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The use of inverse phase gas chromatography to study the change of surface energy of amorphous lactose as a function of relative humidity and the processes of collapse and crystallisation

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Abstract

The purpose of this study was to assess the effect of relative humidity (RH) on the surface energy of amorphous lactose. Two samples of amorphous lactose were investigated; a spray dried 100% amorphous material and a ball milled sample of crystalline lactose. The milled sample had less than 1% amorphous content by mass, but on investigation at 0% RH, yielded surface energies comparable to those obtained from the 100% amorphous material, indicating that the surface was amorphous. The effect of increasing humidity was to reduce the dispersive surface energy of the two samples from 36.0 ± 0.14 and 41.6 ± 1.4 mJ m^{-2} at 0% RH for the spray dried and milled samples respectively, to a value comparable to that obtained for the crystalline alpha-lactose monohydrate of 31.3 ± 0.41 mJ m^{-2}. The change in surface energy due to water sorption was only reversible up to 20% RH; after exposure to higher RH values subsequent drying did not result in a return to the original surface energy of the amorphous form. This shows that the surface is reorganising as the glass transition temperature (T_g) is reduced, even though the sample has not collapsed or crystallised. It was possible to follow the collapse behaviour in the column with ease, using a number of different methods. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Amorphous; Collapse; Glass transition; Inverse phase gas chromatography; Surface energy

1. Introduction

There is growing awareness of the importance of the amorphous state in pharmaceutical products (Hancock and Zografi, 1997). It is well established that materials can become amorphous

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during crystallisation, spray drying and freeze drying, and partially amorphous as a consequence of processes such as milling. The presence of amorphous material in a product can be desirable (e.g. stabilisation of proteins, enhancing bioavailability etc) or undesirable (e.g. poor chemical and physical stability and uncontrolled changes in product performance). Materials with a relatively small amorphous content (in the region of a few percent of the total mass) can exhibit significant changes in behaviour. These effects are not well documented in the literature, as the data are usually held confidentially by pharmaceutical companies, but the changes in behaviour can relate to difficulties in wet granulation of micronised drugs and performance variability in micronised inhalation products. A number of authors have assumed that the reason why small amounts of amorphous content can give rise to a large change in behaviour of the material is that the amorphous content may well occupy most of the surface of the material. Feeley et al. (1998) have shown that there can be differences in surface energy between micronised and unmicronised material, possibly due to surface disorder. Newell et al. (2000) have demonstrated that milled lactose with an amorphous content of less than 1% w/w had a surface energy similar to a sample that was 100% amorphous, whereas a physical mixture of 1% amorphous and 99% crystalline lactose had a surface energy similar to crystalline lactose. This demonstrates that milling can indeed make the surfaces of particles amorphous. This totally amorphous surface may interact differently to crystalline material during processes such as wet granulation or the formation of inhalation products. Thus the fact that amorphous and crystalline forms of the same material have different surface energies can give rise to changes during product manufacture and use (e.g. different dispersion properties of drugs in non-aqueous suspensions for metered dose inhalers, different interactions between drug and carrier particles for dry powder inhalations and changes in wetting by granulation fluids during wet granulation).

A further property of amorphous material is its tendency to allow water sorption. Amorphous lactose will absorb 10% w/w water at 50% relative humidity (RH) at 25°C (Buckton and Darcy, 1996). It is logical that the presence of absorbed water will alter the surface energy of the material. As it is argued that the difference in surface energy between amorphous and crystalline materials can give rise to changes during product manufacture and use, it is highly probable that changes in surface energy due to the sorbed water content could also be significant.

The measurement of the surface energy of particulate samples is extremely difficult (Buckton, 1993). Contact angle methods are not well suited to powdered samples and the presence of liquid probes would result in the chance of changes in the physical form of the sample (e.g. dissolution and/or crystallisation of amorphous regions). It has been argued that vapour sorption methods are the preferred approach to the study of powder surface energetics. Vapour sorption methods include gravimetry (e.g. Buckton and Darcy, 1999; Costantino et al., 1998), isothermal microcalorimetry (Buckton and Darcy, 1999) and inverse gas chromatography (IGC).

IGC has been used recently as a means of studying the surface energies of a number of pharmaceutical systems (Ahfat et al., 2000; Dove et al., 1996; Feeley et al., 1998; Grimsey et al., 1999; Ticehurst et al., 1994, 1996; York et al., 1998) and offers significant advantages over contact angle methods when comparing the surface nature of particulate samples (Ahfat et al., 2000). However, to date there have been no studies of how amorphous pharmaceuticals change surface energy as a function of RH. With IGC it is possible to select any carrier gas and then to make very small injections of probe vapours to assess the surface energy of the solid in the presence of that carrier gas. Consequently it is possible to have the carrier gas at any desired RH and then to measure the surface energy as a function of RH.

