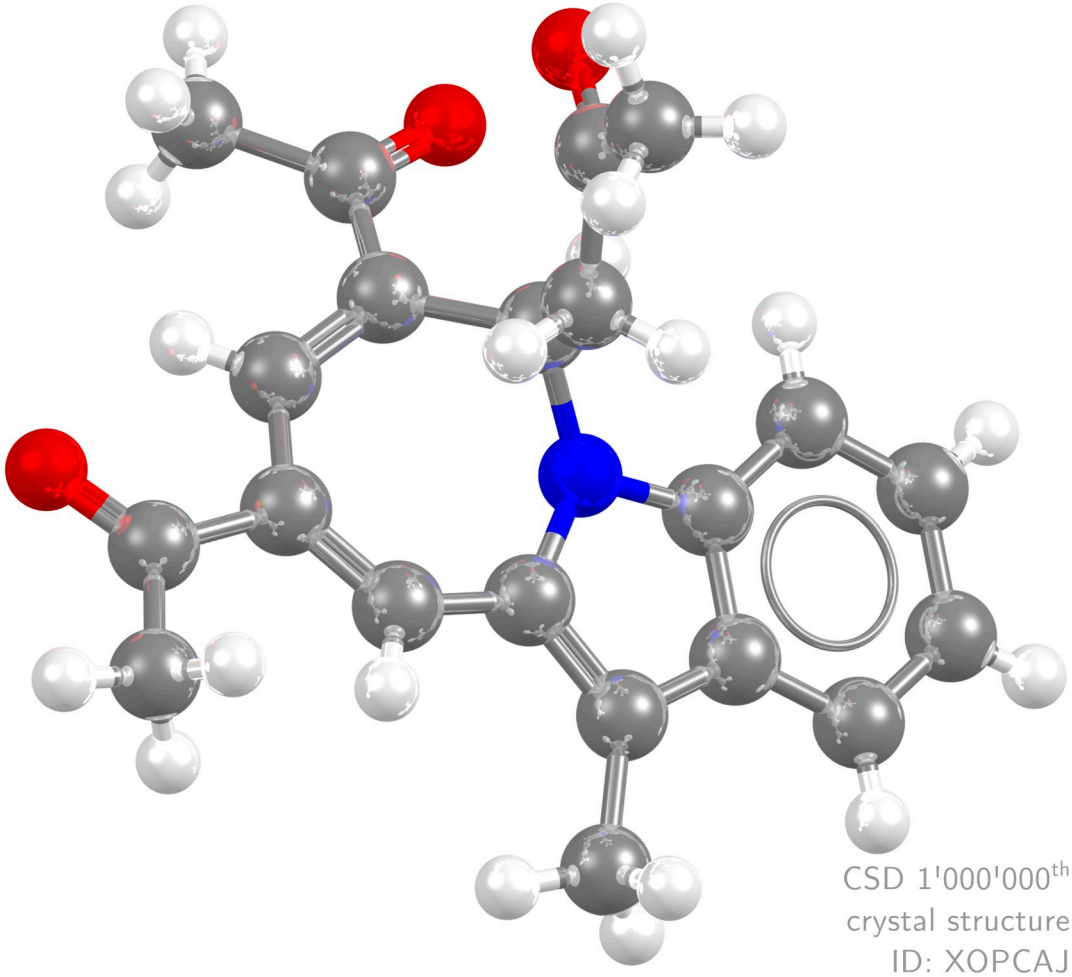
50th annual conference of the

British Association of Crystal Growth

BACG2019



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9-11 July **London**

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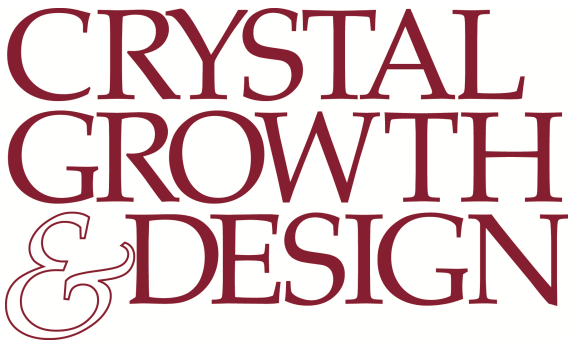
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About

Welcome to the BACG 50th Annual Conference.

Welcome to the 50^{th} meeting of the British Association of Crystal Growth (BACG). We can look back on how much the world has changed since the society was founded, and the role that crystalline materials have played in shaping our society. But the main purpose of our meeting is to look forward and discuss today's new insights into the materials that we have been studying, which will help shape tomorrow's world.

Our venues, in two of London's many Learned Society buildings, emphasises how scientists of like interests have come together to exchange ideas and uphold the best practices of the past in supporting the development of their fields. The Royal College of Obstetricians and Gynaecologists was established in 1929 in Manchester, with a Royal Charter in 1947 and moved to these premises in 1960. It had been considered a minor component of the Royal College of Surgeons, whose origins go back to the fourteenth century with the foundation of the Guild of Surgeons Within the City of London. The oldest national science society emerged from a dining club. The Royal Society, formally The Royal Society of London for Improving Natural Knowledge had its Royal Charter granted in 1660 by King Charles II, and moved to its current location in 1967. The research done by the members of the BACG and being presented at this meeting draws on many traditional disciplines.

The BACG at 50 is still maturing, and we can be agile and modern in our development. The annual meeting is the means when we can come together to exchange ideas, with the discussions of our wide range of lectures and posters, improving the science and disseminating best practice.

So thank you for coming to London to participate in this 50th meeting. I hope that you enjoy the conference, have scientifically worthwhile discussions and meet new people as well as catching up with friends.

Best Wishes
Sally Price

Local Organising Committee

Sally Price, UCL (Co-Chair)
Matteo Savalaglio, UCL (Co-chair)
Ghazala Sadiq, CCDC
Linda Seton, Liverpool John Moores
Joop ter Horst, Strathclyde
Bill Jones, Cambridge University

Scientific committee

Sally Price, UCL (Co-Chair)
Devis Di Tommaso, QMUL
Christoph Saltzmann, UCL
Matteo Savalaglio, UCL (Co-chair)
Jerry Heng, ICL
Luca Mazzei, UCL
Bill Jones, Cambridge University
Kreso Bucar, UCL
Asterios Gavriilidis, UCL

Timetable

Tuesday 9th July

08:30 Registration Opens / Morning Coffee

Plenary Session: Crystal Nucleation and Growth

Chair: Devis Di Tommaso (QMUL)
Room: Lecture Theatre

09:15 Introductory Remarks: Prof Sally Price (UCL, UK)

09:30 **Plenary: Michael Doherty**
University of California at Santa Barbara, US
Towards Digital Drug Product Design for Polymorph Selection and Crystal Growth

10:10 **Invited: Nora de Leeuw**
University of Cardiff, UK
Modelling the nucleation and growth of iron sulfides

10:40 **Kevin Roberts**
University of Leeds, UK
The Crystallisation Structural Pathway of Para amino Benzoic acid: From Solvated Molecule through Solute Clustering and Nucleation to the Growth of Facetted Crystals

11:10 Coffee Break

Crystal Nucleation and Growth

Chair: Elena Simone (University of Leeds)
Room: Lecture Theatre

11:30 **Kieran Hodnett**
University of Limerick, Ireland
Lifetimes of Adsorbed Active Pharmaceutical Ingredients on Heterosurfaces

11:50 **David Mackechnie**
University of Strathclyde, UK
Interfacial Supersaturation as the Driving Force for Heterogeneous Nucleation at Liquid-Liquid Interfaces

12:10 **Sarah Wright**
University of Manchester, UK
Unusual Conformations in Molecular Crystals

Experimental Techniques

Chair: Grahame Woollam (Novartis)
Room: U4/5 - The Collegiate Suite

Anuradha Pallipurath
National University of Ireland, Ireland
The effect of functional group terminations on organic crystal facets: A polarised Raman and computational study

Victoria Hamilton
University of Bristol, UK
In situ observation of organic crystal growth of a pharmaceutical using liquid cell electron microscopy

Elizabeth Willneff
University of Leeds, UK
Near-Ambient Pressure X-ray Photoelectron Spectroscopy: A New Laboratory Technique for Characterising Structure and Bonding at Surfaces of Molecular Crystals

12:30 Lunch & poster session

Executive committee meeting

13:00 **Poster Session & Sponsors Exhibition**

Plenary Session: Characterising, Modelling, and Controlling Polymorphism

Chair: Thomas Vetter (University of Manchester)
Room: Lecture Theatre

14:00 **Plenary: Allan Myerson**
Massachussets Institute of Technology, US
Nucleation of Organic Molecular Crystals on Surfaces and in Confinement

14:40 **Invited: Aurora Cruz Cabeza**
University of Manchester, UK
Joel Bernstein, polymorphism and I

15:10 **Invited: Doris Braun**
University of Innsbruck, Austria
Unravelling complexity in the solid form landscapes of pharmaceuticals

15:40 Coffee Break

Polymorphism

Chair: Linda Seton (Liverpool John Moores)
Room: Lecture Theatre

16:00 **Riccardo Montis**
University of Manchester, UK
Combining Crystal Structure Prediction and Structural Comparison with Experimental Screening: a Potential Route to More Polymorphs, Including a 2-for-the-price-of-1 Special.

