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iGC SEA Case Study 601

Identification of Batch-to-Batch variations in the dissolution rate of a pharmaceutical drug

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Nycomed Pharma (Denmark) supplied three different batches of the same active pharmaceutical material in order to have their surface properties investigated by infinite dilution Inverse Gas Chromatography (iGC SEA). The final aim was to correlate the differences in surface properties between the three batches to observe differences in dissolution rates. The data showed that clear differences were observed in the surface properties despite the chemically identical nature of the samples. Indeed, the sensitivity of the iGC SEA technique was shown to be of considerable use in the identification of batch-to-batch variations. In this particular case, a different surface chemistry was found for the different batches of the drug, which could be correlated to the different processing's and dissolution rates observed between the batches.

Introduction

Batch-to-batch variations of active materials pose a significant problem to the pharmaceutical industry and in general any batch-to-batch variation is unwelcome. The choice of techniques available for the analysis, characterisation and differentiation of chemically identical products can be limited by the nature of the materials and the sensitivity to small physicochemical differences between them. The Inverse Gas Chromatography (iGC SEA) technique very often allows differences to be seen between batches of the same product where other techniques have failed. This is because iGC SEA is a very sensitive surface tool, especially when used at infinite dilution conditions where only the interaction with the highest energy sites dominates in the determination of the dispersive surface energy or the free energies of desorption.

Nycomed Pharma provided a total of three different batches (A, B and C) of a quick release painkiller for investigation by iGC SEA. These three different batches were considered to be chemically identical. However the dissolution rates previously measured were found to be greatly different (see Table 1). While the dissolution rate of Batch A was still within the specification range, the dissolution rate of Batch B was out of the error margin whereas the dissolution rate of Batch C, which was manufactured by direct compression, without wet processing (unlike the two other batches), in order to produce a worst case sample for analysis, was well outside the specification range: A > B > C

Table 1. Dissolution characteristics of the different batches.

Batch	Dissolution rate (% sample dissolved per 20 min)	Specification range
A	95.9%	Within
B	84.9%	Just Outside
C	32.3%	Massively Outside

The aim of this study is to use iGC SEA to determine different surface properties of the three batches of the same chemical entity, to hopefully find differences in the results obtained for each batch, and to finally correlate these differences in





results with the differences in dissolution rates between the batches.

Method

Samples were studied as received. Glass columns of 2mm internal diameter, treated with dimethyldichlorosilane to passivate the surface were packed with around 350 mg of sample and tapped until the powder had settled to a stable level.

Samples were allowed to equilibrate in dry conditions (0% relative humidity) in the carrier gas flow at 303K for two hours prior to recording data.

All data was recorded using the SMS-iGC SEA2000 and analysed using the SMS Standard Analysis Suite v1.12. All experiments were carried out at 303K and under dry conditions. Eluted peaks were measured using an FID at their maximum height from injections of 3% P/P0 vapour in helium. Dead volumes were measured using methane (20% P/P0).

The dispersive component of the surface energy was determined from the net retention volumes V_N measured for a series of alkane elutants (undecane, decane, nonane, octane and heptane) and using the method of Schultz et. al. [1]. This method is based upon a plot of $RT\ln(V_N)$ versus $a(\gamma_L^D)^{1/2}$ which produces a straight line with a slope equal to $2N_A(\gamma_S^D)^{1/2}$, from which γ_S^D, the dispersive component of the solid surface energy, can be determined, a being the molecular area of the probe molecule and γ_L^D, the surface tension of the liquid elutant (see Figure 1).

The specific free energy of different polar probe molecules (including dichloromethane, 1,4-dioxane, ethyl acetate and ethanol) were determined by plotting the corresponding data in a similar manner ($RT\ln(V_N)$ versus $a(\gamma_L^D)^{1/2}$) and measuring the distance of the corresponding point to the alkane straight line (see Figure 1).

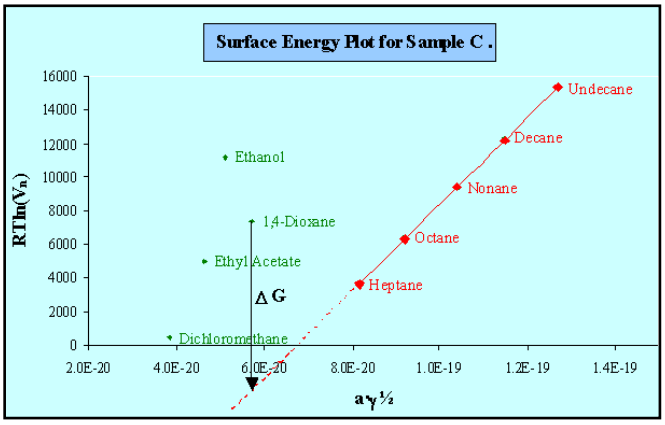

Figure 1. Dispersive surface energy plot (in red) and specific free energy of desorption for several polar probe molecules (in green) eluted through a column of batch C. 0% RH, 30 °C, 0.03P/P_0.

