Use of Inverse Gas Chromatography (IGC) to Determine the Surface Energy and Surface Area of Powdered Materials

Dear Editor:

The paper published by Cline and Dalby (1) claims to have established a "convincing relationship between the surface energy and area parameters derived from IGC and dry powder inhaler performance." As experienced users of IGC for material characterization, we deem it appropriate to highlight several inaccuracies (both technical and fundamental) in this paper, which appear serious enough to require reassessment of the published work. The errors are discussed below.

Surface Energy Determination

The major error made by Cline and Dalby is that they substituted surface tension, as used by van Oss (2), with the free energy of adsorption (denoted by K^A and K^B for specific acidic and basic interactions, respectively, in the paper) in the calculation of the so-called surface energy interaction (abbreviated by SEI). This is evident from the way by which the K^A and K^B parameters are derived. These parameters reflect essentially the free energy of adsorption of a solvent probe on a solid surface and comprise interaction energies contributed by both the probe and the solid surface. In contrast, the γ_S^D value (for dispersive forces) in Eq. 1 of the paper is the true surface tension (or the surface free energy) of the solid, because the algorithm used to derive the equation distinctly discriminates between the surface tension of the material (γ_S^D) under investigation and that of the solvent probe (γ_L^D) and allows calculation of γ_S^D from the free energy of adsorption (ΔG_A). Accordingly, γ_S^D can be computed using Eq. 1* (shown below) from the linear incremental change in ΔG_A per unit surface area of each (essentially nonpolar) probe in the alkane series (3) (i.e., from the slope of the linear plot obtained for the nonpolar probes).

$$\frac{-\Delta G_A^{CH2}}{Na_{CH2}} = 2(\gamma_S^D)^{1/2}(\gamma_L^D)^{1/2} \qquad (1^*)$$

where $\Delta G_A{}^{CH2}$ and a_{CH2} are the free energy of adsorption and surface area per methylene group, respectively; N is the Avogadro's number; and γ_S^D and γ_L^D are the dispersive components of the surface tensions of the solid and the liquid probe, respectively.

To adopt a similar approach for the calculation of γ_S for the polar specific interactions, one would need to "create" an incremental change in the surface area of the polar part of the polar probe and measure the associated change in surface free energy of adsorption. This would require a series of polar probes with similar structures for incremental polar contribution, as in the case with the nonpolar probes. It would be erroneous to calculate the γ_S for polar interactions simply by dividing the $\Delta G_A{}^{SP}$ obtained for a particular polar probe by the probe's surface area, primarily because the probe molecule is composed of both polar and nonpolar parts, and only the polar part contributes to the $\Delta G_A{}^{SP}$ value. Since only two polar probes were used and their structures are dissimilar, it is difficult to envisage the surface area of the polar part of the probe was derived by the authors to calculate γ_S for the chloroform (acidic) and tetrahydrofuran (basic) probes.

Specific Surface Area Determination

The specific surface areas reported were calculated from the IGC data using an erroneous equation, that is, Eq. 1 in (1). The error lies in the intercept term (4, 5).

The correct equation should be:

$$RT\ \ln V_N = 2N(\gamma_S^D)^{1/2}\alpha(\gamma_L^D)^{1/2} + RT\ \ln\left(\frac{S \cdot g\pi_0}{P_0}\right) \qquad (2^*)$$

where R is the gas constant; T is the absolute temperature; V_N is the net retention volume; P_0 is the partial pressure of the solute; π_0 is the bidimensional spreading pressure of the adsorbed film to a reference gas phase state; *a* is the surface area of the probe; S and g are, respectively, the specific surface area and weight of the sample; and γ_S^D and γ_L^D are as defined before.

Comparison of Eq. 2* with the one given below, that is, Equation 1 in (1), clearly shows that the intercept term is in error.

$$RT\ \ln V_N = 2N(\gamma_S^D)^{1/2}\ \alpha(\gamma_L^D)^{1/2} + RT\ \ln\left(\frac{\pi_0}{S \cdot gP_0}\right) \quad \text{Eq. 1 in (1)}$$