16:20 **Jason Potticary**
University of Bristol, UK
Control of polymorphism in the three organic systems through the application of strong magnetic fields during crystal growth

16:40 **Martin Ward**
University of Strathclyde, UK
Recovery of high-pressure solid forms to ambient pressures

Experimental Techniques

Chair: Burak Eral (TU Delft)
Room: U4/5 - The Collegiate Suite

16:00 **Ian McPherson**
University of Warwick, UK
Surface Charge Analysis of Calcite Using Scanning Ion Conductance Microscopy

16:20 **Simon Clevers**
Université de Rouen, France
In situ X-ray for monitoring crystallization in solution : In-situX®

16:40 **Maxime Charpentier**
University of Strathclyde, UK
Phase diagram screening of chiral compounds with UV/CD spectroscopy

17:00 **AGM**

17:30 - 19:30 **Poster Session with drinks and BACG birthday cake**

Wednesday 10th July

09:00 Morning Coffee

Plenary Session: Bio-inspired Crystallization

Chair: Joop Ter Horst (Strathclyde)
Room: Lecture Theatre

09:30 **Plenary: Fiona Meldrum**
University of Leeds, UK
A Crystallisation Approach to Nanocomposite Crystals

10:10 **Invited: Wim Noorduin**
AMOLF, Netherlands
Shaping up bio-inspired functional materials

10:40 **Invited: Dominique Maes**
Vrije Universiteit Brussel, Belgium
Do protein crystals and aggregates go with the flow?

11:10 Coffee Break

Bio-inspired Crystallization

Chair: Jan Sefcik (Strathclyde)
Room: Lecture Theatre

11:30 **Fatima Ibis**
Delft University of Technology, Netherlands
Understanding Kidney Stone Formation: A microfluidic approach

11:50 **Ian Rosbottom**
Imperial College London, UK
A Novel Platform for Continuous Protein Crystallisation

12:10 **Alice Fayter**
University of Warwick, UK
Characterisation of the Effects on Ice Nucleation, Morphology and Growth upon Addition of Ice-active Compounds; a Biophysical Study

12:30 **Noushine Shahidzadeh**
University of Amsterdam, UK
The hopper growth of NaCl crystals

Co-Crystals and Formulation

Chair: Kreso Bucar (UCL)
Room: U4/5 - The Collegiate Suite

Huaiyu Yang
Loughborough University, UK
Jumping into Metastable 1:1 Urea-Succinic Acid Cocrystal Zones by Freeze-Drying

Marvah Aljohani
Galway University, Ireland
Influence of excipients on the stability of pharmaceutical cocrystals

Leila Keshavarz
University of Limerick, Ireland
Influence of Impurities on the Solubility, Nucleation, Crystallization and Compressibility of Paracetamol

Rafel Prohens
Universitat de Barcelona, Spain
Revisiting the Solid-State landscape of Sildenafil: New insights from an old drug

13:00 Lunch & poster session

13:30 **Poster Session & Sponsors Exhibition**

Awards Session

Chair: Bill Jones (Cambridge),
Room: Lecture Theatre

14:30 **BACG Young Investigator Award: Mark Holden**
University of Central Lancashire, UK
The role of active sites in heterogeneous ice nucleation

15:00 **BACG Annual Lecture: Leslie Leiserowitz**
Weizmann Institute of Science, Rehovot, Israel
Mode of action of quinoline antimalarial drugs in red blood cells infected by Plasmodium falciparum, revealed in-vivo

15:45 Break: preparation for the evening dinner at the Royal Society

Reception and Dinner at the Royal Society

18:00 Royal Society opens

18:30 Reception starts

19:00 **Conference Dinner, Awards presentation and Evening talk by Roger Davey**

Thursday 11th July

09:00 Morning Coffee

Plenary Session: Engineering Crystallization

Chair: Aurora Cruz-Cabeza (Manchester)
Room: Lecture Theatre

09:30 **Plenary talk: Marco Mazzotti**
ETH Zurich, Switzerland
On the Manipulation of the Size and Shape of Needle-like Crystals

10:10 **Thomas Vetter**
University of Manchester, UK
Design and optimization of isothermal and non-isothermal deracemization

10:40 **Yuri Abramov**
XtalPi, US
Modeling Support of Finite Pharmaceutical Crystal Growth

11:10 Coffee Break

Engineering Crystallization

Chair: Huaiyu Yang (Loughborough)
Room: Lecture Theatre

11:30 **Jose Capdevila Echeverria**
University of Strathclyde, UK
pH and Temperature Dependent Solubilities and Eutectic Points for the Continuous Chiral Resolution by Integration of Membrane and Crystallisation Technologies

11:50 **Johannes Hoffmann**
University of Strathclyde, UK
Serial Separation and Resolution in Eutectic Solutions

12:10 **Brigitta Bodák**
ETH Zurich, Switzerland
Model-based analysis of solid-state deracemization via temperature cycles

Nucleation and Growth

Chair: Virginia Burger (XtalPi)
Room: U4/5 - The Collegiate Suite

Yumin Liu
University of Manchester, UK
When crystals don't grow – the growth dead zone

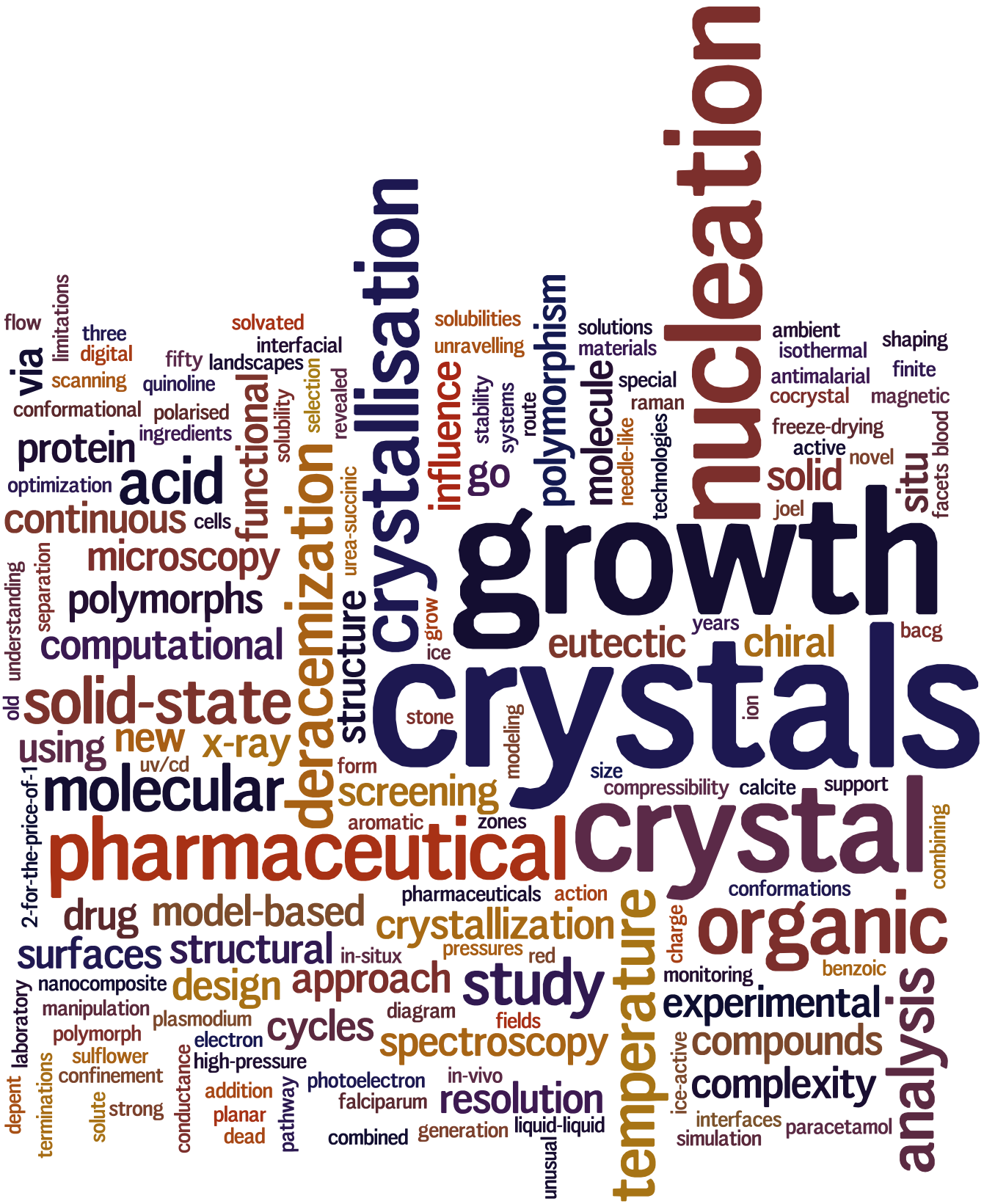
Torsten Jensen
University of Bristol, UK
A Planar Aromatic Molecule that Cannot Crystallise: A Combined Computational and Experimental Study of 2nd Generation Sulflower

