Surface Measurement Systems
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iGC SEA Application Note 301

An overview of iGC SEA – A new Instrumental Technique for Characterising the Phyisco-chemical Properties of Pharmaceutical Materials

Surface Measurement Systems Ltd

This application note gives a brief description of the technique, the instrument and some examples of its application within pharmaceutical physico-chemical analysis.

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 SEA) is a gas phase technique, first developed over 40 years ago, to study the surface and bulk properties of particulate and fibrous materials. IGC SEA 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 led 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.

Figure 1. iGC-SEA instrument.

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 – *iGC SEA*. 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.

iGC SEA – The Technique

The principles of *IGC SEA* 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 SEA* 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 SEA* 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 SEA* can be found in the open literature [1,2].

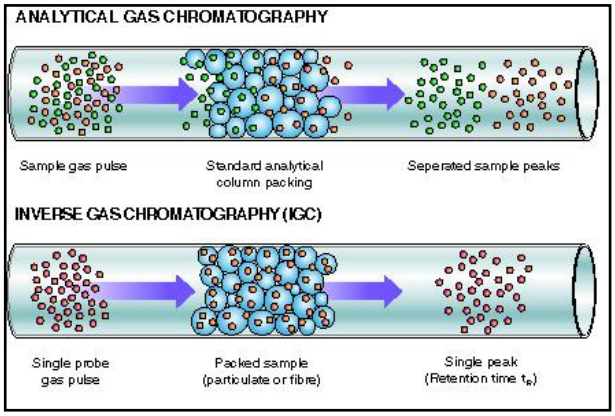
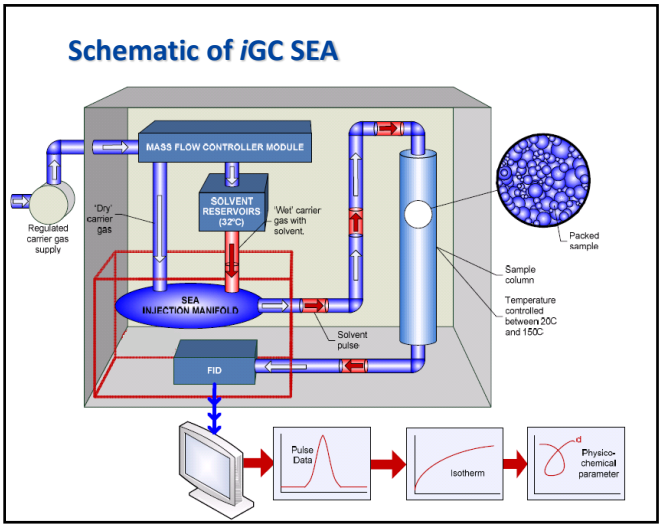


Figure 2. Schematic of IGC principle.

iGC SEA – The Instrument

A cutaway schematic of the SMS *iGC SEA* is shown in the picture below.



The *iGC SEA* 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. A flame ionisation (FID) detector is 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.

iGC SEA – 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 SEA* 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 *iGC SEA* 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 SEA*, 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 (γ^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 *iGC SEA* instrument. The calculated γ^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.

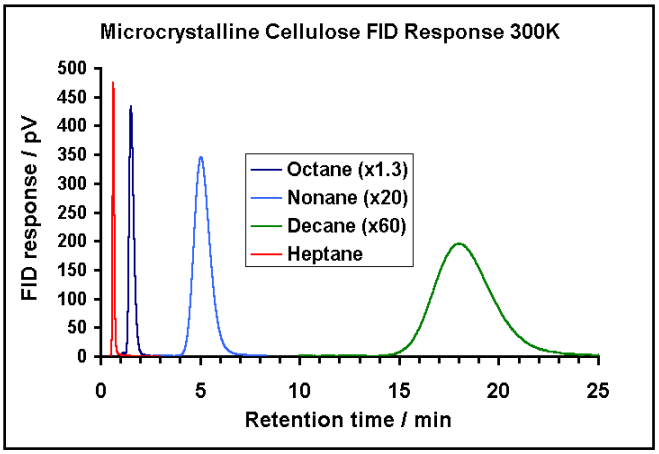


Figure 4. n-alkane injections on MCC.

