylene iodide	40°	58°

In most reported cases (11–13), only water and methylene iodide were used, except in one study (14) where glycerin, formamide, and trichlorophenol were used in addition to water and methylene iodide. Comparison of data obtained for the same low energy solids indicates that Eq. 11 results in slightly different answers than Eq. 12.

Since Wu (11) had shown that the reciprocal mean approach (Eq. 10) provides better agreement between calculated and experimental interfacial tensions in liquid polar–polar systems, it was decided to utilize Eq. 12 to estimate γ_S^d and γ_S^p for the solids of pharmaceutical interest. Most studies were conducted using methylene iodide and water only, but the specific effects exerted by the liquid were considered in a few cases by comparing results with other liquids.

EXPERIMENTAL

Contact Angle Measurement—Measurements were made using a telemicroscope¹ attached to a high precision protractor eyepiece. The sample was contained in a thermostated closed chamber at 25° in an atmosphere saturated with the test liquid. Liquid drops of about 0.03 ml were placed on the solid surface using a microliter syringe². Preliminary measurements revealed this drop size to be convenient, although increasing or decreasing the drop volume did not affect the results.

The advancing angles (7) measured in this manner were independent of time after 5 min. Readings, therefore, generally were made from 5 to 10 min after placement of the drop on the surface. Measurements were repeated at least three times with new samples of solid and liquid. The reproducibility of contact angle values generally was better than 2° and no worse than 3°.

Generally, any nonidealized solid surface will exhibit differences in advancing and receding contact angles (7). Consequently, no contact angle in most studies such as this one is an exact thermodynamic value. However, the excellent reproducibility in the measurements for various conditions and the use of the advancing angle for the standard, paraffin, as well as all other solids provide confidence that the surface energies calculated represent the best estimates possible in systems of practical interest.

In all cases where contact angles are reported, no dissolution of the solid by the liquid was noted over the 5–10-min period of measurement. On more extended exposure of some solids to various liquids, some etching of the surface was noticed. To minimize the possibility of dissolution, it is possible to work with saturated solutions of the drug in each liquid. This approach suffers, however, from the fact that liquids with different surface tensions are being used and constants must be determined for each test liquid. Since dissolution did not seem to be a problem, particularly with those hydrophobic drugs of major interest, it was decided that saturated solutions would not be used. In cases where organic acids were used, 0.1 N HCl was substituted for water; a random check of values for some of these solids with 0.1 N HCl and water, however, revealed no significant differences in contact angle.

Materials³—The various solids used in this study are listed in Tables I–V. They were used as received, after initial drying to remove adsorbed water vapor. Densities for the various solids not reported in the literature were measured pycnometrically (15). In some cases, it was necessary to use dilute surfactant solutions to ensure wetting of the solid in the pycnometer. The solids whose densities were measured were griseofulvin, phenacetin, benzocaine, indomethacin, β -sitosterol, sebacic acid, dodecanedioic acid, thopside acid, salicylic acid, and *p*-hydroxybenzoic acid. All other values were taken from the literature (16, 17) (Table VI).

The liquids used were: water, triple distilled from permanganate; methyl iodide⁴; and ethylene glycol, glycerin, 1,3-butanediol, and

¹ Gaertner Scientific Corp., Chicago, Ill.

² Agla, Wellcome Reagents, Ltd., Kent, England.

³ Magnesium stearate and β -sitosterol were provided by Dr. E. N. Hiestand, The Upjohn Co.; ethinamate was provided by Dr. James Boylan, Eli Lilly Co.; griseofulvin was provided by Dr. Hal Wolkoff, Schering Corp.; indomethacin was provided by Mr. John Allegretti, Merck Sharp and Dohme. Benzocaine, phenacetin, aspirin, and salicylic acid were obtained from Ruger Chemical Co., Hillside, N.J. Benzoic, *p*-fluorobenzoic, *p*-chlorobenzoic, and *p*-bromobenzoic acids were obtained from Eastman Organic Chemicals, Rochester, N.Y. Hydrocortisone and hydrocortisone acetate were obtained from The Upjohn Co., Kalamazoo, Mich.; the various dicarboxylic acids came from Aldrich Chemical Co., Milwaukee, Wis. The *p*-hydroxybenzoic acid was provided by Dr. J. T. Carstensen, University of Wisconsin.

