Crystal Forms @ BO

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This talk is focused on the applications of crystal engineering strategies to the investigation of crystal forms of organic compounds and metal complexes. Our interest in the preparation, characterization and assessment of polymorphs, solvates, cocrystals of molecular materials dates back to the '90s, with the first successes in the investigation of the crystal forms of the drug rifaximine and of other APIs, to then develope in the investigation of other classes of compounds.

In this talk, in particular, I will discuss the problems of antimicrobial resistance, connected with health, and soil enzymes inhibition, connected with environmental issues. These topics are part of the joint national project NICE (nature inspired crystal engineering).

The quest for new antimicrobials or ways to improve the efficacy of known ones is a major undertaking in the pharmaceutical field. Analogously, there is a strong need to decrease the pollution and economical damage caused by decomposition of fertilizers in the soil by the action of enzymes such as urease and ammonia monooxygenase. A number of examples will be used to demonstrate that crystal engineering strategies, especially co-crystallization of organic and inorganic compounds, can be successfully used to obtain new compounds and/or to improve the solid-state properties of known compounds used as antimicrobials or as enzyme activity inhibitors.

The importance, for the success of these strategies, of a close interaction with expert scientists in the application-oriented areas of bioinorganics and microbiology will also be emphasized.

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Solid Form Discovery: Past, Present and Future

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The greatest fear of any pharmaceutical materials scientist is the unexpected disappearance of a desired solid form, accompanied by the appearance of an unwanted, late-appearing stable crystalline phase. Such situations can have dire consequences, exemplified by the case of Norvir (ritonavir), which prompted the withdrawal of a marketed product. During the development and manufacturing processes of drug substances, various types of phase transitions can take place, including the interconversion of polymorphs, solvates, and amorphous forms, as well as the formation of unanticipated cocrystals or molecular complexes. This variability underscores the unpredictability associated with crystal nucleation and polymorphism. The latter has drawn parallels with hurricanes due to the unpredictable nature of the event, the lack of prevention from striking a community (much like how polymorphism can affect any drug) and the devastation that results after the catastrophic event occurs.

This talk will focus on the evolution of solid form development and selection over the past 50 years. Recent advancements including computational predictions, automation and advanced analytical techniques, such as electron diffraction, will be highlighted and discussed. By bridging the divide between computational and experimental disciplines, we may accelerate the time to find solid forms, minimize solid-state risks and offer the potential to design solids with tailored properties,

Key Insights from Computational Tools in Solid-State Pharmaceutical Development

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The polymorphism of a drug substance is a pivotal characteristic that significantly impacts pharmaceutical development (1). Polymorphs represent distinct crystalline forms of an active pharmaceutical ingredient (API), and their solid-state properties fundamentally influence key aspects such as manufacturability, bioavailability, stability, and overall therapeutic performance. A well-established body of scientific literature provides a thorough understanding of the principles driving polymorph selection. However, the complexity of these processes often presents numerous challenges, particularly prior to the new molecular entity (NME) nomination stage (2).

Despite the seemingly straightforward nature of polymorphic screening, various obstacles can arise during the NME nomination process. One prominent challenge is the presence of impurities, which may act as potential inhibitors to the formation of the thermodynamically stable polymorph. These impurities can also influence the morphology of the crystals, particularly during crystallization, affecting the overall properties of the drug product. As a result, a nuanced understanding of these interactions is essential for optimizing polymorph selection and ensuring the successful development of pharmaceutical formulations.

In light of these challenges, there has been significant progresses in developing computational approaches aimed at facilitating polymorph analysis and optimization. By leveraging advanced algorithms and modelling techniques, researchers can probe, predict, and gain insights into the complex thermodynamic relationships between different polymorphic forms (3, 4). These computational strategies not only enhance our understanding of polymorphic behaviour but also enable the rational design of robust crystallization processes. Moreover, they allow for the optimization of morphological characteristics (5) and mechanical properties, thus complementing traditional experimental workflows. This integration of computational methods represents a significant advancement in the field of solid-state pharmaceutical sciences.

Following the chemical synthesis and crystallization of the drug substance, the subsequent phase of pharmaceutical development relies heavily on effective biopharmaceutical strategies (6). These strategies are essential to ensure that the active pharmaceutical ingredient (API) reaches its intended target in the organism. The decision on which formulation strategy to adopt—whether to utilize cocrystals, salts, or amorphous spray-dried materials—depends significantly on the biopharmaceutics classification of the drug and physiologically based biopharmaceutics model (7). Each formulation approach presents distinct physical and chemical properties that can markedly influence the drug's performance and its clinical development timeline.

This presentation aims to articulate these multifaceted challenges by integrating the advancements in computational tools with the foundational principles of drug product development. By doing so, we will provide a comprehensive context that highlights how computational methodologies can be harnessed to navigate the complexities of solid-state properties and biopharmaceutics, ultimately streamlining the path from laboratory synthesis to market-ready drug products.

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Real-Time Monitoring and Temperature Control for Optimized Polymorph Engineering

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Integrating real-time monitoring with precise temperature control and mechanochemical processing represents a transformative approach to the controlled engineering of polymorphic forms in molecular solids. Combining these methodologies overcomes the limitations of traditional solution-based or purely thermal approaches, enabling access to metastable or otherwise elusive polymorphs under milder and more sustainable conditions. Recent studies have shown that mechanochemical transformations proceed through distinct kinetic stages, including prolonged induction periods that can be tuned by adjusting the mechanical energy input[1]. These induction periods are associated with processes of mechanical activation, such as the accumulation of defects and increased surface energy, which lower the effective energy barriers for polymorphic transitions. Crucially, it is the total accumulated mechanical energy, rather than the duration or intensity of milling alone, that dictates the onset of polymorphic conversion, offering a new dimension of kinetic control[2-5].

Variable temperature ball milling reveals that the temperature required to induce polymorphic transformations can be significantly lower than under conventional thermal methods. For instance, transitions that typically require high temperatures under equilibrium conditions can be achieved at substantially lower temperatures in the presence of mechanical activation. This has been demonstrated in cocrystal systems such as nicotinamide-pimelic acid and isonicotinamide-glutaric acid, where the transition temperature was lowered by up to 25°C[2,3]. Real-time, in situ powder X-ray diffraction and temperature monitoring are essential for capturing transient phases and elucidating the interplay between thermal and mechanical effects. This confirms that combining mechanical energy with controlled temperature not only accelerates transformation kinetics, but also expands the accessible polymorphic landscape[2,3].

Collectively, these advances underscore the potential of real-time monitored, temperature-controlled mechanochemistry as a robust platform for the selective design and manufacturing of polymorphs. This approach provides unprecedented control over solid-state reactivity and opens new avenues for the sustainable and targeted engineering of functional materials and pharmaceuticals.

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Navigating phase behaviour in pharmaceuticals to enable phases with desired properties

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Many active pharmaceutical compounds (APIs) exhibit crystalline polymorphism and only one of those polymorphs is the most stable one. Moreover, the solubility of recently developed APIs is often limited leading to formulations containing metastable polymorphs, amorphous material or stabilised supersaturated solutions. Before marketing such formulations, it must be ensured that they persist up to their expiration date, on average about three years.

To obtain a metastable polymorph, understanding the phase behaviour of the API will be helpful. For example, form β of pyrazinamide, which can be obtained by fast cooling of a pyrazinamide solution in methanol, acetone, or chloroform, is often obtained concomitantly with form γ. These experiments are in general carried out around or just below room temperature. With help of the phase diagram of pyrazinamide, it can be observed that form β is stable below -20°C and if crystallisation experiments are carried out at this temperature, pure form β can be obtained and maintained.[1] At temperatures above room temperature, crystallisation experiments with pyrazinamide mainly lead to form γ, which slowly turns into form α depending on the quality of the γ crystals. Thus, if form γ is produced without any precaution, it mostly converts into the α form within a few days, whereas if form γ is obtained in the presence of dimethylurea, it remains form γ for over a year. How dimethylurea causes this increase in persistence is not entirely clear, but it does involve the quality of the crystals, which in the presence of dimethylurea clearly improve.[1, 2] Another example is the ease with which the metastable form of ritonavir can be obtained by grinding as recently reported by Sacchi et al.[3] Although a pathway needs to exist to convert one polymorph into another, from the phase diagram of ritonavir it is clear that very little pressure already will stabilize the so-called metastable form.[4]

Despite considerable progress in crystal structure prediction (CSP), it remains difficult to foresee which of the predicted crystalline forms will be found experimentally and each molecule needs to be studied experimentally to understand its crystallisation behaviour. The COST Action BEST-CSP is contributing to calibrate stability calculations in CSP by preparing a benchmark of experimental physical data on the organic solid state. Hopefully, this will further improve the estimations of the Gibbs free energy for the different polymorphs and therefore predictions on the phase behaviour of an API. If in addition we have a full understanding of the crystallisation kinetics of an API, any viable predicted crystal structure could be crystallised and retained under the right conditions.[5]

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Accessing new polymorphs via solid solutions

