PPXRD-17
Pharmaceutical Powder
X-ray Diffraction Symposium

Program & Abstracts

17th Pharmaceutical Powder X-ray Diffraction Symposium

21 – 24 May 2023 • ICDD Headquarters

Sponsored by ICDD and MDI

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PPXRD-17 Organizing Committee

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PPXRD-17 Program

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Social Events and Posters

Symposium Reception

A reception will be held in conjunction with the Poster Session on Tuesday evening, 23 May, from 4:15 – 6:00 pm EDT, in the ICDD Lounge.

Posters

Posters can be set on Monday evening, 22 May or Tuesday morning, 23 May. Poster boards will be set around the ICDD education wing. All posters should be set by 4:15 pm on Tuesday, 23 May. Posters can remain on display up until the end of the symposium. Please note, ICDD is not responsible for any posters left by the author(s). Posters can be fastened to the board with provided pushpins or Velcro.

Exhibitor Information

Exhibition

Exhibits are located in the back of the symposium room from Sunday, 21 May until Wednesday, 24 May. Please visit with our exhibitors during coffee breaks and lunches. Exhibits will close at the conclusion of the symposium.

Exhibiting Companies

Bruker AXS

www.bruker.com

Representative: *Nathan Henderson, Nathan.Henderson@bruker.com*

Bruker provides cutting-edge instruments for structural and chemical analysis. Powder and single crystal diffraction (XRPD and SCXRD) aid in the discovery of new APIs and polymorphs and in salt and solvate screens. Diffraction experiments find use in the characterization of amorphous processes like hot melt extrusion and spray-dried dispersions. XRPD also helps with complex studies like accelerated aging, variable relative humidity, stability, quality control, and quantification of formulated drug products. For more information, visit us at bruker.com/xrd.

Malvern Panalytical

www.malvernpanalytical.com

Representative: *Kuo-Chih Shih, kuo-chih.shih@malvernpanalytical.com*

When you make the invisible visible, you make the impossible possible. Malvern Panalytical is the leading supplier of innovative chemical, biophysical and structural characterization solutions along with drug discovery and development. Our knowledge and expertise address the analytical challenges in this field, delivering tangible economic impact. XRPD is an invaluable tool for polymorph screening, QA/QC, stability studies and more.

Proto

www.protoxrd.com

Representative: *Izabela Kolodziej, ikolodziej@protoxrd.com*

Proto is an X-ray diffraction (XRD) manufacturer focused on driving scientific advancement. We are proud to offer a high-throughput powder diffractometer that is ideal for rapid screening and drug development. Coupled with our CFR-compliant software, each Proto powder system provides a turn-key package designed to optimize your pharmaceutical work. Our other powder instruments include versatile compact units as well as powerful laboratory systems. Proto's powder XRD systems are highly configurable and come in a range of size/power options, ensuring that you find the ideal platform for your application. Proto is committed to delivering not only a quality product, but world-class service and support that you can count on long after the initial sale.

International Centre for Diffraction Data

www.icdd.com

Representative: *Ben Hish, hish@icdd.com*

For over 80 years, we have focused on meeting the needs of the scientific community through the publication of the Powder Diffraction File™ (PDF®) and providing forums for the exchange of ideas and information. ICDD's material identification databases interface with diffractometers and data analysis systems of the world's leading software developers and manufacturers of X-ray equipment. The Powder Diffraction File is available in PDF-2, PDF-4+, PDF-4/Minerals, PDF-4/Organics, and PDF-4/Axiom. The 2023 release of PDF-4+ features 19,355 new entries.

Rigaku Europe SE

www.rigaku.com

Representative: *Dan Roberts, dan.roberts@rigaku.com*

Rigaku is here to help you navigate through the complex pharmaceutical lifecycle (discovery, pre-formulation, formulation, and manufacturing & control) with an extensive array of analytical equipment and experience. From elemental purity through molecular identity to structure/microstructure and polymorphism, we offer unique solutions for pharmaceutical professionals.

Rigaku supports the future of drug development with revolutionary small-angle X-ray scattering (SAXS) instruments specifically built for automated imaging of large molecules and nano-delivery systems. For elemental and contaminant analysis, our offerings range from high-power, high-performance wavelength dispersive WDXRF systems to benchtop EDXRF systems. Our structural analysis solutions embrace a wide range of diffraction solutions from Electron Diffraction Single Crystal analysis through multipurpose cutting edge SmartLab solutions to the MiniFlex benchtop solution. Our diffraction solutions are integrated with unique software methods and applications for pharmaceutical materials.

Sunday Afternoon Workshop, 21 May 2023

ICDD Headquarters

Fundamentals of Powder X-ray Diffraction

Instructors: **Simon Bates,** Rigaku Americas, USA**, Tom Blanton,** International Centre for Diffraction Data, USA, **Anisha Patel,** Merck, USA, **Raj Suryanarayanan,** University of Minnesota, USA, **Shawn Yin,** Bristol-Myers Squibb Company, USA

1:30 pm **Simon Bates**: Fundamentals of Pharmaceutical Powder X-ray Diffraction – Part 1 (Groups 1 & 2)

- X-rays and X-ray generation
- Scattering and diffraction
- Gas, liquid and solid samples
- Amorphous and crystalline
- Debye ideas and Bragg/Laue ideas
- Debye Scherrer rings
- X-ray optics
- Detector choices
- Common measurement concerns

2:30 pm **Simon Bates**: Fundamentals of Pharmaceutical Powder X-ray Diffraction – Part 2 (Group 1)

- Dealing with organics
- General rules of thumb for sample prep and measurements
- Information content in a powder pattern
    - Peak positions
    - Peak widths
    - Peak intensities
    - Relative intensity and absolute intensity
    - Diffuse scatter
    - Background
- Visual analysis (sameness and difference)
- Identification and discriminate analysis
- Quantification
- Brief overview of common space groups and indexing

2:30 pm **Tom Blanton**: Hands-on Sample Preparation Demonstrations (Group 2)

3:30 pm Coffee Break

4:00 pm **Simon Bates**: Fundamentals of Pharmaceutical Powder X-ray Diffraction – Part 2 (Group 2)

- Dealing with organics
- General rules of thumb for sample prep and measurements
- Information content in a powder pattern
    - Peak positions
    - Peak widths
    - Peak intensities
    - Relative intensity and absolute intensity
    - Diffuse scatter
    - Background
- Visual analysis (sameness and difference)
- Identification and discriminate analysis
- Quantification
- Brief overview of common space groups and indexing

4:00 pm **Tom Blanton**: Hands-on Sample Preparation Demonstrations (Group 1)

5:00 pm ***End of Day 1***

Monday Workshop, 22 May 2023

ICDD Headquarters

Fundamentals of Powder X-ray Diffraction *(continued)*

Instructors: **Simon Bates,** Rigaku Americas, USA**, Tom Blanton,** International Centre for Diffraction Data, USA, **Anisha Patel,** Merck, USA, **Raj Suryanarayanan,** University of Minnesota, USA, **Shawn Yin,** Bristol-Myers Squibb Company, USA

9:00 am	**Raj Suryanarayanan and Tom Blanton**: Applications of Pharmaceutical Powder X-ray Diffraction • Qualitative analysis of drug substance and drug product • Overview of the crystallographic database
10:30 am	Coffee Break
11:00 am	**Raj Suryanarayanan and Tom Blanton**: Applications of Pharmaceutical Powder X-ray Diffraction *(continued)* • Quantitative analysis, sources of error, and advanced applications • Advanced analysis using the crystallographic database
12:30 pm	Lunch
1:30 pm	**Shawn Yin and Anisha Patel**: Industrial Applications of XRD • Industry best practices and PXRD through drug development • Regulatory aspects, GMP analysis, and Industrial case studies
3:30 pm	Coffee Break
4:00 pm	**All Instructors**: Panel Discussion Q&A • Attendees are encouraged to bring real-life problems with data (if allowable)
5:00 pm	***End of Day 2***

Tuesday Sessions, 23 May 2023

ICDD Headquarters

Plenary Session: Intellectual Property

Chair: Tom Blanton, International Centre for Diffraction Data, USA

9:00 am		Opening Remarks **Tom Blanton,** PPXRD Organizing Committee Chair, International Centre for Diffraction Data, USA
9:10 am	P20	Invited - Procuring and Defending Solid Form Patents **Eyal H. Barash,** Barash Law LLC, USA
9:50 am		Exhibitor Introductions
10:10 am		Coffee Break

Amorphous, Mesomorphous, Nano Materials

Chair: **Simon Bates,** Rigaku Americas, USA

10:30 am	P6	Characterization of Polymers Used in Pharmaceutical and Biomedical Applications **Tom Blanton, M. Rost, D. Bohnenberger,** International Centre for Diffraction Data, USA
11:00 am	P4	Quantitative Studies on Mixture of Cellulose and Lanthanum Carbonate **Meredith Shi, S. Bates,** Rigaku Americas Corporation, USA

API Phase Stability / Non-ambient Analysis

Chair: **Raj Suryanarayanan,** University of Minnesota, USA

11:30 am	P11	Simultaneous XRD-DSC Analysis Identifies Correct Solid Form Dissolution in Polymer **Mustafa Bookwala, P. Wildfong,** Duquesne University, USA **J. Shi, S. Bates,** Rigaku Americas Corporation, USA
12:00 pm	P8	Phase Stability and Polymorphism of New Naproxen Salts **Martin Schreyer, G. Nénert, N. Dadivanyan,** Malvern Panalytical B.V., the Netherlands
12:30 pm		Lunch

