SPRING PHARMACEUTICAL SYNCHROTRON X-RAY POWDER DIFFRACTION WORKSHOP

6-8 MAY 2018
PURDUE UNIVERSITY
WEST LAFAYETTE, IN 47907, USA

Excelsus Structural Solutions

PURDUE UNIVERSITY

Sunday, 6th May 2018

14:00 - 18:30 - XRPD Refreshers: an informal tutorial on X-Ray Powder Diffraction (XRPD) and Synchrotron X-Ray Powder Diffraction (S-XRPD)

F. Gozzo, P. Whitfield and M. Reinle-Schmitt, Excelsus Structural Solutions, Switzerland & Belgium
R. Von Dreele, Argonne National Laboratory, USA

Part 1: Crystalline drugs and their diffraction patterns

- Elements of crystallography & X-Ray Diffraction
- Powder diffraction vs Single Crystal Diffraction
- Specificities of organics & qualitative interpretation of their diffraction patterns
- Structural analysis of drug substances and products

Part 2: The importance of powder sample preparation: how can it influence the output of our experiments/measurements?

- Does a powder sample always behave as a powder?
- The choice of the experiment configuration (transmission vs reflection)
- The choice of the detectors: is high-resolution always the best choice?
- How should we prepare samples? Tips
- What if we cannot control all parameters?

Part 3: Laboratory versus synchrotron XRPD: when is lab-XRPD no longer the best choice?

- What is a synchrotron? Why does it enable you to learn more about your sample?
- Laboratory vs synchrotron source: are they complementary?
- LOD & LOQ
- Synchrotron-XRPD: measurements or experiments?
- Synchrotron-based analytical techniques: how does a company access them?

Part 4: In practice – What does a diffraction pattern tell us at glance? What else can it tell us?

- Indexation, Structure Solution and Refinement
- Microstructure analysis of pharmaceuticals
- Trace analysis & Quantitative Phase Analysis
- Pair Distribution Function analysis of pharmaceuticals: definitions, aim of analyses, complexity

Part 5: Can XRPD analyze systems as complex as proteins?

- The pioneer work of Robert von Dreele, Irene Margiolaki and Jonathan Wright

18:30 - 20:00 - Welcome and Networking Reception

Monday, 7th May 2018

08:30 – 08:45 – Workshop introduction

08:30 **Opening remarks; Mission and Structure of the Spring Pharmaceutical Synchrotron XRPD workshop**
S. Byrn, Purdue University, USA
F. Gozzo, Excelsus Structural Solutions, Switzerland & Belgium

08:45 – 10:25 – From laboratory to synchrotron XRPD

08:45 **Applications of XRPD for Phase Identification throughout Pharmaceutical Product Development**
A. Patel – Bristol-Myers Squibb, USA

09:10 **Compression induced phase transformation: a formulator's perspective**
N. K. Thakral - Upsher-Smith Laboratories LLC & University of Minnesota, USA

09:35 **The "Form Selection Process" in the Pharmaceutical Industry: The importance of being Earnest**
M. Daldosso – Aptuit, Italy

10:00 **The impact of qualitative and quantitative synchrotron-XRPD trace analyses on the characterization of pharmaceuticals**
F. Gozzo – Excelsus Structural Solutions, Switzerland & Belgium

10:25 - 10:55 - Coffee break

10:55 - 12:20 - Total Scattering and Pair Distribution Function: an Overview

10:55 **Recent developments in PDF analysis of organics and pharmaceuticals**
S. J. L. Billinge – Columbia University and Brookhaven National Laboratory, USA

11:30 **PDF analysis of organic and molecular systems - quirks and peculiarities**
P. Whitfield – Excelsus Structural Solutions, Switzerland

11:55 **Synchrotron x-ray PDF from amorphous pharmaceuticals**
C. Benmore – Advanced Photon Source, Argonne National Laboratory, USA

12:20 - 13:20 - Lunch, coffee and networking

13:20 - 14:35 – Pair Distribution Function & Industry

13:20 **xINTERPDF: a GUI program for analyzing intermolecular pair distribution functions of organic compounds from X-ray total scattering data**
C. Shi – Abbvie Inc, USA

13:45 **Characterization of Mesomorphous Pharmaceuticals Using Pair Distribution Function**
F. Atassi – Pulmatrix Inc, USA

14:10 **Assessment of Processing Induced Structural Disorder in Pharmaceutical Solids by Synchrotron Total Scattering**
S. Chen - Abbvie Inc, USA

14:35 - 15:50 - In-situ and operando S-XRPD

14:35 **Monitoring phase transformations in formulations**
R. Suryanarayanan – College of Pharmacy, University of Minnesota, USA

15:00 **Probing crystallization of drugs using synchrotron radiation**
L. Taylor – Department of Industrial and Physical Pharmacy, Purdue University, USA

15:25 **Parts per Million PXRD through Nonlinear Optically Guided Analysis**
G. J. Simpson – Department of Chemistry, Purdue University, USA

15:50 - 16:20 - Coffee break

16:20 – 18:00 – Amorphous drugs

16:20 **Structure and Analysis of Amorphous Dispersions**
S. Byrn - Purdue University, USA

16:45 **Polyamorphism of D-mannitol: Structural studies by Synchrotron X-ray diffraction**
L. Yu – Department of Chemistry, University of Wisconsin-Madison, USA

17:10 **Using Containerless Methods to Synthesize and Characterize Amorphous Pharmaceuticals**
R. Weber – Materials Development, Inc. and Argonne National Laboratory, USA

17:35 **Pharmaceutical amorphous solid dispersions characterized by Synchrotron X-ray diffraction and Pair Distribution Function method**
G.L. B. de Araujo – University of Sao Paulo, Brazil

18:00 - 18:30 - Flash presentations of posters

18:30 - 19:30 - Standing dinner during poster session

19:30 - 21:30 or longer - Guidelines for generating reliable experimental PDF of pharmaceuticals (PDF experts discussion, but open to interested participants)

Tuesday, 8th May 2018

08:30 - 08:55 - IP & Industry

08:30 **Current treatment of crystalline forms under US and EP patent law**
D. Weingarten – Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, USA

08:55 - 09:55 - Beamline Overview

08:55 **The XPDF beamline at Diamond Light Source**
P. Chater – Diamond Light Source, UK

09:10 **X-ray Powder Diffraction Facilities available at the Advanced Photon Source**
B. Toby - Advanced Photon Source, Argonne National Laboratory, USA

09:25 **The ESRF powder diffraction beamlines**
Slides provided by A. Fitch – European Synchrotron Radiation Facility, France

09:40 **The MS beamline at the Swiss Light Source**
Slides provided by N. Casati – Swiss Light Source, Switzerland

09:55 **Powder Diffraction Capabilities at NSLS-II (Brookhaven)**
S. J. L. Billinge – Columbia University and Brookhaven National Laboratory, USA

10:10 - 10:40 - Coffee break

10:40 - 12:20 – Database, software and industry support

10:40 **Advanced quantitative phase analysis methods to support the industrial drug development process**
M. Reinle-Schmitt – Excelsus Structural Solutions, Switzerland

11:05 **Crystal Structures of Large-Volume Commercial Pharmaceuticals**
J. A. Kaduk – North Central College, Illinois Institute of Technology and Poly Crystallography Inc., USA

11:30 **Powder Diffraction File™ Coverage of Polymers used in Pharmaceutical and Biomedical Applications**
T. N. Blanton – International Centre for Diffraction Data, USA

11:55 **The GSAS-II software package**
R. Von Dreele & B. Toby – Advanced Photon Source, Argonne National Laboratory, USA

12:20 - 13:20 - Lunch, coffee and networking

13:20 - 14:10 – Laboratory vs Synchrotron XRPD for PDF analyses

13:20 **In house and synchrotron based atomic PDF studies on non-crystalline drugs: is there room for both?**
V. Petkov – Department of Physics, Central Michigan University, USA

13:45 **X-Ray Total Scattering Analysis on Laboratory Instrumentation**
D. Beckers – Malvern Panalytical B.V., The Netherlands

14:10 - 15:30 – Meet the experts

15:30 - 16:00 - Workshop wrap up (what pharma industry needs? what can we provide?)

Characterization of Mesomorphous Pharmaceuticals Using Pair Distribution Function

Faraj Atassi

Pulmatrix Inc., Lexington, USA

Crystalline pharmaceuticals have long and short range three dimensional and translational symmetry order. However, these crystalline materials may lose one or even two-dimensional order to become mesophases (or commonly referred to as liquid crystals). Characterizing pharmaceutical mesophases using Bragg based X-ray powder diffraction has its limitation and generally is not enough to understand the molecular based structure of these unique phases. In this presentation a case study of using pair distribution function (a total scattering technique) calculated using Synchrotron X-ray powder diffraction to characterize lab generated thermotropic mesomorphous materials will be presented. The process used to analyze the synchrotron diffractogram and the techniques used to analyze the calculated pair distribution function and improve its resolution are outlined and discussed. The results of this work illustrate the power of pair distribution function in analyzing disordered pharmaceuticals in order to explore the molecular structures of these materials.

Faraj Atassi is the director of formulation development and analytical and materials characterization departments at Pulmatrix Inc. Before he joined Pulmatrix, he was the director of formulation development at Sage Therapeutics, a principal Scientist at the Chemical and Pharmaceutical Profiling division and the leader of the Novel Drug Delivery group at Novartis, and a research scientist in the preformulation and solid-state group at Eli Lilly and company. Faraj is a licensed pharmacist and holds a MS in Medicinal Chemistry from the Philadelphia College of Pharmacy and a Ph.D. from the department of Industrial and Physical Pharmacy at Purdue University. Faraj's career has focused on building the connection between pharmaceutical materials science and drug delivery and bio-performance.

X-Ray Total Scattering Analysis on Laboratory Instrumentation

Detlef Beckers, Milen Gateshki

Malvern Panalytical B.V., Almelo, The Netherlands

The amorphous and nano crystalline state of active pharmaceutical ingredients (APIs) is of significant interest in pharmaceutical industry as a possible means to enhance aqueous solubility of the compounds. An important practical barrier in the development of amorphous APIs for drug products is the lack of reliable methods for structural characterization and fingerprinting.
It is assumed that often the molecular / short range structural arrangement directly determines the physical stability of the pharmaceutical solid.

