Review

INVERSE GAS CHROMATOGRAPHY – A DIFFERENT APPROACH TO CHARACTERIZATION OF SOLIDS AND LIQUIDS

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Abstract

IGC has become powerful technique in evaluating the properties of solids and liquids. It provides access to several physico-chemical properties of such materials including their surface energy, phase transitions, crystallinity and acid-base characteristics. Kinetic parameters such as diffusion coefficients can be determined. IGC is used to characterize a wide range of product types including pharmaceuticals, natural and synthetic polymers, food ingredients and products, minerals etc.

Key words: inverse gas chromatography, acid base interactions, surface free energy, surface characterization

Introduction

The application of gas chromatography in the study of polymers and other nonvolatile materials has long been hampered by the non-volatility of these materials. The study of nonvolatile materials using gas chromatography was initiated by work of Smidsrød and Guillet,[1] in which polymers were used as the stationary phase and the interactions with known, volatile solutes gave a measure of the physical and chemical state of the material under investigation. The name "inverse gas chromatography" (IGC) was given to this technique.

After the introduction of IGC in 1967 and subsequent theoretical developments, its application in the material sciences has grown rapidly. It has been used for the characterization of polymers, copolymers, blends, biopolymers, fibers, composites, coatings and their ingredients, including pigments, catalysts, chemicals, paper, etc. The major advantages of IGC are its simplicity and user friendliness. The necessary equipment is a standard gas chromatograph, equipped with a short packed column. The sample within the column is mixed with an inert support material (glass beads) or applied on its surface as a thin film. IGC can be used for data collection over a wide temperature range. A large variety of volatile standards with very different characteristics and concentration, can be used. The carrier gas can be either nitrogen or helium. Some authors in recent applications used carrier gas contained a controlled amount of water vapour.[2,3]

IGC has become a widely used technique for the characterization of polymers, in particular their Lewis acidic character and their Lewis basic character[4,5,6,7,8] and their thermodynamic behaviour such as their glass transition temperature. In addition, the transition temperatures of liquid crystals,[9,10] the nature and level of interactions in composite systems such as solid – polymer composites have been studied.[11,12] Adsorption studies of volatile materials on solid surfaces and their heterogeneity, using IGC, have been published recently.[13,14]

Nowadays, a growing number of published papers describing the application of IGC for the characterization of the surface properties of solid surfaces of pharmaceutical materials has proven to be of value.[15,16,17] The correct characterization of drugs and excipients surfaces is important in production processes such as wet granulation, suspension formation, dissolution and film coating. IGC has a part to play in such characterization.

Theoretical aspects of the IGC evaluations

Net retention volume measurements

The surface properties of a material under investigation are determined from net retention volume determinations.

The net retention volume of volatile standard (V_n) is directly related to its thermodynamic interaction with the surface. Thus:

$$V_n = j \cdot F \cdot (t_R - t_o) \tag{1}$$

Here, t_R is the retention time of the probe, t_o is the zero retention reference time of the non-interacting probe, such as methane and j is the James-Martin correction factor for gas compressibility, given by:

$$j = \frac{3}{2} \cdot \frac{\left[\left(\frac{P_i}{P_o}\right)^2 - 1\right]}{\left[\left(\frac{P_i}{P_o}\right)^3 - 1\right]} \tag{2}$$

Here, P_i is the pressure at the column inlet and P_o is the pressure at the column outlet.

Free energy of adsorption

Data from IGC measurements at infinite probe dilution can lead to the determination of the molar free energy of adsorption, ΔG_m^{ads} as given by the following expression:

$$\Delta G_m^{ads} = -RT \cdot \ln(V_n) + C \tag{3}$$

Here, R is the ideal gas constant, T is the absolute temperature of the column and C is a constant, depending on the reference state of adsorption.

If polar probes are injected into the column, dispersive interactions and specific intractions take place between the probe and the material in the column. ΔG_m^{ads} is then given by:

$$\Delta G_m^{ads} = \Delta G^D + \Delta G^{SP} \tag{4}$$

Here, ΔG^D refers to dispersive interactions and ΔG^{SP} to specific interactions.

Fowkes[18] relationship between the work of adhesion and the dispersive component of the surface energy of the solid and the probe is used to calculate the dispersive component of the solid. Thus,

$$RT \cdot \ln(V_n) = 2N \cdot a \cdot \sqrt{\gamma_L^D \cdot \gamma_S^D} + C \tag{5}$$

Here, N is Avogadro's number, a is the surface area of the probe molecule. γ_L^D and γ_S^D are the dispersive component of the surface energy of the liquid (i.e. probe) and the solid, respectively.

By plotting $RT \cdot \ln(V_n)$ as a function of $a \cdot \sqrt{\gamma_L^D}$ for n-alkanes, a straight line is obtained (Figure 1). γ_S^D is calculated from the slope of this line.

