Inverse gas chromatography

A novel finite dilution IGC technique for the physico-chemical characterization and optimization of dry powder inhalation formulations

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Surface Measurement Systems NA

In the October 2007 issue of *Inhalation*, Andrew Otte and M. Teresa Carvajal presented a comprehensive overview of solid surface energy principles and applied measurement techniques for DPI formulations, including infinite dilution inverse gas chromatography (IGC). This follow-up article focuses specifically on the use of IGC for the determination of surface energy as a function of processing conditions for both API and excipient carrier molecules used in inhalable formulations and introduces a novel finite dilution approach that offers a unique new method of profiling surface heterogeneity, which plays a major role in drug-carrier interactions. This extremely sensitive approach provides data of unparalleled specificity that can benefit every stage of the DPI formulation process.

What is IGC?

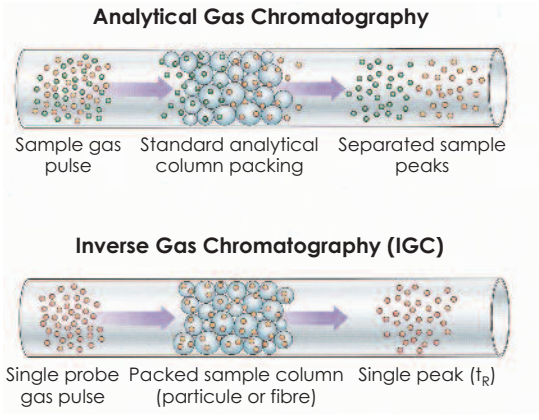
In traditional GC, an unknown mixture of gas or vapor is injected into a column packed with a known separation material; as the various components of the mixture elute through the column, they adsorb and desorb at different rates, causing variances in retention time and allowing the separation of the sample into its constituent components. By contrast, IGC inverts the traditional GC in that the unknown material, which may be an API, excipient, or formulation, is packed inside of a straight glass column and is probed via separate injections of a known vapor or gas probe to determine the unknown's physical and chemical characteristics [1, 2] (Figure 1).

An IGC glass column typically measures 30 cm in length and 2-4 mm in internal diameter, and the inside wall of the column is coated with dimethyldichlorosilane to minimize sample and probe vapor interactions with the column. Packing the sample into the column requires no particular expertise since the analyst accounts for any differences in packing density by measuring the retention time of an inert probe, typically methane. Retention time, which is the time required to elute a given volume of probe through the column, can be measured accurately using standard chromatographic flame ionization and thermal conductivity detectors. Since an inert probe will not interact directly with the sample, subtracting the retention time of the inert probe from the total retention time of each molecular probe injection provides an internal correction to account for packing variations. This procedure thus allows for measurement of retention time attributable specifically to interactions between the probe vapor and the material under investigation, minimizing concerns about measurement reproducibility between columns.

Injecting a pulse of a known concentration of a well-characterized vapor probe, either a straight chain alkane or an acidic/basic probe, via a helium carrier gas at a given temperature and flow rate allows for

Figure 1

Inverse gas chromatography compared to standard analytical GC



the measurement of retention time for each specific probe injected one at a time into the column. Probe molecules used for IGC analysis include dispersive probes such as straight chain alkanes, ranging from heptane to dodecane, to measure non-specific, or Lifshitz-van der Waals, interactions. Polar probes such as toluene and ethyl acetate, which are good basic (electron donor) probes, and good acidic (electron acceptor) probes such as dichloromethane and chloroform measure specific, or acid/base, interactions. Varying the concentration of each probe injected into the column targets surface sites of varying energies, from the highest energy sites at low, or "infinite dilution," concentrations of typically 3-5% partial pressure, to lower energy sites at higher, "finite dilution," concentrations. Taking IGC measurements in both infinite and finite regimes, and utilizing a wide range of well-characterized probes, results in a comprehensive surface energy profile that both isolates important high energy sites and produces a heterogeneity distribution analysis of low energy sites that only IGC can provide.

IGC's unique combination of sensitivity, specificity, and versatility, as well as the simplicity of running an analysis without the troublesome sample preparation issues common to other techniques, makes IGC particularly powerful as a physicochemical characterization tool. Inverse gas chromatography can measure a wide range of properties in addition to surface energy, including phase changes as a function of relative humidity, which traditional differential scanning calorimetry (DSC) systems cannot measure [3], and even bulk properties such as diffusion and solubility parameters [4]. IGC can also analyze virtually any type of material that can be packed into a column, including natural and man-made fibers, polymer films, tablets, and even coatings immobilized onto a carrier surface like glass beads or applied to the inside of the glass column.

