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POSTER Session

Authors & Abstracts

Monday, 5 June
18:00-19:30

This event is organized jointly by:

PolyCrystalLine
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POSTER No. 1

How Good Is My Solid Form? The CSD Approach to a 'Health Check'

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ABSTRACT: Solid form selection of an active pharmaceutical ingredient (API) is a key stage in the drug product development process. Uncontrolled crystal form polymorphism can have a critical impact on pharmaceutical drug product robustness, exemplified by Norvir™[1] (Ritonavir) and Neupro™[2] (Rotigotine). The Norvir™ example illustrates how such polymorphism can be driven by a stronger set of hydrogen bonds in the more stable form. The application of informatics-based assessment[3] of new solid forms complements experimental studies and provides a deeper understanding of the qualities of the structure. The information provided by structural analyses is incorporated into the assessment of risk for the drug candidate.

Structural informatics techniques, which harness the knowledge contained within over 850,000 entries in the *Cambridge Structural Database (CSD)*[3], are quick to apply and are straightforward to use, allowing continuous assessment of progressing drug candidates. Software including such methodologies is being developed under the guidance of the Crystal Form Consortium (CFC), a partnership between the CCDC and several global pharmaceutical and agrochemical companies. The basis of a structural informatics crystal form assessment, or 'Health Check'[4] is to analyse the structure of a specific crystal form in comparison to other similar structures in the CSD and to relate this commonality to thermodynamic stability. Deviation from the norm for the crystal form under investigation can then be taken as an indication that a more stable polymorph might exist for that molecule. The structural features studied typically focus on crystal packing, intramolecular interactions, intermolecular interactions, propensity of hydrogen bonds and the geometry of interactions observed.

Here we will describe what a 'health check' is, which structural informatics tools included in *CSD-Materials* are used to carry out a health check, and how the potential application of these tools can be used to minimise risk in solid form design.

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F. H. Allen, *Acta Cryst.*, B58, 380-388, 2002 [DOI: 10.1107/S0108768102003890]
[4] N. Feeder, E. Pidcock, A.M. Reilly, G. Sadiq, C.L. Doherty, K.R. Back, P. Meenan, R. Docherty (2015) *J. Pharmacy and Pharmacology,* 67, 857-868.

POSTER No. 2

Matched molecular structures in the Cambridge Structural Database: potential use for crystal engineering

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ABSTRACT: With over 850,000 small-molecule crystal structures, the Cambridge Structural Database (CSD) features a wealth of information for understanding molecular packing and crystal engineering. Within this vast dataset are numerous pairs of molecules related by a single well-defined structural transformation. In drug discovery, analysis of such pairs is used to understand how structural modifications will affect the properties or binding affinity of a molecule. This type of investigation is not common for crystal structures, but has the potential to provide critical insights into how simple chemical transformations affect the structure and properties of solid forms.
Here, we outline the process of finding all matched molecular pairs in the CSD. We will then highlight the potential of this repository to inform on crystal engineering in a variety of ways. One example is to explore how transformations around acyclic single bonds (*e.g.* a terminal methyl group becoming a Cl atom) affect the packing of a molecule. There are over 12,000 such transformations represented in the CSD, which allows us to determine which functional group changes are more or less likely to disrupt or change the packing of a molecule in the solid state.

POSTER No. 3

The Effect of Gel on the Phases Stability: The Case of Cd-bpp MOF system

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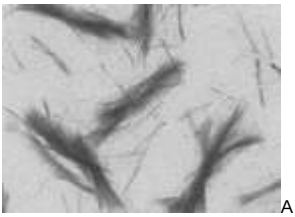
ABSTRACT: It is well known how the crystallization in gel media represents a very useful technique to growth crystals of high quality but also an alternative way to generate new crystalline phases.[1] In particular, for small organic molecules and drugs it has been demonstrated the gel's ability to drive the crystallization process toward specific polymorphs or unusual phases that cannot precipitate from solution.[2]

In the present work we report a similar behaviour observed for the system $CdCl_2$ (M) - 1, 3-bis(4-pyridyl)propane (L), that leads to the formation of different crystalline phases, that is: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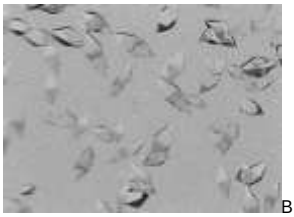
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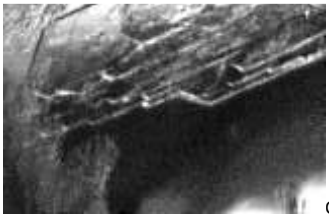
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(A)3D coordination polymer, sra topology 3D $[Cd_2(bpp)_3Cl_2]\cdot H_2O$ (3D-sra). [4]
(B)3D coordination polymer, diamantoid topology $[Cd(bpp)_2Cl_2]\cdot H_2O$ (3D-dia). [3]
(C)1D coordination polymer $[Cd(bpp)3Cl_2]\cdot 2H_2O$ (1D-Cd). [3]

An exhaustive screening has been performed by varying a number of crystallization parameters: total concentration and molar ratio of the reactants, gel strength, experimental set up for counterdiffusion technique. We always carried out the comparison with the behaviour of the same system in solution. We observe significant gel effects of phase stability. In particular increasing gel concentration is related with a global movement of the phase diagram towards lesser values of molar ratio.

The gel also has strongly influenced the morphology of the crystalline material, in particular 3D-dia crystals has revealed different kind of modification. They have displayed surface roughening and crystal elongations until disappearance of a recognizable morphology. This phase also form peculiar aggregates that suggest non-classical crystallization path, as oriented attachment mechanism.

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POSTER No. 4

Engineering of solid-state supramolecular rotors through halogen bonding

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ABSTRACT: Amphydynamic crystals are materials built to possess rapidly moving components in the solid state. Nowadays there is a growing interest in this class of compounds for the development of new functional materials and molecular machines. [1] The aim of our research is to take advantage of crystal engineering principles to assemble stators and rotators into cocrystals showing highly efficient molecular dynamics. This strategy has few advantages such as its intrinsic flexibility and hence the trivial access to a vast number of different supramolecular rotors. Firstly, we were able to synthesize crystalline supramolecular rotors selfassembled by halogen bonding (XB) of diazabicylo[2.2.2]octane (DABCO), a well known D3h-symmetric cylindrically shaped rotator, and a set of five fluorine-substituted iodobenzenes, acting as strong halogen bond donors, that take the role of the stators. The obtained amphidynamic cocrystals show excellent dynamics performance and XB works both as self-assembly driving force and main axle of rotation. [2] Based on these results, we designed and synthesized a series of isomorphous amphidynamic cocrystals based on XB. By carefully studying their inner dynamics and thanks to their structural similarities, we were able to distinguish the enhalpic and entropic components of the rotational free energy barrier. What is more, one of the cocrystal show the lowest ever-reported activation energy of the rotational process. [3]

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POSTER No. 5

Prediction and verification of co-crystal formation

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ABSTRACT: The experimental screening of co-crystal forms of active pharmaceutical ingredients (APIs) is challenging, as well as time and money consuming. For this purpose, there have been proposed several computational methods as possible ways to predict which substances (coformers) would be more likely to form a co-crystal with a given API. [1, 2] Each method depends on different factors that can influence the success of this formation.

