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INVESTIGATIONS OF POWDER SURFACE PROPERTIES OF DRUG SUBSTANCES USING INVERSE GAS CHROMATOGRAPHY (IGC)

I. P. OKOYE

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ABSTRACT

In this study, Inverse Gas Chromatography (IGC) was used to characterize the surface energetics of different batches of two drug substances (Salmetrol Xinafoate, SX and Fluticasone Propionate, FP) manufactured under identical conditions. The results obtained demonstrate the potential of IGC technique to reveal batch-to-batch variability of these drugs. It is shown that the surface energy differences detected by IGC can be ascribed to secondary processing operations such as milling, micronisation and, or blending. This technique in practice therefore, provided an assurance of the same surface energy between batches of materials and eliminates the batches which may ultimately affect the quality and performance of the final products.

KEYWORDS: Gas Chromatography, Dispersive Energy, Acid/base Probe molecules.

INTRODUCTION

Multi-dose dry powder inhalers (MDPI) are now very popular and have taken on an important role in the treatment of asthma and other respiratory diseases (Buckton et al 1999). The active materials for this purpose are ultrafine micronised drugs with particle size between 0.3 and 8.0μm to achieve maximum delivery and deposition to the respiratory track using lactose monohydrate as an inert carrier (Brindley et al, 1995).

The surface properties of powders will affect the way they interact with other phases. Therefore, a change in the surface nature can influence the chemical, physical and micro biological stability of the product. Some characteristics known to be altered by the association of solids with vapour include rates of chemical degradation, crystal growths, powder flow, lubricity, powder compactability and compact hardness (Ganderton and Kassem, 1992).

Inverse gas chromatography has been used successfully in the past decade for studying the surface properties of solids by adsorption of vapour at a gas-solid interface, Lloyde et al (1989), Papirer et al (1988), Feely et al (1998). IGC is a versatile technique capable of providing surface thermodynamic information, determining phase transitions, measuring adsorption properties and calculating the dispersive and non-dispersive forces acting at surfaces and interfaces, Grimsey et al (1999). Rowe et al(1994). The word "inverse" indicates that the component of interest is the stationary powder phase , rather than the injected volatile substances Unlike the conventional adsorption techniques, IGC allows the measurement of adsorption data down to low vapour concentration where the surface coverage approaches zero, adsorbate-adsorbate interactions are negligible and thermodynamic functions depend only on adsorbate-adsorbent interaction, Ticehurst et al (1994), Williams et al (1990). IGC differs from standard gas chromatography in that the properties of the solid stationary phase, the powder, are determined by using known adsorbates as probes and usually only one probe molecule is injected at a time. 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 (n-alkanes) or polar such as acetone Owing to their structures, all n-alkanes have no dipole moment and no functional groups, which undergo specific interaction, hence they interact by induced dipole forces (Dispersive interaction).

In this study, the surface energetics of two drugs (Salmetrol Xinafoate, SX and Fluticasane Propionate, FP), blends for MDPI product have been characterized by inverse gas chromatography. IGC was employed to detect and dequantify differences in the surface thermodynamic properties of the two supposedly equivalent batches of FP and SX manufactured under identical conditions.

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 was acquired using a Dell PC loaded with an electronic Varian Star software.

Two different batches of Salmetrol Xinafoate. SX, (A and B) and two different batches of Fluticasane Propionate, FP,(C and D) unmicronised and micronised were all manufactured and supplied by GlaxoSmithKline Ware Hertfordshire, UK. 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.

Column packing About 0.5m length of ¼" OD (4mm id) silinated glass column was packed with the active drugs. 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 is plugged with silinated glass wool, and the sample dried at 40°C overnight under dry nitrogen carrier at 10ml/min

Each autoinjector vial was prepared so that the head space of the vial was filled with the vapour of each probe The objective is to inject a small volume of vapour instead of liquid In order to achieve infinite dilution conditions (low surface coverage), an equivalent of 10^{-4} to 10^{-7} μl of the liquid is injected into the column via the autosmpler

Typically, one to three drops of the probe were placed into a 2-ml vial using a Pasteur pipette and the vial was sealed with a crimp top Vapour of each probe from each vial was injected separately. The carrier gas and makeup is nitrogen set at

I. P. Okoye. Department of Pure and Industrial Chemistry, University of Port Harcourt, P. M. B 5323 Choba Port Harcourt.

30ml/min, respectively with the FID temperature set at 150°C. The GC oven temperature was set at 30°C for retention of the various probes. The vapour probe molecules at infinite dilution preferentially interact with the most energetic sites on the powder surface. The retention time of each probe was then measured and printed on the PC

RESULTS AND DISCUSSION

The calculation of the surface energy was made following the theory developed by Schultz et al (1987), using a validated Excel Spreadsheet. The net retention volume of the probe (Vn) can be calculated as follows:

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

Where 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).

