Predicting the Quality of Powders for Inhalation from Surface Energy and Area

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Received May 5, 2002; accepted May 30, 2002.

Purpose. To correlate the surface energy of active and carrier components in an aerosol powder to *in vitro* performance of a passive dry powder inhaler.

Methods. Inverse gas chromatography (IGC) was used to assess the surface energy of active (albuterol and ipratropium bromide) and carrier (lactose monohydrate, trehalose dihydrate and mannitol) components of a dry powder inhaler formulation. Blends (1%w/w) of drug and carrier were prepared and evaluated for dry powder inhaler performance by cascade impaction. The formulations were tested with either of two passive dry powder inhalers, Rotahaler® (GlaxoSmithKline) or Handihaler® (Boehringer Ingelheim).

Results. *In vitro* performance of the powder blends was strongly correlated to surface energy interaction between active and carrier components. Plotting fine particle fraction vs. surface energy interaction yielded an R^2 value of 0.9283. Increasing surface energy interaction between drug and carrier resulted in greater fine particle fraction of drug.

Conclusions. A convincing relationship, potentially useful for rapid formulation design and screening, was found between the surface energy and area parameters derived from IGC and dry powder inhaler performance.

KEY WORDS: inverse gas chromatography; dry powder inhalers; surface energy; cascade impaction.

INTRODUCTION

Dry powder inhalers (DPIs) are used to deliver inhaled drug to a patient's lung. DPI formulations typically consist of micronized drug mixed with a carrier of larger particle size. Upon inhalation of the powder blend, the drug and carrier ideally deaggregate through mechanical and shear forces. Smaller particles of drug (1–5 μm) can change direction in the inhaled airstream and deposit deep in the lung, whereas larger carrier particles impact in the throat and are swallowed. This study uses inverse gas chromatography (IGC) to examine the type and magnitude of forces present at the surfaces of the particles and to propose a model correlating those forces to dry powder inhaler performance.

This study was undertaken to establish a theoretical basis for preparing formulations for DPIs. Several papers have been published that examine the influence of different types, grades, and particle size ranges of carrier particles on their ability to maximize a drug's respirable fraction from a DPI (1–3). Similar efforts have been repeated with proteins such as recombinant humanized anti-IgE monoclonal antibodies and recombinant human deoxyribonuclease (rhDNase) (4,5). To date, work in this area has primarily involved a mix-it-and-test-it approach. Although empirical reasoning is usually applied to the selection of excipients and processing conditions, an approach that involves predicting powder behavior would be more expeditious. A correlation between surface energy and *in vitro* performance will greatly enhance formulation efforts and decrease development times. It will also provide a quality control tool for assuring consistent product performance.

IGC is a technique that involves packing a gas chromatography (GC) column with the powder of interest, injecting a series of nonpolar and polar probes and calculating the surface energy of the powders from retention time data. This method has several advantages. It examines the powder in the desired form for the product—there is no need for forming a compact and potentially changing the surface. A wide range of probes can be used; the technique is nondestructive and the material is recoverable (5). IGC has recently gained attention in the pharmaceutical literature, as evidenced by several recent publications examining lactose monohydrate, albuterol, and mannitol (7–12). One limitation of the current technique is that the dispersive component of surface energy is expressed in mJ/m^2 and the polar component is expressed as an acidic (K^A) and basic (K^B) term in units of kJ/mol, or as a unitless number. This limits the investigator's ability to examine combinations of all of the surface energy parameters in an effort to explain powder behavior. As a result, a model for powder behavior or product performance is difficult to generate.

This work proposes a simple approach to the IGC calculations that provides all of the surface energy parameters in the same units and, as an example of the utility of this approach, presents a model relating these parameters to DPI performance.