In this work, we applied two of these methods to evaluate their ability to predict the co-crystallization of two pharmaceutical compounds, Lacosamide and Ivabradine hydrochloride, each with 10 different coformers. These methods are based on the shape similarity of the molecules of API and coformer and on their ability to form hydrogen bonds.[3, 4] More specifically, the first one is a method to predict if 2 molecules will form a co-crystal based on the comparison of each of their molecular descriptors (polarity, dipole moment, 3 simple shape descriptors). The second method is a knowledge-based methodology to assess and predict hydrogen bond formation comparing all their possible homo- and hetero- interactions.

The results of the two methods were quite successful to predict the formation of the experimentally observed cocrystals of Ivabradine hydrochloride with (R)-mandelic acid and (S)-mandelic acid and of the cocrystal of Lacosamide with urea. It is worth noticing that there was a good agreement between the computational predictions provided by the two methods.

As a conclusion, we can say that these two computational methods can facilitate the assessment of the likelihood for a cocrystal to form.

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POSTER No. 6

Suppressing Hydrate Formation in Metoclopramide HCl by Cocrystallization

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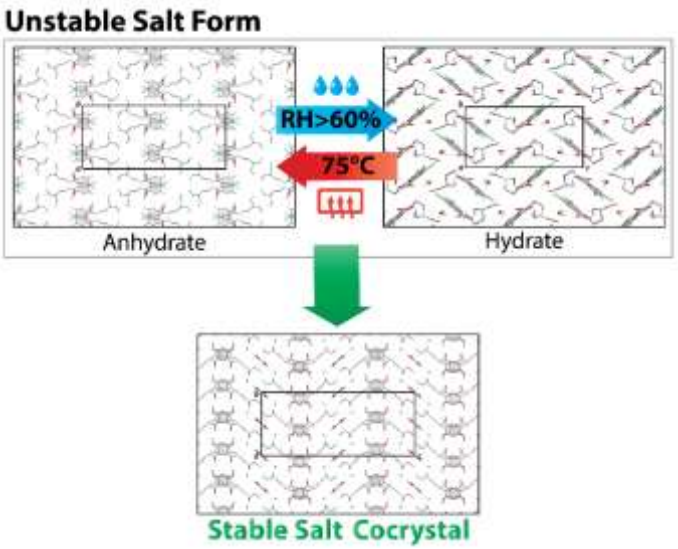
ABSTRACT: From a pharmaceutical point of view, controlling the crystalline form of API in the drug product is crucial in terms of pharmaceutical quality system. Hydrate crystal form is often preferred among commercial drug products due to its stability against high humidity.[1] However, the hydrate form can have an "unsolved pre-formulation problem" because the hydrate-anhydrate transformation by different temperature or humidity conditions can occur during manufacturing process or under storage in ambient condition.[2] In our previous study, the commercially marketed metoclopramide HCl monohydrate form transformed into anhydrate form at 75°C, then it hydrated by exposure to humidity of RH > 60%. Also, their crystal structure features explained the transformation mechanisms.

In this research, we explored more stable crystalline form of metoclopramide HCl by utilizing multicomponent crystal formation with oxalic acid as a coformer. Crystal structure analysis revealed that in this salt cocrystal, all hydrogen bond donors and acceptors were utilized comparable to those observed in the monohydrate form. Importantly, because of this feature, the cocrystal has a good stability under exposure to high humidity environment and also in slurry experiment in water. Besides, this cocrystal form is stable up to 150°C temperature. This research emphasizes the role of cocrystallization on improving the multiple stabilities of highly soluble drug.



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POSTER No. 7

Thorough Study of the Ibrutinib Polymorphs: Emphasizing the Importance of Desolvation

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ABSTRACT: Polymorphism is one big deal for today's pharmaceutical industry as almost all modern active pharmaceutical ingredients (APIs) are highly prone to polymorphism. Different solid forms may have significantly altered properties such as solubility, physical and chemical stability or reproducibility.[1,2] Those variances can dramatically change API's bioavailability and its behaviour in the final drug product,[3] or they can make the production of the desired solid form challenging or even impossible.[4] Therefore, thorough study of the polymorphism is a crucial step for the API and the whole pharmaceutical development. In our research, we focused on the detailed description of the polymorphs of Ibrutinib, a recently approved tyrosine kinase inhibitor used for treatment of non-Hodgkin lymphomas. Ibrutinib has three polymorphs described in the patent literature: form A, form B and form C.[5] In our study, we have prepared single crystals of two of its polymorphs (the most stable form A and metastable form C) and solved their crystal structures using X-ray diffraction. The third polymorph (form B) was obtained only as a powder sample. In addition, we have also prepared a single crystal and solved a crystal structure of Ibrutinib methanol solvate (form F). This solvate was found to be highly unstable channel solvate, desolvating to one of the Ibrutinib polymorphs, form C. The mentioned desolvation process was found to be the only, so far known, method of the preparation of the form C. Further, the single-crystal of the solvate was used to prepare the single crystal of the form C by a single-crystal to single-crystal transformation. Analysis of their crystal structures revealed high similarity between the solvate and the desolvation polymorph, where the major difference is a closure of the vacant channel left after the methanol escape from the structure. Also, the kinetics of the desolvation process of the methanol solvate was measured using a time dependent XRPD. Forms A, B and C were further characterized by a standard solid state methods such as DSC, TGA, DVS and XRPD. To reveal their applicability in the drug production, dissolution profiles were measured for those three forms, with the form B and C having almost 3 times higher dissolution rate in comparison with the form A.

References:
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POSTER No. 8

Polymorphs and surface induced structures in drug thin films investigated by Raman spectroscopy.
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ABSTRACT: The study of polymorphism plays an important role in several fields of materials science, with relevant applications in technology and pharmaceutics. This contribution aims to show how the polymorph phenomenon can be studied by means of confocal Raman microscopy in the *lattice phonons* region (Figure 1). Using this approach allows for an effective *in situ* phase recognition, [1] with the possibility of obtaining a topography of the chemical purity and polymorphism of the sample by mapping the Raman signal at a micrometric resolution. [2] Recently, there is a growing interest in a new generation of crystalline forms obtained in thin films, which are defined as surface-induced polymorphs (SIPs). In pharmaceutical science it has been demonstrated that SIPs might indeed exhibit different performances like enhanced dissolution rates for drug release. A full characterization of the SIPs is still challenging and a number of experimental and computational tools are necessary to unambiguously identify their nature and characteristics. [3]

In the model case of *phenytoin* (5,5-diphenylimidazolidine-2,4-dione) Raman spectroscopy has turned out to be a valuable support to the structural characterization of a SIP. [3] By a careful evaluation of different Raman bands, together with the morphological differences observed in the microscope, regions of distinct polymorphs could be identified. This very information was recently inaccessible, as morphologies could not directly be connected to any morphology.

