

CrystEngComm Symposium Pharmaceutical Polymorphism

4 November 2011

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Welcome from Dr Jamie Humphrey, Editor of *CrystEngComm*

Dear Colleagues

Welcome to the *CrystEngComm* Symposium: Pharmaceutical Polymorphism. We are very pleased to be holding this exciting event, highlighting an important area of crystal engineering research for the pharmaceutical industry. The purpose of these events is to bring together scientists in a stimulating and friendly environment that will foster collaborations and I hope that you will be able to make the most of this opportunity for interaction.

Many thanks to Dr Z. Jane Li who has been fundamental to the organisation of this Symposium. Her help and support has been invaluable to the success of today's meeting.

CrystEngComm, with a high impact factor of 4.0, is the Royal Society of Chemistry's journal that covers crystal engineering and polymorphism. Since its launch in 1999, the journal has grown from strength to strength, to be the popular and high impact journal that it is today. This growth in impact and number of published articles is largely thanks to the authors and referees who support the journal every day. I do hope that we will have the opportunity to publish some of your work in the journal, and if you would like to be a reviewer for the journal, please do let me know.

I hope that you enjoy the Symposium, thank you once again to our hosts and please take the opportunity to interact with each other! I look forward to meeting you.



Dr Jamie Humphrey
Editor
CrystEngComm

CrystEngComm Symposium: Pharmaceutical Polymorphism

4th November 2011

Time	Event
9.30	Tea/Coffee
10.00	Jamie Humphrey/Jane Li Welcome and Introduction
10.10	Orn Almarsson <i>Alkermes Inc., USA</i> Crystal Polymorphism and Pharmaceuticals
10.50	Graeme Day <i>University of Cambridge, UK</i> Crystal Structure Prediction of Pharmaceutically Relevant Molecules: Dealing with Molecular Flexibility
11.30	Ivo Rietveld <i>Universite Paris Descartes, France</i> Determination of the Stability Hierarchy of Polymorphs by Topological and Experimental Pressure-Temperature Diagrams
12.10	Lunch
13.10	Ann Newman <i>Seventh Street Development Group, IN, USA</i> An Overview of Solid Form Screening During Drug Development
13.50	Simon Black <i>Astra Zeneca, UK</i> Stick or Twist?
14.30	Tea/Coffee
15.00	Jamshed Anwar <i>University of Bradford, UK</i> Molecular Simulation of Polymorphic Phase Transitions
15.40	Z Jane Li <i>Boehringer Ingelheim, USA</i> Impact of Polymorph Control in Formulation Development
16.20	Avijit Kelkar <i>Dr Reddy's Laboratories (UK) Limited, UK</i> Intellectual Property Aspects of Pharmaceutical Polymorphism
17.00	Jamie Humphrey/Jane Li Closing Remarks
17.15	Symposium Finishes

Speaker Biographies



Örni Almarsson

Alkermes Inc., USA

Örni Almarsson, Ph.D., has been leading pharmaceutical R&D at Alkermes since 2008. The group has responsibility for active pharmaceutical ingredients, formulations, analytical development and pharmaceutical chemistry. Dr. Almarsson joined Alkermes in 2008 from TransForm Pharmaceuticals/J&J, where he led product generation based on high-throughput materials platforms. Following acquisition by J&J, Dr. Almarsson had cross-site responsibility as Head of Early Development Drug Products/US in Chemical and Pharmaceutical Development at J&J PRD. The role included leadership of early-stage API generation and drug product to support programs from pre-clinical through Phase II candidate evaluation.

Dr. Almarsson received his B.S. degree in chemistry from the University of Iceland in 1988 and a Ph.D. in physical-organic chemistry from the University of California at Santa Barbara in 1994 in the field of bio-organic mechanisms. Following post-doctoral work at MIT, Dr. Almarsson joined Merck Research Laboratories in 1995. In 1999-2000 he was responsible for the pharmaceutical chemistry group at Merck West Point, supporting both discovery and development programs.

Dr. Almarsson is an inventor on several patents, and he has published widely in areas of pharmaceutical chemistry, materials discovery, solid-state characterization, formulation, drug delivery and biopharmaceutical optimization.



Prof. Jamshed Anwar

University of Bradford, UK

Prof. Jamshed Anwar holds a Chair in Computational Pharmaceutical Sciences at the Institute of Life Sciences Research (ILRS), University of Bradford, UK. His research is concerned with developing a molecular understanding of drug delivery systems using computer modelling and simulation. Specific research interests include phase behaviour of solids with applications in crystal engineering and modelling of soft matter including biological lipid membranes. Prior to his appointment at Bradford, he was a Reader in the Molecular Biophysics Group at King's College London. He has also spent periods at the University of Pennsylvania, the Institute of Atomic & Molecular Physics (AMOLF) in the Netherlands, and the University Chemical Laboratory, Cambridge. He was awarded the Pfizer Award in 1999 for his seminal studies on molecular simulations of pharmaceutical systems, and is also a recipient of the RP Scherer Award (1986).