Ilaria Gimondi
University College London, UK
Conformational complexity limitations to the simulation of the nucleation of succinic acid polymorphs

12:30 Closing Remarks - Joop ter Horst
University of Strathclyde, UK

12:40 Lunch

List of Abstracts – Talks



Tuesday 9th July

Plenary Session: Crystal Nucleation and Growth

Lecture Theatre

Towards Digital Drug Design for Polymorph Selection and Crystal Growth

M. F. Doherty[1], **M. Joswiak**[1], **T. Farmer**[1], **B. Peters**[2]

KL

[1] Chemical Engineering Department, UC Santa Barbara, CA, US
[2] University of Illinois at Urbana-Champaign

Most crystalline materials are capable of organizing into multiple distinct solid phases, each exhibiting a unique set of material properties (e.g., mechanical, optical, electronic, catalytic, etc.). This diversity of material properties implies that a specific solid form or structure is typically preferred for a specific application. However, only one polymorph is the thermodynamically stable solid phase, all others are metastable, which makes them difficult to obtain consistently and reproducibly via conventional batch crystallization. Thus, directing and controlling the desired solid form during crystallization is a fundamental solid-state engineering challenge. Here, a general procedure is presented for continuous crystallizers that consistently produces crystals of a preferred polymorph regardless of that polymorph's relative thermodynamic stability. The design rules have been validated both by experimental data generated in our lab and by all of the applicable data in the published literature. The polymorph selection rules depend on the absolute growth rates of each polymorph, which are difficult to measure over a wide range of temperatures and supersaturations. So the challenge is to predict them from molecular models. We report on a procedure using rare-event molecular simulation and mechanistic growth models to predict absolute crystal growth rates (e.g., in units of nm/s). To accomplish this task it is necessary to predict the absolute attachment and detachment rates of growth units into kink sites. This can now be done for sodium chloride crystals grown from aqueous solution.

Modelling the nucleation and growth of iron sulfides

N. H. d. Leeuw[1], **U. Terranova**[1]

[1] School of Chemistry, Cardiff University, Cardiff CF10 3AT, United Kingdom

Iron-sulfur phases have been implicated in the formation of the primordial organic molecules at hydrothermal vents [1]. In particular, mackinawite, conventionally assumed to be the initial precipitate in the iron sulfide series of minerals, has been of increasing interest owing to the fact that its FeS layers may provide compartments for water reacting at the interface. However, the adsorption of ions and molecules on mineral surfaces is also affected by the structural and dynamical properties of interfacial water, with implications for all reactions taking place at the interface. In the first part of this talk, we present a classical molecular dynamics investigation of the properties of water at the interface with the most exposed (001) surface of mackinawite [3]. We find water in the first layer to be characterised by structural properties which are reminiscent of hydrophobic substrates, with the bulk behaviour being recovered beyond the second layer. In addition, we show that the mineral surface reduces the mobility of interfacial water compared to the bulk and discuss also the important differences introduced by simulating water under conditions of high temperature and pressure, a scenario relevant to the conditions at hydrothermal vents. In the context of life's emergence on early Earth, the discovery of an undocumented nano-particulate phase [2], FeS_{nano}, which is a necessary solid-phase precursor to mackinawite, is likely to play a crucial role. In the second part of this talk, we extend the molecular dynamics investigation to a system formed by water intercalated between the sheets of mackinawite, focussing on its energetics. We discuss the energy per water molecule and the spacing between the FeS layers as a function of water content. Finally, we emphasise the significance of these results to FeS_{nano}.

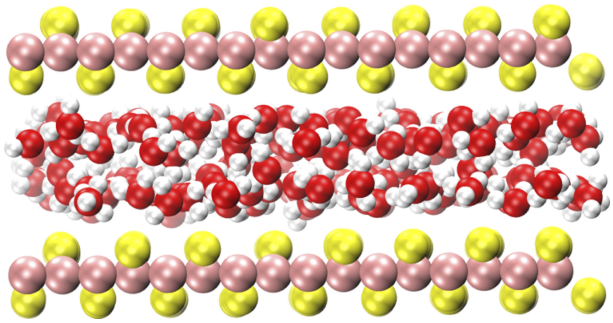


Figure 1: Water intercalated between the sheets of FeS mackinawite.

References

[1] W. Martin and M. J. Russell, Philos. Trans. R. Soc., B 2003, 358, 59-85

[2] A. Matamoros-Veloza, O. Cespedes, B. R. G. Johnson, T. M. Stawski, U. Terranova, N. H. de Leeuw and L. G. Benning, Nat. Commun., 2018, 9, 3125

[3] U. Terranova and N. H. de Leeuw, J. Chem. Phys., 2016, 144, 094706

The Crystallisation Structural Pathway of Para amino Benzoic acid: From Solvated Molecule through Solute Clustering and Nucleation to the Growth of Facetted Crystals

K. Roberts[1], R. Hammond[1], X. Lai[1], C. Ma[1], J. Pickering[1], I. Rosbottom[1], T. Turner[1], G. Xi[1]

[1] University of Leeds, Centre for the Digital Design of Drug Products, School of Chemical Process Engineering, University of Leeds LS2 9JT, UK

In solution phase crystallisation processes, understanding and controlling the transition pathway associated with the assembly of molecules from their solvated state, into three-dimensional, ordered crystalline-solids, represents a significant grand challenge for the physical-chemical sciences. Crystallisation can be sub-divided into three-dimensional nucleation and two-dimensional, surface-mediated, crystal growth stages. Understanding and controlling the various physico-chemical aspects associated with these two stages is important mindful of their impact upon the critical quality attributes of the resulting product crystals. In particular, the nucleation stage directs the crystal size distribution, crystallinity and polymorphic form whilst the crystal growth stage directs crystal purity, morphology, surface properties and inter-particle properties. This paper presents an integrated multi-technique examination of the crystallisation behaviour of the two polymorphic forms of para amino benzoic acid (PABA) encompassing both computational modelling and experimental studies.

Acknowledgements: Funding support gratefully acknowledged from: Molecules, clusters and crystals: A multi-scale approach to understanding kinetic pathways in crystal nucleation from solution (EPSRC Critical Mass Grant EP/I014446/1) and ADDoPT: Advanced digital design of pharmaceutical therapeutics" (Advanced Manufacturing Supply Chain Initiative Grant No. 14060).

Parallel Session: Crystal Nucleation and Growth

Lecture Theatre

Lifetimes of Adsorbed Active Pharmaceutical Ingredients on Heterosurfaces

V. Verma[1], J. Zeglinski[1], S. Hudson[1], P. Davern[1], B. K. Hodnett[1]

[1] Synthesis and Solid State Pharmaceutical Centre (SSPC), Bernal Institute, Department of Chemical Sciences, University of Limerick. Limerick V94 T9PX, Ireland.