⁴ Aldrich Chemical Co.

Table III—Estimated Values for Surface Free Energy (Ergs per Square Centimeter) Using Various Combinations of Liquids

Paired Liquids	Nylon 11			β -Sitosterol		
	γ_S^d	γ_S^p	γ_S	γ_S^d	γ_S^p	γ_S
Water-glycerin	20.4	15.1	35.5	19.3	7.2	36.5
Water-formamide	18.0	16.4	34.4	38.5	2.4	40.9
Water-ethylene glycol	18.8	15.9	34.7	33.1	3.3	36.4
Water-1,3-butanediol	22.2	14.3	36.5	—	—	—
Water-methylene iodide	40.0	9.2	49.2	31.2	3.7	34.9
Ethylene glycol-1,3-butanediol	23.9	9.7	33.6	18.4	14.7	33.1

Table IV—Contact Angles and Surface Free Energies per Square Centimeter for Various Solids Using Water and Methylene Iodide

Solid	Contact Angle		γ_S^d	γ_S^p	γ_S	P_0^a
	Water	Methylene Iodide				
Magnesium stearate	118°	65°	23.0	0	23.0	0
Phenacetin	66°	25°	45.8	12.5	58.3	21
Indomethacin	61°	20°	47.3	14.5	61.8	24
Griseofulvin	57°	26°	45.5	16.7	62.2	27
Hydrocortisone acetate	57°	22°	46.9	16.5	63.4	26
Hydrocortisone	43°	28°	45.1	23.6	68.7	34
Ethinamate	35°	32°	43.3	27.6	70.0	39
Aspirin	37°	41°	39.4	28.1	67.5	42

^a P_0 is the percent polarity; see Eq. 13.

Table V—Contact Angles and Surface Free Energies per Square Centimeter for Various Solids Using 0.1 N HCl and Methylene Iodide

Solid	Contact Angle		γ_S^d	γ_S^p	γ_S	P_0^a
	0.1 N HCl	Methylene Iodide				
Benzoic acid	48°	42°	39.0	22.7	61.7	37
<i>p</i> -Hydroxybenzoic acid	37°	38°	40.6	27.7	68.3	41
<i>o</i> -Hydroxybenzoic acid	39°	34°	42.3	26.2	68.5	38
<i>p</i> -Fluorobenzoic acid	57°	48°	36.0	19.1	54.1	35
<i>p</i> -Chlorobenzoic acid	83°	32°	43.3	5.7	49.0	12
<i>p</i> -Bromobenzoic acid	88°	23°	46.5	3.4	49.9	7
<i>p</i> -Aminobenzoic acid	42°	33°	40.6	25.3	65.9	38
Benzocaine	51°	17°	48.1	19.0	67.1	28
Adipic acid (C ₆)	25°	Spreads	—	—	—	—
Pimelic acid (C ₇)	29°	26°	45.5	29.5	75.0	39
Suberic acid (C ₈)	27°	17°	48.4	29.7	78.1	38
Sebacic acid (C ₁₀)	56°	39°	40.3	18.1	58.4	31
Dodecanedioic acid (C ₁₂)	54°	26°	45.5	18.0	63.5	28
Thapsic acid (C ₁₆)	62°	26°	45.5	14.5	60.0	24

^a P_0 is the percent polarity; see Eq. 13.

formamide, described previously (18). The surface tensions of these liquids were measured using the Wilhelmy plate technique.

Solid Sample Preparation—The paraffin samples used were sheets of Parafilm⁵. These sheets were quite convenient and gave results with water and methylene iodide that were in excellent agreement with previous studies using blocks of paraffin (19). Nylon 11 was used in the form of smooth sheets and gave contact angles for water and methylene iodide that were in good agreement with previous studies (13).

