PPXRD-16 & SPS-XRPD-2 JOINT MEETING

THE 16TH PHARMACEUTICAL POWDER X-RAY DIFFRACTION SYMPOSIUM AND THE
2ND SPRING PHARMACEUTICAL SYNCHROTRON X-RAY POWDER DIFFRACTION WORKSHOP

PPXRD-16
Pharmaceutical Powder
X-ray Diffraction Symposium

SPS-XRPD-2 WORKSHOP

PROGRAM AND ABSTRACTS

Photo by PSI

9-12 May 2019

Paul Scherrer Institute, Switzerland

ICDD
International Centre for Diffraction Data

Excelsus Structural Solutions

PAUL SCHERRER INSTITUT
PSI

SWITZERLAND INNOVATION
PARK INNOVAARE

Sponsored by ICDD and Excelsus Structural Solutions in cooperation with the Paul Scherrer Institute and Park Innovaare

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Local Organizers for PPXRD-16 & SPS-XRPD-2

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Social Events and Posters

Symposium Reception

A Welcoming Reception will be held on Thursday evening, 9 May, from 6:00 – 7:30 pm, immediately following the Opening Plenary: Industry Speaks to Academia. The reception will be held either outside the PSI Auditorium or at the Terrace of Park Innovaare (weather permitting). An announcement will be made at the Plenary session regarding the location of the reception.

Conference Dinner

A conference dinner will be held on Friday evening, 7:30 pm, at the ODEON Brugg. All registered attendees who completed their attendee profile form and signed up to attend the dinner will receive a ticket to enter the dinner. ODEON Brugg is next to the Terminus Hotel, directly opposite of the Brugg railway station, and in the immediate vicinity of a paid 24-hour parking garage.

Posters

Posters can be set on Thursday evening, 9 May or Friday morning, 10 May. Poster boards will be set directly outside the PSI Auditorium. All posters should be set by the first coffee break on Friday morning at 10:30 am.

Posters can remain on display up until Sunday, 12 May. Please remove your poster no later than the afternoon coffee break at 2:30 pm on Sunday, 12 May. Please note, ICDD is not responsible for any posters left by the author(s). Posters can be fastened to the board with push pins. No glue or tape is allowed.

Flash Poster Session:

A flash poster session is scheduled for Saturday morning, 11 May from 9:00 - 10:00 am. Poster presenters will address attendees with a short presentation summarizing the content of their poster.

Poster Viewing:

Attendees may view posters throughout the symposiuåm during coffee breaks, and lunch times. The posters will be set directly outside the PSI Auditorium.

Exhibitor Information

Exhibition

Exhibits are located outside the PSI Auditorium from Friday morning, 10 May until Sunday, 12 May. Please visit with our exhibitors during coffee breaks and lunches. Exhibits will close at 3:00 pm on Sunday, 12 May.

Exhibiting Companies

Avant-garde Materials Simulation GmbH

www.avmatsim.eu

Representative: *Kiran Sasikumar, kiran.sasikumar@avmatsim.eu*

Avant-garde Materials Simulation GmbH - Since 2002, Avant-garde Materials Simulation have been developing the software GRACE for crystal structure prediction of large, flexible organic compounds, including their salts, zwitterions, hydrates, solvates and co-crystals. GRACE is used by the pharmaceutical industry to identify possible Ritonavir cases before they occur. New in 2019 will be the capability to predict the equilibria of different hydration states (anhydrate, hemihydrate, monohydrate, etc.) as a function of temperature and relative humidity, and the capability to calculate temperature-dependent relative free energies with an accuracy better than 0.5 kcal/mol.

Bruker AXS

www.bruker.com

Representative: *Arnt Kern, arnt.kern@bruker.com*

Bruker AXS is a leading global developer and manufacturer of analytical X-ray systems for structure research, materials research and elemental analysis. Our innovative solutions enable a wide range of users in academia and industry - including chemistry, life sciences, nanotechnology, pharmaceuticals, metals and steel, semiconductor, cement, minerals, and many others - to make technological advancements and accelerate their progress. Our solutions are essential for gaining the detailed insight into the relationship between structure, function, and reactivity, which is crucial today for the success of modern science. We provide world-class instrumentation delivering answers to your analytical questions, all the way from the research laboratory or the exploration field to the production floor.

DECTRIS Ltd.

www.dectris.com

Representative: *Dubravka Šišak Jung, dubravka.sisak@dectris.com*

DECTRIS Ltd. - MYTHEN2 microstrip detectors allow you to reach the optimum of your x-ray diffraction and scattering data. Featuring the narrowest strip currently available on the market, MYTHEN2 detectors provide you with the maximal data resolution. This combined with the noise-free performance and extremely high dynamic range allows you to reliably detect trace impurities, solve crystal structures and determine crystallite size of your sample. The wide portfolio of the MYTHEN2 detectors contains optimal solutions for a variety of experimental setups. You can now advance your high-throughput measurements carried out with diverse X-ray energies using weak or bright sources. Radiation hardness and maintenance-free operation make MYTHEN2 detectors the perfect choice for research and industrial sites employing Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) rules.

International Centre for Diffraction Data

www.icdd.com

Representative: *Amy Gindhart, gindhart@icdd.com*

ICDD - ICDD and MDI focus on the needs of the materials characterization scientific community by providing the Powder Diffraction File™ (PDF®) and JADE analysis software. PDF Release 2019 has over 893,000 unique entries for phase identification and JADE Pro software provides the best in X-ray powder diffraction data analysis. For the pharmaceutical market, ICDD offers the PDF-4/Organics database for materials identification of organics and organometallics. PDF-4/Organics 2019 contains over 535,000 entries including 115,520 entries with atomic coordinates. It is a highly targeted collection with a special focus on materials used in commercial and regulatory fields. PDF-4/Organics is the world's largest collection of pharmaceuticals, excipients, and polymers.

Malvern Panalytical B.V.

www.malvernpanalytical.com

Representative: *Maria Orlova, maria.orlova@malvernpanalytical.com*

Malvern Panalytical B.V. - We create superior, customer-focused solutions and services which deliver tangible economic impact through chemical, physical and structural analysis of materials. Underpinned by extensive industry knowledge and technical and applications expertise, Malvern Panalytical instruments help users better understand a wide variety of materials, from proteins and polymers to metals and building materials. Our technologies are used by scientists and engineers in a wide range of industries and organizations to solve the challenges associated with maximizing productivity, developing better quality products and getting them to market faster.

Rigaku Europe SE

www.rigaku.com

Representative: *Uwe Preckwinkel, uwe.preckwinkel@rigaku.com*

Rigaku Europe SE - Rigaku has been at the forefront of X-ray instrumentation since the 1950s, and is a world leader in the fields of general X-ray diffraction (XRD) and X-ray fluorescence spectrometry (EDXRF and WDXRF). Rigaku can provide the unique XRD system for pharmaceutical research. XRD-DSC attachment offers the simultaneous measurement of XRD and DSC, which enables understanding of phase transition behavior. Johansson Kα1 unit enables crystal structure determination from high resolution powder data.

Thursday Program, 9 May 2019

PSI Auditorium

Laboratory and Synchrotron XRPD – Advantages and Disadvantages
Instructors: **Phil Willmott,** Paul Scherrer Institute and University of Zurich, Switzerland; **Tom Blanton,** ICDD, USA; **Fabia Gozzo,** Excelsus Structural Solutions, Switzerland and Belgium; **Pamela Smith,** Improved Pharma, USA

8:30 **Phil Willmott:** "Synchrotron Radiation and SR based techniques"

- General introduction to synchrotron radiation
- Interaction of X-rays with matter, in particular at synchrotron sources
- Overview of techniques that exploit synchrotron radiation for the characterization of matter

9:45 Coffee Break

10:00 **Tom Blanton:** "Laboratory X-ray Powder Diffraction and the Power of Crystallographic Database"

- General introduction to lab-XRPD technique
- Advantages of lab-XRPD for the pharma industry (user-friendliness, GMP certification) and limits
- The power of crystallographic database and overview

11:00 **Fabia Gozzo:** "Synchrotron X-ray Powder Diffraction and Applications to Pharmaceuticals"

- General introduction to Synchrotron-XRPD
- Advantages and disadvantages for applications to pharmaceuticals
- Enhanced Level of Detection (LOD) and Level of Quantification (LOQ)

11:45 **Pamela Smith**: "Pair Distribution Function and Applications to Pharmaceuticals"

- General introduction to Pair Distribution Function (PDF)
- PDF applied to pharmaceuticals

12:30 Lunch

PPXRD-16 & SPS-XRPD-2 Tours of PSI Large Scale Facilities

1:30 Attendees visit PSI Large Scale Facilities, in accordance with their selected tour preference from the "Attendee Profile Form".

4:00 Coffee Break

Opening Plenary "Industry Speaks to Academia" & Reception
Chairs: **Fabia Gozzo,** Excelsus Structural Solutions, Switzerland and Belgium; **Tom Blanton,** ICDD, USA; **Pamela Smith,** Improved Pharma, USA

4:30 Welcome to our Attendees

5:00 Opening Plenary: Industry Speaks to Academia
Invited presentation by **Arnaud Grandeury,** Novartis Pharma, Switzerland

6:00 Welcoming Reception: Please join us after the Plenary for light refreshments and cocktails. The reception will end at 7:30 pm.

Friday Sessions, 10 May 2019

PSI Auditorium ****Signifies presenting author***

Plenary Session "Intellectual Property Rights, Counterfeit Drugs"
Dedicated to the Memory of Prof. Joel Bernstein (1941-2019)
Chair: **Steve Byrn,** Purdue University, USA

8:30	P25	Invited - Patenting Solid Forms: A Review of US Case Law Involving Dr. Joel Bernstein **Jill MacAlpine,** Finnegan, USA	Pg 9
9:10	P26	Invited - Facts and Fictions about Polymorphism: Personal Recollections of our Good Friend, Joel Bernstein **Susan M. Reutzel-Edens,** Eli Lilly and Company, USA	Pg 10
9:50	P24	Invited - Solid Form Patents in Pharmaceutical Development **Eyal Barash,** Barash Law LLC, USA	Pg 11
10:30		Coffee Break	

API Phase Stability
Chair: **Tom Blanton,** ICDD, USA

11:00	P37	Invited – Role of Physical Form of the Active Pharmaceutical Ingredient (API) and Excipients **Raj Suryanarayanan,** University of Minnesota, USA	Pg 12
11:40	P5	High-Throughput Quantum Molecular Dynamics Constrained by Electron Diffraction Aimed at the Prediction of Amorphous Solid Dispersion Stability **Georgios Antipas,** Molecular Modelling Laboratory (MML), Switzerland	Pg 13
12:10		Lunch	

Qualitative & Quantitative Phase Analysis
Chair: **Detlef Beckers,** Malvern Panalytical, The Netherlands

1:15	P11	Invited - The Direct Derivation (DD) Method for Quantitative Phase Analysis: A Practical Approach with the Direct-fitting of Observed Diffraction Patterns **Hideo Toraya,** Rigaku Corporation, Japan	Pg 14
1:55	P8	Method Validation for Quantitative Determination of the (Pseudo) Polymorphs Ratio in DS and DP Samples: Performance and Compliance **Matteo Daldosso*, Silvia Lenzini, Brigida Allieri,** Aptuit, an Evotec Company, Italy **Sarah Le Meur, Michel Wagneur, Luc Aerts,** UCB Pharma, Belgium	Pg 15
2:25	P10	Using Portable X-ray Diffraction (XRD) with Pseudo-Thin-Film Type Analysis for API Verification and Counterfeit Formulation Investigations **Jose Brum,** Olympus OSSA, USA	Pg 16
2:55		Coffee Break	

Synchrotron XRPD Beamlines Overview
Chairs: **Fabia Gozzo,** Excelsus Structural Solutions, Switzerland and Belgium; **Chris Benmore,** APS, USA

3:30	P28	Invited - Overview of Synchrotron X-ray Powder Diffraction: Instruments and Case Studies **Peter Stephens,** Stony Brook University, USA	Pg 17
4:10	P36	Industrial Collaboration: How to make it happen at the Swiss Light Source? **Stefan Mueller,** Paul Scherrer Institute, Switzerland	Pg 18
4:30	P39	Invited - Time and Matter: The Material Science Beamline at the SLS **Nicola Casati,** Paul Scherrer Institute, Switzerland	Pg 19
5:10	P35	ID22 High Resolution Powder Diffraction Beamline at ESRF **Andy Fitch,** ESRF, France	Pg 20

Case Studies

Chair: **Mickael Morin,** Excelsus Structural Solutions, Switzerland

The Case Studies session will run from 5:40 pm – 6:15 pm, followed by the Conference Dinner at 7:30 pm. The Conference Dinner will be held at the restaurant, Brugg ODEON, which is next to the Hotel Terminus Brugg, and in front of the Brugg railway station.

