ALMA MATER STUDIORUM
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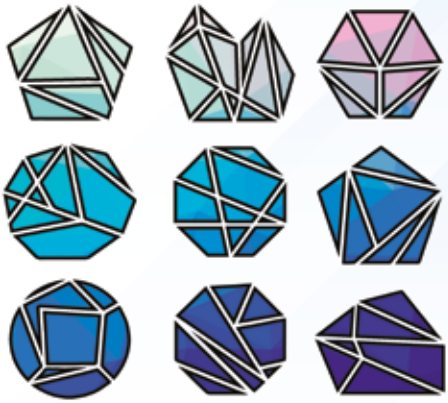
CRYSTAL FORMS @BOLOGNA 2019

CONVENTION / 10th EDITION



Making,
discovering,
protecting,
and using crystals

BOLOGNA (ITALY)
9-11 June 2019

Thanks to our SPONSORS

Welcome to CF@BO N.10

Dear participant,

Welcome to the tenth Bologna's Convention on Crystal Forms, CF@Bo n.10.

This series of meetings was initiated thirteen years ago, in 2006. It began as a joint (ad)venture of the Molecular Crystal Engineering group at the University of Bologna and the company PolyCrystalLine SpA, launched a year earlier as a spinoff of the same group.

The idea was to bring together people from industries and universities who, like us, were interested in comparing results and experiences in the burgeoning field of crystal forms.

It worked. The informal, dense but relaxed two and half days were highly productive. Young and senior scientists convened in Bologna enjoyed a full immersion in the state of the art in the investigation of preparation, crystallization, characterization and properties exploitation of active pharmaceutical ingredients and related organic molecular solids. It worked so well that we decided to repeat the experience a second time, and a third, and so on.

For this 10th edition we have a dense and varied programme. Speakers from sixteen universities and research institutions, from fourteen companies and IPR offices, and from fifteen countries will tell us their stories on crystals, amorphous materials,
co-crystals, hydrates, and will also discuss intellectual property issues, a relevant territory of the crystal forms world.

Please attend the talks and ask questions and also visit the poster session and ask even more questions to those presenting their posters and do not forget to take a look at the sponsors exhibits. We gratefully acknowledge the support to student fellowships provided by Italian Crystallographic Association, CrystEngComm published by RSC, and by some speakers. Thanks to this support, we have been able to guarantee free registration to 13 young participants.

Finally, I recommend you to find some extra time to visit Bologna: a medieval town, site of the oldest university of the western world.

CF@Bo n.10 is dedicated to Joel Bernstein, friend, mentor, and great scientist.
He was due to be with us, as he did for all the past meetings. We will all sorely miss him. He would have asked us to enjoy the science of crystals and their many mysteries and challenges holding a glass of red wine. Let's do that.

Dario Braga
Chairman

Programme SUMMARY

Sunday 9 June

Aula Magna, Chemistry Department "G. Ciamician" - Via Selmi, 2

12:00 **Registration**
14:00 **Welcome address**
14:30 **From Computational Crystal Structure Prediction to the Targeted Crystallisation of Predicted Polymorphs** Sally Price,Univ. College London, UK
15:00 **Amorphous Classification System (ACS): Early Assessment of Physical Stability Risk in Developing Amorphous Solid Dispersions** Geoff G. Z. Zhang, ABBVIE, USA
15:30 **Inconvenient Truths about Solid Form Landscapes.** Susan Reutzel, LILLY, USA
16:00 **Co-crystal Synthesis (and a Few Applications): Fact, Fancy, and Great Expectations** Christer Aakeroy, Kansas State Univ, USA

16:30 Coffee break

17:00 **How Not to Be Wrong About Cocrystals** Naír Rodríguez-Hornedo, Univ. of Michigan, USA
17:30 **Stimuli Responsive Crystals** Mike Zaworotko, Univ. of Limerick, Ireland
18:00 **Cocrystals and Eutectic compounds of Nevirapine** Silvia Cuffini, UniFeSP, Brasil
18:30 **Joel Bernstein Memorial** Fabrizia Grepioni,University of Bologna, Italy

19:00 **Welcome banquet**

Monday 10 June

Aemilia Hotel - Via Zaccherini Alvisi, 16

9:00 **Structural Basis for Designing Mechanical Performance of Solids** C. Malla Reddy, IISER, India
9:30 **The Specificity of Solid-State to Agrochemicals** Adam Keates, Syngenta, UK
10:00 **Structural Investigations of the Form 2 of the SGLT-2 Inhibitor Sotagliflozin** Philippe Ochsenbein, *S*anofi, France

10:30 Coffee break

11:00 **Lessons learnt from the Polymorphism and Crystallisation Behaviour of p-Aminobenzoic Acid** Aurora Cruz Cabeza, Univ. of Manchester, UK
11:30 **Pharmaceutical Cocrystals: Boron APIs, Synthons, and Reactivity** Leonard MacGillivray, Univ. of Iowa, USA
12:00 **From Crystal Structures to New Medicines** Amy Robertson, Astra Zeneca, UK
12:30 **In Search of Sustainable Nutrient Management Solutions for The Planet: from Labile Nitrogen to Localized Phosphorus** Jonas Baltrusaitis, Lehigh Univ., USA

13:00 Lunch

14:20 **From Bench To Market and Return** Dario Braga,Univ. of Bologna, Italy
14:30 **Rifaximine Hydrates: a Never Ending Story** Giuseppe Claudio Viscomi. Alfasigma, Italy
15:00 **U.S. Patent Protection of Solid Forms** Ilaria Goss, EPO, Germany
15:30 **Patenting Crystal Forms** Michelle O'Brien,The Marbury Law Group, USA

16:00 Coffee break

GOLD SPONSOR PRESENTATIONS
16:30 **Solid Form Quantification - A New Benchtop Solution** Benjamin Görling, Bruker BioSpin GmbH, Germany
16:45 **Aqueous Solubility & Bioavailability of Poorly Soluble Drugs: HME, a New Manufacturing Tool** Giuseppe Casassa, Thermo
17:00 **The Importance of Surface Area in Pharmaceuticals** Gianluigi Termine, Anton Paar
17:15 **Accurate Prediction of Hydration States of Molecular Crystals** Jacco van de Streek, Avant-Garde Materials Simulations

17:30 **Poster session**

Tuesday 11 June

Aemilia Hotel - Via Zaccherini Alvisi, 16

8:30 **Non-Standard Crystallization Methods of APIs Electron Diffraction: the Future** Gustavo Santiso-Quiñones, Crystallise, Switzerland
9:00 **Structural Informatics and Solid Form Selection** Kevin Back, Pfizer, UK
9:30 **Understanding the Intriguing Solid-State Phenomena of Dapsone Polymorphs and Solvates** Doris Braun, Univ. Innsbuck, Austria
10:00 **Synthons: Through The Looking-Glass, and What We Have Yet to Find There** Dejan-Krešimir Bučar, Univ. College London, UK

10:30 Coffee break

11:00 **Nanocrystalline Industrial Organics: Solving Crystal Structures from Bad Data** Martin Schmidt, Univ Frankfurt, Germany
11:30 **Co-Crystals of Agrochemicals – New Properties for New Formulations** Martin Viertelhaus, BASF, Germany
12:00 **Crystal Structure Prediction as Part of Pharmaceutical Development** Sandrine Rome, UCB Pharma, Belgium
12:30 **Solid State Properties in Drug Discovery: When It Really Matters** Enrico Modena, PolyCrystalLine, Italy

13:00 Lunch

14:30 **Polymorphism and External Constrains.** Yves H. Geerts, Univ. Libre de Bruxelles, Belgium
15:00 **A Bridge between Drug Substance and Drug Product: the Solid State Matters** Matteo Daldosso, Aptuit an Evotec Company, Italy
15:30 **Supramolecular Gels: Control and Pharmaceutical Application** Jonathan W. Steed, Univ. of Durham, UK
16:00 **Bio-Inspired Metal-Organic Frameworks as a Way to Boost Drugs Properties and Activity** Vania André, Univ. Lisboa, Portugal
16:30 **Concluding Remarks "What Next?" and Poster Prize** Dario Braga, Univ. of Bologna, Italy

