A small amount of water in crystallizations

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A small amount of water in organic solvents can significantly change the solubility of drug substances and new polymorphs can be formed (different hydrates or anhydrates) due to water. During crystallization the polymorph formation depends on the extent of supersaturation. Formation of hydrates changes the solvent composition during the crystallization process along with the solubility and the supersaturation potentially leading to the formation of another solid form. In our study the role of water was examined in some crystallization processes.

Can deuterated solvents change the course of crystallization of organic compounds?

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Crystallization of organic molecules is still a poorly understood process, with a limited knowledge about the factors that govern this phenomenon. Sometimes the outcome of a crystallization experiment seems to be even dependent on the season or the way of obtaining the material that is being crystallized. One of such underexplored areas, which potentially can have a noticeable influence on the outcome of crystallization is using deuterated solvents, instead of their protonated counterparts. For example, very recent computer simulations of a nucleation mechanism of calcium carbonate in H_2O and D_2O have shown that significant differences may be expected in prenucleation clusters formed in these two solvents,[1] and it is anticipated that even more pronounced differences may occur in solvents other than water.[2] There are also reports showing that deuteration of a molecule itself may lead to different polymorphs.[3]

Here, we present preliminary results on the study of crystallization of sulfamerazine (SMN) from methanol. SMN is a sulphonamide antibiotic that is known to exhibit polymorphism. The known polymorphs of sulfamerazine have been identified as Form I (the kinetic form), Form II (thermodynamically stable at lower temperatures, below 51-54 °C), and the rare, difficult to isolate Form III. Our crystallization experiments of sulfamerazine were conducted under controlled heating and cooling conditions using a Crystal16® device, in dried solvents, both conventional and its deuterated counterpart.

Preliminary results indicate the formation of different crystal morphologies of sulfamerazine in a reproducible manner, although the same crystal phase was observed regardless of the type of solvent used. For different supersaturation rates, the crystals grown from deuterated methanol were repeatedly thinner and longer, suggesting a different influence of the solvent on the rate of facets growth. The shape and width of the metastable zone of sulfamerazine in both solvents were similar, but we noticed differences in the nucleation rate and crystallization kinetics.

Acknowledgements

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CORE-SHELL ELECTROSPUN NANOFIBERS FOR STABILIZATION OF AMORPHOUS EMPAGLIFLOZIN

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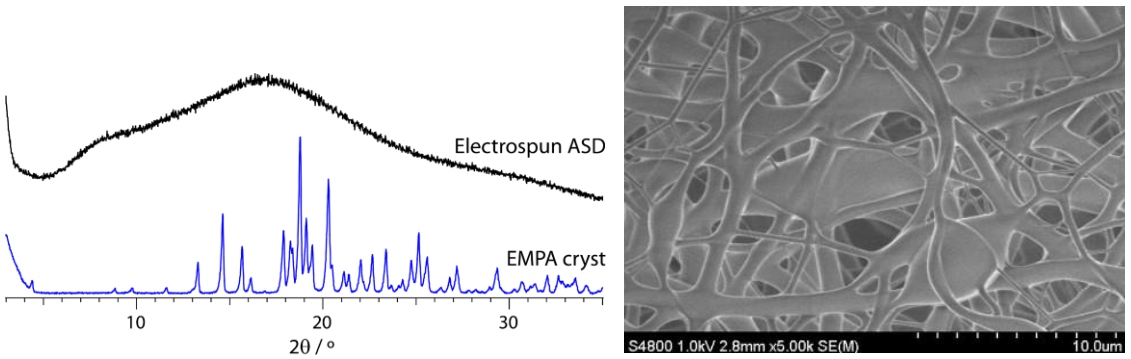
Coaxial electrospinning technology was used to form microfibers with a core-shell structure to obtain a stabilized amorphous solid dispersion empagliflozin, a selective sodium-glucose cotransporter 2 inhibitor. The fibers with optimal properties were obtained by dissolving empagliflozin in a mixture of ethanol and DMSO, adding *Soluplus* as the core polymer and using *Kollicoat* as the shell polymer.

The amorphous state of the obtained solid dispersions was verified by X-ray powder diffraction (XRPD) and differential scanning colorimetry (DSC). The morphology of the obtained microfibers was characterised by scanning electron microscopy (SEM), see Figure 1b. The obtained dispersions were also characterized by Fourier transform infrared spectroscopy (FTIR) and photoluminescence spectroscopy.



(a) (b)

Figure 1. (a) XRPD of electrospun ASD and crystalline EMPA, (b) SEM micrograph of the obtained electrospun ASD.

The obtained structures were demonstrated to prevent long-term recrystallisation of the empagliflozin and protects it from degradation by UV radiation and temperature.

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The impact of intramolecular Hydrogen bonds to intermolecular Hydrogen bonds connectivity in molecular salts

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Insight in non-covalent interactions, especially the extent of the charge transfer in variety of H-bonds (HB) and the directional reproducibility of the utterly smallest patterns (synthons) established depending on donor-acceptor propensity of functional groups and molecular structural fragments within the crystal structures determined and deposited in Cambridge Crystallography database (CCD) [1], impacts previously established skills of serendipity growing crystal toward customized crystallization procedures nowadays to be upraised to Crystal Engineering. This engineering concept enables designing new single phases of single or multicomponent crystalline functional materials with purpose. [2] On the large, macroscopic scale the solid-state structures of the bulk powders may exert improved water solubility, flowability, reactivity or phase transition in photochemical and mechanoshemical processing.

The structural diversity in CCD requires the Etter's General rule "Six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds" to be additionally tested for further exploring the influence of the intramolecular HB (IMHB) to its possible participation in establishing intrermolecular HB, and hierarchy in synthons preference as a predictive tool for the mode of crystal packing. [3]

The crystal structures and packing analyses based on HB motifs of the molecular salts of protonated hydroxypyridine derivative with deprotonated hydroxybenzoic acid derivatives comparable with statistical analyses on the surveyed structures deposited in CDC, selected based on IMHB fragments *ortho* position carboxyl–hydroxyl (carboxylate–hydroxyl) and phenyl hydroxyl–methyl hydroxy groups in phenyl and six-membered-hetero-atom-ring, respectively reveal how the nature and the position of the substituents influence the strength of the IMHBs as per the range of their distances and type of synthons in the formation of intermolecular HBs. [4]

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Mapping the polymorphic landscape of cyclopentobarbital

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Derivatives of barbituric acid (barbiturates) and in particular its 5,5-distubstituted species are model compounds for the study of polymorphism, packing relationships and hydrogen bond interactions [1]. Cyclopentobarbital [5-allyl-5-(2-cyclopenten-1-yl)barbituric acid; Cpl], a compound with sedative and anticonvulsive properties, was investigated as part of an our systematic study of solid forms of barbiturates. Previous reports based on hot-stage microscopy (HSM) studies indicate the existence of at least four polymorphs (I-IV) of Cpl [2].

Solvent selection can exert a direct influence on the formation of specific polymorphic forms [3]. Therefore, a comprehensive solvent screen was conducted, which yielded polymorphs I and III° as well as eight solvate forms. Polymorphs I, II, III° and IV were obtained in HSM experiments by slow heating of the supercooled melt. Crystallization conditions had to be optimized to obtain the polymorphs in phase-pure form. Cpl-II and -IV were produced by melt crystallization via seeding with selected structurally analogous, isomorphic [4] barbituric acids. For this purpose, Cpl was melted and seeded with its isomorphic crystallization partners (Cpl II – Rectidon I; Cpl IV – Nembutal I or Sandoptal I) at 80 °C. In contrast to Cpl-II and -IV, Cpl-I and -III° were obtained without the use of isomorphic additives. Polymorph I and III° are enantiotropically related and were produced by stirring water/ethanol (4:1) Cpl-slurries above or under the phase-transition-temperature of 50 °C.

Cpl-I, II, III° and IV were then characterised by hot-stage microscopy, differential scanning calorimetry, variable temperature powder X-ray diffraction, and variable-temperature infrared spectroscopy. Polymorph III° is the stable form at room temperature. Upon heating polymorphs II, III° and IV transform into form I.

The crystal structures of the polymorphs were determined either from single-crystal structure analyses (I and III°) or by combining powder X-ray diffraction data with crystal structure prediction. Cpl-I displays an N−H···O-bonded tape; Cpl-II an N–H···O bonded ribbon chain; Cpl-III° a second type of N−H···O-bonded ribbon chain whereas Cpl-IV displays a second type of N–H···O bonded tape motif. All four of these types of H-bonded structure have already been known from other barbiturates. Cpl-I and Cpl-III° are also the desolvation products of two distinct groups of solvates, each featuring the H-bonded structure of its parent polymorph.

This study provides new insights into the preparation, identification, structures, and transformation behavior of cyclopentobarbital polymorphs, contributing to a deeper understanding of this fascinating system.

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Investigating Solid-Solid Phase Transitions, and Proton Conduction in Crown Ether-Sodium Hydrogensulfate Supramolecular Complexes

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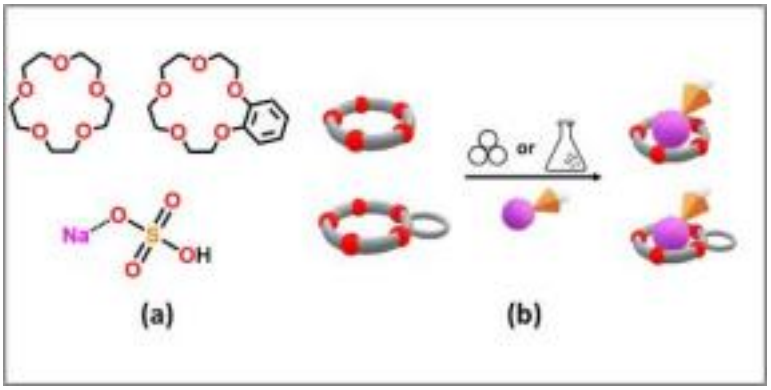
This study deals with the preparation and solid-state characterization as well as structural and phase transition features of supramolecular complexes composed of the solid-acid sodium hydrogensulfate (NaHSO4) and two crown ether ligands,[1] namely the 15-crown-5, and benzo-15-crown-5. Single crystals for each compound were grown, and their structures were elucidated via single-crystal X-ray diffraction analysis (XRD) which highlighted the following compositions: [15-crown-5·Na]HSO_4 (**1**) and [benzo-15- crown-5·Na]HSO_4 (**2**). Microcalorimetric analyses, Hot-stage Microscopy, and variable-temperature powder X-ray Diffraction were employed to analyze thermal stability, and phase transition behaviors. Formation of supramolecular complexes is crucial for inducing solid-solid transitions, leading to superprotonic phases,[2] namely, crystalline solids exhibiting an enhanced ability to conduct protons,[3] as demonstrated through Electrochemical Impedance Spectroscopy measurement.



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Acknowledgments:

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Caffeine vs. Theophylline Co-crystals: Insights into Structure–Mechanical Property Correlation

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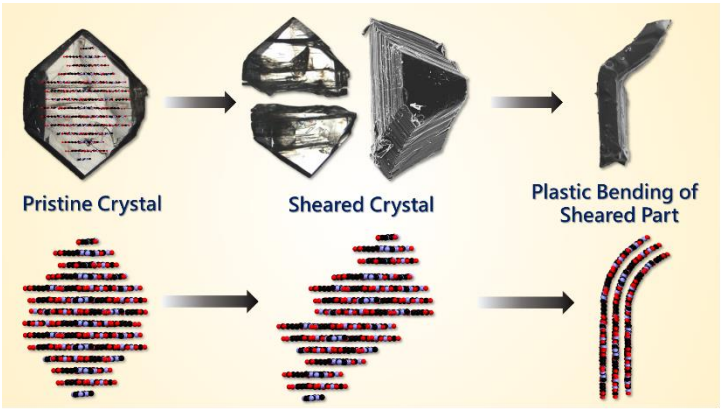

Co-crystallization provides a versatile method to modify the physicochemical and mechanical properties of active pharmaceutical ingredients (APIs). Utilizing crystal engineering principles, we designed co-crystals of structurally similar methylxanthine compounds, caffeine (CAF) and theophylline (THP), with 3,5-dinitrosalicylic acid (DNSA) and 3,5-dinitrobenzoic acid (DNBA) as co-formers. The resulting co-crystals and polymorphs exhibited a range of architectures, including 2D layers, corrugated sheets, and 3D interlocked structures, each displaying distinct deformation characteristics. Special attention was given to the mechanical shearing behavior of the layered co-crystals, THP-DNBA and CAF-DNBA-I, which are particularly relevant for pharmaceutical manufacturing processes like tablet compaction. The THP-DNBA crystal, when sheared, displayed plastic bending deformation, while CAF-DNSA, CAF-DNBA-II, and THP-DNSA co-crystals were brittle due to the lack of flat layer structures. This study highlights the importance of structural features such as flat molecular geometry, π-stacking, and weak interlayer interactions in facilitating plastic deformation through shearing and bending. Additionally, nanoindentation tests on the major crystal faces were performed to quantify the mechanical properties. This presentation provides insights into the relationship between structure and mechanical properties in pharmaceutical co-crystals, emphasizing the potential of co-crystallization to overcome formulation challenges.

