# *i*GC – A new instrumental technique for characterising the phyisco-chemical properties of pharmaceutical materials

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## *i*GC - Introduction

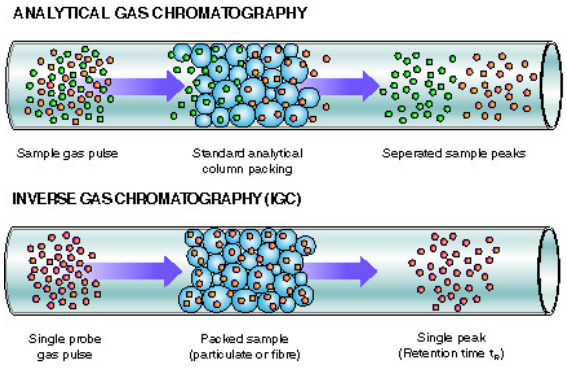
The increasing sophistication of pharmaceutical drugs and drug delivery technologies has created the need for new techniques to measure the physico-chemical properties of a wide range of solid pharmaceutical ingredients and formulations. Inverse gas chromatography (IGC) is a gas phase technique, first developed over 40 years ago, to study the surface and bulk properties of particulate and fibrous materials. IGC has the potential to unlock some of the more difficult to measure physico-chemical properties of pharmaceutical materials such as powder surface energies, acid/base/polar functionality of surfaces, diffusion kinetics, solubility parameters, surface heterogeneity and phase transition temperatures/humidities. These properties affect both the performance and processing of many materials from active drug compounds to excipients and fillers. However, until recently, applications within the pharmaceutical industry have been limited to a few studies of properties such as the surface energy of simple powders. All of these studies have been carried out upon 'home-built' pieces of apparatus, often employing manual or semi-automated experimental methods. This has lead to a diversity of results in the literature, often seemingly contradictory, due to the differences in instrument design, methodology, sample preparation and individual operator skill.

Surface Measurement Systems (SMS), a small innovative scientific instrument manufacturer, noted for its expertise in the moisture sorption behaviour of pharmaceutical materials, has recently developed the world's first commercial inverse gas chromatography instrument – *i*GC. This instrument, which has been developed in collaboration with a pharmaceutical academic/industrial consortium has been specifically designed to address many of the issues faced by physical properties researchers in the pharmaceutical industry, including fully automated operation and the ability to measure samples in a controlled humidity environment. This article gives a brief description of the technique, the instrument and some examples of its application within pharmaceutical physico-chemical analysis.

