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THE EFFECT OF STABILITY TREATMENT ON THE SURFACE ENERGETICS OF INHALATION GRADE LACTOSE

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ABSTRACT

Inverse gas chromatography, IGC was employed to characterize the surface thermodynamic properties of different batches of an inhalation grade lactose. The experiment was carried out using *vapours* of different polar and non-polar probes at infinite dilution. The net retention volume (V_n) of each probe determined from the retention times as sensed by the GC detector, was used to calculate the dispersive and non-dispersive (specific free) energetics of the powder samples. The surface energy values for the inhalation grade lactose subjected to 75% Relative Humidity at 40°C showed that surface reconstruction occurs as indicated by a small but continuous decrease in the specific free energy on prolonged treatment. This trend in surface energetics is demonstrated to reside in the specific interactions with polar probes rather than the non-polar interactions. The observed change in the surface energy, as a result of humidity treatment may be related to minor enhancement in crystallinity or purity of the samples. The results clearly demonstrate the potential of IGC to detect and quantify differences in supposedly equivalent samples of pharmaceutical powder substances.

KEYWORDS: Chromatography, Energy, Detector, Probes.

INTRODUCTION

Batch-to-batch consistency and uniformity of raw materials is crucial for the manufacture of multi dry powder inhaler (MDPI) products. The complexity of particle formation and treatment operations often means that minor differences in the preparation conditions from batch-to-batch can result in variations in the physical properties of routinely manufactured, supposedly equivalent, batch products. This variation can influence processing and formulation characteristics, which may ultimately affect the quality and performance of the final product.

Lactose is commonly employed in the formulation of dry powder inhalers, as an inert carrier, (Byron et al.,1990) . The carrier is used to aid the flow of active drugs. Commercial grade lactose is available in a wide variety of particle sizes with diverse morphology and grades (Wade and Weller, 1994). The physical properties of lactose such as particle size, shape and surface texture have been shown to govern the dispersion and deaggregation of any adhered drugs (Ganderton and Kassem, 1992; French et al., 1996; Steckel and Müller, 1997; Podczeck, 1998). A recent study demonstrated that different grades of lactose produced different deposition profiles of a model drug, Salmeterol Xinafoate (Podczeck, 1998).

As processing operations such as blending, comminution or micronisation produce mechanical activation, the traditional bulk measurement techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction (XRD) and infra-red spectroscopy (IR) highlight some material differences but others remain undetected by these methods. This is so because, mechanical activation rarely distributes uniformly through out the powder mass, but most likely predominate at the surface thus producing disordered phase or amorphous regions on the particle surfaces. IGC may therefore have the potential to unlock some of these more difficult to measure physico-chemical properties that are beyond the reach of the bulk techniques.

A number of recent publications have highlighted the sensitivity of IGC for determining changes in particle surface properties following processing operations. Batch and source variation in the surface properties of α-lactose monohydrate has been measured using microcalorimetry, (Freeley et al.,1998) and IGC method (Ticehurst et al.,1996), but the influence of relative humidity and operations such as comminution have not been reported .

The main objective of the present study is to evaluate the effect of stability treatment (relative humidity) on the surface energetics of two different batches of inhalation grade lactose using IGC. Although not all drugs are prone to batch-to-batch variability, the advantage of this surface measurement lies in the potential for batch-to – batch variability to be identified and eliminated.

EXPERIMENTAL

Material and methods:

IGC study was set up on a Varian CP3800 Gas Chromatography equipped with Flame Ionisation Detector (FID) and a packed glass column system. The data were acquired using a DELL PC loaded with an electronic Varian Star software.

Two different batches (B200 and B300) of α-lactose monohydrate were all supplied by GlaxoSmithKline, Ware, Hertfordshire, UK. Each batch of lactose was subjected to 75% Relative Humidity at 40°C for a period of up to 20 days. Non-polar probes are methane, hexane, heptane, octane and nonane. Polar probes are chloroform, acetone, tetrahydrofuran (THF) and ethylacetate. All the probes were of HPLC grade.

About 1m length of ¼" OD (4mm id) silinated glass column was packed with the lactose. The columns were packed by pouring a known amount of powder sample using gentile vacuum on one end of the column and reducing its volume by vibrating it with the vibro-engraver supplied. Intermediate level of vibration was applied continuously in order to achieve a uniform reduction in inter and intra-column packing density. This procedure was continued until there was no visible gaps in the packing. The end of the column was plugged with silinated glass wool, and the sample dried at 40°C overnight under dry nitrogen carrier at 10ml/min.