Sunday 9 June

Aula Magna, Chemistry Department "G. Ciamician" - Via Selmi, 2

12:00 **Registration**

14:00 **Welcome address**

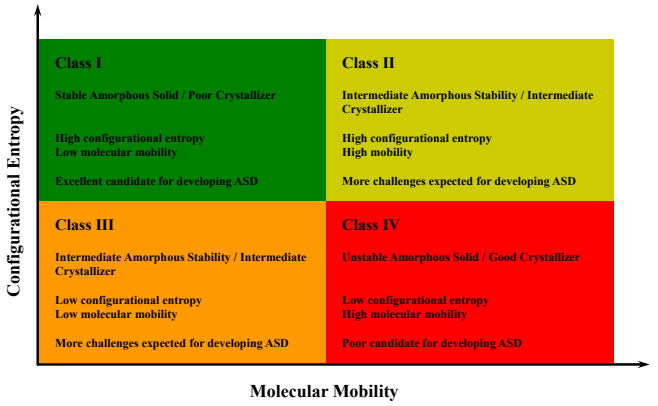
14:30 **From Computational Crystal Structure Prediction to the Targeted Crystallisation of Predicted Polymorphs** Sally Price,Univ. College London, UK

ABSTRACT: Crystal structure prediction (CSP) methods[1] were designed to predict the crystal structure of an organic molecule, prior to synthesis, as an aid to designing new organic materials. However, they are increasingly being used to predict possible polymorphs as an aid to the solid form screening involved in pharmaceutical development.[2] Whilst many of the computer generated crystal structures are probably an artefact of the neglect of temperature in the calculations, there are many examples of these structures being found later as novel polymorphs.[3] The challenge is to develop CSP to account for the kinetics of crystallisation so that it is possible to either design a specific experiment to find the desired polymorph, or be confident that it will never crystallise.[4]
It is sometimes possible to produce the first sample of a polymorph by sublimation onto an isomorphous seed crystal of a closely related compound,[5] but this requires the availability of a suitable template crystal. Other "exotic" crystallisation methods may be suggested by the calculation of specific properties of all the thermodynamically plausible structures; for example, do differences in the crystal diamagnetic susceptibility tensor suggest that the crystallisation kinetics could be affected by a strong magnetic field? However, the serendipitous production of irreproducible polymorphs suggests that we still have a lot to learn about the causes of polymorphism. [6]

[1] S. L. Price, Chemical Society Reviews, 2014, 43, 2098-2111.
[2] S. L. Price and S. M. Reutzel-Edens, Drug Discovery Today, 2016, 21, 912-923.
[3] S. L. Price, Acta Crystallographica Section B, 2013, 69, 313-328.
[4] S. L. Price, Faraday Discussions, 2018, 211, 9-30.
[5] D. H. Case, V. K. Srirambhatla, R. Guo, R. E. Watson, L. S. Price, H. Polyzois, J. K. Cockcroft, A. J. Florence, D. A. Tocher and S. L. Price, Crystal Growth & Design, 2018, 18, 5322-5331.
[6] P. Lucaioli, E. Nauha, I. Gimondi, L. S. Price, R. Guo, L. Iuzzolino, I. Singh, M. Salvalaglio, S. L. Price and N. Blagden, CrystEngComm, 2018, 20, 3971-3977.

15:00 **Amorphous Classification System (ACS): Early Assessment of Physical Stability Risk in Developing Amorphous Solid Dispersions** Geoff G. Z. Zhang, ABBVIE, USA

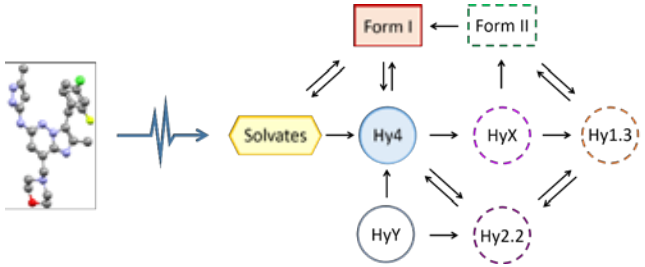
ABSTRACT: The purpose of this study is to develop a classification system utilizing milligram amounts of compound for physical stability ranking of amorphous pharmaceuticals, which can be used as an early risk assessment tool for amorphous solid dispersion (ASD) formulations. Simple thermal analysis utilizing a differential scanning calorimeter is used to characterize amorphous pharmaceuticals with respect to their molecular mobility and configurational entropy. Molecular mobility and configurational entropy are considered as two critical factors in determining the physical stability of amorphous phases. Theoretical arguments and numerical simulations suggest that the fragility strength parameter is a good indicator of the molecular mobility below glass transition temperature (Tg); and the heat capacity change at Tg is a good indicator of the configurational entropy. Using these two indicators, forty structurally diverse pharmaceuticals with known physical stability were analyzed. Four classes of compounds are defined with Class I being the most stable and Class IV the least stable. The proposed amorphous classification system (ACS) and methodology for estimating molecular mobility and configurational entropy provide an accessible framework to conduct early risk assessments related to physical stability challenges in developing amorphous formulations.



15:30 **Inconvenient Truths about Solid Form Landscapes** Susan Reutzel, LILLY, USA

ABSTRACT: An essential first step, and oftentimes a bottleneck, in the design of a solid oral dosage form is identifying at least one suitable crystalline form with which to reliably deliver the drug in the prescribed dose to the patient. The exploration of solid form landscapes can be relatively straightforward, particularly for systems with few, relatively easily crystallized forms, each with clearly distinguishable structures and well-defined properties. However, our investigation of the structural features, stabilities and interconversion pathways between the neat and hydrated forms of a JAK-2 inhibitor, gandotinib (GAN), has revealed many inconvenient truths about the challenges that must sometimes be overcome to generate solid forms and establish structure-property relationships.[1] GAN crystallized in many different forms (neat polymorphs, hydrates and solvates), oftentimes concomitantly, and not always in the most highly crystalline form. Interconversion of the anhydrates and hydrates with small changes in the relative humidity so complicated identifying and characterizing the crystalline forms that some experiments conducted in the humidity of summer could not be reproduced in the winter, and vice versa. Thus, with solid-state transformations being the only route to four of eleven solid forms, elucidating the crystal structure relationships underpinning dehydration – rehydration pathways as a function of temperature and humidity required not only complementary experimental and computational methods, but also extreme patience. A key feature of this system

is that the chlorofluorophenyl ring of GAN in the various neat and hydrated forms is disordered, but to different extents. In this work, we use state-of-the-art experimental methods in combination with developing computational tools, including crystal structure prediction, to paint a molecular picture that captures the extent to which disorder can affect form appearance and stability.



[1] D. E. Braun, J. A. McMahon, R. M. Bhardwaj, J. Nyman, M. A. Neumann, J. van de Streek, S. M. Reutzel-Edens, Cryst. Growth Des. 2019, DOI: 10.1021/acs.cgd.9b00162.

16:00 **Co-Crystal Synthesis (and a Few Applications): Fact, Fancy, and Great Expectations**
Christer Aakeroy, Kansas State Univ, USA

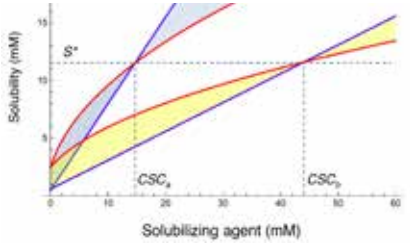
ABSTRACT: When molecules transition from solution into the condensed phase, their behavior and properties are to a large extent governed by intermolecular interactions. Despite the fact that such chemical bonds are relatively weak and reversible they are critically important to solubility, thermal and mechanical stability, optical properties, and many other key performance parameters of modern materials. Consequently, if we want to acquire the ability to design and construct new materials through a bottom-up approach that is both robust and versatile, we need a better understanding of the structural consequences, and balance between, intermolecular forces.[1,2] In addition, we also need to establish more reliable and tangible connections between molecular structure and materials properties. In this presentation we will examine how several fundamental physical properties of a substance can be modified and 'dialed-in' through the use of co-crystallization technologies that are firmly anchored in a fundamental understanding of intermolecular forces. Applications relevant to agrochemicals,[3] and explosives[4] will be presented.