Critical Quality Attributes

Chair: **Shawn Yin,** Bristol-Myers Squibb Company, USA

1:30 pm	P12	Invited - Polymorphs in a Pandemic: Leveraging Synchrotron PXRD to Enable Rapid Development of a Covid-19 Antiviral **Melissa Tan, J.A. Newman, J. Bothe, A. Brunskill,** Merck & Co., USA
2:10 pm	P14	Invited - GMP XRPD: Drug Development Phase Appropriate Method Validation Strategy and the Challenge to Cope With Current Guidelines Versions **Matteo Daldosso,** Aptuit, an Evotec Company, Italy
2:50 pm		Coffee Break

3:10 pm P7 Application of Direct Derivation Method to Accurately Determine Minor Amorphous/Polymorph Impurities in Pharmaceutical Material
Ron Chen, A. Chadha, N. Loka, Y. Gan, Mirati Therapeutics, Inc, USA
S. Bates, Rigaku Americas Corporation, USA

3:40 pm P22 Enhancing the Accuracy of QPA Calibration Curves Close to the Limit of Detection
Fabia Gozzo, M. Reinle-Schmitt, M. Morin, F. Costa, Excelsus Structural Solutions, Switzerland

Poster Session & Reception

4:15 – 6:00pm, ICDD Lounge
Chair: **Tom Blanton,** International Centre for Diffraction Data, USA

P3 Crystal Structures of Large-Volume Commercial Pharmaceuticals
James A. Kaduk, North Central College, Illinois Institute of Technology, Poly Crystallography Inc., USA
T. Ens, N. Boaz, North Central College, USA
A. Dosen, T. Blanton, ICDD, USA

P18 Controlling Pharmaceutical Release via Hydrogen-bonded Networks
Joy-Lynn Kobti, V.N. Vukotic, University of Windsor, Canada

P19 Therapeutic Coordination Polymer Glasses as Controlled Drug-Release Materials
Michelle Dao, V.N. Vukotic, University of Windsor, Canada

P21 Determination of Time-Temperature-Transformation Curve for Sulfonyl Urea Analogues in the Presence of a Crystallization Inhibitor Using Simultaneous XRD-DSC
Mustafa Bookwala, P. Wildfong, Duquesne University, USA
J. Shi, S. Bates, Rigaku Americas Corporation, USA

Wednesday Sessions, 24 May 2023

ICDD Headquarters

Software, Database, Laboratory Instrumentation

Chair: **Tom Blanton,** International Centre for Diffraction Data, USA

9:00 am	P9	High Angle Liquid Cell Tem Tomography and 3D Imaging-Diffraction Studies in Liquid **Partha Pratim Das, A.G. Perez, E. Grivas, S. Nicolopoulos,** NanoMegas SPRL, Belgium **J.G. Casablanca,** Universidad Rey Juan Carlos, Spain **J. Cookman,** University of Limerick, Ireland **S. Plana-Ruiz,** Universitat Rovira i Virgili, Spain **M. Lopez-Haro, J.J. Calvino,** Universidad de Cádiz, Spain
9:30 am	P16	Invited - X-ray Instrumentation and Applications for Pharmaceutics **Bob B. He, N. Henderson,** Bruker AXS, USA
10:10 am	P13	PDF-5+: A Comprehensive Powder Diffraction File™ for Materials Characterization **Soorya Kabekkodu, J. Blanton, T. Blanton,** International Centre for Diffraction Data, USA
10:40 am		Coffee Break

Structure Determination and Refinement

Chair: **Arnt Kern,** Bruker AXS GmbH, Germany

11:00 am	P24	Invited - Structural Studies of Biogenic and Synthetic Uric Acid Salts: Analogous Hydrogen Bonded Frameworks **Tim Fawcett,** International Centre for Diffraction Data, USA **A.M. Thornton, J.A. Swift,** Georgetown University, USA **G.W. Schuett,** Chiricahua Desert Museum & Georgia State University, USA **J.A. Kaduk,** North Central College, USA
11:40 am	P17	Synchrotron X-ray Powder Diffraction: Instruments and Case Studies **Peter Stephens,** Stony Brook University, USA
12:10 pm	P5	Quantitative Matching of Crystal Structures to Experimental Powder Diffractograms Using the Variable-Cell Powder Difference (VC-PWDF) Method **R. Alex Mayo, E. R. Johnson,** Dalhousie University, Canada **K.M. Marczenko,** University of Guelph, Canada
12:40 pm		Lunch

Complementary and Emerging Techniques

Chairs: **Natalia Dadivanyan,** Malvern Panalytical, Germany

Fabia Gozzo, Excelsus Structural Solutions sprl, Switzerland and Belgium

1:40 pm	P27	Invited – The Power of Using Spectroscopic Techniques to Complement X-ray Diffraction in the Development of Pharmaceutical Oral Dosage Forms **Luc Aerts, K. Van Hollebeke, S. Le Meur, C. Rougeot, L. Hutsebaut, N. Darkouch, C. Didelot, N. Bostijn, B. Pignon**, UCB Pharma, Chemin du Foriest, Belgium

2:20 pm P15 XtaLAB Synergy-ED: Single Crystal Structures from Powders
Joseph D. Ferrara, S. Bates, Rigaku Americas Corporation, USA
R. Bücker, F. White, Rigaku Europe SE, Germany
M. Jasnowski, M. Meyer, Rigaku Polska, Poland
S. Ito, A. Yamano, Rigaku Corporation, Japan
Y. Aoyama, E. Okunishi, JEOL Ltd., Japan

2:50 pm P26 Single Crystal X-ray and Electron Diffraction Experiments for the Pharmaceutical Industry: From Non-Standard Crystallization Techniques to Insitu-Crystallization for ED Experiments
Gustavo Santiso-Quinones, Crystallise! AG, Switzerland

Low Angle and Small Angle Scattering

Chair: **Julien Giovannini,** AstraZeneca R&D, Sweden

3:20 pm P10 Structural Characterization for LNPs by Using Small-Angle X-ray Scattering (SAXS)
Kuo-Chih Shih, M. Brown, Malvern Panalytical, USA

3:50 pm Closing Remarks - The symposium with end at 4:00 pm
Tom Blanton, PPXRD Organizing Committee Chair, International Centre for Diffraction Data, USA

Notes

Procuring And Defending Solid Form Patents

Eyal Barash
Barash Law LLC
eyal.barash@ebarashlaw.com

Solid form patents, such as those directed to salts, cocrystals and the like, are commonly listed orange book patents protecting innovator drug products. Between 2015 and 2022, over 80 small molecule drug approvals had at least one patent listed covering a solid form. This presentation will discuss both the concepts behind obtaining such patents as well as how court decisions have evolved in the United States on how such patents stand up to the test of litigation. Explored topics include the concepts of novelty and obviousness in the relationship between solid forms of APIs whose corresponding free base or free acid, as the case may be, is known in the art. In addition, we will discuss recent case law from the United States Court of Appeals for the Federal Circuit, the appellate court which has jurisdiction over all patent appeals in the United States.

Characterization Of Polymers Used In Pharmaceutical And Biomedical Applications

T. Blanton, M. Rost, D. Bohnenberger
International Centre for Diffraction Data, Newtown Square, PA, USA

tblanton@icdd.com

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

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

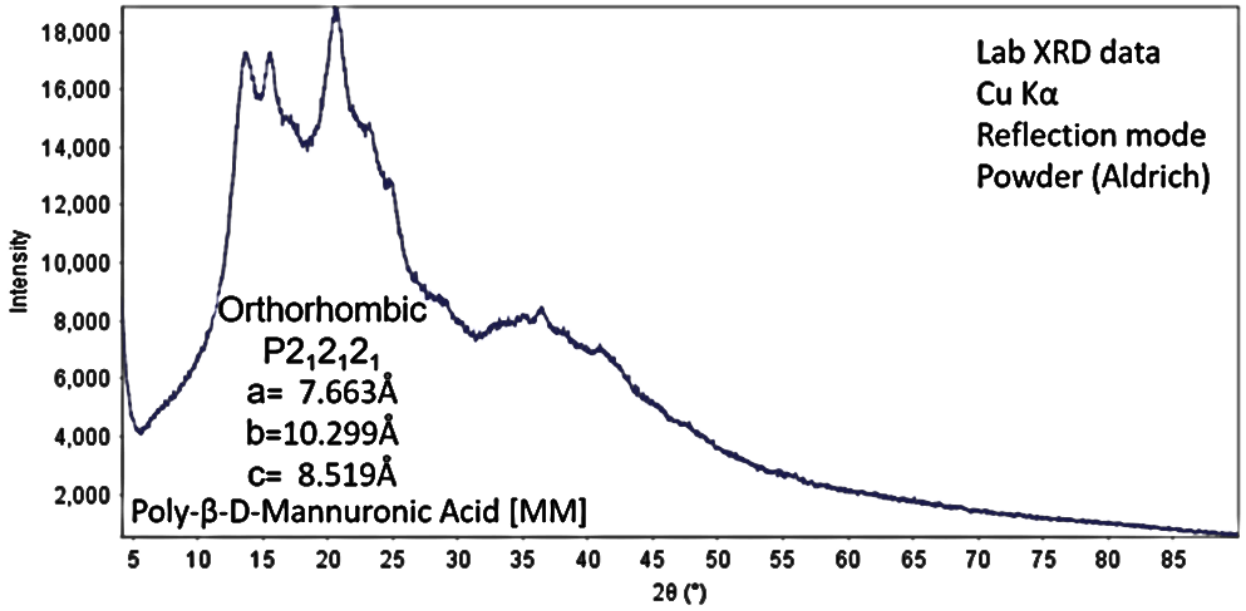

Figure 1. X-ray diffraction pattern (Cu Kα radiation) for alginic acid, poly-β-D-mannuronic acid [MM] type, used as a drug delivery excipient.