All solids used, except for β -sitosterol, magnesium stearate, *p*-aminobenzoic acid, and three dicarboxylic acids, were prepared for study by compaction against a flat surface⁶. The size of the tablet and the force used [up to 4540 kg (10,000 lb)] allowed for pressures of about 90,000 psi. The appearance of the tablets compressed at these pressures was quite smooth when the tablets were kept in the die during the contact angle measurement. Preliminary checks at higher or lower

pressures indicated no significant dependence of contact angle on pressure in the range studied. Magnesium stearate and β -sitosterol were received as compacts compressed at about 16,000 psi.

Another approach used for sample preparation was to melt the solid on a smooth glass plate and then allow it to resolidify. This approach is unsatisfactory if decomposition or crystal structure changes occur. An advantage of this approach, however, is the lack of any pores between compacted solid particles. Comparison of contact angles with a compact and a melt of *p*-hydroxybenzoic acid, *p*-chlorobenzoic acid, and pimelic acid produced excellent agreement, whereas *p*-fluorobenzoic acid and *p*-bromobenzoic acid exhibited changes in surface appearance after melting and solidification. Thus, melted samples were used only when the compact did not appear suitable, *i.e.*, poor cohesion or high porosity, and when no physical changes after melting were apparent. This was found to be the case for *p*-aminobenzoic acid and the 10-, 12-, and 16-carbon dicarboxylic acids.

RESULTS

Earlier studies showed that one can determine γ_L^d and γ_L^p for pure liquids either by measuring interfacial tensions against liquid hy-

⁵ American Can Co., Neenah, Wis.

⁶ Carver Press, Fred S. Carver, Inc., Summit, N.J.

Table VI—Molar Area, A_m , of Molecules at the Surface

Solid	A_m , (cm^2/mole) $\times 10^{-9}$	Molecular Weight	ρ , g/ cm^3
<i>p</i> -Aminobenzoic acid	1.83	137	1.39
<i>p</i> -Hydroxybenzoic acid	1.80	138	1.40
<i>o</i> -Hydroxybenzoic acid	1.80	138	1.40
Benzoic acid	1.75	122	1.32
<i>p</i> -Fluorobenzoic acid	1.77	140	1.48
<i>p</i> -Chlorobenzoic acid	1.86	157	1.54
<i>p</i> -Bromobenzoic acid	1.95	201	1.86
Hydrocortisone	3.59	345	1.28
Hydrocortisone acetate	3.96	403	1.29
Phenacetin	2.32	179	1.25
Benzocaine	2.24	165	1.21
β -Sitosterol	4.64	415	1.02
Griseofulvin	3.22	341	1.44
Indomethacin	3.46	358	1.35
Pimelic acid	2.05	160	1.33
Suberic acid	2.25	175	1.26
Sebacic acid	2.48	202	1.27
Dodecanedioic acid	2.88	230	1.16
Thopscic acid	3.45	286	1.10

drocarbons having a γ_L^P of zero or by measuring contact angles against a nonpolar solid such as paraffin with a γ_S^P equal to zero (8, 18). Equations 9 and 10, respectively, together with Eq. 4 would be applied. An earlier study (18) showed that the choice of nonpolar phase determines the exact values of γ_L^d and γ_L^P obtained. It was suggested that for consistency these values should be determined from wetting experiments using paraffin when such values are to be applied to subsequent wetting data.

Since paraffin was used in this study, all values of γ_S^d and γ_S^P reported are fixed to one standard nonpolar substance, paraffin. To calculate γ_L^d from the paraffin data, a value of γ_S^d for paraffin was taken as 25.5 ergs/cm² (8). Table I lists contact angles for various liquids on paraffin along with values of γ_L^d , γ_L^P , and γ_L for each liquid. Table II lists contact angles of these liquids on nylon 11 and β -sitosterol, while Table III contains calculated values of γ_S^d , γ_S^P , and γ_S for nylon 11 and β -sitosterol using the data in Tables I and II. These values were calculated by solving Eq. 12 simultaneously for each pair of liquids listed. The two nonlinear equations were solved using a zero-finding routine⁷ based upon Brown's (20) method.