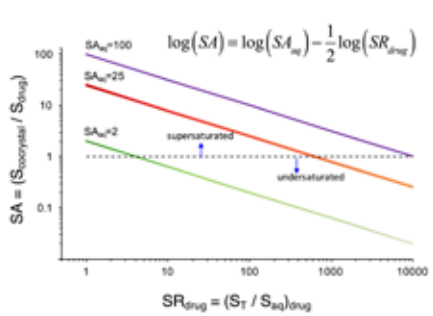
[1] C. B. Aakeröy, *Acta Crystallogr. Sect. B*, **2015**, *71*, 387-391.
[2] C.A. Gunawardana, C.A., C.B. Aakeröy, *ChemComm*, **2018**, *54*, 14047-14060.
[3] B. Sandhu, A.S. Sinha, J. Desper, C.B. Aakeröy, *ChemComm*, **2018**, 4657-4660.
[4] C.B. Aakeröy, T.K. Wijethunga, J. Desper, *Chem. Eur. J.* **2015**, *21*, 11029–11037.

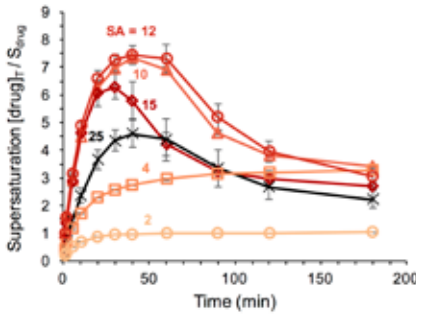
16:30 Coffee break

17:00 **How Not to Be Wrong About Cocrystals** Naír Rodríguez-Hornedo,Univ. of Michigan, USA

ABSTRACT: Cocrystals are an important class of pharmaceutical materials with remarkable potential to fine-tune solubility advantage (SA) over drug. The stoichiometric nature of cocrystals predisposes them to huge, yet predictable, changes in solubility and thermodynamic stability as solution conditions change such as drug solubilizing agents and pH. [1-3] This property differentiates cocrystals from other supersaturating drug delivery systems. Cocrystal thermodynamic properties, while scarce in the literature, provide an unexploited spectrum of cocrystal behaviors that up till now may only show up inadvertently – sometimes to the point of cocrystals appearing risky compared to other solid-state forms. This talk will discuss how cocrystal SA diagrams can be used to (1) tailor cocrystal SA by the rational selection of drug solubilizing agents (SP) and pH, and (2) explain the cocrystal dissolution-drug supersaturation-precipitation behavior.







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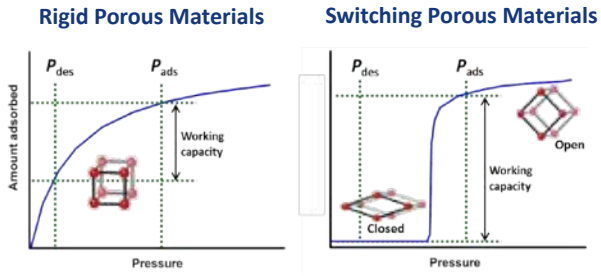
[3] Y. M. Chen; N. Rodríguez-Hornedo, Cryst. Growth & Des. 2018, 18, 1358–1366.

17:30 **Stimuli Responsive Crystals** Mike Zaworotko,Univ. of Limerick, Ireland

ABSTRACT: The discovery of flexible (breathing) porous materials that change their structure when exposed to gases or vapours was initially a scientific curiosity. This has changed in recent years as it is now recognised that such "switching adsorbent materials", SAMs, can offer exceptionally high working capacity for gas storage, including natural gas. This is especially the case when SAMs suddenly convert from a closed phase to an open phase since adsorption isotherms of the type illustrated below in Scheme I can be exhibited.[1-3]
The purpose of this presentation is to (a) provide an overview of the various classes of SAM that are known to exhibit this phenomenon, (b) present selected recent results from our group and (c) to discuss their potential utility. Three classes of SAM to be discussed will be as follows:



Scheme I. Comparison of the adsorption isotherms of rigid sorbents (left) vs. SAMs (right)

(i) ***Flexible MOFs*** (F-MOFs), especially new clases of MOFs based upon diamondoid (dia) and primitive cubic (pcu) topology coordination networks;[1,2]

(ii) ***Switching Adsorbent Layered Materials*** (SALMAs), especially square lattice, sql, topology networks;[3]

(iii) ***Switching Adsorbent Molecular Materials*** (SAMMs), especially anhydrous molecular solids that can reversibly convert to solvated or hydrated crystalline solids.

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[2] A.X. Zhu, Q.Y. Yang, A. Kumar, C. Crowley, S. Mukherjee, K.J. Chen, S.Q. Wang, D. O'Nolan, M. Shivanna, M.J. Zaworotko, J. Am. Chem. Soc., 2018, 140, 15572-15576.
[3] S.Q. Wang, S. Mukherjee, E. Patyk-Kazmierczak, S. Darwish, A. Bajpai, Q.Y. Yang, M.J. Zaworotko, Angewandte Chemie, 2019, 131, DOI: 1021/ange.201901198.

18:00 **Cocrystals and Eutectic Compounds of Nevirapine** Silvia Cuffini, UniFeSP, Brasil

ABSTRACT: In the pharmaceutical area, there are different strategies for low soluble drugs in order to improve the dissolution properties and, as a consequences, their bioavailability and its effectiveness. Nevirapine (NVP) is an antiretroviral drug that presenting low aqueous solubility (BCS Class II), which impacts directly in the bioavailability of the drug, leading to the necessity of high administration dosage[1-2]. Crystallization methods can be used to obtain different crystal forms of NVP in order to improve its dissolution and, consequently, its bioavailability. Co-crystals, eutectics and crystal morphology are among possible crystalline modifications; moreover both co-crystals and eutectics have been used to improve the physicochemical and pharmaceutical properties of drugs.[3-4] Thus, co-formers were used such as, salicylic acid (SA), saccharin (SAC), theophylline (THEOP), theobromine (THEOB), caffeine (CAF), and urea (URE) and also different solvents. Materials were obtained through the liquid-assisted grinding methods and were characterized by solid-state techniques (DRX, DSC, Raman, NMRss, SEM). Results indicates that NVP-SA and NVP-SAC are co-crystals, whereas NVP-THEOP, NVP-THEOF and NVP-CAF are eutectic materials, and NVP-URE is a solid mixture. Although NVP-SA co-crystals, has been already reported at low temperature[3], a phase transition and disorder were study in NVP-SA structure in a range of temperature (100K – 500K). Moreover, hollow crystal morphology for low soluble drugs BCS Class II could be also a promising approach to enhancing the dissolution.