**Simon Black***Astra Zeneca, UK*

Simon studied Natural Sciences at Cambridge, staying on in the Department of Physical Chemistry for his Ph.D. research into structural chemistry. With ICI from 1984 he worked on crystallization of diverse materials at scales from grams to tonnes. He joined AstraZeneca in 2000, where he is currently Principal Scientist for Crystallization in the Physical Sciences Group, which is part of Medicines Development at Macclesfield, England.

Simon describes his role as 'to use crystallization science to develop better medicines'. His interests include promoting and preventing crystallization, through understanding of thermodynamics, crystal structures, and kinetics.

Simon is a Visiting Professor at Manchester and Tianjin Universities. He has over forty external publications and patents, and reviews for pharmaceutical, chemical engineering and crystallization journals.

**Graeme Day***University of Cambridge, UK*

Graeme Day received his BSc in 1996 from Saint Mary's University, Canada, followed by an MSc in theoretical chemistry from the University of Oxford in 1997. He then completed a PhD in computational chemistry, under the supervision of Prof. S. L. Price at University College London in 2003. He joined the Pfizer Institute for Pharmaceutical Materials Science at the University of Cambridge as a postdoctoral research associate, developing methods for predicting structures and properties of molecular organic crystals. Since 2005, he has held a Royal Society University Research Fellowship in the department of chemistry at the University of Cambridge, where his research continues the development of computational methods for understanding the molecular organic solid state, with his main interests in polymorphism, crystal structure prediction and terahertz spectroscopy of molecular materials. Graeme has published over 50 peer reviewed articles in these areas.



Dr Avijit S Kelkar

Dr Reddy's Laboratories (UK) Limited, UK

Dr Kelkar has been associated with Dr Reddys Laboratories for the past 10 yrs, and has been heading the Intellectual property management cell for API BD and Generics divisions of the company. After doing a diploma in the management of intellectual property, he has recently completed the qualification for patent attorney in 2011. After completing his PhD in synthetic organic chemistry from University of Hong Kong, and his postdoctoral research in Universities of Bristol and Sheffield, he moved into the law area of chemistry - namely patents! The immense complexity and the innumerable interpretations of law on the factual conclusions derived from scientific studies is a continuous learning experience that drives his passion for IP. In this seminar, Dr Kelkar will try and highlight the various aspects of patentability, infringement and freedom to operate issues on polymorphic patents in EU, and touchbase upon their interpretations globally.



Z. Jane Li

Boehringer Ingelheim, USA

I am a Senior Research Fellow in Pharmaceutical R&D at Boehringer Ingelheim Pharmaceuticals in Connecticut. I obtained a Ph.D. degree in pharmaceuticals from University of Minnesota with late professor David Grant and have over 20 years experience in pharmaceutical R&D. My work experience includes 8 years at Pfizer, focused on polymorph screen, salt selection, crystallization and solid-state characterization and I actively led or participated in various solid-state research subjects. At Boehringer Ingelheim, I have been working on pre-formulation, formulation development and interface activities involving solid-state pharmaceuticals. I have over 30 publications and patents in the field of solid-state chemistry and pharmaceutical sciences.

**Dr. Ann Newman***Seventh Street Development Group, IN, USA*

Dr. Ann Newman is currently a pharmaceutical consultant at Seventh Street Development Group with over 20 years of large pharma and contract research experience. She received her PhD in Chemistry from the University of Connecticut. For ten years, Dr. Newman performed characterization studies on a wide range of pharmaceutical systems at Bristol-Myers Squibb, covering drug substance and product scale-up from late drug discovery to launch and manufacturing. After that she was Vice President of Materials Science at SSCI, Inc. overseeing characterization of API and drug product samples, crystallization and polymorph screens, salt and cocrystal selections, quantitative assays, amorphous dispersion projects, and problem solving for the pharmaceutical industry. As Vice President of Research and Development at Aptuit, she instituted a companywide R&D initiative over six global sites and covering areas such as API, preclinical (toxicology, safety, pharmacokinetics), formulation, solids, analytical, clinical packaging, and regulatory. She holds an adjunct faculty position in Industrial and Physical Pharmacy at Purdue University and is author/collaborator on over 40 publications, 75 technical presentations, and 40 webinars. Additional information can be found at www.seventhstreetdev.com.