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EXPLORING THE POLYMORPHIC LANDSCAPE OF APREMILAST THROUGH INTEGRATED STRUCTURAL, SPECTROSCOPIC, AND COMPUTATIONAL ANALYSIS

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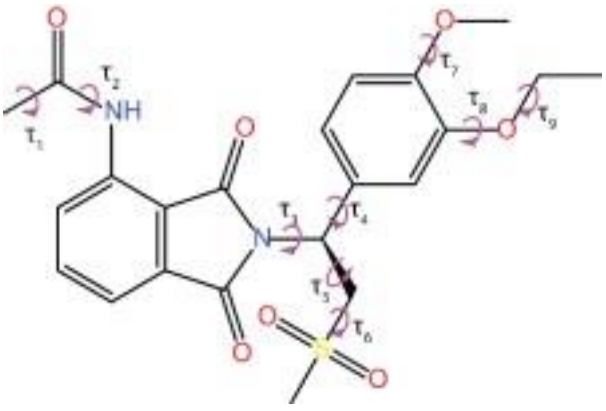
Apremilast, a phosphodiesterase 4 inhibitor used for the treatment of psoriasis, exhibits complex polymorphism. While numerous crystallographically characterized multicomponent crystalline phases of apremilast have been reported—most of them isostructural—only one neat polymorph has been structurally elucidated to date (Dudek et al., 2019).

In this study, we present the structural and thermodynamic characterization of three previously structurally uncharacterized neat polymorphs of apremilast—designated as forms A, II^{RT}, and II^{LT}—alongside the known form B. The crystal structures were determined using single crystal X-ray diffraction powder X-ray diffraction and three-dimensional electron diffraction. The structure of II^{RT} were further validated using solid-state NMR spectroscopy, low-frequency Raman spectroscopy, and density functional theory (DFT)-based geometry optimization. Conformational flexibility, particularly in polymorph II^{RT}, was examined through potential energy surface scans and NMR-guided structure refinement. Thermodynamic relationships among the polymorphs were established using differential scanning calorimetry solubility measurements, and relative lattice energy calculations.

The combined experimental and computational study provide a comprehensive understanding of apremilast's polymorphic landscape underlining the importance of integrating multiple diffraction and spectroscopic techniques for the reliable structure determination and offer insights into the complex conformational flexibility of the apremilast molecule across its polymorphic forms.



Molecular diagram of apremilast with the labeling of flexible dihedral angles

13th Crystal Forms Convention

Dimorphic etoricoxib salts: Phase transformation and interconversion studies

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Keywords: Conformational polymorphism, Multicomponent crystals, Mechanochemistry

Polymorphs possess distinct physicochemical properties, e.g., solubility, dissolution rate, and stability. [1, 2] Etoricoxib is a selective cyclooxygenase-2 (COX-2) inhibitor and helps in alleviating pain and inflammation. It is marketed as the etoricoxib free base (brand name: Arcoxia), a BCS class II drug.[3] We have obtained two new concomitant 1:1 polymorphic salts of etoricoxib with 2,6-dihydroxybenzoic acid (Form 1 and Form 2). The protocol for obtaining the pure polymorphic salt phases was optimized with the help of a liquid-assisted grinding (LAG) approach. The LAG of drug and salt-former in non-polar solvents resulted growth of salt Form 1, whereas the LAG in the presence of polar solvents yielded salt Form 2. A solvent-dependent interconversion of salts (from Form 1 to Form 2) was observed in 1-propanol. The polymorphic salts exhibit ~3-5 times enhancement in the aqueous solubility in comparison to the marketed form. We also noted that these salt forms undergo phase transformation to a new monohydrate salt form in aqueous solutions.

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P10

"WHEN SOLID-STATE NMR MET PAIR DISTRIBUTION FUNCTION…" A NOVEL STRUCTURE DETERMINATION METHOD OF ORGANIC COMPOUNDS

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In recent years, the elucidation of local structure in molecular solids has gained growing importance across various fields and, particularly, in the pharmaceutical one, where understanding the solid-state structure of drugs is critical for predicting and controlling their physicochemical properties, such as solubility, stability, and bioavailability. This becomes especially crucial in cases where the average crystal structure cannot be determined, as in poorly crystalline materials (*e.g.*, nanocrystalline drug forms) or amorphous drugs. In these cases, traditional methods, such as single-crystal X-ray diffraction (SCXRD) and structure determination from powder diffraction (SDPD) approach, fail.

To address this challenge in nanocrystalline organic compounds, we have developed a synergistic approach that combines the Pair Distribution Function, specifically the 'PDF-Global-Fit' approach proposed by Schlesinger et al., with the solid-state NMR (SSNMR) data [1,2]. In the last years, PDF-Global-Fit has emerged as a powerful method for investigating short-range order of organic substances, enabling the local structure to be solved from scratch by a fit to PDF data, without prior knowledge of lattice parameters and space group [2,3]. The method only requires the molecular geometry and an experimental PDF as input and involves PDF-based structure solution and refinement steps, ultimately leading to the determination

of the crystal structure. Nevertheless, in some cases, the method may yield to multiple plausible structures rather than a unique solution [4,5].

The solid-state NMR (SSNMR) spectroscopy can play a key complementary role in this approach, due to its site-specific nature which enables probing the local chemical environment of individual sites. Tailored 1D and 2D SSNMR experiments provide essential structural information, such as the number of symmetrically independent molecules, the tautomeric and protonation states, hydrogen-bond networks, and interatomic proximities [6].

In the integrated method proposed here, the NMR data are used both as restraints for the generation of structures (*e.g.*, number of Z', tautomeric state) as well as for the structure selection steps. In the latter case, the crystal structures can be filtered by analyzing intermolecular H-H and C-H distances, and their agreement with the information provided by SSNMR. In this way, a PDF fit, which requires quite long calculation times, is performed only for the best generated structures. This allows to speed up the overall process and to pinpoint a unique solution. Herein, we present the results obtained so far for a crystalline organic compound of pharmaceutical relevance, the 5-aminosalyicilic acid, demonstrating the strength of this integrated approach in structure determination.

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STRUCTURAL ELUCIDATION OF POWDERED SAMPLES: OVERCOMING CHALLENGES BY COMBINING SSNMR AND MICRO-ED

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Multicomponent crystal forms – including co-crystals, salts, and solvates – have become essential in pharmaceutical science for optimizing the physicochemical properties of Active Pharmaceutical Ingredients (APIs) [1]. Among the various methods for synthesizing crystalline adducts, mechanochemical syntheses have gained significant attention for their efficiency, sustainability, and minimal solvent requirements, aligning with Green Chemistry principles [2]. However, the resulting microcrystalline powders often prevent structure determination by single-crystal X-ray diffraction (SCXRD), due to the difficulty – or impossibility – of obtaining suitable crystals [3]. To overcome this limitation, an integrated approach combining Micro-Electron Diffraction (MicroED) with advanced solid-state NMR (SSNMR) techniques has recently been applied to single-component systems [4]. In this work, the combined approach was extended to pharmaceutical multi-component systems, demonstrating a robust multi-technique approach for the complete structural elucidation of a nutraceutical–API adduct, the pyridoxine-N-acetylcysteine (PN-NAC) salt [5]. PN-NAC was synthesized exclusively by manual dry grinding and, despite numerous attempts, suitable single crystals for SCXRD analysis could not be obtained. These characteristics make it a representative and challenging case for evaluating the capabilities of the combined SSNMR and MicroED approach. Furthermore, high-resolution mass spectrometry and solution NMR were employed to preliminary determine molecular formula and composition, establishing a complete workflow for unknown compound structural determination.

A comprehensive SSNMR study – including ^{13}C and ^{15}N CPMAS, ^{1}H MAS, 2D $^{1}H/\{^{14}N\}$ T-HMQC, $^{1}H\{^{13}C\}$ short- and long-range DCP, ^{1}H DQ/^{1}H SQ, and PM-RESPDOR experiments – enabled near-complete resonance assignment and revealed the formation of a 1:1 salt with two crystallographically independent PN and NAC molecules in the asymmetric unit. Protonation of the pyridine nitrogen of PN was confirmed by a significant low-frequency shift (~86 ppm) of the ^{15}N pyridine nitrogen signal [6], as well as by a strong N–H correlation between the pyridine nitrogen and the NAC carboxylic proton in the $^{1}H/\{^{14}N\}$ T-HMQC spectrum. Moreover, the formation of the N–H bond was unambiguously demonstrated by the short ^{1}H–^{14}N distance (1.16 Å) measured *via* PM-S-RESPDOR [7].

Complementary MicroED analysis on the powder sample provided a three-dimensional structural model fully consistent with SSNMR data, as also confirmed from GIPAW calculations performed on the DFT-D optimized structure. This result highlights the potential of combining these techniques in modern structural chemistry, particularly in pharmaceutical development, overcoming the limitations associated with mechanochemistry. This integrated methodology provides a robust alternative for obtaining detailed structural information when conventional SCXRD is not applicable.

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Exploring the Role of Microstructure and Surface Morphology in the Anomalous Intrinsic Dissolution of Ritonavir Nanocrystals

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Ritonavir (RTV) is an antiretroviral drug which, in addition to its historical use in the treatment of HIV in both adults and children, has more recently received Emergency Use Authorization for the treatment of mild to moderate COVID-19 in high-risk patients, in combination with another drug [1]. It exhibits low aqueous solubility and low permeability and is therefore classified as a Class IV drug in the Biopharmaceutical Classification System (BCS). The reduction of particle size to the nanometer scale (1–1000 nm) has become a well-established and widely adopted strategy to address the challenges encountered during the formulation and development of poorly water-soluble drugs [2]. However, products obtained through high-energy processes (milling to the nanometer scale) cannot be adequately characterized using only conventional techniques typically employed for the solid-state characterization of unprocessed active pharmaceutical ingredients (APIs). In such cases, *microstructural characterization* – such as *crystallite size* and *microstrain* – is essential [3]. The established solid-state characterization techniques include Differential Scanning Calorimetry (DSC), X-ray Powder Diffraction (XRPD), and Intrinsic Dissolution (ID), among others. During the ID of RTV nanocrystals (NCRs), a surprising outcome was observed. The expected result was a higher intrinsic dissolution rate for the nanocrystals compared to the API. However, the nanocrystal compact disintegrated within seconds after the beginning of the test, even in an aqueous dissolution medium in which the API is insoluble. Therefore, the aim of this work is to investigate the anomalous behavior of RTV NCRs observed during the ID. Thus, in addition to the previously mentioned techniques, RTV and RTV NCRs were also characterized by Rietveld analysis, Atomic Force Microscopy (AFM), and Transmission Electron Microscopy (TEM). It is worth noting that no polymorphic changes were observed during the milling and IDT. In this context, preliminary results suggest that the anomalous behavior in ID may be correlated with decreased crystallite sizes and increased microdeformation, larger surface area of nanoparticles, some with spherical morphology. Furthermore, the adhesion of RTV NCRs and RTV differ according to AFM nanomechanical analysis, indicating reduced interaction between the NCRs, in agreement with the ID results.

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New Solid Forms of Valsartan via Antisolvent Vapor-Assisted Crystallization with Monoterpenes

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The discovery of new solid forms of active pharmaceutical ingredients (APIs) remains a key strategy to modulate properties such as solubility or bioavailability. Here, we report three novel crystalline forms of valsartan, obtained through co-crystallization with the monoterpenes menthone, carvone, and eucalyptol.[1]

Conventional crystallization techniques—including ball milling, solvent evaporation, and slurry methods—failed to yield new solid forms. In contrast, antisolvent vapor-assisted crystallization (AVAC) using dichloromethane and hexane reliably afforded crystalline materials for each system.

PXRD confirmed the formation of three new and crystalline compounds, with diffraction patterns clearly differing from pure valsartan and from each other. Solid-state ^{1}H ^{13}C-CP-MAS and INEPT were used to characterize the crystalline compounds. Pure valsartan exhibited no INEPT signals, likely due to insufficient molecular mobility. In contrast, the new solid forms and their corresponding physical mixtures with terpenoids displayed clear and distinguishable INEPT spectra. Each solid form could be unambiguously differentiated from both parent valsartan and the respective physical mixtures, confirming the formation of new solid forms incorporating the terpenoids. Thermogravimetric analysis (TGA) supported the presence of volatile co-formers. All three new solids showed additional mass loss steps below 150 °C, attributable to the respective monoterpenes. Beyond this temperature, the decomposition profiles matched that of pure valsartan.[2,3]

This study demonstrates the utility of small, volatile terpenoids as functional co-formers and highlights vapor-assisted crystallization as a powerful approach to access elusive solid forms of flexible, poorly crystalline APIs.

Figure 1: Molecular Structures of Valsartan (left) and the used terpenoids (right).

