



## Characterisation of drug polymorphs by Inverse Gas Chromatography

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***Two polymorphs of the same active pharmaceutical material were characterised by infinite dilution inverse gas chromatography. Clear differences were observed in the surface properties despite the chemically identical nature of the samples. The sensitivity of the technique may be of considerable use in the identification of batch-to-batch variations, polymorphic forms being one cause of this problem.***

### Introduction

The batch-to-batch variation of active materials poses a significant problem to the pharmaceutical industry. One common origin of such variation is in the presence of two or more polymorphs, often chemically identical, but with different physical material properties. The choice of techniques available for the analysis and characterisation of such polymorphs can be limited by the nature of the materials and the sensitivity to small physicochemical differences between them. One applicable technique is Inverse Gas Chromatography (iGC SEA). Different polymorphs will expose different crystal surfaces and different functional groups at the surface. iGC SEA measures these differences in the surface properties to provide a sensitive tool to compare and identify polymorphs.

In this paper two polymorphs of Xemilofiban (Pharmacia), were studied by iGC SEA to measure their dispersive surface energies and specific polar interactions with a number of solvents. Clear differences were observed between the two polymorphs. Furthermore it was possible to demonstrate that a sample of

polymorph A remained in that polymorphic form after milling and exposure to high humidities.

### Method

Samples were supplied as fine powders by Pharmacia-Pfizer and were studied without further treatment. Glass columns of 2mm internal diameter and 30 cm length, treated with dimethyldichlorosilane to passivate the surface were packed with 150-200mg of sample (see Table 1) and tapped until the powder had settled to a stable level (the 'tapped density').

All data was recorded using the SMS-iGC 2000 and analysed using the SMS Analysis Suite. Eluted peaks were measured using an FID detector at their maximum height from injections of 3% p/p0 vapour in helium. Dead volumes were measured using methane (10% p/p0).

Samples were allowed to equilibrate at the set humidity in the carrier gas flow for a number of hours prior to recording data.



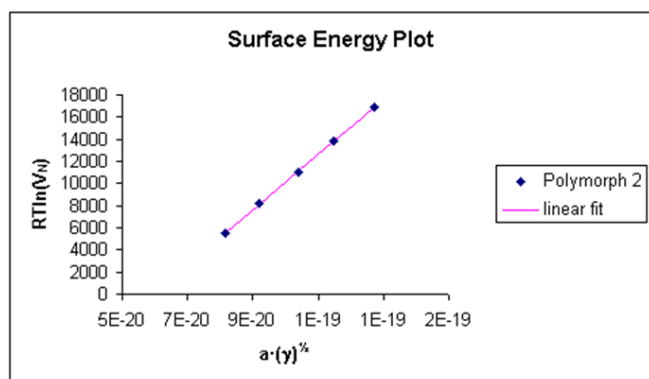


Figure 1. Surface energy plot for heptane, octane, nonane, decane and undecane eluted through a column of Xemilofiban, Polymorph B. 0% RH, 30°C.

## Results

The dispersive component of the surface energy was measured at 0% RH for all samples using the method of Schultz et al. [1] and previously described by our group [2]. An example plot of the data for Polymorph B is shown in Figure 1. Second columns of Polymorph A and a batch of Polymorph A that had been milled and treated at high humidity (75% RH) for a number of hours were packed and measured to estimate the reproducibility of the data. The results of these measurements are summarised in Table 1.

Table 1. Summary of dispersive surface energies at 0% RH, 30°C.

Sample	Mass (g)	Dispersive surface energy at 0% RH (mJ/m <sup>2</sup> )
Polymorph A	0.178 / 0.143	48.3 / 51.4
Polymorph A (milled)	0.178	50.4
Polymorph A (milled and humidified)	0.169 / 0.172	50.5 / 50.6
Polymorph B	0.200	42.9

All the data for polymorph A, including the milled and milled/treated samples lie within  $49.9 \pm 1.6$  mJ/m<sup>2</sup>. In contrast Polymorph B has a distinctly lower dispersive surface energy of 42.5mJ/m<sup>2</sup>.

Polymorph B is known to be the thermodynamically more stable form at ambient conditions, and although other factors are also involved in the overall stability, this is in agreement with the surface energy. However, neither milling nor humidity treatment apparently cause any significant change to the surface energy of Polymorph A.

Milling Polymorph A is believed to introduce a small amorphous content to the material, probably at the surface, observed in moisture sorption studies. The collapse of the amorphous material, together with the expulsion of the absorbed water as the material recrystallised, was found to occur between 50 and 60% RH. In order to investigate this further, the milled material was studied as a function of the relative humidity of the carrier gas. Starting at 0% RH, and increasing in steps, the sample was allowed to equilibrate at each humidity for approximately 6 hours before measuring the retention times.