As a further example of the application of the Raman technique, we also report on the investigation of the relative stability of the *paracetamol* (N-(4-hydroxyphenyl)ethanamide) phases in spin coated films on different substrates over a wide temperature range. In particular, the metastable form III has been found to show the longest lifetime on record when obtained in the film form on suitable substrates.

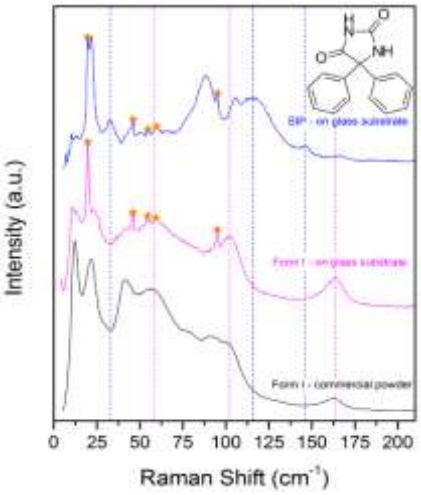

Figure 1: Lattice phonon of phenytoin (and molecular structure) in the bulk and different forms found on substrate. Markers show the peaks of the substrate.

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Controlling needle growth from both stacking and hydrogen-bonding.

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ABSTRACT: A given substance can crystallize in diverse habits. Needle like crystals are an undesired shape in the pharma industry because they have poor flow proprieties, poor filterability and poor compressibility.[1] Two main effects can drive the formation of needle like crystals, one van der Waals contact stacking interactions and H bonding motifs.[2] In this work two molecules with needle like crystal growth were selected, one is 2′-hydroxy-[1,1′-bi(cyclohexane)]-1-carbonitrile with hydrogen bond motifs and the other is Diflunisal with π stacking propriety. In both cases it was possible to modify the crystal habit using different approaches.

In the case of 2′-hydroxy-[1,1′-bi(cyclohexane)]-1-carbonitrile it was shown that the use of solvents of different polarity drastically modify the H-bond motif and the habit of the crystals. The use of a highly polar solvent leads to the formation of block like crystals while less polar solvents cause needle like growth.

In the case of Diflunisal a different approach was selected. A library of tailor made molecules (esters and amides) was synthesized and used as additives in the crystallization process. None of the molecules selected affected the final habit. For this reason a new low attrition method was investigated. A vial with a supersaturated solution was fixed to an engine that move the vial, the spinning frequency is controlled by a variable voltage transformer, using voltages in the range of 10 to 12 volts. During this movement caused by the engine the crystals are slowly changing the dimensions due to a mass action effect.

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POSTER No. 10

Prediction and Experimental Validation of Solid Solutions and Isopolymorphs of Cytosine/5-Flucytosine

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ABSTRACT: The structural, temperature- and moisture dependent stability features of cytosine [1,2] and 5-flucytosine [3] solid forms, two pharmaceutically important compounds, were rationalised using complementary experimental and computational approaches. Moisture sorption/desorption, water activity, thermal analysis and calorimetry were applied to determine the stability ranges of hydrate ↔ anhydrate systems, while X-ray diffraction, IR spectroscopy and crystal structure prediction provided the molecular level understanding.

The computed crystal energy landscapes for the anhydrous forms, monohydrates and 1:1 cocrystals not only revealed that the substitution of C5 (H or F) controls the packing and properties of the solid forms, but also have enabled the finding of novel solid solutions of the two substances, with interesting practical features. All neat, hydrated and solvated solid solutions are isostructural with the 5-flucysosine solid forms and exist only if more than 20% of 5-flucytosine is present. In the case of the monohydrate solid solution, the new phase shows better thermal- and moisture-dependent stability properties than its pure structure, 5-flucytosine monohydrate I.

The chemical exchange of the C5 cytosine proton with a F-atom not only influences the predominance of hydrogen-bonding motifs in monohydrate structures but more important the way in which hydrogen-bonded ribbons are linked through water into three-dimensional packings. In contrast, the hydrogen ↔ fluorine atom exchange in the anhydrous compounds does not affect the predominance of the experimentally observed ribbon motif, but its 3D packing preferentiality.

To conclude, this study is another successful demonstration of the complementarity of computational and experimental screening and characterisation methods. The computed crystal energy landscapes are an important tool not only for interpreting the range of experimental solid forms but also for proposing and targeting crystallisation experiments using isomorphs seeds/templates to produce novel solid forms. Furthermore, the computed structures can support structure solution from laboratory powder X-ray diffraction data.

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POSTER No. 11

Multicomponent crystals of Leucine-Leucine dipeptides

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ABSTRACT: Biologicals are having a more important role as therapeutic agents. They can be composed of proteins, sugar, or nucleic acid and sometimes they might represent the only efficient way to treat a specific disease. The solid-state form of such entities can't be easily used in a dosage form due to the fact that these compounds exist in the amorphous state with consequent disadvantageous therapeutic and pre-formulation properties (e.g. questionable stability, unpredictable solubility and bioavailability).

A possible contemporary solution to this crystallisation ability issue, is the preparation of crystal forms of these biological molecules using and applying the concepts of crystal engineering and molecular complexes.

Leucine-leucine dipeptide has been synthesized through Fmoc Solid Phase Peptide Synthesis and it was co-crystallised along with a list of different co-formers. The Leu-Leu dipeptide is a good starting material due to different structural properties (e.g. small size, good amount of hydrogen bond donors and acceptors, no additional chemical functionalities on the hydrophobic side chains, only solvates are reported in the Cambridge Structural Database).

Single crystal X-ray diffraction analysis show the formation of different novel crystal structures containing both the dipeptide and co-formers with similar multi-layered crystal packings. An interesting nanotube structure has been obtained while trying to co-crystallise the dipeptide and 4-dimethylamino pyridine.

POSTER No. 12

A thermal gradient approach towards polymorph selection in thin films

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ABSTRACT: Polymorphism can be defined as the intrinsic ability of a solid material to exist in two or more crystal forms which may differ in the molecular conformation and/or crystal packing. It is linked to the unpredictability of crystal structures from the first principles as polymorphs differ only in energy ≤ 10 KJ/mol. The phenomenon is generally understood in terms of nucleation, i.e. once a nucleus of a given phase has appeared, growth continue in the same phase without any subsequent phase transition. Due to its dramatic influence on material properties, polymorphism is of great importance for industrial sectors like pharmaceuticals, fertilizers, explosives, pigments, and organic electronics. Although an extensive body of research is available in this topic, some elements key to the understanding of polymorphism is still missing. To this extent we sought to understand the role of heat flux in polymorphic control and phase transitions with a model system, acetaminophen. This is experimentally facilitated by a temperature gradient heating stage which essentially consists of two independent heating elements separated by a distance of 2.5 mm. [1]

One of the heating elements is set at a temperature, above the melting temperature (hot side) while the other at a temperature below the crystallization temperature (cold side) of acetaminophen. Structural evolution is then followed as thin films of acetaminophen are translated from the hot zone to the cold zone. Thin films are ideal model systems, because of the absence of convection, heat transport occurs only by diffusion. In this presentation, we report on the crystallization of polymorphs of acetaminophen as a function of thermal gradient parameters (magnitude of the gradient, sample velocity) in a thin film geometry. The thin film samples were displaced at a given rate ($1 \leq v \leq 75$ µm/s) to control direction and the rate of crystal growth. This allows to decouple nucleation and growth.[2] A detailed structural analysis combining polarized optical microscopy (POM) and X-ray diffraction (out-of-plane, in-plane) has been carried out to characterize different crystalline forms produced by the thermal gradient technique. The resulting polymorphic forms have been found to have high phase purity and exhibit remarkable stability over time.