QUANTITATIVE STUDIES ON MIXTURE OF CELLULOSE AND LANTHANUM CARBONATE

Meredith Shi, Simon Bates

Rigaku Americas Corporations, 9009 New Trails Drive, The Woodlands, TX, 77381

Component analysis methods making use of Total Diffraction data and Fundamental Parameters allow for absolute quantitative analysis of mixed samples without requiring any standard mixture samples or calibration. To test the Component analysis approach against a more traditional quantitative Rietveld approach, a series of mixtures were prepared of cellulose and lanthanum carbonate hydrate for x-ray powder diffraction (XRD) analysis. Lanthanum carbonate is a non-calcium phosphate binder for kidney disease, bone disorder etc. This mixed system of high/low density solid forms is considered to be challenging for quantitative analysis as: 1) cellulose (MCC) is a mixed micro-crystalline/amorphous form with very broad diffraction peaks; 2) the high/low density mixture gives severe micro-absorption contrast adding to the complexity of quantitative analysis; 3) lanthanum carbonate hydrate loses water in the presence of ‘dry’ cellulose acting as a variable hydrate; 4) penetration depth differences between the two phases gives biased particle statistics. The comparative results between Component Analysis and Rietveld analysis, both considered to be standardless quantitative approaches, will be compared.

SIMULTANEOUS XRD-DSC ANALYSIS IDENTIFIES CORRECT SOLID FORM DISSOLUTION IN POLYMER

Mustafa Bookwala[1], Jiawanjun Shi[2], Simon Bates[2], and Peter L. D. Wildfong[1]
[1]Duquesne University, Graduate School of Pharmaceutical Sciences, Pittsburgh, PA
[2]Rigaku Americas Corporation, The Woodlands, TX
bookwalam@duq.edu; wildfongp@duq.edu

Poorly water-soluble drugs can potentially be formulated as amorphous solid dispersions (ASD), allowing improvement in API apparent solubility. ASD polymer selection usually requires estimation of drug solubility in prospective polymer-carriers. Traditionally, differential scanning calorimetry (DSC) is used for measuring the dissolution of the drug in the polymer, however, molecules having polymorphs with difficult-to-resolve melting temperatures (T_m) that undergo interconversions on heating, can result in incorrect solubility determinations. Therefore, the application of simultaneous XRD-DSC was investigated to determine the solubility of the form of interest in the polymer.

The well-established dissolution endpoint (T_{end}) method was used to evaluate the solubility of a sulfonylurea 4-bromo-N-(propylcarbamoyl) benzenesulfonamide (*i.e.,* bromopropamide) in the co-polymer polyvinylpyrrolidone-vinyl acetate (PVPVA). Cryomilled physical mixtures of bromopropamide and PVPVA were prepared, in which polymer concentrations ranged from 0 to 40 %w/w, with the total milling time ranging from 10 – 60 min. Milled samples weighing between 10 – 15 mg were placed on an aluminum DSC pan. The DSC unit heated the samples to 150 °C at 1 °C/min to determine the T_{end}. During all experiments, the sample environment was maintained at less than 5% RH using a humidity controller. The XRD experiments were conducted simultaneously with DSC temperature changes by irradiation of samples with Cu Kα X-rays (λ = 1.5406 Å) generated at 45 kV and 200 mA. The XRD data were collected over the range of 7 – 33 °2θ at an integrated step size of 0.02 °2θ at a rate of 10 °2θ/min.

When heated at 1 °C/min, the low-temperature stable enantiotrope of bromopropamide (form-1) melted at $T_{m,endpoint}$ = 133 °C, followed by recrystallization to the high-temperature stable enantiotrope (form-2), which then melted at $T_{m,endpoint}$ = 140 °C. Simultaneous XRD patterns were collected for each form during the heating of bromopropamide. Diffractograms were used to confirm or identify the T_{end} for the corresponding polymorphs in PVPVA. The addition of increasing quantities of PVPVA to bromopropamide resulted in a reduction of T_{end} to lower temperatures for both forms. At higher PVPVA concentrations, the DSC heat flow signal was suppressed for form-2 relative to form-1. At polymer concentrations above 20 %w/w, the heat flow signal for form-2 was undetectable. Simultaneous XRD measurements, however, revealed that form-1 dissolves and then recrystallizes in the PVPVA matrix to form-2, which then dissolves in the polymer. Simultaneous XRD-DSC aided in confidently measuring the T_{end} for bromopropamide form-2 across multiple PVPVA concentrations. Additionally, XRD-DSC helped to determine the T_{end} for form-1 in PVPVA concurrently with form-2 and identify a polymer concentration above which the conversion of form-1 to form-2 is kinetically restricted, even on heating to higher temperatures.

Materials having polymorphs with similar T_m that undergo solid-form transitions on heating can increase the complexity or possibly mislead the measurement of T_{end} if characterized using only DSC. The application of simultaneous XRD-DSC can, therefore, provide correct conclusions and help select a polymer for ASD development effectively.

PHASE STABILITY AND POLYMORPHISM OF NEW NAPROXEN SALTS

Gwilherm Nénert, Martin Schreyer, Natalia Dadivanyan
Malvern Panalytical B. V., Lelyweg 1, 720E EA Almelo, The Netherlands;
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Sodium naproxen is widely used as a non-steroidal anti-inflammatory active pharmaceutical ingredient (API). The crystal structure of this API has been reported in 1990 [1]. This remains the single known polymorph despite three decades of research on this API. Physicochemical stability is a serious problem during new drug development and thus pseudo-polymorphism has been widely investigated for sodium naproxen. So far, four hydrates have been reported and characterized [2]. So, while the pseudo-polymorphism is rather rich, polymorphism is unusually simple with only one known representative. This is a rather unusual case as polymorphism for APIs tends to be rather rich [3]. Besides the sodium salt, various hydrated naproxen salts of general formula $M[C_{14}H_{13}O_3]_2.xH_2O$ have been reported in the literature: M = Zn (x = 3), M = Ni (x = 10), M = Cu (x = 4) and M = Cd (x =1 and 3) [4].

In this contribution, we report the crystal structure of a new dihydrate naproxen salt and investigate its temperature dependence demonstrating a rich polymorphism as illustrated in Figure 1. This work demonstrates for the first time the existence of polymorphism for an anhydrate naproxen salt. This raises the question of possible polymorphism for other salts of naproxen-based materials.

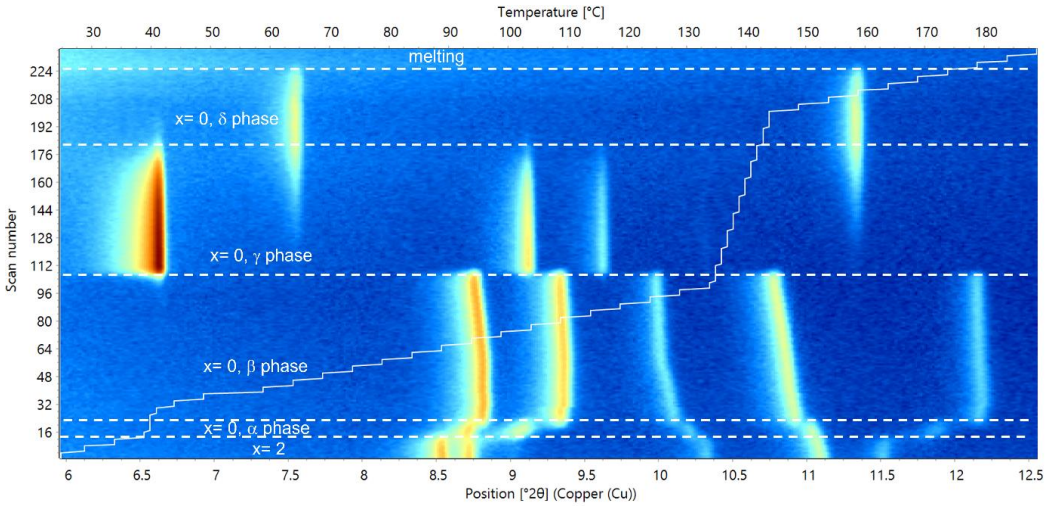

Figure 1:Isoline plot of the temperature dependence of a new naproxen salt of general formula $M[C_{14}H_{13}O_3]_2.xH_2O$ (dihydrate x = 2, and anhydrate, x = 0) in the temperature range 25 < T < 190°C.

[1] Y. B. Kim, I. Y. Park, and W. R. Lah, *Arch. Pharm. Res.*, 1990, **13**, 166
[2] A. D. Bond, C. Cornett, F. H. Larsen, H. Qu, D. Raijada, and J. Rantanen, *IUCrJ*, 2014, **1**, 328
[3] E. H. Lee, *Asian Journal of Pharmaceutical Sciences*, 2014, **9**, 163
[4] Y.-T. Wang, G.-M. Tang, W.-Z. Wan, Y. Wu, T.-C. Tian, J.-H. Wang, C. He, X.-F. Long, J.-J. Wang and S. Weng Ng, *CrystEngComm*, 2012, **14**, 3802.