Samples A & C have been analysed twice in a row on the same column (with a second conditioning of two hours between the two runs) to check for equilibrium and irreversible sorption effects.

Sample B has been analysed once on two different columns to investigate the heterogeneity within the sample.

Results

All results are summarised in Table 2. All values given are average values over the runs measured for each sample.

The values of the standard deviations calculated for the results obtained for two runs carried out successively on the same column (batch A & C) are all within the typical error margin of < 3% [2,3]. We therefore deduce that the sorption exclusively involves a reversible physisorption mechanism and that the two hour pre-treatment was sufficient to dry the samples.

The values of the standard deviations calculated for the results obtained for two runs carried out on the same sample but on two different columns (batch B) are also within the typical error margin of < 4% [2]. We therefore deduce that batch B is homogenous in terms of surface characteristics (and so are probably batches A & C).

Table 2. Dispersive component of the surface energy and specific free energy of desorption of different polar probe molecules for the three batches of painkiller investigated. 0% RH, 30°C, 0.03P/P⁰

Sample			A	B	C
Dispersive component of the surface energy (mJ.m^{-2})		Average value	43.17	41.39	46.76
		Std Deviation (%)	1.60	0.64	1.64
Specific Free Energy of Desorption (kJ.mol-1)	Dichloromethane	Average value	9.62	9.75	8.02
		Std Deviation (%)	0.34	1.06	0.63
	1,4-Dioxane	Average value	14.96	11.38	9.92
		Std Deviation (%)	0.76	0.20	1.00
	Ethyl Acetate	Average value	15.18	11.46	10.50
		Std Deviation (%)	1.19	0.95	0.37
	Ethanol	Average value	-	15.88	15.26
		Std Deviation (%)	-	0.15	0.73

The three batches do not show any significant difference in the dispersive surface energy (see Figure 2). All three samples show a dispersive surface energy value around 45-50 mJ.m^{-2}, which is typical for pharmaceutical ingredients.

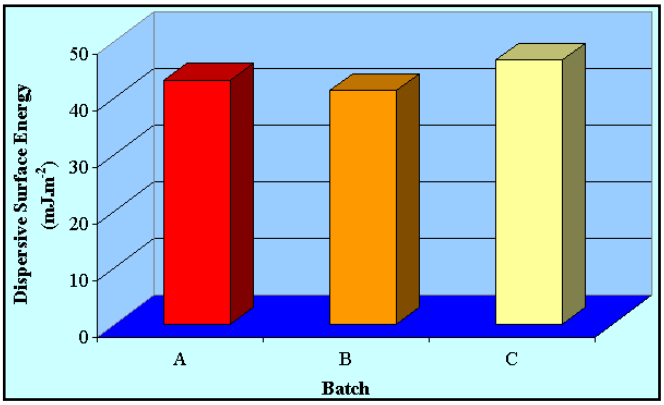

Figure 2. Dispersive surface energy plot for the three different batches of painkiller.

No value is given for the specific free energy of desorption of ethanol for sample A because the peak was so broad that no maximum could be identified. This is most probably due to a very strong interaction of ethanol with batch A. Therefore, we believe that the specific free energy of desorption of ethanol is higher for sample A (> 16kJ.mol^{-1}) than for the others two batches.

The overall trends of the specific free energies of desorption are similar for all three samples (highest for ethanol, intermediate for ethyl acetate and 1,4-dioxane, and lowest for dichloromethane) indicating that the surface chemistry of the three batches is analogous (see Figure 3).

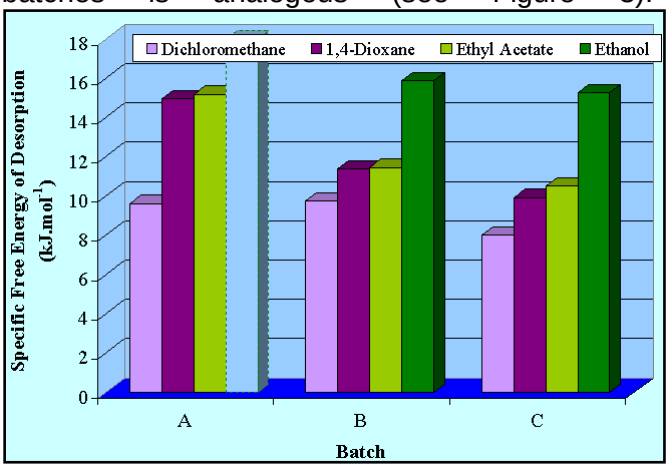

Figure 3. Specific free energy of desorption for the three batches (per batch).