The ability to control a wide variety of parameters provides maximum experimental versatility and access to valuable thermodynamic and kinetic properties at both the surface and within the bulk. A properly equipped IGC system offers tight control of both the vapor injection concentration and the column temperature, and both the column temperature and background relative humidity in the column should be variable (see Figure 2). Operation in the infinite dilution regime allows for the identification of the highest energy sites, therefore identifying amorphous content or contaminants that often dominate at the surface and impact both particle-particle interactions and interactions with moisture in the environment [1]. That high degree of specificity with regard to the chemistry of surface groups that govern the solid-vapor interaction is very difficult to achieve with other techniques.

IGC compared to alternative techniques

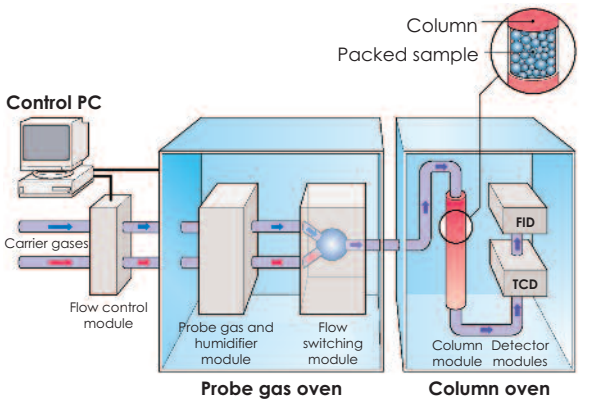
Compared to wetting techniques such as contact angle analysis, IGC provides greater reproducibility, simplicity, and versatility. Wetting techniques probe surface energies by measuring the angle formed at the three-phase solid-liquid-vapor interface when a drop of liquid of known surface tension and acid/base properties is deposited onto the surface of a solid. If the surface under evaluation is flat and smooth, contact angle measurements are straightforward and relatively easy to make. However, because powder surfaces are irregular and inherently subject to swelling, dissolution, and other non-equilibrium effects at the interface, accurate measurements can be difficult to obtain. An alternative wetting technique based on the Washburn equation involves measuring wicking rates of a liquid front in a column packed with powder. Unfortunately, variations in the column packing, particle size, and pore geometry can introduce inaccuracies and reproducibility problems into these measurements [2]. In addition, wetting techniques provide only an estimate of the average energy of all sites covered by the drop of liquid as it sits on the surface of the material without any degree of specificity with regard to the heterogeneity that exists across the entire surface or the distribution of the heterogeneous sites that vary as a function of processing conditions.

Using IGC for DPI formulation and process development

IGC provides a powerful tool for measuring surface energies and for predicting thermodynamic forces of adhesion between dissimilar drug and carrier parti-

Figure 2

Schematic of an inverse gas chromatograph



cles, as well as the forces of cohesion between like particles. The ability to control adhesion between the API and carrier is crucial because sufficient adhesion is necessary to maintain physical stability during processes such as blending and filling, but the adhesive force cannot be so strong that the drug will not detach from the carrier during inspiration [5]. Injecting the column with standard acid/base molecules to probe the polarity of a solid surface allows IGC to predict electron-donor/acceptor tendencies and triboelectrification effects, which are directly related to surface charge and adhesion [6]. By humidifying the carrier gas and injecting relevant probe vapors at different background humidities, IGC can help to determine optimum humidity levels for processing, which is useful since humidity can have a significant impact on DPI formulations [7]. Moisture introduced during processing may interact with surface groups, making them unavailable to other formulation ingredients and reducing the API-carrier interactions that control adhesion. On the other hand, moisture can also increase cohesion and agglomeration, making the product difficult to handle and reducing the inhalable fine particle fraction.

A novel approach to IGC and surface heterogeneity analysis

Whereas wetting techniques are limited to a single number that approximates the average surface energy, finite dilution IGC can produce a histogram that depicts the distribution of the energy sites that are inherent in most materials and subject to change as a function of processing conditions [8]. In this technique, gradually increasing the concentration of the vapor probe outside of the infinite dilution range into the finite dilution regime, between 5 and 95% relative to saturation, provides access to increasingly lower energy sites and creating a profile of the density of each heterogeneous site. The difference in the results between wetting techniques and finite dilution IGC is analogous to the difference between an average particle size and a particle size distribution.

The additional data provided by finite dilution IGC has allowed researchers to expand their analyses of factors critical to DPI formulation. For example, while various techniques, including gravimetric Dynamic Vapor Sorption (DVS), have demonstrated that milling operations can and do introduce a measurable amount of amorphous content onto the surface of lactose particles, profiling the changes in the energy distribution of the active sites induced by processing has until now proven an elusive challenge. Now, finite dilution IGC has been used successfully to analyze the differences in energy distribution on the surfaces of untreated, milled, and recrystallized lactose samples of similar particle size distribution [9]. The enhanced versatility of IGC provided by the finite dilution approach makes available a valuable tool for the development of inhalable formulations.

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