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Determination of the surface properties of two batches of salbutamol sulphate by inverse gas chromatography

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Abstract

The surface properties of two batches of salbutamol sulphate, demonstrated to be chemically and structurally equivalent by FT-Raman spectroscopy and X-ray powder diffraction, were measured using a gas-solid chromatography technique, inverse gas chromatography (IGC). IGC was undertaken using polar and non-polar adsorbates (probes) at infinite dilution with salbutamol sulphate as the solid stationary phase. The retention behaviour of the probes was found to differ markedly between the two batches, implicating a profound difference in surface energetics. This was reflected in the differences in calculated dispersive component of surface free energy (γ_S^D) and acid-base parameters.

Keywords: Salbutamol sulfate; Inverse gas chromatography; Surface properties; Batch to batch variation; Surface free energy; Acid-base interactions

1. Introduction

Minor changes in preparation can result in batch to batch variation of physical properties of powders. Changes in the surface properties of pharmaceutical powders can influence their processing and formulation characteristics, including wet granulation, film coating and suspension formation (Buckton, 1988; Rowe, 1989; Parsons et al., 1992). This ultimately may affect the quality and performance of the final product (Young and Buckton, 1990).

A technique generally used to determine surface properties of pharmaceutical powders is contact angle measurement. However, in order to determine the contact angle of a pharmaceutical powder it is necessary to first compress the particles to form a flat surface. This compression may cause changes in surface properties, and the rough micro-surface produced often leads to contact angle hysteresis, reducing the accuracy of results.

Recently, calorimetric techniques have been utilized to obtain a thermodynamic assessment of powder surface properties (Buckton and Beezer, 1988; Buckton et al., 1988) allowing discrimination between suppliers of lactose in terms of surface adsorption of water (Sheridan et al., 1993).

Physicochemical gas chromatography or in-

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verse gas chromatography (IGC) can be applied to obtain adsorption thermodynamics which also allow the determination of the surface properties of materials. IGC differs from standard GC in that the properties of the solid stationary phase, the powder, are determined by using characterised adsorbates, referred to as probes. IGC has become a standard technique for characterising the surfaces of catalysts, polymers, paper and carbon fibres (Lloyd et al., 1989; Bilinski, 1993). In the pharmaceutical area Djordjevic et al. (1992) employed IGC to ascertain rapidly the surface interactions of cyclosporin A with water.

In this study the adsorption behaviour of a range of polar and non-polar probes has been employed to determine surface characteristics of two batches of salbutamol sulphate. The surface properties calculated using IGC results, using theory established in the literature (Schultz and Lavielle, 1989), were the dispersive component of surface free energy (γ_S^d) and acid-base parameters. Such parameters have recently been used to predict surface interactions of materials (Lloyd et al., 1989; Hegedus and Kamel, 1993).

2. Materials and methods

Two batches of salbutamol sulphate (A and B) were generously donated by Glaxo Manufacturing Services (Ware, U.K.).

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.

X-ray powder diffractograms were produced with copper Kα radiation at 2–72° 2θ using a Siemens D5000 diffractometer.

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were performed on a Perkin-Elmer series 7 at a rate of 10°C min^{-1} between 25 and 225°C.

The moisture content was measured by Karl-Fischer analysis on a Metrohm 701KF Titrino.

Surface area, calculated by the BET method (Brunauer et al., 1938) at 77 K with nitrogen as adsorbate, and pore volume using the BJH method, were measured in a Micromeritics ASAP 2000 apparatus.

Hot-stage microscopy was performed with a Nikon microscope and Stanton Redcroft hot-stage unit between 30 and 240°C, both dry and with silicone fluid.