Total scattering techniques such as Atomic Pair distribution function (PDF) and the Debye Scattering Equation (DSE) have been suggested as possible methods for structural characterization and fingerprinting of amorphous and nano materials and to study the short range order (i.e. inter-atomic distances) of the material. The PDF technique utilizes a Fourier transformation of the X-ray powder diffraction (XRPD) data and gives information about the inter-atomic distances of the material. The accuracy of this assessment of inter-atomic distances depends strongly on the energy of the utilized radiation source. The DSE predicts the scattered intensity in powder diffraction patterns from atomic arrangements like in amorphous materials and randomly distributed nano-clusters in the solid state.

In this presentation we discuss the instrumental requirements and recent advances for the application of these techniques on a laboratory XRD instrument. New generation detectors optimized for hard radiation (like Mo and Ag radiation) allow to minimize artifacts or fluctuations in the PDF arising from statistical noise, resulting in more reliable data. Thus, the amorphous and nanocrystalline materials in the drugs can be studied reliably in the laboratory. We will demonstrate the possibilities of laboratory PDF on a variety of organic samples of different nature. And show with cluster analysis that PDF patterns can reliably be used for fingerprinting of amorphous drugs and drug compounds.

Dr. Detlef Beckers made his PhD in physics in 1996 at the Solid State Physics Institute in the Research Center Jülich in Germany.
He joined PANalytical B.V. in 1996 (at that time Philips Analytical) in the position of Project Manager XRD (X-ray diffraction).
2003 he became Market Segment Manager Pharmaceuticals, Food and Life Science with the responsibility for applications and business development and the co-ordination of the segment activities within PANalytical. In 2009 Detlef Beckers was additionally appointed as Product Manager and responsible for the market introduction of the Empyrean system.
His current position within Malvern Panalytical is Group Leader and Principal Scientist XRD; responsible for the analytical performance of the XRD instrumentation and (pre-) development of new analytical methods and technologies in XRD.

Synchrotron x-ray PDF from amorphous pharmaceuticals

Chris Benmore

Advanced Photon Source, Argonne National Laboratory, Chicago, USA

High energy x-ray Pair Distribution Function analysis of amorphous pharmaceuticals is a powerful tool that has many advantages. Highly penetrating beams lead to small sample corrections, so the measurement is close to the required quantity. The wide accessible Q range makes it possible to achieve high real space resolution. The high flux at synchrotron sources enables high-quality time resolved measurements to be performed during synthesis. Both short and intermediate ordering is probed, providing information on both intra- and inter-molecular structure. However, if meaningful data are to be obtained a careful consideration of the corrections involved and compliance with consistency checks are essential. After all, it is important to remember that the measured x-ray structure factor S(Q) corresponding Pair Distribution Function G(r) are absolute quantities. While a rigorous comparison to amorphous models is often overlooked in the literature, as for most studies on disordered materials x-ray PDF is most useful when used in combination with other techniques such as NMR, neutron and calorimetry. We also briefly consider the benefits of the extended range PDF method which allows the characterization of structural features out to a few hundred nanometers, providing valuable information on nucleation, nanoparticles and mesoporous structures.

Chris Benmore was educated in England receiving his PhD in experimental physics in 1993 from the University of East Anglia. Chris worked as a postdoctoral fellow in Canada and at the neutron scattering center at Los Alamos National Laboratory. Returning to England, he was a neutron scientist at the Rutherford Appleton Laboratory, before crossing the Atlantic again to become a physicist at Argonne National Laboratory, where he has been working for the past 18 years. Chris was in charge of the neutron Glass, Liquid and Amorphous Materials Diffractometer at Intense Pulsed Neutron Source from 2000-2007 and for the past ten years has helped develop the technique of high energy x-ray diffraction for studying the structure of disordered materials at the Advanced Photon Source. Chris has co-authored >200 research publications, primarily on glasses, liquids and amorphous materials, with an emphasis on structures and phase transitions at extreme conditions. Chris has been an adjunct professor in physics at Arizona State University since 2008 and works closely with the Chicago-based company Materials Development Incorporated. In 2012 Chris received the University of Chicago medal for distinguished performance in sustained research, the highest honor awarded by Argonne National Laboratory.

Recent developments in PDF analysis of organics and pharmaceuticals

Simon J. L. Billinge

Department of Applied Physics and Applied Mathematics, Columbia University and

Condensed Matter Physics and Materials Science Department, Brookhaven National Laboratory

The atomic pair distribution function (PDF) analysis is having huge impacts in studies of inorganic nanomaterials. Beginning in the mid oughties we were able to extend this to weakly scattering systems, dilute systems and molecular systems, making this an ideal tool for studying organics and pharmaceuticals. PDF is now having impacts in this area. We have continued to develop the data analysis and modeling capabilities for weak scattering and dilute samples such as organics. The latest x-ray sources and the latest computational methods for data analysis and modeling are giving us an unprecedented view into atomic arrangements at the nanoscale in organics, pharmaceuticals and excipients. I will briefly review where we have come from, but focus on some of the recent developments that look particularly promising for pharmaceutical research.

Also presenting: **Powder Diffraction Capabilities at NSLS-II (Brookhaven)**

Prof. Billinge has more than 20 years experience developing and applying techniques to study local structure in materials using x-ray, neutron and electron diffraction. He earned his Ph.D in Materials Science and Engineering from University of Pennsylvania in 1992. After 13 years as a faculty member at Michigan State University, in 2008 he took up his current position as Professor of Materials Science and Applied Physics and Applied Mathematics at Columbia University and Physicist at Brookhaven National Laboratory.

Prof. Billinge has published more than 200 papers in scholarly journals. He is a fellow of the American Physical Society and the Neutron Scattering Society of America, a former Fulbright and Sloane fellow and has earned a number of awards including the 2018 Warren Award of the American Crystallographic Association and being honored in 2011 for contributions to the nation as an immigrant by the Carnegie Corporation of New York, the 2010 J. D. Hanawalt Award of the International Center for Diffraction Data, University Distinguished Faculty award at Michigan State, the Thomas H. Osgood Undergraduate Teaching Award. He is Section Editor of Acta Crystalographica Section A: Advances and Foundations. He regularly chairs and participates in reviews of major facilities and federally funded programs.

Powder Diffraction File™ Coverage of Polymers used in Pharmaceutical and Biomedical Applications

T.N. Blanton, S. Gates-Rector

International Centre for Diffraction Data, Newtown Square, PA, USA

tblanton@icdd.com

Polymers show a range of order from amorphous to semi-crystalline. Traditional organic analytical techniques, such as infrared spectroscopy (IR), differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and nuclear magnetic resonance (NMR), are typically used for polymer analysis. Though X-ray diffraction (XRD) is not commonly used as the primary technique for polymer characterization, XRD does provide unique information about a polymer particularly when assessing crystallinity and crystallite size. In medical applications, polymers are often used as excipients in pharmaceuticals, and the base material for delivery devices used in biomedical applications.

ICDD has been adding polymer diffraction data to the Powder Diffraction File (PDF®) with the focus on adding raw data diffraction patterns (1D and 2D) as part of the PDF entry. The inclusion of the raw data diffraction pattern is important in correctly identifying the polymer contribution to a composite material diffraction pattern. A traditional d-spacing/intensity stick pattern or simulated diffraction pattern is not capable of accounting for the full-pattern diffraction profile of polymers since all polymers have some amorphous component. The ICDD polymer project focuses on industrially important polymers with an added emphasis on polymers used in medical and biomedical applications. New entries resulting from this project will be presented along with phase identification analysis results for pharmaceutical formulations including an interesting finding for a change in the polymers used in the formulation of opioid based oxycodone pain medication.

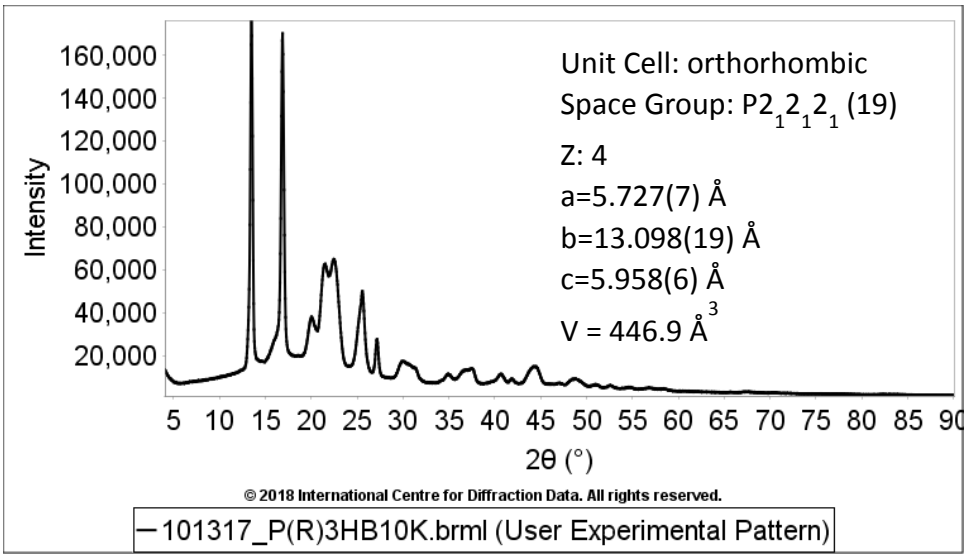


Figure 1. X-ray diffraction pattern (Cu Kα radiation) for poly(R)-3-hydroxybutyrate, investigated for drug delivery and tissue repair applications.

Tom Blanton is the Executive Director and Principal Scientist at the International Centre for Diffraction Data, ICDD. At ICDD, he oversees the development of the Powder Diffraction File™ database and presentation of educational activities. Prior to joining ICDD, Tom was a Senior Principal Scientist at the Research Laboratories of Eastman Kodak Company, responsible for the X-ray Spectroscopy Laboratory as well as leading technical activities in new product development including nanoparticles and antimicrobial materials.

