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International Journal of Pharmaceutics 193 (1999) 13–19

international journal of pharmaceutics

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Isothermal microcalorimetry and inverse phase gas chromatography to study small changes in powder surface properties

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Received 21 June 1999; accepted 1 September 1999

Abstract

It is known that processing can alter the surface energetics of powders. In this study a sample of drug has been processed by use of different drying techniques. The samples were then assessed using inverse phase gas chromatography. It was seen that the original material had a highest surface energy and the tray-dried sample had the lowest energy surface, other samples were intermediate. The use of isothermal microcalorimetry to study water sorption to the powders revealed that the surface of the original material was unstable, as the water sorption response changed on repeat cycling. The tray-dried sample did have a stable surface which gave the same sorption response on repeat exposure to water vapour. It was concluded that the drug had minor variations in surface energy, with the as received material being in a high energy unstable state, which could be due to it being partially amorphous. The tray-dried sample had a lower energy stable surface. In certain applications differences in surface energetics could be expected to lead to changes in processing nature of the powder, so these vapour sorption techniques offer a good way of providing an assurance of the same surface energy between batches of nay material which may be at risk.

Keywords: Inverse phase gas chromatography; Isothermal microcalorimetry; Surface energy; Drying

1. Introduction

The surface properties of powders will affect the way in which they interact with other phases. Thus, a change in surface nature can influence the ease of processing, for example wetting of a powder by a binder fluid or the dispersion of a powder in a suspension. The wettability of the powder surface can also link to the rate of solution of the material.

There are a number of reasons why the surface nature of a powder can change, these include the presence of different crystal habits (where individual faces of the crystal can vary in the proportions of different functional groups of the molecule at

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0378-5173/99/$ - see front matter
PII: S0378-5173(99)00318-X

the surface), a changed polymorphic form, or the presence of amorphous material. The prospect of materials becoming partially amorphous as a consequence of processing has been known for many years (for example Huttenrauch and Keiner, 1979; Huttenrauch, 1988).

The most usual method for the study of the surface properties of solids is to measure a contact angle, however, the difficulties in measuring contact angles for powders have been well documented (Buckton, 1995). A more reliable method of assessing powder surface properties is to use a vapour sorption technique. In this study two vapour sorption approaches have been used, these are isothermal microcalorimetry and inverse phase gas chromatography. Isothermal microcalorimetry is a general technique which is able to detect the heat change associated with physical, chemical or biological processes. In this instance the experiment was designed to measure the enthalpy of water vapour sorption to powders. Through a calorimetric measurement of the interaction between the powder and the water, the water molecules are being used to probe the structure of the surface. Even though commercial instrumentation is available, the use of isothermal microcalorimetry in the gas flow mode has been limited (e.g. Sheridan et al., 1995; Puddipeddi et al., 1996; Jakobsen et al., 1997).

Inverse phase gas chromatography achieves the same outcome as the vapour probes are used to assess the surface nature of the powder. In this method the powder is packed into a column and the probe vapours are injected and their retention time is measured. Naturally the retention time reflects the affinity of the probe for the surface. Different probes are used, which are either apolar (usually alkanes) or partially polar. IGC has been used extensively in the past to study the surface characteristics of polymers and fibres (Fowkes, 1990; Panzer and Schreiber, 1992). In recent years, its use in the pharmaceutical field has been established. Ticehurst et al. (1994, 1996) used IGC to reveal batch-to-batch variation in salbutamol and lactose samples which were not detectable by the use of other techniques. Studies on caffeine and theophylline by Dove et al. (1996) showed that IGC yielded dispersive surface energy data (γ_s^d) data which were comparable to, but consistently greater than, those obtained by the use of the Wilhelmy plate contact angle technique. The reason that higher values were obtained when using IGC is due to the fact that IGC is carried out at infinite dilution. The vapour probe molecules at infinite dilution preferentially interact with the most energetic dispersive sites on the powder surface. The contact angle measurement is an averaged macroscopic event including solid–liquid interactions over regions of the surface which may well have different surface energies.