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Ternary phase diagram of Piracetam-$CaCl_2$ ionic co-crystal in water

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ABSTRACT: Pharmaceutical Cocrystals [1] (CCs) are crystalline solids, which consist of an active pharmaceutical ingredient (API) and at least one cocrystal former (CCF). CCs can potentially improve physicochemical properties, such as solubility, dissolution rate, melting point and even bioavailability compared with their parent APIs. Ternary phase diagram[2]can describe the stability and thermodynamic characteristics of a cocrystal system. That is very important to design the crystallization operation and develop an up-scaled process.

In my project, piracetam and a 1:1 stoichiometric amount of $CaCl_2$ were grinded for 90min at 30Hz by solvent-drop grinding method, leading to form the piracetam$_2$: $CaCl_2$: H_2O co-crystal[3]. To make the ternary phase diagram, we added piracetam and $CaCl_2$ into water with piracetam/$CaCl_2$ ratio from 0 to 1. The suspensions were stirred in sealed vials at 298.15K for 48h to make sure the system reached thermodynamic equilibrium. After that, the sample solids were obtained by vacuum filtration and were characterized by XRPD measurement. Then we determined the solubility of the different compositions to create the liquid surface in this ternary phase diagram.

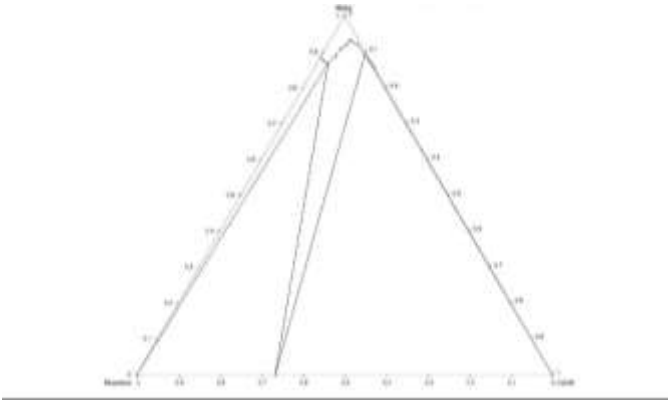

Figure 1. Piracetam-$CaCl_2$ ternary phase diagram in water at 25℃ (mole fraction)

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POSTER No. 14

Greener solid state synthesis: Halogen-Bonded Directed Stereoselective Photodimerization of Vitamin K3

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ABSTRACT: Supramolecular chemistry has been utilized to orient C=C bonds in an appropriate orientation for stereo-selective photodimerization in a non-solvent way. We report herein the stereoselective photodimerization of Vitamin K3 using fascinating templates with ditopic halogen bond donors.[1] As a consequence of cocrystal formation with these templates, reactive C=C bonds of neighbouring Vitamin K3 molecules stay at a center-to-center distance below 4.2 Å and conform to the criteria of Schmidt for photodimerization reaction. Under UV irradiation, Vitamin K3 molecules undergo a [2+2] photodimerization in the solid in a stereoselective and quantitative manner. This is by far the first case wherein both the preparation of the cocrystals and the purification process were achieved in a "green" way. The cocrystals can be prepared through a grinding process. After photodimerization, in the one hand, photodimer can be separated from the crude photoproduct by simply sublimating the templates. On the other hand, the templates are environmentally sustainable that can be recovered and recycled by condensation. Thus, both the preparation and separation of the photodimers are conducted in the absence of solvent.

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Developing Stable Vitamin D_3 through Cocrystallization

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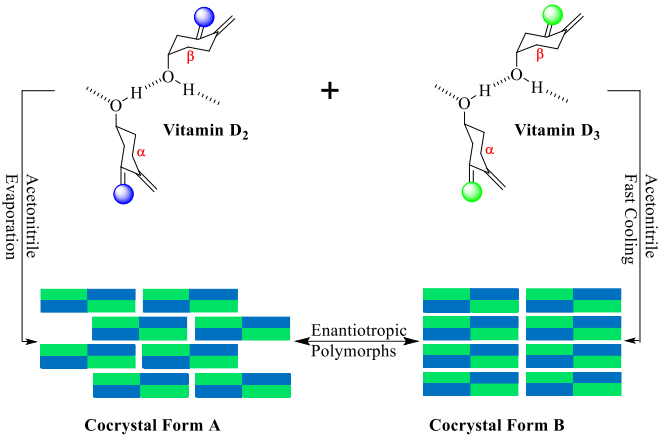
ABSTRACT: 65 million years ago an asteroid hit the Earth and initiated the extinction of dinosaurs. Vitamin D deficiency was thought to be one of main factors, as the global darkness led to the inability to produce the vitamin D which would have been essential for the maintenance of the massive skeletons of the dinosaurs. Vitamin D_3 (VD_3), a steroid hormone, has mainly been known for its effects on bone and osteoporosis. The current therapeutic practices expand into such markets as cancer research, pediatrics, nephrology, dermatology, immunology, and genetics. Although VD_3 has been used in medicine, food and feed industry for several decades, the solid-state of this interesting vitamin is not comprehensively studied. We herein report the discovery of four cocrystals constructed with a set of collective hydrogen-bond interactions.

These cocrystals were formed through an unexpected conformationally selective crystallization process and were found to present superior physicochemical properties compared with vitamin D_3 itself. It was found that two polymorphic forms of VD_2-VD_3 cocrystal exhibited dramatically different physicochemical stabilities due to the packing style and distance of C7-C19. The distance between C7 and C19 is a key factor to indicate the vulnerability of vitamin D to photo- and thermos- induced topochemical cyclization reactions.



