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Characterisation of the surface properties of α-lactose monohydrate with inverse gas chromatography, used to detect batch variation

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Abstract

Inverse gas chromatography (IGC) was employed to characterise the surface properties of four batches of α-lactose monohydrate supplied as chemically and physically equivalent, but reported to exhibit variable processing performance. These batches were found to be indistinguishable by FT-laser Raman spectroscopy, quantitative X-ray powder diffraction, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and surface area measurement. IGC was undertaken using vapours of polar and non-polar adsorbates or probes introduced individually, in very small quantities, onto the α-lactose monohydrate packed column. The net retention volume, V_N, of each probe was determined, allowing the calculation of various surface properties, including the dispersive component of surface free energy (γ^D) and specific interaction with polar probes (ΔG_A^{SP}). Whilst the γ^D values were comparable, ΔG_A^{SP} values for polar probes demonstrated significant differences, indicating batch variation in the polar surface properties of the four batches of α-lactose monohydrate. It is hypothesised that these differences in surface energetics are caused by minor variation in surface crystallinity or purity.

Keywords: α-lactose monohydrate; Inverse gas chromatography; Surface properties; Batch variation; Surface free energy

1. Introduction

Pharmaceutical powders are typically prepared by batch processes, that is, where discrete quantities of powder are produced according to stan-

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dard conditions, rather than on a continuous basis. Minor differences in the manufacturing conditions from batch to batch can result in variation in the physical properties of powders. This batch variation is generally small and subtle, and a robust formulation or further processing can prevent problems. However, where a formulation or additional processing is sensitive to such changes, or batch variation is large, this could lead to a failed or substandard product (Rowe et al., 1994). In addition to batch variation, source variation of materials can occur for so-called equivalent materials produced by different manufacturers (Parker et al., 1992).

Batch and source variation in the physical properties of pharmaceutical powders have been reported on numerous occasions (e.g. Landin et al., 1993, 1994; Phadke et al., 1994). Generally, these differences have been identified in terms of the bulk or particulate properties of the powders. However, variations in the surface properties of materials, although more difficult to detect, could be as influential. Source variation in the surface energetic properties of α-lactose monohydrate in terms of heat of adsorption of water has been measured using microcalorimetry (Sheridan et al., 1993), although the powder surface energetics were not calculated from these results.

Pharmaceutical powders are complex non-homogeneous systems for which characterisation of surface energetics is very challenging. Currently employed methods to determine surface energetics such as contact angles and calorimetric measurements, each have advantages and disadvantages in terms of methodology and complexity, which may affect the usefulness of their measurement (Buckton, 1990). Inverse gas chromatography (IGC) is a complementary technique which can generate further information and may aid in the total description of pharmaceutical powder surfaces. Although there are only a handful of studies utilizing IGC for pharmaceutical systems (Huu-Phouc et al., 1986, 1987a,b; Djordjevic et al., 1992; Ticehurst et al., 1994), the reported data indicate that this technique may be suitable for surface analysis of pharmaceutical powders. IGC can measure surface adsorption below monolayer coverage. This measurement is likely to be important because the first adsorbing layer controls processes such as surface wetting, with further multilayer coverage being controlled by condensation interactions (Braunauer et al., 1938).

In this study the adsorption behaviour of a range of polar and non-polar probes has been used to measure the surface energetics of four batches of α-lactose monohydrate supplied as chemically and physically equivalent from the same source. By applying the theoretical approach of Schultz and Lavielle (1989) the surface properties have been separated into the polar and non-polar components.

2. Materials and Methods

Four nominally equivalent batches of α-lactose monohydrate (named A–D) were supplied from Lactochem (The Netherlands).

FT Raman spectra of 200 scans at 4 cm^{-1} resolution over wavenumber range 3500–50 cm^{-1} were recorded on a Bruker FRA 106-FT Raman module on an IFS 66 Optics bench with a 750-mW Nd : YAG laser at 1064 nm.

Quantitative X-ray powder diffraction was undertaken on < 200-mesh α-lactose monohydrate samples lightly ground with corundum (internal standard) and resieved through a 210 mesh. The diffractograms were produced with monochromated copper Kα radiation (40 kV, 30 mA) at 5–45° 2θ, with 10 s counting at each step of 0.05° 2θ, using a Siemens D5000 diffractometer. Theoretical ideal powder patterns were calculated from single crystal X-ray data, and the experimental powder patterns fitted to the data by full pattern fitting refinement method to obtain the lattice constants.

The anomeric composition of the material was determined by the gas chromatographic method (Dwivedi and Mitchell, 1989) for three samples from each batch of material.