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The identification and characterisation of active pharmaceutical ingredient (API) polymorphs is a vital part of the pre-formulation stage of medicines development. If this is not done comprehensively then there is a risk of phenomena such as the emergence of new polymorphs not identified prior to marketing (e.g. in the case of Ritonavir), which are hugely detrimental to both patients and API manufacturers. On the other hand, being able to precisely control polymorphism can permit the properties of an API – such as solubility and dissolution rate – to be controlled. Traditionally, polymorphic screening is done using liquid solvents, but this is not always fully comprehensive. Using hyphenated synchrotron X-ray diffraction and differential scanning calorimetry (XRD-DSC) we have recently shown that alternate polymorphs and packing motifs can be accessed using solid solutions in the form of amorphous solid dispersions (ASD).[1]

This presentation will begin by introducing the XRD-DSC methodology, before considering a range of recent studies undertaken using this approach. We will discuss the discovery of a new polymorph of olanzapine with an unprecedented packing motif (Fig. 1) via heating a drug-polymer ASD,[1] and explore the effect of the polymer matrix on the crystallisation pathway (Fig. 2).[2] We will further consider systems with flufenamic[3] and mefenamic acids.[4]

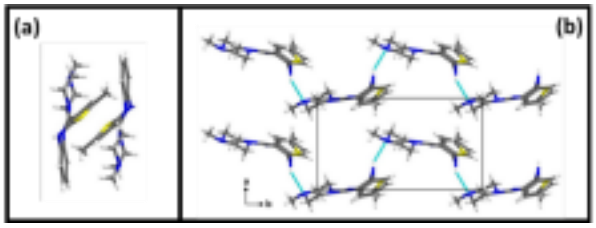

Fig 1: (a) The SC_0 dimer on which virtually all crystalline forms of olanzapine are based, and (b) the H-bonded catemers which make up the recently-discovered form IV.

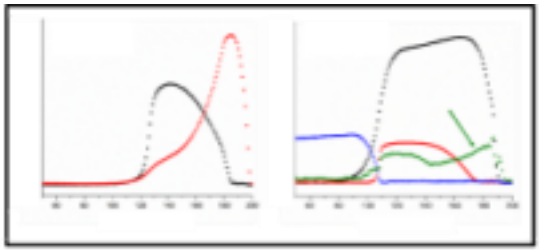

Fig 2: Olanzapine crystallisation behaviour from hydroxypropyl methyl cellulose acetate succinate (HPMCAS) and poly(lactide-co-glycolide) (PLGA) ASDs.

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Particle Engineering Strategies for Challenging APIs: From Structure to Process

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Abstract:
The increasing complexity of active pharmaceutical ingredient (API) molecules in pharmaceutical development presents significant crystallisation challenges, including poor solubility, problematic morphologies, and notably, extremely slow crystal growth kinetics. Delivering APIs with well-controlled physical properties is critical for subsequent formulation and manufacturability. This talk will explore particle engineering approaches designed to address these challenges and provide robust processes that support accelerated development timelines.

Key molecular, crystallographic, and process-related factors contributing to these particle engineering challenges —including high molecular flexibility and inherent kinetic barriers to nucleation and growth—will be reviewed. The presentation will describe approaches for controlling and improving crystallisation outcomes, in the context of industrial case studies, including tailored seeding techniques, selection of solvents and additives, and the application of complementary techniques, such as milling and temperature cycling, to achieve suitable particle size and flow properties for formulation.

Can crystal engineers make food? A few examples of crystallization strategies for the design of food formulations

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Food products are complex multiphase materials often including crystalline phases. To give few examples, ice cream is a semi-solid foam where fat crystals' aggregates stabilize air bubbles, whereas fine ice crystals provide the characteristic texture of this popular dessert. The main ingredient of chocolate is instead cocoa butter, a mixture of triglycerides that result in crystals with a complex polymorphic landscape; choosing the right crystal structure is necessary to ensure the desired texture, mouthfeel and shelf-life.

Precise design and control of food crystallization processes is, hence, essential to guarantee food quality. Furthermore, food crystalline particles can be precisely engineered to obtain novel multiphase formulation with enhanced nutritional and textural properties, as well as flavors.

The purpose of the presented work is to understand how crystal properties such as size, shape and polymorphism, affect the structure (sub-nano, nano and micro) and functionality of food formulations. In order to achieve this goal and enable the design of optimized food formulations, we applied an unprecedented combination of modelling techniques, ranging from the molecular (synthons analysis from crystallographic data, molecular dynamics), meso (population balance equations, interfacial particle stabilization) and continuum (diffusion, dissolution) scales, and experimental activities, including particle characterization (facet-specific and bulk measurements such as nano-IR and electron diffraction) and powder performance determination (kinetic parameters estimation, stability studies) measurements. Different model systems including mixtures of edible triacylglycerides and flavonoids of various nature (e.g., quercetin, curcumin, xanthone) were used and will be illustrated.

Interference between solid solutions and polymorphism: theory and examples

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The relative stability of polymorphs at every temperature is a crucial data for many applications of solids. The stability ranking is not straightforward because of the following problems: ➢ The different varieties are close or very close in energy (ΔG is close to zero). The driving force towards the most stable modification is weak.

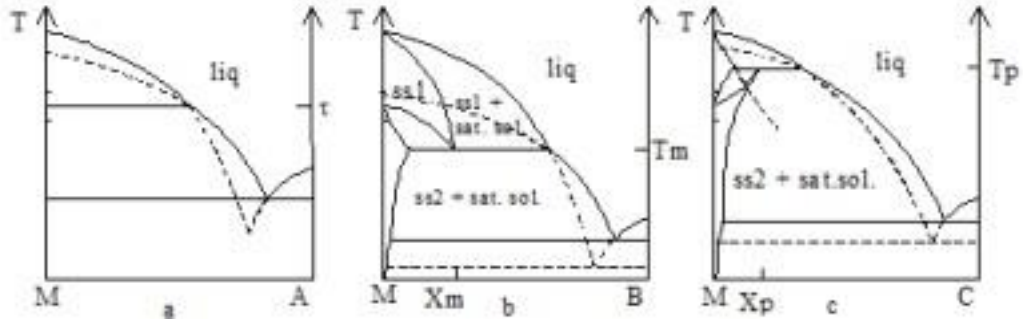
➢ The solid – solid transitions are submitted to slow or very slow kinetics (the activation energy is high), nucleation and/or crystal growth are/is the limiting step(s).

➢ A large fraction of the components cannot be melted without decomposition.

Slurrying a mixture of polymorphs in a solvent, leads to the most stable form at this temperature if the following conditions are fulfilled:

- ✓ No chemical reaction occurs between the solvent and the solute.
- ✓ The solubility in the domain of temperature to be investigated is not too high (viscosity, amount of solute needed) or too low (conversion at a poor rate).
- ✓ The temperature of ebullition is not too close to the temperature investigated.
- ✓ No solvate must be formed in the domain of temperature investigated.
- ✓ *There is no solid solution between the solute and the solvent.*

If the last point is overlooked, erroneous data can be generated. The figure below illustrated such phenomena with three different solvents and the same dimorphic form M.



In figure (a) the temperature of transition T is not impacted by the solvent. In figure (b) the temperature of transition is dropped by different amount of solvent incorporated in the two forms leading to a metatectic invariant [1]. Figure c depict the same problem with an inverted result and a peritectic invariant.

The statement can be reversed: a temperature of polymorphic transition which fluctuates according to the nature of the solvent or the amount of solvent leads (down to ppm level) to predict that there is at least one solid solution.

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Crystals as Intellectual Property

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This short presentation describes an academic scientist's understanding of crystal form patents and their commercial role in the pharmaceutical industry. We'll cover the basic anatomy of a chemical patent, the different types of claims and maybe touch upon some commercial strategies. In particular we'll look at the US 1984 Hatch-Waxman act and how that influences innovator and generic behaviour with regard to chemical patents. We'll cover common patent validity challenges and touch upon some well-known patent litigations, each of which is a story in themselves. Reference 1 gives a good overview of chemical patents for the beginner. Reference 2 explores the fast moving area of cocrystal patents and reference 3 gives a nice story of the patent battles surrounding the antibacterial cefdinir. This presentation and discussion is a general one and the author is not a lawyer so does not constitute legal advice nor a legal opinion. Every case is unique!

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Turning polymorph challenges into patent opportunities

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Crystallizing drug molecules under different conditions may yield different forms (polymorphs, solvates) with characteristic physical properties, particle sizes and shapes. Early in drug development, as a molecule is transformed into a medicine, experimental screening is commissioned to search for solid forms that can be used to isolate, purify and store the drug substance. However, with no way to predict *if* a molecule will crystallize, let alone in a form suitable for use as an API or to reliably deliver safe and efficacious doses of medicines to patients, the solid form properties of a drug molecule inevitably chosen for its biological properties must either be exploited or worked around. Novel solid forms that ensure the safety and efficacy of a pharmaceutical product, lessen the burden of manufacturing or reduce downstream environmental impact, represent new and useful compositions of matter, i.e., patentable innovation. In this presentation, the opportunities that polymorph challenges present in terms of extending market exclusivity through crystal form patents are discussed. Considerations in drafting claims to crystal forms with an eye toward demonstrating infringement are presented and the question underpinning the non-obvious criterion for patentability, “Are polymorphs predictable?”, is addressed.