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POSTER No. 16

Mechanical force and vapor triggered fluorescent color changes among solid forms of Emodin

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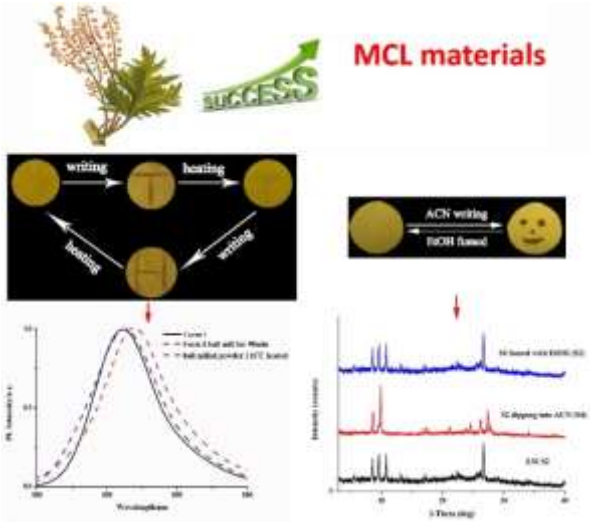
ABSTRACT: In recent years, many strategies such as chemosynthesis and solid-state studies have been taken in attempt to discover reversible mechanochromism luminescent (MCL) materials and alter their fluorescent colors. Here, we report three polymorphs, two hydrates and six solvates of Emodin (EM) – a naturally occurring fluorescent dye. Obvious differences in their fluorescent properties were presented. Notably, form I and amorphous of EM exhibited reversible fluorescent color changes in response to both thermo stress and mechanical stimulation.[1]

Moreover, S2 (ethanol) and S4 (acetonitrile) presented the most significant differences among EM solvates and they showed vapor triggered reversible fluorescent color changes. The reversible processes of both form I to amorphous and S2 to S4 were well exhibited in the writing-erasing process on the cast filter paper made by EM. It was found that different kinds of H-bond and π-π interactions existed in solid states of EM, which illustrated the reasons why they exhibited different fluorescent colors. This work provides a new approach to find eco-friendly and metal-free organic MCL materials that sensitive to vapor, mechanical and thermal stress without chemical synthesis and a demonstration of potential application for EM in organic vapor sensing and security ink material through controlling solid-state transition processes.



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Growth characteristics of beta polymorph of resorcinol in thermal gradient

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ABSTRACT: Fabrication of a thin film of organic electronics materials is very important for the preparation of effective optoelectronic devices [1]. Therefore, fundamental researches about deep understanding of role of molecular structure and supramolecular organization of organic compounds in the formation of preferably oriented thin film over a substrate are much needed. Further, impact of external constraints like rigid wall (substrate) or thermal gradient on the occurrence of polymorph are also equally required. Crystallization of organic compounds on a solid surface can leads to stabilization of one particular polymorphic phase of the compound or formation of a new polymorphic phase [2], termed as substrate induced phase (SIP). In compare with conventional methods like spin coating or drop casting for the preparation of thin film, the use of thermal gradient method can enhance the supramolecular order in the thin film. Hence use of this technique in obtaining of large uniaxially oriented domain over a substrate is recent focus [3].

In current work, a technique of crystallization of different organic compounds, for example, resorcinol, in a thermal gradient over a glass substrate has been performed. Role of molecular and crystal structure of the compound, thermal gradient magnitude, growth rate and polymorphism in formation of preferably oriented or aligned thin film have been investigated. A detail structural and orientation analysis of the thin film over the substrate has been performed by polarized optical microscopy, X-ray diffraction measurement and pole figure analysis. It was observed that in case of resorcinol, only *beta* form is appeared to crystallize over a glass or PDMS coated glass substrate in a thermal gradient. Moreover, well oriented crystals over the substrate were observed to be aligned relative to the temperature gradient.

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POSTER No. 18

Halogen-bonded metal-organic cocrystals: structure and synthesis

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ABSTRACT: Currently, the most important studies of halogen bonding that could find great use in the construction of supramolecular metal-organic architectures have generally been performed on single-component systems. Multicomponent halogen bonded metal-organic systems, where an organic ligand functions as a halogen bond acceptor are still rare in literature.[1,2] Since our previous research has indicated the acetyl fragment as an acceptor species of interest,[3,4] in this work, we were interested in cocrystallizing robust metal complexes containing that fragment on its periphery. We first synthesized two coordination compounds of our selected ligand, n4aa (derived from 2-hydroxy-1-naphthaldehyde and 4-aminoacetophenone), with copper(ii) and nickel(ii) ions, $Cu(n4aa)_2$ and $Ni(n4aa)_2$, respectively, after which they were cocrystallized with selected perflourinated halogen bond donors: iodopentafluorobenzene (ipfb), 1,4-diiodotetrafluorobenzene (1,4-tfib), 1,3-diiodotetrafluorobenzene (1,3-tfib), and 1,4-dibromotetrafluorobenzene (1,4-tfbb).

Cocrystal screening experiments were performed by liquid-assisted grinding mixtures of the metal complexes with the selected halogen bond donors, and the products were then characterized by powder X-ray diffraction. Powder patterns have revealed that cocrystals are formed in all these cases, and also that the corresponding $Cu(n4aa)_2$ and $Ni(n4aa)_2$ cocrystals are isostructural. Single crystals were obtained by traditional solution based crystallization methods.

The supramolecular bonding topology of our obtained cocrystals was found out to be dependent on the topicity of the used halogen bond donor. Cocrystals with the monotopic halogen bond donor, ipfb, contain a discrete I···O halogen bonded complex (0D). These discrete units are then connected into chains that alternates two types of the metal complex subunit, one which participates in two I···O halogen bonds and the other which participates exclusively in C–H···F interactions. In metal complex cocrystals with linear ditopic halogen bond donors, 1,4-tfib and 1,4-tfbb, the dominant supramolecular interaction is the I···O halogen bond which leads to the formation of chains (1D). The chains are then stacked *via* C–H···O hydrogen bonds, perpendicularly to the halogen bond, and further into a 3D network *via* C–H···F interactions. In metal complex cocrystals with 1,3-tfib, a longer and a shorter I···O halogen bond are formed and lead to the formation of a layered architecture (2D). The layers are then stacked *via* long C–H···O interactions.

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Synthesis and characterization of a theophylline-pyridoxine drug-drug salt co-crystal

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ABSTRACT: Pharmaceutical co-crystals represent an emerging class of crystalline solids formed by at least one API (active pharmaceutical ingredient) and an appropriate component, laying in the same crystal lattice and held together by weak interactions (hydrogen bond, halogen bond, π-π stacking).[1] Recently, multi-drug co-crystals (MDC) are turning out to be an alternative method to traditional fixed-dose drug combinations.[2,3] Actually, these particular solid forms of APIs could overcome some disadvantages of combination drugs, such as low solubility and bioavailability and issue with stability of unstable components which can be enhanced through intermolecular interactions. Moreover, MDCs fulfill the criteria for patent eligibility: novelty, utility and non-obviousness.

Structural characterization of co-crystals is extremely important because the outcome properties depend on the 3D arrangement of the molecules in the lattice. Single crystal X-ray diffraction (SCXRD) is usually considered as the best tool for structural studies, always more often supported and complemented by solid-state nuclear magnetic resonance (SSNMR), particularly when dealing with hydrogen atom positions.[4,5]

We report on the synthesis and characterization of a theophylline-pyridoxine drug-drug co-crystal, whose two APIs are known to be concurrently administered for asthma treatment. The co-drug has been characterized by IR-ATR and Raman spectroscopy, thermal analysis (DSC and TGA), powder and single crystal X-ray diffraction, SSNMR measurements and DFT calculation.