Though it appears theoretically feasible to calculate the surface area of the powders from the intercept term using the correct form of Eq. 1 (i.e., Eq. 2*), such an approach is subject to error as the intercept value is obtained by linear extrapolation down to the y-axis over at least five carbons, which can introduce significant errors in its estimation. In other words, a small change in the slope of the plot will cause a substantial difference in the intercept value. In addition, such extrapolation assumes linearity of the relationship in the extrapolated region (i.e., C0–C5) as well, which may not be valid. Another possible source of error is the surface heterogeneity of the materials. Because IGC analysis at infinite dilution probes only the most energetic sites at the surface, the slope (γ_S^D) and hence the intercept (i.e., surface area) will vary with the surface heterogeneity of the powder. That is to say, the approach can yield widely different surface area values for samples of supposedly equivalent surface area, depending on the presence of such high-energy sites. The choice of the reference state (P_0 and π_0) and the presence of other unknown experimental factors will also have an important bearing on the intercept value and hence on the reliability of the estimated surface area. To illustrate this point, we have performed the following surface area calculations based on our published (6) and unreported IGC data and compared them with those measured by the BET nitrogen adsorption technique (see the table).

GSX stands for granular salmeterol xinafoate produced by a patented crystallization process (7). MSX depicts micronized salmeterol xinafoate (which is prepared from GSX by micronization). SX-I and SX-II are the form I and form II polymorphs of salmeterol xinafoate, respectively, prepared by the solution enhanced dispersion by supercritical fluids (SEDS) technique. As shown in the table, there is a large discrepancy in surface area determination between the two

0724-8741/04/0900-1718/0 © 2004 Springer Science+Business Media, Inc.

Sample	Surface area (m^2/g), calculated from the intercept of the linear plot for the alkane series at 40°C (n = 3) using the reference state of de Boer	Surface area (m^2/g), determined by BET nitrogen adsorption analyses (n = 3)
GSX	3.284 (0.510)	10.699 (0.016)
MSX	2.484 (0.298)	9.243 (0.002)
SX-I	1.870 (0.536)	4.449 (0.029)
SX-II	9.243 (1.569)	1.797 (0.038)

methods. Although there appears to be a parallel trend in the surface areas determined by these two techniques, the SX-II sample clearly shows an exception, which is likely due to its relatively polar surface. This indicates that the nature and strength of interactions, which govern the overall surface energy, will also influence the IGC-derived surface area. Consequently, IGC analysis at infinite dilution will not be a suitable technique for specific surface area determination.

A. H. L. Chow and H. H. Y. Tong
School of Pharmacy, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China.

B. Y. Shekunov
Ferro Corporation, Pharmaceutical Technologies, Independence, Ohio, USA.

P. York
School of Pharmacy, University of Bradford, West Yorkshire, UK.

REFERENCES

1. D. Cline and R. Dalby. Predicting the quality of powders for inhalation from surface energy and area. *Pharm. Res.* **19:**1274–1277 (2002).
2. C. J. van Oss. *Interfacial Forces in Aqueous Media,* Marcel Dekker, New York, 1994.
3. G. M. Dorris and D. G. Gray. Adsorption of n-alkanes at zero surface coverage on cellulose paper and wood fibers. *J. Colloid Interface Sci.* **77**:353–362 (1980).
4. J. Schultz, L. Lavielle, and C. Martin. The role of the interface in carbon fibre-epoxy composites. *J. Adhesion.* **23**:45–60 (1987).
5. J. Schultz and L. Lavielle. Interfacial properties of carbon fiber-epoxy matrix composites. In D. R. Lloyd, T. C. Ward, H. P. Schreiber and C. C. Pizana (eds.), *Inverse Gas Chromatography—Characterization of Polymers and Other Materials,* American Chemical Society, Washington, DC, 1989, pp. 185–202.
6. H. H. Y. Tong, B. Y. Shekunov, P. York, and A. H. L. Chow. Influence of polymorphism on the surface energetics of salmeterol xinafoate crystallized from supercritical fluids. *Pharm. Res.* **19**:640–648 (2002).
7. United States Patent No. 5 380 922.

The authors respond:

Surface Energy Determination

We recognized that K^A and K^B are not "true" (theoretically complete) measurements of the acidic and basic components of surface free energy and therefore chose to not label them γ^+ and γ^- as in the approach of van Oss (1). However, derivation of these parameters (K^A and K^B) through the ΔG_{SP} values of chloroform (electron donor, acid) and THF (electron acceptor, base) do provide information of the relative acidic and basic nature of the powder's surface. Other experienced users of IGC for material characterization share this view. Grimsey *et al.* (2) used a similar concept to probe the acidic and basic nature of the surface of mannitol, while York *et al.* (3) used these same probes to examine the surface of milled dl-propranolol hydrochloride.