2. Materials and methods

2.1. Apparatus

Experiments were performed using an inverse gas chromatograph (Surface Measurement Systems Ltd), comprising of three modules (Butler et al., 1999) and illustrated in Fig. 1. An integrated flow control system, employing a series of mass flow controllers (MKS Instruments), was used to prepare a carrier gas stream with mixtures of dry helium and helium saturated with water vapour in the required ratios to give defined RH values. An automated injection valve was used to inject 250 μL of the elution mixture (appropriate mix of elutant vapour and carrier gas) into the gas flow, which carried it through the column to the detectors. All injections of elutant vapours were expressed as concentrations of% v/v of the saturated elutant vapour. A Hewlett Packard 6890 series gas chromatograph (GC) oven was used to control the solvent temperature. The 6890 GC data acquisition system was used to record data from a thermal conductivity detector (TCD) and flame ionisation detector (FID) plumbed in series at the column outlet. This combination of detectors allowed sensitive analysis of both organic vapour elution and on column relative humidity levels. A separate, purpose built column oven was used to control the sample (column) temperature between room temperature and 90°C. The glass columns used were 6 mm OD, 2 and 3 mm ID and approximately 220 mm long. Columns were treated with a dimethyldichlorosilane solution (DMCS, Repelcote®, BDH) and washed thoroughly, to passivate the surface prior to use. DMCS silanised glass wool (Chrompack) was used to hold the powdered samples in place. Pressure transducers were used to record the pressure drop across the column.

The whole system was fully automated by purpose written control software (SMS *i*GC Controller v1.3) and the data analysed using the SMS *i*GC Analysis macros. Chromatography grade stainless steel tubing of 0.75 mm internal diameter was used throughout to minimise dead volume and wall–solute interactions within the system.

Surface energies were determined by eluting 2% v/v injections of solutes. These were methane (BOC, research grade), for the inert reference and the hydrocarbons heptane (Fisher, HPLC grade), octane (Lancaster, 99%+), nonane (Aldrich, 99%+) and decane (Acros, 99%+). The solutes were held at an oven temperature of 300 K throughout the experiments described. Column temperature was 303 K and relative humidity was

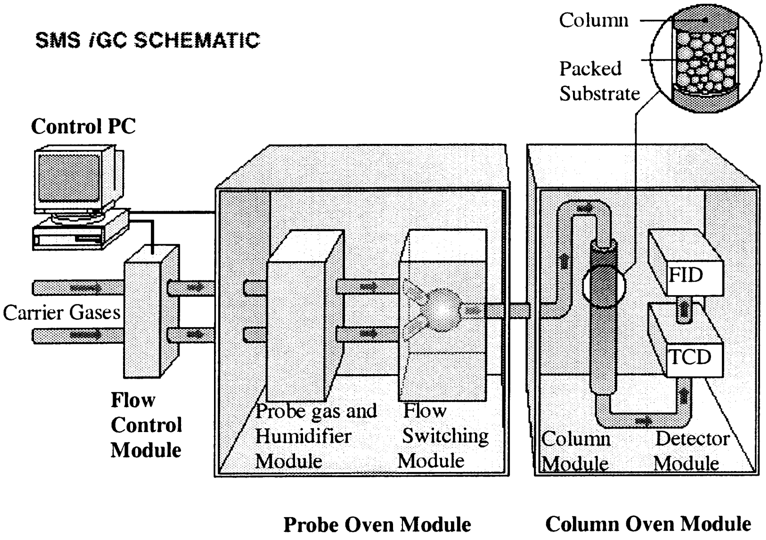

Fig. 1. A schematic diagram of the IGC apparatus.

varied between 0 and 40% (above this value amorphous lactose will crystallise rapidly hence 40% RH was the experimental upper limit). The flow rate used was 10 ml min^{-1}, as this gave a good balance between the speed of elution, the shape of the solute peaks (Gaussian) and the pressure drop experienced across the column. The shape of the peaks is important as a non-Gaussian peak shape indicates that the column and the interactions within are not behaving in an ideal manner.

2.2. Sample preparation

2.2.1. Amorphous lactose

The amorphous lactose was prepared in house by spray drying (Buchi spray drier). Conditions were chosen such that the product would be 100% amorphous, as determined previously (Chidavaenzi et al., 1997). The amorphous nature of the lactose was confirmed by use of isothermal microcalorimetry (Thermal Activity Monitor, Thermometric), using the method of Briggner et al. (1994). The enthalpy of crystallisation (75% RH 25°C) was found to be 48 J g^{-1}, which is in keeping with the value recorded by Briggner et al. (1994) for 100% amorphous lactose.

Between preparation and packing the product was stored in a dessicator at 20°C and 0% RH over P_2O_5. Three different batches of spray dried lactose were prepared.

2.2.2. Milled (partially amorphous) lactose

A sample of the crystalline α-lactose monohydrate was subjected to milling in a simple ceramic ball mill for a period of 4 h. The mill and powder were purged with helium to prevent the crystallisation of any amorphous content induced by the physical process. The product was stored at 20°C in a dessicator at 0%RH over P_2O_5. This amorphous content of the milled sample was assessed using solution calorimetry and by the method of Hogan and Buckton (2000) it was found to have an amorphous content of $0.7 \pm 0.25\%$.