All these experiments have been fundamental to completely describe the molecular structure and the intermolecular interactions. SSNMR and DTF calculation have been crucial to unravel the complex hydrogen bond network and to define the ionic character of the drug-drug co-crystal, which can be more properly defined as drug-drug salt co-crystal.

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POSTER No. 20

Use of crystal structure informatics for defining the conformational space needed for predicting crystal structures of pharmaceutical molecules.

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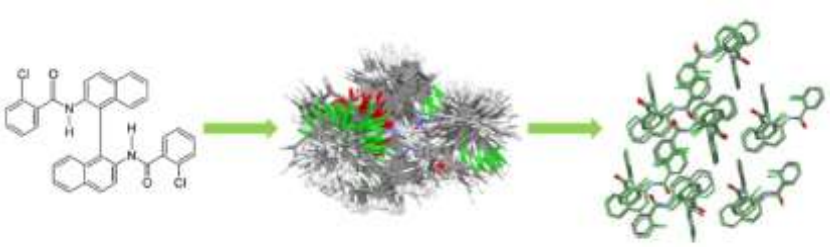
ABSTRACT: Crystal Structure Prediction (CSP) studies aim to predict all the thermodynamically plausible crystal structures of a molecule from the chemical diagram, and so can act as a complement to the solid form screening work carried out in drug development [1]. However, most pharmaceuticals have several bulky molecular fragments linked by flexible torsion angles. Hence, determining the range of conformations that a flexible pharmaceutical could plausibly adopt in a crystal structure is a key to successful CSP studies. We develop a workflow for this purpose based on using conformational information retrieved from the Cambridge Structural Database (CSD) [2], which contains more than 850,000 experimentally-determined crystal structures.

The conformations produced by the CSD Conformer Generator are reduced by considering the underlying rotamer distributions, an analysis of changes in molecular shape, and a minimal number of molecular *ab initio* calculations. This workflow is tested for five pharmaceutical-like molecules, where an extensive CSP study had already been performed, namely molecules XXIII and XXVI from the 6th Blind Test, molecule XX from the 5th Blind Test, GSK269984B and mebendazole [3-6]. The CSD informatics-derived set of CrystalPredictor searches generates almost all the low-energy crystal structures previously found, including all experimental structures, whilst significantly reducing the computational cost. The issues involved in comparing solid-state and isolated-molecule conformations are discussed.



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Facile Synthesis of New Imines for Use as Linker Ligands in Coordination Polymers

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ABSTRACT: Solid-state synthesis (S3) is recognised as an attractive approach to synthesise new and existing molecules with minimal solvent waste and high yield. However, S3 not yet of general utility, being limited by poor understanding of which functional groups and reaction types are best suited for widespread implementation.

In this report, we apply S3 to prepare eight Schiff bases,[1] seven of which are novel, in high yield (>95%) using either mechanochemistry *via* solvent-drop grinding[2] followed by heating or a solution-based method. The synthesised Schiff bases were designed to possess specific functional groups and were selected for their potential utility as linker ligands to generate various types of 3D coordination networks with diamondoid (dia)[3] or primitive cubic (pcu) [4] topologies. All eight compounds were characterised using spectroscopy and single crystal X-ray diffraction, can be prepared in gram quantities and exhibit high thermal stabilities. They therefore are promising for application as linker ligands in Metal Organic Materials, MOMs.

Our synthetic approach will not only afford new materials and enables molecular diversity, but it also provides a rapid and environmentally friendly methodology for the construction of molecular and supramolecular materials.

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Systematics of 4-HOC_6H_4COR (R = H, alkyl) packing: polymorphs and co-crystals

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ABSTRACT: Organic compounds with both hydrogen bond (H-bond) donor and acceptor functional groups connected to a benzene ring have been widely used to investigate how H-bond interactions can be used to engineer crystals with specific packing motifs and physicochemical properties.[1] This type of compounds is also often implicated in discussions of crystallization and polymorphism involving molecular organic solids, which are intimately related to crystal engineering strategies. A fundamental aspect within this scope is the understanding of how systematic changes in molecular structure influence packing patterns, lattice energies, and phase transitions in crystals. Compounds of 4-HOC_6H_4COR type (R = H, alkyl) are interesting systems to investigate these questions, because they are prone to polymorphism[2-5] and have also shown some unique features in terms of crystallization behavior.[6,7] In this work a systematic study covering structural aspects, lattice energies, and phase transitions for the 4-HOC_6H_4COR compounds in Figure 1 will be presented. Also addressed will be the co-crystalization of 4-$HOC_6H_4COCH_3$ with different co-formers to investigate how "exogenous" molecules can interfere with the 4-HOC_6H_4COR packing.

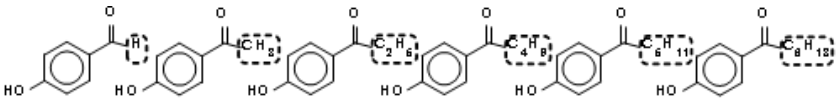

Figure 1. Molecular structures of the compounds studied in this work.

Acknowledgements: This work was supported by projects UID/MULTI/00612/2013 and UID/QUI/00100/2013 from Fundação para a Ciência e a Tecnologia (FCT), Portugal. Post-Doctoral grants from FCT are also gratefully acknowledged by Carlos Bernardes (SFRH/BPD/101505/2014) and Ricardo Simões (SFRH/BPD/118771/2016).

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Crystal forms of the antidepressant venlafaxine: a study to improve the solubility.

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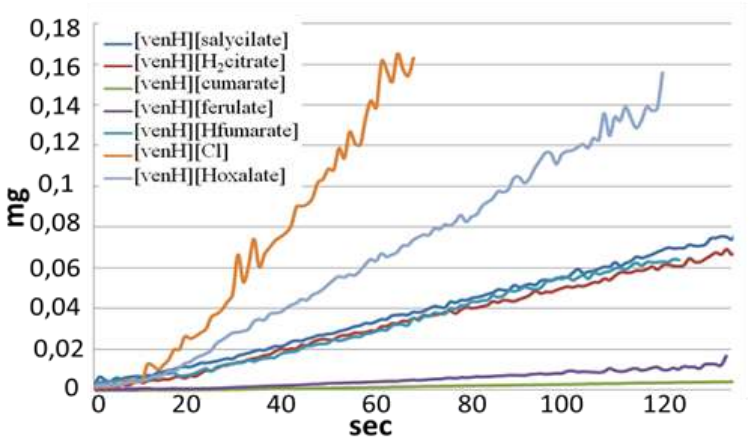
ABSTRACT: In the pharmaceutical field, solid state chemistry and the discovery of new solid forms[1] of active pharmaceutical ingredients (APIs) are very significant. Co-crystallization[2] or salt formation[3] can provide an efficient strategy to obtain new APIs.

This project was focused on the improvement of the solubility properties of venlafaxine (RS)-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol, an antidepressant in a group of drug called Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSNRIs), used for the treatment of Major Depressive Disorder (MDD) and generalized anxiety disorder.