Structure and Analysis of Amorphous Dispersions

Stephen Byrn, Chris Benmore, Gabriel deAraujo, Amrinder Rai

Purdue University, West Lafayette, IN and Argonne National Laboratory, Chicago, IL

For many years, the idea of analyzing atom-atom contacts in amorphous drug-polymer systems has been of major interest, because this method has always had the potential to differentiate between amorphous systems with domains and amorphous systems that are molecular mixtures. In this study, local structure of ionic and nonionic interactions in amorphous solid dispersions were investigated by High-Energy X-ray Diffraction and Pair Distribution Function (PDF) analysis. The strategy of extracting intermolecular drug interactions from the total PDF x-ray pattern was successfully applied to one example system (lapatinib) allowing the detection of distinct nearest neighbor contacts for the HPMC-E3 preparations and the HPMC-P dispersions with high drug loading. However, the HPMC-P 1:3 dispersion (lowest drug loading) showed no nearest neighbor drug-drug contacts. This dispersion was also the most stable dispersion. This result is consistent with the fact that the lapatinib HPMCP dispersion (1:3) is a molecular mixture. The results of this PDF analysis will also be compared to SSNMR analysis based on relaxation time. Additional approaches to analyzing amorphous dispersions using pair distribution functions will also be discussed. Armed with this analytical capability, scientists can now approach amorphous drug product design utilizing a range of methods including levitated drop screening methods. Acoustic levitation is a novel method for fast screening of physically stable solid dispersion formulations. It can assess not only the crystallization tendency of the compounds but also the stability enhancement of polymers. Furthermore, the containerless approach by acoustic levitation eliminates the influence of surface crystallization due to contact. Off-line screening is also possible. These methods use small amounts of material allowing their application to early drug development when small amounts of the API and formulation are available. In many respects, design of a viable amorphous solid form utilizing pair distribution functions is the ultimate in Quality by Design of pharmaceutical formulations.

Dr. Stephen R. Byrn is Charles B. Jordan Professor of Medicinal Chemistry in the Department of Industrial and Physical Pharmacy, Purdue University. Dr. Byrn set in motion the development of the field of Solid State Chemistry of Drugs with his books, short courses, and papers on the subject the first of which were first published in the mid-1970's. He has also educated over 50 Ph. D. students and postdoctoral fellows and taught a wide range of courses at Purdue. Dr. Byrn has had numerous grants including one of the first 13 NIH Centers for AIDS Research. Dr. Byrn is cofounder of Purdue's graduate programs in regulatory and quality compliance. These programs now constitute the Biotechnology Innovation and Regulatory Science (BIRS) MS program. He is also cofounder of the Purdue-Kilimanjaro School of Pharmacy Sustainable Medicines in Africa project in Moshi, Tanzania. Dr. Byrn has served as chair of the Pharmaceutical Sciences Advisory Committee to the FDA and chaired several USP committees. Dr. Byrn is also cofounder of SSCI, Inc. (Solid State Chemical Information) a cGMP research and information company. SSCI, Inc. is now owned by AMRI. Dr. Byrn

	has taught a range of courses and short courses involving Medicinal Chemistry, Industrial Pharmacy, Physical Pharmacy, and Solid State Chemistry. Dr. Byrn is an elected Fellow of the AAPS and has received several awards for his research and entrepreneurial activities including the AAPS David Grant Award for Research Achievement and the AAPS Wurster award in pharmaceutics and formulation.

The XPDF beamline at Diamond Light Source

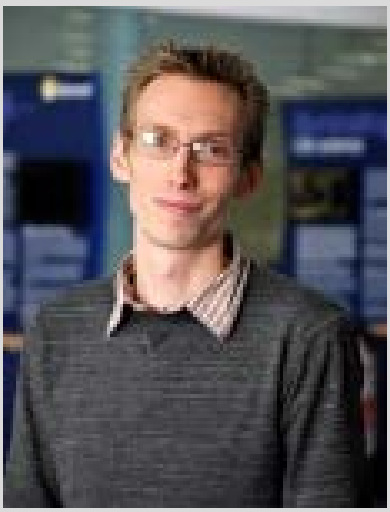
Philip Chater

Diamond Light Source, UK

The XPDF beamline at Diamond Light Source is committed to the fast and reliable production of pair distribution function (PDF) data. In its first year of operation XPDF has welcomed users from a diverse range of disciplines such as materials science, energy materials, earth sciences and pharmaceuticals. Here we present a selection of studies performed using the XPDF beamline and highlight the hardware and software developments which have made these studies possible.

XPDF operates with two large area detectors with one placed close to the sample to the provide the large Q range required for quality PDF data (Qmax up to 40 Å–1) and one mounted further from the sample for simultaneous higher-resolution Bragg data. This set-up is particularly valuable when studying disordered crystalline systems.

Alongside optimised hardware, significant effort has been put into software to produce a user-friendly, automated beamline. Integrated data collection and analysis software has been developed which will perform automatic data processing to deliver real-time Bragg, total scattering and PDF data. 2-D scattering data from an area detector can be corrected, integrated to 1-D and processed to X-ray PDFs, all from within a single interface. The PDF processing pipeline and examples of typical experiments performed on the XPDF beamline will be presented.



Phil obtained a MSci degree in Chemistry from the University of Birmingham (U.K.) in 2004. He continued at Birmingham researching under Dr Paul Anderson first for a PhD and then as a post-doc for the United Kingdom Sustainable Hydrogen Energy Consortium (UK-SHEC) researching complex hydrides for hydrogen storage and the link between reversibility and lithium ion conductivity.

In 2011 Phil joined the University of Liverpool (U.K.) as a post-doc working for Professor Matt Rosseinsky on the local structure of functional oxides, using X-ray and neutron Pair Distribution Function (PDF) analysis to study the short-range structure of materials. Structural characterisation from powders has been a theme underlying all of Phil's research; he has investigated a broad range of systems including complex hydrides, oxide ion conductors, metal organic frameworks, superconductors and ferroelectric materials. As Beamline Scientist at Diamond, Phil will be setting up and running I15-1, the new X-ray PDF beamline, where he is dedicated to constructing a beamline for the rapid and robust production of high-quality X-ray PDF data.

Assessment of Processing Induced Structural Disorder in Pharmaceutical Solids by Synchrotron Total Scattering

Shuang Chen

AbbVie Inc, USA.

Abstract to come

Shuang Chen is currently a principal research scientist at AbbVie. (formerly the proprietary pharmaceutical business of Abbott Laboratories). He received his Ph.D. degree in chemistry from the University of British Columbia, Canada. Before joining AbbVie's Process Research & Development team in 2006, he was a postdoc researcher in the School of Pharmacy of the University of Wisconsin at Madison where he focused his research on the polymorphism and crystallization of organic crystals. At AbbVie, he is engaged in discovering and selecting appropriate API solid forms for pharmaceutical development, developing API crystallization processes for scale up, and characterizing and improving API physical properties for drug product development.

The "Form Selection Process" in the Pharmaceutical Industry:

The importance of being Earnest

Matteo Daldosso[1], Brigida Allieri[1]

[1]*APTUIT (an Evotec Company), Center for Drug Discovery & Development, Verona, Italy*

matteo.daldosso@aptuit.com

Active Pharmaceutical Ingredients (API) shows the tendency to get order and crystallize as solids in different structures (forms). This phenomenon is known as polymorphism.

In general, different polymorphs show different physicochemical characteristics and properties. Therefore, the selection of the API form for drug product (DP) development is more than critical because the API form itself has a great impact on the properties of the final DP: the form selection problem has ethic, therapeutics, commercial and economic implications.

A number of historical and real industrial examples are presented in order to show how the X-Rays Powder Diffraction (XRPD) is an essential technique for the determination and quantification of polymorphic (or pseudo-polymorphic) forms in a given API to effectively support the form selection process for Drug Product Development, coupled with orthogonal techniques.

In particular, in house quantitative XRPD methods and how discovering of late appearing polymorphs has influenced the downstream medicine development is presented.

We will underline the needs to open the standard industrial approach to techniques with higher resolution (like synchrotron XRPD) with the objective to create new culture in the industry. The question: 'Which API form is suitable for pharmaceutical development?' is a crucial point that must a have a solid and earnest answer.

Matteo has a strong background in the solid state characterization of pharmaceutical and inorganic materials with expert understanding of the implications connected to the process of solid state profile determination in the pharmaceutical industry. His major responsibilities focus on crystalline structure elucidation, API form/version selection, x-rays diffraction and scattering, thermal analysis, spectroscopy, regulatory compliance and data integrity.
His career started with working experiences in various European organisations (ESRF, Grenoble, France; ISIS at the RAL, Oxfordshire, UK; University of Wroclaw, Poland; University of Verona, Italy) prior to joining GlaxoSmithKline as an Information scientist in 2006 at its Verona R&D site in Italy. He was eLNB (electronic laboratory notebook) product owner and System Support specialist before moving to the CMC area. In 2012 he became team coordinator, technical and project leader in the physical properties space (XRPD, TGA, DSC, Raman, FT-IR, Optical Microscopy, ESEM, Particle size, GVS, Solid State profile determination) and in the solid state one (Polymorph and Salt Screening, Crystallization Development). He currently manages the Physical Properties Unit within the Analytical and Material Sciences Department at Aptuit, an Evotec Company, in Verona (Italy).

Pharmaceutical amorphous solid dispersions characterized by Synchrotron X-ray diffraction and Pair Distribution Function method

Vinícius D. N. Bezzon[1], Gabriel L. B. de Araujo[1*], Chris J. Benmore[2], Stephen R. Byrn[3]

[1]*Department of Pharmacy, Faculty of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo, SP, 05508-900, Brazil*

[2]*X-ray Science Division, Advanced Photon Source, Argonne National Laboratory, Illinois, 60439, United States*

[3]*Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana, 47906, United States*

** corresponding author:gabriel.araujo@usp.br*

Amorphous Solid Dispersions (ASD) are systems used in pharmaceutical development to enhance the bioavailability of low-soluble drugs, since they may increase drug dissolution. Despite the advantageous properties, ASD are highly unstable and may recrystallize over time, compromising the efficacy of the drug product. In this context, synchrotron X-ray diffraction and Pair Distribution Function (PDF) analysis are powerful tools to understand the complexity of drug-polymer clustering in amorphous molecular structures and to identify interactions that may help to accelerate the polymer selection to improve physical stability of ASDs.[1] In this study we have evaluated ASDs systems composed of flubendazole (FBZ) and lapatinib (LP) dispersed in hydroxypropylmethylcellulose and its derivatives (HPMCP and HPMCAS) with regard to the structural coherence at intra and intermolecular levels by the PDF method. The results are congruent in showing that HPMCP and HPMC-AS are better at dispersing and stabilizing both drugs when compared to the HPMC-E3 matrix.