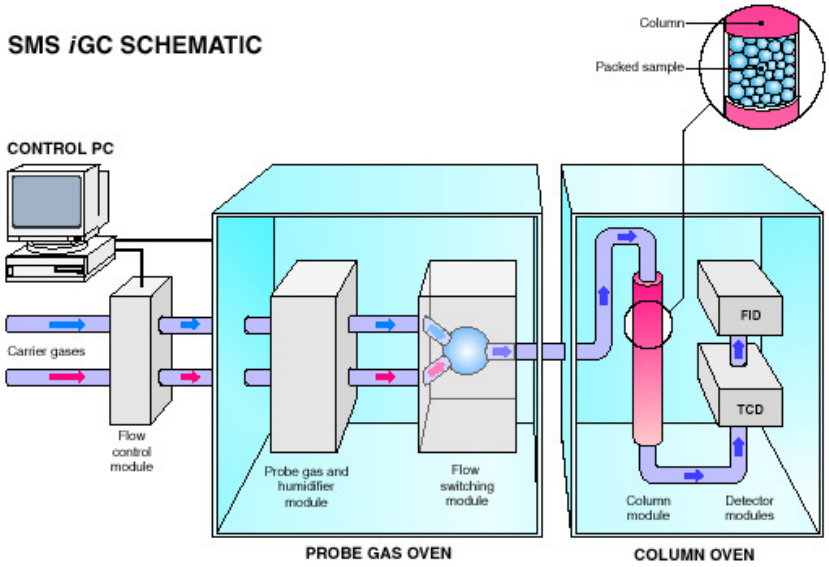
## IGC – The Technique

The principles of IGC are very simple, being the reverse of a conventional gas chromatographic (GC) experiment. An empty column is uniformly packed with the solid material of interest, typically a powder, fibre or film. A pulse or constant concentration of gas is injected down the column at a fixed carrier gas flow rate and the retention behaviour of the pulse or concentration front travelling down the packed column is then measured by a detector. A series of IGC measurements with different gas phase probe molecules allows access to a wide range of phyisco-chemical properties of the solid sample. The fundamental property measured by IGC from which most of these properties are derived is known as the retention volume $V_N$. This is a measure of how strongly a given gas probe molecule interacts with the solid sample. From a series of measurements of $V_N$ a whole variety of thermodynamic and kinetic parameters can be readily calculated. Several in depth reviews of the theory and application of IGC can be found in the open literature [1,2].




## *i*GC – The Instrument

A cutaway schematic of the SMS *i*GC is shown in the picture below. The *i*GC consists of a control PC, a flow control module, a probe gas oven, and a sample column oven. The instrument incorporates a number of

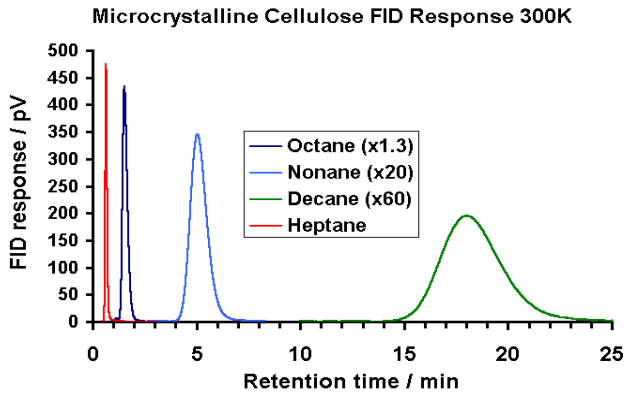


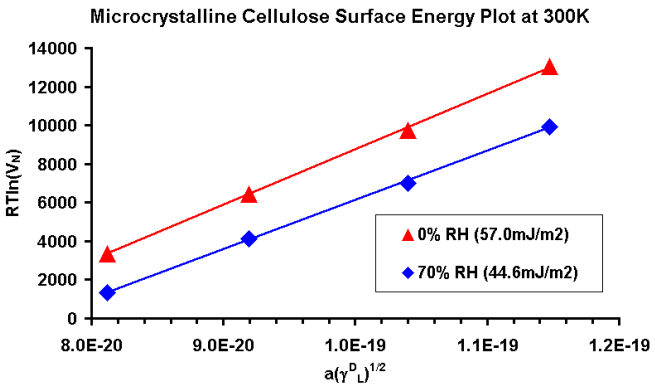
innovative design features including the ability to use up to ten different gas probe molecules in any one experiment and the ability to condition the sample under a wide range of humidity and temperature conditions. The probe gas oven keeps all ten probe vapours/gases and the vapour humidifier at a specified temperature in order to facilitate accuracy and repeatability of injections. A separate sample column oven allows the sample to be studied over a very wide temperature range. The instrument is designed for maximum flexibility, allowing both single peak and frontal injection methods to be employed, all with background humidity control. Thermal conductivity (TCD) and flame ionisation (FID) detectors are fitted as standard, however it is also possible to add further detectors such as mass spectrometers for applications where volatile compounds are released from the sample being studied. SMS have also developed a column packing accessory, which provides a significant advantage in both the time and repeatability of the packing of powdered samples into columns.

### *i*GC – Surface Energy of Microcrystalline Cellulose

The surface energy of pharmaceutical powders can affect their processing behaviour including flowability and miscibility with other powders. Traditionally, surface energies are measured by liquid wetting angle techniques, however these are very difficult to implement reproducibly on free flowing powders. IGC readily lends itself as a technique to measure the surface energies of powders since it does not involve liquid wetting and therefore does not require compression of the particles. In addition, the SMS *i*GC instrument also allows for the first time the measurement of surface energies as a function of humidity.