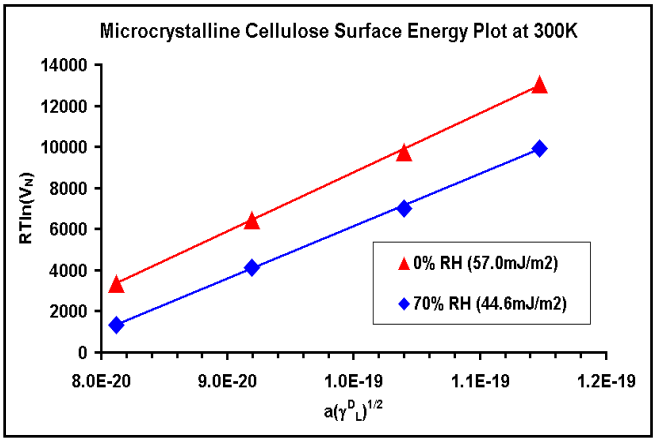


Figure 5. Dispersive surface energy plots for MCC at 0 and 70% RH.

Due to the infinite dilution conditions the surface energy obtained from *IGC SEA* 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 SEA* so successful, e.g. in the characterisation of polymorphs [3] or in the identification of batch-to-batch problems [4].

iGC SEA – 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.

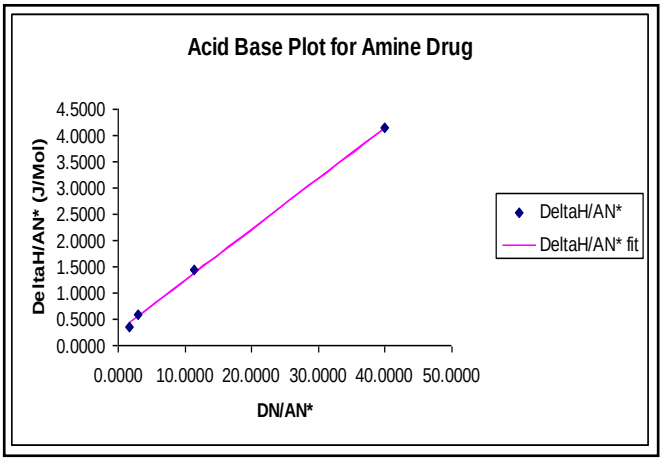


Figure 6. Gutmann acid-base plot on an amine drug.

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.

iGC SEA – 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 SEA* 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 SEA*, 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.

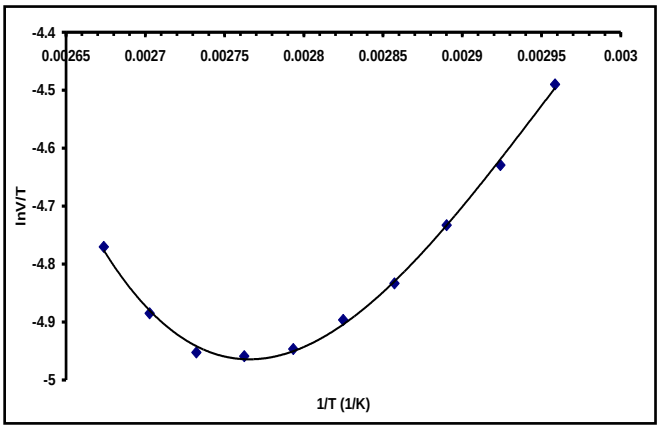


Figure 7. Glass transition results on a α-D-Maltose monohydrate sample.