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

Where Pi is the inlet column pressure and Po is the atmospheric pressure.

Dispersive Energy (γ_s):

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

Where R is the gas constant, α is the area occupied by a molecule of vapour. N is the Avogadro's number while γ_s and γ_l are the dispersive component of the solid and liquid respectively.

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.

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

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

Following Papirer's approach (Papirer et al, 1988), it was shown 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, are determined by a plot of $\Delta G_A^{sp}/AN$ versus DN/AN. The values of DN and AN are given in table 1.

Table 1 gives the physico- chemical parameters of the probes (from table published by Schultz et al (1987). The surface area (α/nm^2) of the probe molecules was determined by injecting the probe onto a neutral solid such as PTFE or polyethylene. The Dispersive component (γ_l) for these probes was measured by contact angle method. 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.

Table 1: Physico- chemical properties of the probes relevant to IGC

Probe	α (nm^2)	γ_l (mJm^{-2})	DN	AN	DN/AN	Specific character
Hexane	0.52	18.41	0	0	0	Neutral
Heptane	0.57	20.30	0	0	0	Neutral
Octane	0.63	21.30	0	0	0	Neutral
Nonane	0.69	22.70	0	0	0	Neutral
Chloroform	0.44	25.90	0	5.4	0	Acid
Acetone	0.43	16.50	17.0	2.5	6.8	Amphoteric
Ethylacetate	0.48	19.60	17.10	1.5	11.3	Amphoteric
THF	0.45	22.5	20.0	0.5	40.0	Base

The retention times and volumes for the range of polar and non-polar probes were used to calculate Dispersive Energy γ_s for non- polar and Specific Free Energy ΔG_A^{sp} for the polar probes. The various polar probe molecules have specific Interactions with the drug-solid surfaces and their energies are indicative of the nature of the functional groups present on the drugs surfaces. Following the theories developed by Drago et al (1971) and Gutmann (1978), the specific interactions are essentially Lewis acid-base interactions or electron acceptor-donor interactions. The acid-base surface properties (Ka and Kd) of the powders were determined from the plot of $\Delta G_A^{sp}/_{AN}$ versus DN/AN (see figure 1).

Table 2 and 3 show the measured Dispersive component and free energy for both Salmetrol Xinafoate. SX and Fluticasane Propionate. FP. The values appear to increase on micronisation. The results clearly demonstrate that both FP and SX are amphoteric and it also showed that the energies of interaction for FP are consistently higher than those of SX. It is an indication that FP is more amphoteric than SX in both micronised and unmicronised samples.

Table 2: The Surface Energy of two different batches of Salmeterol Xinafoate (SX)

Drug sample/ Batch	Dispersive Energy (mJm^2)	Specific Free Energy (kJ/mol				Acid/base Parameters	
		Chloroform	Acetone	THF	EA	Ka	Kd
A-unmic (mean)	41.0037	0.8901	4.7065	4.0059	4.1590	0.1917	0.4185
(Stdev)	0.1052	0.0817	0.1123	0.1333	0.0692	0.0066	0.0158
A – mic (mean)	43.9451	0.6422	4.8892	3.8262	4.2752	0.1817	0.5003
(Stdev)	0.4647	0.0272	0.0745	0.1007	0.0544	0.0051	0.0056
B – unmic (mean)	41.3074	1.2747	5.2470	4.4915	4.5841	0.2144	0.4735

(Stdev)	0.2276	0.0940	0.1303	0.1476	0.1310	0.0071	0.0122
B – mic							
(mean)	43.5244	1.0397	5.3389	4.2943	4.6013	0.2040	0.5283

Unmic = unmicronised, mic = micronised, THF = tetrahydrofuran, EA = ethyl acetate.

Table 3: The Surface Energy of two different batches of Fluticasone Propionate (FP)

Drug sample/	Dispersive Energy/	Specific Free Energy (kJ/mol				Acid/base parameters	
Batch	MJm^{-2}	Chloroform	Acetone	THF	EA	Ka	Kd
C – unmic							
(mean)	55.9625	-0.7272	8.7278	6.8520	6.9740	0.3325	0.5896
(Stdev)	1.1516	0.1092	0.2251	0.0525	0.1996	0.0020	0.0480
C – mic	59.4233	ND	ND	ND	ND	ND	ND
D-unmic							
(mean)	63.5534	-1.0614	9.5301	6.6359	8.4479	0.3156	1.0374
(Stdev)	0.7983	0.2590	0.2000	0.4054	0.5591	0.0221	0.0616
D-mic	ND	ND	ND	ND	ND	ND	ND

ND = not determined, Stdev = standard deviation.