2.2.3. Column packing

The lactose was packed into the glass columns by vertical tapping onto a surface. Progress was monitored visually whilst tapping for at least 15 min. Tapping continued until there were no visible cracks, hollows or channels in the body of the powder. Both ends of the columns were loosely stopped with silanised glass wool. Columns were subject to a conditioning cycle prior to analysis. This consisted of inserting the column into the IGC and the experimental conditions of column temperature, gas flow and humidity were set. The column was left under these conditions for a minimum period of 5 h at 0% RH and over 8 h at elevated humidity. The signal traces from the instrument were checked to ensure that there were no gross changes still occurring. In order to ensure that the equilibration process had been completed the TCD trace as well as the retention time and peak shapes of the eluted peaks were monitored at various stages during the experiments. Any changes in these peaks during the course of the experiment would indicate that the substrate was not yet at equilibrium with the applied conditions and further conditioning was carried out. Whenever the same column was investigated under more than one set of experimental conditions, the sample was allowed to re-equilibrate using a similar procedure.

2.3. Supporting experiments

2.3.1. DVS water sorption

The water sorption experiment was carried out in a Dynamic Vapour Sorption apparatus (SMS Ltd). This was at 303 K, in order to carry out comparisons with the surface energy data. The sample was exposed to 0% RH as a drying step. The sample was then exposed to 10, 20 30 and 40% RH steps.

3. Results and discussion

3.1. Determining dispersive surface energies

The retention times for an homologous series of alkane probes were used to calculate the dispersive surface energy of the surface under investigation. The equations for this analysis have been firmly established for some time (Condor and Young, 1979). The measured parameter is the retention time of the probes, t_r. However, the equations deal with the net retention time, V_N^0, which eliminate any difference in flow rate and temperature of experiments. The method used to calculate the dispersive component of the surface energy of the substrate is that used by Schultz et al. (1987). Eq. (1) is the pertinent equation. The derivation has been demonstrated previously, so the equation is reproduced for reference only.

$$RT\mathrm{Ln}\,V_N^0 = 2N_A(\gamma_S^D)^{1/2}a(\gamma_L^D)^{1/2} + C \qquad (1)$$

By plotting a graph of $RT\mathrm{Ln}\,V_N^0$ versus $a(\gamma_L^D)^{\frac{1}{2}}$, which are both properties of the adsorbate, for a homologous series of hydrocarbons, a straight line is obtained. The gradient yields the dispersive surface energy, γ_S^D.

3.2. Experimentally obtained surface energies at 0% RH

The surface energy of a crystalline sample was previously found to be 31.2 ± 1.1 mJ m^{-2} (Newell et al. 2000). This value was determined from measurements on five different columns with at least three measurements of surface energy performed on each column.

Amorphous (spray dried) lactose was found to have a surface energy of 37.1 ± 2.3 mJ m^{-2} at 0% RH ($n = 25$ determined from mulitple experiments on each of five different packed columns using three batches of spray dried lactose). This value is much greater than the dispersive surface energy that has been reported for the crystalline form, due to the more random orientation of the lactose molecules exposing higher surface energy groups at the particle surface. The greater standard deviation for the amorphous material reflected the fact that the different spray dried batches had slightly different surface energies, thus the standard deviation was low for replicate determinations on any one batch, but was high when the results for different samples were pooled. The data for the effect of RH on the surface energy are reported using one selected batch of spray dried lactose, hence the surface energy is different to the mean value reported above and the standard deviation for replicates is lower. Two columns were packed with this particular batch, with six surface energy measurements on each column, a total of $n = 12$. For this particular batch, the surface energy at 0% RH was measured as 36.0 ± 0.14 mJ m^{-2}.

The milled lactose sample also had a dispersive surface energy value of 41.6 ± 1.4 mJ m^{-2}, the fact that this value is similar to that observed for amorphous lactose indicates that the surface of the milled sample was amorphous (Newell et al., 2000). This being the case, it is to be expected that the behaviour of the milled sample with increased relative humidity will mirror that of the wholly amorphous sample.

3.3. Effect of humidity on surface energy

The effect of RH on the dispersive surface energy of amorphous lactose is shown in Fig. 2. It can be seen that the surface energy decrease is non-linear, with the greatest fall being between 0–10% RH. This is in keeping with sorption isotherms, as displayed in Fig. 3, a sorption isotherm of water to an amorphous lactose sample at 303 K, where the water uptake is greatest at the initial RH increment. Above this the water uptake is approximately linear until the region in which crystallisation occurs, 40% RH in this case.

The surface energy data become more variable as the RH exceeds 35% (Fig. 2), at which point the surface energy has approached that of the crystalline material. It is known that amorphous lactose is plasticised by water such that it will crystallise and collapse when the glass transition temperature (T_g) drops below the experimental temperature. In this experiment the oven temperature was 303 K, which would mean that the T_g would drop below the experimental temperature at ca 6.5% water content (Buckton and Darcy, 1996). Consequently, the data in the region between 35 and 40% RH shows the surface energy of the material as it converts to the crystalline form.