Saturday, 11 May 2019

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Flash Poster Session

Chair: **Barbara Ramirez,** UNAM Mexico (visiting postdoc Excelsus & Swiss Light Source)

The following posters will be displayed permanently in the auditorium hall, available for viewing during coffee breaks and lunches.

9:00	P15	Humidity Effects on Amorphous Pharmaceuticals **Chris J. Benmore*,** Argonne National Laboratory, USA **P. Smith, S.R. Byrn,** Improved Pharma, USA **J.K.R. Weber,** Argonne National Laboratory and Materials Development, Inc., USA	Pg 21
9:08	P18	Quantification of Multiple Amorphous and Crystalline Phases **Maria Orlova*,** Malvern Panalytical B.V., Switzerland **Detlef Beckers, Thomas Degen,** Malvern Panalytical B.V., The Netherlands	Pg 22
9:16	P22	Computed Tomography Analysis for Process Development and Quality Control of Formulations **Detlef Beckers*, Natalia Dadivanyan, Detlev J. Götz,** Malvern Panalytical B.V.,	Pg 23
9:24	P23	Atomic Pair Distribution Function (PDF) and X-ray Scattering Methods to Assess Amorphous Organic Compounds **Detlef Beckers*, Milen Gateshki,** Malvern Panalytical B.V., The Netherlands	Pg 24
9:32	P27	Use of "Cleaning" Algorithm for Model-Free Correction of Instrumental Aberrations in XRPD Patterns **Vladimir Kogan*,** Dannalab, The Netherlands **Detlef Beckers, Alexander Kharchenko,** Malvern Panalytical B.V., The Netherlands	Pg 25
9:40	P31	Total Pattern Analyses of Pharmaceutical Formulations **Timothy G. Fawcett, Stacy Gates-Rector, Megan Rost, Amy M. Gindhart, Tom N. Blanton*, Suri N. Kabekkodu,** ICDD, USA	Pg 26
9:48	P34	Attempts and Approximations for a Background Modeling in Pharmaceutical Samples in Patterns of XRD and S-XRPD **Bárbara A. Ramírez Almaguer*, Lauro Bucio,** Universidad Nacional Autónoma de México, México **Mathilde Reinle-Schmitt,** Excelsus Structural Solutions, Switzerland **Antonio Cervellino,** Paul Scherrer Institute, Switzerland	Pg 27
9:56	Coffee Break		

Amorphous, Mesomorphous, Nano Materials

Chairs: **Shawn Yin,** Bristol-Myers Squibb Company, USA; **Steve Byrn,** Purdue University, USA

10:30	P20	Invited–Magnifying Nano-/Meso- Structural Information of Amorphous Pharmaceutical Solids through Small Angle X-ray Scattering **Amrit Paudel*, Peter Laggner,** Graz University of Technology and Research Center Pharmaceutical Engineering GmbH (RCPE), Austria	Pg 28
11:10	P14	Invited–SAXS-WAXS Studies of Amorphous, Mesoporous and Nanomaterials **Chris J. Benmore*, D. Robinson, G. Jennings, J. Ilavsky, S. Shastri,** Argonne National Laboratory, USA **O.L.G. Alderman, A. Tamalonis, E. Clark,** Materials Development Inc., USA **E. Soignard, J.L. Yarger,** Arizona State University, USA **J.K.R. Weber,** Argonne National Laboratory and Materials Development, Inc., USA	Pg 29
11:50	P40	Invited–Understanding the Disordered State of Matter in Pharmaceutical Development **Vishal Koradia,** Novartis Pharma AG, Switzerland	Pg 30
12:30		Lunch	

Biological & Biosimilar Drugs

Chair: **Pamela A. Smith,** Improved Pharma, USA

2:00	P33	Invited–Macromolecular Powder Diffraction: Ready for Genuine Biological Problems ..... Pg 31 **Irene Margiolaki,** University of Patras, Greece
2:40	P13	Characterizing Proteins Using XRPD and SAXS Techniques on a Laboratory Diffractometer ..... Pg 32 **Natalia Dadivanyan*, J. Bolze, D. Beckers, G. Nénert, T. Degen,** Malvern Panalytical B.V., The Netherlands **S. Trampari,** Kapodistrian University of Athens, Greece **S. Logotheti, A. Valmas, S. Saslis, F. Karavassili, I. Margiolaki,** University of Patras, Greece
3:10		Coffee Break

PDF Guidelines Discussion

Facilitators: **Steve Byrn,** Purdue University, USA; **Pamela A. Smith,** Improved Pharma, USA,
Fabia Gozzo, Excelsus Structural Solutions, Switzerland and Belgium

The PDF Guidelines Discussion will begin at 3:30 pm and end at 5:30 pm.

Sunday, 12 May, 8:30 am - 5:00 pm

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Software, Database, Laboratory Instrumentation
Chair: **Arnt Kern,** Bruker GmbH, Germany

8:30	P29	Invited- How Many Ritonavir Cases are Still Out There? ..... Pg 33 **Marcus A. Neumann*, Jacco van de Streek, Hanno Dietrich, Kiran Sasikumar, Asbjörn Burow,** Avant-garde Materials Simulation Deutschland GmbH, Germany
9:10	P9	ICDD® Polymer Diffraction Data Project – 100+ PDF® Entries and Growing ..... Pg 34 **Tom Blanton*, Megan Rost, Stacy Gates-Rector,** ICDD, USA
9:40		Coffee Break

Structure Determination
Chair: **To be announced**

10:10	P7	Invited - Crystal Structures of Large-Volume Commercial Pharmaceuticals ..... Pg 35 **Jim Kaduk,** North Central College, Illinois Institute of Tech. and Poly Crystallography Inc., USA
10:50	P32	Invited – Structure Determination of Organic Materials from Powder X-ray Diffraction Data: Opportunities for Multi-technique Synergy ..... Pg 36 **Kenneth Harris,** Cardiff University, United Kingdom
11:30	P30	Invited – Walking the Tightrope of Complexity – Assessing Probability of Success of Structure Solution from Powder Diffraction Data ..... Pg 37 **Pamela Whitfield*, Michael Morin, Mathilde Reinle-Schmitt, Fabia Gozzo,** Excelsus Structural Solutions, Switzerland
12:10		Lunch
1:30	P12	Pseudo-centrosymmetric CH-π and π-π Stacking Dimers in Chiral Apremilast Resulting in 4 Polymorphs with Z'>1 ..... Pg 38 **Cristina Puigjaner*, Raquel Cordobilla, Mercè Font-Bardia, Xavier Alcobé,** University of Barcelona, Spain
2:00	P19	Structure Determination of Nanocrystalline Organic Compounds from Unindexed Powder Data by Real-Space and PDF methods ..... Pg 39 **Martin U. Schmidt*, Stefan Habermehl, Carina Schlesinger, Dragica Prill,** Goethe University, Germany
2:30		Coffee Break

Complementary and Emerging Techniques and Methodologies
Chair: **Stavros Nicolopolous,** NanoMEGAS SPRL, Belgium

2:50	P17	Invited - Micro to Nanometer Scale Characterization of Pharmaceutical Compounds by Electron Microscopy ..... Pg 40 **Partha Pratim Das*, Alejandro Gómez Pérez, Stavros Nicolopoulos,** NanoMEGAS SPRL, Belgium
3:30	P6	Extensive Polymorph Screening of the Nucleobase Adenine ..... Pg 41 **Dubravka Šišak Jung*,** DECTRIS, Switzerland **Ivan Halasz,** Institute Rudjer Boskovic, Croatia **Graeme Day, David McDonagh,** University of Southampton, UK
4:00	P21	Study Real Time Crystallization Process in Organic Crystals using Liquid Cell Transmission Electron Microscopy and Electron Crystallography Techniques on PDIs ..... Pg 42 **Alejandro Gomez-Perez*, Partha Pratim Das, Stavros Nicolopoulos,** NanoMEGAS, Belgium **Yael Tsarfati, Boris Rybtchinski,** Weizmann Institute of Science, Israel
4:30	P38	Non-Standard Crystallization Methods of API´s & Electron Diffraction: The Future ..... Pg 43 **Gustavo Santiso-Quiñones,** Crystallise! AG, Switzerland
4:50		Closing Remarks – the Symposium will end at 5:00 pm.

PATENTING SOLID FORMS: A REVIEW OF US CASE LAW INVOLVING DR. JOEL BERNSTEIN

Jill K. MacAlpine, Ph.D.

Finnegan, Henderson, Farabow, Garrett & Dunner, LLP,
Washington, DC, USA

A review of U.S. patent law on patenting of solid forms based on U.S. Court decisions in which the late Dr. Joel Bernstein acted as an expert witness.

General principles of patent law particularly relevant to claiming crystalline forms in the United States will be discussed, including inventive step, sufficiency of description and enablement of claimed forms, and the recent US case of *Grunenthal GMBH et al v. Alkem Laboratories Ltd. et al*, decided by the US Federal Circuit on March 28, 2019.