IGC was undertaken on a Hewlett Packard 5710A gas chromatograph equipped with dual flame ionisation detectors. Industrial grade nitrogen, dehumidified by molecular sieve, was used as the carrier gas. Inlet carrier gas pressure was measured using a Chrompack hand held pressure gauge (accuracy 1%, precision 0.1 lb/inch^2). Outlet carrier gas pressure was assumed to be atmospheric and was measured using a mercury barometer (precision 1 mmHg). Outlet carrier gas flow rate was measured to 0.1 cm^3 min^{-1} using a jacketed bubble flow meter held at 30°C. Variation in outlet column flow rate throughout experimentation was less than 0.5%. Column outlet flow rates used for individual experiments ranged from 12 to 24 cm^3 min^{-1}. A cooling coil was added to the air circulating oven to achieve near ambient column temperature. Column temperature was monitored throughout, using a digital thermometer with thermocouple in contact with column. Injection port temperature was held at 100°C.

Glass columns, 3 mm i.d., were deactivated by a cold silanation (Mohammad and Fell, 1982). The salbutamol sulphate batches A and B were packed into empty deactivated columns, using a vacuum line and mechanical vibrator. The flow properties and surface area of the two batches were different and therefore the mass of powder and columns employed for each batch differed: 0.54 and 0.66 g of batch A was packed into U-shaped columns ($\sim$ 50 cm length), whereas 2.89 and 9.35 g of batch B was packed into columns of $\sim$ 80 and $\sim$ 200 cm length (one and four loops). The ends of the columns were plugged with silinated glass wool. The salbutamol sulphate in the columns was dried at 40°C for 16 h under dry nitrogen prior to use.

Column temperature was set at 29.3 $\pm$ 0.2°C for measurement of retention of probes. Probes employed were pentane (C_5; Aldrich), hexane (C_6; Rathburn Chemicals), heptane (C_7; Sigma),

octane (C_8; Aldrich), nonane (C_9; Aldrich), decane (C_{10}; Sigma), acetone (Ace; Aldrich), diethylether (ether; May & Baker), ethyl acetate (EA; RP Normapur), dichloromethane (DCM; Aldrich), chloroform (Chf; Fisons) and tetrahydrofuran (THF; Rathburn Chemicals), and all 99 + % pure. To achieve infinite dilution conditions, vapours of the probes (equivalent to 10^{-4}–10^{-7} μl of liquid) were introduced into the injection port of the column using a 1 μl syringe. The retention times of the probes were measured with a Hewlett Packard integrator, with the average of at least four injections being taken for each probe.

The fundamental parameter measured in inverse gas chromatography is the net retention volume, which is the net volume of carrier gas required to elute the probe. The net retention volumes of the probes (V_N) were calculated using Eq. 1:

$$V_N = t_r \cdot j \cdot F_c - V_d \quad (1)$$

where t_r is the retention time of the probe, j denotes the James and Martin carrier compressibility correction factor, 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).

3. Results and discussion

3.1. Physicochemical analysis

The FT-Raman spectra of salbutamol sulphate batches A and B, displayed in Fig. 1, have peaks at identical wavenumbers indicating chemical and structural equivalence. This equivalence is confirmed by the X-ray powder diffraction patterns of the two batches (Fig. 2) which show peaks at corresponding 2θ values. The difference in intensity of the peaks on the X-ray diffraction patterns were considered to be due to preferred orientation and minor differences in crystallinity of the powders.