The dispersive surface energy of the milled sample, shown in Fig. 4, exhibits a similar behaviour to the amorphous sample (Fig. 2). The surface energy is observed to decrease with humidity, with the greatest decrease in surface energy between 0 and 10% RH and by 40% RH the surface energy

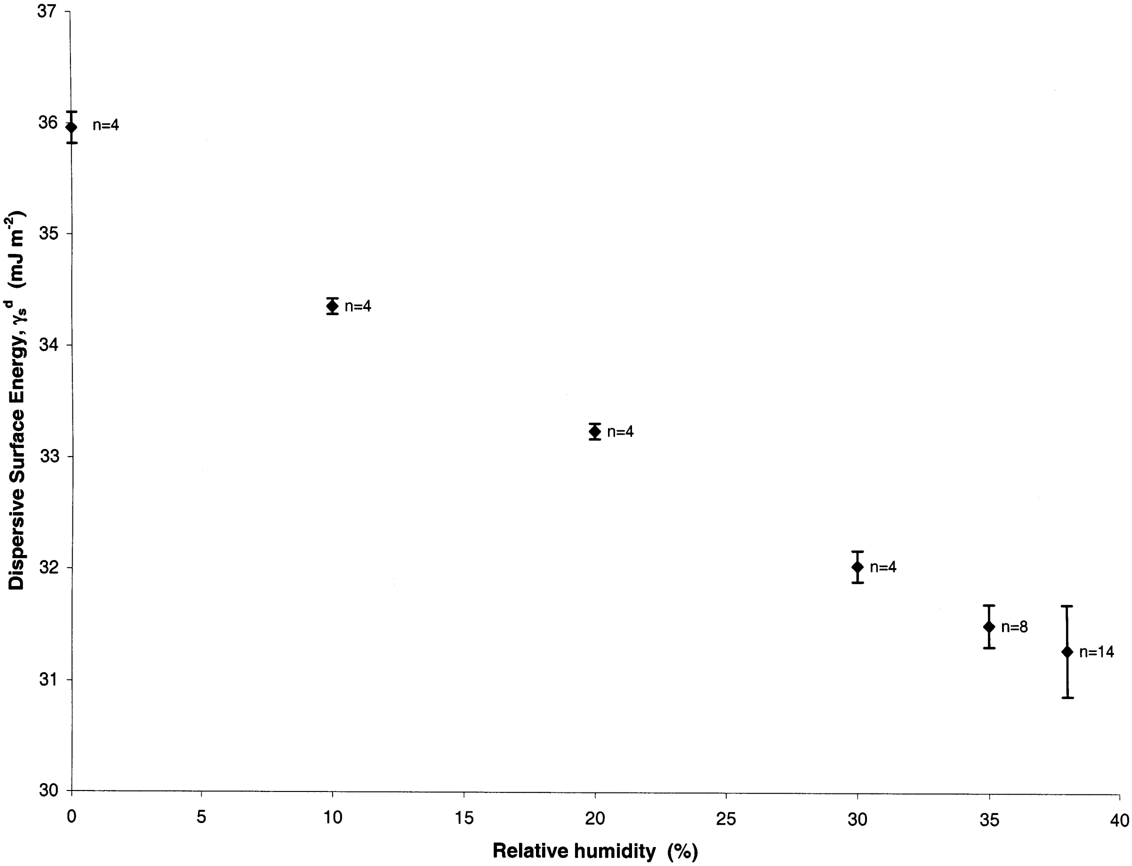

Fig. 2. A graph displaying the measured dispersive surface energy of amorphous lactose at a range of relative humidities.

is within the range determined for the purely crystalline sample.

The surface energy data for both the 100% amorphous and the milled samples were found to be reversible in the region 0–20% RH, in that a change from 0–20% RH would reduce the surface energy of the amorphous sample to 33.2 mJ m^{-2}. If the RH were subsequently reduced to 0%, the surface energy would return to around 36.0 mJ m^{-2}. However, for RH values of 30% and above it was no longer possible to cause the surface energy to return to the starting value. This is further illustrated by the milled sample, the surface energy for this particular column at 0% RH was initially 40.8 mJ m^{-2}. This value decreased to 34.2 ± 0.33 mJ m^{-2} after equilibration at 30% RH. After a period of 30 h at 30% RH the RH was returned to 0% and the surface energy was found to be 38.2 ± 0.11 mJ m^{-2}. This shows that the sample had increased mobility at 30% RH, as T_g had been reduced to be close to experimental temperature such that the surface had a different conformation. For samples that had been exposed to RH values of 35% or greater, a reduction to 0% RH yielded the surface energy value of crystalline lactose monohydrate (and the material was found to be crystalline when removed from the column).

As mentioned above, the spray dried particles will undergo collapse prior to crystallisation, however the surface energy of the material is approaching that for the crystalline form before the collapse takes place. This is evident, as the surface energy equals that of the crystalline form when the RH is 35%, but collapse is obvious only when RH is 40%. Collapse occurs when the particles are no longer able to support themselves under gravity and is a consequence of the T_g dropping below T and the material converting from the glassy to rubbery state. The collapsed form of a material occupies a much smaller volume than the original spray dried particle. In Fig. 5, the pressure drop across the column (measured using the pressure transducers) is shown as a function of RH. It can be seen that the pressure drop rises from 0–30% RH, presumably because of the blocking effect of the absorbed water in the material. At 40% RH however, the pressure drop falls dramatically with time (the three points here are sequential experiments on the same column, showing a substantial fall as a function of time at this RH). After the material has collapsed it crystallises and it can be seen from the TCD that water expulsion occurs (also Fig. 5). The level of the TCD increases as the humidity is increased from 0 to 30% RH. At 40% RH, the level of the TCD rises dramatically and in excess of that expected for just the increase in ambient humidity. The four points shown are again repeated experiments on the same column, showing the increase in TCD with each successive experiment. At 50%, the first experiment yielded a very high TCD value, but this abruptly dropped in subsequent experiments and was stable henceforth. This process of collapse can also be monitored by use of the elution time of methane (the inert marker used to check column integrity). In Fig. 6 the elution time of methane is seen to rise between 0 and 30% RH (the absorbed water making the methane pass more slowly through the column) and then it seems to fall at 40% RH, the