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PLX4720: new perspectives in an old drug thanks to polymorphism

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The crystalline state is considered the most stable state of matter, but polymorphism can occur during crystallisation. Polymorphism is the ability of molecules to arrange stably into multiple crystalline structures, each with a different molecular arrangement and conformation within the crystalline lattice and different thermodynamic parameters. Polymorphism is one of the major concerns of pharmaceutical industry since different polymorphs may have different pharmacological properties and bioavailability [1]. At present, there is no theory able to explain the origin of this phenomenon, but experience suggests that it can be tuned by thermal [2], chemical [3], mechanical stresses [4] or a combination of these [4]. Sometimes, polymorphism can consist in a passage from one crystalline form to another with time, making time an important parameter to be considered. Restricting to thermal stresses, a liquid can be supercooled relative to many crystalline phases due to polymorphism, and to which one spontaneously crystallises is still debated [5]. We here propose the case of PLX4720, a molecule of interest for anticancer research used in targeted therapy against late-stage melanoma, whose pharmacological effect has been extensively characterized, but little is known about its physical behaviour. Structural and thermal properties of PLX4720 have been investigated via 3D electron diffraction (3DED) and calorimetry (conventional and fast), respectively. Calorimetry has been employed to study the glass-forming ability and physical stability of PLX4720 and in the detection of polymorphs, unveiling a rich polymorphic scenario. The crystalline structures of the polymorphs have been revealed thanks to 3DED and confirmed by powder X-rays diffraction. Lastly, the storage stability of the two polymorphs wasstudied, showing a good stability of both forms at room temperature.

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Design and characterization of organic acentric imines for nonlinear optical applications

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Acentric and polar crystal structures have long been the focus of intense research interest due to their distinctive physical properties, which are essential for a variety of advanced technological applications (e.g., ferroelectricity, pyroelectric and piezoelectric responses, second harmonic and terahertz (THz) wave generation, linear electro-optic (Pockels) effect). In optics, high-intensity laser pulses have been demonstrated to trigger a variety of nonlinear optical phenomena, including second harmonic generation (SHG). This process involves the generation of coherent light at a frequency that is twice that of the incident beam. The phenomena in question are governed by odd-rank tensors, which are exclusively allowed or substantially enhanced in polar space groups [1]. However, the identification of new non-centrosymmetric materials remains challenging, approximately 78% of all crystal structures recorded in the Cambridge Structural Database (CSD) are centrosymmetric. Previous studies on a series of imines obtained by condensation of 4-hydroxybenzohydrazide with aliphatic ketones and aromatic aldehydes have shown a persistent tendency to form acentric polar crystal structures (with a frequency of 47% considering the overall structure containing the same moiety) [2]. In the present project, a different benzo hydrazide was used with a methylamino group as the electron donating group. A series of imines has been characterized by single-crystal X-ray diffraction, thus far, showing again a persistent tendency to form acentric polar crystal structures. Hyper-Rayleigh scattering (HRS) measurements demonstrated first hyperpolarizability (β) values consistent with that of organic molecules [3]. Second Harmonic Generation (SHG) spectrum measurements were utilised to confirm the non-centrosymmetric nature of the compounds, thereby excluding contributions from other optical effects. These results serve to both enrich and expand the emerging library of organic acentric crystal structures, opening up further avenues for investigation.

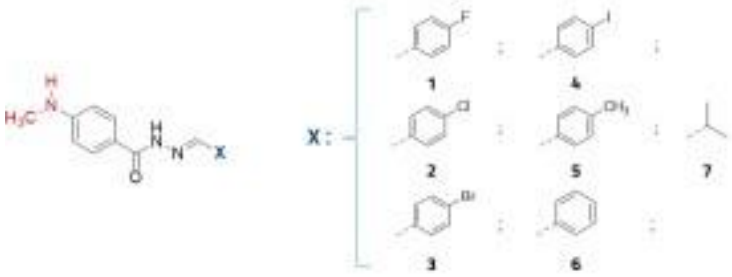

Figure 1. Chemical diagram of the synthesized imines of 4-methylaminobenzohydrazide.

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ANTISOLVENT CRYSTALLIZATION FOR ENGINEERING CO-PROCESSED API-EXCIPIENT PARTICLES – A CASE STUDY WITH AMLODIPINE BESYLATE

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In recent years the transition from batch to continuous manufacturing in the pharmaceutical industry has been gaining importance, with much focus on the process of continuous direct compression (DC) of tablets. A significant challenge to this transition is related to the fact that many APIs (active pharmaceutical ingredients) are unsuitable for it, due to poor flow and/or mechanical properties. Their manufacturability can be improved by co-processing (CP) with excipients, resulting in engineered composite particles which behave in a similar way to bulk excipient [1]. So far, crystallization processes have not been thoroughly explored in the field of co-processed APIs, with most of the focus on alternative methods (e.g. spray drying or crystallo-co-agglomeration). The existing CP research has employed cooling crystallization with a limited range of excipients [2-3].

The aim of this work was to explore the applicability of continuous antisolvent crystallization as API co-processing method, with common direct compression excipients serving as templates for heteronucleation of model API on their surface. The experiments were performed in a milifluidic device (T-mixer I.D. 1 mm, tubing I.D. 3.18 mm) with amlodipine besylate as model drug and water as antisolvent. Nine solvents (methanol, ethanol, isopropanol, acetone, acetonitrile, 1,4-dioxane, N methylpyrrolidone, N,N-dimethylformamide, dimethylsulfoxide) were screened in combination with 42 excipients, representing different grades of microcrystalline cellulose, L-HPC, pregelatinsed starch, lactose, mannitol, maltose and sorbitol. The combination of acetone with excipients based on lactose monohydrate (agglomerated or spray dried) resulted in successful generation of composite excipient particles with embedded API crystals.

Further work was carried out on the systems selected in the screening stage to assess the influence of processing parameters: supersaturation, theoretical drug load (API:excipient ratio) and total flow rate in order to empirically optimize antisolvent crystallization towards prevailing heteronucleation on lactose particles surface vs. bulk nucleation of free amlodipine besylate crystals.

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Novel eutectic mixtures of poorly water-soluble APIs discovered via miniaturised, nanogram scale, high throughput screening.

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Amorphous solids offer significant dissolution advantages over crystalline active pharmaceutical ingredients (APIs) due to their higher free energies. To prevent crystallization, these amorphous solids must be stabilized using polymer matrices to create amorphous solid dispersions (ASDs). The primary methods for preparing ASDs are hot melt extrusion (HME) and spray drying. However, HME struggles with high melting point compounds and chemical instability at elevated processing temperatures, while spray drying, although effective, requires large volumes of solvent and achieves low yields, making it less sustainable than HME.

Eutectic formation, which involves mixing the API with a small molecule excipient to lower the melting point, can make HME more feasible by reducing processing temperatures. In this study, we propose a novel screening process to evaluate eutectic formation, leveraging the miniaturization, addressability, and high-throughput capabilities of 2D picolitre inkjet printing. We have carefully selected poorly water-soluble APIs (BCS Class II or IV) for their diverse chemical structures. These APIs were combined with non-toxic, inactive GRAS materials such as caffeine, gallic acid, saccharin, meso-erythritol, and (3aR)-(+)-sclareolide in a binary mode.

Using picolitre inkjet printing, nano/microarrays were printed onto silanized glass slides. DMSO solutions of pure APIs and carriers were deposited at different weight/weight (w/w) ratios to evaluate eutectic formation. Each microarray consisted of 18 columns and 11 rows, resulting in a total of 198 distinct combinations. The w/w % ratios varied from 100 to 0 % API in a 5 % increment. The spots' mass varied from 250 – 300 ng. Microscopy and thermal analysis methods were employed to identify potential low-melting point binary compositions. This high-throughput method using 2D picolitre inkjet printing enabled precise identification of the optimal weight/weight ratios for eutectic formation paving the way for more effective ASD development via HME.

Polymorphic landscape of benzocaine – the pursuit to stabilize its high-pressure form

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Benzocaine (BZC) is a local anesthetic characterized by high permeability and low solubility, and as such it belongs to class II of Biopharmaceutical Classification System.[1] To this moment four polymorphs of BZC were reported: three (Phases I, II and III) existing at atmospheric pressure (all exhibiting very similar crystal packing, with primary aggregation motif being NH···O bonded ribbons, arranged in a parallel manner), and one high-pressure form (Phase IV).[2–5] The high- and ambient-pressure polymorphs share the same primary aggregation motif, but in case of the former, H-bonded ribbons are arranged at an angle, making it distinctly different from the other known polymorphs, which can translate into more pronounced discrepancy in its physicochemical properties compared to forms I, II and III. The high-pressure polymorph IV can be recrystallized by heating already at 0.45 GPa, or spontaneous recrystallization from BZC I takes place at pressure of 0.60 GPa (if appropriate Pressure Transmitting Medium is in use). Unfortunately BZC IV is not stable at atmospheric pressure and undergoes phase transition when pressure decreases, which hinders its further investigation and possible application.[5]

In the attempt to nucleate and stabilize high-pressure polymorph of BZC at atmospheric pressure, a rational doping was employed. In this method a host compound is mixed with a dopant (compound of a higher molecular volume, compatible in terms of the capability to form intermolecular interactions with the host). So-prepared sample is then melted and subsequently cooled down until complete crystallization. As a result larger molecules of a dopant are randomly incorporated in the crystal lattice exerting pressure from within and hence promoting crystallization of high-pressure crystal form. The method was successfully applied for resorcinol, imidazole, benzimidazole and 2-methylbenzimidazole.[6]

For the experiments with BZC, several organic compounds - Active Pharmaceutical Ingredients (APIs), or GRAS (Generally Regarded as Safe) compounds – were selected as dopants, including three anesthetics with molecules structurally similar to BZC: tetracaine, procaine and lidocaine. BZC (the host) was mixed with the dopants at a different weight ratios and milled using Retsch ball mill to ensure sufficient mixing of the host and dopant. Samples were then melted on a hot plate and subsequently rapidly cooled down. The PXRD patterns were collected for host-dopant samples before and after melting and then compared. The results of the experiments are presented herein.

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Structure, and energetics of nicotinamide:malonic acid bicomponent crystal forms

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The preparation of multicomponent solids, such as cocrystals and salts, is currently one of the main strategies to tune the efficacy of organic functional materials. Within this scope, mechanochemistry has emerged as a very effective, fast and ecological way of performing screening tests and producing organic cocrystals and salts. Because functional materials are in view, a key aspect within this scope is also the accurate characterization of their stability.
Here we report the mechanochemical synthesis of bicomponent crystals consisting of nicotinamide (NIC) and malonic acid (MAL) with 1:1 and 1:2 stoichiometries, and their structural characterization by single crystal and powder X-ray diffraction (XRD). Also described are the results of differential scanning calorimetry (DSC) and solution calorimetry studies that allowed the assessment of polymorphism and thermodynamic stabilities of the different crystal forms obtained relative to decomposition into the precursors.

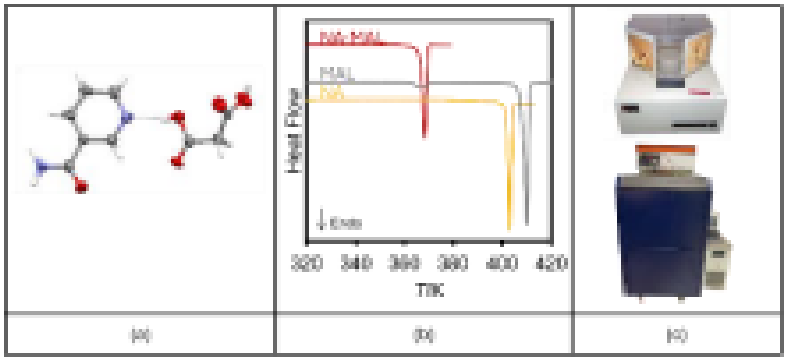

Fig. 1. (a) X-ray diffraction crystal structure of 1:1 NIC_MAL cocrystal; (b) thermograms of the percursors and of the 1:1 NIC_MAL cocrystal; (c) DSC and TAM calorimeters used in the study .

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Is it Possible to Get a Structure With < 100 µg of Sample? Direct Crystallization on TEM Grids for Electron Diffraction Purposes is the Answer.

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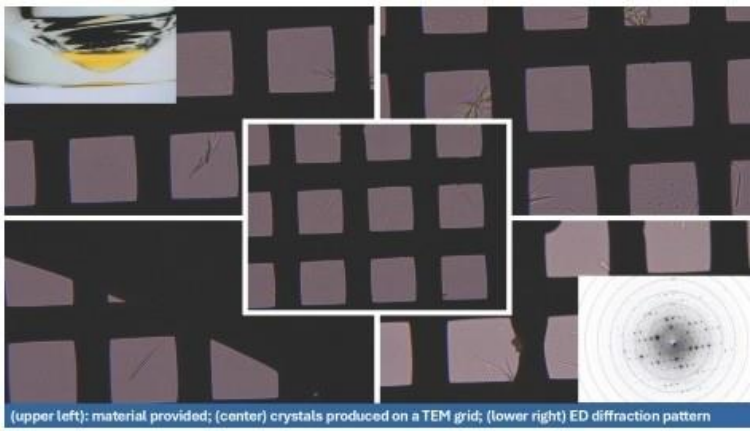
With Electron Diffraction (3D ED / micro-ED) evolving as a complementary technique to SCXRD experiments,[1] any crystalline material having dimensions < 1 x 1 x 1 μm^3 can readily be used for ED structural elucidation purposes. Due to the strongest interaction of electrons with matter, the relatively small size of the crystals does not hinder the collection of the diffraction peaks with good intensities and to high angle resolution for structural elucidation purposes.[2]

Though on the other hand, not every powder is crystalline and not every "crystalline" powder might be suitable for ED experiments. In other words, if the crystallinity of the nano-particles is not "good", then the diffraction pattern will be impacted by this. The intensity of the spots will be affected, and most importantly a low angle resolution will be observed. These two side effects will hamper the process of structural elucidation and make it sometimes almost impossible to achieve.[3]

Therefore, crystallinity plays an important role even for ED experiments. In many cases, good crystallinity can be achieved, especially if the amounts of material available allow usto perform extensive experiments. On the other hand, if the amount of material available is very low (< 1 mg), the question that arises is can we produce "good quality crystals" for diffraction experiments?