To measure the surface energy of solid materials with IGC, a series of pulsed injections are made through the packed sample column using different probe gas molecules. These measurements are carried out at infinite dilution where only very few probe molecules are available for the interaction with the surface. For this reason only the highest energy sites on the surface are covered which provides the highest sensitivity of the measured parameters.




In the case of the dispersive component of surface energy ($\gamma^D$), these probe molecules will be a series of alkanes with different carbon chain lengths as demonstrated in the figures.

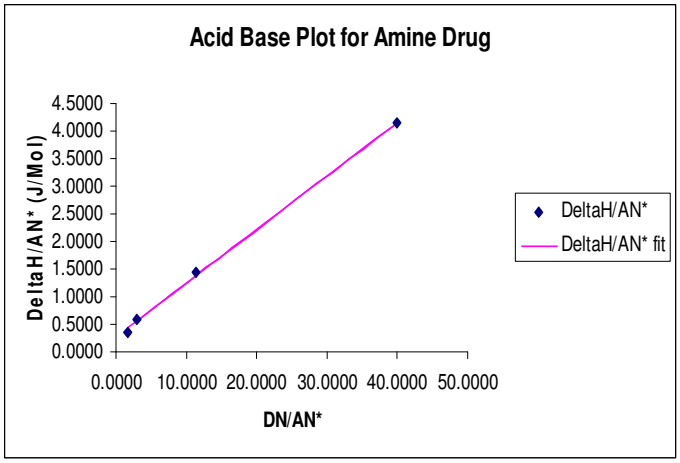
From the surface tension of the probe gases in their liquid phase and their retention behaviour on the solid sample, the surface energy of the solid material can then be calculated. The figure above shows the retention behaviour for a series of alkane probes on microcrystalline cellulose at 300K for both 0% RH and 70% RH measured using an *i*GC instrument. The calculated $\gamma^D_S$ values for microcrystalline cellulose are 57.0 mJ/m$^2$ at 0% RH and 44.6 mJ/m$^2$ at 70% RH. The reduction in dispersive surface energy with humidity may be explained by the physical adsorption of water molecules on the surface. The practical implications of this are that the powder may be expected to exhibit different flowability and mixing properties depending upon the humidity in the environment.

Due to the infinite dilution conditions the surface energy obtained from IGC measurements is an extremely sensitive parameter. The interaction with the highest energy sites allows differences between rather similar materials to be seen, which makes IGC so successful, e.g. in the characterisation of polymorphs [3] or in the identification of batch-to-batch problems [4].

### *i*GC – Acid-Base Parameters of a Drug Component

Apart from the dispersive contribution, for many applications specific polar interactions need to be considered since the acid-base chemistry of the surface plays in important role in formulation.

As mentioned before, alkanes are injected to determine the dispersive contribution of the surface energy. If polar probe molecules are injected in addition then acid-base parameters can be obtained. The experimental points for the polar probe molecules will be located beyond the alkane straight line in the surface energy plot. The distance between each point and the straight line represents the specific contribution of the interaction, which is expressed in the specific free energy, ΔG. By using well-known concepts such as Gutman or van Oss, acid-base parameters can be calculated.




The figure shows the plot of polar probes on an amine drug at 303K for 0%RH. The Gutman approach is used to calculate the acid and base parameters (acceptor number, $K_a$ and donor number $K_b$) from the free energy values [5]. It can be seen in the graph that the probe molecules (methanol, acetonitrile, THF and ethyl acetate) lie along a straight line. The acceptor number $K_a$ yields to 0.1 and the donor number $K_b$ to 0.27. This reflects the basic character of the drug as its surface chemistry is dominated by the amine groups.

The acid-base parameters cannot only be used to characterise the surface chemistry of a drug or excipient but also to predict drug-carrier interactions. For this purpose the acid-base parameters for the drug and the carrier are determined separately as described above. Using the approach of Schultz et al a parameter can be calculated reflecting the strength of interaction between both materials. This allows for the comparison of various excipients and for the prediction of how strongly they will interact with a certain drug.