The interaction being strongest with ethanol, which is a rather hydrophilic acid, it seems that the surface of all three samples is dominated by hydrophilic basic sites. The interaction with ethyl acetate (which is considered hydrophilic and weakly basic) and 1,4-dioxane (which is considered hydrophobic and basic) is relatively strong, implying that acidic sites, both hydrophilic and basic, are well represented at the surface of the sample. The interaction of the dichloromethane (which is acidic and hydrophobic) being lowest, basic hydrophobic sites seem to be least well represented at the surface of the different batches.

When comparing the values of specific free energies obtained for the different batches (see Figure 4), it appears that there are some significant differences between the three batches, especially when the specific free energy of desorption of 1,4-dioxane, ethyl acetate and

ethanol are considered.

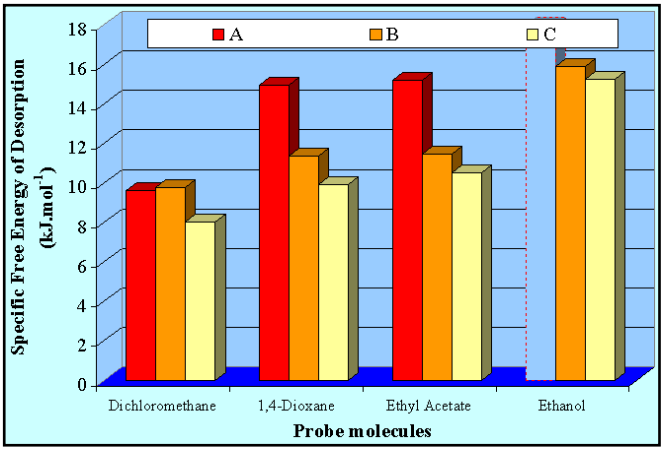

Figure 4. Specific free energy of desorption for the three batches (per probe).

Indeed, batch A shows significantly higher values than sample B which itself shows higher values than sample C. The trend is therefore the following as far as the specific free energies of desorption are concerned: A > B > C.

This is the same trend as the one observed for the dissolution rate. Consequently the difference in specific free energy of desorption can be correlated with the dissolution rate. The higher the specific free energy of ethanol, ethyl acetate or 1,4-dioxane, the faster the dissolution rate. Therefore, the specific free energy of ethanol, ethyl acetate or 1,4-dioxane can be chosen and used separately to predict the dissolution rate of the sample.

For instance, if the specific free energy of desorption of ethyl acetate was superior to 11.5 $kJ.mol^{-1}$ (value obtained for batch B), than the dissolution rate of the corresponding sample would be within the specification range. If it were inferior to this value, the dissolution rate would be out of the specification range.

Conclusion

IGC SEA has been shown to be a sensitive tool for the study of batch-to-batch variations. The three batches of painkiller supplied by Nycomed Pharma showed significant differences in their surface properties. The surface chemistry varies from one sample to the other, and significant differences in the values of the specific free energies of desorption of the polar probes have been shown between the batches. Batch A, which has the fastest and sole acceptable dissolution rate, shows the highest values of specific free energies for most polar probes tested whereas Batch C, which has the worst and slowest dissolution rate, shows the lowest values of specific free energies. Batch B, which has an intermediate dissolution rate shows intermediate values.

Consequently, the difference in surface chemistry can be correlated to the difference in dissolution performance. Furthermore, this study shows that the "wet processing" pre-treatment, which is known to be required to get fast dissolution rates, has a significant effect on the surface properties of the particles. In particular, it increases the number or the strength of available acidic and basic sites at the surface of the particles by removing a surface contaminant or by re-orienting surface groups. The interaction of the particles with the highly polar aqueous media it is dissolved in is therefore stronger and the dissolution rate is increased.

In conclusion, the prediction of the dissolution rate of a batch of painkiller has been shown possible by the measurement of the specific free energy of the sample by iGC SEA. This study also gave some elements of response on how different processing methods can influence the final dissolution properties of drugs.

Note:

The selected vapours used in this study only represent a small selection. IGC SEA allows the use of solvent wide range of solvents, which has a reasonable vapour pressure at the measurement temperature. Other probe molecules would provide complementary information on the acid-base properties of the different batches.

Measurements at different relative humidities or at different probe molecules concentrations could complete the picture by characterising the heterogeneity of the sample.

Acknowledgement:

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References

[1]Schultz, J., Lavielle, L. and Martin, C., J. Adhesion 23 (1987) 45
[2]Reutenauer, S., SMS Technical Note 801 (2002)
[3]Reutenauer, S., SMS Technical Note 802 (2002)

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