The crystallization of seven active pharmaceutical ingredients (APIs) (acetaminophen (AAP), carbamazepine (CBMZ), caffeine (CAF), phenylbutazone (PBZ), risperidone (RIS), clozapine base (CPB) and fenofibrate (FF)) was studied in the absence and presence of heterosurfaces. Two of the APIs, namely AAP and CBMZ, possess hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) functionalities whereas the other five possess HBA functionality only. The smallest nucleation rate enhancement was observed for CBMZ at 1.4 times and the largest was observed for FF at 16 times[1]. Arising from this study, a model of heterogeneous crystallization was developed wherein two influencing factors were identified. The first involves the issue of hydrogen bond complementarity between heterosurface and API. Hence, a HBD-rich heterosurface will provide a hydrogen-bond mediated option for API cluster formation that would otherwise not be specifically available in solution to APIs possessing HBAs only. The second factor identified is that the lifetime of the hydrogen bond made by an individual API molecule or small API cluster with the heterosurface is up to 1,000 times longer than (i) the lifetime of API-API interactions in a solution phase, or (ii) the time required for an API molecule to add to a growing crystal. Molecular modelling using the 'Adsorption Locator' module of Materials Studio indicate that the enthalpy of adsorption for the studied API molecules on Lactose is very similar to the enthalpy of adsorption of the same molecules adsorbed onto its own crystals supporting the concept that the lifetimes of API molecules on heterosurfaces are extended. This lifetime effect arises from the greater stability of an adsorbed species, and this extended lifetime increases the probability that other molecules or small clusters of the API in solution will add to the already adsorbed or attached species thus encouraging the heterogeneous route to crystallization.

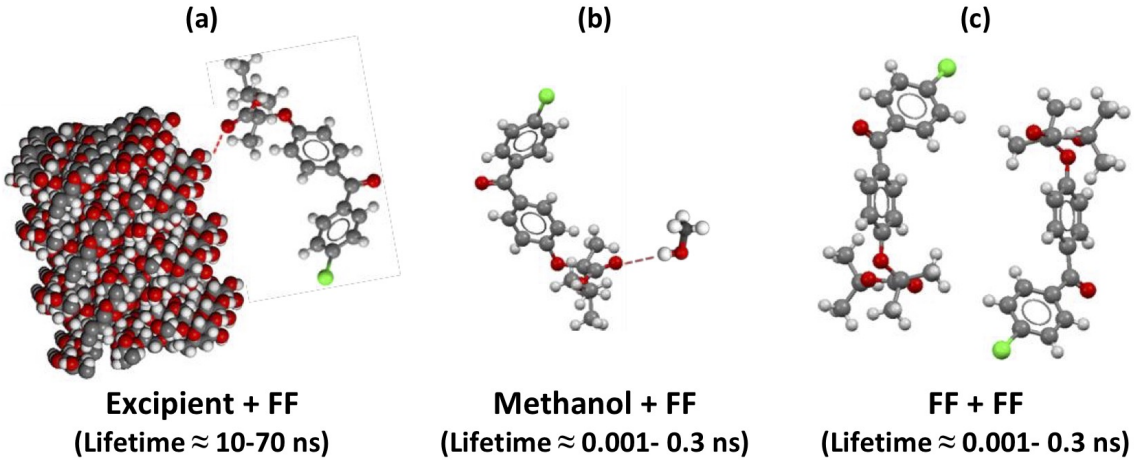


Figure 1: (a) Molecular representation of interactions between (a) excipient and FF, (b) methanol and FF, (c) FF and FF; along with respective lifetime of each interaction.(a) Excipient + FF (Lifetime 10-70 ns), (b) Methanol + FF (Lifetime 0.001- 0.3 ns), (c) FF + FF (Lifetime 0.001- 0.3 ns).

References

[1] Verma, V., J. Zeglinski, S. Hudson, P. Davern, and B.K. Hodnett, Crystal Growth Design, 2018, 18, 7158- 7172

Interfacial Supersaturation as the Driving Force for Heterogeneous Nucleation at Liquid-Liquid Interfaces

D. McKechnie[1,2], **S. Zahid**[1], **P. A. Mulheran**[1], **J. Sefcik**[1,3], **K. Johnston**[1]

[1] Department of Chemical and Process Engineering, University of Strathclyde, Glasgow, UK
[2] Doctoral Training Centre in Continuous Manufacturing and Advanced Crystallisation, University of Strathclyde, Glasgow, UK
[3] EPSRC Future Manufacturing Hub in Continuous Manufacturing and Advanced Crystallisation, University of Strathclyde, Glasgow, UK

Crystallisation experiments are often performed in small-scale setups, such as microfluidics and microwells, to enable high throughput. In these experiments small volumes of solution are partially or fully surrounded by immiscible liquids and the high interface area to volume ratio could allow heterogeneous nucleation at the interface to dominate. The aim of this work is to experimentally measure the heterogeneous crystallisation rate for a model system of aqueous glycine solution in contact with tridecane and use molecular dynamics simulations to provide insight into the observed differenc es in rate between oil and air interfaces. A large number of vials of aqueous glycine solution with concentrations ranging between 275– 333 g/kgsolv ent and with a layer of tridecane covering the solution were prepared at high temperatures, cooled, and monitored by webcam to determine their isothermal induction times. At 275 g/kgsolv ent 63% of samples with an oil interface nucleated within three days, with 83% and 95% nucleating at 307 and 333 g/kgsolv ent respectively. In contrast, vials of aqueous glycine solutions with concentrations in the range 275–450 g/kgsolvent without tridecane had a negligible nucleation rate, with only 5% nucleating at the highest concentration, and 0% at lower concentrations. This significant difference in nucleation rate demonstrates the profound effect the interface has on nucleation behaviour. Classical molecular dynamics simulations of glycine solution in contact with tridecane were used to provide insight to the behaviour of the system at the interface. Figure 1 shows concentration and density profiles. The glycine concentration at the interface is approximately 1.5 times higher than the overall system concentration giving a local supersaturation that would drive crystal nucleation. Simulations of an air interface show the opposite effect with a greatly reduced concentration at the interface. This difference in glycine concentration between the oil and air interfaces explains the difference in nucleation rate observed in experiments. We believe that this effect may often enhance heterogeneous nucleation at liquid-solution or solid-solution interfaces compared to that at air- solution interfaces (e.g., nucleation of glycine at PTFE interfaces [1]). Future work will continue to explore these effects.

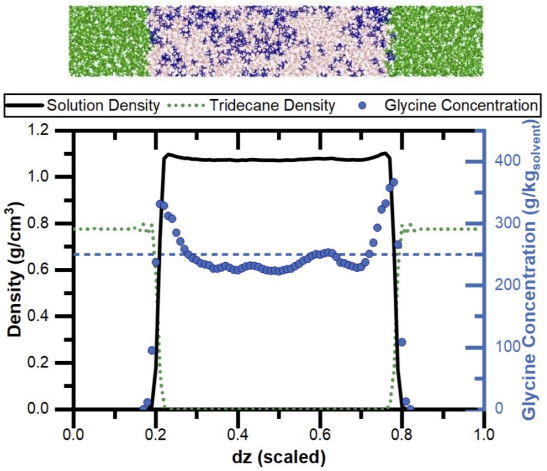


Figure 1: Top: Snapshot of glycine solution with tridecane. Glycine, water and tridecane molecules are blue, red and green, respectively. Bottom: Density profiles (primary axis) of glycine solution and tridecane, and concentration profile (secondary axis) of glycine.

References

[1] M. J. Vesga et al., CrystEngComm, 2019, 21, 2234

Unusual Conformations in Molecular Crystals

S. Wright[1], **M. Bryant**[2], **R. J. Davey**[1], **A. J. Cruz-Cabeza**[1]

[1] School of Chemical Engineering and Analytical Science, University of Manchester, United Kingdom
[2] Cambridge Crystallographic Data Centre, Cambridge, United Kingdom

The molecular complexity and size of novel drug molecules is ever increasing, and so is their conformational flexibility. Complex flexible drug compounds are often challenging to crystallise. Crystallisation is the final step in the manufacture of active pharmaceutical ingredients and with over 90% of pharmaceuticals being crystalline it is important to understand and control this process. The poor crystallisation behaviour of flexible molecules has been linked to conformational diversity in solution.[1,2] In solution, conformers are in equilibrium and their relative populations depend on their relative stabilities. If a crystal conformation is similar to that of a stable conformer in solution, no conformational change or adjustment would need to occur for the system to nucleate and grow.[3] However, if the crystal conformation corresponds to a highly distorted conformation or a higher-energy conformer, then significant conformational adjustment or change would need to occur during crystallisation.[4] Such conformational changes and adjustments may limit crystal growth and are the subject of the present research. We have investigated the occurrence of unusual conformations in the Cambridge Structural Database (CSD) for various subsets of molecular crystals. Torsion angles in flexible molecules were classified as being unusual when they were observed in less populated areas of the CSD torsion distributions. We then applied the concepts of conformational change and adjustment to create new definitions of unusual conformations which reflect the possibility that unusual may refer to two different conformational processes or the combination of both. It may relate to a highly adjusted conformation, a high energy conformer or a highly adjusted high energy conformer. Making these distinctions in the unusual nature of conformers is important and may have different implications for drug polymorphism and ease of crystallisation.