2. Materials and methods

The model drug used was the anti viral compound saquinavir mesylate (Roche). The aqueous solubility is 0.22 g/100 ml. The physical form of the drug was manipulated by adding 90 ml of distilled water to 30 g of drug and then either:

1. drying in a tray oven at 160°C for 2 h,
2. drying in a vacuum oven at 80°C and 200 mbar for 4 h.

A dry batch was heated also at 160°C in a tray oven for 2 h. Each production process was repeated on three separate occasions.

2.1. Inverse phase gas chromatography

Each glass column (50 cm long, 3 mm internal diameter) was silanated in order that the glass surface would be made hydrophobic and non-interactive with any gaseous probe. To achieve this, the glass loops were washed sequentially with distilled water, methanol and finally with toluene. They were then soaked for 12 h in a solution of 5% dichloromethyl silane (DCMS) in toluene, after which they were rinsed with toluene, then methanol to remove any unreacted DCMS and finally water before being dried in an oven overnight. The powder was packed using a mixture of tapping and controlled vibrating using a whirlimixer. The ends of the column were plugged with silanised glass wool and the glass column was connected to a Perkin Elmer F33 gas chromatograph. The powder bed was then completely dried by passing dry nitrogen (20 kN m^{-2}) over

the powder at an oven temperature of 100°C for 24 h. The dry mass of the powder was calculated. The powder bed was allowed to settle for 24 h at an oven temperature of 35°C and a nitrogen flow of 20 kN m^{-2}. Methane was used as a reference probe gas, since it would have no interaction, giving a minimum retention time (t_0). This reference was repeated at several times throughout the experiment to ensure that the retention times were constant and therefore none of the conditions had altered.

The apolar liquids used were *n*-hexane, *n*-heptane and *n*-octane from Sigma. The polar liquids obtained from Aldrich were tetrahydrofuran, acetone, ether and ethyl acetate. The liquid probes were injected manually using a 10 μl Hamilton syringe. The syringe was first rinsed with the probe liquid. It was then flushed out several times with air to achieve infinite dilution. One microlitre of air containing the liquid vapour was injected into the column and simultaneously the chart recorder started. The eluted vapour was detected by flame ionisation using a mixture of air (20 kN m^{-2}) and hydrogen (16 kN m^{-2}). The retention times were taken from the point of injection to the maximum peak height. The existence of infinite dilution conditions was assumed from the fact that the retention times of repeat injections being the same, even if the injection volume was varied to produce different peak heights. An average of five injections was recorded for each liquid probe. The flow rate of carrier gas through the column was measured using a soap bubble flow meter.

2.2. Isothermal microcalorimetry

Experiments were undertaken in a thermal activity monitor (Thermometric), using a commercial gas-flow cell. The gas-flow cell can be programmed to control the RH in the powder cell by mixing the proportions of gas which has remained dry and that which has been humidified to 100% RH. In these experiments the commercial system was modified by using a dry nitrogen source connected to a mass flow controller and then to the flow cell with stainless steel tubing. This adaptation guarantees the input gas is at 0% RH and minimises baseline fluctuation by providing a control over flow rate. The powder sample (50 mg) was placed in the measuring cell and then equilibrated by flowing 0% RH until a zero power response was measured (assumed to be dry powder). Then the RH was changed sequentially to 15, 30, 45, 60, 75, 90% RH. In each case sufficient time was allowed for the calorimetric signal to return to baseline response before moving to the next RH change. The enthalpy change was calculated from the area under the curve of power (rate of change of heat) as a function of time. The surface area of each sample was determined by use of multipoint nitrogen BET and the calorimetric responses were corrected as appropriate. All samples were also studied using differential scanning calorimetry (Perkin Elmer DSC 7, non-hermetically sealed pan scanning at 10°C min^{-1}).