Facts and Fictions about Polymorphism: Personal Recollections of our Good Friend, Joel Bernstein

Susan M. Reutzel-Edens, PhD, FRSC
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN U.S.A.

e-mail: reutzel@lilly.com

Are polymorphs predictable? This question has been periodically raised in the scientific literature, and also in "virtually every legal confrontation on crystal forms", where the *nonobviousness* of polymorphs is debated. If polymorphs were truly predictable, they would all but be eliminated as potentially patentable intellectual property. Certainly, the claim in 1996 that "near future developments in computer speed and force field technology will enable the polymorph prediction of any molecular crystal" was never realized. But what is the state of affairs today? In this presentation, polymorph prediction is analyzed from two perspectives: statistics of polymorph appearance and computational crystal structure prediction (CSP). Facts and fictions about polymorphism revealed through statistical analysis of crystallographic data from the Cambridge Structural Database and over 229 solid form screens conducted at Hoffmann-La Roche and Eli Lilly and Company are presented, along with combined experimental and computational CSP studies of model pharmaceutical compounds. The work, in collaboration with and inspired by Joel Bernstein, not only shows that polymorphism is unpredictable on the basis of molecular structure, but it also shows the substantial gap that still exists between crystal structure prediction and polymorph realization. In Joel's words, "each compound constitutes a new challenge and the prediction and realization of targeted polymorphism remains a holy grail of materials sciences".

Solid Form Patents in Pharmaceutical Development

Eyal H. Barash
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Solid forms of active pharmaceutical ingredients, such as polymorphs, cocrystals, crystalline salts, and amorphous forms are often patented as part of pharmaceutical development and commercialization strategies. This presentation will briefly explain why and how patents on such solid forms are important in the pharmaceutical industry, how they are drafted, and how they are used to protect assets. The issues associated with obtaining these patents and their potential advantages will also be discussed.

Role of Physical Form of the Active Pharmaceutical Ingredient (API) and Excipients

Raj Suryanarayanan (Sury), Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA

The physical form of the active pharmaceutical ingredient (API) can influence the performance and stability of the dosage form. Even if the appropriate physical form of the API is selected, it may not be retained in the final dosage form. Stresses experienced during processing and drug-excipient interactions can lead to both physical and chemical transformations during product manufacture. In order to understand and interpret the effects of such transitions, it is often necessary to monitor the system during all the stages of pharmaceutical processing. While the focus will be on APIs, the processing-induced transitions of excipients can also influence product performance.

Tablet formulations. The amorphous state is increasingly recognized as a means to circumvent the challenge of poor aqueous solubility of compounds. However, during processing, compounds can undergo crystallization thereby negating the solubility advantage of the amorphous state. When amorphous indomethacin was compressed, its crystallization was not uniform throughout the tablets. The spatial information, gained by monitoring the different regions of a tablet (depth profiling), revealed progression of phase transformation from the surface to the tablet core as a function of storage time. Very low levels of crystallization on the tablet surface, while profoundly affecting product performance (decrease in dissolution rate), may not be readily detected by conventional analytical techniques.

Freeze-dried formulations. The phase behavior of the active pharmaceutical ingredient (API) and excipients in multi-component pharmaceutical systems, during the various stages of freeze-drying, is a complex interplay of formulation variables and processing conditions. The behavior of several pharmaceutical excipients, during the different stages of freeze-drying will be presented and the potential implications on product performance will be discussed. In all of these studies, X-ray powder diffractometry serves as a primary tool for phase identification as well as phase quantification.

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High-throughput Quantum Molecular Dynamics Constrained by Electron Diffraction Aimed at the Prediction of Amorphous Solid Dispersion Stability

Georgios S.E. Antipas

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Drug bioavailability is deemed to be enhanced when mixtures of Active Pharmaceutical Ingredients (APIs) and polymer excipients are dosed as Amorphous Solid Dispersions (ASD). ASD design is based on the optimal choice of API and excipients, out of a vast array of different possible compounds and compound compositions, which greatly affect the amount of API in the solid solution (solid solubility limit) and the stability of the ASD; a measure of the latter is the degree of Amorphous Phase Separation (APS, the tendency for separation into API-rich and API-poor clusters within the ASD), as a function of time, temperature and humidity. Although experimental methods do exist for the inference of ASD solubility and stability, all depend on trial and error and none have any a priori prognostic capabilities able to facilitate ASD design.

Aiming to address ASD design, we have developed and implemented a combination of electron diffraction and high-throughput quantum chemical modelling running on High Performance Computing (HPC) segments which enabled the direct detection of ASD density and the ASD solid solubility limit. We determined that this technology allows high-throughput miscibility screening of candidate API/excipient combinations without prior experiments. Additionally, we developed proprietary algorithms which analyze and report APS trends as well as visualize API-polymer and polymer-polymer interactions. We are in the process of extending our ASD stability analysis, taking into account the effect of humidity and solid-state diffusion.

The Direct Derivation (DD) Method for Quantitative Phase Analysis: A Practical Approach using the Observed Diffraction Patterns for Profile Modeling

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Weight of a solid cube can simply be derived by dividing the volume of the cube by the volume per unit weight of the same material. In the same manner, the weight proportion of the kth component material in a K-component mixture can be calculated by dividing the total scattered intensity from that material (S_k) by the total scattered intensity per unit weight (a_k^{-1}). The magnitude of a_k^{-1} can be calculated from the numbers of electrons belonging to the atoms in the chemical formula and the chemical formula weight, and therefore, if we know the chemical composition of each component material. The formula for calculating the a_k^{-1} was first derived by using the relationship between the height and integrated value of the peak at the origin of the Patterson function [1]. It has recently been derived by assuming a general assemblage of atoms in a space like amorphous materials [2]. Therefore, we can derive weight fractions of individual components irrespective of their crystalline states if a set of S_k can be obtained as observed datasets. Whole-powder-pattern fitting is a powerful technique for separating the observed diffraction pattern of the mixture into individual component patterns and, therefore, for deriving the S_k[3]. For a purpose of decomposing the observed pattern, we can arbitrarily combine three kinds of the fitting functions, which have been used in Pawley pattern decomposition, Rietveld structure refinement, and the full-pattern-fitting method using the background-subtracted observed patterns [4]. Recently, we have introduced the background-included observe diffraction pattern of a single phase as the 4th fitting function [5]. This approach requires to prepare the single-phase observed diffraction patterns measured under the same experimental condition as that applied to the target mixture samples, but it is unnecessary to subtract the background intensities. Therefore, it is particularly advantages for the quantification of samples containing low crystallinity materials like hydrates, amorphous component materials, low symmetry materials with many weak peaks in middle and high angle regions *etc*. Some examples of applications, including pharmaceutical materials, will be presented in this report.

References

1) Toraya, H. (2016). *J. Appl. Cryst*., **49**, 1508 – 1516.
2) Toraya, H. & Omote, K. (2019). *J. Appl. Cryst*., **52**, 13 – 22.
3) Toraya, H. (2018). *J. Appl. Cryst*., **51**, 446 – 455.
4) Smith, D. K. et al. (1987). Powder Diffraction, 2, 73 – 77.
5) Toraya, H. (2019). *J. Appl. Cryst*., **52** (in press).

Method Validation for Quantitative Determination of the (Pseudo) Polymorphs Ratio in DS and DP Samples: Performance and Compliance

Matteo Daldosso[a*], Silvia Lenzini[a], Brigida Allieri[a]
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Active Pharmaceutical Ingredients (API) often show the tendency to crystallize as solids in different structures (forms). This phenomenon is known as polymorphism or pseudo polymorphism in case of hydrates - solvates

In general, different polymorphs show different physicochemical characteristics and properties. Therefore, the control of the API form in Drug Substance (DS) and Drug Product (DP) samples is more than critical because the API form itself has a great impact on the properties of the final DP: the form selection has ethical, therapeutic, commercial and economic implications.

X-Ray Powder Diffraction (XRPD) is an essential technique for the determination and quantification of polymorphic (or pseudo-polymorphic) forms in a given DS or DP sample in order to control the API phase purity, its potential conversion during manufacture and stability (not only in the early phase of the drug discovery process but also during the full development path, including batch release, formal stability and so on).

In this contribution the performed activities for the cGMP compliant validation of two XRPD methods to be used for the quantitative determination of the (pseudo) polymorph ratio in a UCB DS (Drug Substance) and DP (Drug Product, ie granules of a fixed composition) are presented.

The methods have the aim to quantify the w/w ratio between the API in its anhydrous form and its n-hydrate. Moreover the methods reliability (in terms of accuracy and precision) and performances (in terms of Limit of Detection and Quantitation) are discussed.

All the activities (Specificity, Linearity, LoD, LoQ, Accuracy and Precision) have been performed in agreement with cGMP (current Good Manufacturing Practices), ICH Q2(R1) (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Validation of Analytical Procedures) and are fully compliant with FDA CFR21 part 11 for data integrity (both raw data acquisition and manipulation).

This work ended up in fully validated and compliant analytical methods based on XRPD for quantitative determination of the (pseudo) polymorph ratio in DS and DP samples to be used in any phase of the DS and DP development.

Using Portable X-ray Diffraction (XRD) with Pseudo-thin-film Type Analysis for API Verification and Counterfeit Formulation Investigations

Jose Brum, Olympus OSSA, USA

All medication formulations have a unique fingerprint of both active and inactive ingredients that identifies the efficacy and brand of each drug. Incorrect formulations containing foreign or substitute ingredients can jeopardize a patient's well-being. Additionally, when incorrect or counterfeit formulations are distributed under a brand name, the reputation of the manufacturer is at risk.

Pharmaceutical manufacturers must protect their business interests by ensuring that the correct formulations of their products are being distributed. This will ensure that patients are receiving the correct API and dosage, and that their branding isn't compromised by counterfeiters. Just as important, they also need to ensure that they have documented fingerprint records of all their drug and formulation steps. X-ray diffraction (XRD) offers a non-destructive fingerprinting method for drug formulations. This is essential for pharmaceutical manufacturers. It offers factual support for patent and other legal records as well as retention of the original powder material if needed.

Olympus offers a unique and viable portable XRD system, meaning it can travel to a site where it is needed rather than having to bring specimens to it. It traces its lineage back to the NASA XRD developed for the current and ongoing Mars mission. The same scientists that invented that configuration also developed the commercial version which Olympus sells today.

Olympus XRD systems employ a technology without moving parts. Essentially, Olympus uses a pseudo-thin-film type analysis, we suspend a very small amount of sample (<15mg) inside two mylar windows, and then apply a frequency to it. This has the effect of convecting a powdered material, and rotating it on its axes, this is commonly referred to as Powder liquefaction.

Due to this type of configuration, we guarantee that within one minute of analysis, every single particle within the windows will at some point cross the x-ray beam in every possible orientation, thereby allowing for 100% randomization. With XRD, the better you randomize your crystallites, the better off your analysis is going to be.

It has been long theorized that if one had a way to do transmittance XRD such as Olympus does, it would be a much better way to achieve diffraction events. Essentially, the pseudo-thin-film transmittance technique avoids the peak broadening issues from which most traditional systems suffer.

Supporting data will presented from both prescription medications, and over-the-counter formulations. Olympus will rely on the user to supply specimens for proof of concept, these can be either from legitimate sources or from counterfeit.

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Overview of Synchrotron X-Ray Powder Diffraction: Instruments and Case Studies

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Synchrotron radiation has revolutionized the technology of X-ray powder diffraction (XRPD). This is particularly apparent in applications of XRPD to pharmaceutical materials. Starting from the hardware, I will describe several configurations of existing synchrotron beamlines in comparison to the common laboratory Bragg-Brentano instrument. It is important to understand the factors that affect resolution and intensity for any powder diffractometer, and I will illustrate with comparisons of data from several instruments on a couple of challenging samples.

In the second part of the talk, I will describe a few of my projects that were enabled by synchrotron powder diffraction.