References

[1] L. Derdour, S. K. Pack, D. Skliar, C. J. Lai and S. Kiang, Chem. Eng. Sci., 2011, 66, 88–102.
[2] L. Yu, S. M. Reutzel-Edens and C. A. Mitchell, Org. Process Res. Dev., 2000, 4, 396–402.
[3] A. J. Cruz-Cabeza and J. Bernstein, Chem. Rev., 2014, 114, 2170–2191.
[4] H. P. G. Thompson and G. M. Day, Chem. Sci., 2014, 5, 3173–3182.

Parallel Session: Experimental Techniques

The effect of functional group terminations on organic crystal facets: A polarised Raman and computational study

Anuradha Pallipurath[1,2], Jonathan M Skelton[3,4], Andre Erxleben[1], Patric McArdle[1]

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[2] School of Chemical and Process Engineering, University of Leeds, Clarendon Road, Leeds, LS2 8JT, UK
[3] Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK
[4] School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Understanding and controlling crystal surfaces is a critical problem in contemporary materials science, especially in the field of pharmaceuticals. Organic crystal surfaces present the additional complexity of multiple possible terminations with different functional groups, which can vary based on the solvent and the method used for crystallisation. These alternate terminations influence the surface chemistry and control many material properties, including morphology, dissolution, and adhesion with excipients and hence downstream processing parameters. While established tools for surface characterization exist, few provide the chemical information required to unambiguously identify functional groups. Polarized Raman spectroscopy is a versatile tool that can provide detailed chemical information on molecular materials, and, when used in a microscope configuration, can be used to map substrates on a micron scale. We have used polarized Raman spectroscopy to study the surface chemistry of aspirin grown from acetone, showing the presence of monomeric carboxylic acid groups H-bonded to water on the <100> surface.[1] These were absent on the surfaces of crystals grown from dimethyformamide and by vacuum sublimation. By analysing crystals grown under a variety of conditions, we relate the growth solvent to the surface termination and reconcile the conflicting results in the literature on the nature of the <100> surface. Our results are supported by detailed first-principles modelling of the surface structure, energetics and vibrational spectra. This study establishes the potential of polarized Raman microscopy as a tool for organic surface science that, particularly when combined with predictive modelling, provides a powerful means to understand and ultimately control surface chemistry.

References

[1] A.R.Pallipurath, J.M.Skelton, A.Erxleben, P.McArdle, Crystal Growth and Design, 2019, 19, 2, 1288-1298

In situ observation of organic crystal growth of a pharmaceutical using liquid cell electron microscopy

V. Hamilton[1], **J. Cookman**[2], **U. Bangert**[2], **S. R. Hall**[1]

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Liquid phase early-stage nucleation and growth of organic crystals have remained hard-to-observe events due to their size and the inherently dynamic and sensitive nature of the system involved. Electron microscopy has typically been overlooked for probing organic crystal growth due to the need to protect beam sensitive materials from the vacuum with coatings or cryo-temperatures [1]. However, recent developments in thin-film technologies allows for liquid sample to be flowed through a cell while inside a transmission electron microscope [2]. This liquid cell electron microscopy (LCEM), allows for observations of liquid phase events in situ. A liquid cell coupled with low-dose capabilities and high-speed camera provides unprecedented temporal and spatial observations of liquid phase events even of beam-sensitive organic materials. Here, a solution of a common non-steroidal anti-inflammatory, flufenamic acid (FFA), in organic solvent (ethanol) was syringe pumped through a liquid cell. Nucleation of dense amorphous clusters and growth of hexagonal FFA crystals were observed using low-electron dose rates (figure 1). These hexagonal crystals agree well with the predicted morphologies of form I FFA, one of the two room-temperature polymorphs of FFA, calculated using the Bravais-Friedel-Donnay-Harker (BFDH) method [3]. However, observation without impacting the system remains a difficulty and compromises between continuous detailed observation and irradiation of the crystallisation remain key difficulties. It is suspected that radiolysis effects from the high-energy beam are inducing the crystallisation process.

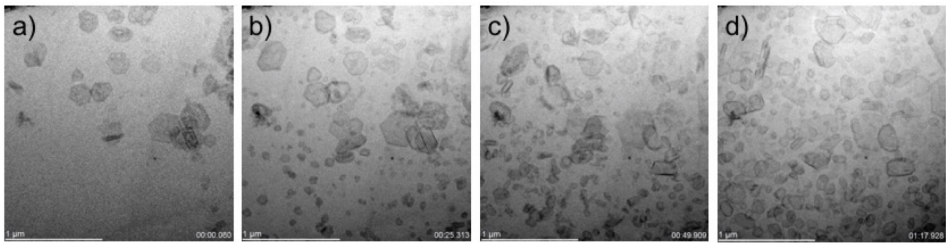

Figure 1: Frames from a video showing the nucleation and growth of flufenamic acid crystals in ethanol at (a) 1s, (b) 25s, (c) 50s and (d) at 77s.

References

[1] Shi, Dan, et al. "The collection of MicroED data for macromolecular crystallography." Nature protocols 11.5 (2016): 895.

[2] Hermannsdörfer, J. de Jonge, N. Studying Dynamic Processes of Nano-sized Objects in Liquid using Scanning Transmission Electron Microscopy. J. Vis. Exp. (2017). doi:10.3791/54943

[3] C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek and P. A. Wood, J. Appl. Cryst., 41, 466-470, 2008

Near-Ambient Pressure X-ray Photoelectron Spectroscopy: A New Laboratory Technique for Characterising Structure and Bonding at Surfaces of Molecular Crystals

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It is commonly recognised that a deep understanding of the molecular structure and composition of surfaces is a central prerequisite for establishing the molecular basis of nucleation and crystal growth as well as the behaviour of organic materials under processing conditions and in formulations[1]. However, the surface science of organic crystals lags almost half a century behind that of inorganic materials. As a result, the experimental basis for understanding phenomena such as crystal growth, adsorption, and facet-specific effects is relatively undeveloped[2]. X-ray photoelectron spectroscopy (XPS) is the most widely used surface analysis technique, but its application in small organic molecule surface science has so far been surprisingly limited. The main reasons for this are: (i) the prohibitively high vapour pressures of most organic materials; the most widely available surface analyses have traditionally relied on electron spectroscopies with electrostatic energy analysers, which require ultra-high vacuum conditions; (ii) the lack of methods for preparing sufficiently clean and well-defined organic surfaces; standard surface cleaning methods employ destructive ion etching followed by high temperature annealing, which cannot be applied to obtain stoichiometric organic crystal surfaces; and (iii) almost all molecular matter is electrically insulating, leading to charge build-up at the sample surface under conditions of electron irradiation and electron emission, making high resolution analysis with electrostatic energy analysers laborious.

In this contribution we will demonstrate how the latest generation of near-ambient pressure XPS equipment overcomes these limitations, permitting studies of local interactions and surface phenomena not only for organic materials, but also for truly volatile matter, for example solutions of organic solutes in water and other solvents and formulations containing volatile components. This will be shown in case studies from a variety of organic materials. For example, in the case of imidazole it will be shown how NAP XPS sensitively probes the protonation state of nitrogen in both the solid and liquid state. Data on paracetamol will show how important cleanliness can be for surface analysis.

References

1. G.R. Desiraju, J Chem Sci, 2010, 122, 667.
2. R.J. Davey, S.L.M. Schroeder, J.H. ter Horst, Angewandte Chemie International Edition, 2013, 52 (8), 2166.

Plenary Session: Characterising, Modelling, and Controlling Polymorphism

Lecture Theatre

Nucleation of Organic Molecular Crystals on Surfaces and in Confinement

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Crystallization is vital to many processes occurring in nature and manufacturing. In chemical, pharmaceutical and food industries, crystallization from solution is widely used for a variety of materials. It is an attractive isolation step during manufacturing as particle formation and purification are combined within a single process. Almost all of the products based on fine chemicals, such as dyes, explosives and photographic materials, require crystallization in their manufacture and over 90% of all pharmaceutical products contain bioactive drug substances and excipients in the crystalline solid state. Hence it is necessary to control the crystallization process in order to obtain products with desired and reproducible properties. The quality of a crystalline product is usually judged by four main properties: size, purity, and morphology (shape) and crystal structure. It is vital in pharmaceutical industry to produce the desired crystal form (polymorph) to assure the bioavailability and stability of the drug substance. It is also important to produce the desired particle shape and size distribution to allow mixing of API with excipient and the formation of the final drug product. Nucleation is the first step of the crystallization process and control of nucleation is crucial in forming crystals of the desired properties and of the desired polymorphic form. Surfaces are well known to influence nucleation and polymorphism. In this talk we will present work on the role of crystalline and polymer surfaces on nucleation and polymorphism or organic molecular crystals. In addition, recent work on biocompatible polymer surfaces imprinted with nanopores of various geometries which are used as heteronucleants will be presented as will work on the nucleation within nanopores of silicon dioxide.