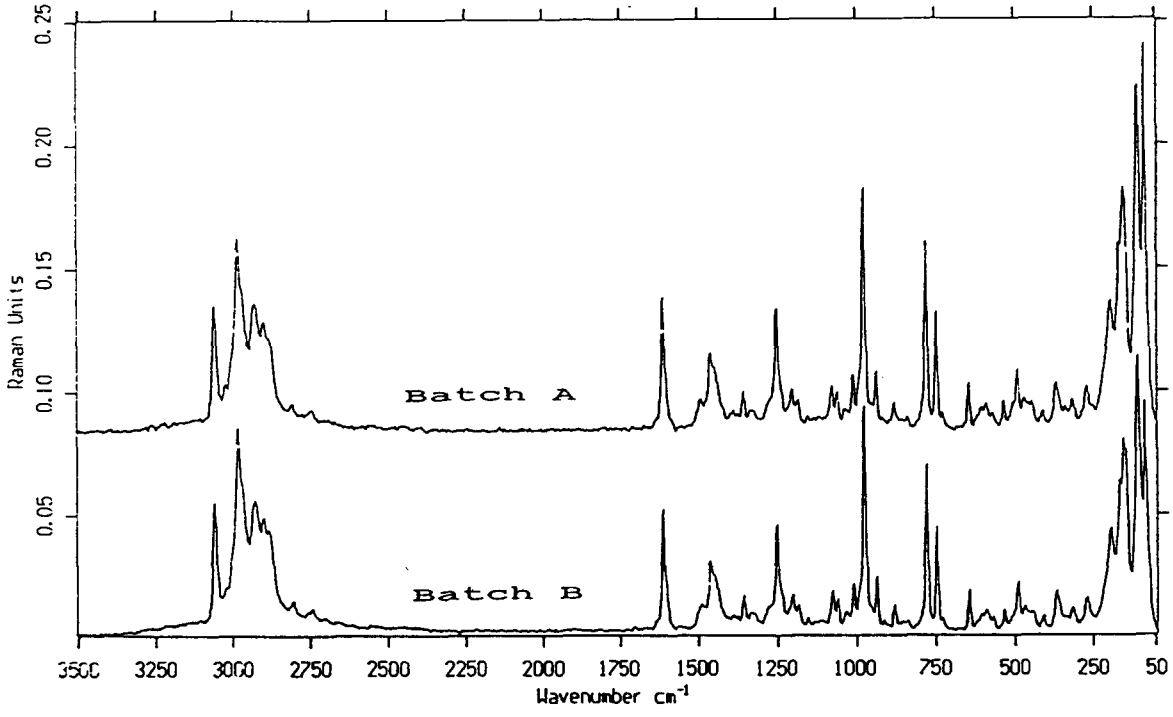

Fig. 1. FT-Raman spectra for salbutamol sulphate batches A and B.

Thermogravimetric and Karl-Fischer analyses indicate the presence of small amounts of water associated with batches A and B. The mean (SD) water contents measured by Karl-Fischer analysis were 0.21% (0.03%) and 0.11% (0.03%) for batches A and B, respectively. DSC demonstrated differences in the decomposition/melting endotherms of the two batches, as displayed in Fig. 3 and 4. Hot-stage microscopy of both batches showed mainly decomposition of the crystals with little melting. It may be that the broader DSC endotherm peak for batch A is caused by an increase in lattice defects producing a thermally less stable material. The presence of increased lattice defects could explain the minor changes in crystallinity detected by X-ray powder diffraction.

3.2. Partition coefficient

The V_N values determined using IGC were used to calculate the partition coefficients (K_s) of the probes between carrier gas and surfaces of salbutamol sulphate batches A and B, according to Eq. 2:

$$K_s = V_N/m \cdot A_{sp} \quad (2)$$

where m is the mass and A_{sp} the specific surface area of the powder in the column.

The values of specific surface area were calculated to be 2.06 and 0.31 $m^2\ g^{-1}$ for batches A and B, respectively. Average values of K_s for octane (non-polar) and THF (polar), from two columns with range, are displayed in Fig. 5. There