References

[1] Hargrave, K. D.; Proudfoot, J. R.; Adams, J.; Grozinger, K. G.; Schmidt, G.; Engel, W.; Trummlitz, G.; Eberlein, W. US005620974A, 1994.
[2] Mui, P. W.; Jacober, S. P.; Hargrave, K. D.; Adams, J. J. Med. Chem. 1992, 35, 201–202.
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18:30 **Joel Bernstein Memorial** Fabrizia Grepioni,University of Bologna, Italy

19:00 **Welcome banquet**

Monday 10 June

Aemilia Hotel - Via Zaccherini Alvisi, 16

9:00 **Structural Basis for Designing Mechanical Performance of Solids**
C. Malla Reddy, IISER, India

ABSTRACT: It is increasingly becoming clear that the information of mechanical behavior of single particles derived from crystal structures is much more reliable for developing the solid product design than that of the traditional empirical and morphology based approaches. In my talk, I will cover the (i) current status of structural basis for understanding mechanical deformation of crystalline molecular solids, (ii) challenges and gaps in the field for structure based prediction of bulk properties and (iii) some first principles for designing mechanical performance of pharmaceutical solids by crystal engineering approach.[1-4]

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[3] M. K. Panda, S. Ghosh, N. Yasuda, T. Moriwaki, G. D. Mukherjee, C. M. Reddy, P. Naumov, Nature Chem. 2015, 7, 65-72.
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9:30 **The Specificity of Solid-State to Agrochemicals** Adam Keates, Syngenta, UK

ABSTRACT: Agrochemicals are typically formulated as colloidal suspensions in water, therefore stability (both chemical and colloidal) of active ingredients (AIs) is not always achievable. It is not unusual to have multiple active isomers, resulting in more than one solid state in the technical material. Understanding the forms and their relationships is key to providing stable formulations.

Salts are common in herbicide chemistry, such as Glyphosate, which can be sold as Soluble Liquid (SL) formulations. But other classes of AI are generally basic and poorly ionisable in nature. The lack of salts restricts the possible solid-state landscape of an AI, although it is possible to form co-crystals, to increase the stability of certain formulation types.[1]

Some examples and utilisation of physical property improvements via the solid state will be presented.

[1] WO 2008/117037 A1

10:00 **Structural Investigations of the Form 2 of the SGLT-2 Inhibitor Sotagliflozin**
Philippe Ochsenbein, *S*anofi, France

ABSTRACT: This is the story of a crystalline polymorphic phase which has resisted disclosing its structure for more than three years. Sotagliflozin is an orally available L-xyloside based molecule inhibiting both sodium-glucose transporter type 1 (SGLT1) and type 2 (SGLT2). It is a chiral fairly rigid molecule of 28 non-hydrogen atoms and its chemical formula (C_{21} H_{25} O_5 Cl S) contains a tetrahydropyrane ring common to most oligosaccharides. Two experimentally known polymorphs Form 1 and Form 2, and two hydrates have been described by powder diffraction and Raman spectroscopy.[1-2] The crystal structures of Form 1 and of hydrate Class 3 (which were briefly presented at this conference)[3] have been published.[4] More than ten solvates have also been characterized; among them, the methanol solvate presents the peculiarity of being quasi isostructural to the Form 1. In contrast to single crystals of Form 1 of which the morphology corresponds to large sturdy plates of which the longest edge can reach a millimeter, Form 2 develops a microcrystalline powder with only a fibrous habitus of submicron thickness. The Form 2 could not be found in an *in silico* crystal structure prediction (CSP) study (performed by Avant-Garde Simulation); whereas CSP calculations could find Form 1 indeed. High resolution powder X-Ray diffraction (ID22@ESRF) shows for polymorphic Form 2 a severe dominant zone problem which has for a while prevented a reliable and successful indexing. After a few diffraction spots were collected using fibers that only diffract to a resolution of about 3 angstroms (beam line Proxima@Soleil); the small cell parameter (of less than 5 angstroms) of Form 2 was unambiguously resolved and Pawley refinements on synchrotron powder data lead to reliable agreement values (Rwp = 0.05). The unit cell of Form 2 was also independently obtained by electron diffraction (ED), but subsequent structure determination by direct methods was not possible since ED data were strongly affected by rapid crystal damaging. The unit cell and symmetry found suggested four independent molecules in the crystal structure; this feature was confirmed by ^{13}C CPMAS solid state NMR. All attempts to solve the crystal structure of Form 2 from powder data alone by applying the global optimization method failed. In a last attempt using hot stage microscopy, long needles of slightly increased size in the intermediate dimension (up to 4-5 microns) could slowly be grown, and a few of these crystals were (after a non-obvious extraction) again analyzed using synchrotron radiation (Proxima@Soleil). In spite of a poor quality dataset (R(sym) > 0.2), the crystal structure of Sotagliflozin Form 2 could finally be elucidated by intrinsic phasing methods.

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[2] S. L. Giaffreda, E. Modena, C. Ianni, A. R. Muthusamy, S. L. Kanniah, **2018** Patent WO/2018/067805.
[3] P. Ochsenbein "*Combining Several Methods to Solve Pharma API Crystal Structures*"
[4] Crystal Forms@Bo June **2017**.
[5] T. Gelbrich, V. Adamer, M. Stefinovic, A. Thaler, U. J. Griesser, Acta Cryst. **2017** C73, 718–23.

10:30 Coffee break

11:00 **Lessons learnt from the Polymorphism and Crystallisation Behaviour of p-Aminobenzoic Acid** Aurora Cruz Cabeza, Univ. of Manchester, UK

ABSTRACT: At Manchester, we have studied the polymorphism and crystallisation behavior of the model pharmaceutical *p*-aminobenzoic acid (*p*ABA) [1]. Despite being a "simple" compound, *p*ABA shows some interesting polymorphic behavior. The best well-known polymorphs, the α and the β forms, are related enantiotropically with β being the most stable form below 13.8 °C [1]. The hydrogen bonding and aromatic interactions of these two forms are very different and whilst the α form is easily grown under most conditions, the β form can only be grown from water in a narrow range of supersaturations. In an attempt to understand the crystallisation pathway and aggregates leading to the nucleation of the β-form in water, we attempted the production of a *p*ABA hydrate from water crystallizations at high pressures and a number of water mixtures with other solvents. Whilst we were unable to obtain a hydrate, we produced several new solvates [2] as well as a new polymorph of *p*ABA, the δ-form [3], which shows some similarities with both the α and the β forms [1]. Kinetic studies of the nucleation of the α form revealed that the kinetics of nucleation and growth of the α-form controlled by aromatic stacking [4]. In light of this, we designed some molecular additives with the view of interrupting aromatic stacking in α-*p*ABA. Crystallisation of *p*ABA in the presence of those impurities led to the observation of β in a much wider range of conditions [5,6]. Understanding crystallization pathways and kinetics is essential for the control and design of crystallization processes involving polymorphic systems.

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11:30 **Pharmaceutical Cocrystals: Boron APIs, Synthons, and Reactivity** Leonard MacGillivray, Univ. of Iowa, USA

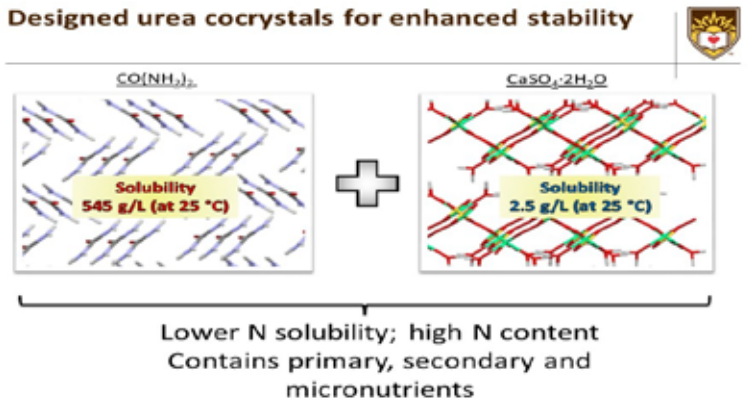
ABSTRACT: In this presentation, we describe the development of pharmaceutical cocrystals involving boron (B)-based active pharmaceutical ingredients (APIs). B-based APIs are highly-promising platforms for the development of new therapies. In this context, organoboron compounds, and particularly those derived from boronic acids, are gaining attention. The now well-documented and evolving supramolecular interactions involving organoboron compounds prompted us to explore the formation of cocrystals of the low molecular weight B-based APIs tavaborole (Kerydin®) and crisaborole (Eucrisa®). Tavaborole was recently approved by the FDA for the treatment of toenail onychomycosis. Crisaborole is a nonsteroidal topical agent recently approved for the treatment of atopic dermatitis. We describe the formation of cocrystals of tavaborole and crisaborole sustained by hydrogen bonds involving the B(OH) group. We also describe the discovery of three polymorphs of crisaborole and suggest that while the growing drug pipeline demands newly-approved APIs to be readily available commercially, there is a growing need of crystal engineers to monitor solid forms of APIs as related to quality control from an increasing number of commercial suppliers. Related work on solid-state photochemical reactions of APIs and involving B-based cocrystals will also be presented.