Unlocking New Antibiotic Forms:

Crystal Engineering and Supramolecular Strategies for Polymorphs, Cocrystals, and Beyond

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The rise of antimicrobial resistance created an urgent need for strategies that enhance the efficacy of existing antimicrobials and enable selective drug delivery. The World Health Organization (WHO) recognizes AMR as a major global health threat, with the potential to cause pandemics comparable to SARS-CoV-2 [1]. Novel antimicrobial strategies are needed, as newly approved antimicrobial drugs have restricted innovation and limited clinical benefit over existing treatments.

Crystal Engineering and Supramolecular Chemistry offer innovative approaches to optimize currently available antimicrobial drugs by improving their solubility, bioavailability, and therapeutic efficacy. While polymorphs and pharmaceutical cocrystals, which represent a key focus of crystal engineering, have been explored for tuning specific drug properties [2]**,** antibiotic coordination frameworks and bio-inspired metal organic frameworks have shown to be effective in increasing the antimicrobial activity of known drugs [3] and newly design molecules with activity.

Mechanochemistry can be transversally applied to the synthesis of all these forms, bringing a note of a green chemistry approach towards these studies.

A wide range of results obtained with different drugs such as praziquantel, sparfloxacin, tazobactam, nalidixic acid and silver-sulfadiazine, as well as newly designed antimicrobial reveal the promising features of the crystal engineering approaches.

Acknowledgments: Fundação para a Ciência a Tecnologia is acknowledged for funding projects UIDB/00100/2020 (https://doi.org/10.54499/UIDB/00100/2020) and UIDP/00100/2020 (https://doi.org/10.54499/UIDP/00100/2020) and LA/P/0056/2020 (https://doi.org/10.54499/LA/P/0056/2020) . The author also acknowledges IMPACTIVE (Innovative Mechanochemical Processes to synthesize green ACTIVE pharmaceutical ingredients) [4], the research project funded from the European Union's Horizon Europe research and innovation programme (European Health and Digital Executive Agency) under grant agreement No. 101057286.

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PHARMACEUTICAL DIGITAL DESIGN: CAN WE GO FROM CHEMICAL STRUCTURE THROUGH CRYSTAL POLYMORPH TO CONCEPTUAL CRYSTALLIZATION PROCESS?

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A "digital design" dream of pharmaceutical development would be to go from the chemical diagram of a molecule, predict its crystal structure and growth, morphology and solubility properties, and use these to design a suitable crystallization process for manufacturing the solid form, without requiring any experimental information on the molecule. The Lilly Digital Design project fleshed out a possible workflow and evaluated the state-of-the-art in the essential steps, using olanzapine and succinic acid as examples.[1] Not surprisingly, polymorphism was a major challenge, requiring a means of determining how primary nucleation, growth and transformation rates determine which of the thermodynamically competitive structures generated in a crystal structure prediction (CSP) study are actually observed. Another problem for polymorphic systems is the ability to model the relative energies and solubilities sufficiently accurately, because of the inadequacies of the electronic structure methods and molecular dynamics force-fields that are currently available.

In order to provide a test-suite for the various developments in modelling that are required for this vision to become a reality, we have published a small test-suite[2]covering just 20 molecules, which are small compared with those in pharmaceutical development, but large compared with those being used for state-of-the-art electronic modelling. For each molecule, a set of crystal structures
are provided, covering known polymorphs, structures of closely related molecules and CSP generated structures with different packing modes. Describing the available experimental data shows the difficulties in defining tests of methods to select which CSP-generated structures are likely to be observable polymorphs.

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A conceptual framework for the crystallizability of organic compounds

Marcus A. Neumann and Jacco van de Streek

The late appearance of a more stable crystal form may render the produc<on of previously known forms difficult or impossible. This so-called phenomenon of disappearing polymorphs can have dire financial consequences, as exemplified by the well-known cases of Ritonavir and Ro<go<ne, and has long been one of the major driving forces for the development of modern crystal structure predic<on. We have spent decades on the development of algorithms for the genera<on of complete crystal energy landscapes, and more recently on accurate temperature-dependent crystal free energy calcula<ons with validated error bars by means of the TRHu(ST) method [1]. The access to the crystal energy landscapes and experimental screening results for dozens of compounds, both confiden<al and in the public domain, has now enabled us to pin-point the major mechanisms that govern the crystallizability of organic compounds, and some<mes prevent the observa<on of the thermodynamically stable form for years.

A crystallizability criterion is presented that captures the ease of crystalliza<on from solu<on, with large values corresponding to poor crystalliza<on dynamics. Replacing crystal energy landscapes by crystallizability landscapes, i.e., plots of the crystal free energy against our crystallizability criterion, many experimentally observed forms are found close to the crystallizability / crystal free energy Pareto curve, corresponding to different compromises between ease of crystalliza<on and thermodynamic stability. Chronologically, crystal forms close to the Pareto curve are oTen observed in order of decreasing (=less favorable) crystallizability and decreasing (=more favorable) free energy. Experimentally observed crystal forms may also be found far away from the Pareto curve, but such forms typically result from solid-solid conversions such as desolva<on, with the ini<al structure of the transforma<ons origina<ng from the Pareto curve of a crystallizability landscape calculated for the appropriate thermodynamic variables and chemical composi<on.

The validity of the concepts outlined above will be demonstrated by comparing a dozen of crystallizability landscapes of industrial compounds to the observed crystalliza<on behaviour. Crystallizability landscapes flagging high disappearing-polymorph risk typically feature a predicted structure that is both substan<ally more stable *and* substan<ally less crystallizable than the experimentally observed forms.

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Hybrid Approaches in Solid Form Design: Virtual Screening and Experimental Validation

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The design and development of suitable solid-state forms of pharmaceutical compounds is a complex and often challenging task. Hybrid approaches that combine virtual screening with experimental validation have become instrumental, offering a comprehensive and rational strategy for navigating the multifaceted solid-state landscape of active pharmaceutical ingredients (APIs). [1] These integrated methods facilitate a deeper understanding of polymorphism, solvate and hydrate formation, as well as cocrystal design, ultimately enhancing stability, solubility, and manufacturability.

This presentation highlights the utility and feasibility of such hybrid approaches through selected case studies. Comprehensive investigations of two APIs revealed an unexpectedly rich polymorphic landscape, including anhydrous and hydrate polymorphs as well as solvates. [2,3] By combining experimental screening and characterisation techniques (X-ray diffraction, spectroscopic methods, and thermal analysis) with crystal structure prediction (CSP), the molecular driving forces behind the observed solid-state forms and their stability could be systematically assessed. Notably, the lowest-energy structures predicted by CSP closely matched experimentally observed forms.

Cocrystallization studies further demonstrate the advantages of integrating computational tools with experimental screening methods. For both metronidazole and griseofulvin [4], virtual screening based on molecular electrostatic potentials and hydrogen-bonding propensity analyses was employed to identify promising coformer candidates. However, experimental results revealed some inconsistencies with these predictions. The experimental screening led to the discovery of several novel cocrystals for both systems. The formation and stability of these cocrystals were found to be strongly influenced by substituent effects, stoichiometric variability, and, in some cases, hydrate formation. Significantly, CSP successfully predicted all coformer combinations that resulted in cocrystal formation.

In conclusion, the chosen examples demonstrate that the synergy between computational and experimental methods significantly enhances solid form design. From unravelling complex polymorphic systems to guiding the identification of coformers for cocrystallisation, hybrid approaches not only streamline the screening process but also deepen our understanding of structural and stability features of pharmaceutical solids.

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Machine Learning within CSP: from one crystal energy landscape to another

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Since differentsolid forms of an active pharmaceutical ingredient (API) have different properties,solid form selection and control of the API forms an important part of a drug development process. A characterization of the solid form landscape enables an informed decision on the solid form selection and as well as on the solid form controlstrategies. The complementary combination of experimental and computational methods providesthe best possibility to perform this characterization.

One of the computational methodsto achieve this goal is Crystal Structure Prediction (CSP). Over the years CSP has evolved from an *in-silico* technique to approach a fundamentalscientic quest [1] to a technique that routinely can be used in drug development processes[2]. The latterstatus has also been reected in the results of the most recent Blind Test of Crystal Structure Prediction [3,4].

Through these developments more and more crystal energy landscapes have become available both in-house and in the academic literature. The subject of this presentation is a discussion of the knowledge that is contained within these energy landscapes and how this knowledge can be exploited by using Machine Learning (ML) techniques. Starting from a discussion on a method how to speed-up the important and , in many cases, time-consuming reranking phase of a CSP by using delta learning (TMFF* energies → DFT** energies) via a regression model based on SOAP*** averaged powerspectra [5],some nextsteps on moving the method further into the realm of cross learning from multiple energy landscapes will be discussed. If time permitssome more technical aspectsin applying and developing the method further will be touched upon as well.