Table IV lists the contact angles of water and methylene iodide obtained from different solids of pharmaceutical interest, while Table V contains such values for various dicarboxylic and benzoic acid derivatives where 0.1 N HCl was used instead of water. The values of γ_S^d , γ_S^P , and γ_S for each solid, calculated as indicated earlier, also are found in these tables. Along with these values is given an index of polarity, P_0 , where:

$$P_0 = \frac{\gamma_S^P}{\gamma_S} \times 100 \quad (\text{Eq. 13})$$

DISCUSSION

Basic to the use of contact angle measurements for estimating solid surface energetics is the assumption that no highly specific interaction and orientation of molecules occur at the solid-liquid interface. If so, using different liquid pairs should lead to the same values of γ_S^d and γ_S^P for a particular solid. The results in Table III for nylon 11 and β -sitosterol clearly indicate the lack of liquid independence, as do the data of Kaoble (14) before he averaged his results.

Molecular orientation might be expected for semipolar molecules such as glycerin, formamide, or ethylene glycol, but it would be expected less for the more symmetrical methylene iodide and water molecules. Indeed, it has been shown that values of critical surface tension, γ_C , for various solids, *i.e.*, surface tension of a liquid required to produce zero contact angle, depend on the type of semipolar liquid used for the determination (15, 21). In addition, mixtures of semipolar solvents and water result in adsorption of the semipolar solvent and a lower value of γ_C as compared to that obtained using liquid hydrocarbons (21).

Indeed, in Table III it can be noted that γ_S values obtained with

Table VII—Comparison of Surface Energy per Square Centimeter Obtained from Contact Angle and from the Parachor Method

Solid	Surface Free Energy, ergs/cm ²	
	Wu (11) Equation	Parachor
Benzoic acid	61.7	45.6
<i>p</i> -Fluorobenzoic acid	54.1	67.8
<i>p</i> -Chlorobenzoic acid	49.0	95.9
<i>p</i> -Bromobenzoic acid	49.9	88.9

the various semipolar liquids generally are lower than those obtained with methylene iodide and water. Consequently, it was decided to utilize only methylene iodide and water data, assuming that the values which are highest are most likely closest to the correct value. At worst, the surface energies are standardized with methylene iodide and water against paraffin but are still characteristic of the solid surface under consideration.

Wu and Brzozowski (22) used methylene iodide and water contact angle data to calculate γ_S^d and γ_S^P for some organic pigments and showed that there was reasonably good agreement between γ_S values estimated in this way and those obtained by the parachor method (23). In the parachor method, parachor values, P , are obtained by adding atomic and group contributions previously estimated with pure liquids. Surface tension, γ , is calculated using ρ (the density), M (the molecular weight), and the equation:

$$\gamma = (P\rho/M)^4 \quad (\text{Eq. 14})$$

Extrapolation of this concept to solids is certainly not as dependable as with liquids, particularly when one considers that errors are amplified by the fourth-power dependence. However, in Table VII are listed calculated and experimental values for four benzoic acid derivatives which are certainly of the right order of magnitude. Thus, it is assumed that these numbers are indeed reflecting the solids under study.

The estimates of surface free energy per unit area, as given in Tables IV and V, are useful in providing some idea of the total energy change that will occur when a given area of contact between phases is increased or decreased. Thus, these are the values of interest when one is concerned with interactions taking place across various interfaces as during powder dispersion. However, the value of γ_S reflects not only the chemical composition of those molecules at the surface but also the number of such molecules per square centimeter.

Thus, to assess further the significance of the values obtained in molecular terms, it is necessary to account for differences in surface density or the number of molecules occupying a unit area of surface. A convenient parameter for comparisons on the molecular level would be the surface free energy per mole, γ_{Sm} :

$$\gamma_{Sm} = A_m \gamma_S \quad (\text{Eq. 15})$$

where A_m is the area in square centimeters occupied by Avogadro's number of molecules. In the absence of any direct method of determining A_m , some estimate may be made by assuming the molecules to be spheres with a molar surface area that is merely the two-thirds power of the molar volume (24). Thus:

$$A_m = fN^{1/3}(M/\rho)^{2/3} \quad (\text{Eq. 16})$$

where N is Avogadro's number, and f is a packing factor generally close to one (24). Table VI lists values of A_m calculated from Eq. 16 for a group of compounds; Table VIII lists the values of γ_{Sm}^d , γ_{Sm}^P , and γ_{Sm} calculated from Eq. 15.