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were performed on a Perkin-Elmer series 7 at a rate of 10°C/min between 25 and 225°C.

Multipoint analysis of N_2 adsorption on a Flowsorb 2300, applying the BET equation (Braunauer et al., 1938), was used to determine the surface areas of samples. Samples were dried at 40°C for 16 h under 30%N_2/70%He prior to measurement.

Details of the IGC rig and experimental procedure used can be found in Ticehurst et al. (1994). The columns were packed with between 0.5 and 1 g of α-lactose monohydrate, and up to four separate columns were used for each sample. The α-lactose monohydrate columns were studied both undried and after drying at 40°C for 16 h. Drying at 40°C for 16 h has been demonstrated to remove surface moisture from the α-lactose monohydrate, but not the water of crystallisation (Ticehurst, 1995).

Column temperature was set at 29.3 ± 0.2°C for measurement of retention of probes. Probes employed were pentane (Aldrich), hexane (Rathburn Chemicals), heptane (Sigma), octane (Aldrich), nonane (Aldrich), decane (Sigma), acetone (Aldrich), diethylether (May & Baker), ethyl acetate (RP Normapur), and tetrahydrofuran (THF) (Rathburn Chemicals), all of which were 99%+ pure. In order to achieve infinite dilution conditions, vapours of the probes (equivalent to 10^{-4}–10^{-7} μl of liquid) were introduced to the injection port of the column using a 1-μl syringe.

2.1. Calculation of surface energetics

The retention time of the probe liquids on the α-lactose monohydrate stationary phase was used to calculate the net retention volume of the probes (V_N) using Eq. (1). V_N is the fundamental parameter measured in IGC:

$$V_N = t_R \cdot j \cdot F_C - V_D \qquad (1)$$

where t_R is the retention time of the probe, j is the James and Martin carrier compressibility correction factor (James and Martin, 1952), F_C is a corrected outlet carrier gas flow rate and V_D the void volume within the column calculated from the homologous series of alkanes (Smith et al., 1978).

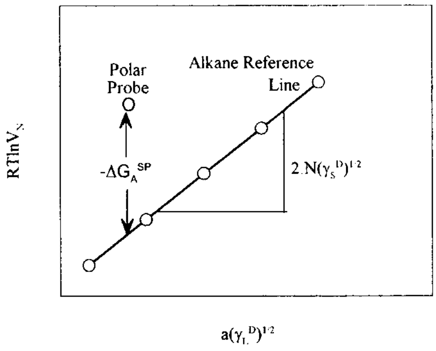

Fig. 1. Schematic diagram showing the determination of the dispersive component of surface free energy (γ_S^D) and specific component of the free energy of adsorption (ΔG_A^{SP}) (approach of Schultz and Lavielle, 1989).

The dispersive component of surface free energy (γ_S^D) and the specific components of the free energy of adsorption (ΔG_A^{SP}) of each polar probe were calculated according to the approach of Schultz and Lavielle (1989), who derived Eq. (2):

$$RT \ln V_N = a \cdot (\gamma_L^D)^{1/2} \cdot 2N \cdot (\gamma_S^D)^{1/2} + C \qquad (2)$$

where N is Avogadro's number, R is the gas constant, a is the surface area of the probe molecule, γ_D^L is the dispersive component of surface free energy of the liquid probe and C is a constant. The values of γ_S^D and ΔG_A^{SP} are determined graphically as shown in Fig. 1. γ_S^D and ΔG_A^{SP} represent the non-polar and polar properties, respectively, of the surface.

3. Results

3.1. Thermal analysis

Fig. 2 is a typical DSC thermal profile for the α-lactose monohydrate batches. The first en-

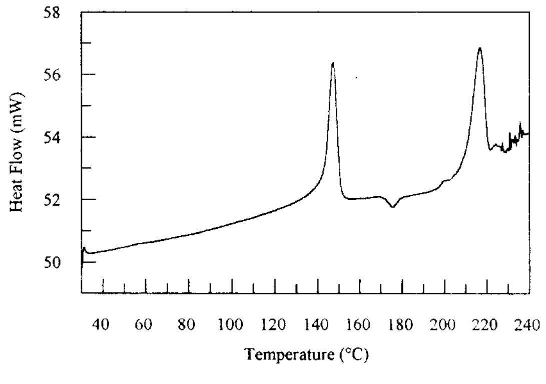

Fig. 2. A typical DSC profile for α-lactose monohydrate.