12:00 **From Crystal Structures to New Medicines** Amy Robertson, Astra Zeneca, UK

ABSTRACT: Obtaining crystal structure data should be one of the first stages in the development of a new drug. This data then plays a key role in the work that follows, from ensuring the correct polymorphic form has been selected, to defining the control strategy and ultimately to support regulatory approvals. Recent developments in the CCDC data mining tools allow us to quickly search commercially available and in-house databases for motifs, structural similarity and hydrogen bonds within a very short time frame. This enables early risk assessment of forms selected for development, and more focused and effective experimental studies to develop crystallization processes. The visualization of the calculated morphology and crystal faces aids in the development of the crystallization process to obtain crystals with optimum morphology to aid downstream processing, e.g. better flow properties.
The presentation will include examples of how crystal structure data and associated database tools have been used to develop control strategies and improve crystallisation processes to increase understanding and improve downstream processing.

12:30 **In Search of Sustainable Nutrient Management Solutions for The Planet: From Labile Nitrogen to Localized Phosphorus** Jonas Baltrusaitis, Lehigh Univ., USA

ABSTRACT: The world is experiencing an unprecedented economic growth and increase in human population, thereby requiring more sustainable utilization of natural resources. Novel materials and processes that can provide sustainable nutrient source or improve major mineral fertilizer utilization are of key importance. Our work is in designing urea molecular and ionic cocrystals utilizing various waste streams and combining them into enhanced efficiency fertilizers. In particular, we utilize diverse set of recycled sulfur feedstock, including gypsum and refinery sulfur, to obtain urea – inorganic acid or their salt adducts for improved nitrogen release fertilizers. We show that NH_3 emissions are decreased when urea is combined into molecular crystals with inorganic compounds. We further design new urea ionic cocrystals with other major nutrients, such as potassium, and micronutrients, such as zinc, to obtain solid state high nitrogen content fertilizers with improved response properties towards urease activity. The corresponding solid product spectral properties, formation kinetics as well as phase diagrams are explored using XRD, Raman spectroscopy and solubility measurements. A broader perspective on nutrient sources, sinks and management is also presented.



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13:00 Lunch

14:20 **From Bench to Market and Return** Dario Braga,Univ. of Bologna, Italy

14:30 **Rifaximine Hydrates: a Never Ending Story** Giuseppe Claudio Viscomi. Alfasigma, Italy

ABSTRACT: Rifaximin is living a sort of “a second life”, started at the beginning of 2000 years with the elucidation and characterisation of the first crystalline forms.
The insight of multiple mechanisms of action of rifaximin, combined with the improved understanding of the properties of the solid material, has made possible an astonishing pharmaceutical development, unpredictable when the compound was invented at the beginning of ’80 years. The significant commercial success of rifaximin, as pharmaceutical drug product, has strongly stimulated the interest on the compound. Several new drug products have been proposed over time since the first discovery of rifaximin crystalline form, wherein in most cases, they rely on alleged properties of new crystalline forms, others on combination of already known forms. In the presentation it will be discussed the complexity of rifaximin drug product development and the impact of rifaximin crystallinity on such development.

15:00 **Patenting Polymorphs at the European Patent Office** Ilaria Goss, EPO, Germany

15:30 **U.S. Patent Protection of Solid Forms** Michelle O’Brien,The Marbury Law Group, USA

ABSTRACT: The discussion will consider how the U.S. Patent Office and U.S. courts treat patents for solid forms (polymorph, salt, solvate, hydrate, amorphous). The criteria for obtaining a patent on a solid form will be discussed from both scientific and legal points of view, including a discussion of challenges in both obtaining and enforcing these patents. Finally, strategic considerations for using solid form patents to gain competitive advantages will be explored.

16:00 Coffee break

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16:30 **Solid Form Quantification – A New Benchtop Solution**
Benjamin Görling, Bruker BioSpin GmbH, Germany

ABSTRACT: In the pharmaceutical industry, about 80% of all Active Pharmaceutical Ingredients (APIs) tend to exist in more than one crystalline form or even as an amorphous fraction. As a change in structure affects the physical and chemical properties of a molecule, polymorphism presents a potential risk to the viability and safety of a drug. Thus, proving the polymorphic purity of the lead API plays a crucial role from early drug development to manufacturing.
Whilst there are methods available that can analyze solid forms in one way or another, there is no universal method to quantify and monitor the different API morphologies.
Over recent years, solid-state NMR has emerged as the major tool for analyzing API polymorphs. However, the method does have some drawbacks. For example, it can be both labor- and time-intensive.
Time-domain NMR is an alternative to classical NMR that offers several advantages over solid-state NMR. First, it can be performed on a benchtop instrument, requiring less space and capital outlay than performing high resolution solid-state NMR experiments. It works at low magnetic fields using permanent magnets, which do not require cryogenic cooling. Additionally, less time is needed to conduct the relaxation measurements. Sample preparation is especially straight forward: The solid powder is filled in a glass tube.
In this talk a method is presented to use time-domain NMR to quantify polymorphs in mixed drug samples. The method works by measuring T1 saturation recovery curves (SRC) of the pure components as reference curves that are subsequently used to quantify the components in a mixture of which the SRC has been measured. Both, 1H or 19F relaxation curves can be used for quantification.

16:45 **Aqueous Solubility & Bioavailability of Poorly Soluble Drugs: Hme, a New Manufacturing Tool** Giuseppe Casassa, Thermo

ABSTRACT: Improving the bioavailability of the active ingredients requires different strategies of galenic formulation, knowing that most of the new molecules in development are in class II and IV. Different formulation strategies can be implemented depending on the root cause of the low bioavailability.
Hot Melt Extrusion (HME) combines thermal and mechanical energy to process polymeric materials above their glass transition temperature (Tg) ensuring molecular level mixing of polymers and active ingredients. The resulting mix is a Solid dispersion keeping the API in the right crystalline form, soluble and bioavailable.

17:00 **The Importance of Surface Area in Pharmaceuticals** Gianluigi Termine, Anton Paar

ABSTRACT: Surface area measurements, specifically according to the B.E.T. method, are part of the pharmaceutical industry but have been adopted sparsely, yet…
Surface area can quite easily reveal an excess of fines that might be challenging for a particle size analysis, can distinguish between different morphologies of similar particle size, can be used to follow the generation of particle-particle bonds under pressure, can be used to confirm brittle fracture under compression, can be part of tighter control on specifications of raw materials so as to avoid surprises during later processing, can be used to monitor temporal morphological stability, and can explain unexpected dissolution behavior.