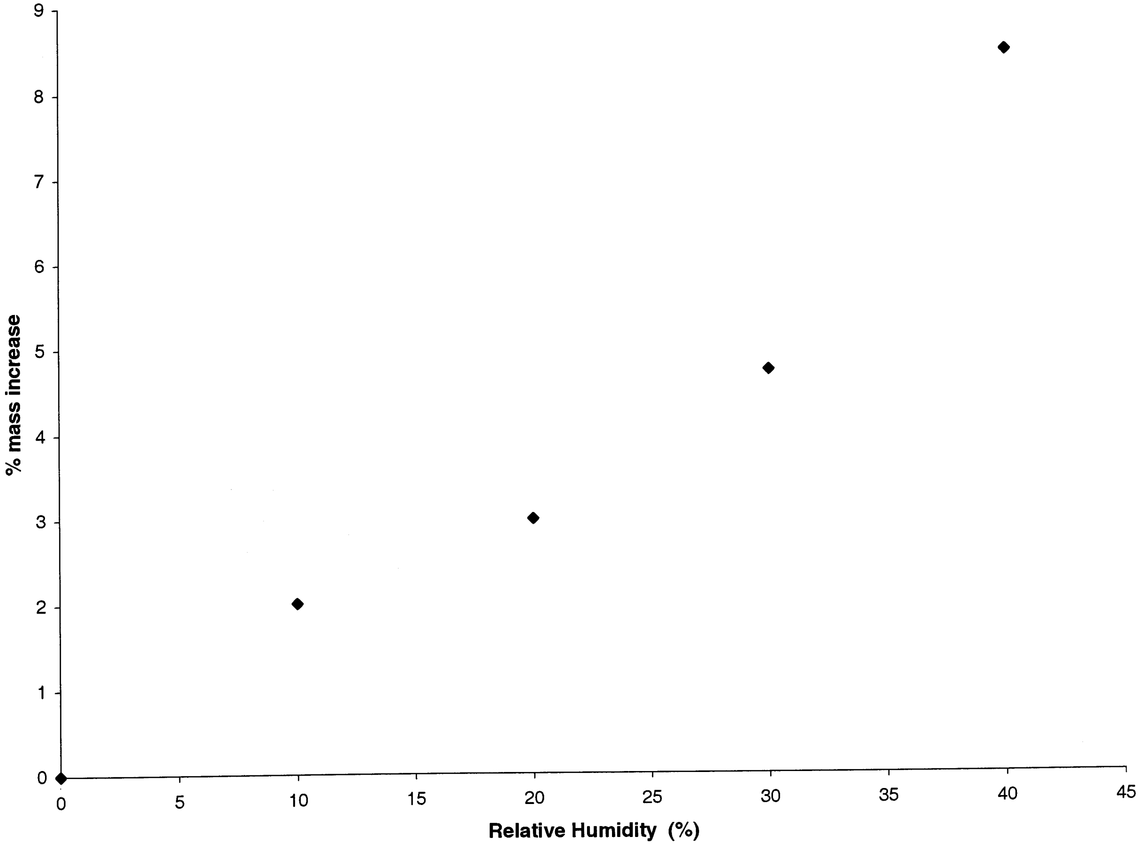

Fig. 3. A water sorption isotherm for amorphous lactose at 303 K.