3. Results and discussion

3.1. Inverse phase gas chromatography

The retention times on the column were used to calculate the dispersive component (γ_s^d) and polar acid–base parameters (K_A and K_D) of the powders. Firstly, the net volume (V_N) of carrier gas required to elute the injected probe molecules from the column was obtained by subtracting the retention time of methane from that of the liquid probe:

$$V_N = JD(t_r - t_0) \quad (1)$$

where t_0 and t_r are the retention times of methane and the probe vapour respectively; D is the flow rate of the eluting carrier gas and J is the correction factor that takes into account the compressibility of the gas as the pressure drops across the column:

$$J = \frac{3}{2}\left[\frac{(P_i/P_0)^2 - 1}{(P_i/P_0)^3 - 1}\right] \quad (2)$$

where P_i is the pressure at the inlet of the column and P_0 is the atmospheric pressure.

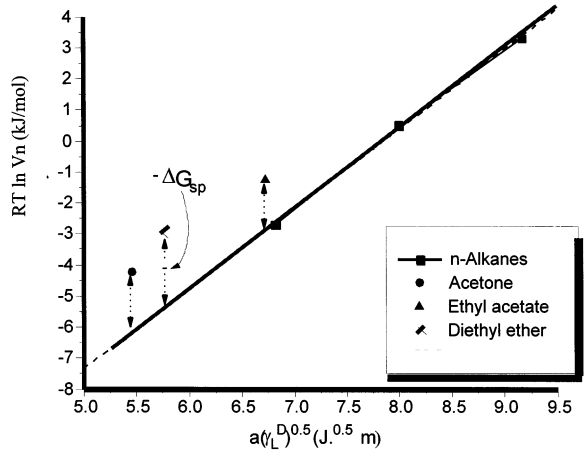

Fig. 1. Plot of free energy of adsorption ($RT \ln V_N$) as a function of the dispersive surface energy of the vapour probe.

3.2. Dispersive component of surface energy

Since apolar liquids interact by dispersive interactions only, the free energy of adhesion, ΔG°_{ads} (which can also be expressed as $RT \ln V_N$ where R is the gas constant and T is the absolute temperature) will be a direct function of the dispersive components of the solid (γ_s^d) and liquid (γ_l^d):

$$RT \ln V_N = 2N(\gamma_s^d)^{1/2} a(\gamma_l^d)^{1/2} + C \quad (3)$$

where a is the area of surface occupied by a molecule of vapour and N is Avagadro's number. If a plot of the free energy of adsorption of liquid probes onto solids '$RT \ln V_N$' was drawn as a function of the dispersion component of the alkanes, a straight line is obtained (Fig. 1). The dispersive component of the solid surface energy can thus be obtained from the slope of the line. The values of a and γ_l^d were obtained from the literature (Schultz et al., 1987; Nardin and Papirer, 1990). The values obtained for the saquinavir samples are shown in Table 1. It can be seen that the as received material has a higher dispersive surface energy than the tray dried material (with the other sample being intermediate). The samples with surfaces which exhibit higher energies can be expected to have different tendencies to interact with other phases.

Table 1
Dispersive surface energy terms as determined using alkanes retention in inverse phase gas chromatography

Sample	Dispersive surface energy (mJ m^2)	S.D.
As received	44.0	3.0
Vacuum dried	38.5	2.7
Heated only	37.1	1.6
Tray dried	32.6	1.5

3.3. Acidic and basic parameters

Polar liquid probes such as acetone or ether have the ability to interact with the solid by polar forces in addition to dispersive forces. These polar interactions are termed specific or acid–base (AB) interactions. If the total free energies of adsorption of polar probes were plotted in the same manner as for apolar alkanes, the polar probes would be located above the alkane line (Fig. 1). The vertical distance between the polar probe and the alkane reference line gives the specific energy of adsorption, ΔG_{ads}^{AB} and is referred to as the specific acid–base interactions of the probe with the solid.