Within this poster, we showcase examples from (new) natural products crystallized and structurally characterized with ED experiments. An impure fraction of an HPLC experiment containing ~ 1mg of an oily yellowish sample (not 100 % pure) was provided to us. By doing micro-filtration and micro-crystallization experiments, it was possible to produce crystalline material directly on a TEM 3 Ø mm grid. The amount of material employed for such experiments was "estimated" to be between 40 – 80 µg. The TEM grid was directly inserted into an electron diffractometer (ELDICO ED-1) and a structure was obtained. The iterative process (crystallization-ED analysis) is required (or is mandatory) as many of the impurities and/or inorganic salts present tend to crystallize better than the target compound. The iteration process culminates once these undesired materials are identified and "separated" from the target substance. The proximity of the ED device close to the lab facility enhances the process and makes it efficient.



(upper left): material provided; (center) crystals produced on a TEM grid; (lower right) ED diffraction pattern

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Novel coamorphous systems of the antibiotic azithromycin

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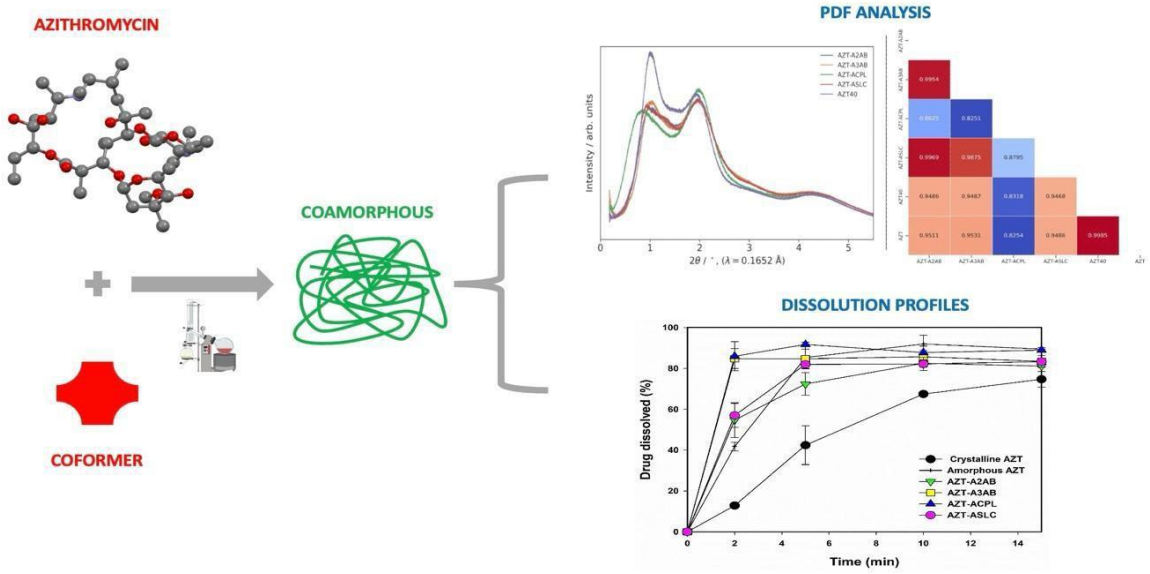

Coamorphous systems offer a promising approach for addressing the solubility challenges associated with crystalline drugs. Through this approach, it is possible not only to improve dissolution kinetics but also to enhance the (inherently low) physical stability of the amorphous phase through the establishment of specific non-covalent interactions between the drug and the conformer [1–8]. Azithromycin (AZT) is a well-known macrolide antibiotic, characterized by a broad-spectrum efficacy and relatively low toxicity [9], yet strongly limited by its very poor water solubility [10].

In this work, the possiblity of obtaining stable coamorphous systems of AZT was demonstrated by solution-based methods, employing ethyl acetate as a bridging solvent. Seven AZT-based systems were prepared via slow and rapid solvent evaporation techniques, consistently yielding amorphous products. Differential scanning calorimetry (DSC) confirmed the coamorphous nature of five systems, formed by AZT and one of –2-, –3-, and –4-aminobenzoic acids, –salicylic acid, and –caprylic acid molecules, all showing a single glass transition temperature (T_g). In contrast, the systems AZT–methyl salicylate and AZT–glycerol did not exhibit T_g, suggesting the formation of phase-separated amorphous mixtures rather than true coamorphous materials.

This hypothesis was further supported by their tendency to recrystallize under stress conditions, whereas the five confirmed coamorphous systems remained stable for more than 140 days at 40 °C. Stability tests demonstrated that coamorphization significantly enhanced the physical stability of AZT compared to its single-component amorphous form, which recrystallized within 72 hours at room conditions.

Advanced structural analysis by Pair Distribution Function (PDF) measurements revealed distinct differences in molecular organization compared to the pure amorphous drug, with the AZT-ACPL system displaying a unique short-range order. This specific packing arrangement correlated with the best dissolution profile observed among the studied systems.

Overall, these results indicate that coamorphous formulations can represent a valuable approach to improve both the physical stability and the bioavailability of AZT, potentially enhancing its therapeutic performance.

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Co-crystal Stability and Polymorphism in Nicotinamide-Dicarboxylic Acid Systems

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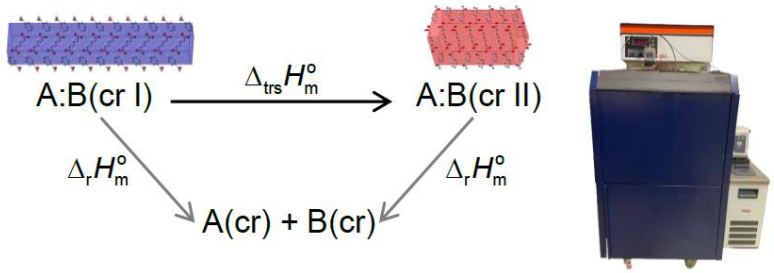
The use of co-crystals is currently one of the most important strategies to tune the properties of functional organic materials. Co-crystals can, however, exhibit polymorphism and, in addition, a given combination of co-formers can yield co-crystals with different stoichiometries. While this widens the possibilities of optimizing the properties of co-crystal-based materials, it also brings more complexity into the task of controlling the selective preparation of the most advantageous co-crystal form for the function in view. A key aspect within this scope is the determination of the relative thermodynamic stability of the different experimentally accessible co-crystals of a given co-former combination. This is particularly important at or close to ambient temperature and pressure, which correspond to the most common handling conditions in most current potential applications of organic co-crystals (e.g. active pharmaceutical ingredients).

Previous studies have suggested that the thermodynamic stability of co-crystals is most often determined by their cohesive strength,[1-2] which is most conveniently given in terms of the experimentally accessible standard molar lattice enthalpy, $\Delta_{Lat}H^{\circ}_{m}$, at 298 K. It should, nevertheless, be noted that, although rarely, experimental evidence of systems where stability seems to be entropically conferred has been reported.[3-5] We recently applied solution calorimetry to determine the relative enthalpic stability of co-crystals consisting of a maleic acid and phenylalanine in 1:1 and 1:2 stoichiometries, at 298 K.[4] An analogous strategy was used in this work to quantify the stability of nicotinamide:adipic acid (NIC:AA) and nicotinamide:sebacic acid (NIC:SEBA) co-crystals relative to decomposition into the precursors. Because both systems exhibit polymorphism, the relative stability of the different polymorphs was also assessed from solution calorimetry measurements, and their enantiotropic relationship and stability domains were also established using differential scanning calorimetry (DSC) and variable temperature X-ray powder diffraction (VT-XRPD). Finally in the case of NIC:AA, where calorimetric determinations could be supplemented with solubility measurements, stability characterization in terms of Gibbs energy, enthalpy, and entropy contributions was possible. The results suggest that this system is a rare example of entropically controlled thermodynamic stability.



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The Effect of Molecular Characteristics on Solvate Formation of Structurally Related Bisphenol Compounds

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Keywords: Bisphenol, structurally related compounds, crystallization from solutions, solvates

Crystallization from solutions remains a fundamental technique in the pharmaceutical sciences, particularly for the final stages of active pharmaceutical ingredient (API) synthesis and purification. This process plays a pivotal role in determining critical attributes such as crystal size, morphology, particle size distribution, and the solid form obtained [1]. Systematic solid form screening is essential, as it can lead to the discovery of new polymorphic or solvate forms, some of which may emerge during late-stage development or even after a drug product has been approved and marketed.

A previous study on the crystallization behavior of the antihyperlipidemic drug probucol (PROB), Figure 1a, under a range of conditions—including several solvent systems—led to the discovery of new polymorphic forms [2], nearly 30 years after the last crystal structures were reported [3]. In addition, several novel solvate forms were identified and characterized.

PROB is a very flexible molecule, however, despite containing two hydroxyl groups, their accessibility is significantly restricted due to the steric hindrance imposed by the adjacent tert-butyl substituents. In this study, two structurally related bisphenol compounds, tetramethyl bisphenol A (TM-BPA, Figure 1b) and 4,4′-methylenebis(2,6-di-tert-butylphenol) (TB-BPF, Figure 1c), were selected for investigation due to their structural resemblance to PROB. While both compounds share key structural motifs with PROB, they exhibit reduced conformational flexibility. Additionally, the hydroxyl groups in TM-BPA are more readily accessible for hydrogen bonding, greatly influencing its crystallization behavior when compared to PROB and TB-BPF. By conducting a solid-state screening of these three bisphenol compounds under identical experimental conditions and comparing their crystal structures, intermolecular interactions, and thermal behavior, this study aims to provide insights into the role of molecular features in directing solvate formation with a common solvent among structurally related molecules.

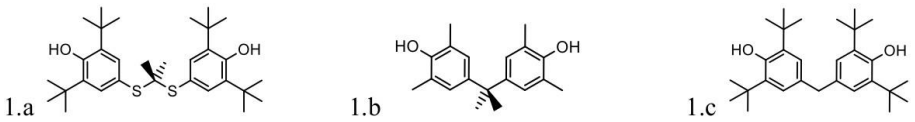

Figure 1. Molecular structures of: 1.a. PROB; 1.b. TM-BPA; 1.c. TB-BPF.

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PRACTICAL APPROACHES FOR DEVELOPING METHODS FOR AMORPHOUS CONTENT DETERMINATION IN CRYSTALLINE ACTIVE PHARMACEUTICAL INGREDIENTS FOR INHALATION

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Developing methods to quantify the amorphous content in crystalline active pharmaceutical ingredients (API) often requires generating an amorphous form of the API. There are many ways of generating amorphous material such as quench cooling, spray drying, freeze drying, rotary evaporation, milling, cryo-milling etc. are often very useful. Although quench cooling from the melt often results in a more homogeneous amorphous material, the degradation that may accompany the melting event (e.g. fluticasone propionate, formoterol fumarate) will pave the way for alternative methods like spray-drying, cryo-milling or freeze-drying. Milling on the other hand produced disordered/amorphous, highly energetic material whose particles will see their cohesive and adhesive balance (CAB) significantly impacted ultimately affecting the dry powder inhalation (DPI) product performance. Another aspect of milled materials is their heterogeneous nature. As differences in particle size, shape, surface area and surface energy will also affect the DPI product performance, a deep understanding of the physical properties and manufacturing processes of milled materials is necessary. As a result, a suitable and robust analytical method to quantify amorphous content is highly recommended.

There are number of techniques that have been used to quantity amorphous materials in processed samples [1,2]. Here we will focus on (1) solution calorimetry, 2) gas perfusion microcalorimetry and 3) dynamic vapour sorption, arguably the three most sensitive techniques capable of detecting around 1% amorphous content. A review of these three techniques will be presented together with key factors to be considered, practical aspects and pros and cons of each technique with respect to the API to be analysed.

This thorough review of accumulated data from all three different techniques should give a valuable insight when selecting the best and most sensitive technique for detecting and quantifying low level of amorphous content. This review and examples illustrating some practical challenges for each technique and for various APIs used in inhalation products should also provide valuable information to anyone from the scientific community interested in developing and validating an analytical method for amorphous content determination including accuracy, repeatability and intermediate precision, specificity, detection and quantitation limits, linearity, range and robustness as per the ICH Q2 guidelines [3].

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MECHANOCHEMICAL INVESTIGATION OF KINETICALLY-DRIVEN NOVEL POLYMORPH OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITOR DRUG MOLECULE

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Abstract

Medicinal mechanochemistry is a fast-evolving methodology that holds a promising future for the sustainable development of APIs in the pharmaceutical domain. The application of mechanochemistry in the pharmaceutical sciences has been used widely for the assessment of diverse solid forms of API such as polymorphs, cocrystals, salts solvate etc. The most important challenges in pharmaceutical development are the polymorphic transformations that may alter the biopharmaceutical attributes of drug products. Therefore, it is important to adopt high throughput screening to decipher the solid-state landscape of possible polymorphs throughout the life cycle of a drug product.