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* TMFF: Tailor Made Force Field

** DFT: Density Functional Theory

*** SOAP: Smooth Overlap of Atomic Positions

An integrated approach combining experimental and computational for solid form design and selection

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Crystal engineering is broadly utilized in pharmaceutical industry to design solid state forms with optimum properties with respect to manufacturability, stability and performance to obtain the quality drug product. Commercial solid form selection is one of the key milestones during drug product development. It is also critical as product recalls due to solid state form issues compromises patient safety, damages company's reputation and puts economic burden in redeveloping the drug product. Experimental screening is typically utilized to explore the solid form landscape of drug candidates and select the solid form with optimum properties. With the advancement of computations as well as due to immense pressure to shorten development timelines, computational approaches to support solid form design and selection are of greater importance. Over the past decade, pharmaceutical industry has witnessed an ever-increasing utilization of these tools to complement experimental efforts. In this presentation, we will be discussing the value of application of combined experimental and computational approaches for solid form design and selection process for rule of 5 (Ro5) and beyond rule of 5 (bRo5) drug candidates. Also, case studies will be discussed where experimental and computational approaches were used in conjunction to gain fundamental understanding at molecular and crystal structure level underpinning the link between structure, properties and performance to obtain optimum drug product.

CRYSTALLOGRAPHIC LANDSCAPE OF ELECTRON DIFFRACTION: NOVEL APPLICATIONS FOR THE PHARMA AND AGROCHEMICAL INDUSTRY

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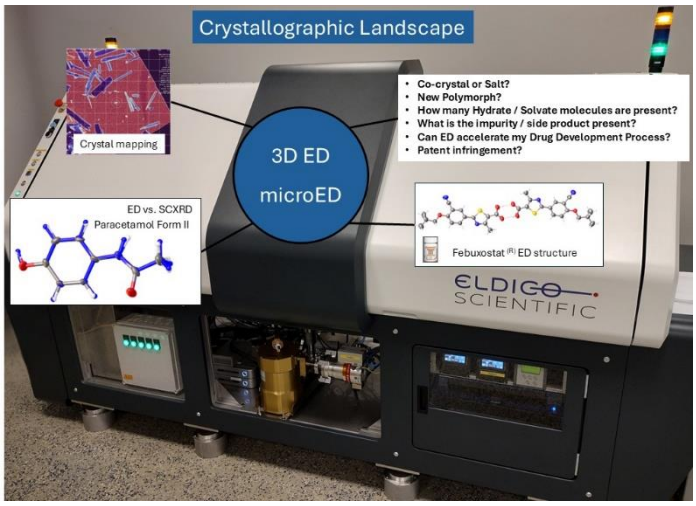
Electron Diffraction (3D ED / microED) has been rapidly evolving as a complementary technique for SC-XRD experiments.[1] Continuous rotation ED experiments work in the same manner as SC-XRD experiments, overcoming the bottle-neck problem: crystal size. Though the bottleneck now becomes the instrumentation. Dedicated electron diffractometers[2] make the technique more accessible, resulting in ease of use. In fact, in the last 3 years, there has been an increase in the number of publications arising from such devices.[3] Especially in the field of pharmaceutical solid forms.

We would like to show case, not only the technology, but emphasize in the advantages and capabilities of having a dedicated device for electron diffraction experiments. Especially for the Pharmaceutical and (Agro-)Chemical companies. Moreover, we would compare the technology to existing technologies like SC-XRD or XRPD, highlight new fields of applications like automation in "crystal mapping" for phase or impurity identification and present some studies where ED has been a game changer for API's structure elucidation.[4]

Furthermore, you will learn about the new applications of ED:

- For polymorph screening
- Benefits on amorphous materials,
- Relevance in process development,
- Applications in Quality Control and Formulation
- Importance in the IP world.

Especially, when very little amounts of sample are present or other available analytical techniques fail to provide an answer.



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GS2

Discovering solid forms: new amorphous and crystalline polymorphic forms of sodium naproxen

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The solid form of an active pharmaceutical ingredient (API) is usually governing its material properties such as solubility or tableting characteristics. Several strategies have been put in place to improve solubility as this is often a major issue. Naproxen is a poorly soluble API, but its solubility can be improved by synthetizing corresponding sodium salt. Another alternative to improve solubility is to stabilize an amorphous state [1], however it has been shown that naproxen is a typical non glass former [2].

For ceramic materials, it has been demonstrated that crystallization from melt can be a successful approach [3] to stabilize new polymorphic forms of technological relevance. In this contribution, we have been applying a similar approach investigating sodium naproxen as an example. When heating up sodium naproxen above its melting point, various phases can be stabilized upon cooling at room temperature depending on the heat treatment: a new polymorph, or a glass phase. This is in significant contrast to behavior of pure naproxen. In Figure 1 the temperature dependence of this substance is shown as function of temperature. Upon consecutive heating, the initial amorphous state (1) evolves towards a second amorphous state (2) before recrystallizing into previously unreported crystalline polymorphic forms of sodium naproxen (regions (3) and (4)). For instance, the crystal structure present in the region (4) of the isoline plot can be stabilized at room temperature and varies from the initially reported crystal structure of sodium naproxen [4] only by the orientation of the methoxy group (Figure 1 b).

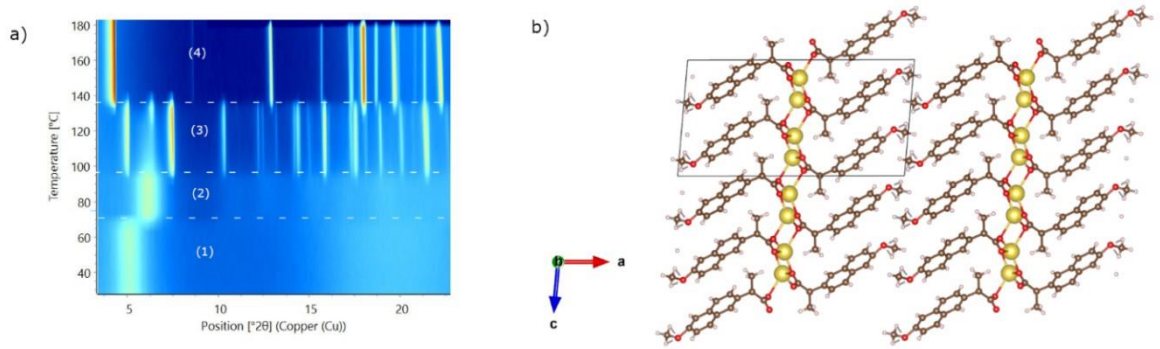

Figure 1. a) Isoline plot of the recrystallization of amorphous sodium naproxen as function of temperature and b) crystal structure of the new polymorph of sodium naproxen appearing at high temperature (section 4).

While molecular glasses are investigated to attempt stabilizing amorphous phases of APIs with the goal of bioavailability-enhancing formulations, this work demonstrates that their crystallization can be an alternative route for the stabilization of new polymorphic forms of this poorly soluble API.

Keywords: small molecule pharmaceuticals; X-ray diffraction; polymorphism; amorphous API, solubility

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EFFICIENT TOOLS FOR SOLID-STATE RESEARCH

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The exploration and control of solid-state forms remain critical challenges in pharmaceutical development, with implications for bioavailability, stability, intellectual property, and regulatory approval. Advances in experimental methodology now allow for more systematic and resource-efficient investigation of crystallization behaviour, polymorphism, solubility, and phase transitions.

This presentation will introduce a set of laboratory-scale instrumentation platforms— ***CrystalBreeder™, Crystal16®, and Crystalline™***—designed to support high-throughput and information-rich studies in solid-state research. These tools enable parallel screening with minimal material input, offer precise temperature and agitation control, and integrate in situ analytics such as turbidity measurements, video microscopy, and particle tracking.

The Synergy of Computational Modeling, Machine Learning, and Experiments in Pharmaceutical Solid-State Research and Development

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The importance of computational modeling and machine learning are well known in pharmaceutical drug discovery. Using computational modeling, machine learning and automation technologies,XtalPi has developed a series of methods to guide and enhance experimental workflows for drug development:

- Virtual multicomponent screening to predict the likely salts, cocrystals, and solvates of a compound and recommend solvents for formation experiments. These virtual screenings can be used to reduce the number of wet-lab experiments performed and increase the likelihood of generating the desired result.
- Crystal structure prediction (CSP) predicts all possible polymorphs of a compound and ranks them by thermodynamic stability. The CSP structure-energy landscape can reveal if the most stable polymorph has been discovered and complements experimental XRPD, SC-XRD, and MicroED techniques for crystal structure determination.
- AI-enhanced crystallization (Xtal2) is a machine learning model—constructed from more than 100k virtual and 10k experimental data—used to recommend crystallization strategies based on molecular structure information. Combining Xtal2 with autonomous work stations allows intelligently designed experiments to be run 24x7.
- Morphology prediction calculations reveal how variables like solvent and additives affect the particle shape of a crystallized compound. These calculations reveal if an undesirable morphology (e.g. needles) is expected and can be avoided by crystallization conditions, or if engineering solutions (e.g. milling) will be required.