**Ivo Rietveld***Universite Paris Descartes, France*

Chemistry degree from Utrecht University (NL) in 1996
Ph.D. in physical chemistry of polymers from Leiden University (NL) in 2000
Postdoctoral study at Delft University (NL) on electrospray in 2000
Postdoctoral study at the University of Pennsylvania (USA) on dendrimer based oxygen probes for in vivo measurements in blood and tissue in 2001 and 2002
Researcher at the University of Kyoto (JP) on electrospray and polymer thin films from 2003 to 2007
Assistant professor at Université Paris Descartes (FR) on polymorphism of drug molecules from 2007 onwards.

Abstracts

Crystal Polymorphism and Pharmaceuticals

Örn Almarsson, Ph.D.

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The talk will be an overview of crystal polymorphism from the vantage point of pharmaceutical research and development. The goal is to provide a clear definition of polymorphism in the context of pharmaceuticals, survey characterization techniques, and discuss the advent of high-throughput methodology in the discovery and study of crystal form diversity. Examples will be taken from the various form types considered in the preparation of a pharmaceutical drug substance (API) and formulation, including the free form, salts and cocrystals. Implications of polymorphism – known and unexpected – for solubility, stability and product performance, as well as for patents on the material, will be discussed.

Molecular Simulation of Polymorphic Phase Transitions

Jamshed Anwar

Computational Biophysics Laboratory, Institute of Life Sciences Research, University of Bradford,

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Crystal-crystal phase transitions are of considerable scientific interest and industrial importance. The interest spans numerous fields that include Earth sciences, materials science, biomineralisation, explosives, and speciality chemicals and pharmaceuticals. For pharmaceuticals, unpredicted phase transitions in crystals of the drug compound can adversely affect both the product activity and its stability. Whilst we can characterise the structural, thermodynamics and kinetic aspects of crystal-crystal phase transitions, the molecular mechanism by which such transitions occur still eludes us. However, molecular simulations do offer a way forward. These simulations have the potential to make the underlying molecular processes transparent, which should enhance our fundamental understanding and enable us to develop a framework for possibly controlling crystal-to-crystal phase transitions, and assisting in the rational design and development of materials and processes where such transitions are important.

I shall outline the molecular simulation methodology and its application to phase transition phenomena, and give illustrative examples of simulation of crystal-crystal transitions as a function of temperature and pressure. I shall also identify the limitations and challenges that confront such simulations.

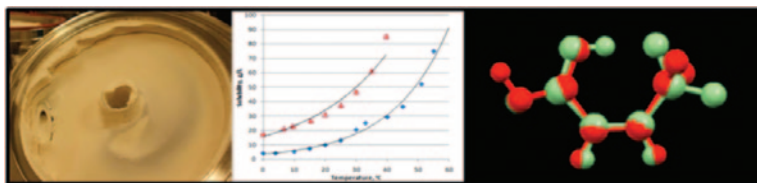
Stick or Twist?

Simon Black

Suspecting a new polymorph is only the beginning. Case studies, in-house and from the literature, illustrate what happens when a new polymorph is suspected and confirmed. Reference samples are required as an important step on the way to transformation diagrams summarising the thermodynamic relationships between different forms.

Comparison of crystal structures suggests that 'twisting' of molecules may be significant, with 'unusual' conformations featuring in forms that nucleate later. Different solubilities and crystallization

kinetics demand alterations to the crystallization process design. Different material and particle properties demand changes to the formulation process. In one case study, a decision is required between two polymorphs, one of which has very poor flow properties. Which would you choose?



Crystal Structure Prediction of Pharmaceutically Relevant Molecules: Dealing with Molecular Flexibility

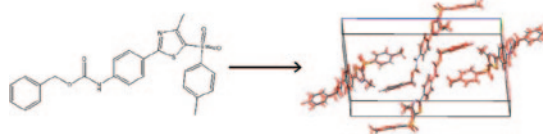
Graeme Day

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Given the chemical diagram of a molecule, is it possible to predict how it will crystallise (i.e. space group, unit cell parameters and all atomic coordinates)? The development of computational methods to address this problem has been a great challenge for computational chemistry. Prediction methods based on global searches of the lattice energy surface are now becoming reliable, at least for conformationally rigid molecules, so that computational results can be confidently applied to understanding the crystallisation behaviour of organic molecules.

These methods are of particular interest for pharmaceutical materials science, where predictive tools to anticipate new crystal forms could complement or even guide experimental polymorph screening.

In this context, there has been considerable recent effort put into developing methods for global lattice energy minimisation methods for conformationally flexible molecules. The presentation will examine the challenges posed by flexible molecules and describe some of the emerging promising approaches, with reference to recently published studies and the results of the 2010 blind test of crystal structure prediction, which included a highly flexible pharmaceutical-like molecule.