IGC THEORY

In an IGC experiment, the powder of interest is packed into an empty GC column. The column is installed in the GC and a series of organic probe vapors are injected onto the column at infinite dilution. Probe retention times are measured and reflect the magnitude of interaction with the powder surface. From the retention times of nonpolar and polar probes, a methodology has been established to calculate the powder's surface energy. The methodology is described by Schultz *et al.* (13), and the theory is summarized by Conder and Young (14). The basic relationship employed is:

$$RT \ln V_n = 2N(\gamma^D_{SOLID})^{1/2} a(\gamma^D_{LIQUID})^{1/2} + RT \ln (\Pi_0 / A_{SP} G P_o) \quad (1)$$

In Eq. (1), R is the gas constant, T is the temperature (K), V_n is the net retention volume of the probe, N is Avagadro's number, a is the molecular surface area of the probe, γ^D_{Liquid} is the dispersive component of surface tension of the probe, Π_0 and P_o are constants, G is the mass of powder in the column, and A_{SP} is the specific surface area. Plotting RT ln V_n vs. $a\ (\gamma^D_L)^{1/2}$, for the nonpolar probes, yields a straight line. The dispersive component of the solid is calculated from the slope and the specific surface area is calculated from the intercept in Eq. (1), where all terms are known except for A_{SP}.

Because polar probes will act through both dispersive and polar interactions, plotting their values on the same graph

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0724-8741/02/0900-1274/0 © 2002 Plenum Publishing Corporation

will yield values above the alkane line, resulting in a measure of the specific interaction ΔG_{SP} (Fig. 1).

Typically, four or more polar probes are injected and their specific interactions are plotted vs. Gutman electron donor and acceptor values as per the approach of Shultz *et al.* (13). This approach results in polar components calculated in kJ/mol or as a unitless value, depending on the investigator's approach.

We utilized chloroform (slightly acidic) and tetrahydrofuran (basic) to assess the basic and acidic nature of the solid. The distance above the alkane line, ΔG_{SP} (kJ/mol), for each polar probe, was converted to mJ/m^2 through Avagadro's number (molecules/mol) and the cross-sectional area of the probe (*a,* angstroms/molecule). This allows calculation of γ^D, K^A and K^B of the powder all in the same units (mJ/m^2).

Harmonization of the units now allows the use of a model for predicting DPI performance based on the interaction of two surfaces, similar to that proposed by van Oss (15) for the interfacial tension of two liquids:

$$FPF = 2(\gamma^D_1\gamma^D_2)^{1/2} + 2\,(K^A_1\,K^B_2)^{1/2} + 2\,(K^B_1\,K^A_2)^{1/2} \quad (2)$$

In our treatment, subscripts 1 and 2 represent drug and carrier, respectively.

When setting a specification for a carrier powder a researcher may stipulate particle size, the size distribution, and/or the amount of fines, all of which play a significant role in affecting powder behavior. The specific surface area of a powder is a single value that is influenced by all of these parameters. Therefore, it may be more appropriate to examine powder surface energies and the specific surface area as one term expressed as energy/gram (mJ/g). The specific surface area, in units of m^2/g, of each powder was determined by IGC and used to convert surface energies from mJ/m^2 to mJ/g. This calculation has the advantage of describing how energetic the surface is and the amount of surface available for interaction.

MATERIALS AND METHODS

All IGC probes were purchased from Sigma (St. Louis, MO, USA). Deactivated glass columns were purchased from Alltech Associates (Waukegan, IL, USA). Lactose monohydrate samples were purchased or obtained from Foremost (Rothschild, WI, USA) and Quest International (Hoffman Estates, IL, USA). Mannitol and trehalose dihydrate were purchased from Sigma (St. Louis, MO, USA). Micronized albuterol was used as received from Cipla (Bombay, India), and micronized ipratropium bromide was used as received from Boehringer Ingelheim (Ingelheim, Germany).

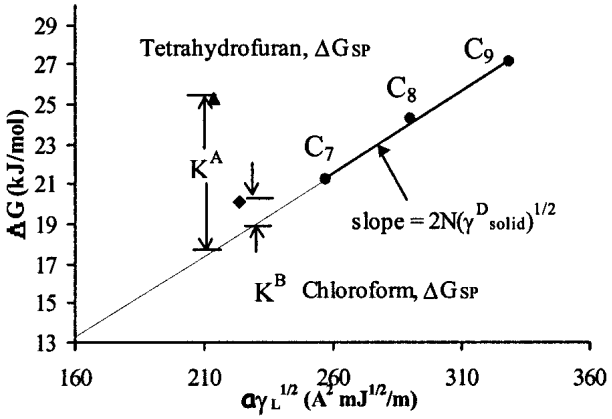

Fig. 1. Representative IGC plot demonstrating calculated surface energy parameters of the solid under investigation.