When polar probes are being used, the vertical distance between the polar probe data point and the vertical projection to the reference n-alkane line represents the specific polar component of the free energy of adsorption. By plotting ΔG^{SP} of polar molecules as a function of temperature, we can calculate the specific enthalpy (ΔH^{SP}) and the specific entropy (ΔS^{SP}) of adsorption from the following expression:

$$\Delta G^{SP} = \Delta H^{SP} - T \cdot \Delta S^{SP} \tag{6}$$

The specific interactions between polar molecules and the material of interest can be used to determine the acidic constants and basic constants using the donor (DN) and acceptor (AN*) numbers for the polar probes (Table 1).[19]

Table 1. Properties of liquids used in IGC experiments.[19,20,21]

	A(Å^2)	γ_l^d (mJ/m^2)	DN	AN	AN*
C_6H_{14}	51.5	18.4	0	0	0
C_7H_{16}	57.0	20.3	0	0	0
C_8H_{18}	62.8	21.3	0	0	0
C_9H_{20}	68.9	22.7	0	0	0
THF	45	22.5	20.0	8.0	0.5
Diethyl ether	47	15	19.2	3.9	1.4
$CHCl_3$	44	25.9	0	23.1	5.4
CCl_4	46	26.8	0	8.6	0.7
C_6H_6	46	26.7	0.1	8.2	0.17
Acetone	42.5	16.5	17.0	12.5	2.5
Ethylacetate	48	19.6	17.1	9.3	1.5

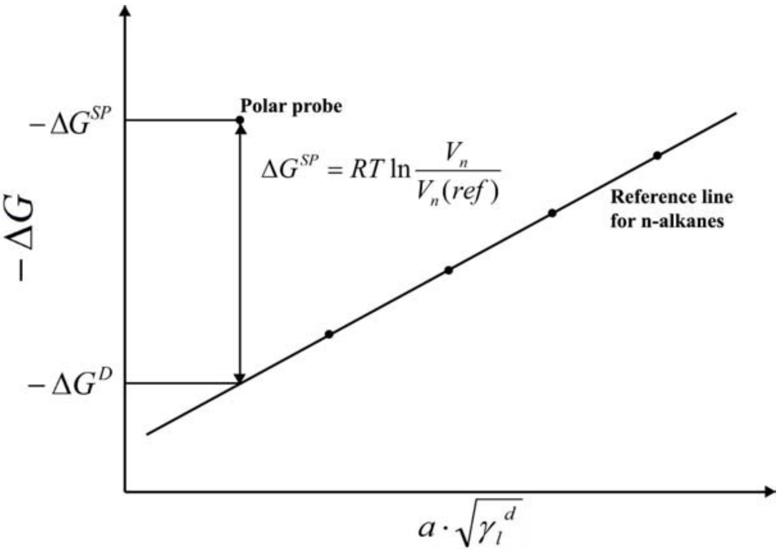

Figure 1. Schematic representation of a RT·ln(V_n) vs. $a \cdot \sqrt{\gamma_L^D}$ diagram for n-alkanes and polar probes.

Gutmann's equation is used to calculate of the acid-base components of the surface energy:

$$\frac{\Delta H^{SP}}{AN^*} = K_D + K_A \cdot \frac{DN}{AN^*} \tag{7}$$

K_A is the acceptor constant and K_D is the donor constant of the stationary phase. Equation (7) has been generally used to determine the acid-base character of many solid materials as well as those of liquid polymers. [22,23,24]

Prediction of interactions

Using the acid number and the base number of two different interacting materials that are used in a coatings formulation, for example a polymeric film former and a pigment, it is possible to define a specific interaction parameter, A, describing the acid/base interaction between the two types of materials. This is the basis of Equation (8), where

$$A = AN_R \cdot DN_P + AN_P \cdot DN_R \tag{8}$$

The index, R denotes the polymeric film former and P the pigment. This approach was used by Schultz and Lavielle[25] for the definition of the specific interaction parameter for a system consisting of carbon fibers and an epoxy polymeric matrix. Several authors have used this approach for the characterization of different materials, used in composites and coatings. Balard and Papier[26] characterized fillers for paints. Voelkel[27] applied this concept to polymers, fillers, surfactants and other materials. Lara and Schreiber[28] used a similar expression for polymer - pigment systems, defining a pair-interaction parameter, I_{SP}, as shown in Equation (9).

$$I_{sp} = \sqrt{AN_R \cdot DN_P} + \sqrt{AN_P \cdot DN_R} \tag{9}$$

The I_{SP} values may be regarded in a more arbitrary manner. Researchers have found the good agreement between the I_{SP} value and the adsorption process parameters for film formers and a phthalocyanine green pigment. However, this is not always the case. Despite the presence of a high I_{sp} values, sometimes a lack of adhesion indicates that specific interactions do not prevail in the process. Thus, interpretation of the acquired data and development of derived interrelationship needs to bear in mind the characteristic properties of the resultant composite. Thus, there is a need to be sure that the predictions made on the basis of AN/DN logic are actually realized for the coating system under evaluation.

Sorption isotherms

Inverse gas chromatography is a useful technique for providing data relating to the adsorption of gases and of vapours onto a solid surface, whether polymeric or otherwise.

In order to determine an adsorption isotherm by the IGC technique, the net retention volume V_N has to be measured at different probe concentrations. According to the theory of the gas chromatography, the probe vapours are adsorbed and desorbed in and through the chromatographic column. Because of the increased volume of the injected probe, the shape of the eluted peak is affected and distorted. The process is carried out at a finite concentration as the volume of the gaseous probe is between 0.1 μL and 2.5 μL. The front profile of the eluted peak becomes increasingly diffuse while the rear profile (tail) remains almost vertical with increase in the volume of the probe. The relationship between the net retention volume (V_N) and the number of moles of probe, adsorbed per gram of adsorbent is shown in Equation (10).

$$n = \frac{1}{m \cdot R \cdot T} \int_0^p V_N dp \tag{10}$$

Here, n is the number of moles of probe, adsorbed per gram of adsorbent, m is the weight of the adsorbent in the column, R is the gas constant, T is the absolute temperature of the column and p is the partial pressure of the probe.