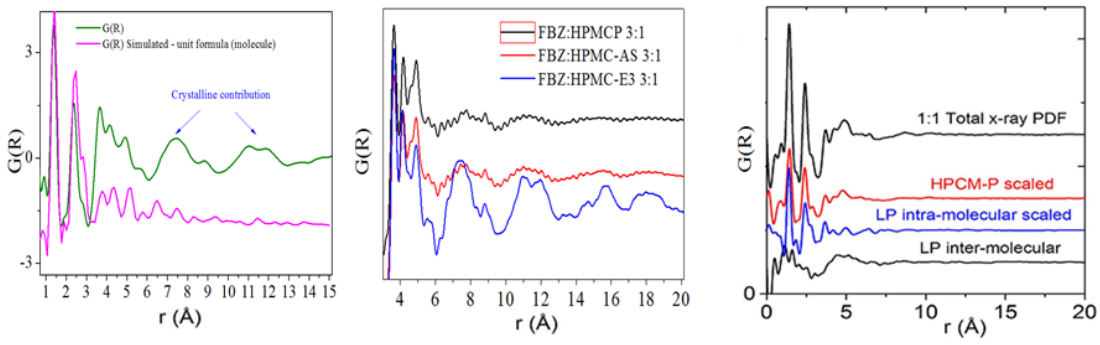


Figure 1*. Comparison of PDF patterns of pure FBZ (left), FBZ ASDs (center) and LP ASD (right).*

1. De Araujo, G. L.B., Benmore, C.J., Byrn, S.R., Scientific Reports, 7, 46367 (2017).

Dr. Araujo holds a PharmD from the University of São Paulo (São Paulo, SP, Brazil) and received his Ph.D. in Production and Quality Control of Drugs and Medicines from the same institution. In 2016-2017 he conducted post-doctoral research at Department of Industrial and Physical Pharmacy at Purdue University (West Lafayette, IN, USA) with Prof. Stephen R. Byrn. He accumulated more than 11 years of industrial experience working on Research, Development, and Innovation at large pharmaceutical companies. Since 2013 he has been an Assistant Professor of Pharmaceutical Technology at the University of São Paulo. His research interests include: Nanostructurated Drug Delivery Systems; Advanced solid state technologies and techniques (in special thermal analysis and high-energy X-ray and Pair Distribution Function) to improve and accelerate the development of medicines and Pharmaceutical Manufacturing.

The ESRF powder diffraction beamlines

Slides provided by Andy Fitch

ESRF, CS40220, 71, avenue des martyrs, 38043 Grenoble Cedex 9, France

fitch@esrf.fr

The ESRF operates several diffraction beamlines that between them allow single-crystal and powder X-ray diffraction and scattering experiments over a wide range of photon energies and under varied experimental conditions.

ID11, the Materials Science beamline, was one of the first to operate at the ESRF, and, following several upgrades, is dedicated to moderate to high energy powder or single-crystal diffraction and/or imaging studies Very high spatial (<100 nm) and time (1 ms) resolution is available.

ID15A, Materials Chemistry and Materials Engineering, recently refurbished as part of phase I of the ESRF upgrade, is a highly versatile instrument that allows a wide range of in-situ measurements in the areas of materials chemistry and catalysis, among other areas. It is equipped with a CdTe-based Pilatus 2M photon-counting area detector providing rapid counting and outstanding data quality, with sensitivity into the hard-energy regime.

ID22 is the high resolution powder diffraction beamline. The heavy-duty diffractometer, equipped with its nine-crystal Si 111 multi-analyzer stage, provides high resolution data for the solution and refinement of crystal structures from powders, quantitative analysis, in-situ studies, etc. Data can routinely be collected as a function of temperature. The beamline is also equipped with a large Perkin Elmer medical imaging detector for complementary measurements, for samples where angular resolution is less of a priority, including data for pair-distribution function (PDF) analysis. The robotic sample changer allows the processing of up to 75 samples as a series.

ID31, High-Energy Beamline for Buried Interface Structure and Materials Processing, is one of the new, long, microfocus, beamlines constructed during the ESRF Phase I upgrade program. The beamline also has a CdTe Pilatus detector, and offers a number of hard X-ray characterisation techniques including reflectivity, wide and small angle diffraction, imaging methods, and auxiliary techniques, coupled with versatility in choosing beam sizes, energy and energy band with. Data for PDF analysis can also be obtained as a routine technique.

Between them, these beamlines offer opportunities to study the crystal structures of materials via classic diffraction techniques, and to study the evolution of materials as they are heated or cooled, undergo chemical reaction, adsorb or desorb gasses, or generally are operated upon or processed under realistic operating conditions. Where appropriate, by tuning the photon energy to an element's absorption edge, anomalous scattering can be exploited to enhance contrast between elements close to each other in the Periodic Table.

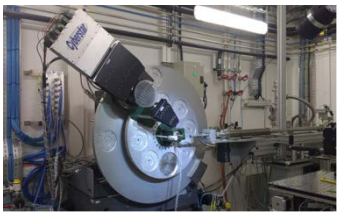


Figure 1.The ID22 high resolution powder diffractometer

Defective, poorly-crystalline materials, amorphous phases, glasses and liquids can be investigated structurally via the PDF technique, exploiting measurements to high Q values accessible via the hard energies available, to yield a picture of short-range order and longer-range interatomic distances. Tomographic and other imaging techniques can yield detailed 3-d information such as the distribution of different phases in polycrystalline and composite materials, yielding microstructural information on length scales up to mm.

The impact of qualitative and quantitative synchrotron-XRPD trace analyses on the characterization of pharmaceuticals

Fabia Gozzo

Excelsus Structural Solutions – Switzerland & Belgium

The ability of reliably detecting and quantifying impurities in the range 0-1%wt is always a difficult exercise, which becomes particularly difficult when dealing with pharmaceutical organic compounds due to their often poor scattering power and their sensitivity to radiation damage. In the pharmaceutical world, impurities are often synonymous of undesired polymorphic forms of the same active ingredients characterized, therefore, by the same elemental composition of the selected Active Pharmaceutical Ingredient.

The need of assessing the purity of the desired polymorphic form very often occurs after formulation, making the exercise of detecting and quantifying traces much more challenging due to the presence of the excipients signal.

The ability of synchrotron high-resolution and dose controlled X-Ray Powder Diffraction of directly detecting the presence of such impurities can play a crucial role in all phases of both the development and the IP protection of drug substances and products. We discuss the latest development and progresses in the field of synchrotron XRPD applied to pharmaceuticals and their impact on the characterization of pharmaceuticals.

Dr Fabia Gozzo is CEO and Founder of Excelsus Structural Solutions (Switzerland and Belgium). She has more than 25 years of practical experience with synchrotron facilities, in developing complex instrumentation and using it for the study of pharmaceuticals, pigments, food components, concrete and semiconductors. Before founding Excelsus Structural Solutions, she was working as a senior researcher and beamline scientist at the Powder Diffraction Endstation of the Material Science Beamline, Swiss Light Source. At the Paul Scherrer Institute, she has contributed to the growth of the Swiss Light Source synchrotron facility where she has developed for more than 10 years a state-of-the-art powder diffractometer, recently acknowledged in several scientific publications as one of the best ones in the world. Dr Gozzo has built there a substantial industrial and academic user community, including some large pharmaceutical companies. She is recognized as a synchrotron- and powder diffraction expert and as such, is regularly invited at the international level as a speaker, lecturer and scientific advisor. She is author and co-author of more than 80 scientific articles and book chapters.

Crystal Structures of Large-Volume Commercial Pharmaceuticals

James A. Kaduk[1], Austin M. Wheatley[2], Amy M. Gindhart[3] and Thomas N. Blanton[3]

[1]*North Central College, Naperville IL - Illinois Institute of Technology, Chicago IL - Poly Crystallography Inc., Naperville IL*

[2]*North Central College, Naperville IL*

[3]*ICDD, Newtown Square PA*

As part of a continuing project, the room-temperature crystal structures of several commercial pharmaceutical APIs have been solved using synchrotron X-ray powder diffraction data (11-BM at APS), and optimized using density functional techniques. The molecules to be discussed include: 1. terazosin hydrochloride dihydrate (Hytrin), which was originally solved (but only approximately) using data contained in the Powder Diffraction File database. 2. bretylium tosylate (Bretylol and others), which exhibited significant decomposition in the beam. 3. oxybutynin hydrochloride hemihydrate (Dytropan and Lyrinel XL), which has not been described as a hemihydrate, and which exhibits X-ray induced photoreduction of a triple bond. 4. levocetirizine dihydrochloride (Xyzal), which solves and refines better in P21/n rather than the true space group P21. 5. methylpednisolone acetate (Medrol). The presentation may also include progress (or lack thereof) on februxostat Form G (Uloric and Adenuric), as well as other new structures as they are solved.

Jim Kaduk is President of Poly Crystallography Inc., a company which provides crystallographic problem solving and consulting services. He is also a Research Professor of Chemistry at Illinois Institute of Technology, and a Senior Research Scientist (Physics) at North Central College. He began his crystallographic career as an undergraduate at Notre Dame. After obtaining a Ph.D. in inorganic chemistry at Northwestern in 1977, he joined Amoco Chemicals and did catalysis R&D for eight years. Through a number of corporate changes he ran the X-ray diffraction lab at Amoco/BP/Ineos from 1985-2009. The lab characterized a very wide range of materials, including catalysts, inorganics, corrosion deposits, organics, and polymers. Jim is well known for his expertise in solving and refining crystal structures using powder diffraction data, and for combining crystallography and quantum mechanics to understand not just where the atoms are, but why they are there.

Jim is Treasurer of the International Centre for Diffraction Data, the organization which produces the Powder Diffraction File database, and is a past Chairman of its Board of Directors. He is a former treasurer of the American Crystallographic Association and served in many other roles. He is a Co-Editor of the forthcoming Volume H of International Tables for Crystallography on powder diffraction, and author of multiple chapters. He is a consultant to the IUCr Commission on Powder Diffraction, and a member of the Commission on Crystallographic Nomenclature and the Committee

for the Maintenance of the CIF Standard (COMCIFS). He is a co-editor of Powder Diffraction and Advances in X-ray Analysis. He is a member of the faculties of the ACA's summer course, the ICDD's Clinics on Advanced Methods in XRD and the Rietveld Method, and teaches short courses and workshops around the world. He has been a member of the Northwestern University Library Board of Governors since 2001.