IGC Experiments

All IGC experiments were conducted using a Hewlett Packard 5890 GC with flame ionization detection. Three to four IGC columns were analyzed per powder. All glass columns were ¼ inch O.D. × 2 mm I.D × 2, 3, or 4 ft in length. The GC was operated with an inlet temperature of 100°C, an FID temperature of 250°C, and a column oven temperature of 32°C. Nitrogen was used as the carrier gas. Typical flow rates ranged from 4–8 ml/min and typical column head pressures ranged from 18–25 psi (104–173 kPa). Injections of probe vapor were made manually, at infinite dilution, with a 10 μl Hamilton syringe. Infinite dilution was verified by injecting smaller amounts of probe until the probe retention time did not change significantly with the amount of probe injected. The IGC column was equilibrated for approximately three hours at 32°C prior to analysis. N-alkanes C_7, C_8, and C_9 were injected as nonpolar probes. Tetrahydrofuran and chloroform were injected as polar probes.

DPI Formulations

Albuterol or ipratropium bromide (1%w/w) and carrier were blended and 25 (±2 mg) of blend was loaded into #3 hard gelatin capsules and tested using either a Rotahaler® (GlaxoSmithKline) or Handihaler® (Boehringer Ingelheim) DPI.

Cascade Impaction

Aerosol performance was examined using a Multi Stage Liquid Impinger (MSLI, Copley Scientific, UK) operating at 60 l/min as described in USP 24, <601> apparatus 4. The MSLI consists of a series of four vertically stacked impaction stages wetted with liquid (20 ml). Each stage captures particles according to their aerodynamic diameter. Larger particles collect on the top (>13 μm) while smaller particles deposit on the lower stages and the filter. The cumulative percentage of drug that passes stage 2 (<6.8 μm) and deposits on stages 3, 4, and the filter represents the fine particle fraction (FPF), which is often used as an *in vitro* surrogate for estimating the percentage of drug likely to be delivered into the lung. MSLI experiments were performed in triplicate.

Drug deposition in the MSLI was quantitated using high performance liquid chromatography (HPLC). The HPLC system was operated at a flow rate of 1 ml/min, the mobile phase consisted of 60% (0.01 M citric acid and 0.003 M heptane sulfonic acid sodium salt, pH adjusted to 3.5 with 1 M NaOH) and 40%methanol. A 25 cm Phenomenex Prodigy® 5 μm C-18 analytical column was used in the analysis with ultraviolet detection at 225 nm.

Particle Size and Statistics

Particle size of all lactose monohydrate, trehalose dihydrate, and mannitol samples were determined with a Malvern Matersizer® (Worcestershire, UK) using forward laser light

Table I. IGC Parameters for Individual Powders

Powder	γ^D mJ/m^2	K^A mJ/m^2	K^B mJ/m^2	SSA[a] m^2/g	γ^D mJ/g	K^A mJ/g	K^B mJ/g
Trehalose A	42.9 (0.52)	26.1 (0.32)	5.9 (0.18)	0.125 (0.009)	5.35 (0.33)	3.27 (0.27)	0.73 (0.04)
Lactose A	43.4 (0.57)	27.2 (0.44)	7.6 (0.67)	0.057 (0.006)	2.48 (0.22)	1.56 (0.14)	0.43 (0.01)
Lactose B	47.9 (0.66)	28.0 (0.11)	5.7 (0.17)	0.026 (0.003)	1.26 (0.11)	0.74 (0.07)	0.15 (0.02)
Lactose C	47.9 (1.18)	29.4 (0.29)	6.6 (0.18)	0.017 (0.003)	0.80 (0.10)	0.49 (0.07)	0.11 (0.01)
Lactose D	48.3 (2.75)	28.8 (2.03)	6.2 (1.22)	0.003 (0.001)	0.15 (0.03)	0.09 (0.02)	0.02 (0.00)
Mannitol A	57.7 (2.40)	19.9 (0.69)	0.0 (0.00)	0.018 (0.002)	1.06 (0.10)	0.37 (0.03)	0.00 (0.00)
Mannitol B	68.6 (1.04)	21.3 (0.27)	0.0 (0.00)	0.049 (0.008)	3.35 (0.51)	1.04 (0.18)	0.00 (0.00)
Albuterol	41.5 (0.26)	19.3 (0.03)	5.8 (0.03)	1.723 (0.074)	71.5 (3.32)	33.3 (1.48)	10.0 (0.43)
Ipratropium	44.9 (0.37)	8.7 (0.36)	26.0 (0.44)	1.564 (0.161)	70.2 (6.78)	13.5 (0.82)	40.6 (3.64)