The amount of the adsorbed probe can then be calculated as shown in Equation (11).

$$n = \frac{w \cdot S_a}{m \cdot S_c} \tag{11}$$

Here, S_a denotes the area, as shown in Figure (2). This area is bounded by the adsorption envelope of the peak maximum of superimposed chromatograms with different probe concentrations and a time axis, starting at t_M. This time axis value (t_M) is the retention time of methane. S_c denotes the calibration peak area of the known amount w of the probe injected and m is the amount of the adsorbent in the column.

Katz and Gray[29] used this method for the determination of adsorption isotherms of n-alkanes on cellophane. Due to sufficient precision of measured adsorption isotherms, they were able to determine the adsorption heat values and adsorption entropy values.

The same principle was used by Doris and Gray[30] for the adsorption isotherm determination of hydrocarbons on cellulose and on wood fibre surfaces. Gray and Guillet[31] determined adsorption isotherms from the shape of the single gas chromatographic peak for n-decane and n-hexanol on poly(styrene) and on poly(methyl methacrylate). Papier et al.[32] evaluated adsorption isotherms for benzene and for hexane on glass fibres and silicas. Many other researchers have used this chromatographic approach for the determination of adsorption isotherms. Among these are Shiyao et al.[33], Demertzis and Kontominas[34], Gilbert[35] and Papier et al.[36]. Three reasons for choosing this technique are: it is quick, simple and gives meaningful results. The limitations are the same as for the IGC in general. Among these could be the structural changes in the support material due to exceeding the T_g values and events related to preferential adsorption phenomena, which can occur when using strongly interacting polar probes.

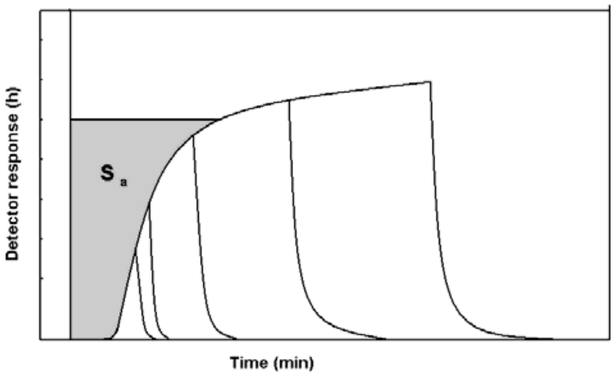

Figure 2. Gas chromatographic representation of larger probe injections. Shaded area denotes S_a.

The glass transition and crystallinity of polymer stationary phases

A graph representing the variation of the retention volume versus the reciprocal of the absolute temperature of the column is a retention diagram or Van't Hoff retention diagram. This variation is, in general, linear and the slope is related to the enthalpy of the process, solution in the liquid stationary phase or adsorption on the solid surface, if solid material is in the column. The relationship is shown by Equation (12). Thus:

$$\frac{\partial \operatorname{Ln} V_g}{\partial (1/T)} = -\frac{\Delta H}{R} \tag{12}$$

Here, $-\Delta H$ is the corresponding enthalpy and R is the gas constant.

The retention diagram could also reveal certain singularities due to transitions of the stationary phase. Such graphic representation is shown in Figure (3):

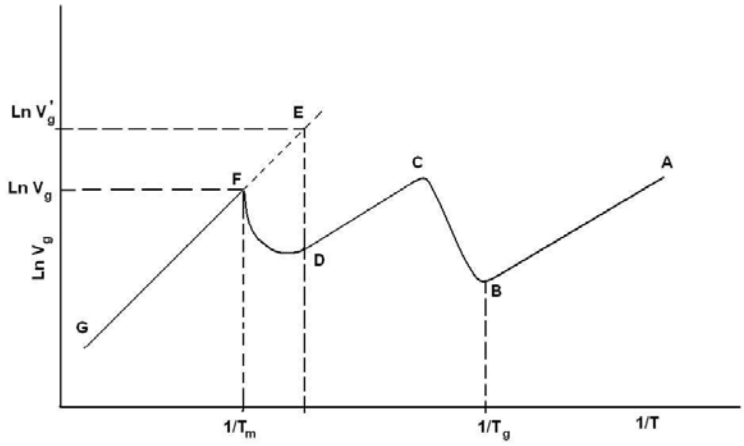

Figure 3. Retention diagram.

In the temperature region corresponding to segment AB of Figure 3, the polymer is below its glass transition temperature (T_g). Retention is caused solely by the surface adsorption and the relationship is linear. At point B, corresponding to the glass transition, penetration of the solute into the bulk of the polymer stationary phase begins and nonequilibrium conditions prevail. At temperatures below the melting point of the polymer, in region CD, retention is limited to bulk sorption of the solute into the amorphous domain of the stationary phase. Upon melting, in region DF, the amount of the amorphous phase increases, leading to an increase in retention volume. At temperatures above the melting point (T_m), segment FG, a linear retention diagram is again obtained, corresponding to bulk sorption into the completely amorphous polymer stationary phase. By extrapolating the straight line from point D to point E, the retention volume for the theoretically amorphous polymer can be computed. Comparison with the experimental retention volume (in point D) yields the amorphous fraction of the stationary phase. The crystallinity can then be calculated as shown below:

$$wt\%\ (crystallinity) = 100\left[1-\left(\frac{V_g}{V_g^{'}}\right)\right] \tag{13}$$

where V_g and V_g’ are specific retention volumes in points E and F from the retention diagram.

