

Is It Possible To Predict The Milling Behaviour of Indomethacin Polymorphs Using Standard Computational Techniques?

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Summary

Milling induced disorder can be a problem when formulating drugs for inhalation as polymorph conversions and the generation of amorphous regions can occur. This study aimed to predict which cleavage planes would be exposed during milling of γ and α indomethacin using attachment energy calculations and comparing these with experimental results obtained from Inverse Gas Chromatography (IGC). It was found that the software was able to predict the exposed cleavage planes for the stable γ polymorph but not the metastable α polymorph. Analysis of milled samples suggested that the α form underwent a transition to a slightly amorphous state on milling (the γ form remained unchanged) which may explain the poor predictions.

Introduction

Milling is a commonly used technique when processing powders for inhalation. The process however can lead to problems as surfaces with increased energy levels and areas of amorphicity are produced. This increase in the surface energetics can lead to the powder having poor flow properties due to the increased cohesive forces of the particles. Amorphous materials can take on more moisture than their crystalline counterparts which can be a problem on storage.

The aim of this project was to determine whether or not it is possible to predict, using standard computational chemistry techniques, the milling behaviour of polymorphs.

Indomethacin was chosen as a suitable polymorphic system for the study. Crystal structures (for the γ and α polymorphs) were obtained from the Cambridge Crystallographic Data Centre (CCDC). Both polymorphs were ball milled for up to 4 hours and were characterised before and after milling using TGA, DSC, DMA, XRPD and IGC.

Results - Experimental

The study showed that the γ form was stable under all of the milling conditions employed. The DSC plots only showed one peak corresponding to the melting point of the γ form (figure 1). The XRPD patterns showed no changes in peak positions after milling (figure 2) and the DMA plots did not contain a peak at approximately 45°C corresponding to the glass transition temperature (T_g) of indomethacin (figure 5). DMA was found to be sensitive to 2% amorphous indomethacin content.

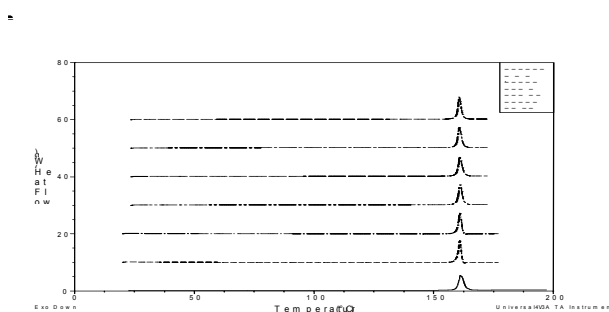


Figure 1. DSC plots for γ IMC samples milled using the porcelain ball mill: a) before milling, b)2 min, c)5 min, d)30 min, e)1 hour, f)2 hours, g)4 hours

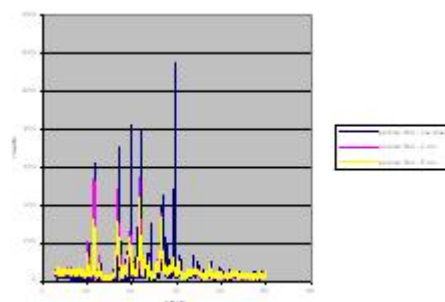


Figure 2. XRPD patterns produced by γ IMC before and after milling using the stainless steel ball mill.

The α form however underwent an apparent conversion to the γ form under the milling conditions (this conversion has been reported to occur via the amorphous phase but this was not observed in the time scale between milling and data collection. This behaviour was determined using DSC, DMA and XRPD. The DSC profile of the α form before milling showed only one peak corresponding to the melting point of the α form. After milling two peaks were observed corresponding to the melting points of the α and the γ forms respectively (figure 3). The XRPD

did not indicate any polymorphic changes although less intense and slightly broader peaks indicate the possible presence of some amorphous form (figure 4).

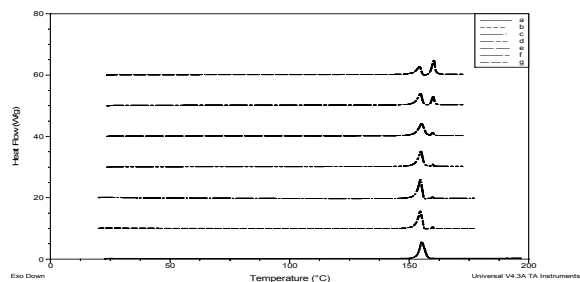


Figure 3. DSC plots of α IMC samples milled using the porcelain ball mill: a) before milling, b) 2 min, c) 5 min, d) 30 min, e) 1 hr, f) 2 hr, g) 4 hr

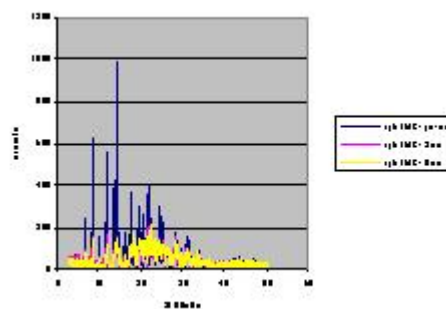


Figure 4. XRPD patterns produced by α IMC before and after milling using the stainless steel ball mill.