The goal of the project was the preparation of new venlafaxine salts by salt formation between venlafaxine free base and co-formers accepted in *Pharmacopeia* and the subsequent tablet formulation with excipients. Three of the new salts were chosen for the tablet formulations with excipient and the in vitro dissolution tests in accordance to the United States Pharmacopeia (USP). Dissolution tests were compared with those of the commercial form of venlafaxine: venlafaxine hydrochloride.



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Pseudo-polymorphic forms of new molecular salts of the antiplated drug with thienopyridine structure S(+)Clopidogrel

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ABSTRACT:
After expiration in 2012 of the patent protection for the blockbuster drug Clopidogrel (Plavix®, Sanofi-Aventis), it has been challenging for drug manufacturers to launch generic forms with improved physicochemical properties and biopharmaceutical performances [1]. Therefore our aim was a cocrystallization screening by crystal engineering approach for new molecular salts of the more active and better tolerated form of clopidogrel, the dextrorotary isomer S(+)clopidogrel, followed by structural determination. Few structures of this drug exist so far in the Cambridge Structural Database (CSD v.5.35): the two polymorphs of S(+)clopidogrel hydrogen sulfate used in pharmaceutical formulations, orthorhombic form II (refcode FUQMOU) and monoclinic form I (FUQMOU01) [2,3], as well as the S(+)clopidogrel camphosulfonate (JASHUG) [4] and S(+)clopidogrel isopropylsulfate (YEXHOZ) [5].

The crystal structures of two new *pseudo*-polymorphic forms of S(+)clopidogrel-picrate salt obtained by co-crystallization are reported. Compound 1 (CDCC 1448941), prepared by treating clopidogrel hydrogen sulfate with picric acid, crystallizes in the monoclinic space group $P2_1$ with a ionic couple S(+)ClopH+•Pic- and a molecule of solvent ethanol in the A.U.. Crystals of Compound 2 (CDCC 1448942), grown dissolving clopidogrel free base and picric acid in a methanol/*n*-propanol mixture, crystallize in the monoclinic space group *C*2 with two ionic couples in the A.U.. The configurations and conformations of the ionic couples, held together by quite strong ionized +N–H···O– hydrogen bonds (H-bonds), are almost identical in both crystals.

The two compounds are compared with known structures of clopidogrel salts, including those used in pharmaceutical formulations, and the H-bonds discussed in reference to the general behavior of the *N*-bases-picrate H-bond and to the coformers acid-base properties. *d*(N···O) contact distances are in the range 2.752-2.815 Å with calculated H-bond energy from 2.68 to 3.45 kcal mol-1 and ΔpK_a of -4.26. These medium-strong H-bonds fit well the reported correlations among *d*(D···A), E_{HB}, and pK_a [6] aimed to verify the validity of the pK_a equalization principle [7-9].

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POSTER No. 25

Quantification of polymorphs form in Pharmaceutical Compounds Based on Powder X-Ray Diffraction with partial least square

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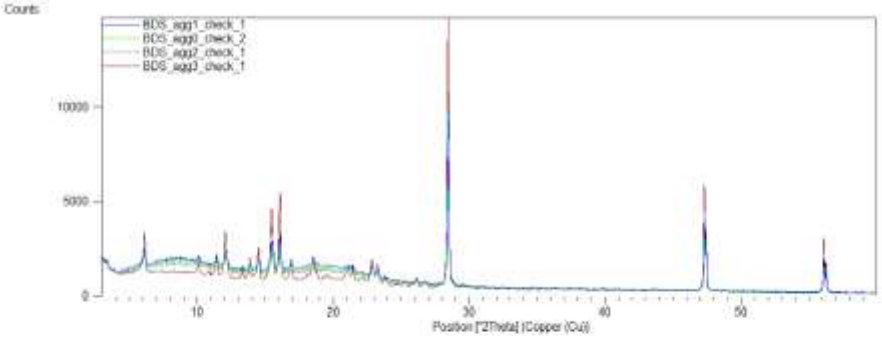
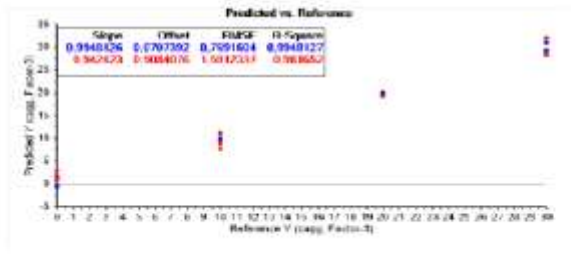
ABSTRACT: Over the last few years, studies on quantification and determination of various polymorph forms in complex matrices have become a key point in research by pharmaceutical industries. Studies on their quantification are also requested by the FDA, because the various polymorphs are characterized by a different bioavailability in the organism. In our studies we would like to improve simple method for the quantification of a crystalline phase in presence of a complex matrix which comprises several phases and amorphous. The method consists in an X-ray diffractometric analysis combined with the partial least square. The analyzed drugs are the Budesonide (BDS), a glucocorticoid used for the treatment of asthmatic pathologies and the Tachifludec, whose API is paracetamol, commonly used for inflammatory diseases. This work is done by preparing – through the method of standard addition – specimens that will be submitted to XRPD. The obtained diffractograms are then submitted to multivariate analysis through partial least square 1, by using the Unscrambler 10.4 software. The main advantage of chemometrics is its easy applicability. Moreover, thanks to the data obtained by the multivariate regression, it can be confirmed that the chosen method is extremely valid to solve these kinds of problem.



XRPD Patterns of Mixed Budesonide and HPMC



PLS model calibration and validation plot of standard of Budesonide and HPMC mixed

POSTER No. 26

Engineering co-drug solid forms: the mechanochemical synthesis of an indomethacin-caffeine system

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ABSTRACT: Nowadays, the exploration and synthesis of novel crystal forms is a well-established strategy for tuning physicochemical properties of a certain molecule while preserving its inherent activity.[1] A particular type of crystal form is represented by pharmaceutical cocrystals where at least one component is an Active Pharmaceutical Ingredient (API).[2] If both co-formers are APIs, a co-drug, or drug-drug cocrystal, is formed. This is a convenient approach, when the two APIs are used in combination to treat a specific disease, to reduce the pill burden and also minimize any possible mistake by patients.[3] Moreover, sometimes drug-drug cocrystallization may represent also a strategy to tune the performances of APIs.[4]

This poster reports on the preparation and solid-state characterization of an indomethacin-caffeine co-drug in a 1:1 stoichiometry. These two active ingredients are frequently co-administered as part of a therapy against strong migraines, in a commercially available fixed dose combination formulation. The X-ray crystal structure of the co-drug is characterized by a hydrogen bond interaction between the carboxylic moiety of indomethacin and the purinic nitrogen atom of caffeine. Dissolution kinetic tests revealed superior bioavailability of indomethacin in the co-drug compared to indomethacin alone. On the other hand, the thermal stability of indomethacin was lower in the cocrystal rather than in the pure drug.