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“Solid Form Matters: Microenvironmental Influences on API Stability in Drug Products”

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Abstract

The solid-state form of an active pharmaceutical ingredient (API) is a critical quality attribute that can significantly influence the performance, stability, and regulatory compliance of the final drug product. While solid form selection is typically addressed during early development according to well established guidance, its behavior under real-world formulation conditions—especially during shelf life—remains underappreciated.

This presentation explores how microenvironmental factors such as pH, temperature, and excipient interactions within the drug product matrix can induce solid-state transformations, including disproportionation, crystallization, or amorphization. These changes may occur during storage or use, potentially altering bioavailability or triggering regulatory concerns.

We will illustrate this with several anonymized case studies involving different formulation principles and some real case experiences.

These examples underscore the importance of integrating solid form risk assessment into formulation design and stability protocols. We advocate for a paradigm shift where final product conditions are not just a downstream consideration but a central element in solid form strategy.

CO-CRYSTALS, SALTS AND SUBLIMATION

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Sublimation, or crystallisation from the gas phase, has not been well-explored for the crystallisation of molecular materials [1]. Our group has begun to investigate sublimation as a crystallisation technique, particularly with regards to organic multi-component crystals [2]. We have studied the competition between hydrogen bonding and halogen bonding in the gas phase [3], as well as the sublimation of hydrates [4]. We have also shown that crystals of organic salts can be prepared by sublimation [5], and that selective crystallisation of either a salt or a co-crystal of the same components is possible by changing the sublimation conditions [6]. Additives can also have a significant effect on the product that crystallises from sublimation, and the polymorphic form of the co-formers used can also change the outcome of a sublimation crystallisation. Sublimation can also give crystals of forms that are difficult to obtain from solution.

In this presentation, our results on crystallisation from the gas phase will be presented, and discussed in terms of what can be learned about control of crystal form in the sublimation process. It has become clear that sublimation has great potential in exploring the crystal form landscape.

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Amorphous forms of drugs: from preparation to poly*A*morphism

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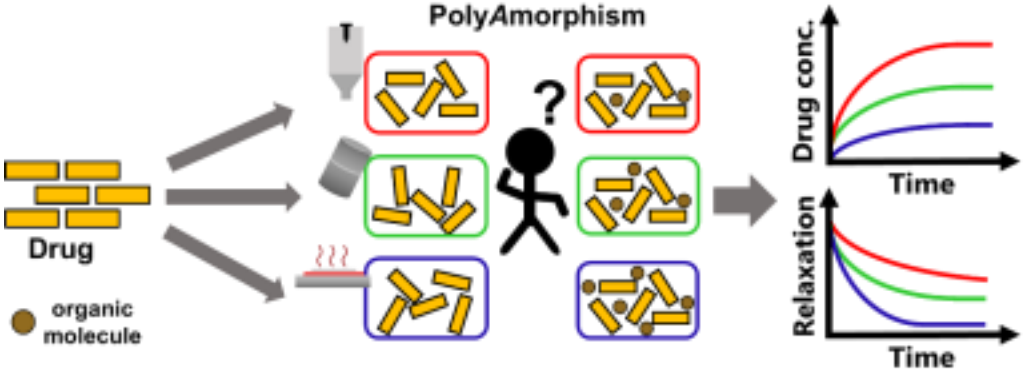
Most drug delivery today utilizes solid dosage forms, especially for small molecules. However, the solid state of drugs can take many forms, and increasingly high energy solids are used, with different degrees of disorder, ranging from stable to metastable crystalline forms, to supercooled liquid crystalline forms, to amorphous forms.
Amorphous forms are ideal candidates to improve the solubility and thus potentially the oral bioavailability of poorly water-soluble drugs. When searching for amorphous forms, only one "amorphous state" is currently considered as a result from the screening process *via* different preparation methods. However, depending on the preparation conditions, distinctly different amorphous forms with distinct molecular-level organizations as well as physicochemical properties can be isolated and even interconverted between each other in a phenomenon termed poly*A*morphism.[1-3] The occurrence of *diversity* among amorphous forms of the same drug is therefore a topic of great interest in the investigation of oral drug formulations.
In this presentation, we will start by discussing various solid-state forms and their potential applications in drug delivery. We will then aim to deepen our understanding of the amorphous forms of drug molecules as a rational basis for the development of amorphous solid dispersions (ASDs) and co-amorphous systems.[4,5] In the second part of the presentation, we will examine the *diversity* within amorphous forms, particularly poly*A*morphism, and discuss how their structural and physicochemical properties are significantly influenced by the preparation methods used.



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Abstract

Amy Woods-Ryan, Durham University

HEPES of conformational, multi-zwitterionic polymorphs

The common buffering agent known as HEPES (2-[4-(2-Hydroxyethyl)piperazin-1-yl]ethane-1-sulfonic acid) was found to have heaps of polymorphs and hydrates. Five new solid forms of HEPES (including two hydrates) were found under different crystallisation conditions. These were characterised and their relationship and transformations investigated. Most interestingly, since HEPES is amphoteric as well as flexible, the solid forms contain different zwitterions as well as different conformers.

Our study highlights the complex behaviour of zwitterionic and flexible molecules in the solid state, the difficulties faced in controlling their crystallisation and the challenges associated in developing them for pharmaceutical applications.

Continuous flow chemistry as a tool for crystallisation of porous organic materials

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Abstract:

Reversible processes, such as dynamic covalent/non-covalent chemistry and crystallisation, are exploited by chemists to make complex, and potentially porous, structures from simple precursors. However, they are profoundly influenced by reaction environment and thus challenging to direct.[1] Reaction conditions significantly affect yield and selectivity; poor *control* over reaction conditions limits reproducibility, scalability, crystallinity, and sustainability, ultimately limiting our ability to form robust structure-function relationships.

In this talk, I will present continuous flow chemistry as a tool that can overcome these challenges, and that dynamic processes are particularly well-suited to benefit from. Using recent case studies including the efficient flow synthesis of porphyrins,[2] molecular knots,[3] and the flow crystallisation of a molecular material,[4] I will illustrate the available benefits for the porous materials community, and how automation can further accelerate the discovery, optimisation, and translation of organic materials.

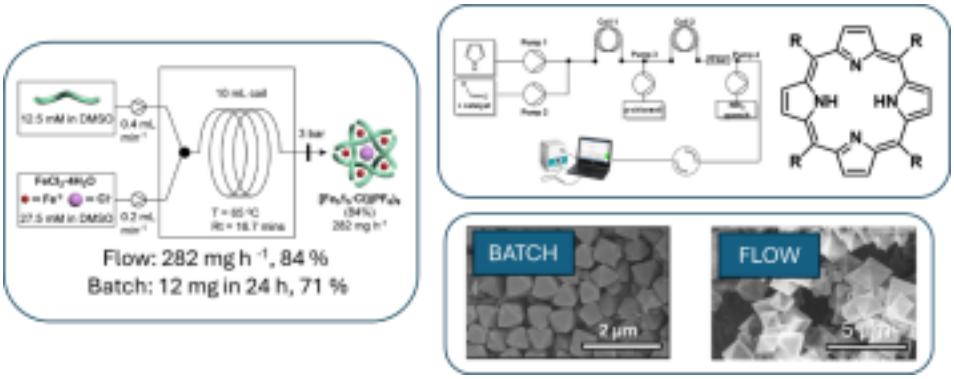

Figure 1 *Flow synthesis of a molecular pentamer*[3] *and meso-porphyrins*[2]*; flow crystallisation of a porous organic cage improves crystallinity*[4]

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Mechanisms of Cocrystal Formation and Coformer Exchange in Ethenzamide Systems – From In Situ Studies to Pharmaceutical Applications

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Understanding the mechanisms underlying cocrystal formation and coformer exchange is critical for the rational development of multicomponent pharmaceutical solids with improved physicochemical properties. Ethenzamide (ET), a model active pharmaceutical ingredient (API) with limited solubility, serves as an excellent system to investigate these processes due to its ability to form a broad range of binary cocrystals with structurally diverse coformers. The aim of this presentation is to provide an integrated overview of how *in situ* and *ex situ* studies have elucidated the pathways of cocrystallization and coformer selection in ethenzamide systems, and how these findings translate into pharmaceutical applications.

Recent studies have demonstrated that the synthesis of ET cocrystals can be achieved through a range of solvent-free methodologies, including ball milling, melting, and MAS NMR-induced transformations. Solid-state NMR experiments, in combination with differential scanning calorimetry and theoretical modelling, have revealed a multistep mechanism of cocrystal formation involving eutectic phase generation, molecular rearrangement, and thermodynamically driven partner selection in the molten or semi-molten state. It is particularly noteworthy that, in multicomponent mixtures, ET exhibits a high degree of selectivity toward specific coformers. This phenomenon is driven by relative stabilization energies and molecular electrostatic potentials of the resulting cocrystals [1].