Table 1
Thermal analysis of four batches of α-lactose monohydrate

Lactose sample	DSC results				TGA results (% weight loss by dehydration)
	Enthalpy of dehydration (J/g)	Onset of dehydration (°C)	Enthalpy of melting (J/g)	Onset of melting (°C)	
A	110.3	144.1	101.0	213.4	5.3
B	112.7	144.0	125.0	212.6	5.1
C	114.3	143.7	87.3	211.7	5.1
D	109.8	144.0	91.9	208.5	5.2

dotherm is the dehydration of the monohydrate (130–150°C), which is followed by the endotherm for the melting of the anhydrous form (200–220°C). The results from the thermal analysis of the four batches α-lactose monohydrate are displayed in Table 1. The analysis of the dehydration of the α-lactose monohydrate samples indicates that the water contents were similar. The apparent differences observed in the enthalpies of melting are difficult to quantify due to non-base line return after melt and concomitant sample degradation. Additionally they reflect the sample in an artificial anhydrous state, and thus do not represent a measure of the crystallinity of the lactose in its original monohydrate form.

3.2. Anomeric composition

The anomeric composition of the four batches of α-lactose monohydrate is displayed in Table 2. The variation in the content of β-lactose could be due to the natural variation in both the ingredients used in the crystallisation process, and the drying steps employed following crystallisation. However, as IGC has been demonstrated to detect differences in the surface energetics of α and β-lactose (Ehler et al., 1979), variation in surface β-lactose content may be expected to affect the overall surface energetics.

Table 2
Anomeric composition of four batches of α-lactose monohydrate

Lactose batch	Anomeric composition, $n = 3$ (% β-lactose)
A	4.2 ± 0.53
B	3.1 ± 0.18
C	4.2 ± 0.38
D	3.4 ± 0.40

3.3. Surface area

The values for surface area for three of the four batches of α-lactose monohydrate are shown in Table 3, indicating the batches were comparable. The small quantity available of the fourth batch prevented a surface area measurement.

3.4. FT-laser Raman

The FT-Raman spectra were found to be equivalent with peaks at the same wavenumbers. Most importantly the peaks in the range of 50–500 cm^{-1}, which are generally associated with secondary order and crystallinity, showed no differences.

3.5. Quantitative X-ray powder diffraction

The lattice dimensions for α-lactose monohydrate batches A, B and D, determined using X-ray powder diffraction with full pattern fitting, are given in Table 4. The minor differences in lattice

Table 3
Specific surface area of batches of α-lactose monohydrate

Batch	A	C	D
Specific surface area (m^2/g)	0.39 ± 0.01	0.38 ± 0.01	0.40 ± 0.01

Table 4
Lattice dimensions of α-lactose monohydrate determined by quantitative X-ray powder diffraction

Lactose batch	Lattice constants (Å)			
	a	b	c	β
A	7.934	21.592	4.814	109.77
B	7.935	21.577	4.813	109.80
D	7.932	21.590	4.808	109.88

dimensions are of the order expected from experimental errors, and do not represent a structurally significant change.

3.6. Inverse gas chromatography

The retention times and volumes for a range of polar and non-polar probes on the undried and dried α-lactose monohydrate surfaces were used to calculate γ_S^D and ΔG_A^{SP}.

For IGC of all the batches of undried α-lactose monohydrate V_N of the polar probes decreased throughout the experiment, as illustrated by the retention of THF on batch A in Fig. 3. In contrast, non-polar probes were found to have consistent retention throughout the run, as shown for octane in Fig. 3. These results indicate that changes in the surface during experimentation are predominantly related to polar interactions. The decrease in the affinity of polar probes for the surface was considered to be caused by the dehydration of the α-lactose monohydrate surface by the dry carrier gas during experimentation. Interestingly, some polar probes, such as ethanol, were found to be totally retained on the undried α-lactose monohydrate, presumably because they exhibited a strong affinity for the surface moisture.

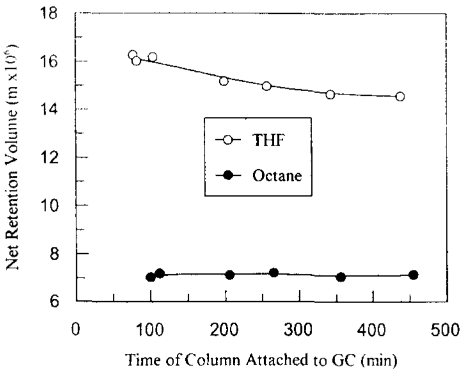

Fig. 3. Change in the net retention volume (V_N) of octane and THF on α-lactose monohydrate with the time during which the column is attached to the GC.