- Determining that a particular API was a pure single phase, when NMR suggested otherwise.
- Resolving whether a particular API contained multiple phases, or if preferred orientation was creating confusion.
- Laying the groundwork to challenge the validity of claims in a particular patent, by showing that they could apply to a pharmaceutically acceptable solvate of the same API.

Industrial Collaboration: How to make it happen at the Swiss Light Source?

Stefan Müller, Paul Scherrer Institut & SLS Techno Trans AG, stefan.mueller@psi.ch

The scope for industrial research and development at the Swiss Light Source (SLS) is greater than ever before. Clients from all over the world are able to probe their systems with greater resolution and more closely matching realistic operation conditions than can be achieved at their home laboratories. For industry use, the SLS offers a variety of instruments and a team of scientists covering a wide range of expertise including macromolecular and small molecule crystallography, X-ray powder diffraction, X-ray absorption spectroscopy, small-angle X-ray scattering and imaging.

In 2018, as in previous years, the SLS has provided the resources for academic and industry users to access photon beams for research at the SLS. SLS Techno Trans AG supports these activities by maintaining an ecosystem with stakeholders in the region and around the SLS to provide industry customers with straightforward access to the SLS.

In 2018, the SLS hosted 1675 individual users who performed 1000 academic and 338 industry (proprietary) projects. The total number of proprietary days across the SLS increased from 173 in 2016 up to 223 in 2017 and finally to 234 in 2018, which is 11.5% of the total available beamtime.

SLS Techno Trans AG focused its marketing outreach activities during 2018 by strengthening European collaboration with the European project CALIPSOplus. Within this project the European Light Source for Industrial Innovation (ELSII) task was launched. This collaboration provides resources to allow us to further strengthen our ecosystem in the region around the light source and to improve the European network with our colleagues from the other synchrotron radiation facilities and FELs. The Tailor-made for SMEs Trans-national Access (TamaTA) work package (http://www.calipsoplus.eu/taa-tamata/) is a concrete action within CALIPSOplus aiming to lower the barriers of accessing the European research infrastructures to foster SME innovation and competitiveness. The access procedure is based on a specific review system for SME proposals in parallel to the established academic access, but following the same principles. Through a “voucher scheme”, successful SMEs obtain a pre-defined amount of beam time and data analysis hours.

With this presentation I would like to encourage greater use of our facilities by industrial partners and present pathways to facilitate collaborations between industry and PSI.

Time and Matter: The Material Science Beamline at the SLS

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The Material Science beamline is specialized in advanced diffraction experiments and measurements, for a wide community ranging from Geo to Pharma, Physics to Metallurgy, Chemistry to Materials. The X-ray beam provided by the in vacuum undulator is monochromatized, and if needed focused, through a double crystal monocromator and two mirrors, with an available energy range between 5 and 38 keV. The large flux delivered to the sample is then coupled with advanced automatization, modern detectors and a range of conditioning devices, in order to answer the needs of the large community we serve.

The Powder Diffraction station has two separate experimental tables: the first equipped with a 120° position sensitive detector, the Mythen-II. It serves mainly capillary powder samples in Debye-Scherrer geometry, delivering high resolution data. The time needed for acquisition is reduced by the lack of detector scanning , with intrinsic advantages for radiation damage, *in situ* studies etc.. The second table is equipped with a Pilatus 6M detector, at variable distance and position from the sample. It serves transmission experiments on oriented or otherwise statistically problematic powder samples, as well as for single crystal studies. Acquisition time is typically faster for comparable signal/noise making it ideal for high throughput. At last, very fast experiments can be served with an Eiger detector, a special development of the PSI detector group capable of reaching in excess of 22 kHz frame rate.

ID22 High Resolution Powder Diffraction Beamline at ESRF

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The 6 GeV European Synchrotron Radiation Facility in Grenoble has operated a high resolution powder diffraction beamline since May 1996. Originally built on bending magnet BM16, and moved in 2002 to insertion device ID31, since 2014 the beamline has been located at ID22, with an in-vacuum undulator source. The beamline produces very high resolution powder diffraction patterns at relatively hard photon energies, with routine operation in the range 25 – 40 keV, (λ = 0.5 – 0.3 Å), thus allowing the use of capillary specimens without worries about sample absorption for a wide range of sample types. In 2015 a Perkin Elmer XRD 1611 medical-imaging detector was installed to provide data to high Q (25 – 30 Å^{-1}) for PDF analysis at energies up to ≈70 keV. In 2017 a new powder diffractometer, based on air-bearing technology, replaced the original machine that had operated reliably for more than 20 years.

On 10 December 2018 the ESRF storage ring ceased operation and is being replaced by a new, low-emittance storage ring of the new generation, offering greatly enhanced brightness. Full user operation will resume in August 2020, though on ID22 we expect to restart experiments for industrial and in-house projects well before that. The deadline for user proposals is 1 March 2020. On ID22 we will be replacing the bank of nine scintillation counters behind the nine-crystal multianalyzer stage with a Dectris Eiger-2 pixel detector with CdTe sensor. Tests [1] made with a Pilatus detector showed that there are advantages for high resolution powder diffraction by adopting this approach, including improved resolution and peak shape at low angle, improved statistics at high angle, improved signal to noise, filtering of bright diffraction spots from a grainy sample for improved powder averaging, etc. Along with the new-generation ring, this should lead to significant improvements for the quality of powder diffraction data.

ID22 high resolution powder diffractometer

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Humidity Effects on Amorphous Pharmaceuticals

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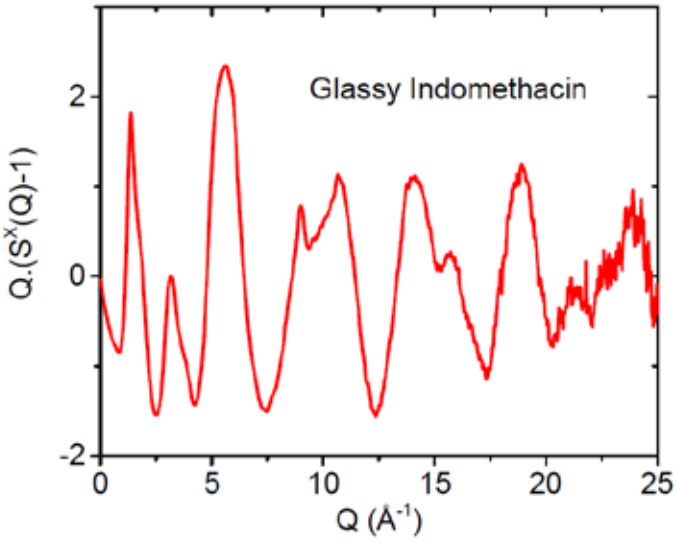
The kinetics and disorder of hydration (or dehydration) of pharmaceutical hydrates is of the utmost importance in the processing and storage of drug products, especially since the crystallization of amorphous drugs during dissolution often reduces their bioavailability. Temperature and humidity effects have been studied for decades & many pharmaceutical hydrates and solvates show dehydration or rehydration behavior that affect their properties & stability. However, what is not understood are the kinetics involved in the hydration process and the degree of atomic and molecular disorder created during these solid-gas reactions. Here we present *in-situ* high energy x-ray measurements of humidity induced effects in two amorphous pharmaceutical hydrates, namely indomethacin and carbamazepine, where dissolution rates of different phases vary. Experiments performed on a custom built humidity chamber are described together with the effects on amorphous structure over time as the materials swell and ultimately crystallize.

Indomethacin is a model compound due to the wealth of information about the formation and characterization of the more soluble amorphous form and the effect of humid storage conditions. However, the more soluble amorphous solid form of indomethacin is not the most thermodynamically stable and the propensity to revert back to the stable crystalline form under high temperature and humidity results in the drug becoming less effective. Here we describe in-situ bulk measurements on amorphous pharmaceuticals exposed to varying humidity levels using high energy x-ray diffraction. Experiments performed as a function of relative humidity show how surface water is absorbed into amorphous Indomethacin prior to crystallization at the molecular level.



Quantification of Multiple Amorphous and Crystalline Phases

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The physico-chemical properties of pharmaceuticals are depending on their solid-state form. The crystallinity of an active ingredient has a strong influence on both processing behavior as well as its bioavailability. Due to higher thermodynamic stability, the desired solid-state form of an active pharmaceutical ingredient is usually crystalline. However, the amorphous state is sometimes required to achieve sufficient efficacy for low soluble compounds. During the processing of pharmaceutical solids, certain processes can disrupt the crystalline structure and lead to formation of amorphous regions. To establish the integrity of the finished product it is therefore important, to be able to determine the existence and quantify the amount of amorphous material within a crystalline matrix and vice versa. In this presentation we compare different methods to quantify crystalline and amorphous organic compounds including multiple phase mixtures. Results from different full pattern quantification methods are compared on accuracy and limitations in application.

Computed Tomography Analysis for Process Development and Quality Control of Formulations

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The use of (micro-) Computed Tomography (CT) for the characterization of pharmaceutical materials has become increasingly important. CT gives valuable information about the morphology of tablets like e.g. porosity and porosity distribution; it helps in understanding the relationship between processing parameters and resulting morphology as well as the influence on drug product dissolution properties. CT provides a means to non-destructively visualize the internal structure of materials, which can be used to investigate the distribution homogeneity of drug delivery systems or other functional material in the formulation. CT can also be used to investigate the homogeneity of tablet coating in process development and quality control.
The direct correlation with the phase composition of the formulation is often of paramount importance. Recent developments allow for a significant improved resolution in CT on an X-ray diffractometer. This enables to directly correlate high quality diffraction data with the morphology study on formulations.

We present the application of the CT set-up on different formulations. Application examples include the distribution analysis of MUPS in a tablet, wall thickness analysis of capsules, investigation of morphology and its homogeneity in pressed tablets and the analysis of the interior of capsules, e.g. the occurrence of compound aggregates and compound distributions.

Atomic Pair Distribution Function (PDF) And X-ray Scattering Methods To Assess Amorphous Organic Compounds

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The amorphous state is of significant interest as a possible means to enhance aqueous solubility of APIs. Either by spray drying the API itself or creating solid dispersions of the API with different polymers. Often the short-range structural arrangement directly determines the physical stability of the pharmaceutical solid.

An important practical barrier to the development of amorphous APIs for drug products is the lack of reliable methods for structural characterization and fingerprinting. The Atomic Pair distribution function (PDF) have been suggested as an alternative approach for fingerprinting of amorphous 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.

Recent advances in laboratory X-ray diffractometer technology like e.g. 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.

Use of “Cleaning” Algorithm for Model-Free Correction of Instrumental Aberrations in XRPD Patterns

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XRPD patterns of pharmaceutical substances are often constituted by a significant number of peaks at low angles. As a result, XRPD patterns of pharmaceuticals are strongly influenced by instrumental aberrations, particularly by the aberration originated from the axial divergence of X-Rays. These instrumental aberration effects result in additional peak broadening, peak asymmetry and peak center gravity shifts from the "ideal" Bragg position.

Traditionally, methods for the correction of instrumental aberrations were based on modeling of individual peaks. In this poster we present a methodology for the correction of instrumental aberration effects by considering an XRPD pattern as single "unknown" continuum without the need for introduction of separate peak models. No prior knowledge about the crystallographic unit cell or peak indexes is required.