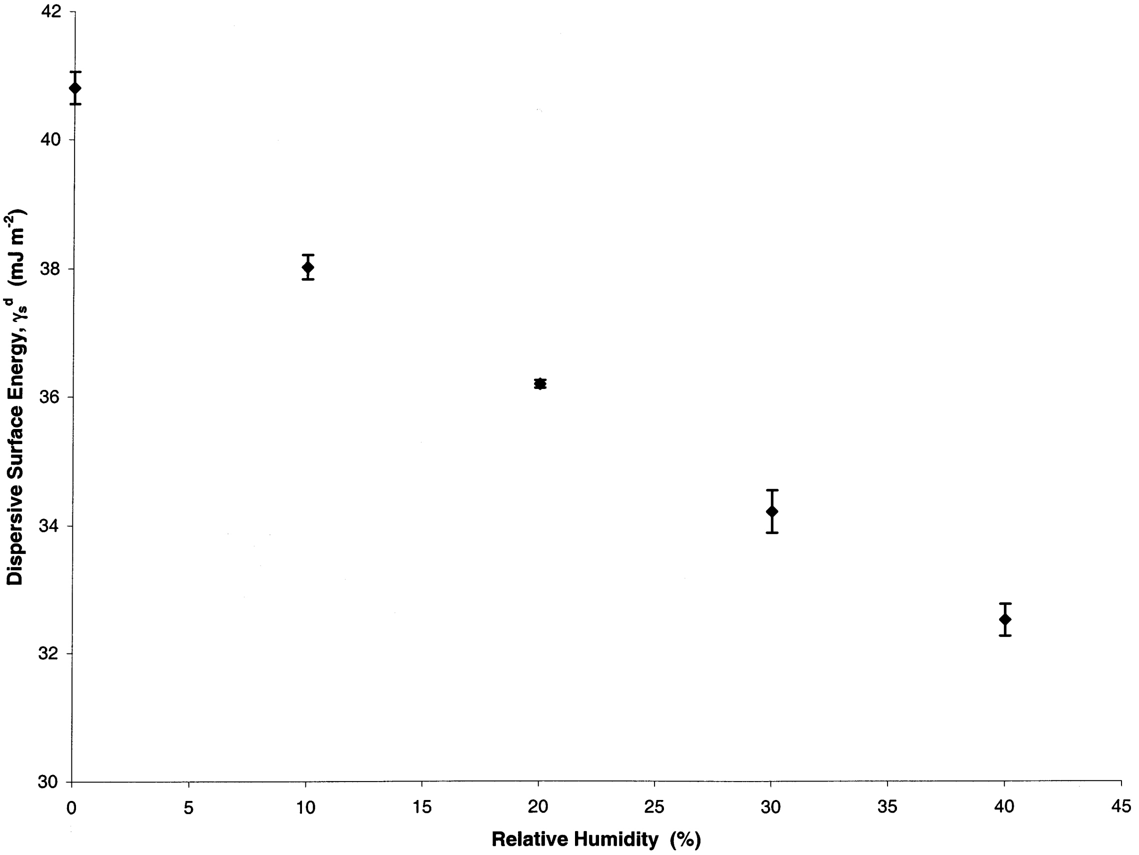

Fig. 4. Dispersive surface energy values obtained for a milled lactose sample at a range of humidities.

three points again being successive injections; and stabilise at 50% RH. It can be seen that at 50% RH the retention time of methane is much less than that observed for the original column of amorphous lactose (Fig. 6). The reason for this is that the crystallised material exists as a thin thread of powder in the column (not touching the column walls), whereas the original column was packed to avoid spaces and cracks. It is surprising that it is possible to determine a surface energy at all when the material has collapsed, crystallised and occupies a small fraction of the column. Furthermore, it is surprising that the surface energy of the original crystal form (packed column of particulates) is the same as that for the thin crystalline thread of material that remains in the column after the amorphous form has collapsed and crystallised in situ. This gives great encouragement for the use of IGC, as it shows that column packing and sample shape do not alter the measured dispersive surface energy to any great extent.

It was also possible to use the retention times of methane to follow the collapse rate at a selected RH (Fig. 7). In Fig. 7 it can be seen that the retention of methane starts to decrease at a linear rate between 200 and 1400 min after exposure to 40% RH, after which the retention time drops in an exponential manner to a value of 0.23 min. The difference in actual values shown by the methane elution times in Fig. 6 and Fig. 7 are due to measurements being taken on columns of different internal diameters and different masses being packed into them. The TCD response provides data on the release of water from the column as the sample crystallises. Also shown on

Fig. 7 are the TCD values obtained from the same injections as each of the methane elution times. As the methane elution time decreases, the TCD value is shown to increase. Again, this seems to initially be linear in the region 0–600 min. This initial rate of increase then appears to decrease somewhat over the range 600 to 1300 min, before increasing dramatically after 1400 min. This dramatic upturn mirrors the increased rate of decrease of the methane elution time over a similar time period.

For the milled sample, the behaviour obvious in the TCD and pressure drop of the wholly amorphous sample is not observed. This is because the behaviour of the amorphous regions of the sample data is swamped by the stability of the 99% of the sample that is crystalline. The physical collapse observed in the wholly amorphous sample is not replicated in the milled sample, as the remaining 99% that is crystalline is supporting the collapsing, amorphous regions. In this case the dead volume would decrease, but by a much smaller value than that of the pure amorphous sample. There is a change in the dead volume observed, but it is less than 1 in 1000 of the dead volume and thus too small to be distinguished from the random error present in the experiment as a whole. Similarly, the pressure drop and TCD do not show any changes across the humidity range that are distinguishable from those observed in crystalline lactose. It is only the surface energy that is markedly altered by the presence of less than 1% amorphous material.