The IGC method is particularly attractive becouse it requires no apriori information concerning the polymer. Consistency of the crystallinity, as determined by IGC and other methods, is usually quite good.

Thermodynamics of the solute – polymer interactions

The fundamental information concerning the solute-polymer interactions, obtained by IGC, is the specific retention volume, the volume of the carrier gas under standard conditions that is required to elute the probe, per gram of stationary phase:

$$V_g^0 = \frac{V_n \cdot 273{,}2}{T \cdot m} \tag{14}$$

Here, V_g^0 is the specific retention volume, V_n is the net retention volume, T is the column temperature and m is the mass of the polymer in the column.

The weight fraction activity coefficient of the probe at infinitive dilution, Ω_1^∞, is obtained from the following equation:

$$\mathrm{Ln}\Omega_1^\infty = \mathrm{Ln}\left(\frac{273{,}2 \cdot R}{V_g^0 \cdot p_1^0 \cdot M_1}\right) - \frac{p_1^0\left(B_{11} - V_1^0\right)}{R \cdot T} \tag{15}$$

Here, R is the gas constant, p_1^0, M_1, B_{11} and V_1^0 are the saturated vapour pressure, molecular weight, gaseous state second virial coefficient and molar volume of the solvent at the column temperature T, respectively.

The Flory-Huggins interaction parameter (χ_{12}^∞) at infinitive dilution of solvent[37] is given by the following equation:

$$\chi_{12}^\infty = \mathrm{Ln}\left(\frac{273{,}2 \cdot R \cdot v_2}{V_g^0 \cdot p_1^0 \cdot V_1^0}\right) - 1 - \frac{p_1^0\left(B_{11} - V_1^0\right)}{R \cdot T} \tag{16}$$

Here, v_2 is specific volume of the polymer.

The partial molar heat of sorption ($\Delta\overline{H}_{1,sorp}$) of the solvent that is sorbed by the polymer is given as:

$$\Delta\overline{H}_{1,sorp} = -R\frac{\partial\left(\mathrm{Ln}V_g^o\right)}{\partial\left(1/T\right)} \tag{17}$$

The partial molar heat of mixing ($\Delta\overline{H}_1$) at infinitive dilution of the solvent is given as:

$$\Delta\overline{H}_1 = R\frac{\partial\left(\mathrm{Ln}\Omega_1^\infty\right)}{\partial\left(1/T\right)} \quad (18)$$

The molar heat of vaporization (ΔH_v) of the solvent is related to $\Delta\overline{H}_{1,sorp}$ and $\Delta\overline{H}_1$ as follows:

$$\Delta H_v = \Delta\overline{H}_1^\infty - \Delta\overline{H}_{1,sorp} \quad (20)$$

The solubility parameters of the polymer (δ_2) can be calculated by combining the Hildebrand-Schathared theory and the Flory-Huggins theory:

$$\left(\frac{\delta_1^2}{R\cdot T} - \frac{\chi_{12}^\infty}{V_1^0}\right) = \frac{2\delta_2\delta_1}{R\cdot T} - \frac{\delta_2^2}{R\cdot T} \quad (21)$$

Here, δ_1 is the solubility parameter of the solvent.

Practical applications

Pharmaceutical powders

The behavior of pharmaceutical solids during either processing or use can be noticeably affected by the surface free energy of the constituent particles. Inverse gas chromatography as a highly sensitive technique can provide an insight into the potential problems that may be encountered during dosage form production and use. A number of articles demonstrating the relevance of IGC to pharmaceutical processing and manufacture have appeared in the literature. Simplification of the equation for calculating the surface properties of a sample has been used in the pharmaceutical literature in such a way that the enthalpy of adsorption (equation 7) was replaced by the free energy of adsorption, which is then correlated with K_A and K_D parameters. This enables calculation of solid surface properties only at one temperature. It has been shown that the method can be used to discriminate between batches of samples that were chemically and structurally equivalent, as determined by standard analytical techniques. Ticehurst et al.[38] applied IGC successfully to discriminate between two batches of salbutamol sulphate, although no differences could be observed with analytical techniques such as FT–Raman spectroscopy and X-ray powder diffraction. Polar probes and nonpolar probes were injected at infinite dilution into the column filled with sample. The retention times of the probes differed significantly between the two batches, both the dispersive component of surface free energy ($\gamma_S{}^D$) and the acid-base parameters differing markedly (Table 2).

Table 2. Measured surface energy parameters for two batches of salbutamol sulphate.[33]

		$-\Delta G^{SP}$(kJmol^{-1})				
Batch	$\gamma_S{}^D$(mJm^{-2})	Acetone	Diethylether	Ethyl acetate	THF	Dichloro-methane
A	83 (±2)	9.9 (±0.0)	9.4 (±0.0)	9.6 (±0.2)	9.4 (±0.2)	3.8
B	38 (±1)	6.2 (±0.2)	2.8 (±0.2)	4.4 (±0.1)	6.2 (±0.1)	2.2

In the case of α-lactose monohydrate[39], batches differed only in specific interactions, while the values of dispersive component of surface free energy were comparable (Table 3). It was presumed, that this deviation appeared because of the different degree of crystallinity or because of the presence of impurities on the lactose monohydrate surface.