In situ studies have demonstrated the critical influence of mechanical pressure, grinding duration, and even friction induced by MAS on the initiation and progression of cocrystal formation [2]. These parameters not only influence the kinetics of formation but also determine the emergence of different polymorphic forms, as demonstrated in the case of the ET–gentisic acid system, where different polymorphs exhibited varying stability and behaviour during tableting processes [3].

Overall, this presentation will highlight the interplay between solid-state chemistry, thermodynamics, and pharmaceutical functionality. The insights gained into the mechanisms of action pave the way for the design of cocrystals with optimised therapeutic profiles, in line with modern trends in green chemistry and precision drug development.

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API: Don't Forget the I. From the Right Molecule to the Right Particle

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Once an effective and potentially safe new chemical entity moves from the discovery phase to the development, this so called "**Right Molecule**" (a.k.a. lead candidate) needs to be transformed into the "**Right Particle**" and the "**Right Powder**" to become the Active Pharmaceutical Ingredient (API) of the future new medicinal product for human use.

The knowledge acquired with the solid-state investigation of drug substances (DS, a.k.a. API), drug products (DP), and even intermediate of the manufacturing production helps to control and optimize the product performance and the drug delivery.

At Molecular, Particle and Bulk levels there are a huge number of characteristics and attributes that require attention and control from the Material Science point of view (see Figure 1 below). It is well established that the control of the **API form** (due to polymorphism) in DS and DP is more than critical since the API form itself has profound influence on the properties of the final DP with ethical, therapeutic, commercial and economic implications. Furthermore, **other Critical Quality Attributes (CQAs)** may be subject of control to ensure the success of a given formulation strategy in terms of performance and manufacturability. Particle size distribution (PSD), particle morphology, mechanical properties and other attributes play a key role for the DP performances and manufacturability. We will discuss the influence of different API attributes may have on drug products' performance showing how a deep knowledge of the relevant CQAs is important for formulation and product development as well as batch-to-batch variability investigations.

This simply because **we do not have to forget the "I": the API is an Ingredient** of a complex DP: for sure (one of) the most critical component that need to have the proper characteristics to be part of a DP composition considering the final dosage form, formulation and dose.

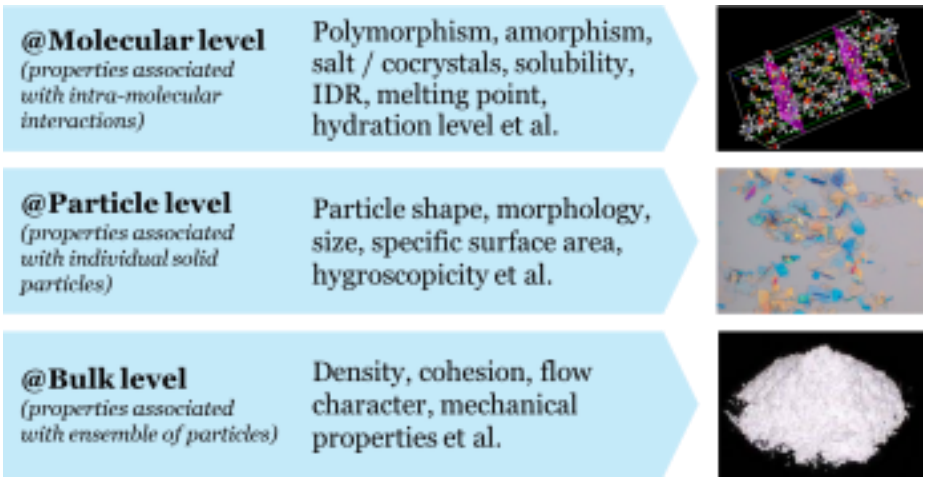

Figure 1: API properties at different "levels"

Challenges in crystallization scale-up of an API

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This presentation describes the discovery, characterization, and process optimization of a novel nanocrystalline form of an anti-cancer agent. Through a series of crystallizations trials and internal research, the new form was identified and isolated, exhibiting advantageous properties such as enhanced solubility, promising chemical and physical stability and good processability. Comprehensive solid-state characterization and multivariate analysis (PCA) confirmed the distinctiveness of the new form compared to known polymorphs. The crystallization process, consisting in an anti-solvent precipitation, was systematically optimized with in-line monitoring using image and IR probes, enabling real-time tracking of key events such as oiling-out, gel formation, and precipitation. Solubility curves and metastable zone width (MSZW) were determined as functions of anti-solvent fraction, dosing rate, temperature, and seeding, supporting robust process design for industrial scale-up. This work demonstrates an integrated approach to the development of new pharmaceutical crystal forms, from discovery to process transfer, and highlights the value of advanced analytical and process monitoring techniques in solid-state pharmaceutical development.

Optimizing complex multicomponent solid form discovery & crystallization process design

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Crystallization is a critical industrial separation process, producing crystalline products of which the value is closely tied to the product quality [1]. This product quality is defined by the form, size, shape, and purity of the crystals. While trying to achieve a high product quality, sufficient yield and productivity are important specifications as well in the design of a crystallization process. These specifications necessitate a systematic approach to process design.

Key enablers of efficient crystallization process design are accurate solubility data and crystallization kinetics. Advancements in commercial equipment have made it easier to obtain high-quality solubility measurements, even for complex multicomponent systems [2,3]. This simplifies the determination of the conditions under which specific yields and productivities can be achieved, but also specific polymorphs or multicomponent crystals can be obtained. Equally important is a thorough understanding of crystallization kinetics [4]. Methods such as induction time distribution measurements offer insights into nucleation rates and mechanisms [5,6].

Such insights on solubility and crystallization kinetics lead to product quality control strategies that improve the crystallization process design, for instance by controlling the polymorphic form. The solubility and kinetic measurements are integrated in a crystallization process design workflow to address quality challenges and optimize production by crystallization.

Crystallization, due to the very specific solid structure of crystals, is usually highly effective in rejecting impurity from entering the growing crystals. However, insufficient impurity rejection during crystallization can occur [7]. A challenging case of impurities is the unwanted enantiomer in crystallization-enhanced chiral resolutions and deracemizations. A clever choice of solid form can open up such routes for crystallization-enhanced chiral resolutions and deracemizations [8].

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The Critical Role of 3D Molecular and Biomolecular Structures in Innovative Drug Discovery

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Understanding and controlling the 3D molecular structure of active pharmaceutical ingredients (APIs) is fundamental to overcome pharmacokinetic challenges in drug development. In this presentation, we explore crystal engineering[1]—through cocrystallization and salification—as a versatile strategy to modulate solubility[2], dissolution rate, and membrane permeability[3] of selected APIs without altering their chemical structure. By designing new solid forms with small organic acids, we achieved significant improvements in dissolution profiles and permeability, enabling more controlled and effective drug release. Structural and computational analyses revealed that molecular interactions in the solid state and in solution play a key role in tuning these properties.

The same principles can be extended to the design of co-amorphous systems, offering valuable solutions for structurally complex molecules such as selective PI3K inhibitors, where solid-state behavior critically impacts formulation success. These findings highlight the versatility of crystal engineering in addressing diverse challenges in drug development and in supporting the creation of innovative, bioavailable therapies. Our results underscore the potential of rational solid-state design to overcome pharmacokinetic limitations and enhance drug performance, offering a promising alternative to complex formulations.

Beyond small molecules, the three-dimensional conformation of biomolecular therapeutics—such as peptides, proteins, and nucleic acid-based drugs—plays a pivotal role in determining their stability, efficacy, and biological activity. Subtle conformational changes can influence binding affinity, aggregation propensity, and degradation pathways, directly impacting therapeutic outcomes. In this context, structural characterization techniques such as small-angle X-ray scattering (SAXS) have become essential tools for probing the solution-phase architecture of biotherapeutics[4]. SAXS enables the investigation of global shape, flexibility, and conformational dynamics under near-physiological conditions, providing critical insights into formulation behavior and stability. Integrating solid-state design with advanced structural biology approaches allows for a more comprehensive understanding of drug behavior, ultimately guiding the development of next-generation therapeutics with improved performance and reliability.

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Solubility – Easy Parameter with Hurdles in Determination and Interpretation

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Chemical, Material & Regulatory Science, BASF SE

Solubility is an ubiquitous physicochemical parameter determined for active ingredients. Especially in pharmaceutical discovery projects solubility often competes with biological activity and it is often the activity that wins the match. This presents a unique challenge: solid-state scientists and formulation scientists may find an open playground or a hard nut to crack.

Everybody understands solubility and it seems to be an “easy to determine parameter”. This parameter is not part of Lipinski’s rule of 5, but these rules are associated with solubility.

We measure thermodynamic solubility, saturation solubility and kinetic solubility. And sometimes it is hard to differentiate. For each measured solubility a set of parameters has to be determined and reported to deliver a clear picture.

- Is solubility really such an easy parameter?
- Where between thermodynamic and kinetic do we measure?
- Which parameters/side conditions do we need to keep in mind?
- Is every solubility increase an achievement (see Figure)?

