Pharmaceutical Special Interest Group Autumn Meeting

5th November 2008, AstraZeneca, Charnwood.

Programme and Abstracts:

Morning Session, Chair: Matthew Johnson (GlaxoSmithKline)

9.45: Talbir Austin (AstraZeneca), Opening Remarks and Safety

10.00: Robert Docherty, Pfizer:
The Future Application of Computational Methods in Solid Form Selection.

The selection of the solid form for development is a milestone in the conversion of a new chemical entity into a drug product. An understanding of the materials science and crystallisation of a new active pharmaceutical is crucial at the interface of drug substance manufacturing and drug product processing. In this presentation the broad challenges facing pharmaceutical scientists, as a consequence of polymorphism, hydrate and solvate formation during product design will be highlighted. The opportunities presented by structure based computational tools to help address these challenges will be presented in terms of a framework that addresses both the business need and the new emerging regulatory environment.

10.45: Graeme Day, University of Cambridge:
Discovering and Understanding New Crystal Forms: Guiding Experiments by Crystal Structure Prediction and Modelling

The goal of *ab initio* crystal structure prediction has served as a driving force for improvements in methods for modelling the crystal structures of organic molecules. Such methods are now becoming reliable for certain types of molecules, so that computational results can be confidently applied to understanding the crystallisation behaviour of organic molecules. In a practical sense, computational methods are now in a position to guide our experimental studies in discovering and characterising new polymorphs and solvates.

To illustrate this, the results of several computational studies on small organic molecules will be presented, with emphasis on how they have both guided and helped interpret experimental work that has led to the discovery and characterisation of new crystal forms and improved our understanding of solvent incorporation in crystal structures.

11.15: Refreshments

11.45: Frank Leusen, University of Bradford:
A Major Advance in Crystal Structure Prediction

The goal of predicting the crystal structure of an organic molecule from its molecular structure alone has attracted considerable industrial interest. The difficulty of the task is demonstrated by the regular 'Crystal Structure Prediction Blind Test' which is hosted by the Cambridge Crystallographic Data Centre [1]. Participants are provided with three or four molecular structures and invited to predict, within six months, up to three crystal structures which they think each compound will adopt. The experimental crystal structures have been determined but are not available until after the participants have supplied their predictions. The limited number of successful predictions reported in the previous Blind Tests reveals just how difficult crystal structure prediction (CSP) can be [1]. 'Success' in this context means that the observed, experimental crystal structure is found among the three submitted predictions of a participant. All of the previous successful predictions were based on force field methods, where the intermolecular and intramolecular forces are represented by analytical functions. In this contribution, the previous Blind Tests are briefly reviewed and the successful application of a new CSP approach to all four compounds of the 2007 Blind Test is presented [2]. The central part of the new approach used in this study is a hybrid method for the calculation of lattice energies that combines density functional theory simulations with an empirical van der Waals correction.

[1] G.M. Day, W.D.S. Motherwell, H.L. Ammon, S.X.M. Boerrigter, R.G. Della Valle, E. Venuti, A. Dzyabchenko, J.D. Dunitz, B. Schweizer, B.P. van Eijck, P. Erk, J.C. Facelli, V.E. Bazterra, M.B. Ferraro, D.W.M. Hofmann, F.J.J. Leusen, C. Liang, C.C. Pantelides, P.G. Karamertzanis, S.L. Price, T.C. Lewis, H. Nowell, A. Torrisi, H.A. Scheraga, Y.A. Arnautova, M.U. Schmidt and P. Verwer, *Acta Cryst. B*, **61**: 511 – 527 (2005).

[2] M.A. Neumann, F.J.J. Leusen and J. Kendrick, *Angew. Chemie Internat. Ed.*, **47**: 2427 – 2430 (2008).

12.15: Xue Wang, University of Leeds:
Crystal Morphology: Measurement, Modelling and Closed-loop Control

Research on particle shape is extremely important to many industrial applications such as pharmaceuticals, biopharmaceuticals, human health products and speciality chemicals. For example, for pharmaceuticals, the morphology can affect important properties such as dry powder density, cohesion, and flowability, that can have major impact on a company's ability to formulate drug particles into finished products. Moreover, crystal morphology can affect drug dissolution, potentially affecting formulated product bioavailability and, in extreme, resulting in a company's loss of the license to making the drug product.

Despite the importance, direct characterisation of particle shape has been quite limited largely relying on off-line instruments and methods. In addition, prediction of crystal morphology was often restricted to single crystals, while population balance process modelling uses a definition for crystal size that is based on the volume equivalent diameters of spheres. There was lack of knowledge on how to incorporate the information about crystal morphology for single crystals into population balance process modelling which handles tens of thousands of particles in a crystalliser. As a result, for quiet some time, automatic closed-loop control of crystal morphology has been considered by many researchers and industrial practitioners as too much a challenge.