Table 3. Measured surface energetic parameters for four batches of α-lactose monohydrate after conditioning at 40 °C for 16 hours.[34]

		$-\Delta G^{SP}$(kJmol^{-1})			
Batch	$\gamma_S{}^D$(mJm^{-2})	Acetone	Diethylether	Ethyl acetate	THF
A	44 (±2)	9.1 (±0.3)	6.0 (±0.2)	8.6 (±0.2)	7.3 (±0.2)
B	40	5.7	2.9	5.4	4.4
C	41 (±3)	8.2 (±0.3)	5.2 (±0.2)	7.8 (±0.2)	6.6 (±0.2)
D	42	8.7	5.4	7.7	6.9

The size of powder particles is often very important for sufficient bioavailability. It is hard to prepare directly a powder of optimal size, for instance with crystallization. Instead of directly preparing powders of appropriate size, milling is used. Milled material can give rise to variability in performance. An example is given by changes that can occur during the wet granulation processing of inhalation aerosol and the variation in their performance. It is known that crystalline materials can become partially amorphous during milling. Thus it is reasonable to believe that changes in surface energy that accompany the conversion should be detectable by means of IGC. Roberts and coworkers[40] proposed that crystalline particles, composed of different planes that are bonded together with different strengths, break at the cleavage plane with the smallest attachment energy. The particles will preferentially fracture along these planes. With the reduction in the size of the particles, the surface chemistry of these planes becomes more and more representative, as long as the material behaves in a brittle way. This hypothesis was confirmed by IGC analysis of DL-propranolol hydrochloride milled particles, in combination with molecular modeling. For smaller particles, the interaction with alkanes and dichloromethane (as an acidic probe) became stronger, while the interactions with basic tetrahydrofuran became weaker. This trend continued until the particle size reached a value that was comparable with the theoretical brittle ductile transition, after a reversal was observed. Molecular modeling supported results that were obtained by IGC, since it showed that the primary cleavage plane of DL-propranolol hydrochloride was dominated by the π-electron-rich naphthalene moiety (York et al.[41]). Roberts's hypothesis was also confirmed by work of Trowbridge et al.[42] who investigated the effect of milling on the surface energy of acetaminophen. They discovered that the dispersive and the basic components of surface energy increased with milling while the acidic component decreased (Table 4). Again results were in correlation with those provided by molecular modeling, where it was shown that the portion of hydrophobic methyl, benzyl and carbonyl groups on powder surface is increasing while the phenol-OH group is sterically hindered and inaccessible to probe molecules. On this basis the authors concluded that milling causes an increase in the dispersive and in the basic nature of material and, on the contrary, a decrease in the acidic nature.

Table 4. Surface energetic parameters for milled acetaminophen.[37]

			$-\Delta G^{SP}$ (kJmol^{-1})	
Batch	Particle size (μm)	γ_S^D (mJm^{-2})	Chloroform	THF
Fine crystals	38.9	50.9	0.33	7.11
Powder	11.3	59.1	0.42	6.34
Fine powder	10.4	58.2	0.43	6.22

Feeley et al.[43] measured the surface energetic changes of salbutamol sulphate that were induced on micronisation. They showed that surface energy differences detected by IGC can be related to important secondary processing properties such as powder flow.

Samples of different crystal morphologies and habits were also studied using the IGC method. The surface energy of ibuprofen batches showed an increase in the polar interactions when the polarity of the crystallization solvent was increased (Table 5). This was linked with the increase in the proportion of the crystal surface that was taken up by the slightly polar face, due to the habit modifications. Changes in the nonpolar component of the surface free energy were correlated to the percentage area of the nonpolar face. The results showed that changing the shape of the particles can alter the proportion of the functional groups that were present at the surface and consequently gave information concerning overall dissolution properties of different batches.[44]

Table 5. Surface energetic parameters for Ibuprofen crystallized from different solvents.[39]

Crystallization Solvent		$-\Delta G^{SP}$(kJmol^{-1})			
	γ_S^D(mJm^{-2})	Methanol	1-Propanol	THF	Chloroform
Hexane	31.1 (5.8)	2.96 (0.77)	2.30 (0.05)	2.45 (0.04)	0.59 (0.07)
Acetonitrile	36.3 (3.6)	3.83 (0.45)	2.61 (0.52)	2.54 (0.53)	1.42 (0.64)
Methanol	38.2 (1.7)	5.94 (0.74)	4.47 (0.46)	2.27 (0.71)	1.74 (0.49)

Inverse gas chromatography (IGC) has been successfully used to characterize the nature of the surface of two optical forms of mannitol, DL and βD. It has been shown that the surface free energy of the two forms is significantly different, with the DL form having higher values for the interactions with the dispersive probes and the basic probes. Molecular modeling was used to predict the slip planes by utilizing attachment energy calculations and so the dominant faces exposed upon milling could be predicted. A visual comparison of the faces indicated that the DL form had a higher density of acidic and dispersive sites, exposed at the surfaces, than did the βD form. The results from the modeling agree with the trends seen in the changes in surface free energy as measured by IGC. This suggests that the components of the surface energy terms reflect the density of exposed groups at the particle surfaces.[45]

Grimsey et al.[46] compared the surface free energy properties of poly (l-lactide) microparticles (PLLA) of the primary sample with particles that had been produced either with crystallization from supercritical fluids by the Solution Enhanced Dispersion with Supercritical fluids (SEDS) technique or with spray drying. The spray dried PLLA was found to be X-ray amorphous while SEDS processed and unprocessed PLLA were semicrystalline.