Polymorphs In A Pandemic: Leveraging Synchrotron PXRD To Enable Rapid Development Of A Covid-19 Antiviral

Melissa Tan[1], Justin A. Newman[1], Jameson Bothe[1], Andrew Brunskill[1], [1]Analytical Research & Development, Merck & Co., melissa.shuk.chaen.tan@merck.com

In May 2020, Merck and Ridgeback Biotherapeutics announced a partnership to develop an oral antiviral compound, originally discovered at Emory University, as a treatment to reduce hospitalization and death associated with the novel coronavirus. This essential medicine promised to change the outlook of the pandemic by achieving sustained recovery.

During the development of molnupiravir and prior to achieving Emergency Use Authorization (EUA) from the FDA and other global regulatory agencies, two anhydrous polymorphs of molnupiravir—Form 1 and Form 2—were discovered, introducing questions around the stability, solubility, and bioavailability of each form. The crystal structure of Form 1 was confirmed by single crystal X-ray diffraction, and served as an important data point in assigning the tautomeric state of the compound in the solid state. In contrast, the structure of Form 2 was determined by Rietveld refinement with synchrotron powder diffraction data and corroborated by crystal structure prediction (CSP).

This talk focuses on how the development team leveraged high resolution powder diffraction data to assist in characterization of the new polymorph, providing confidence in the form landscape, and positioning the team to successfully achieve EUA both domestically and abroad.

GMP XRPD: DRUG DEVELOPMENT PHASE APPROPRIATE METHOD VALIDATION STRATEGY AND THE CHALLENGE TO COPE WITH CURRENT GUIDELINES VERSIONS

Matteo Daldosso
Aptuit, an Evotec Company, Verona, Italy
matteo.daldosso@evotec.com

Crystal structure of new chemical entities (NCE) became among the years a critical quality attribute of new API and drug products. Different Polymorphs may have different physico – chemical properties, affecting the performance in terms of efficacy and potentially safety of the pharmaceutical products (remember the Ritonavir Case?).

X-ray powder diffraction (XRPD) is a key tool for characterizing the structural order or disorder of solid APIs or DP, identifying the solid forms of any given polymorph, solvate, co-crystal or salt by distinctive combinations of diffraction peaks and order parameters. Unique X-ray powder diffraction (XRPD) patterns can also distinguish the different phases, or polymorphs, within a particular material, confirmed by comparing profiles against reference materials and a library database of expected polymorphs. XRPD is crucial for pharmaceutical products characterization and control.

Solid state scientists must face the challenge of obtaining XRPD data in compliance with the regulations (e.g., GMP), guidelines (e.g., ICH) and authority's requirements and expectations since the objective of the characterization and QC activities is to ensure and assure that the pharmaceutical product can be released safely and in an accurate manner for human use with all the critical quality attributes under control. This means to have in place an overall quality system of the lab that includes the solid-state techniques, like XRPD.

Despite the importance of the solid form control in API and Drug Products from the early phases of development up to commercial, the international guidelines (e.g., ICH) are not always crystal clear on the requirements to perform XRPD in full compliance (as well as other solid state analytical techniques).
The requirements in terms of XRPD method development and validation according to an incremental approach to validation based on development phase and the related criteria to prove method specificity, precision, accuracy et al., will be matter of discussion considering pharmacopeia indications and the current and future versions of the ICH guidelines (including Q2 and Q14).

Application of Direct Derivation Method to Accurately Determine Minor Amorphous/Polymorph Impurities in Pharmaceutical Material

Ron Chen*[1], Aastha Chadha[1], Nikhil Loka[1], Yonghong Gan[1], Simon Bates[2] and Cletus Nunes[1]

1. Mirati Therapeutics, Inc, 3545 Cray Court, San Diego, CA 92121
2. Rigaku Americas Corporation, 9009 New Trails Drive, The Woodlands, TX 77381-5209

X-ray powder diffraction (XRPD) is a powerful analytical technique to characterize the physical quality and structural attributes of pharmaceutical material (drug substance, intermediate and drug product). It is widely used qualitatively in crystalline form identification, polymorph screening and API crystallization as well as quantitatively in crystallinity, phase purity and composition analysis in pharmaceutical research and development.

Quantitative phase purity and composition analysis using peak intensity(area), or ratio of peak intensity(area) is the most common method in pharmaceutical QC labs. However, for pharmaceutical materials, accuracy and precision can be challenging as the samples will typically exhibit a wide particle size distribution, crystal habits favoring preferred orientation, disorder, and other crystal quality issues. In addition, the diffraction signal can show variability depending on sample preparation.

Hideo Toraya et al at Rigaku developed a new method for quantitative phase analysis called Direct Derivation and has demonstrated the utility of the method in quantifying crystalline mixtures as well amorphous components in mixtures (J. Appl. Cryst. (2019). 52, 13-22). The method was implemented into the Rigaku Smartlab Studio II software as a plugin that users can utilize to develop quantitative phase analysis method. In this presentation, we will share our experience with two real life applications: one is amorphous content formation during tableting that resulted in impurity growth in stability studies. We need an accurate and sensitive method to quantify the small amount of amorphous content to help with tableting process development and in-process quality control. The second application is a method for quantification of a minor polymorph that may be produced in API crystallization. In both cases, we were able to achieve 1-2% LLOQ for the amorphous content and the minor polymorph impurity. The method was found to be accurate across the whole concentration range (LLOQ-100%). XRPD raw data were acquired with Rigaku benchtop MiniFlex 6G. Critical parameters related to sample preparation and data processing will be discussed in detail.

Enhancing the Accuracy of QPA Calibration Curves Close To the Limit of Detection

Fabia Gozzo – Excelsus Structural Solutions – Switzerland

Quantification of crystalline phases via Rietveld refinement is an established and powerful analytical approach of quantification. The Rietveld method, however, requires that we dispose of a valid structure model for every single crystal form present in the mixture and the validity requirement of structure models becomes very stringent when we aim at accurately quantify small amounts of crystal forms, i.e. below 0.1-0.5%wt. The stability of the refinement also strongly depends on our ability to accurately model the extrinsic (not sample-dependent) and intrinsic (sample-dependent) background, which is often a hard exercise in the case of pharmaceutical compounds. Amorphous component is quantified as a whole, provided we spike the analyte with a known amount of a known standard.

When one or more of such requirements cannot be fulfilled, the Rietveld method is not appropriate approach and model-free approaches based on total scattered intensities and/or multivariate analysis are a better option. Model-free approaches, however, rely of calibration curves and their accuracy relies on the accuracy of such calibration curves. Accurate calibration curves are, furthermore, a powerful tool to quote accuracy in Rietveld QPA (Quantitative Phase Analysis) as well.

Constructing calibration curves implies the generation of *ad-hoc* physical mixtures to cover the %wt interval we are interested in. Typically, we aim at calibration curves with at least 5-10 points besides the 0% and 100% extrema. Physical mixtures are accurately prepared and made as homogeneous as possible via geometric addition of the minority phase, via a turbula® or milling, when this is tolerated by the materials under investigation. Then, a subsample of such physical mixtures is measured, which is expected to be representative of the entire mixtures. Volumetric inhomogeneities are, however, very often observed, especially when dealing with electrostatic pharmaceutical powders. Often such inhomogeneities become worse when powders are loaded in capillaries as a phase separation occurs at this stage, therefore mitigating all efforts of getting a homogeneous mixture via patient and careful mixing. We present here a new methodology we have developed and tested that allows us to get accurate calibration curves based on the accurate measurement of the mass of the mixture components and totally independent of the homogeneity of the mixtures. Results will be presented on ad-hoc atorvastatin mixtures as well as with an interesting example of the methodology applied to a real industrial case.

CRYSTAL STRUCTURES OF LARGE-VOLUME COMMERCIAL PHARMACEUTICALS

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As part of a continuing project, the room-temperature crystal structures of eight commercial pharmaceutical APIs have been solved and refined using synchrotron X-ray powder diffraction data (11-BM at APS), and optimized using density functional techniques. *Danofloxacin mesylate* $(C_{19}H_{21}FN_3O_3)(CH_3O_3S)$ crystallizes in space group *P1* with $a = 6.77467$, $b = 12.4975$, $c = 12.8277$ Å, $\alpha = 84.8277$, $\beta = 87.7524$, $\gamma = 74.9923°$, $V = 1044.67$ Å^3, and $Z = 2$. *Meglumine diatrizoate* $(C_7H_{17}NO_5)(C_{11}H_8I_3N_2O_4)$ crystallizes in space group $P2_1$ (#4) with $a = 10.74697(4)$, $b = 6.49364(2)$, $c = 18.52774(7)$ Å, $\beta = 90.2263(3)$, $V = 1292.985(5)$ Å^3, and $Z = 2$. *Encorafenib* $C_{22}H_{27}ClFN_7O_4S$ crystallizes in space group $P2_1$ (#4) with $a = 16.17355(25)$, $b = 9.52338(11)$, $c = 17.12368(19)$ Å, $\beta = 89.9928(22)$, $V = 2637.49(4)$ Å^3, and $Z = 4$. *Omadacycline dihydrate* $C_{29}H_{40}N_4O_7(H_2O)_2$ crystallizes in space group *R3* (#146) with $a = 24.34435(8)$, $c = 14.55213(5)$ Å, $V = 7468.849(29)$ Å^3, and $Z = 9$. *Nicarbazin* $(C_{12}H_{10}N_4O_5)(C_6H_8N_2O)$ crystallizes in space group *P-1* (#2) with $a = 6.90659(8)$, $b = 12.0794(4)$, $c = 13.5040(7)$ Å, $\alpha = 115.5709(11)$, $\beta = 102.3658(6)$, $\gamma = 91.9270(4)°$, $V = 982.466(5)$ Å^3, and $Z = 2$. *Oxfendazole* $C_{15}H_{13}N_3O_3S$ crystallizes in space group $P2_1/c$ (#14) with $a = 18.87326(26)$, $b = 10.40333(5)$, $c = 7.25089(5)$ Å, $\beta = 91.4688(10)°°$ $V = 1423.206(10)$ Å^3, and $Z = 4$. *Butenafine hydrochloride* $C_{23}H_{28}NCl$ crystallizes in space group $P2_1$ (#4) with $a = 13.94807(5)$, $b = 9.10722(2)$, $c = 16.46676(6)$ Å, $\beta = 93.9663(5)°$, $V = 2086.733(8)$ Å^3, and $Z = 4$. *Besifloxacin hydrochloride* $C_{19}H_{22}ClFN_3O_3Cl$ crystallizes in space group *P1* (#1) with $a = 5.36596(8)$, $b = 10.3234(4)$, $c = 17.9673(14)$ Å, $\alpha = 98.122(5)$, $\beta = 92.9395(9)$, $\gamma = 96.1135(3)°$, $V = 977.483(13)$ Å^3, and $Z = 2$. All of structure solutions presented "interesting" features. Other new structures may be presented as they become available.