Note: Values are mean and (standard deviation).
[a] Specific surface area

scattering analysis. Statistical significance was evaluated using one-way analysis of variance with Tukey's post hoc analysis.

RESULTS

Injections of probe vapors produced chromatograms with approximately Gaussian peaks. Data for the IGC analysis of carrier and drug powders are presented in Table I. The first four columns of Table I list the dispersive (γ^D) acid (K^A) and base (K^B) values for the various lactose, trehalose, mannitol, ipratroprium bromide, and albuterol powders in mJ/m^2. The surface free energy parameters are similar for the lactose and trehalose samples, whereas the surface free energy parameters for mannitol are different. Albuterol and ipratropium bromide have similar values for the dispersive component, but different values for the K^A and K^B components. Individually, these surface free energy values are not predictive of FPF data of drug and carrier blends.

The fifth column of Table I lists the specific surface area (SSA) of each powder determined by IGC. The specific surface area determined by IGC followed the same order as the specific surface area of the powders calculated from the Malvern software (laser light scattering, data not shown). A trend between SSA of the carrier particles and FPF of drug can be seen in Fig. 2, where plotting FPF vs. SSA results in an $R^2 = 0.8488$.

The remaining columns in Table I list the surface energy data calculated in mJ/g. Using this approach, greater differences between γ^D, K^A, and K^B exist and correlate well with FPF using the model described in Eq. (2) (Table II). Least squares linear regression with FPF on the Y-axis and the term $2(\gamma^D_1\gamma^D_2)^{1/2} + 2(K^A_1K^B_2)^{1/2} + 2(K^B_1K^A_2)^{1/2}$ on the X-axis yields an $R^2 = 0.9283$ (Fig. 3).

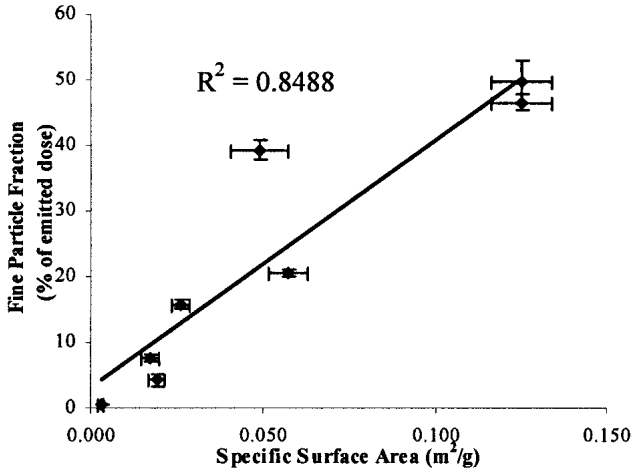

Fig. 2. Fine particle fraction of drug (blended with carrier) vs. specific surface area (m^2/g) of carrier.

DISCUSSION

Although a trend exists between the SSA of the carrier particles and FPF of the drug, incorporating the surface energy components improves the correlation. This is especially the case when considering the formulation of mannitol B and ipratropium bromide where the SSA relationship (Fig. 2) would have predicted a lower FPF than the lactose A/albuterol formulation. The surface energy interaction relationship (Fig. 3) predicts a higher value for the same formulation. Similar but subtler differences can be seen with the mannitol A/albuterol and ipratropium bromide/trehalose formulations. Least squares linear regression of SSA data yields an $R^2 = 0.8488$, whereas the surface energy interaction relationship yields an $R^2 = 0.9283$.

With this approach we are able to examine the impact of each surface energy parameter on the surface energy interaction between drug and carrier. This provides a formulator with a tool to rationally select the best combination of drug and carrier for optimal DPI performance.