The dispersive component of the surface free energy γ_S^D for all three samples was found to be comparable. Polar interactions of SEDS processed PLLA were smaller compared to those of unprocessed sample. For the spray dried material none of the probes were eluted. This indicates complete adsorption and absorption of the polar probes to the high energy surface of the amorphous material.

The authors concluded that the process of PLLA particle formation had a significant effect on the polar component of the surface free energy of PLLA, which is due to different degree of crystallinity of the sample.

Table 8. Surface energetic parameters for poly (l-lactide) formed by different techniques.[41]

		$-\Delta G^{SP}$(kJmol^{-1})		
Process Route	γ_S^D(mJm^{-2})	Ethylacetate	Acetone	Chloroform
Unprocessed	36.6	9.32	12.05	6.11
SEDS processed	34.5	4.96	7.07	2.97
Spray Dried	35.7	No probe eluted	No probe eluted	No probe eluted

When Ticehurst et al.[35] studied the surface energy of α-lactose monohydrate, they noted that the retention behaviour of some of the probes altered if the analysis was carried out immediately after the column was attached to the chromatograph. They found that the retention times of the polar probes decreased over the time until a constant result was achieved. They suggested that this effect was due to the dry carrier gas used that caused drying of the lactose sample.

The interaction between water and drug substances or pharmaceutical excipients is of essential importance for short- and long-term chemical, physical or microbiological stability of both intermediate pharmaceutical products and final pharmaceutical products. Sorption of water to solid substance can alter the rates of chemical degradation, crystal growth and dissolution, wettability and dispersibility, powder flow, lubricity, powder compactability and hardness of the final solid dosage form. Due to these changes, it is important to be familiar with the principle of water bonding and with the effect of the presence of bonded water. Water can associate with solids in two ways. Water molecules can interact only with the surface of the solid (adsorption) or penetrate the bulk solid structure (absorption). To understand the effects that water can have on the properties of solids requires an understanding of the location and mobility of molecules of water as well as its physical state. The difference in mobility can be observed through such measurement as heats of adsorption, freezing point, NMR, dielectric properties and diffusion.

IGC can be adapted so that the carrier gas is humidified to produce ambient conditions (moisture values) within the column. In this way, samples of pharmaceutical powders can be analyzed under conditions that reflect a more typically ambient environment for powder handling and processing. The effect of humidity on the surface free energy of the powders can also be studied and the particular interaction sites of the water molecules on the surface identified using molecular modeling procedures. This is very applicative for studying the properties of powder in real conditions; for example in industry.

Djordjevic et al.[47] used the IGC technique to measure the adsorption of water at zero surface coverage and at finite surface coverage of the orthorhombic form of cyclosporine A. From the sorption-desorption isotherms measured by IGC, the surface area was determined from the calculated monolayer capacity. BET adsorption isotherms of water at 373 K and nitrogen at 77 K were utilized. When nitrogen was used as adsorbate a lower value for the specific surface area was obtained. This was explained in terms of the size of the adsorbate molecule and its ability to access the internal surface of the adsorbent.

Sunkersett et al.[48,49] used IGC to study the surface energetic parameters of selected pharmaceutical materials under dry conditions and at an ambient relative (47% RH) humidity. The values of the dispersive component of the surface energy either remained constant or showed a small decrease at the increased relative humidity. The specific component of the free energy of adsorption remained constant, increased or decreased, depending on the material and the probe. This was explained using a molecular modeling approach. In the cases where a decrease in interaction of a probe molecule with increased humidity was observed, the modeling showed that the preferable interaction site of water was the same as that of the probe molecule. For the instances of an increase in humidity causing an increase in the interaction of the polar probes with the surface, Sunkersett proposed that the adsorbed water must be capable of altering initial partial charges at sites where the probes would preferentially interact.

Ohta and Buckton[24] studied the changes in the acidic properties and the basic properties on the surface of amorphous cefditoren pivoxil powder using IGC under various relative humidities (RHs). The basic nature on the surface of amorphous cefditoren pivoxil decreased with increasing RH, with a dramatic fall between 0 and 10% RH. This was attributed to water preferentially shielding the exposed carbonyl groups from acidic polar probes. Since water molecules would be adsorbed to the most hydrophilic sites at an initial RH increment, it seems reasonable to suppose that the most hydrophilic adsorption sites on the surface of amorphous cefditoren pivoxil are the exposed carbonyl groups.