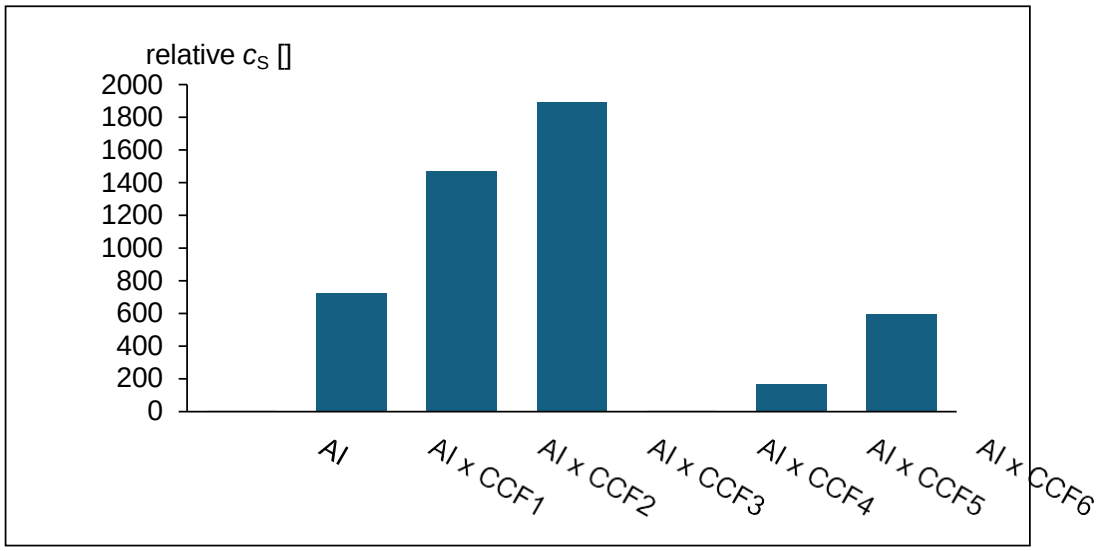

Figure: Aqueous solubility of active ingredient (AI) and co-crystals after 2 h.

Kerns and Di: Drug-like Properties: Concept, Structure Design and Methods, Elsevier, **2008**

Mixed Crystal Form Screening: Molecular, Co-Crystalline and Ionic Co-Crystalline Solid Solutions

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Pharmaceutical solid solutions allow properties fine tuning and precise dose control for multidrug solid forms and personalised medicines. Despite recent examples demonstrate that old designing principles were too restrictive these phases remain relatively rare, their controlled synthesis challenging and their characterization complex. In this view, a crystal engineering strategy to maximise their successful realization for practical applications.
Here such idea is well demonstrated by Piracetam and Oxiracetam that can be crystallized as molecular, co-crystalline and ionic co-crystalline solid solutions. Each form shows full solid state solubility of the parent drugs and give access to different ranges of properties, which can additionally be fine-tuned with composition. Ultimately the solid solution screening results in a co-crystalline form that is sufficiently stable and easy to synthesize, and enables full dose control.

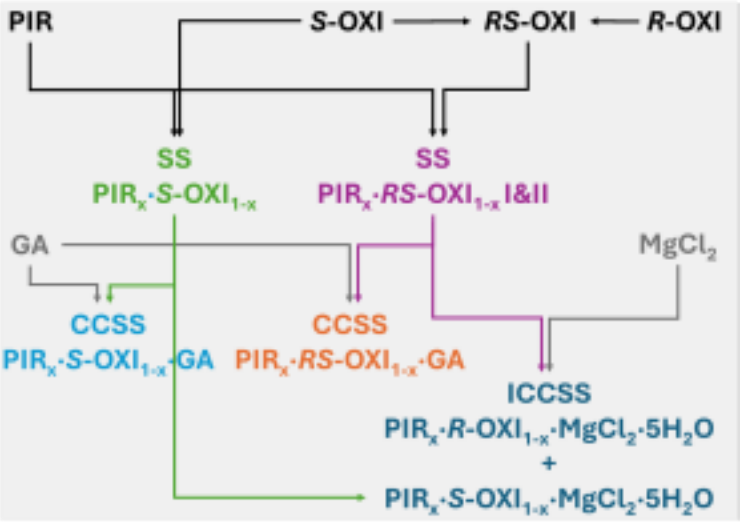

Figure 1. Molecular, co-crystalline and ionic cocrystalline solid solutions of Piracetam and Oxiracetam

Co-crystallization as a versatile tool in pharmaceutical development

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Solid State Development Sciences, UCB Pharma, Braine-l'Alleud, Belgium

It goes without saying that co-crystals have become a powerful tool in the pharmaceutical field essentially due to their potential to tune the physicochemical properties of an API (solubility, dissolution rate, stability…) without compromising its molecular structure.
Pharmaceutical co-crystals enable better formulation strategies, improved drug performance, simplified storage conditions, and, potentially, can extend product lifecycles via new intellectual property opportunities. However, the use of co-crystals in the pharmaceutical industry is not necessarily limited to the modification of the physicochemical properties of interest.

In our presentation, we show an example of going beyond the use of co-crystals for mere property adjustment, demonstrating the successful implementation of co-crystals in the development process: as a tool for purification, meaning selective isolation of the desired molecule or in the context of chiral resolution. Both approaches were developed in parallel in one project but for two different synthetic routes – 'enantiopure' and 'racemic'. The
challenge of the former synthetic route dealt with the complexity of the isolation of the final product, where a recrystallization step without additional purification by chromatography was not possible. The co-crystallization was used to selectively isolate the target molecule from the crude material obtained after synthesis.

The alternative synthetic route led to a racemic intermediate of the target molecule that was then separated by chiral chromatography. Since this separation approach is quite expensive, the co-crystallization approach was successfully used as a tool for chiral resolution.

Computational approaches for the prediction of particle properties of organic molecular materials

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Since 1965 the Cambridge Structural Database (CSD)[1] has been used by scientists around the world to explore the link between the structure of crystalline materials and their properties. Building on the wealth of data in this collection of over 1.3 million structures, Solid Form[2] and Particle Informatics[3] methods have been developed hand in hand with partners across academia and the formulated products industries. Nowadays, these data-centric approaches are routinely used to assess the risk of polymorphism, predict the shapes of crystalline particles, and identify links between bulk structure and surface properties.

This contribution will explore our recent advances in the calculation and description of *digital particles*, with a few examples of how calculated particle properties can assist the development of solid form and crystallisation research with particular focus on solid form selection.

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Insights into Pharmaceutical Drug Substance and Product Using Multinuclear Solid-State NMR Spectroscopy

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High resolution characterization of pharmaceutical solid dosage forms represents an ever-challenging problem facing pharmaceutical scientists. Detailed solid-state analysis of a drug product should include active ingredients as well as excipients, and potential interactions among them. Historically, pharmaceutical solid-state NMR has primarily been applied to cases of relatively simple solid form determination, where it naturally excels, particularly in formulated products. This presentation will focus on modern applications of solid-state NMR spectroscopy to gain insights into complex solid dosage forms, including crystalline and amorphous materials, protonation states, drugs and excipients, and ubiquitous water.

Historically for pharmaceutical solids, ^{13}C is the most widely studied nucleus due to the information content available, its presence in nearly all pharmaceutical ingredients, and high resolution spectra that can be obtained. It is primarily accessed via cross polarization (CP) experiments due to its low natural abundance and relatively long relaxation times, which have hindered its use in quantitative analysis. We will illustrate practical examples of quantitative CP experiments in amorphous solid dispersion tablets, a commonly used modern dosage form.

^{19}F is a friendlier nucleus from an NMR standpoint due to its relative sensitivity, and continues to become more widespread in pharmaceutical materials. It is highly useful when present in active ingredients and enables exquisitely selective analysis of the physical state of the active within a formulated product, even at very low drug loading. We will examine how it can be used for solid form characterization in relevant drug products.

^{15}N is particularly useful in protonation state investigations, but suffers from extremely poor sensitivity and sometimes prohibitively long experiment times. We will examine a case where it was utilized to show proton transfer from drug to excipient in an amorphous solid dispersion, and help to gain a better understanding of the overall landscape of these materials.

Finally, water content is a frequently measured quantity is solid dosage forms, and is often considered a critical quality attribute. The methods used to quantitate water content, such as Karl Fischer titration, loss on drying, or thermogravimetric analysis, generally sample a bulk powder or tablet and report back the overall water percentage in a given quantity of material. However, the distribution of this water is far from homogeneous. We will demonstrate how ^{1}H NMR relaxation times, detected through ^{13}C CP experiments, can be used to ascertain how ubiquitous water is distributed among various ingredients in a formulation. This deeper understanding of the distribution of water molecules throughout a given formulation can provide valuable insight into dosage form design for more robust drug products and processes.

Linking crystal structures with material properties

Helen Blade

Principal Scientist, Global Product Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield

An overview of computational approaches to link crystal structure to particle morphology for pharmaceutical product development will be presented. By combining experimental insights with advanced modelling techniques, we demonstrate how the solid-state landscape of an API fundamentally shapes its manufacturability and therapeutic performance.