Intellectual Property Aspects of Pharmaceutical Polymorphism

Dr Avijit S Kelkar

Abstract unavailable at time of print. Please visit www.rsc.org/crystengcommsymposium for further details.

Impact of Polymorph Control in Formulation Development

Z. Jane Li

Boehringer Ingelheim Pharmaceutical Inc., Ridgefield, CT USA

In formulation development, the crystal form of the active Pharmaceutical Ingredient (API) can play an important role in determining the performance, stability and manufacturability of a drug product. It is known that more than 50% of APIs may exist more than one crystal form and formation of hydrate is rather common. During the unit operations, such as milling, wet granulation, there is a potential to induce phase changes of an API. The API phase transformation in a formulation can be complex depending on process and formulation, and may lead to undesired changes in dissolution, stability and manufacturability of a drug product. Understanding of the potential for process induced phase transformation is critically important to ensure the robustness and quality of a drug product. In this presentation, case studies will be given to demonstrate effect of API phase change in formulation development and how to develop a strategy to mitigate the risks.

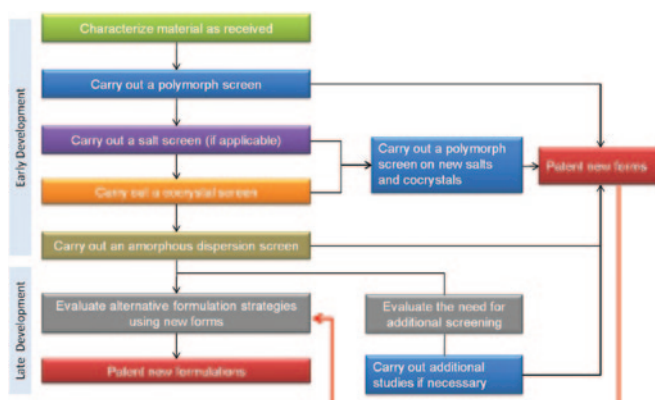
An Overview of Solid Form Screening During Drug Development

Ann Newman

Seventh Street Development Group, IN, USA

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The solid form of an active pharmaceutical ingredient (API) used in development has become an important aspect of drug development based on possible issues with manufacturability, solubility, bioavailability, and stability differences between materials. During early and late drug development, solid form screening is commonly performed to find a candidate with optimal properties for early development or to find a form with different properties to improve a formulation in later development. A variety of solid forms can be investigated in these screens including polymorphs, salts, cocrystals, amorphous, and amorphous dispersions. This presentation will give an overview on what is involved in common screens such as why screening should be performed, when to perform various screens, and what to think about when designing experiments. Case studies on polymorph and salt will also be presented.



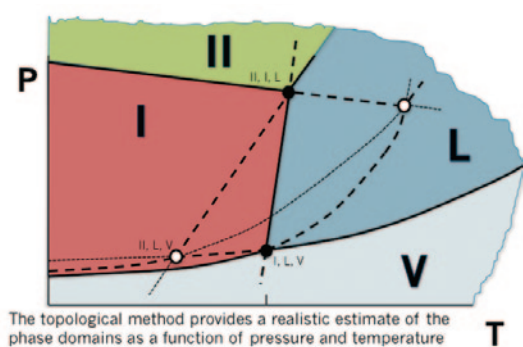
Determination of the Stability Hierarchy of Polymorphs by Topological and Experimental Pressure-Temperature Diagrams

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Even if an active pharmaceutical ingredient is known to exhibit polymorphism, it is often unclear which is the stable form under ambient conditions and under which conditions phase changes may occur. Direct experimental evidence of solid – solid transitions can be difficult to obtain. Surprisingly, it is often not realized that the regions of polymorph stability can be mapped out in the pressure – temperature domain with the help of classic thermodynamics. Ideally, the necessary data are the transition temperatures, heats of transition (calorimetric data) and the density as a function of temperature (crystallographic data) for each polymorph and the liquid phase. Even if certain information is experimentally inaccessible, often, thermodynamics still allows drawing conclusions about the stability regions of polymorphs.



Phase diagrams based on calorimetric and crystallographic data and classic thermodynamics are called topological phase diagrams, because part of the phase boundaries is obtained by extrapolation and application of thermodynamic principles. High resolution X-ray diffraction provides thermodynamic work by measuring density as a function of temperature with reasonable precision. It complements DSC (differential scanning calorimetry) data and together they give rise to the Gibbs energy as a function of temperature and pressure.

To verify the topological approach, high-pressure differential thermal analysis (HP-DTA) has been carried out and it has been shown that the measured and topologically obtained phase boundaries coincide reasonably well.

In conclusion, the topological approach supported by experimental data involving heat and work related properties of polymorphs leads to a reliable phase diagram reflecting the stabilities between different polymorphs.