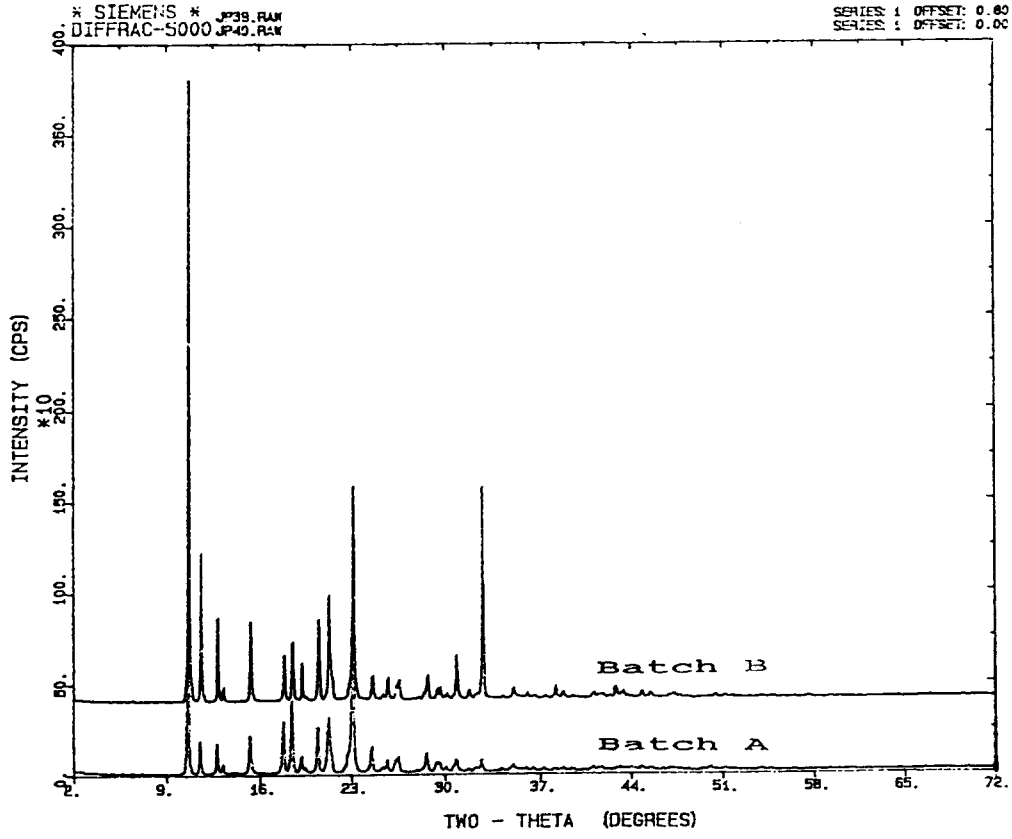

Fig. 2. X-ray powder diffractograms for salbutamol sulphate batches A and B.