Jim received the 2017 Jenkins Award from the Denver X-ray Conference for lifetime achievement in the advancement of the use of X-rays in materials analysis, and is a Distinguished Fellow of ICDD. His > 225 published papers center on powder crystallography, and he has contributed > 870 patterns to the Powder Diffraction File.

Pharmaceutical amorphous solid dispersions characterized by Synchrotron X-ray diffraction and Pair Distribution Function method

Vinícius D. N. Bezzon[1], Gabriel L. B. de Araujo[1*], Chris J. Benmore[2], Stephen R. Byrn[3]

[1]*Department of Pharmacy, Faculty of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo, SP, 05508-900, Brazil*

[2]*X-ray Science Division, Advanced Photon Source, Argonne National Laboratory, Illinois, 60439, United States*

[3]*Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana, 47906, United States*

** corresponding author:gabriel.araujo@usp.br*

Amorphous Solid Dispersions (ASD) are systems used in pharmaceutical development to enhance the bioavailability of low-soluble drugs, since they may increase drug dissolution. Despite the advantageous properties, ASD are highly unstable and may recrystallize over time, compromising the efficacy of the drug product. In this context, synchrotron X-ray diffraction and Pair Distribution Function (PDF) analysis are powerful tools to understand the complexity of drug-polymer clustering in amorphous molecular structures and to identify interactions that may help to accelerate the polymer selection to improve physical stability of ASDs.1 In this study we have evaluated ASDs systems composed of flubendazole (FBZ) and lapatinib (LP) dispersed in hydroxypropylmethylcellulose and its derivatives (HPMCP and HPMCAS) with regard to the structural coherence at intra and intermolecular levels by the PDF method. The results are congruent in showing that HPMCP and HPMC-AS are better at dispersing and stabilizing both drugs when compared to the HPMC-E3 matrix.

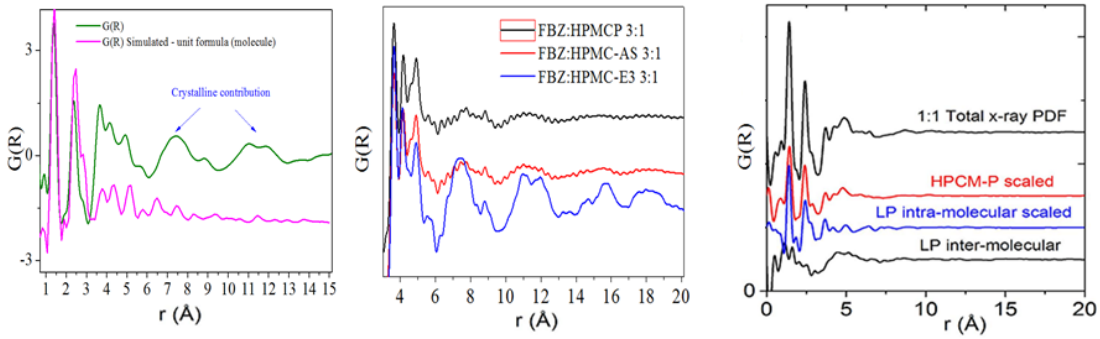


Figure 1. Comparison of PDF patterns of pure FBZ (left), FBZ ASDs (center) and LP ASD (right).

1. De Araujo, G. L.B., Benmore, C.J., Byrn, S.R., Scientific Reports, 7, 46367 (2017).

Applications of XRPD for Phase Identification throughout Pharmaceutical Product Development

Anisha Patel

Bristol-Myers Squibb, New Brunswick, NJ, USA

Small molecule APIs can exist in a variety of distinct solid-state forms with drastically different physicochemical properties. During development of these APIs, many factors are considered during form selection, such as stability, manufacturability, bioavailability, and intellectual property. If solid-state changes are observed during development, these selection factors can be negatively impacted, which can have detrimental effects to the development process and timeline. The "gold standard" tool to characterize solid-state forms is XRPD, which is used to ensure product quality from the late stages of Discovery as well as throughout Product Development, Commercialization, and Life Cycle Management.

We will discuss several case studies in order to illustrate the use of XRPD in screening of solid forms of APIs and in determining the impact of DS and DP unit operations on the solid-state form of APIs. We will further discuss the use of XRPD to troubleshoot processing or stability failures due to contamination or raw material variability. Throughout the presentation, comparisons to other solid-state characterization techniques, such as Raman, NIR, IR, and ssNMR, will be discussed to illustrate gaps in areas of implementation of XRPD.

Anisha Patel is a Senior Research Scientist within the Materials Science department at Bristol-Myers Squibb, New Brunswick NJ. Prior to joining BMS, Anisha worked at the NJ Center for Biomaterials at Rutgers University, NJ. Anisha holds a Bachelors in Medical Materials Science and Engineering from the University of Sheffield, UK. Her research interests include: solid-state characterization of pharmaceutical materials with emphasis on powder x-ray diffraction; salt and co-crystal dissociation mechanisms in the solid-state; understanding API Form changes during drug product manufacture and storage.

In house and synchrotron based atomic PDF studies on non-crystalline drugs: is there room for both?

V. Petkov

Dept. Physics, Central Michigan university, Mt. Pleasant, MI-48858

Pharmaceutical industry is *entering* a *new era* in drugs development involving a transformation from crystalline to non-crystalline drug formulations. The driving force of the transformation is the largely improved bioavailability of the latter in comparison to the former. Non-crystalline drugs, however, are both an opportunity and challenge for pharmaceutical research and development (R&D). In particular, assessing the quality of a non-crystalline drug requires precise information about its 3D structure type, phase content, amount of different non-crystalline ingredients eventually present, stability, and others. With crystalline drugs, such information is almost straightforward to obtain by traditional powder x-ray diffraction (XRD). A non-traditional "powder XRD-type" technique using x-rays of higher (> 15 keV) than usual (Cu Kα ~ 8 keV) energy, often referred to as total x-ray scattering coupled to atomic pair distribution function (PDF) analysis, is emerging as a powerful analytical tool for structural characterization of non-crystalline drugs [1]. We will present results from recent total x-ray scattering studies utilizing in house equipment (Panalytical XRD instrument) and state-of-the-art synchrotron x-ray sources. Examples will include indomethacin, aspirin and ingredients used in non-crystalline drugs, such as starch, trehalose, polyvinylpolypyrrolidone, and others. Special attention will be given to demonstrating the viability of in house PDF studies on non-crystalline drugs since experiments at National Synchrotron Radiation Facilities are not necessarily an affordable (e.g. proprietary issues) and/or time-efficient pharmaceutical R&D option.

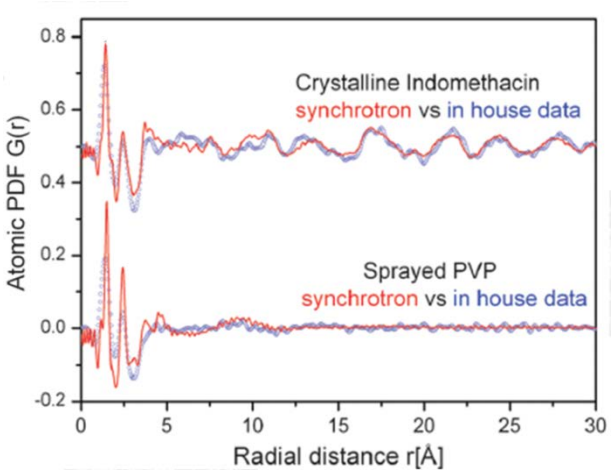


Figure 1. Comparison between atomic PDFs for indomethacin and Polyvinylpyrrolidone (PVP) obtained on an *in-house* XRD instrument (Ag K_α) and using high-energy x-rays (115 keV) at the 11-ID-C beamline, Argonne.

1. Petkov, V., Ren, Y., Kabekkodu, S., Murphy, D., *PhysChemChemPhys* **15**, 8544-8554 (2013).

Education: M.S. & PH.D., U. of Sofia, Bulgaria
Post-docs: Tohoku U., Japan and U. Rostock, Germany
Prof. in Physics at CMU since 2002 (Department of Physics, Central Michigan University)

Research interests: 3D structure studies on materials with a limited degree of structural coherence ranging from liquids and glasses to nanoparticles and crystals with intrinsic disorder by high-energy XRD and computer modeling.

Publications: 180+

BM: a python code for modelling physically based background for XRD

Bárbara A. Ramírez-Almaguer[1], Saúl García-Jiménez[1], Lauro Bucio[1]

[1]*Laboratorio de Cristalofísica y Materiales Naturales, Instituto de Física, Universidad Nacional Autónoma de México.*

Bara219@gmail.com

A graphic interphase has been developed in python code to run a program to calculate the background in diffraction patterns for different organic materials (ciprofloxacin, sildenafil citrate, ampicillin, acetylsalicylic acid, sucrose) modelled as a contribution of: (i) Thermal Diffuse Scattering (TDS) of the present crystalline phases; (ii) Air scattering.

A program to model the background in a powder diffraction patterns based in correction factors for absorption and air scattering under a symmetrical reflection geometry with a given sample thickness, divergence and receiving slit width, scale factors, average temperature factors and specimen density of packing has been developed.

The background has been calculated considering the Bragg and the diffuse scattering (Thermal Diffuse Scattering plus static disorder, Compton and air scattering). Compton scattering was also corrected for the bandpass function of the monochromator. (Figure 1)

To made the code accessible to the users, a graphic interphase has been codified. The program asks for the diffraction pattern, a run in the diffractometer without sample and other run with sample holder and other equipment parameters. Then the user defines typical parameters for the sample (Structure, density, volume etc.) and adjusting another parameter, a background based in the physical bases of the equipment and the sample is obtained. The code has been proved in pure organic substances and mixed with good results.

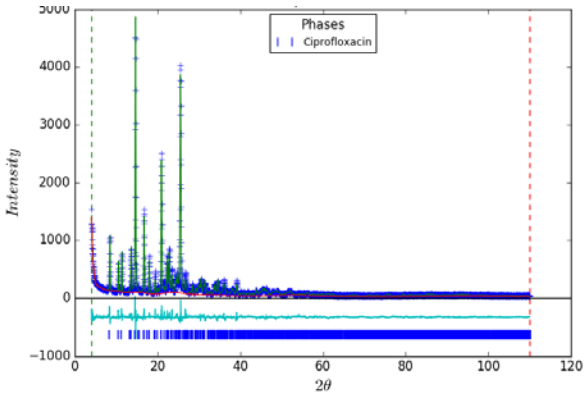


Figure 1. Rietveld refinement of CIP sample, wR = 0.09. Calculated background is plotted as red line.