From Table VIII, it is possible to compare values of γ_{Sm}^d and γ_{Sm}^P with changing chemical structure and to see if the calculated values are consistent with expected behavior. This, in turn, would support the fact that the wetting results are, in part, reflecting the chemical structure of the molecules in the solid state. In the benzoic acid series, it is apparent that the absence of a *para*-substituted group of high polarity such as hydroxyl and amino and the introduction of increasingly nonpolar halogens produce a reduction in the γ_{Sm}^P term in the rank order expected. Addition of *para*-substituents on benzoic acid does increase γ_{Sm}^d , which is what is expected on the basis of

⁷ Available at the Academic Computing Center, University of Wisconsin.

Table VIII—Surface Free Energy per Mole^a

Solid	γ_{Sm}	γ_{Sm}^d	γ_{Sm}^p
<i>p</i> -Aminobenzoic acid	121	74	47
<i>p</i> -Hydroxybenzoic acid	123	73	50
<i>o</i> -Hydroxybenzoic acid	123	76	47
Benzoic acid	108	68	40
<i>p</i> -Fluorobenzoic acid	96	64	32
<i>p</i> -Chlorobenzoic acid	91	81	10
<i>p</i> -Bromobenzoic acid	97	91	6
Hydrocortisone	246	162	84
Hydrocortisone acetate	251	185	65
Phenacetin	135	106	29
Benzocaine	150	107	43
β -Sitosterol	162	144	18
Griseofulvin	200	147	53
Indomethacin	214	164	50
Pimelic acid	154	93	61
Suberic acid	176	109	67
Sebacic acid	145	100	45
Dodecanedioic acid	183	131	52
Thopside acid	207	157	50

^a Values are (ergs per mole) $\times 10^{-9}$

increased polarizability. Esterification of a normally polar alcohol or carboxyl group as in benzocaine versus *p*-aminobenzoic acid and hydrocortisone versus hydrocortisone acetate likewise can be seen to reduce polar contributions while increasing the dispersion force component.

In the dicarboxylic acid series, the general trend is that the dispersion component increases as the number of methylene groups per mole increases whereas the value of γ_{Sm}^p remains fairly constant, as does the number of polar groups per mole. Sebacic acid seems somewhat of an exception in this regard, which could indicate that the calculation of area per mole, as in Eq. 16, may not always be correct.

At this point, if it is assumed that the values of γ_S , γ_S^d , and γ_S^p do reflect properties unique to the solid surface, one can make generalizations concerning the overall surface properties of the pharmaceutical solids studied here. It is clear, for instance, that except for magnesium stearate and β -sitosterol on a per square centimeter basis, all of these solids can be considered moderate in their surface energy as compared to paraffin, a low energy substance, and metals, on the other end of the scale. It is clear also that the fatty acid chains dominate the surface properties of magnesium stearate, thus making it a good lubricant and a good waterproofing agent.

In Tables IV and V, it is interesting to note the rather constant value for γ_S^d and the large variation in γ_S^p . This finding suggests that comparison of P_0 values for such a diverse series of compounds is a valid means of comparing the expected level of polarity on a per square centimeter basis. It is clear from a comparison of P_0 values and contact angles that even 42% polarity can lead to a nonwetting solid. It is difficult to assess at what point the hydrophobicity becomes significant enough to influence a particular process without knowing all factors influencing that process. However, with these numbers as an index of polarity and the various surface free energy terms, it should be possible to see whether a meaningful correlation with various surface-controlled phenomena does exist. Such studies involving the dispersion and dissolution of low energy pharmaceutical solids are now being performed.

CONCLUSIONS

The contact angle obtained with water and methylene iodide on various organic solids was used to calculate surface free energies for these solids. The overall free energy term, when expressed on a molar basis, appears to reflect the chemical structure of the molecule; however, on a per square centimeter basis, the results also reflect the number of molecules occupying a unit area. From such measurements,

an index of polarity was determined which indicates that, per square centimeter, drug molecules that present wetting problems may be as high as 40% polar. Although some theoretical uncertainties still exist as to the surface free energy per square centimeter of a solid, as determined from contact angle, the numbers estimated here provide systemic standard parameters which reflect solid surface properties.

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