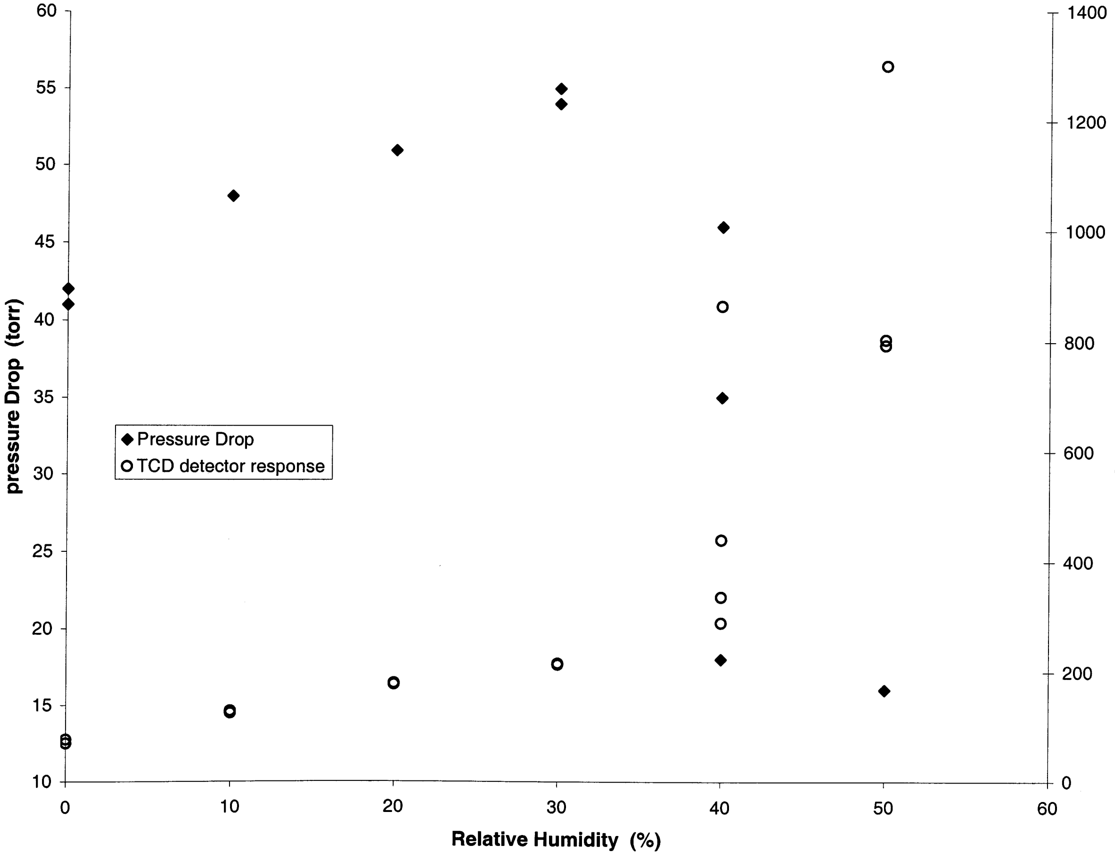

Fig. 5. A graph showing the complimentary behaviour of the column pressure drop and TCD detector response of an amorphous lactose column at a range of relative humidities.

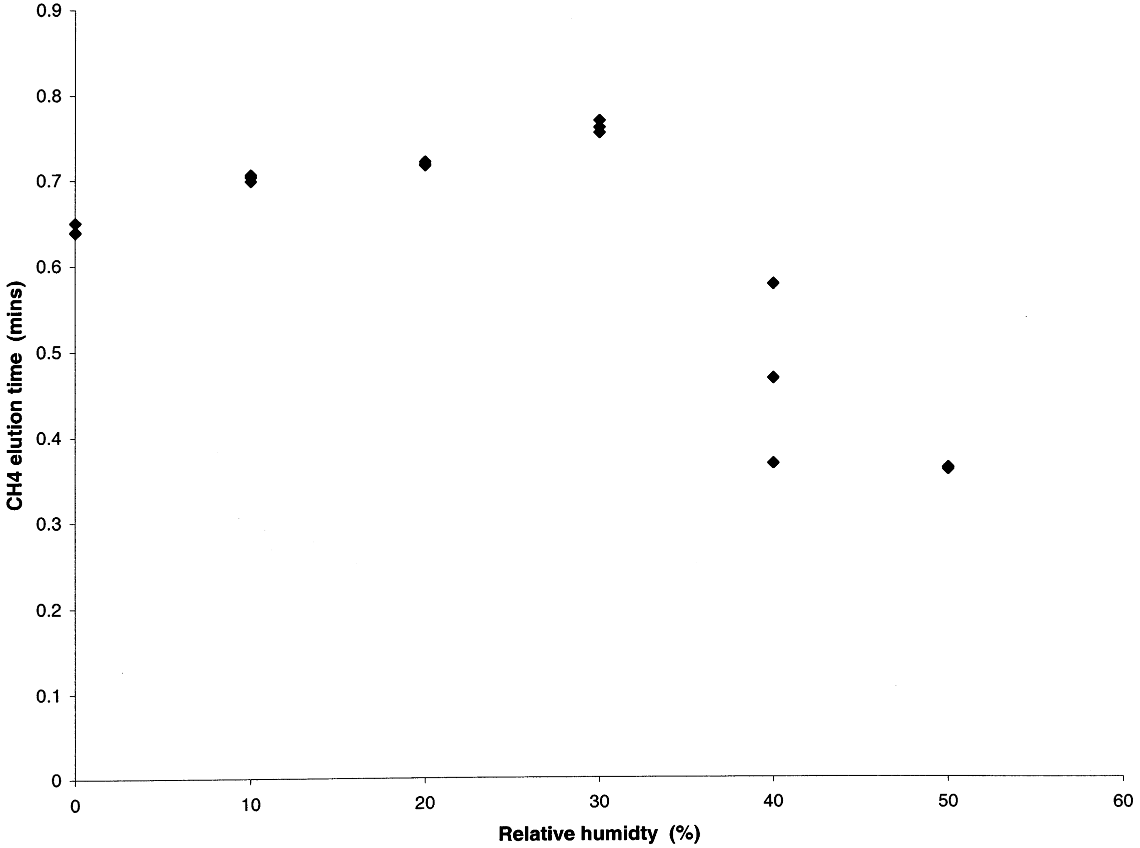

Fig. 6. A graph showing the methane elution time of an amorphous lactose column as measured at a range of relative humidities.