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 SEA* can be used to predict the conditions under which stable processing and storage of materials can be performed.

iGC SEA – 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 (δ_d), polar (δ_p) and hydrogen-bonding (δ_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 [7]. 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: δ_d =19.9, δ_p= 21.7 and δ_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 [8] and nanoparticle formation [9].

iGC SEA-Surface Heterogeneity of Mannitol

Since real solid surfaces are fundamentally inhomogeneous, a single value of surface free energy is not necessarily representative of the entire surface. Real solids in fact exhibit a range of lower and higher energy sites on their surfaces due to presence of different types of surface functional groups, surface topographies, surface irregularities or impurities [10].

In this study, detailed surface energetics of a model pharmaceutical excipient: D-mannitol, with and without surface methylation was determined using *iGC SEA*. D-mannitol is a particularly interesting example since it is known to have, energetically, a high level of inhomogeneous surface on the native mannitol crystal [11].

Surface Energy Heterogeneity

Dispersive, γ_S^D and specific (acid-base), γ_S^{AB} surface energy profiles obtained directly from the *iGC SEA* for silanised and AR samples are shown in Figure 8 and Figure 9, respectively.

It can be clearly observed that AR D-mannitol is energetically more active and more heterogeneous, meaning the surface energy changes as a function of surface coverage. There is a notable difference between maximum and minimum γ_S^D values, ranging from about 37.50 and up to 53.00 mJ/m^2.

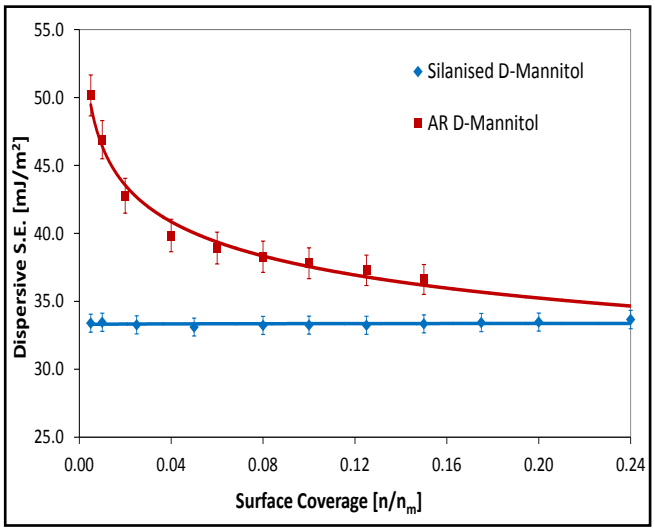


Figure 8. Dispersive surface energy profiles (as a function of surface coverage).

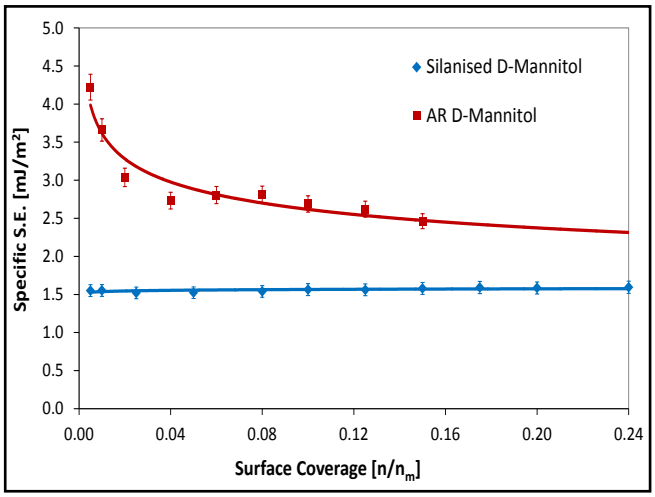


Figure 9. Specific (acid-base) surface energy profiles.

Full description of surface heterogeneity is available in Application note 224.

Conclusion

The above data demonstrates the potential of *iGC SEA* 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 *iGC SEA* 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 *iGC SEA* to particulate and fibre characterisation.

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