Herein, we investigate the new polymorph of canagliflozin (CNG) belonging to the sodium-glucose co-transporter 2 inhibitors of the antidiabetic class employing ball milling. Surprisingly, solution methods resulted in different hydrate forms of the selected drug. However, ball milling in the presence of a catalytic amount of ethyl acetate resulted in an anhydrate form (labelled as form G). DSC was used to study the thermal behaviour that showed a unique melting endotherm at 107.4 ^{o}C different than commercial form. Besides, the emergence of new diffraction peaks at 2θvalues of 3.84, 11.37, 16.72, 17.53, and 24.81 in PXRD data further confirms the existence of a new phase. FTIR spectra showed two characteristic vibration bands of O-H stretching at 3477 & 3303 cm^{-1} and C-O bending vibration appeared at 1227 cm^{-1}. These changes in the vibration bands of new crystalline forms are ascribed to the differences in the crystal packing as compared to the commercial form. The anhydrate nature was confirmed by TGA analysis revealing no weight loss in the range of 100 ^{o}C which indicates that there is no water present in the crystalline form G. Solubility and intrinsic dissolution release (IDR) study was performed in phosphate buffer pH 6.8 and showed significant improvement in solubility (2.7 times) and IDR (1.9 times) than commercial form.

In a nutshell, the generation of a novel polymorph (form G) of CNG by a change in crystal packing is kinetically driven by mechanochemical reactions that have a significant contribution to improving biopharmaceutical performance.

Keywords: *Ball milling, Canagliflozin, Medicinal Mechanochemistry, Polymorphs, Solid forms*

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SOLVENT FREE MECHANOCHEMICAL DERACEMIZATION OF NAPROXEN METHYL ESTER

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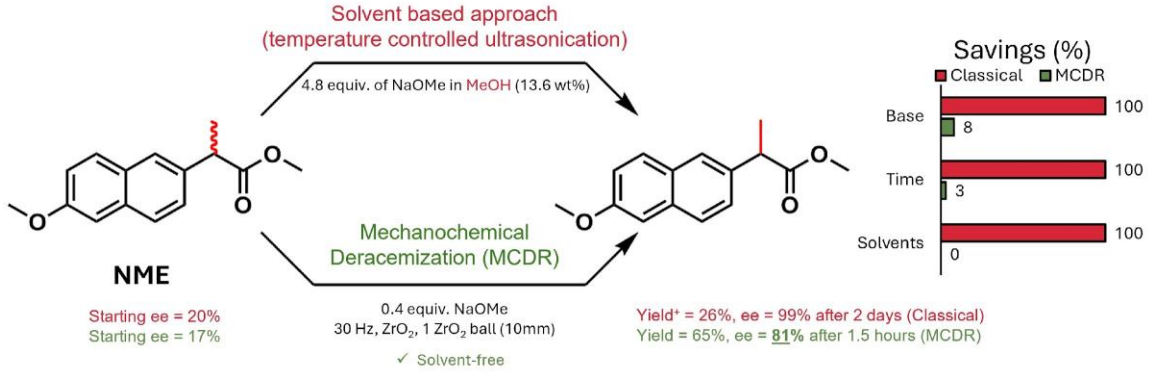
Enantiopurity is crucial in the pharmaceutical industry, as one enantiomer can have a desired medicinal effect while the other may be harmful to health. Naproxen, a common NSAID, is a good example of this: the S enantiomer treats the pain while the R enantiomer causes liver damage. Despite progress in asymmetric synthesis, most industrial processes still pass through a racemic compound, which is resolved while 50% of the compound is lost. Tremendous effort was put into developing deracemization processes which avoid this loss by combining racemization and stereoselective crystallization. But these approaches, like Viedma ripening (VR)[1], also applied to the Naproxen methyl ester[2], suffer from tremendous drawbacks: They require large amounts of toxic solvents and the often takes several days. In this work, we present a greener, safer, and economically viable approach to deracemization based on mechanochemistry: with Naproxen methyl ester as a model compound, we show that a successful adaptation of VR to a ball mill, allows deracemization in only 90 minutes while avoiding any solvents in the reaction.[3]



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An Aciclovir Intermediate Can Prevent Drug-Induced AKI

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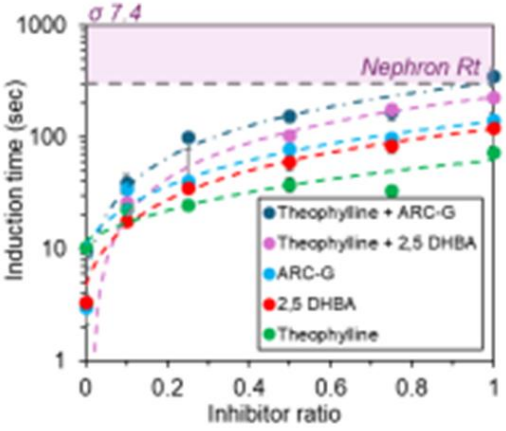
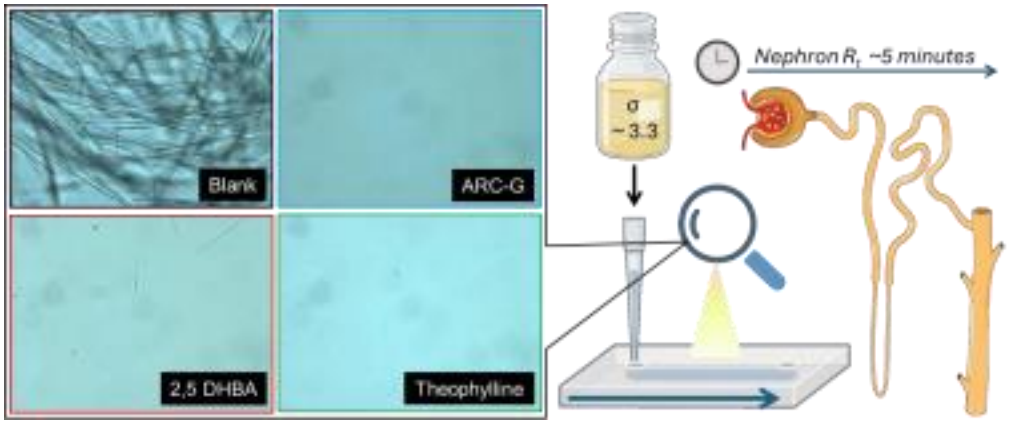
Aciclovir is commonly prescribed and is accompanied with a very high risk of adverse drug reaction (ADR). With >85,000 IV doses each month in English hospitals alone and 12-48% of patients experiencing precipitation-induced acute kidney injury (AKI), this equates to between 10,000 – 41,000 people every month in England.[1,2] ThisAKI is due to the kidney concentrating aciclovir past its solubility limit, resulting in precipitation in the nephron. In our work, we force the kidney filtrate to maintain this highly supersaturated state to allow the filtrate to safely pass through the nephron before precipitation occurs.

We highlighted important bonds in aciclovir dihydrate, the clinically precipitating phase. Analysis of the Cambridge structural database helped identify 3 strategies which we predicted would bind these locations. A small screen (of 12) revealed 3 promising inhibitors, all drastically extending induction time. For example, in the presence of ARC-G induction time was extended from ~5 sec to ~2 min 21 sec - a 28-fold increase at a supersaturation (7.4) higher than the maximum predicted clinical, ~6. Furthering this, combining two inhibitors such as ARC-G and theophylline, extends induction time to ~5 min 50 sec, beyond the retention time of the kidney at ~ 5 min.



For additional validation, we set up an *in vitro* nephron using a microfluidics chip. Supersaturated aciclovir was flowed through the 'nephron' and any precipitation at the nephron retention time of 5 min was observed. Catastrophic precipitation occurs in the absence of inhibitor; in the presence of ARC-G no crystals were observed. In the presence of 2,5 DHBA and theophylline a small number of crystals appear at this 5-min timepoint.



At clinical supersaturation, our small inhibitors extend aciclovir induction time by forcing the solution to remain in a supersaturated state by preventing crystal nucleation, thus allowing the renal filtrate to flow safely out of the collecting duct before precipitation occurs.

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Characterization and Comparison of Curcuminoid Solvate Phases

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Key words: curcuminoids, solvates, solid-state form characterization, crystal structures

Curcuminoids are natural coloring agents derived from turmeric (*Curcuma longa* L.) and are widely recognized for their therapeutic potential and use as natural food additives. While Curcumin is the most studied of the three Curcuminoids, its analogues — Demethoxycurcumin (DMC) and Bisdemethoxycurcumin (BDMC) — may exhibit distinct bioactivities that remain poorly understood due to their limited availability and challenging isolation.[1] These difficulties arise from the structural and physicochemical similarity among the three compounds, which complicates their separation from the naturally occurring Curcuminoid mixture. Recently, our research group has identified several solid-state forms of BDMC,[2] and investigated processes such as the cooling crystallization of Curcumin.[3]

To enable cost-effective purification strategies such as selective crystallization, access to crystalline forms of each compound is essential. However, until now, no crystal structure of DMC has been reported. We synthesized three DMC solvates and one new BDMC solvate, and characterized them using thermal analysis, NMR spectroscopy, powder X-ray diffraction (PXRD), and single-crystal X-ray diffraction (scXRD). The solvates were compared not only with each other but also with previously reported solvate structures and isostructural Curcuminoid compounds to evaluate the influence of the methoxy group substitution on the crystal packing. Our findings provide new insights into the crystallization behavior of the three Curcuminoids and lay the groundwork for developing a separation method based on solvate formation, targeting crystalline Curcuminoid components.

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Phenylpiracetam: Solid Solutions and Attempts at Chiral Resolution

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Phenylpiracetam (PPA) is an API belonging to the racetam family, a class of nootropic compounds known for their cognitive-enhancing properties used in the treatment of neurological disorders such as cognitive impairment and restless leg syndrome.[1] Despite its therapeutic potential, the crystallographic behaviour of phenylpiracetam is remarkably complex. Enantiopure PPA is known to crystallize in two enantiotropically related polymorphs, Form A and Form B (stable and metastable at room temperature, respectively). Additionally, miscibility of the phenylpiracetam enantiomers in the solid state is possible over a wide compositional range, hindering the chiral resolution of (RS)-PPA.[2]

This work aims to investigate whether solid solution formation, an intrinsic feature of PPA hindering chiral resolution, can be circumvented through crystal engineering strategies. First, cocrystallization with chiral coformers was attempted but, despite testing over 150 chiral coformers, no racemic conglomerate was isolated. Then, given that co-crystallization with inorganic salts has proven successful for the chiral resolution of other racetam derivatives,[3–5] we extended our investigation to metal salts. Co-crystallization with $ZnCl_2$, $ZnBr_2$ and $CaCl_2$ led to the formation of several novel PPA complexes, which were structurally characterized. However, these structures still exhibited features of enantiomeric solid solution formation.

To further elucidate the structural landscape of PPA and rationalize its strong tendency to form enantiomeric solid solutions, computational studies were carried out. Conformational analysis highlighted the conformational flexibility of the PPA molecule around the chiral centre, suggesting that its ability to adopt multiple low-energy conformations may contribute to the formation of substitutionally disordered solids.

These results suggest that enantiomeric solid solution formation is a recurring feature accompanying PPA crystallization, posing a challenge for its chiral resolution in the solid state. Further studies with different molecular systems and salts are ongoing to assess whether this trend is general or system specific.

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Solid solution quantification from full powder X-ray diffraction profile: novel application of multivariate calibration

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Non stochiometric crystals, such as solid solutions, represent a valid strategy for fine-tuning materials properties, from inorganic pigments to active pharmaceutical ingredients (API).[1] The change is achieved by substitution of structurally similar compounds within the crystal lattice, resulting in a minor variation of cell parameters: according to Vagard's law in a solid solution a linear correlation exists between composition and unit cell dimensions.[2] The cell modulation can be experimentally observed as a shift of the XRD profile, with the shift depending on the substitutional amount.

With the present work we demonstrated how, after proper alignment of the diffraction data, chemometric methods can detect the evolution of the solid solution profile and correlate it to the molar composition, creating rapid quantitative models. The solid solutions chosen for this work are NA2·FAxSA(1-x) and IN2·FAxSA(1-x)[3], i.e., the co-crystals of nicotinamide (NA) and isonicotinamide (IN) with fumaric (FA) and succinic (SA) acids in different proportions; they are used as model systems for the development of PCR and PLS[4] models for the quantification of solid solution composition. Different alignment strategies are presented (unshifted peak, internal standard, instrumental alignment), and the results obtained on test samples show the predicting efficacy of the proposed approach.

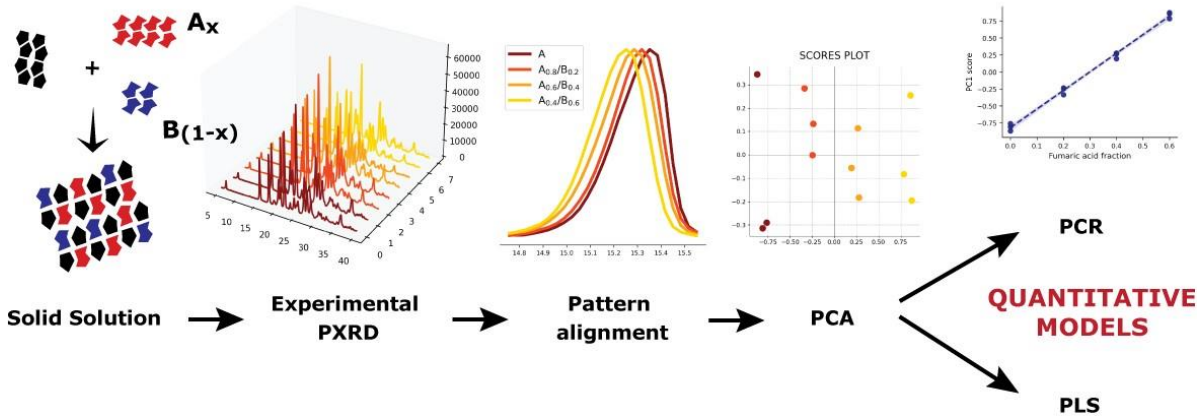

Figure 1. Workflow proposed for the quantitative model.