### *i*GC – Glass Transition Temperature of Maltose

Many pharmaceutical materials display polymorphism (more than one form or phase in coexistence) which can be highly dependent upon both temperature and humidity. In particular, excipients or active compounds can show very unstable polymorphic behaviour in the presence of moisture which is detrimental to the long term stability of the formulated product. This is often due to the amorphous character induced in the material by milling or spray drying of the powder. Although techniques already exist for measuring the glass transition temperatures of materials (e.g. DSC, DMTA), IGC is unique in being able to measure the glass transition behaviour both as a function of temperature and humidity.

In order to measure a phase transition temperature by IGC, a series of measurements of $V_N$ for a given gas probe molecule at different temperatures is performed. A plot of the retention behaviour as a function of 1/T will yield a straight line, which is equivalent to the heat of sorption, provided there is no phase transition. However, where a phase transition does occur, an inflexion point is expected. The figure shows such a plot for α-D-maltose monohydrate [6], a commonly used sugar, at 0%RH with decane as the probe molecule. In this case the sample shows a pronounced minimum at the glass transition temperature, and the calculated value of $T_g$ agrees well with literature data. A series of measurements at different background humidities then allows the glass transition temperature to be determined as a function of relative humidity as outlined in Table 1.

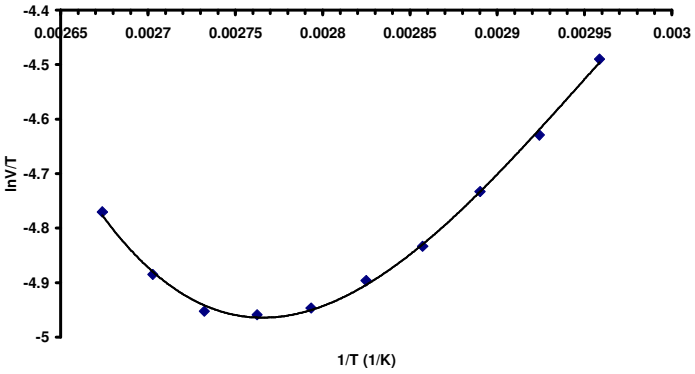



*Table 1. Humidity dependence of $T_g$ of α-D-Maltose monohydrate.*

| RH (%) | Tg (K) |
|---|---|
| 0 | 361.6 |
| 5 | 348.6 |
| 10 | 338.8 |
| 15 | 332.5 |

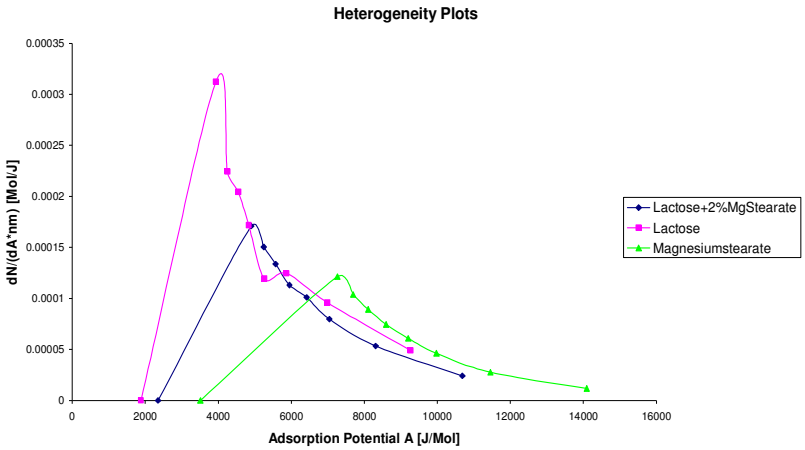
 

These results clearly show that as the humidity is increased, the glass transition temperature decreases rather markedly even at relatively low RH values. This is due to the absorbed moisture plasticising the amorphous regions in the maltose, thus allowing the glass transition to occur at lower temperatures. The practical implications of such data for pharmaceutical materials is that IGC can be used to predict the conditions under which stable processing and storage of materials can be performed.

