# Interactions of model drugs in HFAs and crystals dissolution: an AFM *in situ* investigation using functionalised probes

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## Introduction

To investigate interactions of model drugs in HFAs (Hydrofluoroalkane), relevant to pressurised metered dose inhalers (pMDI), using a custom built pressurised AFM cell for the atomic force microscope. It is not unreasonable to suggest that a fundamental knowledge of the interactions between probe-drug-propellant will expedite the rational formulation of suspension type pMDIs (Fig. 1). While the development of a pressurised AFM cell is still in the conceptual/development stage and giving the early stages of the project, preliminary studies have been initiated using two model drugs and a model propellant (2H, 3H-decafluoropentane).

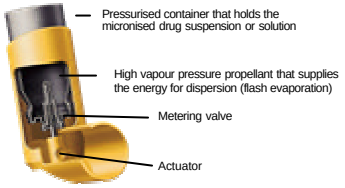


*Figure 1. Schematic diagram of the AFM optical head*

## AFM Measurements

The atomic force microscope (1) (AFM) (Fig.2) has recently been applied to a number of pharmaceutical related problems. This is mainly due to its ability in characterizing the surface morphology of materials at very high resolution, and its capability in measuring fundamental interactive forces between contiguous surfaces. Furthermore, with the use of functionalised AFM probes, the *in situ* AFM technique can provide an invaluable tool into the behaviour of individual particulate interactions.

The aim of this work was to apply an *in-situ* AFM technique to investigate interactions between two different drug crystals in a model propellant system (2H, 3H-decafluoropentane (mHFA), Apollo Scientific, Derbyshire, UK) using two functionalised AFM probes.

All AFM experiments were conducted using a commercially available AFM (Multimode AFM with Nanoscope IIIa controller, DI, Cambridge, UK) equipped with an *in situ* Multimode AFM liquid cell (Fig. 3, Fig. 4). A model hydrofluoroalkane propellant (2), which has similar properties to propellants used in a pMDI, was used for the study.

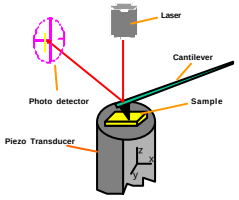


*Figure 2. Schematic diagram of the AFM optical head*

*Figure 3. Multimode AFM in situ cell*

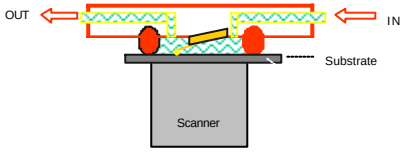


*Figure 4. Schematic diagram of the Multimode AFM in situ cell*

Multiple force measurements were conducted on 4 well-defined crystalline faces of single crystals of two model drugs (Model drug **A**, monoclinic crystal and model drug **B**, orthorhombic crystal) using polar (COOH) a-polar ($CH_3$) (BioForce Nanoscience, USA) and $SiN_4$ (Digital Instruments, UK) functionalised AFM probes. Force measurements were conducted in a saturated solution of a model hydrofluoroalkane solution to eliminate potential crystal etching. In addition, AFM Imaging of the previously investigated crystals was performed *in situ* using saturated and un-saturated - hydrofluoroalkane solutions. This allowed observation of real-time changes in the surface topography individual crystal faces at the mesoscopic scale.

## Results and Discussion

Significant differences in the adhesion profile between functionalised probes were observed. In addition, analysis of the adhesion values with respect to crystal face indicated the dominance of specific polar groups. Variation in such polarity could clearly influence particulate interactions in a pMDI and may also dominate specific face etching prior to saturation. Representative AFM force plots of the two model drug substrates are shown in Figures 5a, b, c, d and Figure 6a, b, c and d respectively. Summary of force of adhesion results is presented in Table I.

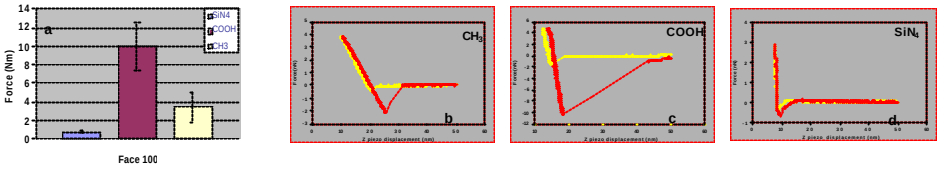


*Fig. 5 a, b, c and d: Force Plots for model drug A*

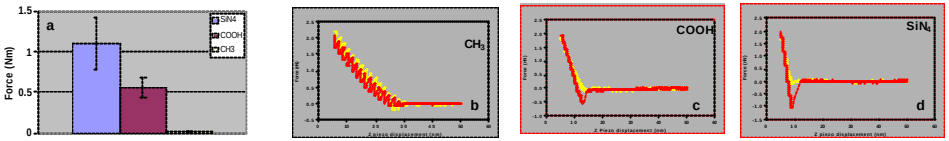


*Fig. 6 a, b, c and d: Force Plots for model drug B Note: Experiment performed also on other 3 well defined faces of model drug B (Face {101}, {011} and {10(-1)}) and results presented similar trend*

| | Drug B | | | | Drug A |
|---|---|---|---|---|---|
| | Force of Adhesion (nN) | | | | |
| | {002} | {011} | {101} | {10(-1)} | {100} |
| $SiN_4$ | 1.1±0.3 | 0.9 ±0.4 | 1.4 ±0.3 | 1.1 ±0.6 | 0.7 ±1.3 |
| COOH | 0.6 ±0.1 | 0.7 ±0.4 | 0.1 ±0.0 | 0.7 ±0.1 | 3.4 ±1.5 |
| $CH_3$ | Non measurable force detected | | | | 1.0 ±2.6 |

Analysis of the adhesion force values (n = 100) indicates a rank adhesion of $SiN_4$ > COOH > $CH_3$ for drug B and COOH>>$CH_3$>>$SiN_4$ for drug A

*Table I. Force of Adhesion summary*

Visualisation of the un-saturated and saturated model drug-hydrofluoroalkane solutions suggested progressive crystal dissolution in the unsaturated system. Within minutes the previously atomically flat surface of drug B (exposed to unsaturated solution) indicated crystal dissolution (etching) to occur via a layer-by-layer process (Fig. 8). As expected, no etchings of the model drug A crystals were observed when exposed to both saturated and unsaturated hydrofluoroalkane solutions (Fig. 7)

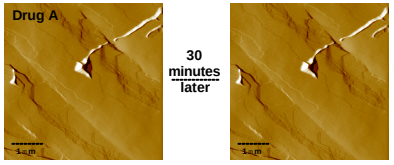


*Figure 7. Visualization of drug S in saturated solution of hydrofluoroalkane*

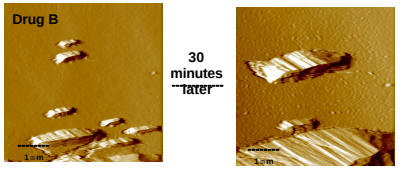


*Figure 8. Visualization of drug B in saturated solution of hydrofluoroalkane*

## Conclusions

The use of the AFM to determine variations in particle substrate interactions, under model propellant, clearly opens up the possibility for rapid material screening. Such techniques could prove invaluable during the early phases of formulation product development. Future innovations, including the development of a pressurised AFM cell, may allow a better insight into the interactions of such a complex system.

### References

1. Binnig, G., Quate, C. F., and Gerber, C., *Phys. Rev. Lett.* 56, 930 (1986)
2. Rogueda, P.G.A, *Drug Development in Industrial Pharmacy,* Issue Volume 29, Issue 1,pages 29-39 (2003)

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