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Mechanochemically Induced Loss of Stereochemistry in Atropisomers

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Keywords: racemization, atropisomerism, mechanochemistry

Abstract: Atropisomerism is a form of axial chirality arising due to hindered bond rotation. [1] Unlike compounds with stereocenters, which often racemize via bond breaking and formation processes, atropisomers racemize via bond rotation. Biaryls such as 1,1'-bi-2-napthol (BINOL), and its derivatives have attracted interest in the scientific community since these axially chiral scaffolds can be utilized as chiral catalysts and ligands in asymmetric synthesis. [2,3] Asymmetric synthesis is typically solvent-based, but greener methods like mechanochemistry are gaining momentum due to solvent-related waste and toxicity. [4] With mechanochemistry increasingly used in asymmetric synthesis and catalysis, studying milling's impact is essential. [5] It is yet unknown whether a change in stereochemistry of these biaryl atropisomers can be induced by using solely mechanical energy. Therefore, in this study, we investigate the stereochemical integrity of different biaryl atropisomers under typical mechanochemical conditions for asymmetric synthesis. We explored a variety of biaryl substrates, different organic and inorganic bases, the presence of liquid during milling, and different reaction times. It was found that under various conditions, biaryl atropisomers undergo degradation, which can be attributed to different reaction mechanisms. The most prominent ones are racemization and side product formation via intermolecular ring closure, like C-O and C-C bond formation, resulting in extended, insoluble π-π stacked structures. These findings indicate that use of ball milling leads to changes in stereochemistry, but also loss of it, as well as formation of side products. This leads to a decrease in catalytic activity, which can be crucial for the effectiveness of asymmetric synthesis. Such findings remain critical for the employment of mechanochemistry in asymmetric synthesis and need to be deeply investigated on other substrates.

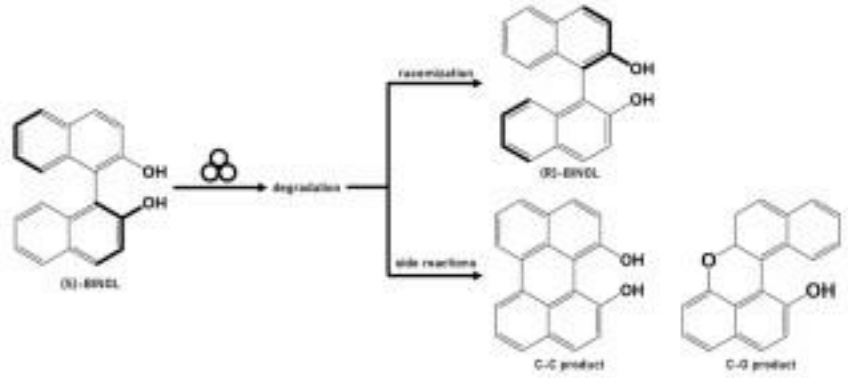

Figure 1. Reaction scheme of milling of (S)-BINOL.

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Stimuli-Responsive Photophysical Behavior of Cu(I)-Based Coordination Polymers: A Structural Investigation

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We present a comprehensive study on the structural characterization and stimuli-responsive photophysical behavior of Cu(I)-X hybrid coordination polymers (HCPs), with a specific focus on their mechanochromic properties. These materials, composed of coordination clusters, exhibit significant and reversible changes in their emission spectra when exposed to external stimuli, including mechanical and thermal inputs.

Our investigation primarily focused on the mechanochromic response induced by mechanical stress. The synthesized materials displayed notable shifts in emission characteristics correlated with the intensity and duration of the applied mechanical stimulus. Spectroscopic analyses highlighted how these variations are associated with structural changes induced by the external perturbation.

To further understand the impact of mechanical stress, structural analysis revealed that, despite the introduction of lattice distortions, the crystalline integrity of the material was preserved. Additionally, complementary studies were conducted to investigate the thermal response, exploring the relationship between structural dynamics and photophysical behavior.

This work provides valuable insights into the dynamic luminescence of Cu(I)-based HCPs, emphasizing their potential applications in responsive optical devices and adaptive materials. The results contribute to advancing the understanding of structure-property relationships in coordination polymer systems.

Mechanistic Insights into Co-Crystals Formation via Mechanochemistry: In-Situ Monitoring and Kinetic Modeling

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Co-crystals are of significant interest to the pharmaceutical industry as a platform to supply APIs (Active Pharmaceutical Ingredients). In fact, by combining an API in the solid state with other chemically distinct entities, it is possible to enhance its physico-chemical properties, including thermal stability, water solubility, dissolution rate, as well bioavailability and processability.

Within the possible methods for the synthesis of co-crystals, those based on mechanochemistry are drawing the attention of the pharmaceutical industry, which is asked to reduce its environmental footprint on behalf of governments and institutions. In fact, the drastically reduced use of solvents and energy, along with reactions that often result in 100% yields of single products, make mechanochemistry a sustainable and eco-friendly method.[1]

However, though mechanochemical methods are very promising, their translation to industry remains hindered by a lack in their mechanistic understanding and selectivity, and this is exacerbated as the kinetic and thermodynamic rules of conventional solution chemistry tend not to apply. To tackle this challenge, methods for time-resolved in-situ (TRIS) monitoring of mechanochemical reactions have been developed, thus paving the way for obtaining (in)accessible information on intermediates or new products.[2,3] Moreover, the collection of TRIS data also provides access to kinetic profiles which, when modelled analytically, offer exciting insights into fundamental behavior of solids under mechanochemical conditions.[4]

These insights are presented in the context of the Horizon project IMPACTIVE, aimed to scale-up the synthesis of target active pharmaceutical ingredients via mechanochemistry. The synergistic contribution of TRIS-PXRD and other experimental and theoretical approaches is shown to represent a key step in the understanding of the mechanistic behaviour.

By gaining a better understanding of how this type of chemistry works, the novel reaction pathways offered by mechanochemistry may no longer be seen as limitations, but rather as valuable assets unlocking numerous opportunities for the pharmaceutical industry.

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Spontaneous solid-state formation and self-propagation of a polymer-based cocrystal

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Spontaneous solid-state reactions can involve a chemical reaction or a change of the crystal structure that occur between solid reactants without the need of an external energy source (e.g., heat, light, or mechanical input). These reactions are well documented for single-component crystals, while the number of studies regarding multicomponent solids such as cocrystals is limited [1].

We report an intriguing example of solid-state spontaneous formation and self-propagation of a polymer-based cocrystal [2] obtained from the cocrystallization of one small molecule and a polymeric macromolecule. Specifically, the spontaneous formation of a binary system made of 6-fluoroanthranalic acid and polyethylene glycol (PEG) was observed in the solid state, initially by simple manual mixing of the two components and subsequently through the use of different techniques including mechanochemistry, melt crystallization and solution-based techniques. Samples that were kept repaired from light and at room temperature ended in the cocrystal formation with different kinetics, depending on the energetic input given to the system. Indeed, when the energy transferred to the starting materials was high (e.g. milling or melting) and the reactants were intimately mixed, the polymer-based cocrystal nucleated and self-propagated within days or even hours, depending on the treatment. On the other hand, the nucleation and self-propagation kinetics appeared much lower when the energy input the system receives was extremely low (simple manual mixing) (Figure 1).

Different aspects of the formation mechanisms were investigated. The semicrystalline nature of the pure polymer seems to play important role: in-situ PXRD studies showed a correlation between the crystallization of pure polyethylene glycol and the nucleation of the multicomponent crystal. Additionally, a specific range of polymer molecular weight is necessary for the cocrystal formation.

The spontaneous and self-propagating of a polymer-based cocrystal represents an intriguing phenomenon that requires further investigation, possibly leading to the full understanding of the molecular movements involved.

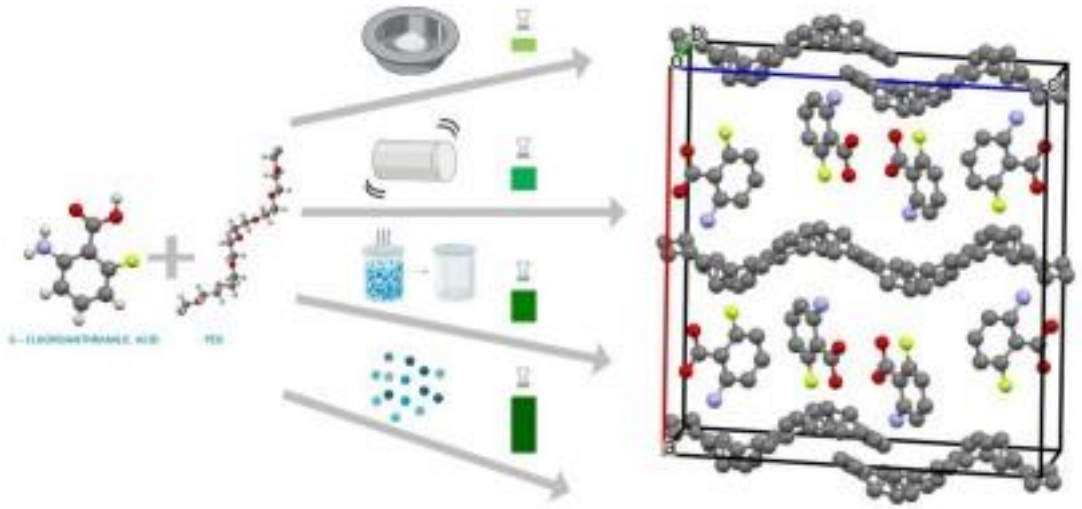

Figure 1. Summary of the crystallization methods used in this study for obtaining the polymer-based cocrystal.

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Probing nanoscale features of electrospun amorphous solid dispersions

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Background

>75% of emerging active pharmaceutical ingredients (APIs) suffer from low aqueous solubility which severely constrains their application in the clinic. One approach to overcome this issue is to disperse APIs in water-miscible polymer carrier to generate molecular dispersions of the API in the polymer (amorphous solid dispersions; ASDs) and remove the lattice energy barrier to API dissolution. However, the lower free energy of the crystalline form means that there is a major risk of APIs recrystallization upon storage. To comprehensively understand API recrystallization behavior in an ASD, in addition to the extent of crystallization as a function of time, gaining insight into the early-stage behavior of the drug within the polymer matrix is crucial for the development of stable and effective formulations. Small angle neutron scattering (SANS) has recently been shown to capture nanoscale drug domain of ca 10 nm and lower [1].

Aim

In this study, poly(ε-caprolactone)(PCL) was used as the carrier polymer, and aspirin was used as model drug to study how the physical form of the aspirin changes in nanoscale dimensions within a PCL matrix upon wetting.

Methods

ASDs were prepared by electrospinning at drug loadings of 10%, 20%, and 30% (w/w, drug to polymer). Sans2d instrument was used to analyze the nanoscale dimensions of phase-separated drug domains in the dry state and during D_2O buffer immersion at 0, 8, 15, and 19 hours.

Results

Scanning electron microscopy(SEM) images show that samples with lower aspirin loading (10% and 20%) exhibit a uniform morphology, characterized by smooth, cylindrical fibers without any beads-on-string features observed. For 30% aspirin, there are deposits of aspirin on the fiber surface. The SANS profiles for all membranes in the dry state can be fitted using a power-law model. For membranes with low drug loading, the scattering exponent approaches 4, consistent with the Porod's law, indicating smooth surfaces of fibrous membranes. In contrast, the membrane with 30% drug loading exhibits a lower exponent ($3 < n < 4$), characteristic of surface fractals and suggestive of a rougher interface[2]. The SANS profiles for drug-loaded membranes upon D_2O immersion show scattering features related to drug-rich domains, indicating the formation of drug aggregates. Higher drug loadings lead to a higher extent of aggregation. Dissolution testing reveals that the release rate decreases with increasing drug loading, due to a longer time being needed to dissolve the aggregates.

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Salts and cocrystals of 2,4-diaminopyrimidine drugs with 4-aminosalicylic acid - SC-XRD and ESI-MS study

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2,4-diaminopyrimidine drugs, compounds structurally related to folic acid (FA) belong to the class of antifolates, involved in folate metabolism by inhibiting the dihydrofolate reductase (DHFR). Antifolates inhibit the transformation of folic acid to the tetrahydrofolate (THFA) preventing the synthesis of DNA, RNA, and proteins, leading to the restrictions in cell growth. Pyrimethamine (PYR) and trimethoprim (TMP) belong to the BCS (Biopharmaceutics Classification System) class II drugs with low water solubility, which can be significantly improved by the formation of suitable salts or cocrystals. In the present work pyrimethamine and trimethoprim were cocrystallized with 4-aminosalicylic acid (4ASA). The obtained crystals were studied by SC-XRD, while ESI-MS, as soft ionization technique, enabled the observation of peaks corresponding to noncovalently bonded molecules, giving insight into their aggregation in solution/gas phase environment.