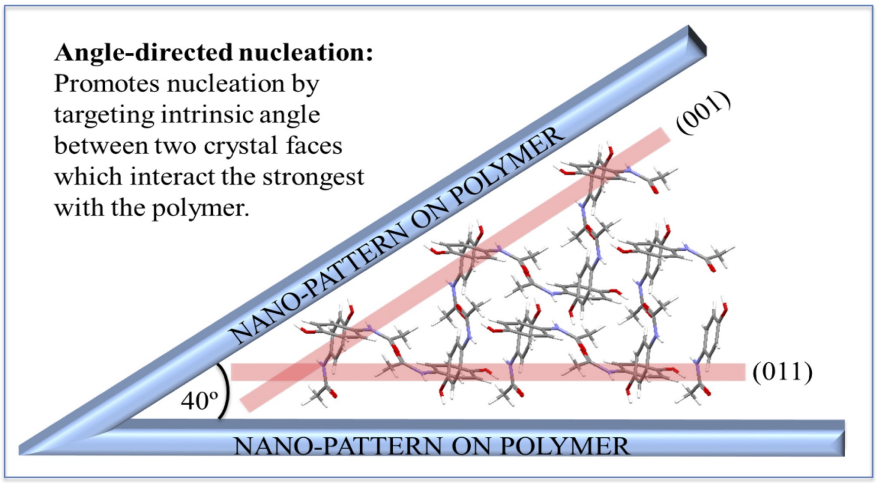

Figure 1: Angle Directed Nucleation.

References

[1] J. Stojaković, F. Baftizadeh, M. A. Bellucci, A. S. Myerson, and B. L. Trout, Crystal Growth Design, 2016.

Unravelling complexity in the solid form landscapes of pharmaceuticals

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Crystalline forms are essential to all industries that rely on fine-tuning material properties for optimal product performance. [1] Yet, elucidating the solid form landscape, structure relationships, transformation pathways and thermodynamics of any fine chemical can be an enormous challenge. This is exemplarily demonstrated for two pharmaceuticals, whose solid-state behaviour could only be unravelled by combining experiment and theory. [2,3] Experimental and computational screening for dapsone solid forms resulted in five neat forms (I – V), fifteen solvates, a hydrate and its isomorphic dehydrate. Calorimetric measurements, solubility experiments and lattice energy calculations revealed that a new polymorph, form V, is the thermodynamically stable form from absolute zero to at least 90. The discovery of form V, 100 years after the compound was first synthesised, was complicated by the fact that the metastable but kinetically stabilised form III shows a higher nucleation and growth rate than the most stable form. Only seven of the eleven observed forms of gandotinib crystallised directly from solution, form I, two hydrates and four solvates. The four remaining forms (II and three hydrates) were produced by (de)hydration processes. Interconversion of the anhydrates and hydrates with small changes in the relative humidity complicated identifying and characterising the forms. A key feature of this system is that the chlorofluorophenyl ring of gandotinib in the various solid forms is disordered, but to different extents. The computed crystal energy landscape of the compound showed that stable form I belongs to a large family of very similar low energy structures, all higher in lattice energy than the global minimum. By taking into account the contribution of disorder to the total free energy, form I is calculated to be energetically competitive with lowest energy structure. To conclude, the survey of the crystal chemistry of dapsone and gandotinib has revealed inconvenient truths about solid form landscapes and the efforts that are sometimes required to identify solid forms and to characterise relevant properties. Only a careful exploration of solid form landscapes will deepen our understanding of solid form properties and uncover nuances in crystallisation behaviour that can guide process and product design.

References

[1] J. Bernstein, Polymorphism in Molecular Crystals, Clarendon Press: Oxford, 2002

[2] D. E. Braun and U. J. Griesser, DOI:10.1021/acs.molpharmaceut.9b00419

[3] D. E. Braun, J. A. McMahon, R. M. Bhardwaj, J. Nyman, M. A. Neumann, J. van de Streek and S. M. Reutzel-Edens, Cryst. Growth Des. 2019, 19, 2947

Parallel Session: Characterising, Modelling, and Controlling Polymorphism

Lecture Theatre

Combining Crystal Structure Prediction and Structural Comparison with Experimental Screening: a Potential Route to More Polymorphs, Including a 2-for-the-price-of-1 Special.

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Although our current knowledge on polymorphism had been advancing significantly over past years, this fascinating topic still represents a challenging aspect of structural crystallography and solid-state chemistry. Despite the major enhancements in experimental and computational methods, the highly successful calculations invariably predict far more feasibly acceptable structures than are experimentally found, even when extensive experimental screenings are made. Possible reasons for this discrepancy have been previously suggested but still questions such as Why don't we find more polymorphs? remain open. [1] In this work we explore the idea that detailed crystal structure comparisons of predicted and experimental polymorphs may represent a further useful tool for polymorph screening. The identification of structural similarities and differences might help in discriminating which structure, within the crystal energy landscape, would seem likely to be experimentally isolated. [2] This information might be also used to identify whether pairs or groups of structures are so closely related to convert one into the other, during the nucleation/crystal growth stages or by proper solid-solid phase transitions, preventing the observation of some potential metastable forms. To follow these objectives, we compared experimental and predicted structures from the previous results of a CSP study by Asmadi et al. [3] on a group of three rigid, planar small molecules of known crystal structures, 2-methyl-, 3-methyl- and 2,3-dimethyl-benzo[b]thiophene 1,1-dioxide. The results of the crystal structure comparison of the ten lowest energy predictions from the CSP calculations for each derivative with the known, unique experimental crystal structures are discussed. A short experimental screening leading to the discovery of three new polymorphs is also presented.

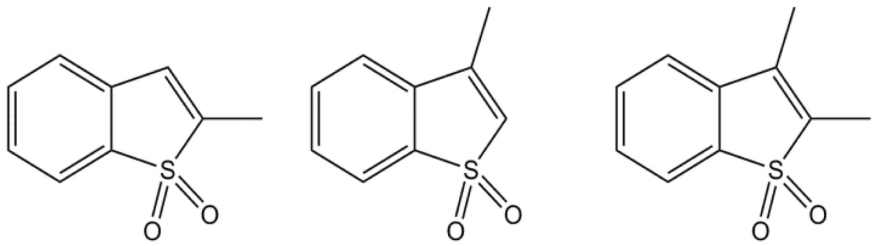

Figure 1: 2-methyl-, 3-methyl- and 2,3-methyl-benzothiophene-1,1-dioxides (2-MBTD, 3-MBTD and 2,3-DBTD.

References

[1] S. L. Price, Acta Cryst,. 2013. B69, 313–328
[2] L. Price, D. E. Braun and S. M. Reutzel-Edens Chem. Commun., 2016, 52, 7065-7077
[3] A. Asmadi, J. Kendrick, and F. J. J. Leusen, Chem. Eur. J., 2010, 16, 12701–12709

Control of polymorphism in the three organic systems through the application of strong magnetic fields during crystal growth

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Crystals of three separate organic molecules, the anti-epilepsy drug carbamazepine, an analgesic and anti-inflammatory flufenamic acid and the polyaromatic hydrocarbon coronene have been shown to exhibit preferential growth of a specific polymorph when grown during the application of strong magnetic fields. Here we report the first systematic experimental and computational investigation of polymorph control by magnetic fields during crystallization. In these three polymorphic systems, experimental crystallization inside a homogeneous and static magnetic field has been able to reproducibly produce one polymorph over the one which normally crystallizes outside the magnetic field. In some cases, significant undercooling of the crystallization process is also observed. In an attempt to explain this phenomenon, these data, combined with first principles calculations of crystal diamagnetic susceptibilities, we consider the thermodynamic effects of the magnetic field. We propose that polymorphs close in free energy, but which possess a large difference in the anisotropy of their diamagnetic susceptibility tensors, can have their relative thermodynamic stability affected by a magnetic field. When this is not possible, the magnetic field may still be able to control the crystallization process by inhibiting the crystallization of a more stable form, thus facilitating the crystallization of the metastable form according to Oswald's rule of stages. Consideration is also given to the size of stable clusters in solution within these systems in order to further determine the precise role of the field.