The relative basic and acidic nature of the probes can be expressed by the ratio of their Gutman numbers (DN/AN) (Gutmann, 1978), chloroform is acidic and has a value of zero while THF is basic with a DN/AN ratio of 40. Consequently chloroform will interact more with the basic sites and THF with acid sites exposed at the crystal surfaces. The base parameter, Kd is higher than Ka for SX indicating that the surface is predominantly basic in character while the reverse is the case in FP and increases on micronisaton.

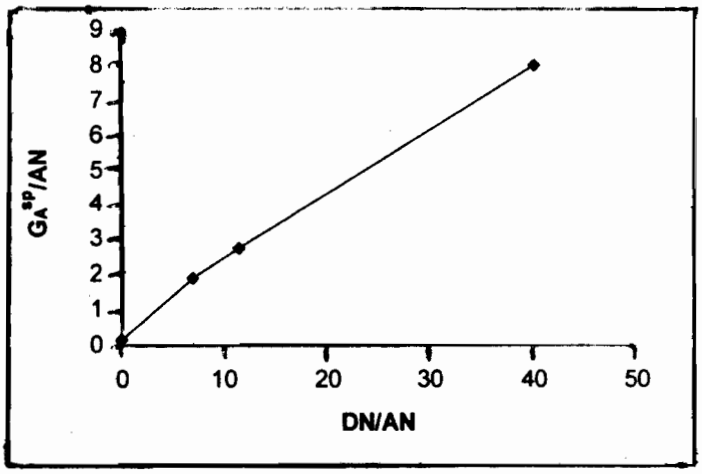

Figure 1: The plot to show how Ka and Kd are calculated

Salmeterol Xinafoate (SX) posses a nitrogenous base, which is predominantly exposed at its surface. The results in table 2 showed that SX electron donor character appear to dominate and increase on micronisation (increase in Kd), while its electron acceptor character decreases on micronisation (decreases in Ka). It is suggested that the electron donor ability of the amino group in SX may have been enhanced on micronisation, due to exposure of more of the functional groups on a molecular scale (at the particle surface), after particle breakage as a result of micronisation.

Chloroform, an acidic probe molecule, in contrast showed a very weak interaction with FP, which is clearly indicated by a negative energy (see table 3). The observed negative energy also suggest that the entire FP surface are strongly acidic. There are greater number of electrons withdrawing functional groups on FP to account for these greater acidity than SX. Generally, the micronised samples are observed to have more energetic surfaces than the unmicronised samples.

Batch to Batch Variation of Drug Substances:
The IGC results indicate that there is a profound difference in the surface energies of batch A and B of SX and also batch C and D of FP. The reason for the differences may be due to a number of factors such as temperature and pressure, agitation, time or rate of crystallization / crystallinity or impurities including amorphous phase. As shown in table 2 and 3, drugs from batches B were found to have more surface energies than those from batch A. The mean and standard deviation of these data demonstrate that the differences are statistically significant. The results demonstrate that both FP and SX from batches B and D are more amphoteric (higher Ka and Kd) than those from batches A and C, possible due to higher moisture content of batches B and C. The difference in moisture content could possibly cause a minor change at the crystalline level, explaining the observed differences.

Furthermore, minor changes in preparation can result in batch to batch variation of physical properties of pharmaceutical powders. Again changes in the surface properties of pharmaceutical powders can influence their processing and formulation characteristics, including wet granulation, film coating and suspension formation. These ultimately may mean that drugs from batches B and D would likely interact with materials much more than those from batches A and C, thereby influencing the quality and performance of the final MDPI products. The results obtained, thus far demonstrate the potential of IGC to detect and quantify differences in supposedly equivalent samples of pharmaceutical powder substances.

CONCLUSION

IGC is a surface sensitive technique and appear to be a powerful tool for studying the surface properties of drug powders. The use of alkane probes and acid/base probes allows the characterization of the surfaces in terms of their Dispersive energies and their acid and base or acceptor/donor characteristics.The concept of acid/base interactions constitutes an interesting approach to a better understanding of the surface and interfacial properties of solid - drug substances.

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