Controlling Pharmaceutical Release via Hydrogen-bonded Networks

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A recent 2020 study estimates that it requires 10+ years and costs up to $2.8 billion to bring a new drug to market.[1] Considering this, it would be highly advantageous to be able to improve the therapeutic effect of medications we already have available. Many drugs suffer from a narrow therapeutic index (i.e., the difference between toxic and therapeutic levels) and poor solubility, which ultimately limits their bioavailability and efficacy.[2] Controlled-release systems can improve the solubility and performance of hydrophobic drugs, enhancing their bioavailability. Previous work on crystalline solid-state formulations such as polymorphs, solvates, and co-crystals has been extensively studied to address this issue. However, the drug's release rate can potentially be improved by embedding the neutral drug into a hydrogen-bonded network. Previous work has shown that guanidinium cations and disulfonate anions can be used to encapsulate small organic molecules.[3] My work explores using guanidinium cations and 4,4-biphenyldisulfonate anions to form a hydrogen-bonded salt network capable of encapsulating various hydrophobic pharmaceuticals (**Fig.1**). The networks are synthesized via solution techniques. Crystal structures, as well as phase purity, will be established by X-ray diffraction techniques, and the solubility enhancement in comparison to the drug's free form will be reported.

References

1. Wouters, O. J., McKee, M., & Luyten, J. (2020). Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *Jama*, *323*(9), 844-853.
2. Habet, S. (2021). Narrow Therapeutic Index drugs: clinical pharmacology perspective. *Journal of Pharmacy and Pharmacology*, *73*(10), 1285-1291.
3. Russell, V. A., Evans, C. C., Li, W., & Ward, M. D. (1997). Nanoporous molecular sandwiches: pillared two-dimensional hydrogen-bonded networks with adjustable porosity. Science, 276(5312), 575-579.

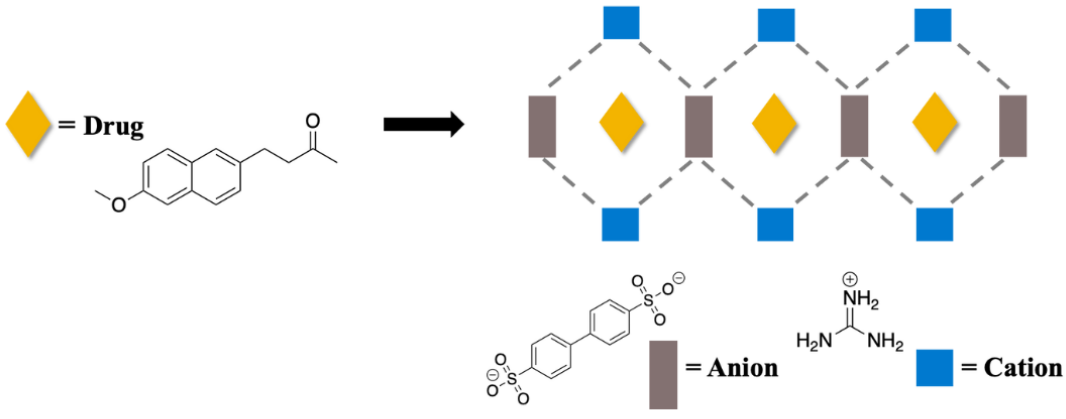

Figure 1. Hydrogen-bonded network for the controlled release of hydrophobic drugs.

Therapeutic Coordination Polymer Glasses as Controlled Drug-Release Materials

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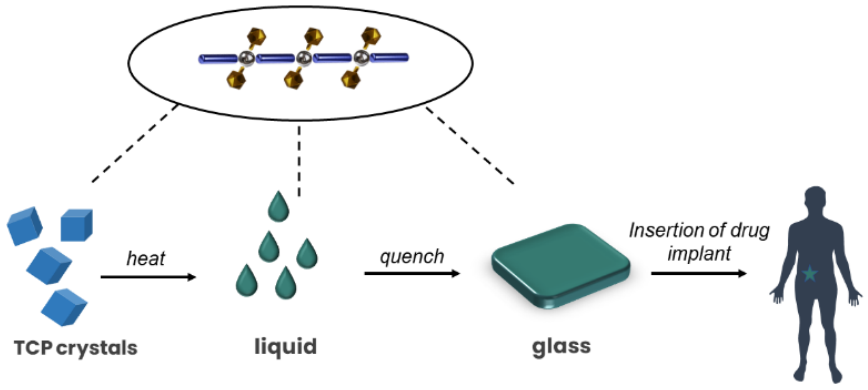
Driven by the increasing demand for rapid advancements in biomedicine, billions of dollars are spent annually on discovering novel pharmaceuticals that offer safer and more effective treatments and diagnoses. New classes of hybrid materials, namely, coordination polymers (CPs) have emerged as promising new platforms for controlled drug release systems. Herein, we have recently developed novel imidazole- and pyridine- based Cu (II) therapeutic coordination polymers (TCPs) for the controlled release of Non- Steroidal Anti-Inflammatory Drugs (NSAIDS), diclofenac and ibuprofen. In our approach, the pharmaceutical is encapsulated during the synthetic procedure and released based on a surface degradation mechanism to avoid undesirable drug release kinetics and reproducibility issues. Our materials have demonstrated high drug loading capabilities, facile synthesis, and most notably, extended slow controlled drug release under simulated bodily conditions. In addition, we report the rare event of melting of crystalline nicotinate-based Cu (II) TCPs consisting of ibuprofen which result in amorphous glasses upon cooling. We successfully demonstrated the moldability of our materials in its melt form, which highlights its potential for real clinical therapies as drug-releasing implants for the controlled release of the NSAID ibuprofen. The melting behavior of our materials were characterized with DSC, TGA, and VT-PXRD. The molecular structure and physical properties of the crystalline and glass forms of our TCPs were also investigated with VT-EPR and PDF, which will be presented.



Scheme 1. Graphical representation of abstract.

DETERMINATION OF TIME-TEMPERATURE-TRANSFORMATION CURVE FOR SULFONYL UREA ANALOGUES IN THE PRESENCE OF A CRYSTALLIZATION INHIBITOR USING SIMULTANEOUS XRD-DSC

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Molecularly homogeneous drug-polymer dispersions are known to physically stabilize amorphous drugs against recrystallization. Identification of crystallization induction times (T_{ind}) under several isothermal conditions allows the construction of time−temperature-transformation (TTT) plots, which inform about the physical stability of an amorphous binary system. In this research, we constructed the TTT curves for chlorpropamide and tolbutamide in the presence of 5 %w/w polyvinyl pyrrolidone-vinyl acetate co-polymer (PVPVA), using a combined X-ray diffraction-differential scanning calorimeter (XRD-DSC) instrument.

The T_{ind} was identified for both chlorpropamide and tolbutamide at 7 different isothermal conditions between the glass transition temperature (T_g) and melting temperature (T_m). The TTT curves for both molecules in the presence of PVPVA show the phase boundary, representing T_{ind}, partitioning the completely amorphous phase from the amorphous/crystalline phase mixture. The curve was characterized by a "nose temperature" that exhibited the minimum time for glass destabilization between the T_g and T_m. Although the nose temperature was the same (T_g + 50) for both systems, the onset time at T_g + 50 was 2.4X longer for chlorpropamide (73.98 ± 3.31 s) than tolbutamide (30.96 ± 4.84 s) in the presence of 5 %w/w PVPVA. The T_{ind} was consistently longer for chlorpropamide relative to tolbutamide at temperatures lower than the nose temperature. In contrast, at temperatures greater than the nose temperatures, the recrystallization onsets for both materials were within the deviation of each measurement. These data suggested that the glass stability for chlorpropamide was higher than tolbutamide in the presence of 5 %w/w PVPVA at temperatures closer to its T_g, whereas both drugs had similar recrystallization onsets near their respective T_m.