17:15 **Accurate Prediction of Hydration States of Molecular Crystals**
Jacco van de Streek, Avant-Garde Materials Simulations

ABSTRACT: For solid-state forms of pure compounds, crystal structure prediction has matured to the extent where it has become a routine tool in pharmaceutical development [1,2]. The major success of crystal structure prediction for neat forms is crucially dependent on two factors: First, because polymorphs share the exact same numbers and types of elements and bonds, there is substantial error compensation, greatly contributing to the high accuracy of the relative energies and thereby to the success of the predictions. Second, the stoichiometry of the crystal structure of a single compound is known *a priori* and remains fixed across all candidate structures.
However, because water is omnipresent, depending on the conditions, organic compounds can unexpectedly crystallize as, or transform into, hydrates, *i.e*. crystal structures that contain water molecules that are incorporated into the crystal structure. The presence of the water molecules causes the solid-state structure to rearrange and substantially changes the physical properties of the solid-state phase such as thermodynamic stability and bioavailability. The variable—and *a priori* unknown—water content invalidates the two assumptions that made the crystal structure prediction of pure compounds so successful. In the past, attempts have been made to put anhydrates and hydrates with different numbers of water molecules onto the same energy scale by determining an energy value for a single water molecule in the gas phase, but unless true free energies are used, which depend on the temperature and the relative humidity, such attempts can never provide a complete picture of the inherently complicated phenomenon of hydrate formation.
In this contribution we present the results of a thermodynamic model that predicts the equilibria between the crystal structures of different hydration stages of a molecular compound (including the anhydrate), some or all of which may be the result of a computational crystal structure prediction study, as a function of temperature and relative humidity. The model was validated against nine anhydrate-hydrate pairs for which the equilibrium conditions were known, and for these nine cases the model achieves an average accuracy of 1 kJ/mol.

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17:30 **Poster session**

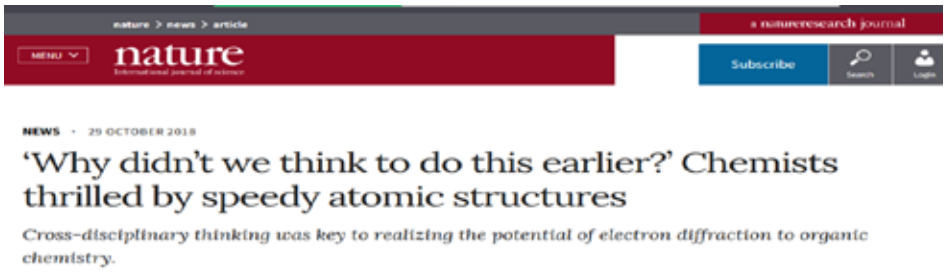
Tuesday 11 June

Aemilia Hotel - Via Zaccherini Alvisi, 16

8:30 **Non-Standard Crystallization Methods of APIs Electron Diffraction: the Future**
Gustavo Santiso-Quiñones, Crystallise, Switzerland

ABSTRACT: 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 the crystallization of liquid compounds, "gel-like" or "oil-like" substances. Most important, Crystallise! will show how single crystals and X-ray structure analysis can help to understand and solve problems many other analytical techniques fail to answer.

Furthermore, the topic of Electron Diffraction (ED) of organic molecules will be addressed. Very recently, Dr. G. Santiso-Quinones and Dr. G. Steinfeld published in collaboration with Dr. T. Grüne a new methodology and approach to do ED.[1,2] Using a modified TEM and a crystallographic approach,[3] data acquisition, data process, data analysis become easier and more reliable compared to other previous methods used before.[4] This technology / methodology was a runner-up by Science, among 12 candidates, for breakthrough of the year 2018.[5] A 5th place (peoples' choice) was obtained. Eldico Scientific AG is the outcome of this work. A new company which will produce devices optimized and dedicated for Electron Diffraction of nano-crystalline powders. The future of crystallography and characterization of such systems will be addressed. Case example(s) on organic molecules will be presented.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NEWS · 29 OCTOBER 2018

'Why didn't we think to do this earlier?' Chemists thrilled by speedy atomic structures

Cross-disciplinary thinking was key to realizing the potential of electron diffraction to organic chemistry.

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[4] L. Palatinus, *et al*., *Science*, **2017**, *355*, 166-169.
[5] https://vis.sciencemag.org/breakthrough2018/finalists/#rapid-structure

9:00 **Structural Informatics and Solid Form Selection** Kevin Back, Pfizer, UK

ABSTRACT: The selection of an Active Pharmaceutical Ingredient solid form suitable for particle, product and patient is an important milestone in drug development, traditionally underpinned by experimental studies. Risk based structural informatics tools compare the crystal structure of a new API with related structures found within the curated data of the Cambridge Structural Database. These tools, developed by the CCDC and embedded in the Cambridge Structural Database System, have been integrated into the solid form selection workflow.[1]

The application of these state-of-the-art tools to a new chemical entity allows the risk of polymorphism to be assessed through statistical insights into the qualities of the structure. Through an in-depth comparison with the vast array of knowledge gleaned from over a century of crystallography, unusual conformations and intermolecular interactions can be quickly highlighted to the project team, articulating risk and instigating further tailored experimental screening.

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9:30 **Understanding the Intriguing Solid-State Phenomena of Dapsone Polymorphs and Solvates** Doris Braun, Univ. Innsbuck, Austria

ABSTRACT: Solid form screening and crystal structure prediction (CSP) calculations were carried out on the model pharmaceutical dapsone (DDS), resulting in five neat forms (**I** – **V**), twelve solvates, a hydrate (**Hy**) and its isomorphic dehydrate (**Hy$_{dehy}$**). All literature forms comprising four polymorphs,[1] three solvates[2] and the hydrate,[3] were reproduced and characterised together with ten new solid forms of DDS. The kinetic and thermodynamic stabilities, solid form interrelationships and structural features were unravelled.

Calorimetric measurements, solubility experiments and lattice energy calculations revealed that the new neat polymorph, Form **V**, is the thermodynamically stable polymorph from absolute zero to at least 90 °C. At higher temperatures Form **II** and then Form **I** becomes the most stable DDS solid form. The computed 0 K stability order was confirmed with calorimetric measurements as follows: **V** (most stable) > **III** > **Hy$_{dehy}$** > **II** > **I** > **IV** (least stable). The discovery of Form **V** was complicated by the fact that the metastable but kinetically stabilised Form **III** shows a higher nucleation and growth rate. By combining laboratory PXRD data and ab initio calculations, the crystal structure of Form V (Z'=4) was solved. The Forms **I** and **IV** crystallize exclusively from the melt. Their structures were derived from the computed crystal energy landscape and show distinct packing features compared to the Forms **II**, **III**, and **V**.

Depending on the relative humidity **Hy** contains between 0 and 0.33 molecules of water per molecule DDS. The crystal structure is retained upon dehydration, indicating that DDS hydrate shows a nonstoichiometric (de)hydration behaviour. Unexpectedly, the water molecules are not located in structural channels but at isolated-sites of the host framework, which is counterintuitively for a non-stoichiometric (de)hydration behaviour. Water-DDS interactions were estimated to be weaker than water-host interactions that are observed in stoichiometric hydrates and the lattice energies of the **Hy$_{dehy}$** and **V** differ only by 1.6 kJ mol^{-1}.

To rationalise and understand DDS solvate formation and solvate stability, a careful control of the experimental crystallisation and storage conditions, a range of analytical methods and CSP were required. Structural similarity and diversity of the (at ambient conditions) unstable solvates were apparent form the computed crystal energy landscapes, which had the experimental packings as lowest energy structures. Packing comparisons of the solvate structures indicated that both size/shape of the solvent molecule and the possible DDS···solvent interactions are the important factors for DDS solvate formation.

To conclude, this study expands our understanding about the complex crystallisation behaviour of pharmaceuticals and highlights the big challenges in solid form screening. Only the appropriate combination of experimental and computational strategies made it possible to rationalise the form stability and structural features of DDS.