Advanced quantitative phase analysis methods to support the industrial drug development process

Mathilde Reinle-Schmitt, Pamela Whitfield, Mickael Morin, Fabia Gozzo

Excelsus Structural Solutions Switzerland and Belgium

Over the last decade, the fast development of synchrotron sources and instrumentation has enabled a more systematic use of Synchrotron X-Ray Powder Diffraction (S-XRPD) to analyze solid forms at several stages of the industrial drug development process. A complementary tool to capable conventional instrumentation, S-XRPD enables issues to be addressed that are beyond the capabilities of laboratory XRPD instrumentation. Typical applications include quantification in complex mixtures and the detection of very low levels of crystalline impurities (<0.1%). The complexity of the instrumental setting, choice of data collection/analysis strategy and challenging beamtime access has traditionally limited the use of this technique to a small number of academic experts.

Bridging the gap between synchrotron specialists and pharmaceutical companies, Excelsus Structural Solutions (ESS) develops advanced S-XRPD data collection strategies tailored to solve problems related to drug discovery. This gives pharmaceutical companies the opportunity to add this very powerful technique to their analytical toolbox whilst respecting specific constraints linked to industrial R&D such as confidentiality, deadlines, validation and budget.

In order to fulfil at best complex characterization needs and demanding regulatory requirements to bring a drug to market, ESS has always centered its activities on advanced Quantitative Phase Analysis. In pharmaceutical development, the accurate control of drugs composition is indeed crucial, since any deviation from the expected formulation due for instance to unwanted recrystallization or conversion of the active pharmaceutical ingredient (API) can lead to dangerous side-effects for the patient. In this context, monitoring the evolution of small traces at the earliest stage of conversion is essential and in this talk, we will show how it was possible to push the level of detection of crystalline traces down to 0.01 wt%. In the recent years, novel amorphous dosage forms with improved solubility are increasingly developed by the pharmaceutical industry. Their lack of long-range order makes it more challenging to find suitable analysis techniques to address some of the key issues related to physical and chemical stability. In this context, ESS has recently developed its activities towards amorphous quantification. This talk will also highlight the latest results obtained by ESS team in the field of quantification of amorphous mixtures.

Mathilde Reinle-Schmitt did a PhD in Experimental Physics at the Swiss Light Source and University of Zurich during which she used a variety of synchrotron techniques (Surface X-Ray Diffraction, Angle-integrated and angle-resolved X-ray Photoelectron spectroscopy…) to study 2D electron systems at polar-oxide interfaces. After a postdoctoral appointment at the Swiss Light Source Materials Science beamline, she joined Excelsus Structural Solutions in 2016 where she is involved in the development of methods and measurement strategies mostly related to quantitative phase analysis and pair distribution function measurements of pharmaceuticals via synchrotron-radiation x-ray powder diffraction.

xINTERPDF: a GUI program for analyzing intermolecular pair distribution functions of organic compounds from X-ray total scattering data

Chenyang Shi

AbbVie Inc, USA.

Structures of organic compounds are more complex than their inorganic counterparts, which have usually a network structure, representing a giant "molecule". Organics, on the other hand, have strong intramolecular bonds but much weaker intermolecular interactions, making them prone to structural disorders. Another complexity comes from the weak X-ray scattering of light elements (C, H, O, N etc) which are the building blocks of organic compounds. The atomic pair distribution function (PDF) calculated from synchrotron X-ray total scattering has been demonstrated to be a valuable tool for investigating structures of disordered and amorphous organics compounds (Shi et al., 2017; Prill et al., 2015; Prill et al., 2016). Although existing tools such as DiffPy-CMI (Juhás et al., 2016) and XISF (Mou et al., 2015) can be used for solving this problem, a new software program is still of great value that provides a user-friendly graphical user interface (GUI, as opposed to command-driven in DiffPy-CMI) and analyzes the data in real-space (as opposed to reciprocal space in XISF). In my talk I will introduce xINTERPDF, a GUI program for analyzing intermolecular pair distribution functions in organic compounds from X-ray total scattering data. I will briefly discuss its design, distribution and application examples. The program is freely available at https://github.com/curieshicy/xINTERPDF.

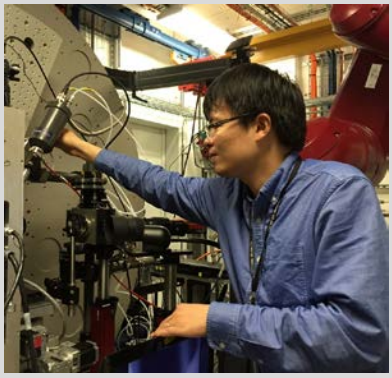
Shi, C., Teerakapibal, R., Yu, L. & Zhang, G. G. Z. (2017). IUCrJ 4, 555-559.

Prill, D., Juhás, P., Schmidt, M. U. & Billinge, S. J. L. (2015). J. Appl. Cryst. 48, 171-178.

Prill, D., Juhás, P., Billinge, S. J. L. & Schmidt, M. U. (2016). Acta Crystallogr. A 72, 62-72.

Juhás, P., Farrow, C. L., Yang, X., Knox, K. R. & Billinge, S. J. L. (2015). Acta Crystallogr. A 71, 562-568.

Mou, Q., Benmore, C. J. & Yarger J. L. (2015). J. Appl. Cryst. 48, 950-952.



Chenyang Shi did PhD study at Department of Applied Physics and Applied Math at Columbia University with Prof. Simon Billinge. His thesis investigates local structure and lattice dynamics study of low dimensional materials using atomic pair distribution function and high energy resolution inelastic x-ray scattering. After graduation, he joined AbbVie Inc as a Senior Scientist where he has been advancing synchrotron X-ray techniques (e.g. total scattering and fluorescence imaging) in pharmaceutical research. Outside work, he loves watching and playing soccer, and programming with Python.

Parts per Million PXRD through Nonlinear Optically Guided Analysis

Garth J. Simpson

Department of Chemistry, Purdue University, West Lafayette, USA

Second harmonic generation (SHG) imaging enables selective detection of trace quantities of chiral crystals, enabling targeted, localized synchrotron diffraction analysis. Matching the dimensions of the X-ray source to the ~5 micrometer dimensions of the crystalline domains greatly suppresses the diffuse background, enabling detection of crystallinity in the parts per million (ppm) regime with high signal to noise ratios (SNR > 1000). Under favorable conditions, localization of the diffraction analysis to individual single crystalline particles enables indexing for qualitative analysis. Applications using SHG-guided synchrotron PXRD for quantitative and qualitative analysis of pharmaceutical materials will be summarized and critically evaluated.

Prof. Simpson started working in the field of nonlinear optics >20 years ago, starting first through an unauthorized side project as a graduate student with Kathy Rowlen at the University of Colorado, Boulder from 1995-2000. Following a post-doctoral appointment with Dick Zare at Stanford torturing single cells with microelectrodes, he has been at Purdue since 2001. His group initially worked to develop a systematic molecular-based theoretical framework for describing and precisely measuring polarization-dependent phenomena in nonlinear optical analyses of chiral assemblies. More recently, this esoteric topic has (surprisingly) turned out to be potentially useful in the selective detection and analysis of chiral crystals using nonlinear optical imaging. Microscopes originally developed by the Simpson group are now routinely used for protein crystal detection in high throughput screening and for quantitative analysis of crystallinity within pharmaceutical formulations.

Monitoring phase transformations in formulations

Seema Thakral[1], Sampada Koranne[1], Ramprakash Govindarajan[2], Raj Suryanarayanan[1]

[1]*College of Pharmacy, University of Minnesota, Minneapolis, MN 55455*

[2]*College of Pharmacy, University of Iowa, Iowa City, IA 52242*

The disproportionation of pioglitazone hydrochloride in intact tablets was mapped by transmission-mode synchrotron X-ray diffractometry (SXRD; Argonne National Laboratories). Tablet mapping was performed in situ at the beamline using a custom-built temperature and humidity controlled setup. Presence of basic excipients (magnesium stearate or croscarmellose sodium) caused disproportionation, yielding the crystalline free base. The disproportionation reaction, influenced by sorbed water and microenvironmental acidity, was initiated at the tablet surface and progressed toward the core. The transformation was solution-mediated, and the spatial heterogeneity in disproportionation could be explained by the migration of sorbed water. SXRD also revealed spatial heterogeneity in mannitol phase composition in intact 'unperturbed' lyophilized cakes. When lyophilized alone, mannitol appeared to crystallize completely, predominantly as the delta anhydrous polymorph. On the other hand, a second non-crystallizing component influenced the crystallization behavior of mannitol and there was pronounced intra vial heterogeneity in mannitol phase composition. Vertical mapping of 'as is' lyophiles using SXRD revealed the formation of mannitol hemihydrate and spatial heterogeneity in its distribution across the depth of the lyophile. Such intra vial heterogeneity can have a pronounced "local" effect and hence serious implications on the stability of lyophilized formulations. Processing conditions for lyophilization (annealing at different temperatures) and formulation composition influenced the formation and distribution of mannitol hemihydrate in the final lyophile.

Raj Suryanarayanan (Sury) is Professor and William and Mildred Peters Endowed Chair in the College of Pharmacy, University of Minnesota. He obtained his B.Pharm. and M.Pharm. degrees from Banaras Hindu University, India and M.Sc. and Ph.D. degrees in Pharmaceutics from the University of British Columbia, Vancouver, Canada. The overall goal of his research is to apply principles of pharmaceutical materials science to the design of robust pharmaceutical dosage forms with reproducible and predictable properties. His research group has developed low temperature powder X-ray diffractometric techniques to study frozen and freeze-dried pharmaceutical systems. He is a consultant to numerous pharmaceutical companies and was a member of the USP Expert Committee (Excipients test methods). He is a fellow of the American Association of Pharmaceutical Scientists (AAPS) and is a past chair of the Teachers of Pharmaceutics Section of the American Association of Colleges of Pharmacy. Sury is a member of the Academy of Distinguished Teachers at the University of Minnesota, is the recipient from AAPS of the Outstanding Educator Award and the David Grant Research Achievement Award in Physical Pharmacy and the PhRMA (Pharmaceutical Research and Manufacturers of

America) Foundation Award. He is an Associate Editor of *Molecular Pharmaceutics*.