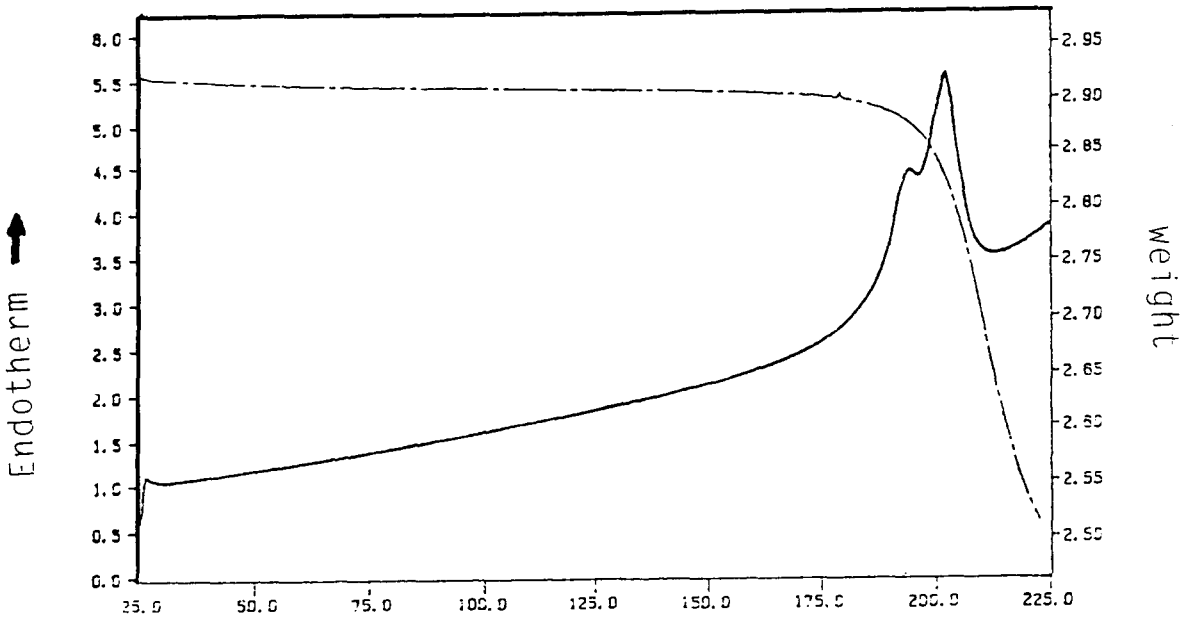

Fig. 3. DSC and TGA trace for salbutamol sulphate batch A.

was an order of magnitude difference between the value of K_s for THF and octane on batches A and B which was exhibited by all other probes. This indicates profoundly different adsorption properties for the surfaces of the two batches of salbutamol sulphate.

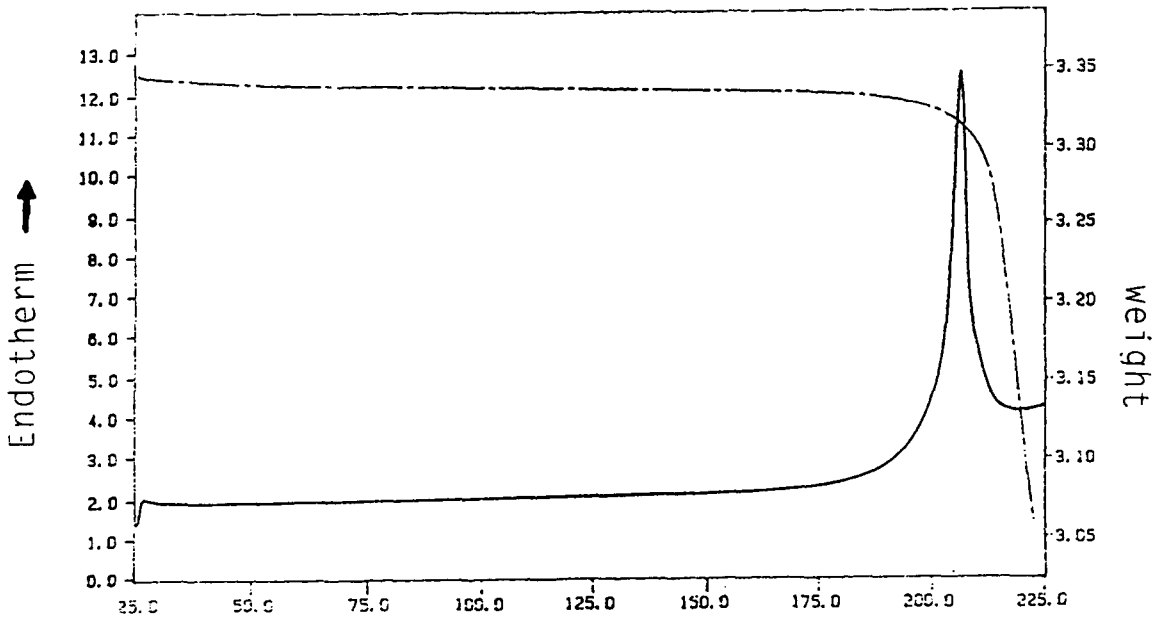

Fig. 4. DSC and TGA trace for salbutamol sulphate batch B.

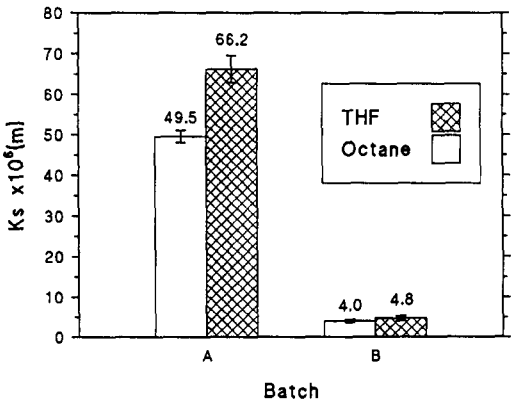

Fig. 5. Partition coefficients calculated by IGC, K_s, of octane and THF with salbutamol sulphate batches A and B.