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10:00 **Synthons: Through The Looking-Glass, and What We Have Yet to Find There** Dejan-Krešimir Bučar, Univ. College London, UK

ABSTRACT: This presentation will critically evaluate the concepts, theories, and ideas underpinning modern crystal engineering efforts, with a view to stimulating a constructive, community-wide conversation about the current state of the art.[1] Some of our recent efforts to further develop existing guidelines for the design of molecular cocrystals and solid solutions will also be discussed, along with a brief description of an alternative and underused method for the preparation of novel cocrystals.[2]

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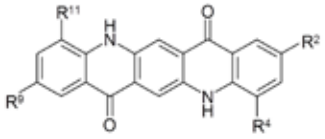
10:30 Coffee break

11:00 **Nanocrystalline Industrial Organics: Solving Crystal Structures from Bad Data**
Martin Schmidt Univ Frankfurt, Germany

ABSTRACT: Industrial organic compounds are frequently nanocrystalline. In this case, their crystal structures cannot be solved by the usual methods, even not by the standard methods of structure determination from powder data. Therefore, we developed a new method, called FIDEL ("Fit with Deviating Lattice parameters"). [1] FIDEL performs a global fit to the powder diffraction data, even in the case of unknown lattice parameters, and can, thus, be used to determine crystal structures of nanocrystalline industrial organic compounds from bad powder data without previous indexing. The molecular geometry is used as input. The optimisation starts from a large set of random crystal structures with random lattice parameters in various space groups. For the optimisation, FIDEL uses a similarity index based on cross-correlation functions, which allows a comparison of simulated and experimental powder data even if the lattice parameters do not match. [1,2] The lattice parameters, molecular position and spatial orientation as well as selected intramolecular degrees of freedom are optimised simultaneously in an elaborated multi-step procedure. Subsequently, the promising hits are subjected to an automated Rietveld refinement with TOPAS. [3] Finally, a user-controlled Rietveld refinement with TOPAS is performed.
Examples of industrial organic compounds, including quinacridone derivatives (see Figure) and metal complexes are shown. [4]



Quinacridone
R = H, F, Cl

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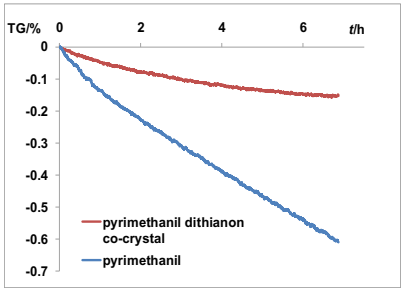
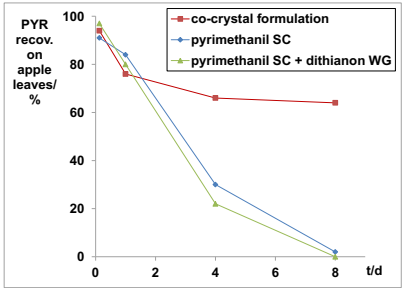
11:30 **Co-Crystals of Agrochemicals – New Properties for New Formulations**
Martin Viertelhaus, BASF, Germany

ABSTRACT: Co-crystals of active ingredients give us the chance to modify solid state properties of the actives. Which properties are in focus for agrochemical industry? And what can be the impact of co-crystallization?
Improved solubility is the most prominent solid state property to be modified by co-crystals, mainly discussed for active pharmaceutical ingredients. Solubility can also be decreased. For suspension concentrate formulations, widely used for agrochemical active ingredients, this is the only direction that can work to end up with a stable formulation. In combination with solubility enhancing excipients, a formulation with increased solubility and strong immediate effect and decreased solubility and retard effect can be prepared. Furthermore, the discussed co-crystal reduces volatility, so that rain and sun have less interference with the efficacy of the new formulation.





12:00 **Crystal Structure Prediction as Part of Pharmaceutical Development**
Sandrine Rome, UCB Pharma, Belgium

ABSTRACT: The development of a new drug implies to choose the crystalline form with the most suitable physico-chemical properties and have an overview of the polymorph landscape. Experimental polymorph screenings aim to discover as much as possible crystalline phases and the relative stability between the forms. However unexpected polymorphs can still pop up due to a complex interplay between thermodynamics and kinetics. In silico screening by computational molecular Crystal Structure Prediction (CSP), which yields the thermodynamic stability for a wide variety of different crystal packing arrangements, can assess the likelihood of a late-appearing polymorph and can be a complementary tool to experimental screening. At UCB, a collaboration was put in place with AMS (Avant-garde Materials Simulation), founded by Marcus Neumann. The company's main goal is the development of software for Crystal Structure Prediction (GRACE).
The presentation will focus on two UCB molecules.
The first one is rotigotine, a dopamine agonist for the treatment of Parkinson's and restless legs disease. Only one polymorphic form was known since 1985 until the appearance of a new and more stable form in 2008. The goal of the simulation was to evaluate retrospectively if, with the present prediction abilities, the tool would be able to predict this late-appearing polymorph and hence maybe would have been able to avoid a massive batch recall and a reformulation of the patch.
The second example is a molecule in development at UCB. Despite several polymorph screenings on different batches no other form has been detected. In support to experimental data, an in silico screening was performed to have an overview of the theoretical polymorph landscape and assess the stability of the known form.

12:30 **Solid State Properties in Drug Discovery: When It Really Matters**
Enrico Modena, PolyCrystalLine, Italy

ABSTRACT: The knowledge of solid-state properties in drug development helps to avoid manufacturing problems, optimize the performance of APIs and provide space for innovations. Polymorphism represents a key issue that significantly impacts on all those aspects. But not the right crystal form only has to be achieved: the control of other aspects like granulometry, morphology, crystallinity degree and absence of phase contamination, allows a more accurate design of the final drug properties. Some examples of solid-state properties studies are proposed, embracing different stages of drug development from early discovery to manufacturing.

13:00 Lunch

14:30 **Polymorphism and External Constrains** Yves H. Geerts, Univ. Libre de Bruxelles, Belgium

ABSTRACT: Polymorphism is generally abundant for molecular crystals, i.e. many compounds exhibits two or more polymorphs. Chemists often try to correlate molecular structure with the relative stability of polymorphic forms. We have chosen another research line by exploring how external constrains, for example the presence of a rigid wall [1] or temperature gradient (Figure 1) impact on the occurrence of polymorphism [2-6]. In our approach, we consider both nucleation and growth phenomena and try to separate them in well-selected experimental conditions. I will report on recent results.

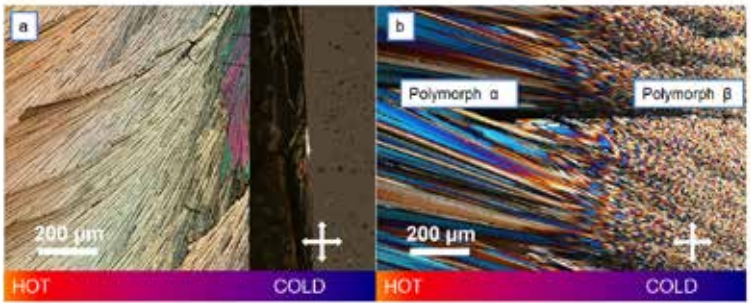


Figure 1. Polarized Optical micro-scopy images as the film is translated from hot to cold zone: a) Observation of large elongated domains formed upon crystallization in a temperature gradient. b) observation of the conversion of polymorph β into α induced by a temperature gradient.

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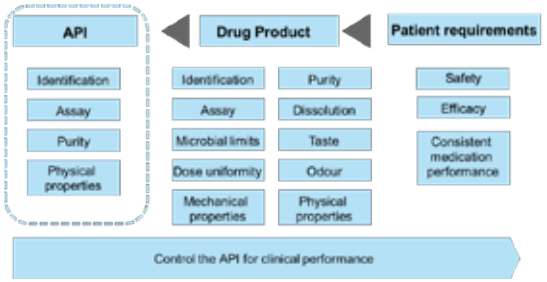
15:00 **A Bridge between Drug Substance and Drug Product: The Solid State Matters**
Matteo Daldosso, Aptuit an Evotec Company, Italy

ABSTRACT: The solid state characteristics of an Active Pharmaceutical Ingredient (API) have great impact on the fundamental properties of a medicinal product: solubility, dissolution rate, bioavailability, activity and toxicity, stability (shelf life identification) and manufacturing among others.
The knowledge acquired with the solid state investigation of drug substance, drug products, and even intermediate of the manufacturing production helps to control and optimize the product performance and the drug delivery. In the context of the QbD this became even more important because solid-state chemistry plays a critical role in many of the steps required to achieve QbD. In this system, the product is designed to meet patient requirements, the process is designed to meet product quality attributes, critical sources of process variability are identified and controlled and the process is continually monitored to ensure consistent quality over time. Moreover, the definition of the CQAs of the API (e.g. crystal form, particle size distribution, crystal morphology, etc.) influences the drug product attributes both in term of manufacturability and final bioavailability: the solid state knowledge acts as a bridge between the DS and DP. This presentation will provide examples on how the solid state knowledge can influence a pharmaceutical product development through all the clinical phases to the market lunch and beyond.