Another approach used in the pharmaceutical, IGC literature (4,5) to estimate the acidic and basic nature of a solid's surface is that proposed by Shultz *et al.* (6). This approach uses a series of empirically derived electron acceptor and electron donor values (7,8) for various probe molecules to calculate corresponding acceptor (K_A) and donor (K_D) values of the solid's surface. However, it is limited by the fact that it expresses these values as unitless numbers that do not provide an opportunity for comparison or combination with γ^D values, expressed in mJ/m^2.

ΔG_{SP} values for THF and chloroform have units of kJ/mol. Our reason for converting ΔG_{SP} values by dividing by Avogadro's number (molecule/mol) and an estimate of the surface area of the probe (angstroms^2/molecule) was to harmonize the units, with γ^D values, to allow for mathematical combinations. We made this point very clearly in the IGC Theory section on page 1275. Such a transformation provides a mechanism to compare the surface energy interaction (dispersive, acidic and basic components) of different combinations of materials.

Specific Surface Area Determination

The version of Eq. 1 that we submitted was incorrect. We inadvertently transposed the "–" sign with a "+" and included Π_0 in the numerator and P_o in the denominator. However, the data we reported was calculated with the correct equation, using the reference states of de Boer ($P_o = 1.01 \times 10^5$ N/m^2, $\Pi_0 = 3.38 \times 10^{-4}$ N/m). The correct equation is:

$$RT \ln V_n = 2N(\gamma^D_{solid})^{1/2} a(\gamma^D_{liquid})^{1/2} - RT \ln(P_0/A_{SP}G\Pi_0)$$

We thank Dr. Chow for pointing out our error.

In our manuscript, we noted that the specific surface area (SSA) of powders we examined by IGC correlated with values calculated from particle size distribution data obtained from laser light scattering (Malvern Mastersizer S) (see the table below). The correlation coefficient was 0.84 when data from similar shaped lactose monohydrate and trehalose dihydrate was used in the calculation.

Mannitol's needle-like particle shape was not amenable to laser diffraction sizing, and could not be included in the data set. While by no means a perfect correlation, this relationship shows that IGC-derived specific surface areas rank order powders in the same way as measurements based on an instrument widely used in aerosol science. Though there are

Material	Specific Surface Area IGC (m^2/g)	Specific Surface Area Malvern (m^2/g)
Trehalose	0.125	0.576
Lactose A	0.057	0.513
Lactose B	0.026	0.224
Lactose C	0.017	0.166
Lactose D	0.003	0.108

assumptions, such as linearity when extrapolating to the y-axis and effects due to surface heterogeneity, we continue to believe an IGC approach to estimating specific surface area remains a benefit of this emerging development tool. Furthermore, estimates of specific surface area for a given powder were reproducible from one column preparation to another.

We concede that IGC is an emerging technique with potential flaws and few standardized procedures. We thank Dr. Chow for furthering the discussion on what we believe could become a useful formulation tool.

D. Cline and R. Dalby
Department of Pharmaceutical Sciences, University of Maryland, Baltimore, Maryland, USA

REFERENCES

1. C. Van Oss. *Interfacial Forces in Aqueous Media*. Marcel Dekker, New York, 1994.
2 . I. Grimsey, M. Sunkersett, J. Osborn, P. York, and R. Rowe. Interpretation of the differences in the surface energetics of two optical forms of mannitol by inverse gas chromatography and molecular modeling. *Int. J. Pharm*. **191:**43–50 (1999).
3. P. York, M. Ticehurst, J. Osborn, R. Roberts, and R. Rowe. Characterisation of the surface energetics of milled dl-propranolol hydrochloride using inverse gas chromatography and molecular modeling. *Int. J. Pharm.* **174:**179–186 (1998).
4. H.Tong, B. Shekunov, P. York, and A. Chow. Characterization of two polymorphs of salmeterol xinafoate crystallized from supercritical fluids. *Pharm. Res.* **18:**852–858 (2001).
5. H. Tong, B. Shekunov, P. York, and A. Chow. Influence of polymorphism on the surface energetics of salmeterol xinafoate crystallized from supercritical fluids. *Pharm. Res*. **19:**640–648 (2002).
6. J. Schultz, L. Lavielle, and C. Martin. The role of the interface in carbon fibre-epoxy composites. *J. Adhesion*. **23:**45–60 (1987).
7. V. Gutmann. *The Donor-Acceptor Approach to Molecular Interactions*, Plenum, New York, 1978.
8. F. Riddle and F. Fowkes. Spectral shifts in acid-base chemistry. 1. Van der Waals Contributions to acceptor numbers. *J. Am. Chem. Soc*. **112:**3259-3264 (1990).