The value of K_s calculated at infinite dilution, where the elution peak is essentially Gaussian and retention is independent of quantity of probe injected, can be used to calculate the standard free energy of adsorption, ΔG_A, of the probe. This requires the use of arbitrary standard adsorbed and vapour states. Standard states generally utilised are 101 kN m^{-2} (p_{sg}) (1 atm), the standard vapour state and 0.338 mN m^{-1} (p) for standard surface pressure (De Boer, 1953):

$$\Delta G_A = -RT \ln(K_s \cdot p_{sg}/p) \quad (3)$$

The differences obtained for K_s of the two batches were reflected in the values of the standard free energy of adsorption of the probes (ΔG_A), calculated as Eq. 3 and displayed in Table 1. The values of ΔG_A in Table 1 demonstrate the more thermodynamically favourable adsorption of probes onto salbutamol sulphate batch A. This more favourable adsorption implies a more energetic surface for batch A.

3.3. Dispersive component of surface free energy (γ_s^d)

The net retention volume of probes (V_N) can be used to calculate the dispersive component of surface free energy of the two batches. This is achieved by relating V_N to free energy of adsorption ($-\Delta G_A$) shown in Eq. 4:

$$-\Delta G_A = RT \ln V_N + C^a \quad (4)$$

where R represents the gas constant and C^a is a constant dependent on powder surface area and standard states chosen. $-\Delta G_A$ can be related as a first approximation to the work of adhesion (W_A) of the probe on the surface as in Eq. 5:

$$-\Delta G_A = NaW_A + C^b \quad (5)$$

where N denotes Avogadros number and a is the surface area of the probe molecule. Using Eq. 4 and 5 and applying the theory determined by Fowkes (1964) for non-polar probes, as shown in Eq. 6, Eq. 7 can be derived:

$$W_A = 2\left(\gamma_l^d \cdot \gamma_s^d\right)^{1/2} \quad (6)$$

$$RT \ln V_N = a \cdot \left(\gamma_l^d\right)^{1/2} \cdot 2N \cdot \left(\gamma_s^d\right)^{1/2} + C \quad (7)$$

γ_l^d and γ_s^d are the dispersive component of surface free energy of the liquid probe and solid, respectively. Plotting $RT \ln V_N$ vs $a \cdot (\gamma_l^d)^{1/2}$ for the alkanes produced a straight line for batches A and B, as shown in Fig. 6 and 7. This was expected as alkanes are non-polar and interact purely by dispersive forces, thus obeying Fowkes theory. The gradient of the alkane line is equal to $2N \cdot (\gamma_s^d)^{1/2}$ and was used to calculate the dispersive component of surface free energy of batches A and B, as shown in Table 2.

The greater than doubling of the dispersive component of surface free energy (γ_s^d) of batch A compared to batch B indicates a more energetic

Table 1
Mean ($n = 2$) and range of free energies of adsorption ($-\Delta G_A$) of probes on salbutamol sulphate batches A and B

Probe	$-\Delta G_A$ (kJ/mol)	
	Batch A	Batch B
Pentane	12.3 [a]	not measured
Hexane	16.4±0.2	12.6±0.3
Heptane	20.2±0.1	15.1±0.3
Octane	24.1±0.1	17.9±0.3
Nonane	27.8 [a]	20.5±0.2
Decane	not measured	23.3 [a]
Acetone	21.1±0.1	15.1±0.5
Ethyl acetate	25.2±0.2	16.4±0.4
THF	24.9±0.2	18.2±0.4
Ether	21.6±0.2	12.5±0.5
Dichloromethane	10.5 [a]	14.1 [a]
Chloroform	12.9 [a]	not measured

[a] Result from one column.