The method is based on the integral transformation algorithm disclosed in reference [1]. As input for the correction the algorithm uses Fourier coefficients of instrumental functions as described in reference [2].

The algorithm converts the measured pattern into a corrected pattern without influencing the resolution. The resulting peaks appear to be symmetrical and located in the ideal (Bragg) positions regardless of the instrumental setup. This method is beneficial for indexing, search-match, full-pattern refinement and polymorph discrimination. The main advantage of this approach is the possibility to make the peak positions of "cleaned" patterns independent from the instrumental setup without the need for immediate analysis.

We will present examples of this methodology as general pretreatment for patterns of pharmaceutical substances.

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Total Pattern Analyses of Pharmaceutical Formulations

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Diffraction analyses of pharmaceutical formulations have historically been hindered because of the wide spread use of non-crystalline and nanocrystalline ingredients and the difficulties in analyzing these materials. To address this issue the International Centre for Diffraction Data, over the last decade, has developed a system for analyzing whole patterns containing noncrystalline materials. The system includes several components; 1) the systematic additional of experimental pattern references for noncrystalline API's and excipients, 2) the development of application software that can correct for common instrumentation and specimen effects 3) a suite of graphics programs to scale, sum and display various combinations of reference and experimental data. Reference pattern simulations include adjustments for crystallite size and orientation.

To evaluate the effectiveness of the analysis applications, 65 pharmaceutical formulations were analyzed. The poster will demonstrate total pattern analysis for several of these formulations including those containing the most commonly occurring excipients. The analyses were conducted on high volume pharmaceutical including Azor®, Prilosec® OTC, Tramadol®, Eliquis®, Singulair®, Diazepam®, Invokana®, Myrebetriq® and Seroquel®.

The X-ray powder diffraction pattern of Diazepam® (top red pattern) compared to the reference patterns of its identified ingredients, lactose monohydrate, diazepam, calcium stearate, cellulose 1β, amorphous cellulose. The insert shows a comparison of summed phases (black) to the experimental data (red).

Attempts and Approximations for a Background Modeling in Pharmaceutical Samples in Patterns of XRD and S-XRPD

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Pharmaceutical solids can exist in several forms: polymorphic crystalline and amorphous arrangements. They present differences in their physicochemical properties, for instance, melting point, density, morphology, solubility, and color. These characteristics may have an impact on the stability (physical and chemical), bioavailability and bioequivalence1; e.g., amorphous substances are unstable than crystalline substances. Differences in degrees of drug crystallization affect chemical and physical stability, rather than crystalline polymorphism of the substance. Tablets are solids preparations of active pharmaceutical ingredients and additives; many of the additives commonly used are poorly crystalline or amorphous, determining the final solubility in the drug.

A proper background modeling is the first step for correcting amorphous fraction quantification in active pharmaceutical ingredients, additives, and mixes.

A python-code based program to model the background of the diffraction patterns as a contribution of diffuse scattering -Thermal Diffuse Scattering (TDS) plus static disorder, Compton and air scattering-, according to the present crystalline phases; Air scattering based in correction factors for absorption and air scattering under a symmetrical reflection geometry with given sample thickness, divergence and receiving slit width, average temperature factors and specimen density of packing has been developed and probe in blends of ciprofloxacin (API-Cipro) and microcrystalline cellulose (MC) in different blends had been performed using the program.

As a second approximation to this subject, a series of S-XRPD diffraction patterns from three highly crystalline reference samples had been collected at the MS beamline (PD End station) in the Swiss Light Source to understand the contribution of the capillary, air and sample absorption besides the packing density in the contributions to the diffuse background.

Magnifying Nano-/Meso- Structural Information of Amorphous Pharmaceutical Solids Through Small Angle X-Ray Scattering

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Amorphous state is intentionally (eg. amorphous solid dispersion) or unintentionally (induced by processing) present in solid pharmaceutical intermediates and/or finished dosage forms.[1] In either case, in-depth characterization of the structural properties of amorphous states is an important step towards prediction and control of the quality of final products such as dissolution performance and physical and chemical stability. Likewise, a thorough structural analysis of inherently amorphous macromolecule drugs (eg. protein) and polymeric excipients is inevitable to ensure their desired functionality.

Powder X-ray diffraction (pXRD) is one of the most used quantitative tools for the analysis of crystalline phases and crystallinity of pharmaceuticals[2] and recently for the characterization amorphous forms.[3] On the other hand, the rich information achievable by small-angle X-ray scattering (SAXS) has gained limited attention for the analysis of pharmaceuticals so for. A particularly useful technique is simultaneous small- and wide-angle scattering (SWAXS)[4], which combines the meso-scale (2-50nm) with the nano-scale (<2nm), i.e. the supramolecular domain structure with the high-resolution atomic/molecular structure and forms the link to pXRD. In this presentation, we describe various nano-/meso-scale structural parameters that can be derived from solid-state SAXS analysis of amorphous pharmaceuticals. This includes the specific inner surface, mean square density fluctuation, domain size, correlation length, etc. The applications will be discussed through some relevant case studies. For amorphous forms of APIs like desvenlofaxine, simvastatin, and sulfamerazine, obtained by milling the SAXS invariant directly provide the information of the degree of nanoscale heterogeneity that was related to physical stability.[5] Furthermore, SAXS parameter enabled the differentiation between the nanostructures of amorphous drug-polymer dispersions obtained via melt quenching and milling. In a case of lyophilized protein formulation exposed to different humidities, the change in specific inner surface obtained by SAXS as a function of water content was found to systemically correlate with their reconstitution kinetics.[6] The extended applications of SAXS methods will be further exemplified for microstructure characterization of excipients.[7]

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SAXS-WAXS Studies of Amorphous, Mesoporous and Nanomaterials

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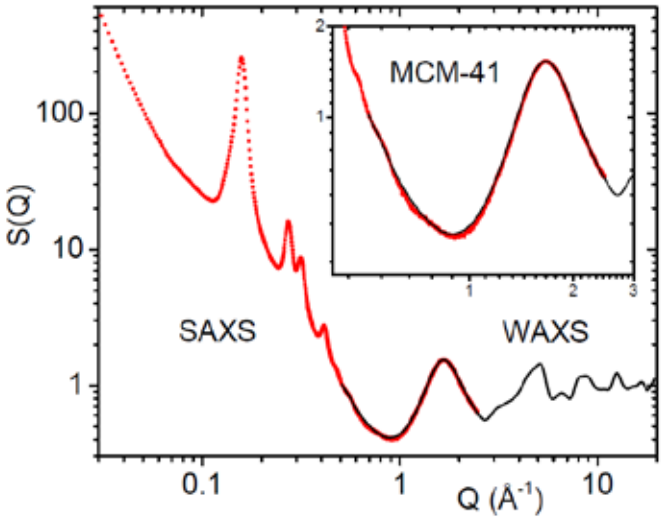
High energy x-rays (>50 keV) are extremely penetrating and provide a bulk probe of a material's structure. A wide region of reciprocal space is reduced to a small angular cone allowing access to high momentum transfers and high real space resolution in the associated pair distribution function. Here we describe a dual detector system for high-energy x-ray, simultaneous, small and wide-angle x-ray scattering (SAXS and WAXS). The instrumentation provides continuous reciprocal space coverage over many length-scales (0.01 to 20 nanometers), opening the door to *in-situ* and time-resolved studies of atomic to mesoscopic scale processes. The varying resolution, splicing of data and normalization on an absolute scale are discussed with a focus on applications to amorphous, mesoporous and nanomaterials. Examples will include glassy itraconazole and the amorphous mesoporous silicas MCM-41 and SBA-15.

The combination of SAXS and WAXS theory is considered with a view to enabling Fourier transformation of the structure factor spanning multiple length-scales in reciprocal space into real space, to obtain an extended-range pair distribution function. Several examples are used to illustrate that when the SAXS intensity in the structure factor, S(Q), is similar to the WAXS intensity, the contributions to the extended-range pair distribution functions are minimal. However, when the SAXS intensities are significantly stronger than the WAXS, the observed density fluctuations can provide unique information on the local, intermediate and nanometer length-scales. Most notably, the method strongly reflects the periodicity associated with intense low-Q reflections and is useful in obtaining direct information on maximum particle sizes and their distributions.



Understanding the Disordered State of Matter in Pharmaceutical Development

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Many pharmaceutically relevant materials - active pharmaceutical ingredients, excipients, and formulations possess disordered arrangement. The significance of disordered state towards pharmaceutical product performance in terms of stability, bioavailability and processing is well established. A deliberate use of the disordered material in formulations such as solid dispersion provides an important tool to enhance bioavailability. On the other hand, disordered state may unintentionally introduced during pharmaceutical processes of milling and compression among others. In either of these cases, a thorough characterization and understanding of the disordered state is required. This presentation will focus on approaches of grazing incidence measurements and pair distribution function analysis to probe the disordered material in pharmaceutical development. It will also present evaluation of difference in the disordered state produced by different processes.

Macromolecular Powder Diffraction: Ready for Genuine Biological Problems

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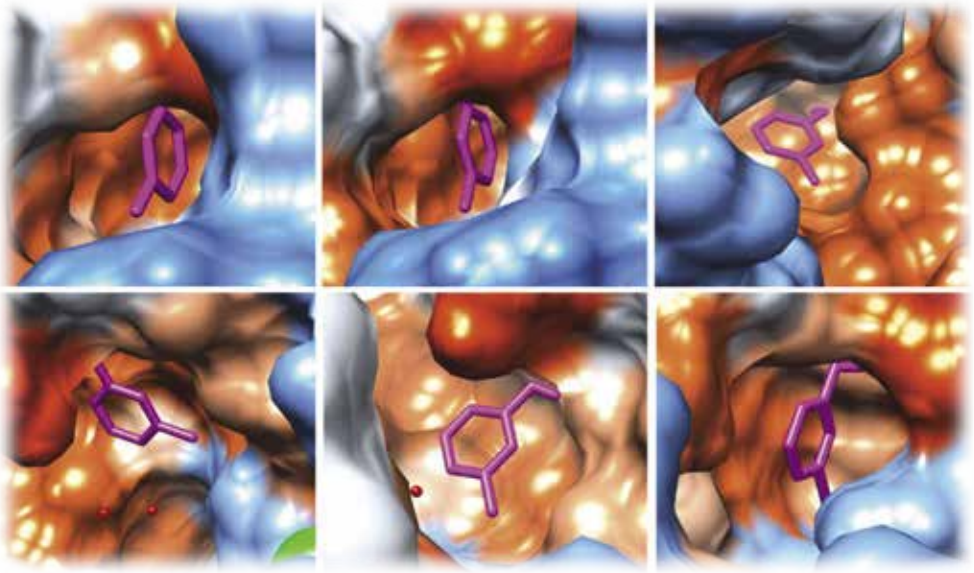

Ligand identification in protein structures via XRPD.

Identification of 6 m-cresol hydrophobic binding sites in a new monoclinic form of Human Insulin. (Valmas et al., 2015; ESRFNews 2015; Karavassili et al., 2017).