### *i*GC – Surface Heterogeneity of Lactose and Magnesium stearate

In a previous chapter it was shown how surface energy determinations can provide useful information in various pharmaceutical applications. These measurements were carried out at infinite dilution, where small differences between materials can be detected due to the interaction of the probe molecule with the highest energy sites on the surface. Although this method is extremely sensitive it provides information about the high energy sites only. For many applications it is desirable to study the entire surface and therefore to bring lower energy sites into consideration as well. This is particularly useful for the understanding of sorption mechanisms and the prediction of the interaction at interface boundaries of blends and composites.

An interesting example is the impact of small amounts of Magnesium stearate on Lactose carrier systems in drug delivery [7]. It is well known that surfactants such as Magnesium stearate alter the properties of the system but infinite dilution measurements of the surface energy show no significant differences for Lactose with and without the surfactant. For this reason, surface heterogeneity profiles have been determined by a variation of the concentration of hexane as a probe molecule. The retention volume obtained can be converted into the distribution function Φ and the corresponding partial pressure into the adsorption potential A. The figure shows the heterogeneity profiles of pure Magnesium stearate, partially amorphous Lactose, and a mixture of this Lactose with 2% Magnesium stearate.




It can be seen that there are significant differences in the population of the energy sites. Magnesium stearate shows a distribution with one significant maximum around 7.2 kJ/Mol while the distribution

curve of Lactose is located at much lower adsorption potentials (around 3.9 kJ/Mol). The shoulder at 5.5 kJ/Mol indicates an amorphous contribution. The mixture with 2% Magnesium stearate shows only one single peak with a maximum located at a similar adsorption potential to the amorphous peak of Lactose. These results are interesting for two reasons: first of all, it shows that even small amounts of a surfactant cause an increase in the mean adsorption potential. Secondly, it explains why infinite dilution measurements show no significant difference between Lactose with and without surfactant since the high energy sites of Lactose (the amorphous contribution) are located at similar energy levels as those of the mixture. It may be concluded that the improvements of the Lactose processing behaviour are due to a more uniform energy distribution caused by the surfactant.

### *i*GC – Solubility Parameters of Lactose

The solubility parameter is a property, which was originally derived from the characterisation of polymers but has become increasingly applied in the characterisation of pharmaceutical materials in recent years. This is due to the direct relationship of the solubility parameter with the cohesion energy. It is for this reason that in some papers the expression “cohesion parameters” is used. The cohesion energy is an important parameter as it describes the intermolecular forces inside a material and is therefore directly related to stability and formulation issues.

There are different approaches for the determination of the solubility parameters. This calculations are usually either based on the Hansen theory, which involves the splitting of the solubility parameter into dispersive ($\delta_d$), polar ($\delta_p$) and hydrogen-bonding ($\delta_H$) contributions or on the Hildebrandt theory, which calculates the total solubility parameter.

A typical example is the determination of the solubility parameters for Lactose according to Hansen [8]. In this experiment the retention volume is measured for an injection of various probe molecules which have a considerable interaction with the solid component. The retention volume can be transformed into an activity coefficient. If then the solubility parameters of the probe molecules are known the solubility parameter of the sample can be calculated. The calculation yields the following results for Lactose: $\delta_d$ =19.9, $\delta_p$= 21.7 and $\delta_H$ = 25.6 $MPa^{1/2}$. The total solubility parameter is 39.1 $MPa^{1/2}$.

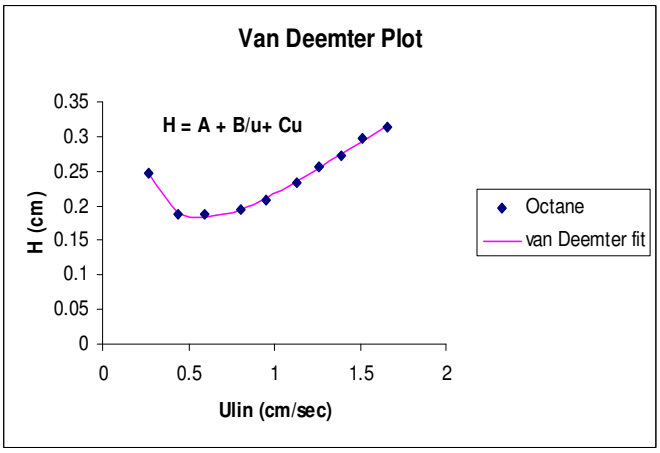
Solubility parameters may predict the absorption of simple solvents or complex drug molecules across a variety of substrates. They have been also correlated with oral absorption [9] and nanoparticle formation [10].