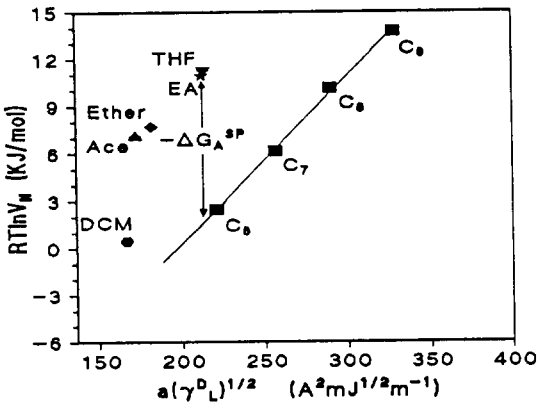

Fig. 6. Plot of RT ln V_N vs $a\cdot(\gamma_l^d)^{1/2}$ of non-polar and polar probes for salbutamol sulphate batch A.

surface. This is in agreement with the more favourable adsorption of non-polar probes onto the batch A surface.

The γ_s^d values determined by IGC could not be compared to those derived by other techniques as it relies on a different theoretical approach. Also IGC at infinite dilution is by definition only measuring a small portion of the powder surface; with a heterogeneous surface, probes would tend to interact with the more energetic surface sites.

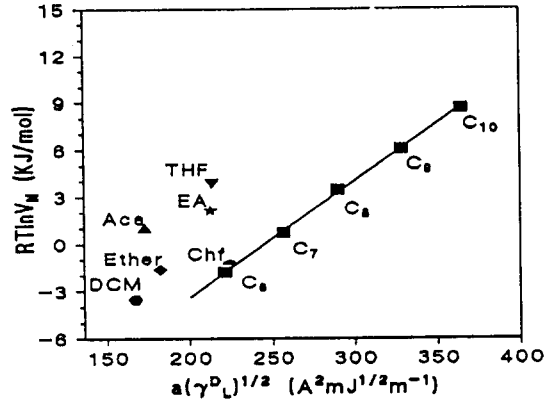

Fig. 7. Plot of RT ln V_N vs $a\cdot(\gamma_l^d)^{1/2}$ of non-polar and polar probes for salbutamol sulphate batch B.

Table 2
Mean ($n = 2$) and range of dispersive components of surface free energy (γ_s^d) for salbutamol sulphate batches A and B

Batch	γ_s^d (mN m^{-1})
A	83 ± 2
B	38 ± 1

Interestingly the c constants derived from the BET analysis (Braunauer et al., 1938) of nitrogen adsorption were calculated as 35 and 21 for batches A and B, respectively. The c constant is a measure of the difference between the heat of adsorption of the first adsorbed layer and the heat of liquification of nitrogen. The larger c for batch A indicates a more favourable adsorption and thus a more energetic surface. Nitrogen is a non-polar molecule and thus interacts purely by dispersive forces; therefore the larger c for batch A implies the stronger dispersive interaction. This implies the increased energetics are caused by the dispersive energy at the surface, which is in agreement with IGC results.

3.4. Specific or acid-base interactions

The interaction of polar probe over and above the dispersive forces is a measure of their specific interaction. An estimate of this specific interaction, $-\Delta G_A^{SP}$, can be obtained from a RT ln V_N vs $a(\gamma_l^d)^{1/2}$ plot, where $-\Delta G_A^{SP}$ is the displacement of the probe above the alkane line. Fig. 6 and 7 show plots employed to determine $-\Delta G_A^{SP}$ values for polar probes on batches A and B. The values of $-\Delta G_A^{SP}$ derived from Fig. 6 and 7 are displayed in Table 3.