Knowledge of 3D structures of biological molecules plays a major role in both understanding important processes of life and developing pharmaceuticals. Among several methods available for structure determination, macromolecular X-ray powder diffraction (XRPD) has transformed over the past decade from an impossible dream to a respectable method. XRPD can be employed in biosciences for various purposes such as observing phase transitions, characterizing bulk pharmaceuticals, determining structures via the molecular replacement method, detecting ligands in protein–ligand complexes (Karavassili et al., in preparation), as well as in situ detection of novel protein crystal forms upon controlled relative humidity variation using laboratory XRPD. This presentation aims to provide necessary elements of theory and current methods, along with practical explanations, available software packages and highlighted case studies. We will demonstrate the value of in-house and synchrotron XRPD as an analysis tool in industrial protein-based drug screening, and its potential to help troubleshooting the production process and to provide information for further refining the manufacturing of pharmaceuticals. Selected examples will be presented regarding studies of pharmaceutical proteins and their complexes with organic ligands including Human Insulin, Urate Oxidase as well as peptide drugs (Fili et al., Acta Cryst. B, in press).

Characterizing Proteins Using XRPD and SAXS Techniques on a Laboratory Diffractometer

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Proteins often form microcrystalline precipitates. The protein molecules are then surrounded by solvent and their packing arrangement is retained by limited intermolecular contacts. A change in the crystal environment first affects the bulk solvent that fills the intermolecular space, with resulting changes in the crystal structure. Protein crystals, when exposed to controlled humidity environments can show a large change in unit-cell parameters when the humidity is decreased. The effect of relative humidity (rH) on the crystal structures of protein polycrystalline precipitates can be monitored via in-situ laboratory X-ray Powder Diffraction (XRPD) measurements.

On the other hand, Small-Angle X-ray Scattering (SAXS) applied to protein solutions has become an accepted and rapidly growing structural biology technique. Measurements can be done under native conditions, while varying concentration, pH, ionic strength or temperature. Such data provides information about molecular weight, size, shape and stability of the biomolecules and ultimately allow for a (low-resolution) molecular shape envelope reconstruction. The information is complementary to that obtained from XRPD, NMR or cryo-EM. Although the setup for SAXS is easy in theory, it is in practice demanding with respect to the instrumentation and until recently it required dedicated, costly laboratory instruments or the usage of synchrotron beam lines.

Here we present how a multipurpose Empyrean diffractometer can be configured for XRPD and SAXS measurements at ambient conditions and for in-situ rH and temperature (T) experiments. The performance is demonstrated on a number of protein examples.

How Many Ritonavir Cases Are Still Out There?

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On rare occasions, a crystal structure that has been prepared for years is unexpectedly "superseded" by a thermodynamically more stable polymorph, rendering the initial crystal structure almost impossible to obtain—a so-called "disappearing polymorph" [1]. Famous cases included the drug compounds Ritonavir and Rotigotine: the thermodynamically more stable polymorph is substantially less soluble and required a costly reformulation before a product with comparable specifications could be manufactured again.

On a case-by-case basis, the probability of a kinetically hindered but thermodynamically stable polymorph having been missed in an experimental polymorph screen can be assessed by a computational crystal structure prediction study: the calculations do not suffer from kinetics and will in principle enumerate all possible crystal structures for a given compound; comparison against the experimental structures identifies any missed polymorphs. In a recent paper, we presented the results of 41 such computational crystal structure prediction studies to draw up statistics regarding the number of hidden Ritonavir cases [2]. The main finding of the paper was that between 15 and 45% of all experimental crystal structures are in fact thermodynamically unstable.

The large spread in our estimate was due to the computational error in the calculation of the relative free energies of the predicted polymorphs. Even though the computational error is estimated to be as small as 0.5 kcal/mol, about half the size of the gold standard referred to as "chemical accuracy", the experimental energy differences between polymorphs are also around the 0.5 kcal/mol mark, and to reduce the large spread in our estimate an even more accurate energy model was needed.

The shortcomings of our old energy model—neglect of temperature, relatively poor accuracy of the exchange part of the functional used in the DFT calculations, and the assumption that Van der Waals interactions are pairwise additive—are well documented, and in this contribution we will present the results of an energy model in which these shortcomings have been addressed [3]. With the availability of more accurate relative lattice energies, we are able to narrow down our estimate of how many pharmaceutical compounds are out there for which the most stable crystal polymorph has not yet been observed.

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ICDD® POLYMER DIFFRACTION DATA PROJECT – 100+ PDF® ENTRIES AND GROWING

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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 results of an interesting finding for a commercial excipient polymer sold as one phase but turned out to be three different and incorrect phases.

CRYSTAL STRUCTURES OF LARGE-VOLUME COMMERCIAL PHARMACEUTICALS

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As part of a continuing project, the challenging room-temperature crystal structures of six commercial pharmaceutical APIs have been solved by Monte Carlo simulated annealing techniques using synchrotron X-ray powder diffraction data (11-BM at APS), and optimized using density functional techniques. **Bisoprolol fumarate**, $(C_{18}H_{33}NO_4)_2(C_4H_2O_4)$, crystallizes in $P\bar{1}$, with a = 8.16570(5), b = 8.51639(12), c = 16.75179(18) Å, α = 89.142(1), β = 78.155(1), γ = 81.763(1)°, V = 1128.265(10) Å^3, and Z = 1. The structure was difficult to solve because the two ends of the bisoprolol cation are similar but not identical. **Hyoscyamine sulfate monohydrate**, $(C_{17}H_{24}NO_3)_2(SO_4)(H_2O)$, (generally described as a dihydrate) crystallizes in $P2_1$ with a = 6.60196(2), b = 12.95496(3), c = 20.93090(8) Å, β = 94.8839(2)°, V = 1783.680(5) Å^3, and Z = 2. The multiple fragments led to a low success rate. **Atropine sulfate monohydrate**, $(C_{17}H_{24}NO_3)_2(SO_4)(H_2O)$, (racemic hyoscyamine) crystallizes in $P2_1/n$ with a = 19.2948(5), b = 6.9749(2), c = 26.9036(5) Å, β = 94.215(2)°, V = 3610.86(9) Å^3, and Z = 4. The success rate of solution using DASH was only 1%, and required Mogul Distribution Bias and {010} preferred orientation. Despite being apparently orthorhombic **cefprozil monohydrate**, $C_{18}H_{19}N_3O_5S(H_2O)$, crystallizes in $P2_1$ with a = 11.26503(5), b = 11.34017(4), c = 14.72628(10) Å, β = 90.1249(4)°, V = 1881.24(2) Å^3, and Z = 4. DFT calculations suggest that the carboxylic acid proton on one (but not the other) of the two independent cefprozil molecules is transferred to an amino group, forming a salt. This suggestion needs to be confirmed by spectroscopic experiments and calculations of the vibrational spectrum. Despite being apparently monoclinic, **metolazone**, $C_{16}H_{16}ClN_3O_7$, crystallizes in $P\bar{1}$ with a = 8.1976(5), b = 14.4615(69), c = 16.0993(86) Å, α = 115.009(18), β = 90.096(7), γ = 106.264(4)°, V = 1644.52(9) Å^3, and Z = 4. The broad 02$\bar{1}$ peak indicates stacking faults in the structure. **Linagliptin**, $(C_{25}H_{28}N_8O_2)_2$(solvent)(H_2O), crystallizes in $P2_12_12$ with a = 24.85078(12), b = 21.5691(8), c = 9.74377(4) Å, V = 5222.77(3) Å^3, and Z = 8. The structure was solved by TEM electron tomography. Initial fit to the X-ray powder data was relatively poor, but the structure contains a channel, which is filled with water and solvent. Hydrogen bonding is important in all these crystal structures.

Structure Determination of Organic Materials from Powder X-ray Diffraction Data: Opportunities for Multi-technique Synergy

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Structure determination of organic materials directly from powder X-ray diffraction (XRD) data [1,2] is nowadays carried out extensively by researchers in both academia and industry. Most work in this field exploits the direct-space strategy for structure solution [3,4] followed by Rietveld refinement. Although these techniques are now readily accessible and relatively straightforward to use, it is essential that the structural results obtained from such analysis are subjected to rigorous scrutiny before they can be assigned as incontrovertibly correct, and the lecture will present an overview of important issues that must be given careful attention in validating the correctness of crystal structures determined using these techniques. The lecture will discuss several aspects of validation that are important with regard to: (i) validation of the appropriate structural model for use in direct-space structure solution calculations, and (ii) validation of the final structure obtained from Rietveld refinement [5]. The lecture will emphasize that significant advantages can be gained by the synergistic utilization of information obtained from other experimental and computational techniques as an important component within the strategy for structure determination from powder XRD data [6-10], focusing on the important roles that solid-state NMR spectroscopy and periodic DFT calculations may play in extending the scope of structure determination of organic materials from powder XRD data.

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Walking the Tightrope of Complexity – Assessing Probability of Success of Structure Solution from Powder Diffraction Data

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This presentation will attempt to outline some of the thought processes and logic that can contribute when answering the question 'can you solve this?' Answering this question with what can be a bare minimum of information (and sometimes none!) is always going to be difficult but a reasonable assessment of risk must nonetheless be made. Even where the complexity seems manageable there are always going to be occasions when a structure does something unexpected such as possessing a rare space-group or maybe the data exhibits a nasty microstructure. Some such problems can be identified and tackled given sufficient time but clients may not want to invest additional resources into something edging ever closer to a research project than a timely result.

The brute-force computational nature of real-space methods such as simulated annealing invite the use of code-breaking as an analogy. In code-breaking 'cribs' (or clues) are used to either point in the correct direction or exclude portions of search-space to reduce the computational requirements. Similarly in indexing and simulated annealing, key pieces of information such as absolute density, stereochemistry, water content, etc., can improve the chances of finding a solution in a reasonable amount of time given limited computing resources. Most researchers will have one or more apparently simple structures that should have solved readily but inexplicably refused to produce a satisfactory solution. However, a probabilistic approach is a good guide to assessing risk in a structure solution process. Good examples of this are the tables of space-group frequencies in the crystallographic literature produced via data mining from entries in the Cambridge Structure Database.

A real example will be used to demonstrate ways a problem can be assessed at different stages of the structure solution process, and how prior knowledge is leveraged to improve the probability of success within a manageable timescale.

Pseudo-centrosymmetric CH-π and π-π Stacking Dimers in Chiral Apremilast Resulting in 4 Polymorphs with Z'>1

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Understanding, controlling and predicting the structure of crystalline solids is a matter of great current relevance, especially in the pharmaceutical industry where crystal structure directly affects properties such as solubility, bioavailability, hygroscopicity, processability and chemical and physical stability. Typically, the knowledge of the atomic coordinates of one molecule and the symmetry of the crystal lattice usually allows the 3D crystal structure to be determined. However, for about 13% of the crystal structures deposited in the Cambridge Structural Database, some chemically identical molecules are not related to one another by crystallographic symmetry and occupy distinct independent positions, being Z' the number of symmetry-independent molecules in a crystal structure and Z the number of molecules in the unit cell [1]. The interactions between crystallographically independent molecules can give some clues for understanding solid state packing and also has conceptual relevance in the propensity of a molecule to form potential multicomponent solids such as solvates, cocrystals and host-guest complexes. Moreover, examination of the cases in which more than one molecule occupies the crystallographic asymmetric unit helps the rationalization of the crystallization issue, the development of space group prediction and increases statistical surveys.