Building TTT curves for a drug helps determine temperature-related glass stability for the solid. Determination of T_{ind} can be analytically challenging, especially for drug-polymer systems. Simultaneous XRD-DSC helped measure onset times while also providing extensive information about the polymorphs that grew from the melt. The TTT diagrams constructed for the two sulfonylureas showed that amorphous chlorpropamide in the presence of PVPVA was more stable at temperatures close to its T_g relative to tolbutamide.

HIGH ANGLE LIQUID CELL TEM TOMOGRAPHY AND 3D IMAGING-DIFFRACTION STUDIES IN LIQUID

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Liquid-Cell (LC) electron microscopy (EM) is a rapidly emerging field in Transmission Electron Microscopy (TEM) [1]. While 2D LC observations are common for inorganic, Organic and biological samples, studies of objects using electron tomography (Imaging, Chemical Mapping or Diffraction) in liquid are scarce mainly due to very limited available tilt range of the current LC holders (e.g. usually ± 35 º). To perform such electron tomography, LCs need to reach high angular ranges, preferably > 140º (± 70 º) to extract reliable 3D information. Since such LC do not exist currently, we have developed a prototype "tomographic" LC (label Tomochip) by modifying a commercial LC (K-Kit from Bio MA-TEK), whose original total inclination angular range is about 60º (±30º), to extend its range to about 120º (± 60 º) [2]. Central part of such LC viewing window can be tilted ±70º with an effective observation area of 100µm x 25µm. We found that when LC spacer is 100-200 nm, it is very probable that samples (e.g. 3D objects) may stay still inside the observation area for long periods of times (e.g. several minutes), which is adequate in order to perform tomography experiments within the liquid.

For image Tomography, as a proof of concept we have studied beam induced crystal growth of Form III of Flufenamic acid (FFA) in our Tomochip at 100 kV. We minimized total tomography acquisition time by performing 10° tilt steps from -50° to 50°, while crystals were maintained still inside the liquid during tilt. We have also studied 3D carbon particles within water in a Tomochip where images were collected from 70°to 70° with every 5° tilt step. In both cases TomoJ (v2.6) plugin for tomographic reconstruction of the ImageJ (v1.53e) image processing program has been used. 3D image tomography was reconstructed using Total Variation Minimization reconstruction algorithm.

For diffraction Tomography/3DED, as a proof of concept we have studied CeO2 nanoparticles in water medium and data was collected between -60° to 60° with 1° tilt step. From 3D ED data it was possible to unit cell determination which matches with the reported unit cell (a = 3.88 Å b = 3.88 Å c = 6.06 Å, 90 ° 90 ° 120 °) of CeO2.

[1] F. Ross (Ed.) (2016) "Liquid Cell Electron Microscopy (Advances in Microscopy and Microanalysis)", (Cambridge University Press, Cambridge)
[2] Devices and Methods for High angle liquid Electron Tomography, WO2021123305A1

Keywords: In situ, Liquid, Pharmaceuticals, Crystal Growth, Tomography

X-RAY INSTRUMENTATION AND APPLICATIONS FOR PHARMACEUTICS

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This presentation explores recent advancements in X-ray instrumentation and applications for pharmaceuticals. These advancements include new X-ray sources, optics, detectors, and designs. For example, the microsource is a new X-ray source that runs on low power but delivers high-quality, brilliant X-rays. Additionally, advancements in detector technology have expanded the variety of detector choices for specific configurations and applications. The newly-introduced Hybrid Photon Counting (HPC) pixel detector, for instance, enables diffraction data collection with high frame rates, high dynamical range, and high resolution in either 1D or 2D mode. This makes it suitable for fast data collection with large angular coverage, such as high-throughput screening and in-situ measurement of time-sensitive phase transformations and chemical reactions.

X-ray diffraction plays an essential role in drug discovery and development, covering many applications such as phase identification, structure solution and refinement, crystallinity, particle size and distribution, amorphous phase characterization, in-situ monitoring of phase transformations or chemical reactions, and high-throughput screening. Different sample forms and quantities, including solid, liquid, gel, or powder, can be analyzed. However, one configuration of an X-ray diffractometer may not be optimal for all applications and sample forms. Therefore, a diffractometer with a suitable X-ray source, optics, detector, and easy switch between several configurations would benefit labs requiring various XRD applications and productivity.

X-ray Microscopy (XRM) is another powerful instrument that provides 3D insights into pharmaceutical products. It is nondestructive and requires minimal to no sample preparation.

References:

[1] Bob He, "*Two-dimensional X-ray Diffraction, 2nd Edition*", John Wiley & Sons, (2018).

[2] Thakral, S., Terban, M. W., Thakral, N. K., & Suryanarayanan, R. (2015). Recent advances in the characterization of amorphous pharmaceuticals by X-ray diffractometry. Advanced drug delivery reviews, (2015).

PDF-5+: A Comprehensive Powder Diffraction File™ For Materials Characterization

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For more than 80 years, the scientific community has extensively used International Centre for Diffraction Data's (ICDD®) Powder Diffraction File (PDF®) for materials characterization, mainly by powder X-ray diffraction. Historically the Powder Diffraction File was made available in two major formats: one for inorganic analysis and the other for organic analysis. In the early years of the PDF, it was deliberately done like this due to the typical computer capabilities of that time. In the upcoming release of 2024, ICDD will provide a comprehensive database consisting of the entire Powder Diffraction File in one database called PDF-5+. This database will have more than one million entries (1,061,898). The PDF-5+ with a relational database (RDB) construct houses extensive chemical, physical, bibliographic, and crystallographic data, including atomic coordinates and raw data, enabling qualitative and quantitative phase analysis. This wealth of information in one database is advantageous for phase identification, characterization, and several data mining applications in materials science. A database of this size needs rigorous data curation and structural and chemical classifications to optimize pattern search/match and characterization methods. Every entry in the Powder Diffraction File has an editorially assigned quality mark. An editorial comment will describe the reason an entry does not meet the top-quality mark. Among several classifications implemented in PDF-5+, subfiles (such as Bioactive, Pharmaceuticals, Minerals, etc.) directly impact the search/match in minimizing false positives. Scientists with specific field expertise continuously review these subfiles to maintain their quality.

ICDD has responded to the growing need for database requirements in pharmaceutical characterization using powder X-ray diffraction by implementing a unique project targeting pharmaceutical data acquisition, including raw data and customized subfiles. Several database features that enable material characterization with an emphasis on pharmaceuticals will be discussed in this presentation.

Structural Studies of Biogenic and Synthetic Uric Acid Salts: Analogous Hydrogen Bonded Frameworks

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Abstract

The structural characterization of some uric acid salts, especially those associated with biological processes, has been a difficult challenge owing to their propensity to rapidly precipitate as powders or poorly formed microcrystals. The present study arose from ongoing investigations of urates produced by several reptile species. Commonalities observed across their various powder diffraction patterns, along with prior literature studies and associated PDF entries, identified potential candidates for Rietveld refinement. VASP and DFT calculations were utilized to identify likely motifs and three new hydrate structures of ammonium urate and potassium urate. Each structure is characterized by extensive networks of hydrogen-bonded urates where the water serves to interlink layers of anions.

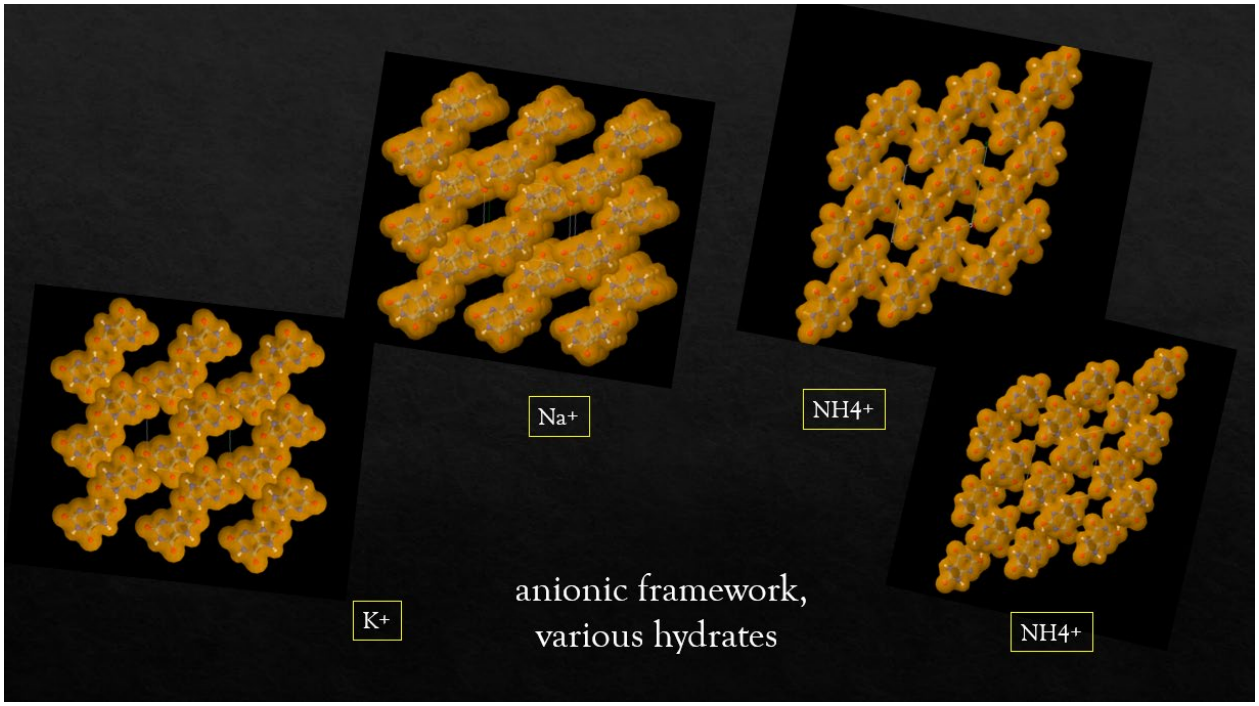

Figure 1. Several hydrated salts of uric acid. The cations and water are located within the channels.