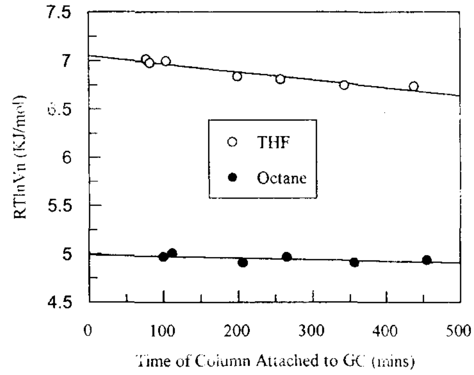

Fig. 4. Change in the $RT \ln V_N$ (relative interaction free energy) of octane and THF on α-lactose monohydrate with the time during which the column is attached to the GC.

The minimum lag time, i.e. the time interval between the column being attached and the first measurement being taken, was approximately 1 h. The lag allowed for the required equilibration of the column and the oven. An approximate linear relationship between $RT \ln V_N$ (relative interaction free energy) and the time period over which the column had been attached to the GC was found, as shown in Fig. 4. The value of $RT \ln V_N$ was extrapolated to time zero to achieve an estimate of the undried surface energetics.

The surface energetic properties of α-lactose monohydrate, shown in Tables 5 and 6, indicate that within experimental error the four batches have equivalent γ_S^D values in each of the two surface states. In addition, drying has little effect on the magnitude of γ_S^D.

In contrast, there were large differences in the ΔG_A^{SP} values of the polar probes between batches, indicating differences in the specific interactions. The magnitude of differences between the batches were similar both unconditioned and after drying at 40°C, suggesting that they are not related to adsorbed surface water. Interestingly, the poor precision of ΔG_A^{SP} values for polar probes with batch C was improved following drying at 40°C

Table 5
Surface properties of α-lactose monohydrate with no conditioning (figures in parentheses represent the standard deviation of the measurements)

Batch	γ^D (mN/m)	$-\Delta G_A^{SP}$ (KJ/mol)			
		Acetone	THF	Diethyl ether	Ethyl acetate
A	42 (2)	10.0 (0.2)	8.1 (0.2)	6.7 (0.2)	9.5 (0.2)
B	40	6.2	4.8	3.2	5.7
C	40 (3)	8.7 (0.7)	7.1 (0.8)	5.3 (0.2)	8.4 (0.7)
D	44	10.5	8.6	7.2	9.6

suggesting that the variability in the undried state was caused by differences in the initial surface moisture.

The reason for the differences in surface energetics is not clear. There is no obvious differences in the crystal structure, measured by X-ray powder diffraction, or chemistry and secondary structure, measured by FT-Raman. The rank order of magnitude of the specific interaction strength of polar probes, batch D > A > C > B, shows no correlation with the rank order of β-lactose content, batch A = C > D > B, suggesting the β-lactose impurity is not important in controlling surface energetics. In addition, the surface moisture, although causing a change in surface energetics, does not explain the batch variation.

During this experiment, IGC was carried out at infinite dilution which relates to approximately 1–3% surface coverage of the surface by the probe molecules (Ticehurst, 1995). It is therefore extremely sensitive to surface high energy sites. A possible cause for the batch variation is minor differences in the surface crystallinity, which would lead to 'hot spots' of high energy which could be detected by IGC. If this disorder is predominantly at the surface it need only be a very low proportion of the total bulk powder, thus it would not be detected by bulk techniques such as X-ray powder diffraction, which has a resolution down to only about 10% disorder content (Altree-Williams et al., 1981). This type of surface disorder could cause a change in the processing performance of a powder. An alternative reason for the differences is variable levels of high energy impurities within the batches, which again would not be detected by the bulk techniques.

In summary, four batches of α-lactose monohydrate from the same source, supplied as equivalent with regard to chemical and physical properties, have been demonstrated by IGC to have different surface energetics. These differences were shown to reside in the specific interactions with polar probes rather than non-polar interactions. It is possible that the differences are related to minor variation in the crystallinity or purity of the batches. These variations in surface proper-

Table 6
Surface properties of α-lactose monohydrate batches determined after conditioning at 40°C (figures in parentheses represent the standard deviation of the measurements)

Batch	γ^D (mN/m)	$-\Delta G_A^{SP}$ (KJ/mol)			
		Acetone	THF	Diethyl ether	Ethyl acetate
A	44 (2)	9.1 (0.3)	7.3 (0.2)	6.0 (0.2)	8.6 (0.2)
B	40	5.7	4.4	2.9	5.4
C	41 (3)	8.2 (0.3)	6.6 (0.2)	5.2 (0.2)	7.8 (0.2)
D	42	8.7	6.9	5.4	7.7

ties, hitherto unrecognised, may assist in explaining variation in processing properties of pharmaceutical powders.

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