The results of this study are plotted in Figures 2 and 3. Figure 2 shows the dispersive component of the surface energy of the milled sample as a function of the relative humidity at 30°C. It is clear that the non-polar surface energy decreases continuously between 0 and 70% RH as the amount of water adsorbed on the surface increases. However, no discontinuity can be observed between 50 and 60% RH that could be connected to the collapse of the amorphous content. Furthermore, after exposing the sample to 70% RH the sample was re-tested at 0% RH. Both points at 0% RH are plotted in Figure 2 and are clearly very similar. No irreversible change can be observed, in agreement with the surface energy of the milled sample pre-treated at 75% RH.

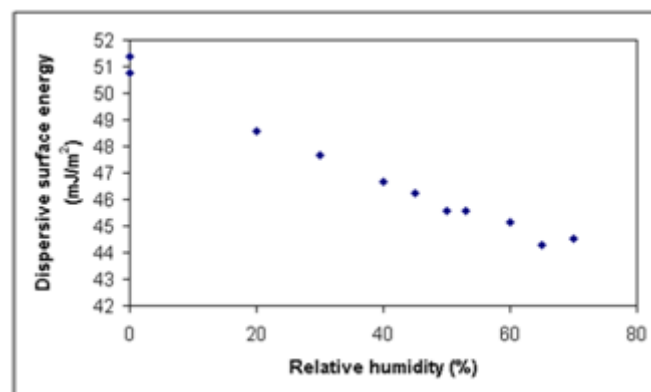


Figure 2. Surface energy of milled Xemilofiban, Polymorph A, plotted against the relative humidity. 30°C.

In contrast to the dispersive component of the surface energy, the interaction of the milled sample with polar molecules shows a clear change when exposed to high humidities. Figure 3 shows the retention time of ethanol and nonane (a non-polar molecule with a comparable elution time) plotted against the relative humidity of the sample. As with the non-polar surface energy, nonane exhibits a continuously decreasing retention time, consistent with a decreasing interaction at higher humidities. The retention time of ethanol also decreases up to 50% RH, but then shows a sudden and significant increase. This effect has been observed in other systems such as maltose [1] where the presence of a small amount of amorphous material causes an increase in the retention time due to bulk diffusion around the glass transition temperature ( $T_g$ ). In this case the experiment was performed under a constant temperature, but absorbed moisture provided by the increasing humidity acts as a plasticiser and causes  $T_g$  to decrease. The humidity at which the change occurs is exactly the same point seen in the DVS water sorption data at which the amorphous material collapses in the vapour sorption studies. The reason why the effect is observed with ethanol but not nonane is because the polar solvent interacts much stronger with the sample than the non-polar solvent. On the timescale of the iGC SEA experiment no crystallisation of the amorphous material is observed. This would be seen as a decrease in the retention time.

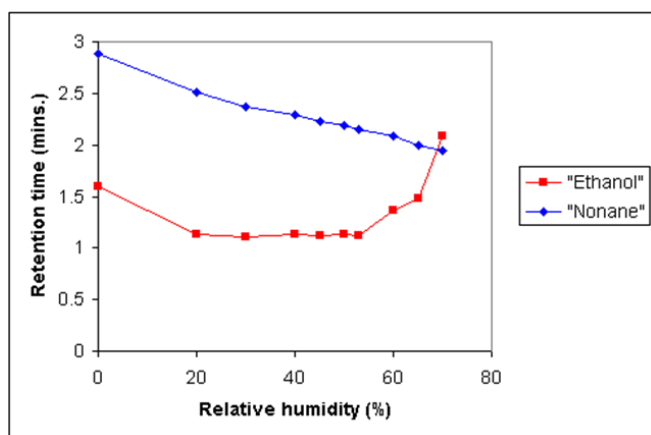


Figure 3. Retention times of ethanol and nonane from milled Xemilofiban, Polymorph A, plotted against the relative humidity. 30oC.

This shows that milling Polymorph A has indeed introduced an amorphous component into the material, but no irreversible change was seen suggestive of a morphology change in the analysis of the Polymorph A sample that had been milled and recrystallised at 75% RH. Within the sensitivity of the technique, no evidence that such treatment causes recrystallisation into Polymorph B can be observed, despite the higher thermodynamic stability of Polymorph B.

Apparently the underlying Polymorph A directs any recrystallisation.



## Conclusion

iGC SEA has been shown to be a sensitive tool for the study of pharmaceutical polymorphs. The surface energy has been used to distinguish and identify two polymorphs of the same drug and this was found to be consistent in line with the known thermodynamic stabilities.

Milled samples of Polymorph A were shown to contain a proportion of amorphous material, also seen in sorption studies, with a glass transition at approx. 55% RH at 30oC. Humidity treatment to recrystallise this material resulted in a sample identical to the original Polymorph A, suggesting that the underlying sample morphology rather than thermodynamic stability drives the recrystallisation.

### Acknowledgement:

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## References

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  - [ 2 ] Thielmann, F. and Butler, D.A., SMS Application Note 202 (2000)
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