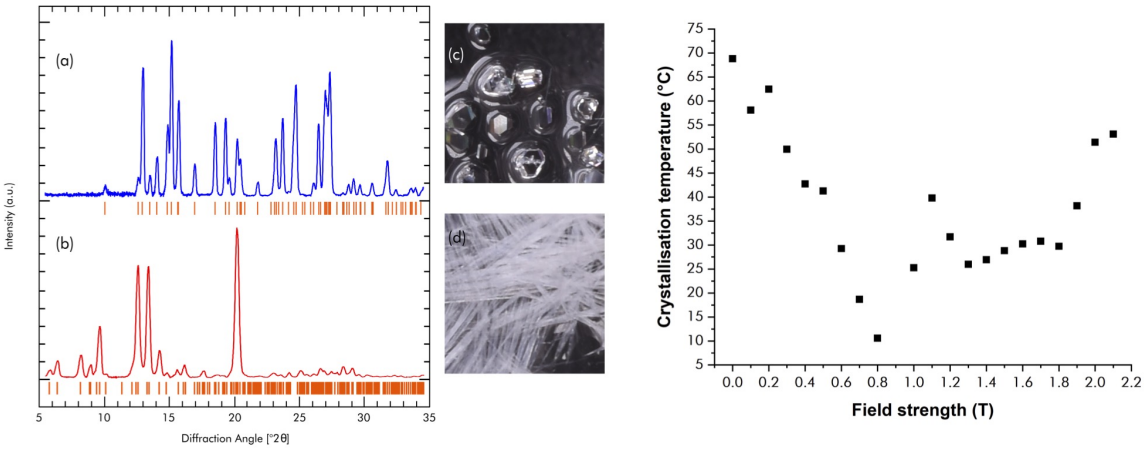

Figure 1: How carbamazepine is affected by a magnetic field when grown. Powder diffraction patterns and optical images of carbamazepine grown without ((a) and (c) – Form III) and with ((b) and (d) Form I) a magnetic field present. (e) demonstrates how a magnetic field can increase the supersaturation of the system is increased via inhibition of crystallisation.

Recovery of high-pressure solid forms to ambient pressures

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The discovery and study of new solid forms is a continual challenge in the field of solid-state science. The driving force behind this is the possibility that a new solid form of a given material might exhibit improved properties in comparison to the former e.g. increased solubility, improved mechanical properties. The use of high-pressure crystallographic methods has proven to be a highly efficient way to obtain new solid forms.1–3 Typically, these studies make use of a diamond anvil cell (DAC) to provide a high-pressure environment (0.1-100's GPa) with the sample crystal monitored by single crystal X-ray diffraction (SCXRD) during compression/decompression. The main limitation of traditional high-pressure methods is that if a new solid form is discovered that is also recoverable to ambient pressure then only a small, single particle of the material is obtained. Harvesting a single particle does not allow for straightforward evaluation of important material properties such as flowability, rheology and thermal properties. Furthermore, using a single crystal to seed a crystallization process to scale up production is challenging. In recent work, we have investigated the use of a large volume press to obtain high-pressure solid forms and successfully recover them back to ambient pressure in significant quantity (100-1000's mg) through compression or by anti-solvent addition at high pressure (approx. 0.8 GPa). Through these studies we have demonstrated the ability to obtain high pressure solid forms of para-aminobenzoic acid (delta polymorph),4 gamma-aminobutyric acid (GABA monohydrate), paracetamol (Orthorhombic, polymorph II) and maleic acid (polymorph II).

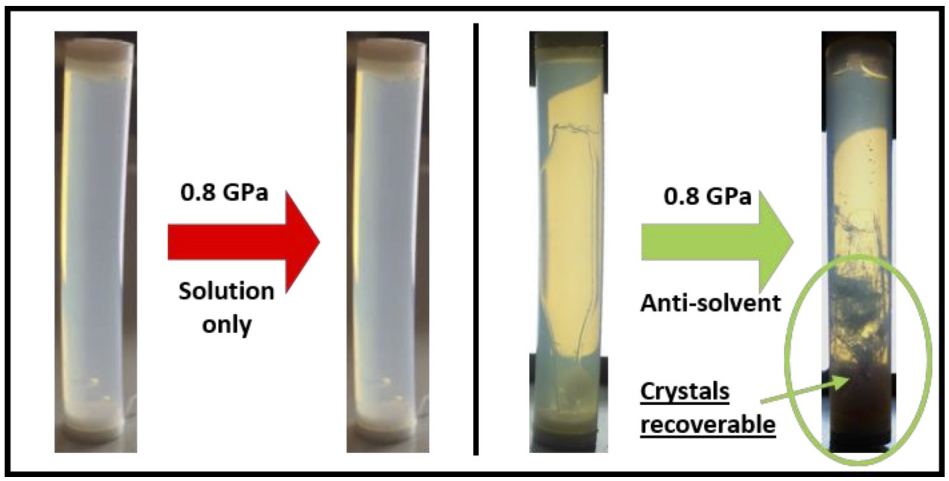

Figure 1: Illustration of anti-solvent addition process at high-pressure conditions

References

[1] M. A. Neumann, J. van de Streek, F. P. A. Fabbiani, P. Hidber and O. Grassmann, Nat. Commun., 2015, 6, 7793.
[2] R. D. L. Johnstone, A. R. Lennie, S. Parsons, E. Pidcock and J. E. Warren, Acta Crystallogr. Sect. B-Structural Sci., 2009, 65, 731–748.
[3] I. D. H. Oswald, I. Chataigner, S. Elphick, F. P. A. Fabbiani, A. R. Lennie, J. Maddaluno, W. G. Marshall, T. J. Prior, C. R. Pulham and R. I. Smith, CrystEngComm, 2009, 11, 359–366.
[4] M. R. Ward, S. Younis, A. J. Cruz-Cabeza, C. L. Bull, N. P. Funnell and I. D. H. Oswald, CrystEngComm, 2019, 21, 2058–2066.

Surface Charge Analysis of Calcite Using Scanning Ion Conductance Microscopy

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The charge on mineral surfaces in solution has implications for both fundamental understanding, e.g. of crystal growth mechanisms, and applications, e.g. describing ion adsorption and speciation in the environment.[1–3] However, measurement of surface charge is non-trivial, often requiring the sample to be either a finely dispersed powder, to allow titration or electrophoresis measurements, or be a macroscopic single crystal, to carry out streaming potential measurements. Furthermore, as ensemble measurements, they are not sensitive to the local variation in charge with topography, as predicted by simulation.[3] Scanning ion conductance microscopy (SICM), in contrast, utilises a 100 nm glass pipette to detect local ion conductance (and hence concentration) as a function of position in 3D space (Figure 1). Previously we have shown that with a knowledge of how ion conductance changes at the surface compared to the bulk it is possible to determine the charge on the surface.[4] Here we use this technique to study the surface charge of calcite microcrystals under a range of solution conditions. Results are compared to existing surface complexation models as well as molecular dynamics simulations.

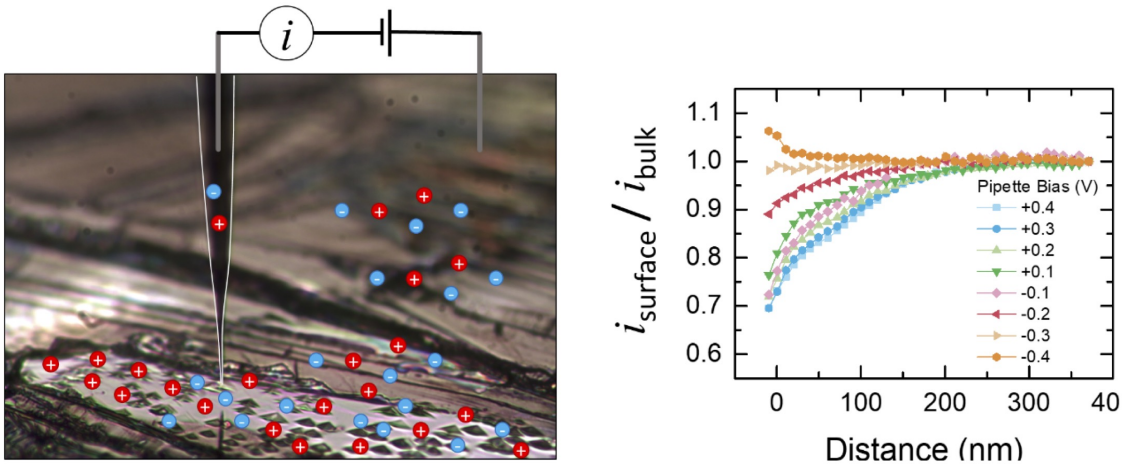

Figure 1: Scanning ion conductance microscopy uses current flowing through a glass nanopipette to measure local ion concentration as a function of position. Measurements show an increase in cation concentration at the surface of a cleaved calcite crystal.