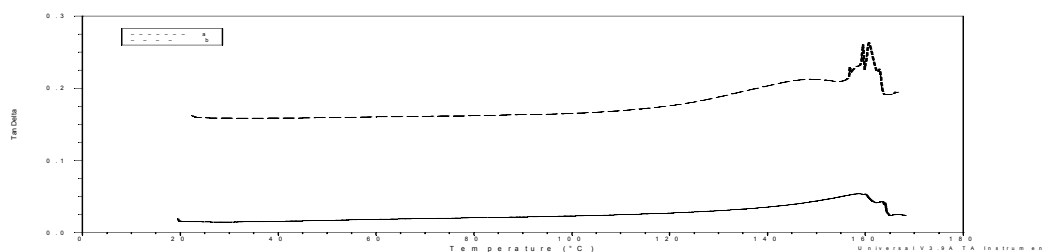


Figure 5. DMA plots ($\tan \delta$) for both polymorphs milled in the porcelain mill for 4 hours: a) γ -IMC, b) α -IMC

Results – Computational

Materials Studio 4.0 was used to predict morphologies of the two polymorphs based on data obtained from the CCDC. Force fields were applied to the structures to optimise the geometry of the structure taking into account charges and bond length. Attachment energies for each face were calculated and the faces with the lowest attachment energies were studied in terms of atoms/functional groups present to interpret the results from Inverse Gas Chromatography (IGC).

Investigation of the faces with the lowest attachment revealed that for both polymorphs it was predicted that an increase in the acidic nature of the surface would occur. This is due to the exposure of both the chlorine atom and some free carboxylic acid groups. Examples of these faces are given in figures 6-8. Figure 6 shows a representation of the (0 1 1) face of the γ form showing that all atoms are below the surface level and that hydrogen bonding is contained within the slice. Figure 7 gives a representation of the (0 0 1) face of the γ form showing that there are hydrogen atoms above the surface level and that hydrogen bonding may occur through the surface (free COOH group). Figure 8 gives a representation of the (0 0 1) face of the α form showing a chlorine and a hydrogen atom above the surface and that hydrogen bonding is contained within the slice.

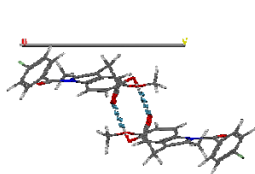


Figure 6.

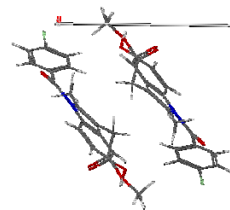


Figure 7.

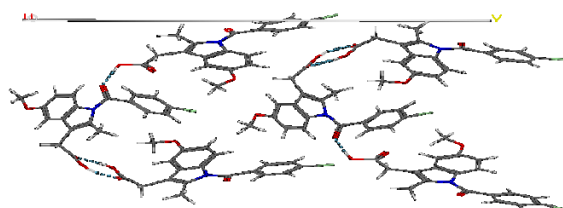


Figure 8.

Inverse Gas Chromatography was used to study the surface of the samples before and after milling to determine whether or not the chemistry of the surfaces produced experimentally on milling correlates with the cleavage planes calculated from the crystallographic modelling software. A series of alkanes and polar probes were used to study the surface with increases in the retention time, and hence specific energy, of the basic probes (and a decrease seen with the acidic probe) expected if the predictions were correct.

Evaluation of the IGC results shows that the predicted cleavage planes are in good agreement with the experimentally produced surfaces for the stable γ polymorph but the metastable polymorph could not be modelled successfully. The specific energies for both polymorphs before and after milling are given in tables 1 and 2 respectively. The energy values in the table are in mJ/m^2 .

	Pre-milled	Milled
THF	1689.8	2920.7
Chloroform	115.7	-832.6
Ethyl Acetate	1479.9	3632.3
Acetone	4183.9	3792.6

Table 1. Specific energies obtained for the pre-milled and milled γ -IMC samples.

	Pre-milled	Milled
THF	2854.2	2623.5
Chloroform	97.1	124.2
Ethyl Acetate	3756.3	3333.2
Acetone	4210.3	3696.1

Table 2. Specific energies obtained for the pre-milled and milled α -IMC samples.

Discussion

The results obtained using DSC and DMA (and also XRPD) show that the γ form of indomethacin is stable as no conversion to either the α form nor the amorphous form took place under any of the milling conditions. The DSC and DMA results obtained for the α form suggest the conversion of this form to the γ form on milling due to the presence of two peaks corresponding to melting points and the absence of peaks corresponding to the T_g or crystallisation of amorphous indomethacin. This is an unlikely situation since the two polymorphs are monotropically related and therefore no transition temperature exists between the two below the melting point of the α form.

A more likely explanation for the findings is the conversion of the α form to the amorphous phase as reported by Otsuka, 1986 and Crowley and Zografis, 2001. If this did happen then the conversion of the amorphous form to the stable γ happened very quickly as the time period between milling and analysis was less than one hour.

Another explanation for the findings may be the formation of amorphous regions on the surface of the particles which may encourage recrystallisation to the more stable polymorph when the sample is heated slowly. Surface amorphicity may not be picked up by the DMA as it is not a bulk property.

The probe interactions observed by the IGC indicate the exposure of acidic groups on the surface of the γ molecules due to the increased affinity of the basic probes (THF and ethyl acetate) for the milled sample. This supports the predictions made during the modelling work as the software predicted the exposure of chlorine atoms and some free carboxylic acid groups on the surface. These changes were not observed for the metastable α polymorph. This may be due to attachment energies for the cleavage planes being too high.

The IGC results suggest that the computational chemistry approaches are able to make predictions on the cleavage planes exposed on milling with a stable polymorph. The ability of the software to predict cleavage planes for metastable polymorphs however has not been established. This is most likely due to the fact that the software does not predict polymorphic changes or the production of amorphous regions within the powder or on the surface of the molecules.

Conclusions

This study has looked at the use of molecular modelling techniques to predict the cleavage planes exposed during the milling process. We have shown that for a stable polymorph the computational approach was able to predict the cleavage planes based on attachment energy calculations. This was shown using IGC. For a metastable polymorph it was not possible to predict the cleavage planes based on attachment energies. Further investigation is needed to establish why this is so.

Acknowledgements

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