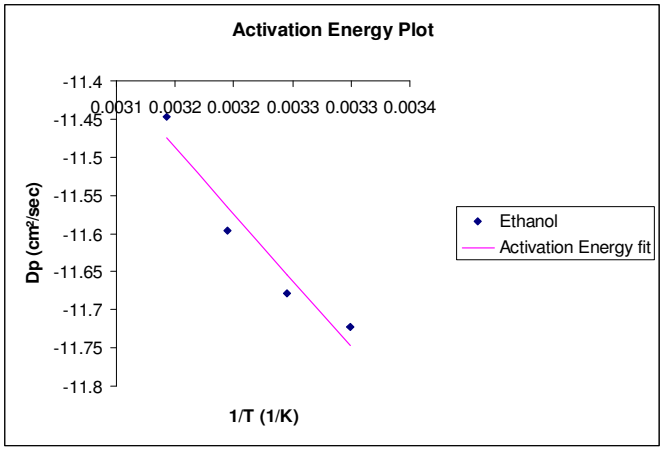
### *i*GC – Diffusion and Activation Energy of Diffusion for an Anti-Obesity Drug

Bulk absorption behaviour has a considerable impact in manufacturing and storage stability. The diffusion coefficient is an important property since it provides valid information about bulk absorption behaviour of drugs and excipients.

There are different approaches known in the literature. A simple and fast determination of the diffusion coefficient uses the van Deemter approach. For this calculation the retention time of the probe molecule is measured at different carrier gas flow rates. The retention time is then transformed into the theoretical plate height H, which is plotted versus the linear flow rate u. The resulting curve is fitted with the van Deemter equation as shown in the figure.




A, B and C are constants describing different diffusion regimes. C represents all non-equilibrium properties and is therefore directly related to the bulk diffusion constant. In the actual example [11], the diffusion of ethanol and octane into an anti-obesity drug was measured. The diffusion coefficient for ethanol yields to $8.12*10^{-6}$ while octane gives $4.12*10^{-5}$ $cm^2$/sec (for a particle size of 18.2µm). The values clearly indicate that the permeability of octane is higher than the permeability of ethanol. This could be due to the stronger interaction of ethanol with the hydrophilic material. Thus, polar molecules are retained more strongly and pass more slowly through the drug particles than non-polar probe molecules. The absolute values are rather high for diffusion coefficients due to the relatively large particle size.

If the experiment is carried out at different temperatures the activation energy of diffusion can be obtained. This is another very useful parameter since it allows an estimation of how fast a solvent can penetrate the bulk structure of a material. This information can be helpful in predicting the storage stability of a particular component if water is used as a probe molecule in the measurement. A low activation energy for water would mean that water can easily diffuse into the material and may cause phase transitions or other unwanted effects while a high activation energy means that there is a high activation barrier for water and therefore a much slower water uptake. In the latter case the material would have a rather high storage stability.

**Conclusions**

The above data demonstrates the potential of *i*GC as a new technique available to researchers within the pharmaceutical industry. For the first time, new advances in instrumentation have made it possible to measure physico-chemical properties of pharmaceutical powders which were previously very difficult or impossible to perform. In particular it is now possible to measure surface and bulk properties of powders reproducibly and accurately under controlled humidity conditions. Thus pharmaceutical researchers can use *i*GC to characterise their materials under temperature and humidity conditions most relevant to their real world applications. The interested reader is directed towards the articles listed below which explain the detailed theory and many more potential applications of *i*GC to particulate and fibre characterisation.

**References**

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