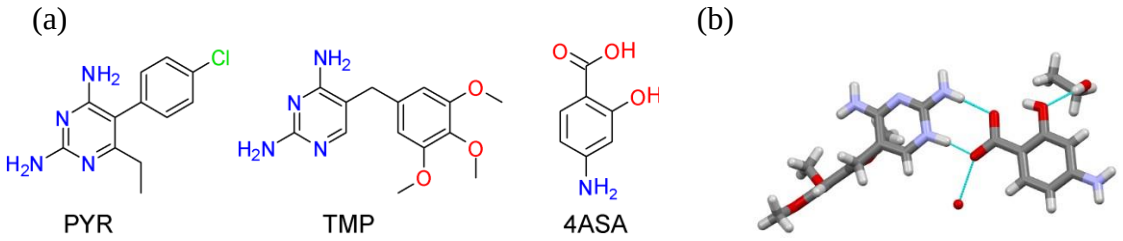

Figure 1 (a) Chemical structures of PYR, TMP, and 4-ASA (b) crystal structure of TMP/4-ASA salt

New strategy to crystallize elusive polymorphs of drugs

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Many Active Pharmaceutical Ingredients (APIs) can crystallize in more than one crystal forms, some of which are very difficult to crystallize in their pure forms (the so-called elusive polymorphs). This can hinder the elucidation of their crystal structure and determination of their physicochemical properties, all of which is important for understanding polymorphs stability and behaviour. Our work is focused on searching new experimental approaches, which can lead to such elusive polymorphs of drug molecules. Inspired by the reports that some of the polymorphs can be obtained only through desolvation [1,2], we envisaged a similar strategy, which is based on the process we termed 'decocrystallization' (or cocrystal decomposition). The idea is to first obtain a cocrystal of an API with a volatile coformer, which can be relatively easily removed afterwords, forcing a reorganization of a crystal lattice and leading to the desired polymorphs. The advantage of decocrystallization over desolvation processes lies in a great number of coformers, which can be used for cocrystallization in comparison to much fewer solvents. Here we report the first three examples of this crystallization method, including the design and synthesis of appropriate cocrystals, their crystal structure determination and subsequent decocrystallization. All processes led to elusive polymorphic forms of APIs belonging to non-steroidal anti-inflammatory drugs (NSAID): meloxicam form V, piroxicam form III and flurbiprofen form III. Figure 1 shows a scheme illustrating this process for piroxicam. The proposed method entailed mixing solid piroxicam and pyrazine together, heating it to 120°C in a sealed container for 10 minutes and then for 15 minutes at 100°C in an open container. In the course of only 25 minutes the whole process was completed. We believe that this method can lead not only to elusive crystal forms, but also to the discovery of new polymorphs, impossible to crystallize otherwise.

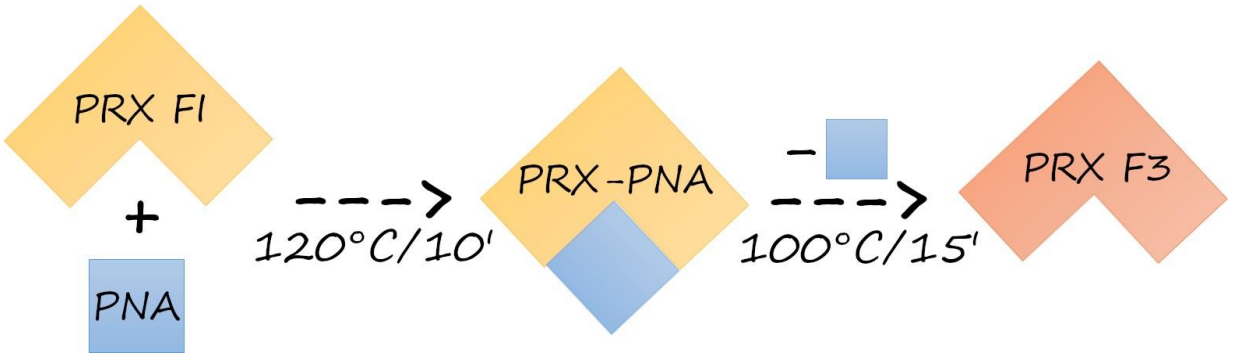

Figure 1. Schematic representation of decocrystallization process: PRX F1 – piroxicam from 1; PRX-PNA – piroxicam:pyrazine cocrystal; PRX F3 – piroxicam form 3

Acknowledgements
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The Design and synthesis of ternary multi-component crystals through sublimation

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Crystal engineering is the design and synthesis of new molecular solids with desirable properties and is an active area of research. Cocrystals are solid crystalline materials which contain two or more different neutral compounds coexisting in the same crystal structure. Many cocrystals are binary (i.e. consist of two coformers) but few are ternary (three coformers) or higher. Furthermore, most cocrystals are produced using solution-based methods (such as solvent evaporation), with very little work done on sublimation of cocrystals. Sublimation is the process in which a solid material transitions from the solid to gas phase (usually as a result of heating under vacuum), or the formation of solid directly from the gas phase (desublimation); usually in the cooler zone of a sublimation apparatus). This work explores the potential of the sublimation method to produce ternary multi-component crystals directly from the gas phase. We investigated the synthesis by sublimation of two ternary multi-component crystals that have been previously obtained using solution-based methods. The first multi-component crystal contains 3,5-dinitrobenzoic acid, 4-aminobenzoic acid and 4,4'-bipyridine[1] while the second contained 3,5-dinitrobenzoic acid, 3-aminobenzoic acid and isonicotinamide.[2] We also report a novel ternary multi-component crystal containing 3,5-dinitrobenzoic acid, 3-aminobenzoic acid and 4,4'-bipyridine, which was obtained from sublimation. Different experimental variables such as the sublimation temperature and stoichiometry were varied to determine which factors affect the formation of ternary cocrystals by sublimation.

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Use of different types of industrial mills for the mechanochemical kg synthesis of pharmaceutical co-crystals

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We present the application of batch mechanochemical processes for the synthesis of pharmaceutical co-crystals using the example of ibuprofen nicotinamide (rac-IBP:NCT) on a kilogram scale in different types of industrial mills. For the synthesis of the co-crystals, eccentric vibrating mills, drum mills and attritor mills were used. After optimization of the synthesis processes in the different mills, high conversion rates and high product yields without decomposition products could be observed in all cases.

In contrast to conventional solution-based processes, which generally consume significant amounts of solvents and energy, the use of ball mills is a more environmentally friendly and efficient mechanochemical process for the production of co crystals on a kilogram scale.
Examination of the resulting co-crystals showed minimal metal contamination from abrasion, with levels well within acceptable regulatory standards for daily intake.

Our results show that it is possible to use common industrial mills for the potential large-scale production of pharmaceutical co-crystals. These experiments may point the way to more sustainable industrial drug production.

The author (M.F.) acknowledges IMPACTIVE (Innovative Mechanochemical Processes to synthesize green ACTIVE pharmaceutical ingredients), 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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Poster Presentation at 13th CF@BO, 7-9 Sept. 2025, University of Bologna, Italy

Abstract

Drug-drug multicomponent system of tadalafil and finasteride: Preparation, characterization, simulation studies and pharmaceutical performance

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We report a modified bi-component solid-state form of two drugs, namely Tadalafil (TDF) and Finasteride (FNS), an USFDA approved fixed dose combination, for the treatment of benign prostate hyperplasia, under the trade name Entadfi. Individually, both the constituent drugs suffer from the limitation of low aqueous solubility, belonging to class-II of the biopharmaceutical classification system. A drug-drug coamorphous system of TDF and FNS was prepared by the mechanochemical synthesis. Characterization of this novel phase was carried out by powder X-ray diffraction, thermal analysis, FT-IR spectroscopy and solid state NMR. Particle characteristics and morphological features of the coamorphous system were studied by scanning electron microscopy and 3D-laser scanning microscopy. Possible intermolecular interactions between TDF and FNS, facilitating the formation of the coamorphous phase, were probed by the spectroscopic analyses. Various homo vs. hetero dimeric interactions were conjectured from the respective crystal structures of individual drugs and were validated by the computational study employing the density functional theory. Interestingly, *in-vitro* dissolution studies showcased significant improvement in the dissolution profile of coamorphous system compared with the physical mixture, which was successfully translated to the *in-vivo* study in SD rats. Physical stability of the developed coamorphous system evaluated under accelerated as well as long term stability conditions, indicated reasonable stability for potential drug product usage. Considering its industrial applicability due to obvious benefits *viz.* single solid phase, improved solubility, dissolution and better pharmacokinetic parameters leading to higher bioavailability, the developed coamorphous system could prove to be a better therapeutic alternative over the marketed physical mixture.

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From Molecules to Materials: How Packing and Interactions Define Solid-State Stability of Elafibranor

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Elafibranor (**EFR**) is used to treat a rare genetic liver disease called primary biliary cholangitis (PBC)[1]. It is currently sold under the trade name IQIRVO® after being approved by the FDA and EMA. Three anhydrates, one monohydrate, multiple solvates and salt forms, as well as the amorphous phase of **EFR** are reported in the patent literature.[2-9]

In this study, we aimed to identify and characterize the solid-state landscape of **EFR** and to elucidate the relationships between its solid-state forms. A comprehensive solid-state screening was conducted using multiple crystallization techniques, including solvent evaporation, cooling crystallization, antisolvent addition, slurry conversion, and reproduction of patent-reported methods. This approach led to the identification of 16 distinct solid forms, twelve of which were successfully upscaled. These include two anhydrous polymorphs (**AH_I°**, **AH_{II}**), one monohydrate (**Hy1**), eight solvates (**S_{DMA}**, **S_{DMC}**, **S_{DMF}**, **S_{FA}**, **S_{HOAc}**, **S_{NiMe}**, **S_{NMP}**, **S_{Pyr}**), and the amorphous phase. While several forms correspond to those reported in the patent literature, three solvates (**S_{DMC}**, **S_{NiMe}** and **S_{Pyr}**) were identified as novel. All forms were thoroughly characterized using complementary experimental techniques, including X-ray diffraction, infrared spectroscopy, and thermal analysis methods.

Crystal structures were determined for ten forms, nine of which were elucidated using single crystal X-ray diffraction. The structure of the metastable anhydrate **AH_{II}** was solved from powder X-ray diffraction (PXRD) data and shows a catemeric arrangement of **EFR** molecules. Other H bonding motifs include dimers (**AH_I°**), tapes (**Hy1**) or discrete H-bonds (**S_{DMA}**). Of the solvates, three distinct types of **EFR**···solvent H-bonding interactions were identified: O–H···O (with amide solvents and water), O–H···N (with pyridine), and absence of any H-bonding between **EFR** and the solvent (e.g., **S_{HOAc}**, **S_{DMC}**, and **S_{NiMe}**). A correlation between H-bonding and solvate stability was established. Solvates exhibiting H-bonding between **EFR** and solvent molecule, particularly with amide-based solvents, were stable, while those lacking such interactions were unstable and transformed within a day upon removal from their mother liquor.

With the help of DSC- and solubility experiments, **AH_I°** was identified as the thermodynamically stable polymorph, which is monotropically related to **AH_{II}**. Phase-pure **AH_{II}** was obtained through controlled desolvation of selected solvates, primarily those exhibiting the **EFR** catemer motif.

Computational analyses were performed to complement the experimental findings, which included periodic electronic structure and pairwise intermolecular energy calculations. The results highlight the value of integrating experimental and computational approaches to better understand the stability and transformation behavior of complex solid-state landscapes of APIs.

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Substituent-Induced Modulation of ROY's Polymorphic Landscape

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The ROY molecule is a model compound in polymorphism studies, famous for its ability to crystallize in 14 different forms due to its high conformational flexibility.[1–4] In this work, we explore how two specific modifications—tert-butylation and N-methylation—affect ROY's polymorphic behavior and molecular packing. Our single crystal X-ray diffraction results show that both modified derivatives, tBu-ROY and *N*-Me-ROY, consistently crystallize in just one form, even after extensive polymorph screening. This indicates a significant suppression of polymorphism. Hirshfeld surface and fingerprint plot analyses reveal narrower distributions of intermolecular interactions, dominated by H···H, O···H, and N···H contacts. The bulky tert-butyl group limits torsional freedom, while N-methylation disrupts key hydrogen bonding motifs—both contributing to simpler, more rigid packing arrangements. These findings offer valuable insights into how subtle molecular changes can be used to control polymorphism, which is crucial in fields like pharmaceuticals where solid-state form affects solubility, stability, and bioavailability.

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Application of Mechanochemistry in Pharmaceutical Materials Design

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In the recent past, mechanochemistry has gained tremendous attention due to its clean and green method of preparation. As mechanochemical reactions take place under non-equilibrium conditions, there is always a possibility for the formation of kinetically "trapped" metastable polymorphic phases. Moreover, there are several factors that can influence the outcome of a mechanochemical transformation compared to solution-phase crystallization. Here in my talk I will discuss about our work[1] related to mechanochemical synthesis of pharmaceutical multi-component solids and their characterization (Figure 1).