Here we present the case of Apremilast (AP), an oral novel anti-inflammatory chiral drug molecule, which is placed by the Biopharmaceutics Classification System in class 4 due to is low solubility and permeability. Four anhydrous polymorphs of AP have been found through a polymorph screening. The crystal structure of the most stable form I has been solved from single crystal X-ray diffraction in the monoclinic space group $P2_1$, showing four independent molecules in its asymmetric unit, whereas form IV of APR crystallizes in the same monoclinic space group $P2_1$ but with Z' = 2 (crystal structure solved from single crystal XRD too).

Attempts to grow quality crystals of forms II and III were unsuccessful limiting the use of SCXRD to determine their structures. Over the last years, structure solution from powder diffraction data has become a real chance, while it is still not routine (structures from powder diffraction data today represent the 0.5% in the Cambridge Structural Database) [2]. Thus, the resolution of both crystal structures was achieved by using the direct space methodology, using high statistics laboratory powder XRD data. Their PXRD data were perfectly indexed to triclinic cells by means of Dicvol04 [3], and the space groups determined to be $P\bar{1}$ with two symmetry-independent molecules in their asymmetric units (Z' = 2). Both crystal structures were determined by starting from a molecular model using the two different conformations found in the crystal structure of form I, by means of the program FOX [4] with the parallel tempering algorithm. The refinement of the structures II and III has been performed by the Rietveld method using FullProf [5]. The four forms combine pseudo-centrosymmetric π–π and/or CH-π stacking motifs with molecular chirality, which explains the presence of Z' > 1 in these structures.

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Structure Determination of Nanocrystalline Organic Compounds From Unindexed Powder Data by Real-space and PDF Methods

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In my presentation I will show three methods for structure determination of nanocrystalline pharmaceutical compounds from uindexed powder data.

1. Fit with Deviating Lattice parameters (FIDEL) [1]

Classical real-space methods and Rietveld refinement require the lattice parameters to be known. If the lattice parameters are incorrect, the simulated peaks do not overlap with the experimental peaks. For this task, we developed a fit with deviating lattice parameters (FIDEL), which uses cross-correlation functions to compare simulated and experimental powder patterns. Starting from a large number of random structures with random lattice parameters in various space groups, the structures are fitted to the experimental powder pattern. The best matching structures are subsequently treated by Rietveld refinements. If the molecules are too flexible and/or the powder data are too bad, there can be multiple propsed crystal structures, which all fit to the experimental powder pattern sufficiently well.

2. Structure determination by fit to the PDF curve [2]

We are developing a similar procedure for structure determination, which performs a fit to the pair-distribution function instead of to the powder pattern itself.

3. Comparison of the PDF of an amorphous sample with the PDF of known polymorphs [3]

If polymorphic forms are known, the experimental PDF curve can be used to determine the local structure of pharmaceutical compounds, even if the compound is amorphous.

Application examples are shown for all methods.

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Micro to Nanometer Scale Characterization of Pharmaceutical Compounds by Electron Microscopy

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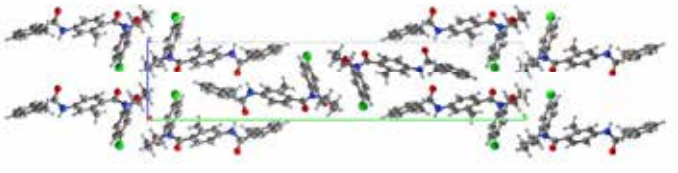
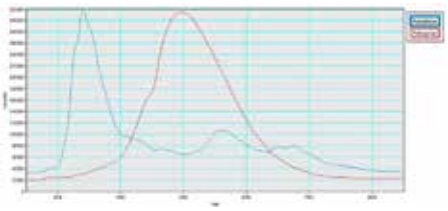
Scientific community have shown a growing interest in using Electron Microscopy based techniques to characterize pharmaceutical compounds due to inherent advantages for structure characterization at micron to nm scale. The major advantage of using Electron Microcopy based techniques are based to the fact that imaging, diffraction and spectroscopic analysis can be combined at the same time where in case of Transmission Electron Microscope (TEM) up to 1 nm image resolution can be obtained. In our work, we have used a TEM based technique (electron diffraction tomography [1] also known as MicroED) and Scanning Electron Microscopy (SEM) based technique (Cathodoluminescence/CL) imaging and spectroscopy to characterize pharmaceutical organic compounds in nm and micro meter resolution respectively. Using electron diffraction tomography in TEM under low dose conditions and using novel pixelated detectors, we have studied ab-initio structure solution of several known and unknown pharmaceutical compounds [2,3].The principle of TEM electron diffraction tomography method is sampling the reciprocal space in small steps (usually 1 degree tilt) by focusing the electron beam on a nanometer size crystal, which can be used to determine further crystallographic information. Using this novel diffraction technique it was possible to characterize compounds with short to long with unit cell (> 35 Å) and/or up to 2 molecules in the asymmetric unit (e.g. like carbamazepine, nicotinic acid, Ramelteon, Tolvaptan, Loratadine Form II, Linagliptin etc.) [2, 3]. In the inserted above image, structure solved from ED tomography data of Tolvaptan compound is shown.



On the other hand, we have used spectroscopy based technique like CL in SEM to fingerprint several organic pharmaceutical compounds.e.g. Linagliptin, Tolvaptan, Rivaroxaban, Ramelteon, Lacosamide, Clofarabine, Piroxicam, Loratadine etc. where we found that most of the compounds show unique characteristic CL spectra [4]. Therefore a proposed strategy to characterize a pharmaceutical sample could be to first use SEM -CL spectroscopy and compare its CL spectra with reference CL spectra of known phases; in case that does not match , proceed to further analysis using TEM electron diffraction tomography for full characterization of the compound of interest. In the right image, comparison of CL spectra of Ramelteon (blue colour curve) and Tolvaptan (red colour curve) is shown.



Therefore a combination of these two techniques could be a powerful tool to monitor pharmaceutical modifications and phase identifications.

Keywords: Electron Microscopy, Diffraction Tomography, Cathodoluminescence, Spectroscopy, Imaging

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Extensive Polymorph Screening of the Nucleobase Adenine

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Crystal structure prediction algorithms often result in densely populated energy landscapes, featuring a (very) high number of polymorphs. However, the experience tell us that a successful polymorph screening of small molecule is not likely to yield more than three polymorphs and a (couple of) amorphous phase(s). Success of the polymorph screening depends the optimization of three factors (i) the use of many different synthetic procedures to create new polymorphs, (ii) resolution and sensitivity of the X-ray diffractometer to detect the new polymorphs (iii) good understanding of the energy landscape and a possibility to rank the predicted structures.

This work presents how a combination of experimental techniques and theoretical methods can result in a surprising number of polymorphs, even if the molecule in question is very simple. The target molecule of this research is adenine, one of the smallest molecules of life. However, *ab initio* structure prediction conducted only in the common space groups resulted in more than 1500 low-energy structures. In order to explore the energy landscape, several synthetic paths were used: crystallization from a solution, sublimation, slurrying and thermally-induced phase transition. This resulted in four adenine polymorphs, of which only one was obtained as a single crystal. Further two were detected as a component in a powder mixture. This was possible only due to the fact that highly resolving diffractometers were used for the measurement, including a diffractometer optimized for *in situ* x-ray diffraction. As last, structure determination of these polymorphs was based on four different techniques: single crystal diffraction, powder diffraction, total scattering and *ab initio* structure prediction.

This focus of this work are the procedures used to obtain and characterize polymorphs, particularly on polymorphs detected in *in situ* powder diffraction studies. One new polymorph is characterized as a liquid crystal. The other polymorph cannot be isolated from the mixture, so a*b initio* structure prediction was used for its characterization. The novel laboratory diffractometer will also be presented.

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Keywords: crystal structure prediction, in situ, polymorph screening

Study Real Time Crystallization Process in Organic Crystals using Liquid Cell Transmission Electron Microscopy and Electron Crystallography Techniques on PDIs

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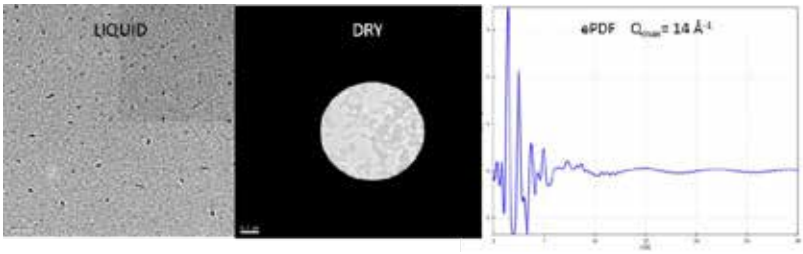
The industrial and scientific importance of organic crystals is revealed in a wide number of applications in various fields (pharmaceutical, biology, material science, etc.). Comprehension of the precipitation and crystallization process in those materials is of great importance; however, the mechanisms behind those processes are still not well understood [1]. It has been reported that "non classical" crystallization via amorphous intermediate precursors in solution is quite common [2]. The study of organic precursors evolution into final crystalline and defined morphologies poses real challenges to understand the process behind this [1]. Since the major part of such process occurs in solution, direct observation of the different reaction steps is usually followed either by spectroscopy methods and/or by drying the solution at different reaction time intervals and using TEM (Cryo) electron microscopy [3]. However, for a better consistency between "in-vivo" experiments carried out in solution and TEM cryo-electron microscopy observations, samples should have been prepared under exactly same conditions (i.e. avoid the drying process at different reaction time intervals)

In the last decade, new type of sealed liquid cells has been emerged for sample observation in a liquid environment in a TEM microscope. In those cells, thin (20 nm) amorphous Si_3N_4 films have been used as membranes containing a liquid layer (200 nm to several microns) and supported on Si microchips, usually placed on specially designed TEM holders; such design has allowed a number of exciting new experiments in materials and life science applications (crystal growth and catalysis, "in-situ" electrochemical processes, etc.)

On the other hand, using Electron Pair Distribution Function (e-PDF) allows to study local order of different substances (liquids to high/medium/low-range ordered solids) where is actually possible to perform such experiments in a TEM microscope at local nm scale. e-PDF technique (or alternatively X-Ray PDF) allows to monitor precisely crystallization and ordering effects in various systems [4]. Using ePDF within the LC has allowed to monitor also precisely the onset of crystallization from amorphous aggregate during the chemical reaction process.



Following the work done by [3] about the crystallization process in organic crystals and combining the power of novel TEM related techniques ("in situ" LC-TEM imaging + ePDF). We found exciting new evidences from the morphological to crystallographic point of view and crystallization process in case of organic compounds.

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Non-Standard Crystallization Methods of API´s & Electron Diffraction: The Future

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Crystallise! AG (Switzerland), a start-up company on its 4th year of operations, uses "non-standard" crystallization techniques to succeed where others have not succeeded to produce single crystals. Case examples of APIs and agro-chemicals will be showcased, including comparison of experimental and simulated powder patterns. Furthermore, Crystallise! will address the topic of Electron Diffraction. Based on a recent publication, where Crystallise! is co-author, the technology employed was nominated by Science, among 12 candidates, for breakthrough of the year 2018. An Electron Diffractometer and the potential for disrupting the analytical process in R&D and Quality Control departments will be addressed.