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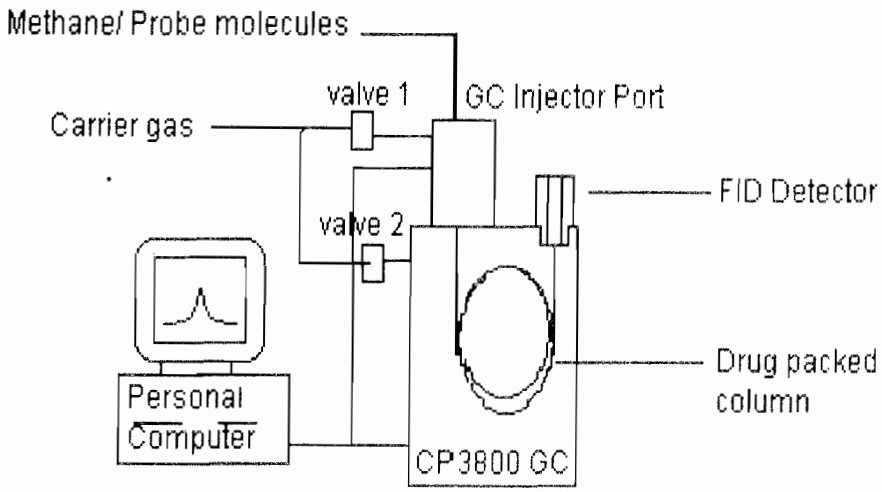

Figure1: Schematic diagram for Inverse Gas Chromatography (IGC)

Autoinjector vials were prepared so that the head space of each vial was filled with the vapour of each probe. In order to achieve infinite dilution conditions (low surface coverage), an equivalent of 10^{-4} to 10^{-7} µl of the liquid was injected into the column via the autosampler. Typically, one to two drops of the probe were placed into a 2-ml vial using a Pasteur pipette, and the vial sealed with a crimp top. The Vapour of each probe from each vial was injected separately and the retention time of each probe was then measured and printed on the PC.

Calculation:

The calculation of the surface energy was made following the theory developed by Schultz et al (1987), using a validated Excel Spreadsheet.

$$V_n = JD(t_r - t_o) \quad (1)$$

Where V_n is the net retention volume of the probe, t_o and t_r are the retention times of the methane and the vapour respectively, D is the flow rate of the eluting carrier gas and J is the correction factor that takes account of the gas compressibility as the pressure drops across the column (De Boer 1968).

$$J = 1.5[(P_i/P_o)^2 - (P_i/P_o)^3 - 1] \quad (2)$$

Where P_i is the inlet column pressure and P_o is the atmospheric pressure.

Dispersive Energy (γ_s):

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

Where R is the gas constant, α is the area occupied by a molecule of vapour. N is the Avagadro's number while γ_s and γ_l are the dispersive component of the solid and liquid respectively. The slope of equation 4 is equal to $2N(\gamma_s)^{1/2}$ where γ_s can be calculated.

Specific or Acid – Base interaction(non-dispersive energy, ΔG_A^{sp}):

An estimate of the specific interaction, ΔG_A^{sp}, is obtained from equation 4.

$$\Delta G_A^{sp} = RT\ln(Vn/Vn^{ref}) \quad (4)$$

where Vn^{ref} is the retention volume of the alkane.

Following Papirer's approach (Papirer and Saint-Flour,1982), it was assumed that:

$$\Delta G_A^{sp}/AN = Ka(DN/AN) + Kd \quad (5)$$

where Ka and Kd are numbers describing the acid and base characteristics of the powder- solid, and are determined by a plot of $\Delta G_A^{sp}/AN$ versus DN/AN.

The electron acceptor number (AN) defines the acidity or electron – acceptor ability of the probe while the donor number (DN) defines the basicity or electron –donor ability of the probe. The values of DN and AN are published (Papirer and Saint – Flour, 1982; Schultz et al 1987).

RESULTS AND DISCUSSION

The measured surface energies of the two different batches of inhalation grade lactose are presented in table1, and the results indicate that the two samples are completely different in terms of the measured surface energies. However, the Dispersive energy (γ_s) values of the two samples are quite close. In contrast, there are large differences in the value of ΔG_A^{sp} between the two samples. The reasons for the differences in surface energetics relating to the polar probes only are still being debated. The samples were supplied as chemically and physically equivalent with no obvious differences in the measured X-ray powder diffraction pattern, DSC or other bulk techniques. However, a possible reason for the batch variation may come from minor differences in the surface crystallinity or impurities within the batches. IGC is a surface sensitive technique, therefore the probe molecules interact with the high energy sites located at the surface of the solid lactose powder, which invariably would not be detected by the bulk techniques.