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Exploring Chiral Resolution in the Solid State *via* Ionic Co-Crystal formation

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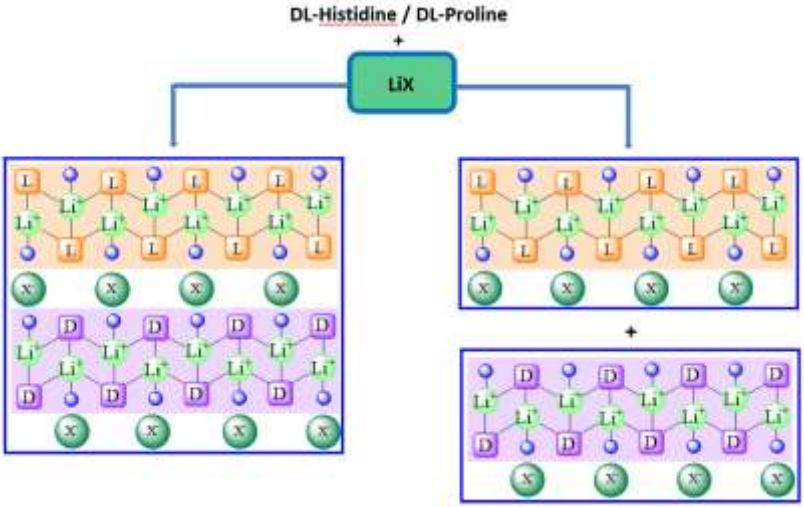
ABSTRACT: An ionic co-crystal (ICC) is a multicomponent solid formed by at least an organic molecule and an inorganic salt in a defined stoichiometric ratio. ICCs have the potential to alter physicochemical properties (such as solubility and thermal stability) of a pure organic material of interest. The purpose of the current work was to investigate the possibility of chiral resolution by ICC formation. ICCs of DL-proline and DL-histidine[1] with lithium halides were synthesized and investigated whether a racemate ICC or a conglomerate of L- and D-ICC was formed. Green chemistry methods were used for synthesis.

The performed investigations highlighted the potential for chiral resolution in the solid-state induced by Li^+; depending on the chosen halide we were able to observe the formation of a conglomerate and/or a racemate ICC. The racemate ICC can be described as a special type of co-crystals made of enantiopure L- and D-amino acids chains of the same type as those obtained with enantiopure L-amino acid. The obtained results encourage further research to establish the homochiral preference of lithium cation and to identify the factors that promote conglomerate formation versus the formation of a racemate ICC through co-crystallization.



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POSTER No. 28

X-ray powder diffraction: a powerful tool in the structure determination of new salts of the anti-Parkinsonian drug amantadine

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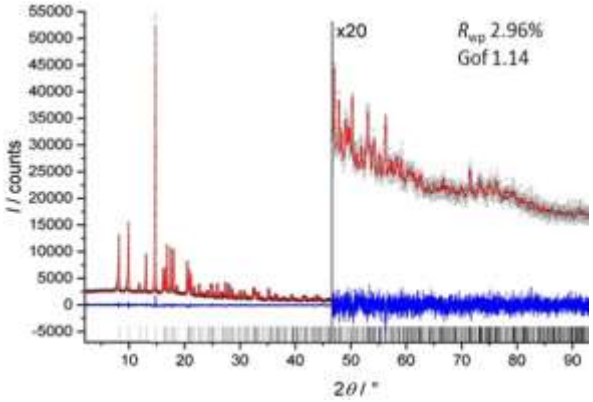
ABSTRACT: Over the last years, Pharmaceutical Industry has faced some drawbacks regarding the poor aqueous solubility and low bioavailability of several Active Pharmaceutical Ingredients (APIs) during drug development process. To overcome these issues, without changing the pharmacological behavior of the APIs, methods such as co-crystallization and salt formation are being employed.[1]

Amantadine is an anti-Parkinsonian API used to reduce some of the symptoms, such as askinesia and rigidity, and to improve motor fluctuations. This API has a very low aqueous solubility and also bioavailability limitations, when administrated as hydrochloric and sulfate salt forms.[2] In order to improve its physicochemical properties, we synthesized several new salts using different organic acid derivatives. The structural characterization of the compounds was performed using single crystal X-ray diffraction, DFT calculations, solid-state NMR and X-ray powder diffraction. DSC-TGA analysis and solubility tests are underway.[3] Here we report and discuss some of the interesting results, with major focus on structure determination using X-ray powder data.



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Hydrogel-membrane composite materials: promising materials for protein crystallization

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ABSTRACT: X-ray diffraction techniques allow obtaining of molecular structures at a resolution level at the moment not still surpassed by other techniques. However, obtaining crystal samples having quality suitable for diffraction experiment represents the bottleneck in the structure determination process, particularly in the case of protein molecules due to their weak intermolecular interactions, flexibility, and to the contribution of solvent on their aggregation. A turning point in this field could be represented by the use of new materials which could be able to extend the range of the experimental conditions able to trigger nucleation.[1] An example is represented by gel-mediated protein crystallization that is able to produce high quality crystals[2] that are particularly suitable for soaking experiments with drugs of foreign molecules due to their resistance to the osmotic stress.[3] However, the low consistency and fragility of the gel materials restricts the use of such technique for which a support for gel is required. Hydrophobic membranes have been already tested as support for protein crystallization, showing ability to modulate the solvent exchange and to trigger heterogeneous nucleation.[4] In addition, their flexibility makes them suitable as support for gels during crystallization experiments.

Here, we purpose an innovative approach for protein crystallization that exploit a material made of hydrogel and membrane able to combine the advantages of crystallization in gel with those of membrane-assisted crystallization.[5] Crystallization by hydrogel-membrane material has been tested on two proteins, leading to crystals that grow at lower protein concentration and having improved diffraction properties than those produced by means of conventional technique. As prospective, the material can be optimized to promote membrane proteins crystallization, for biomineralization, and non-classical mesocrystal structures.

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POSTER No. 30

Absolute Structure Determination of a light atom penta-peptide API using synchrotron radiation

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ABSTRACT: In drug discovery of new chiral active pharmaceutical ingredients, the determination of the absolute structure configuration is extremely important. Having the wrong enantiomer could be crucial or even devastating [1]. Single crystal X-ray diffraction is the most precise analytical method to confirm the absolute configuration. However, in order to do so, a single crystal is needed. In many cases growing single crystals could be very difficult or even "impossible". Crystallise! AG (Switzerland), a company dedicated to single crystal growth and X-ray characterization, has achieved unprecedented results in this area [2,3]. A single crystal of a light atom (C, H, N, O) penta-peptide API, was grown in only four weeks after receiving the sample. Other competitors had tried for a period of four years without success. Using synchrotron radiation Crystallise! succeeded not only in getting the crystal structure but also in confirming the absolute configuration [4].

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[3] https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/learn-more.html
[4] Crystal size: < 0.1 x 0.01 x 0.01 mm^3. The final criteria parameters for the Hooft Y = 0.01(16) and Hooft P3 statistic values = 0.991, 0.009, 0.000 were reliable enough to confirm the absolute configuration of the structure refined.

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