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 projects that were enabled by synchrotron powder diffraction:

- Determining that a particular active pharmaceutical ingredient (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.

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* This talk is dedicated to the memory of Joel Bernstein.

Quantitative Matching of Crystal Structures to Experimental Powder Diffractograms Using the Variable-Cell Powder Difference (VC-PWDF) Method

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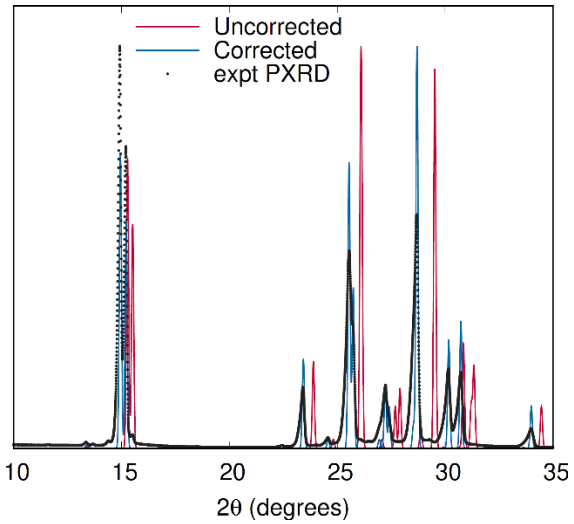
The identification and classification of crystal structures is critical in pharmaceutical drug development, both from a performance and intellectual property standpoint. Being able to identify the same crystallographic form from unique origins (e.g. different temperatures, pressures, or *in silico*-generated) is a complex challenge. The use of the variable-cell powder difference (VC-PWDF) method[1] to match collected experimental powder diffractograms to both experimental crystal structures from the Cambridge Structural Database, and *in silico*-generated structures, will be discussed. The VC-PWDF method is shown to correctly identify the most similar crystal structure to both moderate and "low" quality experimental powder diffractograms for a set of 7 representative organic compounds. Features of the powder diffractograms that are more challenging for the VC-PWDF method are discussed (i.e. preferred orientation), and comparison with the Fit with DEviating Lattice (FIDEL) method[2] showcases the advantage of the VC-PWDF method provided the experimental powder diffractogram can be indexed.



[1] Mayo, R.A.; Otero de la Roza, A.; Johnson, E.R., *CrystEngComm*, **2022**, *24*, 8326-8338.
[2] Habermehl, S.; Mörschel, P.; Eisenbrandt, P.; Hammer, S.M.; Schmidt, M. U., *Acta Crystallogr.*, **2014**, ***B****70*, 347-359.

The Power Of Using Spectroscopic Techniques To Complement X-Ray Diffraction In The Development Of Pharmaceutical Oral Dosage Forms

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Control of the physical form of active pharmaceutical ingredients (APIs) and excipients is of prime importance in pharmaceutical development of solid dosage forms like tablets and capsules. A specific form of an API is mostly chosen for reasons of physical stability, while also guaranteeing an appropriate dissolution and absorption behavior. A change of physical form can on top also entail differences in chemical stability as each solid form provides its specific chemical protective environment to the molecules.

To control the physical form of the API during the development of an oral dosage form, powerful analytical techniques are hence of utmost importance. With this respect, it can be stated unambiguously that X-Ray Diffraction (XRD) is the golden standard. Applied on single crystals it is the reference technique to assess the crystalline structure and can even provide an experimental proof of the chirality of a molecule. Via powder diffraction, XRD is the reference technique to identify different forms like (pseudo-)polymorphs or salts or co-crystals. Crystallinity can also be assessed, as well as ratios of forms. Via enhanced techniques like synchrotron radiation even very subtle changes can be detected.

XRD remains nevertheless a 'structural' technique and is little sensitive to chemical aspects. This is even more prominent when amorphous phases are involved, as XRD as such shows hardly any specificity towards amorphous systems. Therefore, at UCB, we have been embracing the last decade a set of complimentary techniques, all spectroscopical. Most prominent ones are Solid State NMR, Raman and Infra-Red (IR) spectrometry. The power of these techniques is that they respond more to changes in the chemical environment and in that sense also show a high sensitivity for changes in intra- and intermolecular interactions. While XRD is the reference for structural phenomena, it needs to be acknowledged that there is no rule indicating which of the spectroscopic techniques mentioned above will be most powerful to detect specific transitions. Often a screening of the different techniques is needed to select the most appropriate one for a specific case.

A welcome feature of both Raman and IR is the possibility to complement the bulk data with chemical imaging providing a spatial view on the observed changes throughout the oral dosage form.

The presentation aims to illustrate the power of a combination of XRD with NMR, Raman or IR, by showing a few case studies. The possibilities in quantification of the different physical phases by the mentioned techniques will also be discussed.

XtaLAB Synergy-ED: Single Crystal Structures from Powders

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The Rigaku XtaLAB Synergy-ED is a fully integrated electron diffractometer, with a seamless workflow from data collection to 3D structure determination. The Synergy-ED is the result of Rigaku's collaboration with JEOL, synergistically combining each partner's core technologies: Rigaku's hybrid pixel array detector (HyPix-ED) and CrysAlis^{Pro} software, and JEOL's long-standing excellence in electron beam generation and control.

Using MicroED, a three-dimensional electron diffraction method, single crystals of all classes below one micron in size can be studied. The Synergy-ED offers the ability to determine the single crystal structure from a single grain from powder samples. In fact, one can determine the single crystal structure of multiple compounds present in a single powder sample.

There are two well-characterized polymorphs of acetaminophen with known single crystal structures. In this presentation we will explore the case of a third polymorph of acetaminophen generated in an XRD-DSC experiment with a structure determined by MicroED. This result is a major step in understanding the properties of acetaminophen and demonstrates to potential to solve many more unsolved problems in structural science.

Single Crystal X-ray and Electron Diffraction Experiments for the Pharmaceutical Industry: From Non-Standard Crystallization Techniques to *Insitu*-Crystallization for ED Experiments

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Abstract:

Single crystal X-ray diffraction (SCXRD) and Electron Diffraction (ED) (also known as micro-ED) experiments are complementary techniques to XRPD which can provide answers which XRPD techniques might not be able to address. For example, SCXRD can provide a direct confirmation of the absolute configuration of an Active Pharmaceutical Ingredient (API). Furthermore, from SCXRD experiments, a simulation of the powder pattern can be produced which then can be compared to the experimental XRPD. Impurities, or other phases present in the bulk can be easily identified by a simple comparison, i.e, the finger print of the crystal measured is as pure as it could be.

ED is an emerging technique which has a lot of potential. ED experiments are equivalent to SCXRD experiments with the great advantage that nano-crystalline powders can be used instead of micro-sized crystals. Because in ED experiments, each nano-crystalline particle studied is treated as a single (nano)-crystal, electron diffraction can provide information which might not be detected or be available in standard XRPD experiments of the bulk. Furthermore, even when high resolution XRPD might detect a low-level impurity or an extra phase in the bulk, ED can provide easier the structure and therefore, a better understanding of the underlying problem.

Crystallise! AG will showcase some none-common crystallization experiments of APIs and chemical compounds and exemplify on the potential of SCXRD experiments as complementary technique for XRPD. Furthermore, we will talk about ED and the potential this technology has. Some case studies will be showcased too. Last but not least, Crystallise! will show a case study of a direct crystallization on TEM grids using < 10 μg of sample for ED experiments.

Structural Characterization for LNPs by Using Small-Angle X-ray Scattering (SAXS)

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Small-angle X-ray scattering (SAXS) is a powerful technique that can be used to characterize the structure of nanomaterials. These materials include, but is not limited to, liposomes and lipid nanoparticles (LNPs). LNPs have been used for the 3rd generation vaccines and has drawn a lot of attention since the surge of COVID-19. Malvern Panalytical provides a slit smear SAXS solution (ScatterX78) that can be used as an accessory for the current floor standing Empyrean XRD system [1]. A discoidal shape lipid nano disc, also known as Bicelles, are used to validate the data obtained by ScatterX78. The same structural parameters can be used to fit the data obtained from the synchrotron source as well as the data from Empyrean, showing that ScatterX78 is capable of performing effective SAXS experiments. Like all other scattering techniques, SAXS is based on the contrast i.e., electron density differences, to distinguish different structural characteristics. Hence, SAXS is a perfect tool to answer a question that has long existed in the development of 3rd generation vaccines: where is the payload? Figure 1 (a) shows three simulated scattering curves with the slit smear function put into consideration. Figure 1 (b-d) are the schematic representations for each scenario including: 1. no payload (green trace); 2. the payload is at the aqueous core of the liposome (orange trace) and 3. the payload is not only in the aqueous core of the liposome but also at the surface of the liposome (red trace). It is clear to see that by using SAXS, one is able to distinguish all these three scenarios. In addition, SAXS can also help to probe the structural differences before and after freeze-thaw cycle (stability test).