Since the specific free energies of adsorption of polar probes on a solid are known, the solid surface can be described in terms of its acidic and basic nature. According to the Gutmann (1978) acid–base concept, liquids are characterised as either a Lewis base (or an electron donor) and assigned a donor number (DN) or a Lewis acid (an electron acceptor), characterised by a corrected acceptor number (AN*). Assuming entropic contributions are neglected (Papirer et al., 1988), the acid–base interaction of polar probes with solids can be described in terms of the acid and basic parameters and corresponding donor (DN) and corrected acceptor (AN*) numbers:

$$\Delta G_{ads}^{AB}/AN^* = (DN/AN^*)K_A + K_D \quad (4)$$

The acid and basic parameters are thus determined from the slope and intercept of the line, respectively, and are shown in Table 2. As with the dispersive surface energy terms (Table 1), the tray-dried material has the lowest energy and the as received is the most energetic surface.

Table 2
Polar surface energy as assessed by use of inverse gas chromatography for the same drug as received and after two different drying techniques

Sample	K_a (S.D.) acidic nature	K_b (S.D.) basic nature
As received	0.0353 (0.003)	0.193 (0.053)
Heated only	0.0278 (0.004)	0.207 (0.073)
Vacuum-dried	0.0196 (0.004)	0.208 (0.084)
Tray-dried	0.0185 (0.003)	0.156 (0.059)

Table 3
Surface areas of the powders as assessed by nitrogen sorption

Sample	Surface area ($m^2\ g^{-1}$)	S.D.
As received	0.91	0.11
Heated only	0.70	0.01
Vacuum-dried	0.71	0.02
Tray-dried	0.84	0.09

3.4. Isothermal microcalorimetry

The calorimetric data can either be expressed in terms of the mass of sample in the cell or the surface area which is available. The surface area data are given in Table 3. It is logical to consider the results in terms of unit mass for amorphous samples, as water will absorb into the material, however for crystalline samples the water will adsorb to the available surface, so expression of the results per unit area would be preferred. Whilst the nitrogen surface area is not necessarily exactly the same as that seen by water molecules it is usual to correct data by use of nitrogen sorption surface areas.

The plot of cumulative heat flow (the sum of the total heat flow at each RH) normalised per mass of sample yielded a different response for each material (Fig. 2), however, when corrected for surface area only the tray dried sample was distinctly different from the others (Fig. 3). Considering the fact that differences were seen between all the samples when using inverse phase gas chromatography, it could be that unit mass is more appropriate for these samples, perhaps due to some amorphous content at the surface.

In order to investigate why the tray dried sample was so different to the as received material samples were held in the cell of the isothermal microcalorimeter after reaching 90% RH, and were then re-equilibrated to 0% RH. The experiment was then repeated in 15% RH steps up to 90% RH. The sample was retained in the cell and dried again before exposing to a third cycle of humidification. The data in Fig. 4 show the mean (S.D.) data for three repeat cycles on the as received material. The results are plotted in a non-cumulative fashion, which means that the point at 15% RH is the heat change for the 0–15% RH step, and the point plotted at 30% RH is the heat change for the 15–30% RH step and so on. It can be seen that there are significant

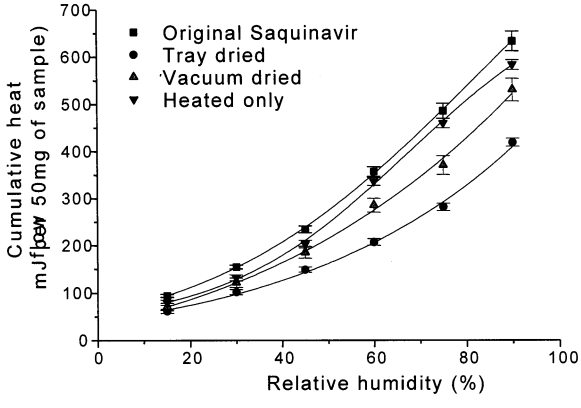

Fig. 2. Cumulative heat flow (expressed per mass of sample) as a function of RH.