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JOINT MEETING

68TH ANNUAL DENVER X-RAY CONFERENCE & THE 25TH INTERNATIONAL CONGRESS ON X-RAY OPTICS AND MICROANALYSIS

5 - 9 August 2019

The Westin Lombard Yorktown Center, Lombard, IL, USA

Program Available Online

www.dxcicdd.com

DXC SPECIAL TOPICS IN X-RAY ANALYSIS SESSIONS

- New! Student Session - Education in X-ray Analysis
- New Developments in XRD/XRF Instrumentation (vendor/commercial presentations permitted)
- X-ray and Forensic Investigations
- Machine Learning Techniques in X-ray Analysis
- Cultural Heritage

DXC XRD SESSIONS

- General XRD
- Rietveld
- Stress/Texture/In-Situ
- Pair Distribution Function
- Applied and Functional Materials
- Small Angle X-ray Scattering of Advanced Functional Materials

DXC XRF SESSIONS

- General XRF
- Industrial Applications of XRF
- Quantitative Analysis of XRF
- Trace Analysis including TXRF
- Food Safety and Agriculture Applications

ICXOM-25 SESSIONS

- X-ray Optics
- New Detectors and Instrumentation
- Advanced XRF and SR Nanoprobes
- Data Analysis
- Biological Applications
- Earth & Environmental Sciences
- Cultural Heritage
- Functional Materials

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INTERNATIONAL CENTRE FOR DIFFRACTION DATA

LET OUR TEAM OF EXPERTS HELP YOU TAKE YOUR SKILLS TO THE NEXT LEVEL!

Practical X-ray Fluorescence Clinic:

April/May 2020

From theory to hands-on exercises, this course offers techniques and skills to improve lab performance. Discover the latest in cutting-edge instruments such as TXRF, hand-held devices, energy dispersive and wavelength dispersive spectrometers through live demonstrations.

The XRF course covers the basics of X-ray spectra; instrumentation design; methods of qualitative and quantitative analysis; specimen preparation and applications for both wavelength and energy dispersive spectrometry. The course emphasizes quantitative methods, use of automated X-ray spectrometers, review of mathematical matrix correction procedures, and new developments in XRF.

Fundamentals of X-ray Powder Diffraction Clinic:

3 – 7 June 2019

For the novice with some XRD knowledge or for the experienced with an interest in the theory behind XRD, this clinic offers a strong base for increased lab performance.

The clinic covers instrumentation, specimen preparation, data acquisition and qualitative phase analysis through live demonstrations. It also covers hands-on use of personal computers for demonstration of the latest software including data mining with the Powder Diffraction File (PDF) and use of the powder diffractometer: optical arrangement, factors affecting instrumentation profile width, choice and function of divergence slit, calibration and alignment, detectors, and X-ray optics.

Advanced Methods in X-ray Powder Diffraction Clinic:

10 – 14 June 2019

For the experienced XRD scientist, this session offers enhanced analysis skills through intense problem solving, as well as an introduction to the Rietveld Method. The course emphasizes computer-based methods of data collection and interpretation, both for qualitative and quantitative phase analysis.

The advanced clinic covers factors affecting d-spacings of crystals, as well as factors affecting diffraction-line intensities; structure-sensitive properties (atomic scattering and structure factors), polarization effects, and multiplicity. Additionally, the clinic covers specimen-sensitive effects (orientation, particle size), measurement-sensitive effects (use of peak heights and peak areas), and choice of scanning conditions will also be addressed.

Rietveld Refinement & Indexing Clinic:

23 – 27 September 2019

Powder pattern indexing and Rietveld structural refinement techniques are complementary and are often used to completely describe the structure of a material. Successful indexing of a powder pattern is considered strong evidence for phase purity. Indexing is considered a prelude to determining the crystal structure, and permits phase identification by lattice matching techniques. This clinic introduces the theory and formalisms of various indexing methods and structural refinement techniques along with quantitative analysis. One unique aspect of this clinic is the extensive use of computer laboratory problem solving and exercises that teach method development in a hands-on environment.

Please visit the ICDD website for more information.

Register today at WWW.ICDD.COM

Please note: A minimum of 10 registrants per course is required, otherwise the course will be cancelled and your registration fee will be refunded. You will be notified of a course cancellation no later than two weeks prior to the start of the course.

ICDD® International Centre for Diffraction Data

ISO 9001:2015 QUALITY MANAGEMENT SYSTEM CERTIFIED BY DEKRA CERT. NO. 110409.01

For More Information Contact

Eileen Jennings, Education Coordinator
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Email: clinics@icdd.com

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ICDD Headquarters, 12 Campus Boulevard
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2020 LUDO FREVEL Crystallography SCHOLARSHIP AWARDS

DEADLINE

Applications must be submitted online by

17 OCTOBER 2019

All applications must be submitted via the ICDD website at
www.icdd.com/index.php/ludo-frevel-scholarship

Over $494,750
in scholarships awarded since 1991!

DONATIONS: Scholarship awards are made possible by donations from both individuals and corporations. Contributions can be directed to the Ludo Frevel Crystallography Scholarship Fund at **http://www.icdd.com/index.php/ludo-frevel-scholarship/#donate**. 100% of all donations to the scholarship fund are applied to student funding, as defined by the program's charter. The Ludo Frevel Scholarship Program is a registered non-profit charity, and all donations are tax-deductible.

The science of crystallography has played a key role in the development of X-ray diffraction, electron diffraction and neutron diffraction for the elucidation of the atomic structure of matter. Crystallography is an interdisciplinary branch of science that is taught in departments of physics, chemistry, geology, molecular biology, metallurgy and materials science.

SCHOLARSHIP COMMITTEE

A committee, consisting of the ICDD Scholarship Committee Chairman, the ICDD Chairman, the Chairman of the ICDD Education Subcommittee, the ICDD Corporate Secretary, and three individuals without conflicts of interest, administers the awarding of the scholarships. One or more accredited professors (with no conflicts of interest) may be invited to assist in the selection of successful candidates.

APPLICANT QUALIFICATIONS

The applicant should be enrolled in a graduate degree program during the 2020 calendar year with major interest in crystallography — e.g., crystal structure analysis, crystal morphology, modulated structures, correlation of atomic structure with physical properties, systematic classification of crystal structures, phase identification and materials characterization. Students with a graduation date prior to 1 July 2020 are not eligible for the 2020 scholarship award. The term of the scholarship is one year. The recipient may submit an application for one renewal at the end of the first year. Because a limited number of scholarships are awarded, renewal applications will be considered on a competitive basis in conjunction with all applications that have been submitted up to the closing date.

EVALUATION OF APPLICATIONS

The amount of available funding limits the number of scholarships that can be granted in any given year. A selection committee will evaluate the applications received to determine which are most deserving of a scholarship. These evaluations consider both the proposal (impact, innovativeness, originality, efficacy of approach, and relationship to crystallography) and the student (recommendation letter, educational track record, prior work and/or research, honors, awards, and professional activities) in determining which applicants will receive the award.

There is a limitation of one award per educational institution. In the event that two or more candidates from one institution are considered to be among the top applicants, only one will be given an award.

SCHOLARSHIP FUND RESTRICTIONS

The scholarship award is to be used by the graduate student to help defray tuition and laboratory fees. A portion of the award may be applied to registration fees and travel costs to attend accredited scientific meetings related to crystallography, where the recipient is presenting results of work performed as part of his or her graduate studies.

HOW TO APPLY

Applications must be submitted online by 17 October 2019

1. A description of the candidate's proposed graduate degree research (*two-page limit*) including:

- Purpose and rationale for the research
- Proposed methodology to be used in the study
- References and/or descriptions of the scientific background for the proposed research

2. A curriculum vitae including:

- Educational preparation (institutions, dates, degrees obtained and in progress, and particularly-pertinent course work)
- Awards, honors received
- Any research publications and/or presentations given
- Any work experience (dates, employers, positions)
- Professional activities, memberships

All applications are to be submitted online at the ICDD website: **http://www.icdd.com/index.php/ludo-frevel-scholarship**. Please follow the instructions on that web page.

The preferred method of application is via the web; however, if you require an alternate method, please contact **Stephanie Jennings** at **sjennings@icdd.com** or **610.325.9814**.

Submission of the two documents below must be in PDF format. You will also be asked for the contact information of your primary research advisor. An email will be sent to this advisor seeking a letter of recommendation on your behalf. His/her letter must be submitted on or before the deadline date.

International Centre for Diffraction Data
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ICDD 04/19

PPXRD-16 and SPS-XRPD-2 Program-at-a-Glance

Thursday, 9 May – Sunday, 12 May 2019

All events will be held at the PSI Auditorium, unless otherwise noted.

Day	Time	Event
Thursday 9 May Workshop	8:30 am	Workshop: Laboratory and Synchrotron XRPD – Advantages and Disadvantages Instructors: **Philip Willmott, Tom Blanton, Fabia Gozzo, Pamela Smith**
	12:30 pm	Lunch
	1:30 pm	Tour: Visit PSI Large Scale Facilities
	4:00 pm	Coffee Break
	4:30 pm	Welcoming Remarks; Chairs: **Tom Blanton, Fabia Gozzo, Pamela Smith**
	5:00 pm	Opening Plenary: Industry Speaks to Academia
	6:00 pm	Reception *(ends at 7:30 pm)*
Friday 10 May Sessions	8:30 am	Plenary: Intellectual Property Rights, Counterfeit Drugs - Dedicated to Joel Bernstein**;** Chair: **Steve Byrn**
	10:30 am	Coffee Break
	11:00 am	API Phase Stability; Chair: **Tom Blanton**
	12:10 pm	Lunch
	1:15 pm	Qualitative & Quantitative Phase Analysis; Chair: **Detlef Beckers**
	2:55 pm	Coffee Break
	3:30 pm	Synchrotron XRPD Beamlines Overview; Chairs: **Fabia Gozzo; Chris Benmore**
	5:40 pm	Case Studies*;* Chair: **Mickael Morin** *(ends at 6:15 pm)*
	7:30 pm	Conference Dinner at Brugg ODEON
Saturday 11 May Sessions	9:00 am	Flash Poster Session; Chair: **Barbara Ramirez**
	10:00 am	Coffee Break
	10:30 am	Amorphous, Mesomorphous, Nano Materials; Chairs: **Shawn Yin**, **Steve Byrn**
	12:30 pm	Lunch
	2:00 pm	Biological & Biosimilar Drugs; Chair: **Pamela Smith**
	3:10 pm	Coffee Break
	3:30 pm	PDF Guidelines Discussion; Facilitators: **Steve Byrn, Pamela Smith, Fabia Gozzo** *(ends at 5:30 pm)*
Sunday 12 May Sessions	8:30 am	Software, Database, Laboratory Instrumentation; Chair: **Arnt Kern**
	9:40 am	Coffee Break
	10:10 am	Structure Determination; Chair: **To be announced.**
	12:10 pm	Lunch
	1:30 pm	Structure Determination – *Continued*
	2:30 pm	Coffee Break
	2:50 pm	Complementary and Emerging Techniques and Methodologies; Chair: **Stavros Nicolopolous**
	4:50 pm	Closing Remarks (*Symposium closes at 5:00 pm*)