This presentation will report recent developments in on-line measurement, modelling and automatic control of the morphology of crystals grown from solution. It will cover the following topics:

1. On-line characterisation of crystal shape using 2D and 3D imaging and image analysis.
2. Morphological (or multi-dimensional) population balance process modelling of the dynamic evolution of both crystal shape and size.
3. Techniques for the estimation of facetted growth rates of crystals - a key component in morphological population balance modelling and morphology control.
4. Closed-loop control of morphology and size simultaneously - recent simulation and experimental results will be presented to demonstrate that the crystal shape and size can be close-loop manipulated using either simple feed-back control, or more complicated model-based control.
5. Future research and development needs will also be discussed in order to develop practical tools that can be used in industry.

12.45: Lunch

Afternoon Session. Chair: Brett Cooper (Merck Sharp & Dohme)

14.00: Amy Robertson, AstraZeneca:
Process Analytical Technology Applications in Crystallisation Development

Demands for improving pharmaceutical productivity and quality, as well as the encouragement of recent process analytical technology (PAT) initiatives have caused PAT to become increasingly embraced by pharmaceutical companies in both research and manufacturing. PAT has been recognized as a key tool in understanding and designing crystallisation processes and a number of different probes are routinely used. These include Focus Beam Reflectance Measurement (FBRM), Particle Vision Monitor (PVM), ATR UV/Vis spectroscopy, FTIR and Raman probes. The use of these probes in conjunction with off-line analytical techniques such as XRD and optical microscopy can provide information to ensure the crystallisation is designed to produce the correct polymorphic form, with the desired purity, yield, crystal size and habit.

14.30: Claire Thompson, GlaxoSmithKline:
Pharmaceuticals in a State of Disorder - But How Much?

Formulations designed for inhaled delivery require micronisation of the active pharmaceutical ingredient (API) to produce the desired particle size distribution. Conventional micronisation methods involve a high energy input, which can lead to disruption of the crystal lattice at the surface of the particles. These disordered or amorphous regions can be chemically and/or physically unstable in comparison to the crystalline state. Subsequent recrystallisation can lead to agglomeration of the particles, thus increasing the particle size distribution. It is, therefore, imperative to have methodologies in place for the detection and characterisation of amorphous material.
A plethora of techniques have been utilised to detect and quantify amorphous material in pharmaceutically important compounds. However, the sensitivity of these techniques has been reported to vary widely. Here, we discuss some of the techniques used, and sensitivities reached, for the detection of amorphous material in pharmaceutical compounds.

15.00: Refreshments

15.30: Matt Tucker, ISIS:
Looking Beyond the Bragg Peaks with Total Scattering

The importance of disorder in crystalline materials is increasingly being recognised as a key property of many functional materials. From negative thermal expansion to solid state amorphisation, a clear picture of the local atomic structure is essential to understanding these phenomena and solving the associated problems.

A powerful technique for exploring the local structure of materials is total scattering, also known at the PDF method. Here synchrotron X-ray and/or neutron powder diffraction data are carefully corrected and normalised onto an absolute scale, they can then be used to obtain information on the local, medium and long range atomic structure simultaneously.

In order to gain the maximum information from this valuable data specialised refinement methods are required. One of the most powerful methods currently available for producing three dimension models using this type of data is RMCProfile[1]. I will give several brief examples where RMCProfile has been used to successfully study the structural and dynamical disorder of a wide range of materials to illustrate its potential.

To give an example of how an amorphous structure can be successfully modelled using this technique, I will discuss a study of pressure induced amorphisation in the negative thermal expansion material ZrW_2O_8 [2,3].

Finally, I will briefly discuss the potential and possible limitations of applying this technique to pharmaceuticals and whether lab based measurements could be of use for this method of characterisation.

[1] *RMCProfile: reverse Monte Carlo for polycrystalline materials* M G Tucker, D A Keen, M T Dove, A L Goodwin, Q Hui *J. Phys.-Condes. Matter* **19** 335218 (2007)
[2] *Structural description of pressure-induced amorphization in ZrW2O8* D A Keen, A L Goodwin, M G Tucker, M T Dove, J S O Evans, W A Crichton, M Brunelli, *Phys. Rev. Lett.* **98** art. no. 225501 (2007
[3] *Negative thermal expansion in ZrW2O8: Mechanisms, rigid unit modes, and neutron total scattering* M G Tucker, A L Goodwin, M T Dove, D A Keen, S A Wells, J S O Evans *Phys. Rev. Lett.* **95** art. no. 255501 (2005)

16.00: Anne Kavanagh, BCA Industrial Group Chair:
Closing Remarks.

16.15: Close