4. Conclusions

The data presented here demonstrate that it is possible to use IGC to determine the surface energy of a substrate under any selected humid atmosphere. Whilst the determination of surface energy under humid conditions has been reported for clay samples (Ballard et al., 1997), the range of humidities investigated here is wider. For the first time the effect of absorbed water on the surface energy of amorphous lactose has been determined. Over the RH range 0–40%, the dispersive surface energy fell from 36.0 ± 0.14 mJ m^{-2} to 31.3 ± 0.41 mJ m^{-2} which is the dispersive surface energy of crystalline lactose monohydrate. Surprisingly the surface energy could still be measured with confidence after the spray dried material collapsed and crystallised in the column, even though the sample then occupied only a proportion of the original packed volume. The milled sample that contains only a small proportion of amorphous material exhibits similar behaviour, with the surface energy decreasing from 40.8 ± 0.27 mJ m^{-2} at 0% RH to 32.5 ± 0.25 mJ m^{-2}at 40% RH, which is within the range of surface energies observed for crystalline lactose. For the milled sample, the physical collapse associated with the amorphous sample is not observed, as the bulk of the sample is in the form of crystalline lactose. The small proportion of amorphous lactose undergoes a physical collapse, but has the remainder of the sample to support it; hence the overall decrease in sample volume is so small as to be negligible.

The amorphous material was found to change confirmation, such that the surface energy became

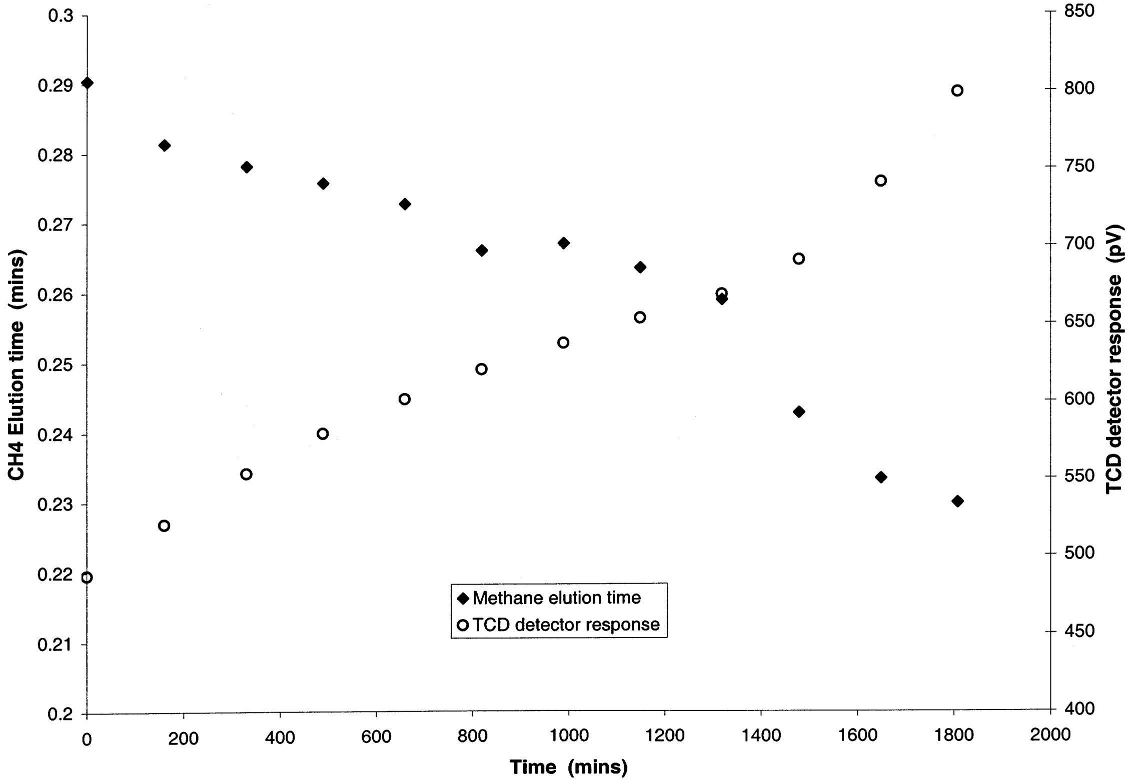

Fig. 7. A graph showing the behaviour of methane elution time and TCD detector response of an amorphous lactose column at 40% relative humidity with respect to time.

similar to that of the crystalline form before collapse or crystallisation occurred. Also, after a certain amount of water was absorbed the surface energy of the starting dry sample could not be recovered following drying. It is clear from these data that the surface gains sufficient mobility to repack quickly well below the collapse or glass transition temperature.

The IGC could be used to study the collapse process with ease, either by monitoring the pressure drop over the column or the retention time of methane. There are very few methods that allow the collapse process to be studied in defined undisturbed environmental conditions, hence the IGC method has a positive advantage for the study of physical transitions in amorphous samples.

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