The acid and base parameters (Ka and Kd) are large showing that the surface of lactose is strongly amphoteric. The acid sites are due to the exposed hydroxyl groups while the Dispersive sites are presumed to be the exposed carbon atoms in the chain

Table 1: The Surface Energies of the inhalation grade lactose

Batch/ Sample	Dispersiv Energy/	Specificfree Energy. ΔG_A^{sp} /kJ/mol				Acid/Base Parameter	
	mJm^2	Chloroform	acetone	EA	THF	Ka	Kd
B200							
(Mean)	46.361	2.327	9.859	9.246	8.010	0.383	1.139
(Stdev)	1.733	0.118	0.281	0.242	0.229	0.011	0.048
B300							
(Mean)	45.081	1.750	7.471	7.561	6.121	0.281	1.057
Stdev)	1.707	0.114	0.220	0.167	0.122	0.005	0.001

Table 2: The effect of stability treatment (75% RH at 40oC for 0 to 20 days) on the surface energy of batch **B200** of inhalation grade lactose

Batch/	Dispersiv Energy/	Specificfree Energy/kJ/mol				Acid/Base Parameter	
sample	MJm^2	Chloroform	Acetone	EA	THF	Ka	Kd
B200							
0 days	46.351	2.398	10.02	9.255	7.920	0.376	1.105
5 days	44.497	2.114	9.467	8.881	7.272	0.343	1.075
10 days	43.326	1.878	8.884	8.212	7.001	0.335	1.056
15 days	42.972	1.661	8.120	7.729	6.892	0.310	1.015
20 days	43.012	1.502	7.544	6.867	6.455	0.301	1.001
B300							
0 days	44.775	1.772	8.107	7.544	6.760	0.288	1.040
5 days	43.306	1.662	7.662	7.309	6.487	0.265	1.040
10 days	43.565	1.580	7.333	7.045	6.305	0.252	1.020
15 days	43.821	1.574	7.200	6.836	6.286	0.250	1.001
20 days	43.354	1.521	7.313	6.765	6.297	0.251	1.001

Table 2 shows the surface energy values for the inhalation grade lactose subjected to 75% Relative Humidity at 40oC for a period of up to twenty days. These results showed that surface reconstruction occurs as indicated by a small but continuous decrease in the specific free energy of interaction on prolonged treatment. This trend in surface energetics is demonstrated to reside in the specific interactions with polar probes rather than the non-polar interactions.

It is possible that these changes in surface energetics, as a result of humidity treatment, are related to minor enhancement in crystallinity or purity of the samples. Figure 2 shows the plot of specific energy for acetone and ethyl acetate, and these values are observed to decrease with time of treatment and became equal on prolonged treatment. It shows that there was a surface reconstruction, a stabilization process for both samples. During this experiment, IGC was carried out at infinite dilution, which relates to very low surface coverage by the probe molecules. It is therefore extremely sensitive to high energy sites, which strongly suggests that any reconstruction would occur predominantly at the surface. Furthermore, such a reconstruction would only be a very small proportion of the total bulk powder, thus it would not be detected by bulk techniques such as X-ray powder diffraction.

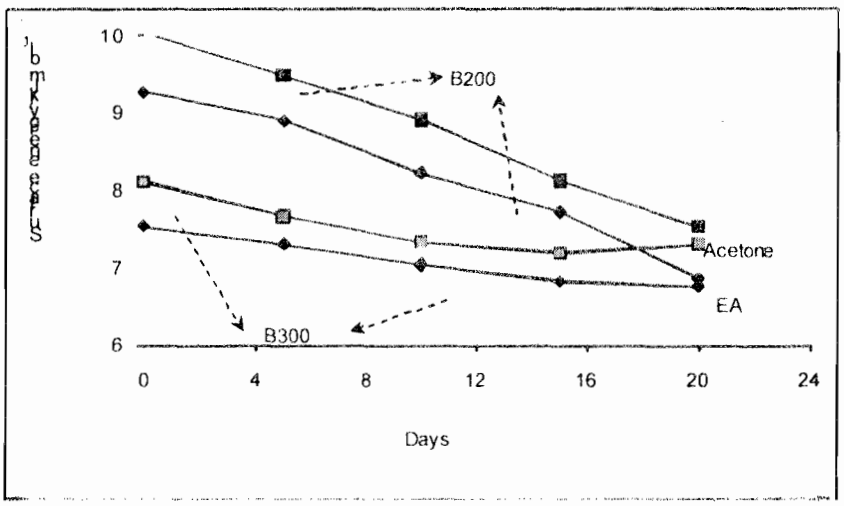

Figure 2: The plot of specific energy, ΔG_A^{sp} versus days at 75% relative humidity for both lactose samples, using ■ Acetone and ♦ Ethyl Acetate(EA) as probes.

CONCLUSION

The two batches of inhalation grade lactose supplied as equivalent in terms of chemical and physical properties, have been demonstrated by IGC to have different surface energetics. It was shown that the differences emanated from the polar probes interactions with high energy sites resident at the surfaces of the solid. It is also suggested that the differences are related to minor variation in the crystallinity or impurities within the batches.

The results obtained, thus demonstrate the potential of IGC to detect and quantify differences in supposedly equivalent samples of pharmaceutical powder substances. A continuous change in the surface energy was observed as the samples were subjected to related humidity treatment, supporting the idea of surface reconstruction at the crystallite level.

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