Probing crystallization of drugs using synchrotron radiation

Lynne S. Taylor

Department of Industrial and Physical Pharmacy, Purdue University, USA

Many emerging drug candidates exhibit low aqueous solubility. Consequently, formulations that promote the generation of supersaturated solutions in vivo following dissolution are of interest to enhance oral drug delivery. Drug crystallization kinetics are essential to the success or failure of this strategy. Both crystallization in the solid formulation, and from the solution generated upon dissolution, are of importance. Herein, we describe our studies using synchrotron radiation to monitor the kinetics of crystallization from highly supersaturated solutions, demonstrating that different drugs have vastly different tendencies to crystallize from aqueous solution. We discuss the impact of polymeric crystallization inhibitors. Finally, the challenge of monitoring crystalllization in a low dose commercial formulation that consists mainly of excipients is highlighted.

Lynne S. Taylor is the Retter Professor of Pharmacy in the Department of Industrial and Physical Pharmacy and a Professor of Chemical Engineering (by courtesy) at Purdue University. Prior to moving to academia, she spent several years working at Astra and then AstraZeneca in Sweden developing new drugs. Lynne received a Bachelor of Pharmacy degree with First Class Honors from the University of Bath in the United Kingdom. Her doctoral thesis work at the University of Bradford, UK, was in the area of Pharmaceutical Technology. In between her degrees, she spent some time working in pharmacy in both the UK and Zimbabwe. After her PhD, Lynne was a postdoctoral researcher with Professor Zografi at the School of Pharmacy, University of Wisconsin-Madison. Research in Lynne's group is directed toward exploring the science underlying the preformulation, formulation and manufacturing of drugs and other bioactive substances, in particular poorly water soluble compounds. She has published more than 250 peer reviewed articles.

Compression induced phase transformation: A formulator's perspective

Naveen K. Thakral[1,2], Seema Thakral[1], Raj Suryanarayanan[1]

1. *Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455.*
2. *Upsher Smith Laoratories LLC., Maple Grove, Minnesota 55369.*

Compression induced polymorphic transformation has been reported for a number of drugs1. Crystallization of the amorphous indomethacin, during compression has also been reported2. When a powder bed is compressed in die cavity, it is subjected to a combination of hydrostatic and shear stress. In present research, our goals were to evaluate the effects of (i) hydrostatic pressure alone and (ii) the combined effects of pressure and shear stress during compaction, on the polymorphic transformation. Our model drug was anhydrous chlorpropmide, which can exist in stable form A and metastable form C. The lines with d-spacings of 5.89 and 7.49 Å are unique to forms C and A respectively, and the extent of transformation (form C →A) was based on the integrated intensities of these lines. No polymorphic transformation of form C →A was observed only when the powder (form C) was subjected to a hydrostatic pressure of 25 MPa. But at higher pressures of 50, 100 and 150 MPa, the extent of transformation increased progressively with pressure. Form C was compacted (uniaxial) to the same pressures, in a universal material testing machine (Zwick), the tablets were powdered and subjected to XRD. At all the pressures, the extent of transformation observed following compaction was much higher than that observed when subjected to hydrostatic pressure alone. This difference in polymorphic transformation may be attributed to the additional contribution of shear stress, experienced during compaction. The spatial distribution of phase transformation (in the radial direction), in compressed tablets, was monitored using a microdiffractometer system (Bruker D8 Discover 2D; CoKα radiation) with a two-dimensional area detector. Following compression at 25 MPa, there was a pronounced gradient in the extent of phase transformation when monitored from the radial surface to the core. This gradient decreased with increase in compression pressure. Formulation strategies to reduce the extent of transformation have been discussed.

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2. Thakral, Naveen K., et al. "Compression-induced crystallization of amorphous indomethacin in tablets-characterization of spatial heterogeneity by two-dimensional X-ray diffractometry." *Molecular pharmaceutics* (2014).

Naveen Thakral is pharmaceutical scientist with 24 year experience in the manufacturing, material characterization, pre-formulation and formulation development.
In pharmaceutical material characterization he developed a method to analyze the intact dosage form, for studying *in situ* phase transformation, using 2D-XRD at University of Minnesota.
He uses XRD as main tool for the study of drug-excipient compatibility studies, solid state characterization of amorphous dispersions, polymorphs & salts screening etc. His research has been published in number of reputed journals.

He is presently working as Senior Scientist with Upsher-Smith, a subsidiary of Sawai Pharmaceuticals, a Japanese Generic Company.

X-ray Powder Diffraction Facilities Available at the Advanced Photon Source

Brian Toby & Robert Von Dreele

Advanced Photon Source, Argonne National Laboratory

toby@anl.gov, vondreele@anl.gov

The facilities at the APS for powder diffraction includes the very high resolution 12-crystal analyzer/detector diffractometer (11-BM-B) which operates at medium energy (20-33keV) and a high throughput 2D imaging detector instrument (17-BM-B) that operates also at somewhat higher energy (27-51keV). Canonical measurement times on 11-BM are circa 1 hour/scan, while 17-BM can collect a dataset in seconds. The APS also has other diffraction beamlines optimized for PDF measurements, surface scattering, small-angle scattering and engineering studies. 11-BM operates ~50% of the time via a mail-in system that allows rapid turnaround (2-6 weeks) producing data often suitable for structure solution and Rietveld refinement for complex materials, with the balance used for on-site users. The 17-BM instrument, coupled with Argonne's data processing/analysis software (GSAS-II) allows tracking of experiments in real time with both powder patterns and pair distribution function (PDF) data produced from image integrations done as in situ experimental or operando conditions (temperature, gas atmosphere, humidity, etc.) are varied. The GSAS-II software package is a fully developed, open source, crystallographic data analysis system written almost entirely in Python. For powder diffraction, it encompasses the entire data analysis process beginning with 2D image integration, peak selection, fitting and indexing, followed by intensity extraction, structure solution and ultimately Rietveld refinement, all driven by an intuitive graphical interface. Significant functionality of GSAS-II also can be scripted to allow it to be integrated into workflows or other software. This talk will cover these capabilities with some examples.

Brian Toby is a Senior Physicist, the group leader for Computational X-ray Science and the Chief Computational Scientist within the Advanced Photon Source of Argonne National Laboratory. Previously he led the Materials Characterization Group, where he led the construction of the 11-BM robot-enabled powder diffractometer, now the most productive beamline at the APS, and designed and implemented its mail-in access system.

Brian has an undergraduate degree from Rutgers University and a Ph.D. from Caltech, both in Chemistry. Over the past three decades he has worked in powder diffraction crystallography, with employment in one academic lab, two industrial labs and two government labs, primarily working with synchrotron and neutron instrumentation. He is a Fellow of the International Centre for Diffraction Data and of the American Crystallographic Association. He has served as vice-chair and chair of the US National Committee for Crystallography for the National Academy of Science. His research interests include structure refinement determination techniques, informatics for powder diffraction and crystallographic studies of metal oxides and zeolitic materials. He has coauthored

over 130 refereed papers with a total of >10,000 citations (h-index 39).

He has written several popular crystallographic software packages, CMPR, CIFTOOLS (pdCIFplot) and EXPGUI and is also the principle author of the powder diffraction implementation of the crystallographic information file, pdCIF. In 1989 he developed, with Takeshi Egami, the first code to fit local structure in real-space for crystalline materials using pair-distribution functions. In 2005, he received a Bronze Medal from the U.S. Department of Commerce for his software work. In 2006, Brian and Jim Kaduk launched a new section within the journal Powder Diffraction, dedicated to crystallographic instruction and in 2011 joined Robert Von Dreele in the creation of a new universal crystallographic computation package, GSAS-II. In 2015 was the 16th recipient of the Barrett Award from the Denver X-ray Conference

Dr. Von Dreele was born December 10, 1943 and grew up in northern Delaware. In 1966 he graduated with a BS degree in Chemical Engineering from Cornell University and then entered the PhD program in Chemistry at Cornell where he received his degree in 1971 with a specialization in inorganic chemistry and an interest in crystallography. He immediately joined the faculty in the Chemistry Department at Arizona State University teaching mostly introductory chemistry to freshmen and pursuing research in crystallography. In 1972-3, while on leave, he was a National Science Foundation postdoctoral fellow at the Inorganic Chemistry Laboratory at Oxford University where he began his pursuit of powder diffraction crystallography, an endeavor he continues to this day. He attained the rank of Full Professor in 1981.

In 1986 he decided to pursue his main interests in neutron scattering and joined Los Alamos National Laboratory, New Mexico, as a Scientific Staff member at the LANSCE spallation neutron source located at that facility where he was the Instrument Scientist responsible for two of the neutron powder diffractometers. During this time he was a Fulbright Fellow at the ISIS neutron scattering facility, Rutherford-Appleton Laboratory in Chilton, England (1986), received a Los Alamos National Laboratory Distinguished Performance Award (1998) for his work in protein powder diffraction, presented the 5th Joseph Morgan Lecture at Texas Christian University in 2000, and was made a Fellow of the Mineralogical Society of America in 2001.

In 2003 he left Los Alamos and joined Argonne National Laboratory as a Senior Physicist with a joint appointment between the Intense Pulsed Neutron Source and the Advanced Photon Source Argonne. In early 2008 the former facility was closed down and he is now full time at the APS. In 2007 he was elected Vice-President of the

American Crystallographic Association and served as President in 2009. He was a member of the US National Committee for Crystallography 2006-2009. He received the Barrett Award at the 58th Annual Denver X-ray Conference.

Since 1985, Dr. Von Dreele has continued development of the widely used software, General Structure Analysis System (GSAS), for analysis of both neutron and x-ray powder diffraction data; this package has been cited more than 7000 times in the scientific literature. He is the author of some 150 publications which includes the 1st protein structure solved from x-ray powder diffraction data. Most recently he has been developing GSAS-II, a replacement for the GSAS software using a modern computer language with a fully integrated graphical user interface, display graphics and computational analysis system for diffraction data.