According to theory developed by Gutmann (1978) and Drago et al. (1971), specific interactions can be described in terms of acid-base properties. Gutmann (1978) derived Gutmann numbers in order to describe the electron donor or base (DN) and electron acceptor or acid (AN) properties of liquids. DN or the basic property is defined by the reaction enthalpy of the liquid with a reference acceptor $SbCl_5$. AN or the acidic property is defined as the NMR chemical shift of ^{31}P contained in $(C_2H_5)_3PO$ when reacting with the liquid. Riddle and Fowkes (1990) found that

Table 3
Specific free energy of adsorption (kJ/mol) of polar probes on salbutamol sulphate batches A and B

Batch	$-\Delta G_A^{SP}$ (kJ/mol)					
	Acetone	Ether	THF	Ethyl acetate	Dichloromethane	Chloroform
A	9.9 ± 0.2	9.4 ± 0.0	9.4 ± 0.2	9.6 ± 0.2	3.8 [a]	not measured
B	6.2 ± 0.2	2.8 ± 0.2	6.2 ± 0.1	4.4 ± 0.1	2.2 [a]	0.3 [a]

[a] Result from one column.

part of the shift in NMR of the ^{31}P contained in $(C_2H_5)_3PO$ was due to dispersive forces and hence calculated a more suitable acceptor number, AN*. As an approximation, neglecting entropic effects, $-\Delta G_A^{SP}$ was used to calculate acid (K_A) and base (K_D) parameters for the salbutamol sulphate surface, according to Eq. 8:

$$-\Delta G_A^{SP} = K_A \cdot DN + K_D \cdot AN^* \quad (8)$$

Eq. 8 was rearranged to form Eq. 9 in order to determine K_A and K_D graphically:

$$-\Delta G_A^{SP}/AN^* = K_A \cdot (DN/AN^*) + K_D \quad (9)$$

The data from Table 3 were plotted according to Eq. 9 in Fig. 8. The values of K_A and K_D derived, shown in Table 4, indicate trends in acid-base behaviour.

The values for K_A and K_D for batches A and B indicate that batch A has larger acid and base parameters than batch B, implying it will interact more strongly with both acidic and basic materials. The negative value for K_D is difficult to explain on a theoretical basis, however, it may be an artifact of the poor linearity of the plot for batch B ($r = 0.977$), where the 90% confidence intervals of the intercept pass through zero.

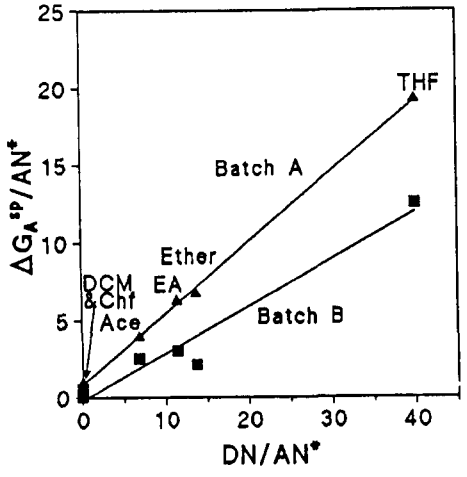

Fig. 8. Plot of $-\Delta G_A^{SP}/AN^*$ vs DN/AN* of polar probes for salbutamol sulphate batches A and B.

3.5. Concluding remarks

The results of X-ray powder diffraction and FT-Raman spectroscopy demonstrated salbutamol sulphate batches A and B were chemically and structurally equivalent with minor differences in crystallinity. DSC indicated a difference in the decomposition/melting endotherm of the two batches which could be caused by the minor differences in crystallinity together with particle size effects. In contrast, IGC measured large differences in the surface interactions of the two batches with both polar and non-polar probes. The IGC measurements were used to calculate the surface energetics of the two batches. Batch A was found to have a more energetic surface than batch B both in terms of its dispersive and specific components. The specific component was used to calculate the acid-base properties of the surface, where batch A was found to be more energetic both as an electron donor and an electron acceptor.

These results demonstrate the potential of IGC to detect and quantify differences in the surface

Table 4
Acid (K_A) and base (K_D) parameters for salbutamol sulphate batches A and B

Batch	K_A	K_D
A	0.46	0.83
B	0.30	−0.15

properties of chemically and structurally equivalent pharmaceutical powders.

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