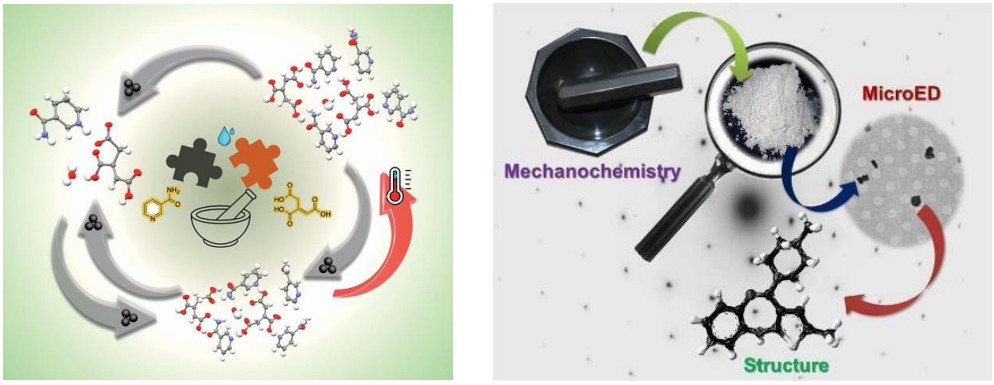

Figure 1. Mechanochemical synthesis and characterization of pharmaceutical materials.

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Impact of Droplet Evaporation on Polymorphism of Suberic Acid

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Polymorphism of organic molecular systems continues to be an important topic in crystallization, ranging from interests in structure screening, food products performance, and patent protection. While new potential pharmaceutical compounds regularly generate challenges in polymorphism, the identification of new polymorphs of more commonly studied compounds also continues. Suberic Acid is the eight carbon straight chain dicarboxylic acid, and it is used as a food additive, as a pharmaceutical precursor, and as an API conformer. Suberic Acid was thought to form only a single α polymorph until a second β polymorph was identified through DSC analysis and subsequent crystallization in nanoscale chambers (Ha et. al.). Among many techniques available to form crystalline particles is droplet evaporation, which can be done using a spray dryer at elevated temperatures, or using a vibrating orifice aerosol generator (VOAG), a Collison type aerosol generator, and a syringe pump constant flow aerosol generator.

In this poster, we highlight our work on forming crystalline suberic acid particles from a syringe pump constant flow aerosol generating atomizer as well as a Collison type aerosol generator, each in combination with appropriately designed diffusion dryers. While the α polymorph is formed using several solvents including water and ethanol, particle formation at low concentrations from isopropanol demonstrates the formation of a newly reported γ polymorph of suberic acid. The γ polymorph also has indications of being formed in acetone. The formation of the unique structure is identified uniquely from the α and β using powder X-ray diffraction (pXRD). Thermogravimetric analysis is further used to demonstrate that the new form is not a solvate. Differential Scanning Calorimetry together with variable temperature pXRD are used to demonstrate that the new polymorph is energetically similar to the α polymorph; however, it transforms to the α polymorph over time at temperatures below the known α/β transition point. The size distributions and impact of solution concentrations are also identified. Finally, we will discuss the broader opportunities/challenges/insights potentially available from using these droplet evaporation methods more commonly used to study atmospheric aerosols in a crystallization context.

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FIFTEEN SOLID SOLUTIONS OF FOUR THIOXANTHONE HALOGEN DERIVATIVES: STRUCTURES, MISCIBILITY LIMITS, AND LUMINESCENCE

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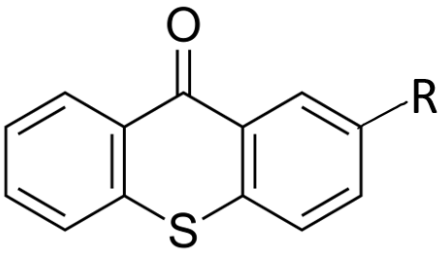
Solid-state luminescent materials based on organic molecular crystals are increasingly important for applications in sensing, security, and optoelectronics. Among the various methods for tuning solid-state properties, the formation of solid solutions offers a unique route for continuous and composition-dependent property modulation but remains unexplored in organic systems.[1,2]

A systematic study was conducted on four halogenated thioxanthone derivatives (Figure 1): 2-fluoro-, 2-chloro-, 2-bromo-, and 2-iodothioxanthone – to map their solid-form landscape, miscibility behaviour, and luminescence characteristics.[3] Six distinct crystal packings were identified among the pure compounds. Fifteen binary solid solutions were experimentally prepared and structurally characterized. Miscibility limits were found to depend on halogen size compatibility and the presence or absence of specific intermolecular interactions such as halogen and hydrogen bonding. Several solid solutions exhibited pronounced shifts in luminescence colour as a function of composition, allowing fine control of optical emission. In contrast, other systems showed broad miscibility ranges with minimal changes in photophysical behaviour.



R = **Cl** (TXANT-Cl), **I** (TXANT-I), **Br** (TXANT-Br) or **F** (TXANT-F)

Figure 1. Molecular structure of thioxanthone halogenated derivatives.

Solid solution formation in halogenated thioxanthones systems demonstrates a powerful approach to rationally engineer luminescent properties in organic crystals. These findings provide fundamental insights into structure-property relationships and expand the design space for functional crystalline materials.

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Schrödinger's Modeling Platform and Solutions to Accelerate Drug Substance and Drug Product Formulation and Delivery Processes

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Early assessment of stereoconfiguration, degradation, reactivity, catalysis, polymorphism and solubility of active pharmaceutical ingredients (API) is critical for small molecule drug discovery and development processes. We have developed automated computational platform leveraging physics-based methods, chemistry informed AI and ML models to efficiently predict 1) Boltzmann-averaged spectra of small molecules without crystallizing the molecule or using X-ray spectroscopy, 2) bond dissociation energies and decomposition products to elucidate reaction mechanisms, 3) crystal polymorphs to aid selection of a stable solid form, 4) solubility enhancement via organic cosolvents using free energy perturbation (FEP+) method, 5) polymer excipients that can interact strongly with the API and reduces the risk of recrystallization, and 6) apparent pKa values of ionizable lipids and simulate the self-assembly and structural properties of lipid nanoparticles.

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Functionalized Hydroxyapatite with Metronidazole-Based Metal Complexes for Antimicrobial Applications

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Introduction

Hydroxyapatite (HA), thanks to its excellent biocompatibility and structural similarity to bone, is widely used in biomedical applications such as bone regeneration, drug delivery, and implant coatings [1][2]. Its use is particularly common in dental implants, where HA serves as a coating material to promote osseointegration. However, infections related to implants remain a significant clinical challenge. One strategy to mitigate this issue involves functionalizing HA with antimicrobial agents [3].

Among the active pharmaceutical ingredients explored for this purpose, metronidazole (MET) functionalization has attracted attention due to its proven efficacy against anaerobic bacteria, including pathogens commonly associated with dental implant infections [4]. However, its antimicrobial spectrum is limited to anaerobes. A promising strategy to broaden its activity involves the formation of metal complexes, which may enhance its efficacy toward aerobes [5].

In this context, we investigated the functionalization of HA with silver and zinc salicylate (Sal) - metronidazole complexes ([Ag(Sal)(MET)] and [$Zn(Sal)_2(MET)_2$]). These complexes were synthesized and characterized, and their incorporation into HA composites was evaluated with the aim of improving the antimicrobial performance of HA-based materials for safer and more effective use in medical and dental applications.

Results and discussion

PXRD confirmed hydroxyapatite as the main crystalline phase in all composites, while the successful integration of the metal complexes was assessed with TGA, SEM, and FTIR. Electron microscopy showed preserved HA morphology. Antibacterial tests confirmed the composites retained the antimicrobial activity of the metal–metronidazole complexes.

The composites are structurally stable, and exhibit enhanced antibacterial properties, supporting their potential for medical applications.

Conclusion

Hydroxyapatite (HA) was used as a core to synthesize antibacterial composites with AgSal(MET) and $Zn(Sal)_2(MET)$ complexes. XRD confirmed HA structural integrity, with AgSal(MET) visibly incorporated and $Zn(Sal)_2(MET)$ detected via ATR-FTIR. TGA and microscopy confirmed the presence of organic ligands and preserved HA morphology. The composites are structurally stable and exhibit enhanced antibacterial properties, supporting their potential for medical applications.

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EXPLORING SOLID-STATE LANDSCAPES: ADVANCES IN PHARMACEUTICAL POLYMORPHISM OF PHENPROCOUMON

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Keywords: Polymorphism; Phenprocoumon; Racemate; Conglomerate

Background:
Pharmaceutical polymorphism plays a critical role in determining the physical and chemical properties of drug substances. Different polymorphs can exhibit significant variations in solubility, bioavailability, stability, and manufacturability, which directly impact drug efficacy, safety, and regulatory approval [1-3]. As such, identifying, characterizing, and controlling polymorphic forms is essential throughout the drug development process, from early discovery to commercial production. This study focuses on the solid-state behaviors of phenprocoumon, a widely used anticoagulant drug, exploring its polymorphic landscape through a combination of analytical techniques. The findings contribute to a deeper understanding of solid-state transitions and provide insights into the selection of optimal crystal forms for formulation development.
Methods:
Through a combination of powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and meticulous data analysis, we successfully identified four previously unreported polymorphic forms of phenprocoumon. Single crystal X-ray diffraction and powder structure resolution techniques enabled us to determine the crystal structures of three of these forms.
Results:
Five polymorphic forms of phenprocoumon were identified and characterized. Among them, three forms were structurally resolved, exhibiting distinct packing motifs and thermal behaviors. The differences in their melting points, enthalpies, and PXRD patterns clearly confirmed their unique crystalline nature.
Conclusion:
This study reveals the rich polymorphic landscape of phenprocoumon and underscores the necessity of comprehensive solid-state screening during drug development. Our findings not only expand the crystallographic database for this widely used anticoagulant drug but also enhance the understanding of thermal transitions in polymorphisms, thereby guiding future polymorphism screening efforts.

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Searching for Fenofibrate Substrate-Induced Phases

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Abstract

Polymorphism, the ability of a compound to crystallize in more than one crystal structure, has profound implications in pharmaceutical science, as different polymorphs can exhibit distinct solubility, stability, melting points, and bioavailability. While substrate-induced polymorphism (SIP) has been extensively explored in organic semiconductors, its application to active pharmaceutical ingredients (APIs) remains limited. In this study, we investigated SIP in Fenofibrate, a poorly water-soluble, BCS Class II lipid-lowering agent known to exhibit four polymorphic forms. Using pristine and chemically functionalized silicon dioxide (SiO_2) substrates—including surfaces modified with covalently grafted fenofibrate derivatives, we explored how surface chemistry and solution concentration modulate polymorphic outcome and crystal growth behavior in thin films.

Polymorph formation was found to be strongly dependent on solution concentration: low concentrations favored metastable forms (Forms II, III, IV), while higher concentrations promoted stable Form I. Surface functionalization dramatically influenced polymorph selection. All modified substrates exhibited enhanced nucleation and crystal growth compared to unmodified SiO_2, highlighting the nucleation-enhancing role of engineered surface chemistry. Surface properties, including hydrophobicity, molecular coverage, and drug–substrate interactions, played a critical role in determining both the crystallization kinetics and polymorphic form. These findings establish substrate induced polymorphism (SIP) as a versatile and effective approach for controlling the crystallization behavior of active pharmaceutical ingredients (APIs). By applying rational surface engineering principles, SIP offers a powerful pathway for the selective stabilization of metastable forms, potentially enabling improved drug formulation strategies, enhanced stability profiles, and new opportunities in intellectual property management.

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From Prediction to Attempted Realisation: Mapping the Polymorph Landscape of Sulfamerazine and Sulfadiazine

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Crystal Structure Prediction (CSP) is increasingly employed to complement experimental form screening in the pharmaceutical industry, aiming to mitigate risks in the drug development process [1,2]. However, a significant challenge with CSP is the tendency for overprediction, resulting in the prediction of many more structures than are likely to be found experimentally [3], which can complicate the process of identifying potential forms that might be found by further experimentation.

In this study, we conducted a CSP search on two chemically similar pharmaceutical molecules, sulfadiazine (SDZ) and sulfamerazine (SMZ), which exhibit different solid-form behaviours. Throughout this study, SDZ has one known polymorph, while SMZ now has five. We utilised CSP and further ab initio methods, including harmonic phonon free energy estimates, to investigate the reasons behind these observed differences. Additionally, we applied a molecular dynamics (MD) based workflow [4] to rationally reduce the number of predicted structures by modelling the effect of temperature on static CSP_0 crystal structures. From our computational investigation, we were able to predict a new and recently published fourth form of SMZ [5].

To validate our computational predictions, we employed non-classical crystallisation techniques, such as templating by sublimation, to try to discover new polymorphs of either molecule. During this process, we identified a novel solid solution of SDZ and SMZ and were able to identify a novel fifth form of SMZ that our experiments show is the new most stable form at high temperature. Furthermore, we collected experimental data on the transition between the SMZ forms I and II to contribute to the BEST_CSP benchmark.

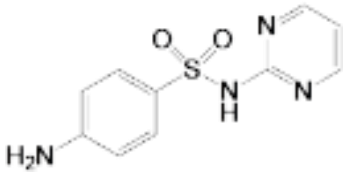

Figure 1. Sulfadiazine (left) and sulfamerazine (right).

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