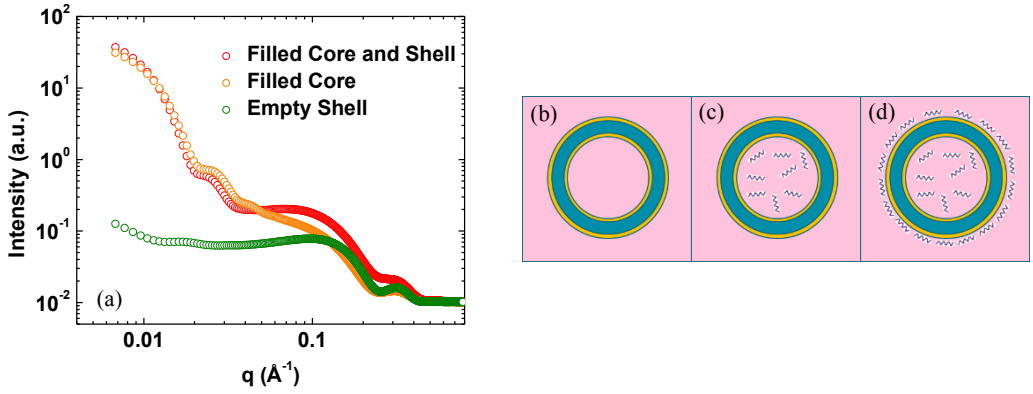

Figure 1. Simulated SAXS pattern from liposomes with 100 nm in radius with no payload (a, green trace & b), payload in the aqueous core (a, orange trace & c) and payload in both aqueous core and the surface of liposome (a, red trace &d) Note: the data shown here is generated by SASView to prove the concept. None of the data is from the actual sample from MP's customer.

References

[1] Bolze, Joerg, Vladimir Kogan, Detlef Beckers, and Martijn Fransen. "High-performance small-and wide-angle X-ray scattering (SAXS/WAXS) experiments on a multi-functional laboratory goniometer platform with easily exchangeable X-ray modules." Review of Scientific Instruments 89, no. 8 (2018): 085115.

Notes

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For More Information Contact:

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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.

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- 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:

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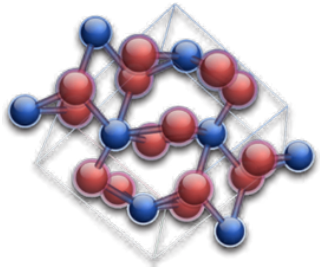

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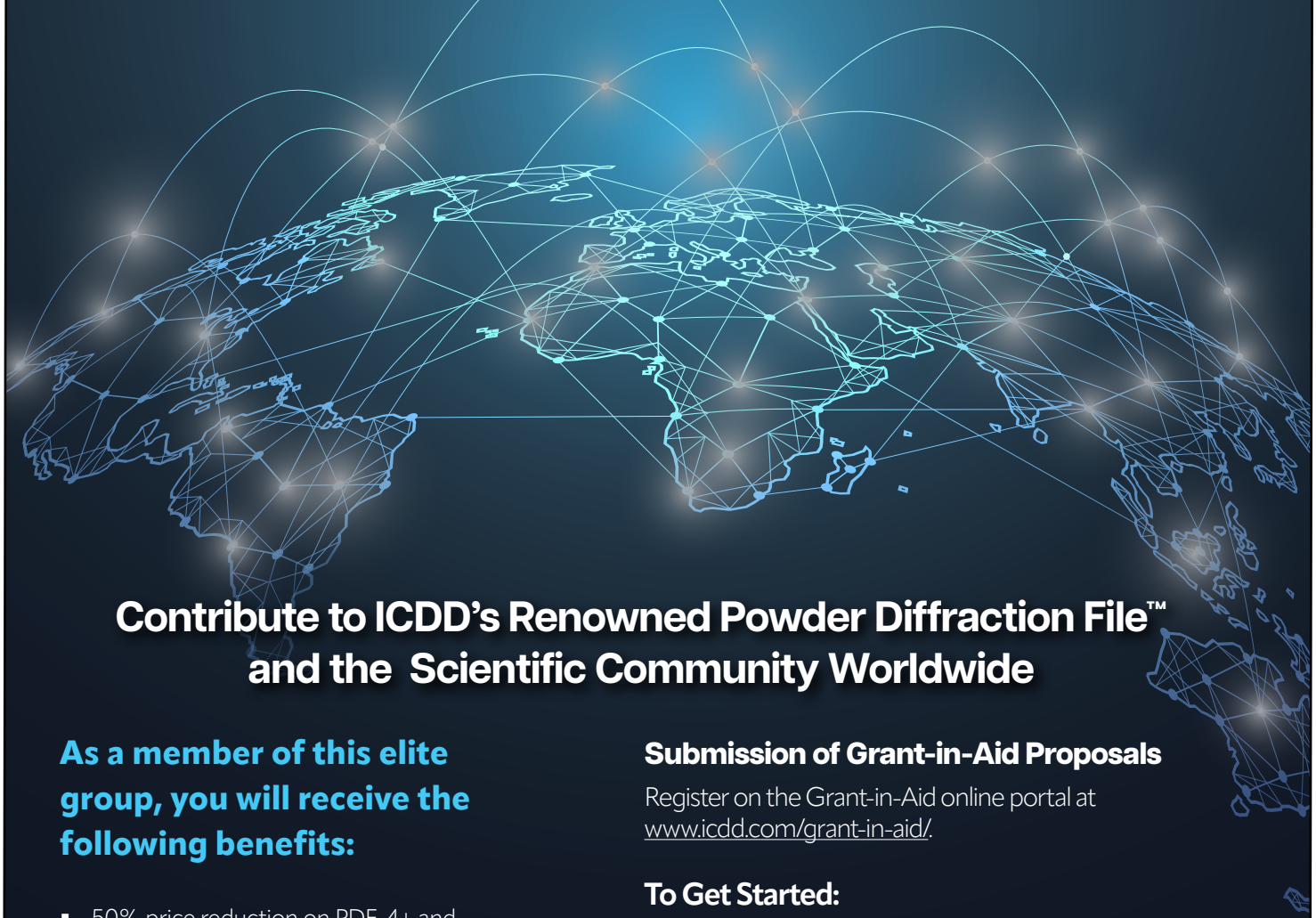

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Pharmaceutical Powder X-ray Diffraction Symposium

21-24 May 2023
ICDD Headquarters • Newtown Square, PA, USA

PPXRD-17 Program-at-a-Glance

DAY	TIME	EVENT
Sunday 21 May Workshop	12:30 pm	Lunch / Attendee Check-in
	1:30 pm	Workshop: Fundamentals of Powder X-ray Diffraction – Part 1 (Groups 1 & 2); Instructor: **Simon Bates**
	2:30 pm	Workshop: Fundamentals of Pharmaceutical Powder X-ray Diffraction – Part 2 (Group 1); Instructor: **Simon Bates**
	2:30 pm	Workshop: Hands-on Sample Preparation Demonstrations (Group 2); Instructor: **Tom Blanton**
	3:30 pm	Coffee Break
	4:00 pm	Workshop: Fundamentals of Pharmaceutical Powder X-ray Diffraction – Part 2 (Group 2); Instructor: **Simon Bates** *(ends at 5:00pm)*
	4:00 pm	Workshop: Hands-on Sample Preparation Demonstrations (Group 1); Instructor: **Tom Blanton** *(ends at 5:00pm)*
Monday 22 May Workshop	9:00 am	Workshop: Applications of Pharmaceutical Powder X-ray Diffraction; Instructors: **Raj Suryanarayanan** and **Tom Blanton**
	10:30 am	Coffee Break
	11:00 am	Workshop: Applications of Pharmaceutical Powder X-ray Diffraction *(continued)*; Instructors: **Raj Suryanarayanan** and **Tom Blanton**
	12:30 pm	Lunch
	1:30 pm	Workshop: Industrial Applications of XRD; Instructors: **Shawn Yin** and **Anisha Patel**
	3:30 pm	Coffee Break
	4:00 pm	Workshop: Panel Discussion Q&A; Instructors: **All** *(ends at 5:00pm)*
Tuesday 23 May Sessions	9:00 am	Opening Remarks; Organizing Committee Chair: **Tom Blanton**
	9:10 am	Plenary Session: Intellectual Property; Chair: **Tom Blanton**
	9:50 am	Exhibitor Introductions
	10:10 am	Coffee Break
	10:30 am	Amorphous, Mesomorphous, Nano Materials; Chair: **Simon Bates**
	11:30 am	API Phase Stability / Non-ambient Analysis; Chair: **Raj Suryanarayanan**
	12:30 pm	Lunch
	1:30 pm	Critical Quality Attributes; Chair: **Shawn Yin**
	2:50 pm	Coffee Break
	3:10 pm	Critical Quality Attributes *(continued)*; Chair: **Shawn Yin**
	4:15 pm	Poster Session and Reception; Chair: **Tom Blanton** *(ends at 6:00pm)*
Wednesday 24 May Sessions	9:00 am	Software, Database, Laboratory Instrumentation; Chair: **Tom Blanton**
	10:40 am	Coffee Break
	11:00 am	Structure Determination & Refinement; Chair: **Arnt Kern**
	12:40 pm	Lunch
	1:40 pm	Complementary & Emerging Techniques; Chairs: **Natalia Dadivanyan** and **Fabia Gozzo**
	3:20 pm	Low Angle and Small Angle Scattering; Chair: **Julien Giovannini**
	3:50 pm	Closing Remarks; Organizing Committee Chair: **Tom Blanton** *(Symposium closes at 4:00 pm)*