His main research interests are the development of x-ray and neutron powder diffraction and its application to a wide variety of scientific problems. This has included the initial development of a practical application of the Rietveld method to neutron time-of-flight (TOF) powder diffraction data, development of in situ neutron TOF powder diffraction at high pressure, development of high precision texture analysis with neutron TOF powder data, and most recently the first application of high resolution x-ray powder diffraction to protein crystal structure problems. Current research is in further extensions of protein powder diffraction including investigation of crystal growth, phase transformations, radiation damage and exploring possible routes to de novo protein structure determination from powder data.

Using Containerless Methods to Synthesize and Characterize Amorphous Pharmaceuticals

Richard Weber

Materials Development, Inc. and Argonne National Laboratory

This talk will focus on the application of non-contact (containerless) methods, such as acoustic levitation, to access metastable and amorphous forms of organic compounds. The complete absence of extrinsic nucleation sites in containerless conditions enables deep supercooling and/or extreme supersaturation to be achieved for a wide variety of compositions. The ability to extend the glass forming range in metal oxides by using containerless methods is well established; a similar capability to make amorphous and non-equilibrium forms of organic compounds is a relatively recent innovation. The presentation will be illustrated with details of instruments, examples of using containleress methods to synthesize new materials and to make in-situ measurements on materials during processing. The potential for using the tools to investigate and characterize large scale processing methods such as spray drying will be outlined. Ongoing experiments and plans for expansion of the current capabilities will be described and discussed in the context of developing pipeline drugs that require delivery in special dosage forms.

Richard Weber founded Materials Development, Inc. (MDI) in 2006 and he is the company president. MDI develops and sells innovative instruments for processing materials in extreme environments and uses them for R&D on materials. Current research and collaborations include measurements of the atomic structure of molten nuclear fuels, development of a combined SAXS/WAXS instrument, microgravity measurements of melt properties and development of amorphous pharmaceuticals. Prior to forming MDI, Weber was VP for Research at Containerless Research, Inc. a company that he co-founded and where he led the team that developed REAl(TM) Glass. The glass technology was sold to a fortune 50 company in 2006. In addition to operating MDI, Weber is an Argonne Associate at DOE's Advanced Photon Source where he collaborates to develop beamline experiments to measure the structure of materials in extreme conditions. He earned a BSc first class in Metallurgy from Sir John Cass College in 1983 and a PhD and DIC from the Department of Materials, Imperial College London in 1986. He became a Chartered Engineer in 1990. He regularly presents at conferences and has authored/co-authored about 160 papers and 5 patents.

Current Treatment of Crystalline Forms Under US and EP Patent Law

David Weingarten, Ph.D.

Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Atlanta, USA

Patent law pertaining to prosecution and litigation of patents claiming crystalline forms continues to develop in view of scientific advances in the ability to detect, analyze, characterize, and distinguish crystalline forms. General principles of patent law particularly relevant to claims to crystalline forms in each of the United States and Europe will be discussed, followed by a focused discussion of the current treatment of such claims by courts and patent offices in each of the United States and Europe. Scientific concepts and technical information deemed useful under current patent laws for showing patentability and validity of claims to crystalline forms will be reviewed. Case studies and examples based on publically available patents, prosecution histories of patent applications, and documents from litigations will be used throughout to highlight issues, considerations, and potential strategies and pitfalls under current patent laws for protecting crystalline forms.

David Weingarten, Ph.D., has a diverse intellectual property practice focusing on patent litigation before U.S. district courts and the U.S. International Trade Commission (ITC), post-grant trial proceedings at the U.S. Patent and Trademark Office (USPTO), prosecution, and strategic portfolio management. His practice encompasses the chemical, pharmaceutical, biotechnology, and consumer product areas.

David's practice focuses on U.S. district court litigation, primarily concerning Abbreviated New Drug Applications (ANDA) under the Hatch-Waxman Act, and Section 337 proceedings before the ITC. He also drafts opinions on patent infringement, validity, and enforceability, and prepares intellectual property agreements, such as those relating to license and supply. In addition, David prepares and prosecutes U.S. patent applications on behalf of domestic and foreign clients.

David has experience with strategic management of worldwide patent portfolio for a clinical-stage biotechnology company developing treatments for pseudomonas, cardiovascular, inflammatory, cancer, and sickle cell diseases. Additionally, as part of Finnegan's pro bono program, he has successfully represented several disabled veterans in proceedings before the U.S. Court of Appeals for Veterans' Claims.

Prior to practicing law, David spent more than a decade in the pharmaceutical industry developing drugs across a wide range of therapeutic areas, including cardiovascular, metabolic, respiratory, and inflammation. As a member of senior management, he was responsible for leading research and development efforts in drug discovery, process research and development, and manufacturing. He also prepared New Drug Application (NDA) submissions,

conducted due diligence, and managed technology transfers.

During his doctoral studies, David investigated the rhodium(II)-catalyzed reaction of α-diazo ketones and its application toward organic synthesis. As a National Institutes of Health post-doctoral fellow at Columbia University, he designed and developed new combinatorial methods for determining enantioselective chemical processes and implemented molecular modeling to analyze complex experimental results.

While at Emory University School of Law, David was awarded first place, Emory University School of Law Transactional Negotiation Meet; was a Robert W. Woodruff Fellow; a Dean's teaching Fellow; and received awards for outstanding academic achievement in contract drafting, negotiations, deal skills, and patents and global health. David completed TI:GER®program in Intellectual Property and Technology Transfer, Emory University School of Law and Georgia Institute of Technology. He was an Achievement Rewards for College Scientists (ARCS) scholar and an American Chemical Society, Organic Division graduate fellow at Emory University.

PDF analysis of organic and molecular systems – quirks and peculiarities

Pamela Whitfield

Excelsus Structural Solutions Switzerland

Organic and molecular systems present some additional challenges over the traditional samples subjected to PDF and total scattering analysis. Their poor scattering power compared to the heavier elements constrains their signal to background and increases the importance of properly subtracting the signal from the empty container and air scattering over say a CdSe nanomaterial. Commonly, anharmonic behaviour in molecular systems lead to a discontinuity between intra- and intermolecular thermal parameters which must be considered in the important overlap region where both intra- and intermolecular interactions are visible in the PDF. There is usually little diversity in the elements present in organic materials, most commonly C, H, N and O, so many organic PDFs look quite similar, especially as PDF can't properly resolve the differing C-C bond lengths that can exist. The high hydrogen content of most sample can make neutron PDF measurements problematic due to wavelength-dependent incoherent scattering and significant absorption, but where feasible the negative scattering length of 1H can be useful in better localizing hydrogen within the structure. One point in the favour of organic materials however is that their molecular connectivity is usually well known which often places some limits on the expected PDF from single molecule. Although smaller molecules can be relatively rigid, rotational torsions from single bonds can drastically change longer-range atom-atom interactions. Such torsions can be modelled using techniques borrowed from conventional diffraction analysis with minimal additional parameters, vital with a form of data which is by definition information-poor.

Dr Whitfield has over 25 years of practical experience with powder diffraction using both X-rays (laboratory and synchrotron) and neutrons (constant wavelength and time-of-flight). She developed and managed the largest XRPD facility at the National Research Council Canada, supporting government, academic and industrial groups across Canada, developing custom sample environments and new analytical methodologies with samples ranging from battery materials and cements, to polymers and organic systems. Latterly she was an instrument scientist on the POWGEN time-of-flight neutron powder diffractometer at Spallation Neutron Source in the USA, helping develop new data collection and analysis techniques as well as custom sample environments.

Dr Whitfield is known internationally as an expert in powder diffraction techniques and instrumentation and a beta-tester of the TOPAS software since 2000. She has served on numerous national and international bodies, including 9 years as chair of the IUCr Commission on Powder Diffraction, vice-chair of the Canadian National Committee for Crystallography, chair of the Synchrotron and Neutron Scattering Techniques sub-committee of the ICDD and is presently serving on the European Powder Diffraction Conference committee. She is a frequent instructor at schools and workshops, and regularly invited to present at international meetings. In March

	2018 she was made a Fellow of the International Centre for Diffraction Data.

Polyamorphism of D-mannitol: Structural studies by Synchrotron X-ray diffraction

Chengbin Huang,[4] Men Zhu,[1] Chris J. Benmore,[2] Chenyang Shi,[3] Geoff G. Z. Zhang,[3] and Lian Yu[1,4]*

[1]*Department of Chemistry, University of Wisconsin-Madison, Madison, WI 53706*

[2]*X-ray Science Division, Advanced Photon Source, Argonne National Laboratory, IL 60439*

[3]*Drug product development, AbbVie, North Chicago, IL, 60044*

[4]*School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53705*

E-mail: lian.yu@wisc.edu

We report recent progress in determining the structures of the two amorphous phases of D-mannitol. Polymorphism is common in crystals but rare and even controversial in liquids or glasses. The polyalcohol D-mannitol has a low-density amorphous phase (LDA) and a high-density amorphous phase (HDA). The HDA is obtained by cooling the normal liquid, and the LDA by spontaneous transformation just above the glass transition temperature. The LDA has lower energy, larger volume (2.1%), and stronger hydrogen bonds. This transition is similar to water's HDA to LDA transition with the same anomaly of heat release coupled with volume expansion. In both systems, polyamorphism arises from the competing demands of hydrogen bonds (loose packing) and van der Waals forces (close packing). Total X-ray scattering has provided accurate structural details for changes in the second and third molecular neighbors and these are interpreted with the aid of reverse Monte Carlo simulations. D-mannitol is expected to play an important in understanding polyamorphism and suggests a general occurrence of the phenomenon in hydrogen-bonded systems.

Zhu, M.; Yu, L. Polyamorphism of D-manntitol. *J. Chem. Phys.* **2017**, 146, 244503.

Lian Yu is a Professor of Pharmaceutical Sciences and Professor of Chemistry at the University of Wisconsin-Madison. He received a B.S. in chemistry from Peking University and a Ph.D. in physical chemistry from The Ohio State University. Before joining UW-Madison, he worked for Eli Lilly. His laboratory studies crystallization, polymorphism, glasses, and amorphous solids. His honors include Fellow of the American Association of Pharmaceutical Scientists (AAPS), Lilly Research Laboratories President's Award, Invited Visiting Professorship at University of Manchester and Tsinghua University, and AAPS David Grant Research Achievement Award in Physical Pharmacy.