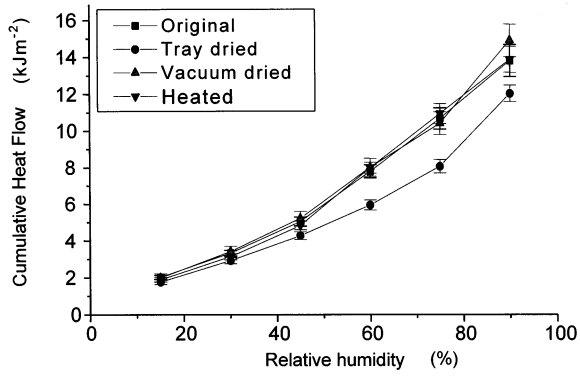

Fig. 3. Cumulative heat flow (expressed per unit area of sample) as a function of RH.

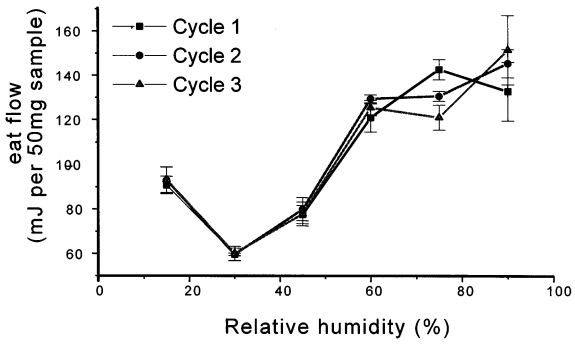

Fig. 4. Heat flow as a function of RH for as received sample, showing that the surface nature changes with each repeat exposure to RH.

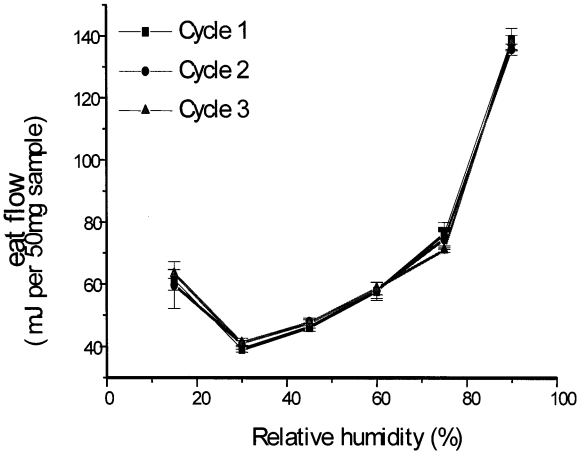

Fig. 5. Heat flow as a function of RH (non-cumulative) for tray-dried drug, showing three repeat cycles superimposed.

changes between the three cycles, which shows that the surface is unstable and changes gradually with each exposure to RH. This is unusual behaviour as unstable surfaces which are affected by RH usually will make a complete transition to the stable form on one isotherm. The tray dried material (Fig. 5) however, has a stable surface (as it does not change on repeat cycles). It is probable that the original material has a partially amorphous surface, but that the tray dried form is the stable crystalline material.

When measured using differential scanning calorimetry all the saquinavir samples had a single melting endotherm at 248°C. There was no indication of any other peaks. The data are typical of a crystalline material, but DSC is not able to detect amorphous material unless it amounts to over 5–10% by mass of the sample, so it is possible that some amorphous material could be in some of the samples at this low level. It follows that the difference in surface nature seen between these samples is a small difference in structure which cannot be detected by DSC. However, the change in properties between these samples can be detected readily by the vapour sorption techniques.

4. Conclusion

Isothermal microcalorimetry and inverse phase gas chromatography provide a very sensitive method by which it is possible to study minor changes in the surface properties of powders. Both vapour sorption techniques show consistent data, indicating that the drug can exist in a high energy unstable form at the surface (presumably partially amorphous). Changes in the processing used can cause the drug to change to have a lower energy, stable surface. Although not all drugs are prone to batch-to-batch variability, it is known that on some occasions changes in processing properties can occur due to variability in powder surface nature. The advantage of using these surface measurements is that any potential for batch-to-batch variability can be eliminated.

Acknowledgements

Thanks to Roche Products for support to JWD.

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