Considerations about proper use of IGC method

IGC measurements may be carried out both at finite surface coverage (finite concentration region) and zero surface coverage (Henry's law region or infinite dilution region). In the finite concentration region, retention volumes are dependent upon the adsorbate concentration in the gas phase. The IGC method can provide the energy distribution of "surface active sites", i.e. sites with adsorbing energies for gaseous probes. In the infinite dilution region, injection of minor amounts of adsorbates to approach zero surface coverage, permits neglect of lateral interactions between adsorbed molecules and the retention volumes are independent of injection sample size. An important aspect of IGC at infinite dilution is that it is mainly sensitive to the presence of sites with high interaction energies. In the case of a heterogeneous solid surface, the recorded chromatographic peaks are strongly asymmetrical, even for low volumes of the injected liquid probe. During investigation of the adsorption equilibrium at low coverage of a heterogeneous surface, the most active sites will be covered first. These sites correspond only to the initial part of the adsorption isotherm and they are not representative of all of the active sites. Therefore, the components of the surface free energy determined by the use of extremely low volumes of the test probes are related only to those strongest (and highly energetic) adsorption sites that form only a small fraction of all active sites. Owing to the surface energetic heterogeneity, the correct parameters of surface adhesion ability in the monolayer region should be distributions on the dispersive and donor/acceptor components of the surface free energy and their initial moments, rather than the parameters that are related to the Henry region.[50]

When performing IGC with glassy polymers or with semi crystalline polymers, the influence of bulk absorption has to be considered. There are always difficulties in trying to separate the thermodynamic interactions of the injected molecules with the bulk and the surface of the polymer.[51,52,53,54,55]

On the contrary Cseremuszkin et al.[56] came to different conclusions in measuring the surface properties of cellulose. The adsorption behaviour of the sample was examined from elution characteristics of chemically different adsorbates. The neutral probes were eluted completely during IGC measurements while acidic, amphoteric and basic probe molecules were eluted incompletely. In this work, complete elution was defined by the flat post peak FID signal within the noise limits of the detector. An understanding of incomplete elution is thereby reached by introducing the efficiency of vapors and their enthalpies of acid-base interactions. Delayed elution of acid-base vapors was interpreted as being due to a nonequilibrium sorption process and calculations have shown that diffusion into the bulk is unlikely under the measurements conditions.

Planinšek and Buckton[57] used inverse gas chromatography to assess surface properties of a range of pharmaceutical powders. The powders examined were two sources of hydroxypropyl methyl cellulose (HPMC), microcrystalline cellulose, magnesium stearat and acyclovir. It was found that many powders gave a similar value for the dispersive surface energy, which is surprising given the differences in chemical nature. It is likely that this is due to the use of infinite dilution giving rise to the study of specific regions of the powder surface only. The values obtained for dispersive energies were not influenced by the packing mass or the flow rate of the carrier gas. The retention of polar probes on the column was a concern for the amorphous HPMC samples. This gave rise to derived values for acid-base nature that varied depending on sample mass and carrier gas flow rate. The data show that care must be taken when studying amorphous samples for which it is possible to obtain diffusion into the material rather than just surface adsorption of probes. Despite these problems, it was still possible to differentiate between the samples (including differences between the two HPMC samples) by use of polar probes. Planinšek et al.[58] investigated how the measurement conditions or type of the column used influence surface free energy parameters of lactose monohydrate. Glass columns and stainless steel columns of different lengths were filled with lactose powder. Dispersive and polar components of surface free energy were determined at different flow rates of carrier gas using lactose alone or lactose that had been diluted with calcinated diatomite (Chromosorb W). It was found that measurement conditions did not influence the value of the dispersive parameter of surface free energy. On the contrary, K_A and K_D values were dependent on dilution of lactose with Chromosorb W. This was assumed to be probably due to different packing of the sample in the column. Nevertheless, it was suggested that dilution of the sample with Chromosorb W increases the access to the area of the surface that interacts with the polar probes. The researchers proposed that the analysis of any powder surface by the IGC method should involve dilution with Chromosorb W. Decreasing of the carrier gas flow in the same column and increasing of the stainless steel column length, at the same carrier gas flow rate, increased the interaction of polar probes with the surface. The results suggested that higher surface area of the sample could be available for interactions in a longer column using a low flow rate. The results seemed to provide a better representation of the surface energy properties.

Glass transition temperature measurements

Kunaver et al.[59,60] used IGC for the determination of the T_g and T_m values for the polymer/oligomer systems, their combinations and for a high solid thermosetting coating system. Figure 4 gives a graphical representation of the retention diagram for an epoxy resin. The solvent used as the probe was n-butyl acetate. Figure 4 clearly shows that the T_g is 70.6 °C. Thus, at this temperature a deviation from the linear relationship is observed. The DSC measurements supported the value of 69.5 °C as the T_g point. The IGC procedure was carried out on a high solids coating system. It should be noted that the composition of the system consisted of polyester resin and a melamine resin in 7:3 proportions. The column was assembled in the usual manner, with the uncured high-solids coating system as the stationary phase. Curing was achieved by heating the column at 150 °C for 30 minutes in the chromatograph oven. The retention times of n-decane were then obtained at different temperatures. The T_g value, determined as in previous example, was 54 °C. Figure 5 represents the retention diagram for the cured high solids coating system. The determination of the T_g value for the cross linked thermosetting coating system, indicates that the T_g has a significant effect on the interlayer adhesion properties. There is also an advantage offered by this technique. High solid coating systems, heavily loaded with pigments, are difficult to analyze using

DSC equipment because of the low sample capacity offered by DSC. IGC columns can be loaded by up to 20% with the sample. Longer columns can also be used. Thus, the quantity of the sample can be sufficiently great to ensure that reliable T_g values are obtained.