The talk will showcase how digital tools such as polymorph and particle mapping, are used to anticipate material attributes and variability before experimental material is available. These methodologies underpin solid form selection, inform process decisions, and help develop robust control strategies—ultimately supporting accelerated development pathways and digital twin

A NICE POEM: COCRYSTALS FROM LIQUID INGREDIENTS

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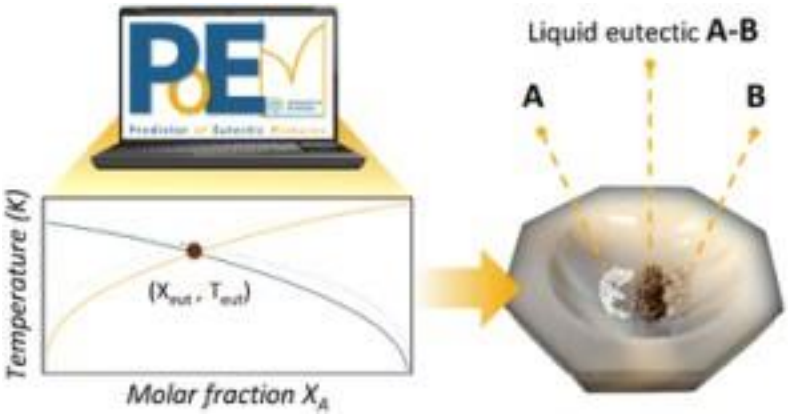
This study introduces PoEM (Predictor of Eutectic Mixtures), a novel predictive tool designed to estimate the melting point variations in binary mixtures used in mechanochemical syntheses and cocrystallizations. The prediction of the phase behaviour of a mixture of solid components when they come into contact is of high interest in fast growing research fields such as crystal engineering, mechanochemistry, and deep eutectic solvents (DESs). Mechanochemistry has emerged as a sustainable and efficient method for chemical synthesis and especially for cocrystal fabrication, significantly reducing solvent waste and enabling unique reaction pathways. A critical aspect of mechanochemical processes of cocrystal formation is the presence of eutectic mixtures, which can enhance reaction efficiency by facilitating mass transport and molecular mobility.

PoEM utilizes an empirical model based on regular solution theory and the Schroeder-van Laar equation to predict the eutectic point, accounting for deviations from ideal behavior due to intermolecular interactions. The tool's predictions are validated against experimental data from a training set of 36 binary mixtures, demonstrating its accuracy and reliability.

The application of PoEM is illustrated through the identification of coformers for the synthesis of a cocrystal containing thymol, showcasing its practical utility in designing mechanochemical processes. By providing a user-friendly interface and rapid calculations, PoEM offers a valuable resource for researchers in the field of mechanochemistry and cocrystals, enabling the rational design of solvent-less synthetic procedures.

This presentation will detail the development, methodology, and validation of PoEM, highlighting its potential to advance the efficiency and sustainability of mechanochemical reactions.



This tool has been developed within the NICE – Nature Inspired Crystal Engineering – PRIN2020 project, granted by MIUR (PRIN2020 Y2CZJ2).

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Free download: https://cristallografia.org/blog/2024/09/12/poem/

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Pharmaceutical Cocrystals via Halogen Bond

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Keywords: Halogen bond, pharmaceutic cocrystals, self-assembly, crystal engineering

The halogen bond is the attractive interaction wherein halogen atoms of organic derivatives act as electrophiles and attractively interact with electron rich sites (e.g., lone pair possessing atoms, π electrons of unsaturated moieties, anions) which function as nucleophiles. These interactions can be strong enough to drives cocrystal formation and we will describe cases wherein the halocarbon is of pharmaceutical interest. For instance, we will describe the cases of the 3-iodo-2-propynyl-N-butylcarbamate (IPBC), an iodinated antimicrobial product used globally as a preservative [1], and (1,2,4-trichloro-5-[(3-iodoprop-2-yn-1-yl)oxy]benzene) (Haloprogin), an antimycotic topical drugs [2] (Figure). Clearly, the halogen bond nicely complements the opportunities offered by the hydrogen bond when the obtainment of pharmaceutical cocrystal is pursued. The approach appears of particular relevance if it is considered how often halogen atoms are present in commonly used drugs.

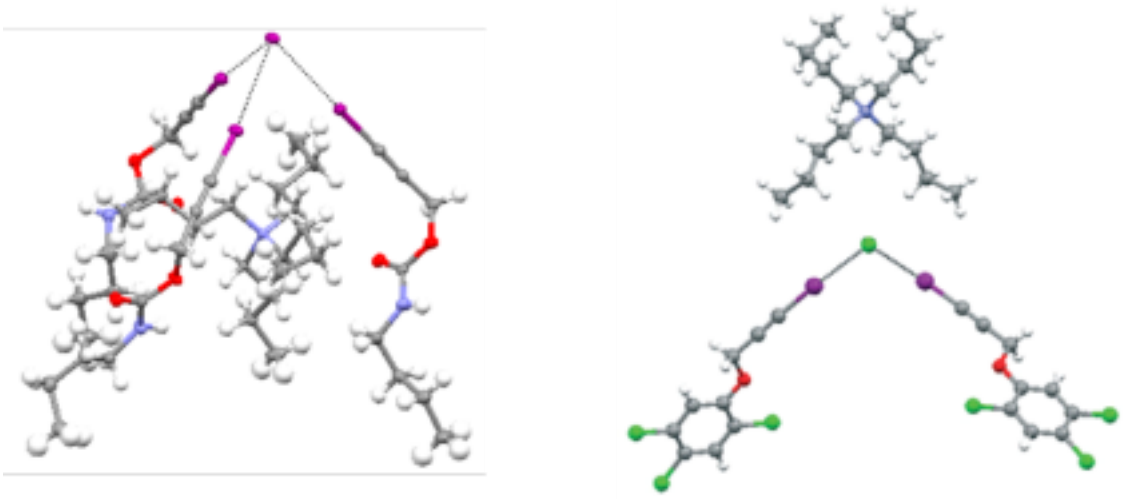

Figure. Cocrystals between: IPBC and an iodide acting as nucleophile (left), Haloprogin and a chloride acting as nucleophile (right).

Acknowledgements. Ministero dell'Università e della Ricerca (PRIN-2020, project NICE, no. 2020Y2CZJ2) is gratefully acknowledged for financial support.

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Advanced Solid-State NMR tools for Crystal Engineering:
From Structure Elucidation to Phase Purity Assessment

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In crystal engineering applied to drug development, the identification, characterization, and quantification of different forms of an active pharmaceutical ingredient (API) are critical, as the properties of the resulting crystal depend on its structure and phase purity. While X-ray diffraction is the preferred technique, it may encounter limitations when dealing with poor crystal quality, small crystal size, hydrogen atom positions, or disordered/amorphous samples. Over recent decades, solid-state NMR has emerged as an indispensable tool in crystal engineering, offering a highly complementary approach to X-ray diffraction for investigating the structures of crystalline molecular materials.
This talk highlights new applications of solid-state NMR in the study of polymorphs, co-crystals and molecular salts, focusing on its ability to:
-investigate hydrogen bonds in terms of proton transfer;[1, 2]
-determine the tautomeric or zwitterionic character of molecules;[3, 4]
-solve structures by combining crystal structure prediction with solid-state NMR data;[4, 5] -quantify mixtures of crystalline and amorphous forms.[6]

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Study of pillared MOFs with Zn-paddlewheel state switching

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Metal-organic frameworks (MOFs) with zinc paddlewheel nodes represent a versatile class of porous materials with potential for dynamic structural transformations. This study investigates the unusual behavior of PUM168, a pillared MOF with **pcu** topology that exhibits remarkable paddlewheel state switching triggered by methylene blue dye absorption from acetonitrile solution. Unlike previously reported paddlewheel transformations that require harsh conditions such as heating or gas absorption, PUM168 undergoes closed-to-open paddlewheel conversion upon minimal dye uptake occurring exclusively at crystal surfaces. To understand this phenomenon systematically, we analyzed 409 crystal structures containing zinc paddlewheel from the Cambridge Structural Database. The frameworks in this comprehensive dataset are built from 94 different dicarboxylates (with bdc, ndc, and bphdc being most prevalent) and 124 different N-ligands (dabco, bipy, and bis(4-pyridyl)ethane being most widespread). Using SOAP descriptors and HDBSCAN clustering, we identified distinct paddlewheel geometries: open paddlewheels cluster into three distinct types, while closed paddlewheels form a conformational continuum. A simple logistic regression model utilizing structural descriptors reflecting pillar N-ligand length, square layer acute angles, dicarboxylate angular characteristics, and framework void fraction successfully predicts paddlewheel states. Our analysis revealed 15 structures with potential open-closed transformation capability, with experimental validation confirmed for several cases. Notably, for structures like TOTMUN, VITDEK, and WOSPUS, alternate crystal forms with open paddlewheels have been experimentally observed, supporting our predictions. This work establishes a predictive framework for searching for MOFs with paddlewheel switching and demonstrates that subtle guest-framework interactions can trigger significant structural transformations under mild conditions.