It should be noted that Handihaler exhibited a larger pressure drop than Rotahaler, and that a larger pressure drop could lead to a larger dispersion force. Although three of the

Table II. Surface Energy Interaction and Fine Particle Fraction of Powder Blends

Carrier	Drug	SEI[a] (mJ/g)	FPF of Blend
Trehalose A	Ipratropium^H	68.1	49.7%
Trehalose A	Albuterol^H	60.4	46.6%
Mannitol B	Ipratropium^H	43.7	39.3%
Lactose A	Albuterol^R	42.1	20.5%
Lactose B	Albuterol^R	28.9	15.8%
Lactose C	Albuterol^R	23.4	7.6%
Mannitol A	Albuterol^H	21.3	4.2%
Lactose D	Albuterol^R	10.1	0.5%

[H] Handihaler, 14.5 kPa pressure drop at 60 l/min.
[R] Rotahaler, 0.5 kPa pressure drop at 60 l/min.
[a] Surface energy interaction.

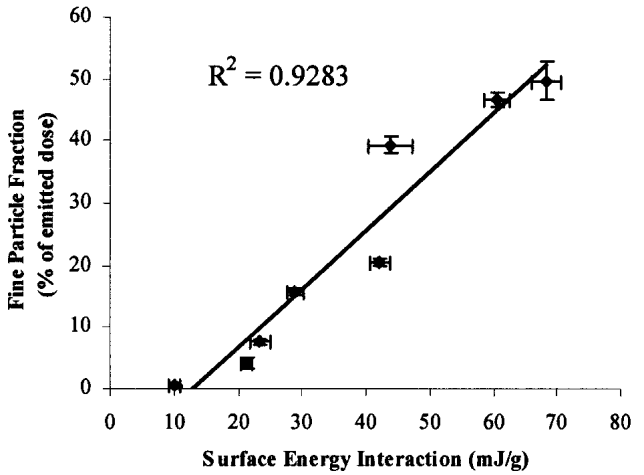

Fig. 3. Fine particle fraction of drug (blended with carrier) vs. surface energy interaction (mJ/g) between drug and carrier.

formulations with the highest FPF were tested with Handihaler, the fourth formulation tested with Handihaler had an FPF that was lower than all but one of the Rotahaler formulations. With these test conditions it appears that the surface energy interaction was the dominant predictive parameter and not the pressure drop.

Interestingly, the FPF improves with increasing surface energy interaction (mJ/g). Previous investigators have proposed that stronger drug/carrier interaction would lead to less particle separation and decreased DPI performance. Staniforth *et al.* (16) proposed that mixing a portion of micronized carrier in with larger carrier blocks the high-energy sites on the larger carrier particles leading to less drug/carrier interaction and increased FPF. When considering IGC values for the lactose carriers in terms of mJ/m^2, there is no substantial difference between surface free energy values, even when the only difference is the amount of fine particles present, as indicated by higher specific surface area.

By examining the powders in terms of mJ/g with Eq. (2), we see an increase in DPI performance with an increased surface energy interaction. An explanation of this counterintuitive finding is that a certain minimum surface energy interaction between carrier and drug particles is needed to pull highly cohesive, micronized drug particles apart during the initial blending process and when the powder is being aerosolized. If the drug particles remain aggregated in the formulation or upon aerosolization, they will not disperse into primary particles in the 1–5 μm range.

CONCLUSIONS

Examining the surface energy of powders in terms of mJ/g by IGC may be more useful than the traditional approach that reports the dipsersive component (γ^D) in mJ/m^2 and the polar components (K^A, K^B) in kJ/mol or as a unitless number. This approach, coupled with a predictive model for the interaction of two different powder surfaces, correlated well with *in vitro* measurements of dry powder inhaler performance. The model proposed can be used to anticipate interparticulate interactions and allows a researcher to judiciously choose powder combinations (surface energy and surface area) to ensure optimal dry powder inhaler performance.

ACKNOWLEDGMENTS

The authors would like to thank the United States Pharmacopeia for the financial support David Cline has received through the USP fellowship program. We would also like to thank Dr. Helmut Bender from Boehringer Ingelheim for his participation in this study.

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