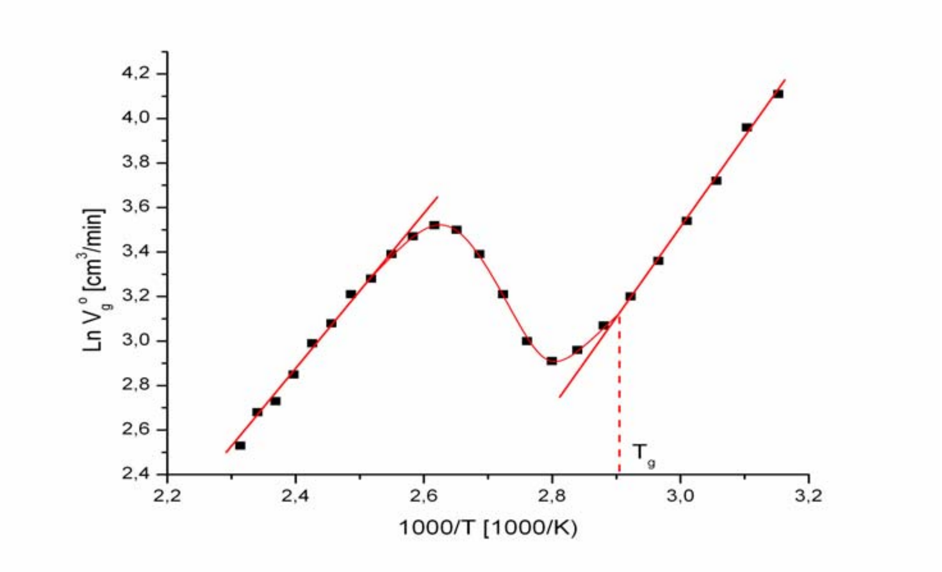

Figure 4. Retention diagram of the epoxy resin.

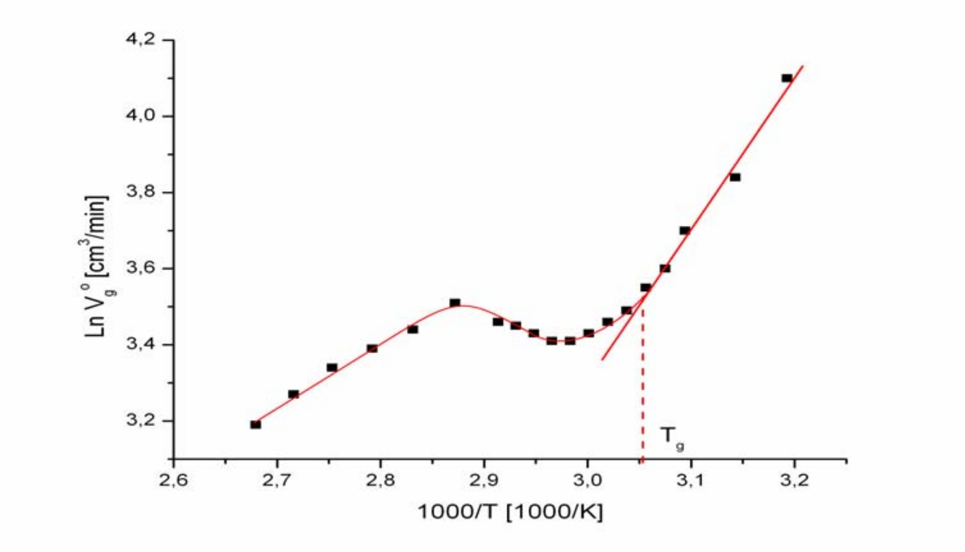

Figure 5. Retention diagram of the cured high solid coating material.

Conclusions

IGC can be a valuable tool for the characterization of nonvolatile materials, in particular pharmaceutical materials and polymers. Measurements of the dispersive component of the surface energy and the Gibbs energy of acid-base interactions were found to provide an effective tool for the determination of a batch to batch variations and the evaluation of the change in the surface energy as a consequence of milling processes. The results were in good agreement with some other methods used: the contact angle measurements or spectrometric methods. The IGC technique was also successfully used for the determination of the glass transition temperature of different polymers and coating materials. Here again, the results were in good agreement with those provided by the DSC measurements. IGC has proven to be a very sensitive technique. Different, relevant measured parameters can be changed, such as the investigation temperature, the length of the column, the amount of the material within the column, the carrier gas flow, the standard selection etc., in order to achieve greater sensitivity in the method applied. This paper illustrates some applications of IGC with the aim of characterizing nonvolatile materials of very different origin. Because of its simplicity and precision, IGC has become the method of choice for the study of thermodynamic interactions of volatile standards with nonvolatile materials. IGC is a powerful and valued technique.

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Povzetek

Inverzna plinska kromatografija (IGC) je v zadnjem času postala pomembna metoda za proučevanje trdnih in tekočih snovi. Metoda omogoča proučevanje fizikalno-kemijskih lastnosti snovi kot so površinska energija, fazni prehodi, kristaliničnost in kislo-bazične lastnosti. Določimo lahko tudi kinetične parametre kot je npr. difuzijski koeficient. Inverzno plinsko kromatografijo uporabljamo za ovrednotenje različnih materialov: farmacevtskih učinkovin in pomožnih snovi, naravnih in sintetičnih polimerov, hrane in njenih sestavin, mineralov in podobno.