15:30 **Supramolecular Gels: Control and Pharmaceutical Application**
Jonathan W. Steed, Univ. of Durham, UK

ABSTRACT: Gels are formed by hierarchical self-assembly either because of hydrophobic effects in water or by more directional interactions such as hydrogen bonding in less polar solvents (Fig. 1). Low molecular weight gelators based on small-molecules (LMWG) are emerging as pharmaceutical crystallization media. Particular attractions of LMWGs to the scientific community are the reversible nature of the interactions between the gelator molecules, the wide (essentially unlimited) range of solvents that can be gelled and the possibility of tuning the gels' behaviour by introducing responsive or switching functionality. This presentation focuses on the control crystallization by manipulating the materials properties of small molecule (supramolecular) gels and the nature of the gel fibre surface. We show how concepts firmly rooted in supramolecular host-guest chemistry and supramolecular self-assembly can be married with the materials science of soft matter in order to control and manipulate bulk materials properties.[1] The application of these kinds of switchable gels as novel media for pharmaceutical crystal growth is emerging [2] and the lecture will demonstrate by a number of case studies how gel phase crystallization fits into the wider toolbox of solid form screening.

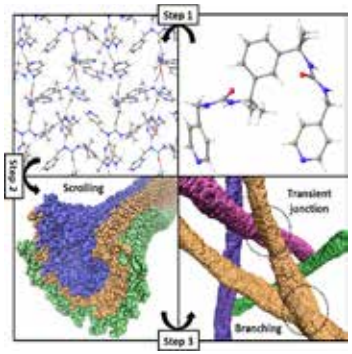


Figure 1. Assembly of a supramolecular gel by (1) layering, (2) scrolling and (3) entanglement.

[1] C. D. Jones and J. W. Steed, *Chem. Soc. Rev.* **2016**, *45*, 6546.
[2] D. K. Kumar, J. W. Steed *Chem. Soc. Rev.* **2014**, *43*, 2080.

16:00 **Bio-Inspired Metal-Organic Frameworks as a Way to Boost Drugs Properties and Activity**
Vânia André, Univ. Lisboa, Portugal

ABSTRACT: The awareness of the possibilities that metal-organic frameworks offer towards pharmacological applications has been increasing, especially for controlled drug delivery and release.[1] However, the coordination of drugs to metals[2] can also be envisaged as an alternative way to induce significant changes in previously known active pharmaceutical ingredients, changing important properties such as solubility and bioavailability, with the further advantage that synergetic effects of the metal can be explored to enhance its performance. This can be particularly relevant in the quest against the global threat of multidrug-resistant bacteria.
In fact, bactericidal agents, including antibiotics, drastically reduced the number of deaths caused by infections over the last 70 years, but due to their misuse and abuse, many microorganisms developed resistance mechanisms, causing thousands of deaths/year, and leading to an increased economic burden and productivity losses. Bearing these concerns in mind, the goal of this work is to develop new coordination frameworks enclosing drugs (mainly antibiotics) and safe metals to increase their solubility and consequently bioavailability, trying simultaneously to explore synergetic effects with the metal to increase the antimicrobial activity.[3] Another important point of this project is that mechanochemistry is the main synthetic pathway proposed. This is an environment-friendly technique that drastically reduces the amount of solvents and it has proven to be very efficient in different areas including MOFs' synthesis.

Acknowledgements: Fundação para a Ciência e a Tecnologia (FCT, Portugal) and FEDER are acknowledged for funding (projects UID/QUI/00100/2019 and PTDC/QUI-OUT/30988/2017)

[1] V. André, S. Quaresma, J. L. Ferreira da Silva, M. T. Duarte, *Beilstein J. Org. Chem.* **2013**, *13*, 5007-5017.
[2] S. Quaresma, V. André, A. M. M. Antunes, L. Cunha-Silva, M. T. Duarte, *Cryst.Growth Des.* **2013**, *13*, 5007-5017.
[3] V. André, F. Galego, M. Martins, *Cryst.Growth Des.* **2018**, 18, 2067-2081.

16:30 **Concluding Remarks "What Next?" and Poster Prize** Dario Braga, Univ. of Bologna, Italy

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10 things to do in BOLOGNA

1. The main plaza of Bologna is PiazzaMaggiore and there is a lot to see here including the Basilica of San Petronio. This church was meant to be the largest church in the world, but when the Vatican caught wind of the construction, they put a halt to that. This Basilica isn't Bologna's main church contrary to popular belief. The aetual main church of Bologna is locirted on the main street of dell'In-dipendenza, Cattedrale di San Pietro.

2. Visit the Basilica di Santo Stefano. The Basilica is a complex of sacred buildings that form the "Sette Chiese" (Seven churches). The complex is placed in a triangular shaped square (it has been recently restored) and is made by Chiesa del Crocifisso, Basilica del Sepolcro, Chiesa di San Vitale e Sant'Agricola, Cortile di Pilato, Chiesa del Martyrium, Chiostro Medievale (the medieval c1oister) and Museo di Santo Stefano.

3. Wander the streets of the Ouadrilatero, the medieval market where you can browse through the outside stands and old shops selling ali sorts of delicacies.

4. Eat ali the Bolognese specialtiesl Tortellini, sage and butter tortelloni, tagliatelle al ragù, morta-della, crescentine with cold cuts and soft cheese like stracchino and squaquerone; ali to be washed down with the local white wine Pignoletto or red Lambrusco.

5. Hike to the top of San Luca. under the longest portico in the world: 3,8 km and 666 arcades. The reward is the beautiful sanctuary of the Basilica of San Luca at the top of the hill. One can begin the walk up to the Sanetuaryof the Madonna of San Luca at the Meloncello Arch situated along via Saragozza.

6. The towers are one of the main features of Bologna. Between the XII and XIII century many towers were built, but nowadays they are less than twenty. These towers had a military and civil function: they gave prestige to the families which paid for their construction. The two most important towers are The Asinelli's tower and the Garisenda.

7. Visit the Archiginnasio, the first seat of the University of Bologna, the oldest university of the Western world, founded in 1088. Before the Archiginnasio was built between 1562 and 1563, lessons were held in private or rented houses, in religious venues and sometimes on the squares. Make sure you peek inside the gorgeous and fascinating Teatro Anatomico: this is where corpses were dissected for the first scientific studies of the human body.

8. Few people know that Bologna have always been a city of water The most charming part of this unusual Bologna is discovered by opening a small window located in Via Piella. Other "views" have been opened on Canale delle Moline from via Oberdan and via Malcontenti. In the Jewish Ghetto, under which flows the Aposa river or between via delle Moline and via Capo di Lucca, you can hear the roar of Salto del Reno river.

9. Visit the Museum of the History of Bologna. Housed inside PalazzoPepoli, the old residence of one the most important families in medieval Bologna, this museum traces the entire history of Bo-logna, from the Etruscan settlement known as Felsina to Roman Bononia to the height of its power during the Middle Ages and on through modern times.

10. Stroll the Porticoes. Because Bologna was booming due to its thriving university, extra housing was needed for students. The university was located downtown and instead of building outside the city, Bologna built facades on the front of their buildings into the streets. These student housings were built on the front of already existing buildings with a stipulation that they must be wide and high enough to allow horse carts to pass.

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