References

[1] P. Van Cappellen, L. Charlet, W. Stumm, P. Wersin, Geochimica et Cosmochimica Acta 1993, 57, 3505–3518.
[2] M. Wolthers, L. Charlet, P. Van Cappellen, American Journal of Science 2008, 308, 905–941.
[3] M. Wolthers, D. D. Tommaso, Z. Du, N. H. de Leeuw, Phys. Chem. Chem. Phys. 2012, 14, 15145–15157.
[4] K. McKelvey, S. L. Kinnear, D. Perry, D. Momotenko, P. R. Unwin, J. Am. Chem. Soc. 2014, 136, 13735–13744.

In situ X-ray for monitoring crystallization in solution : In-situX®

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Introduction Crystal growth from solution is widely used in many fields for industrial crystallizations (e.g. pharmaceuticals, food chemistry) as well as for academic purposes (e.g. solvent-assisted phase transitions). To fully understand crystallization processes, it is essential to know all of the solid phases that may appear in suspension. In this context, a new laboratory prototype based on X-ray diffraction to perform in-situ analyses directly in the crystallization reactor was developed: In-situX® technology [1]. In-situX® is designed to monitor crystallizations directly inside a reactor by means of XRPD. The sample (e.g. mixture of solid and liquid) is placed in a double-jacketed reactor and analyzed in suspension without any sampling (Figure 1). The reactor is mounted in a Bruker® D8 diffractometer inverted geometry ($-\theta$ /$-\theta$) goniometer. The temperature of the reactor can be accurately controlled in a wide temperature range (-70degC/+70degC) without any icing. The sample is analyzed in real-time at the bottom of the reactor (thin membrane transparent to X-rays, mechanically and chemically resistant) all along crystallization processes. Applications of the In-situX® technology In-situX® has already proved its efficiency to deal with characterization of new solid forms, for polymorphic identifications, polymorphic screening, solvent assisted solid-solid transitions, crystallization of hydrates, solvates or co-crystals, for purification and resolution processes and during maturation of solid phases.[1] In-situX® can be also used for studying solid/vapor equilibria in order to analyze the stability of solvates (hydrates). Through selected examples among possibilities cited above, this presentation aims at proving the efficiency of In-situX® technology to characterize suspensions during a crystallization process.

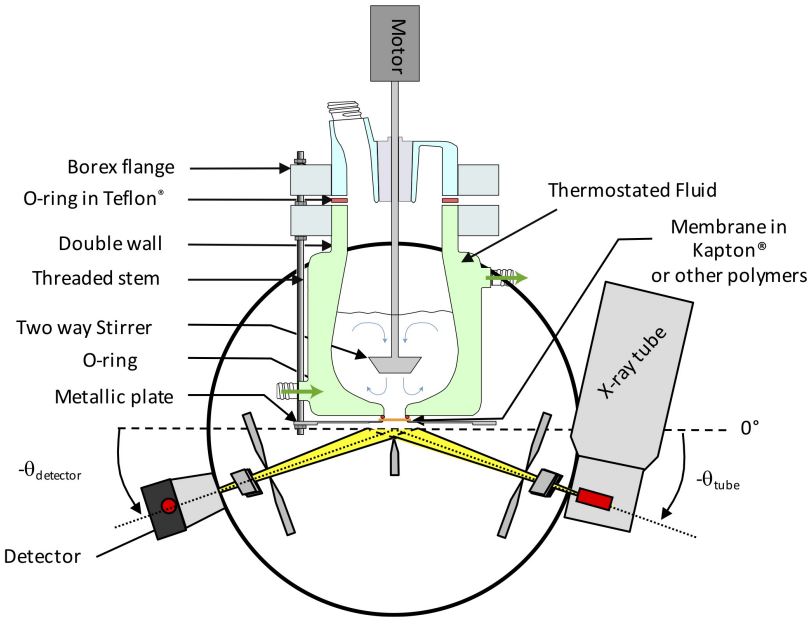

Figure 1: Schematic view of the reactor and the goniometer geometry in the In-situX® technology

References

[1] G. Coquerel, M. Sanselme, and A. Lafontaine, US9255898B2 patent, 2014 Coquerel G., Clevers S., EP18305580.5 patent, 2018

[2] H. Takahashi, S. Iwama, S. Clevers, S. Veesler, G. coquerel, H. Tsue, and R. Tamura, Crystal Growth Design, vol. 17, no. 2, pp. 671–676, 2016.

Phase diagram screening of chiral compounds with UV/CD spectroscopy

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Phase diagrams are important for understanding thermodynamics of multicomponent systems and to determine crystallization processes, especially for the development of chiral resolution processes for chiral compounds. Phase diagrams become quite complex as the number of components increases, leading, for example for co-crystal formation in a racemic solution, to quaternary systems (Figure 1 (left)). Building chiral compound phase diagrams usually requires the use of a chiral HPLC, which is an expensive and time-consuming analysis technique. In this work, we propose an alternative approach for building chiral phase diagrams using UV/Circular Dichroism (CD) spectroscopy. This is, to our knowledge, the first time that this technique is applied to phase diagram determination. This study presents the UV/CD spectroscopy method for measuring equilibrium component concentrations and enantiomeric excess in suspension liquid phases. In this new approach, we re-evaluate phase diagrams of two model systems obtained from previous work using chiral HPLC [1]. The first model system is levetiracetam and its opposite enantiomer in acetonitrile, describing a racemic compound ternary phase diagram type. UV and CD signal calibration using the pure enantiomer solution leads to the determination of total enantiomer concentration in solution, and enantiomeric excess, respectively. The predicted results from the fit, agree well with the reference data, validating the method and the phase diagram shown on Figure 1. The second model system is a co-crystal forming phase diagram between levetiracetam and (S)- mandelic acid in acetonitrile. Due to signal superimposition for both UV and CD, a multivariate technique was used on CD spectra to fit a model for both components compositions. Results slightly differ from the original work and a new phase diagram has been proposed. In both cases, the measured saturated concentrations have been validated by identified solid phases by XRPD, sampled from equilibrated suspensions. Obtained phase diagrams gave consistent and promising results, proving this technique could be a good alternative to chiral HPLC. The multivariate technique suggests the possibility to work in more complex systems like chiral quaternary phase diagrams, which is currently being pursued.

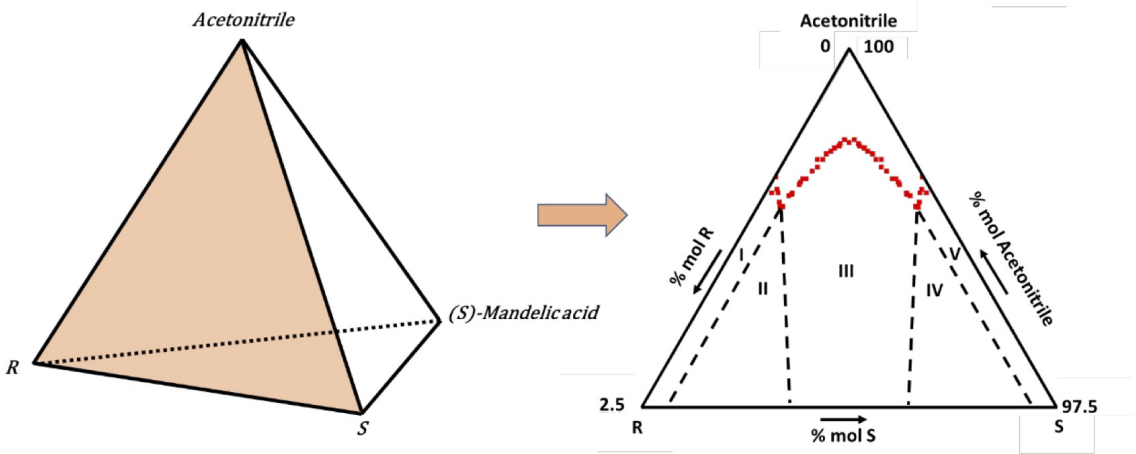

Figure 1: Zoom in R/S/Acetonitrile isothermal ternary phase diagram from the model quaternary system

References

[1] Springuel, G.; Collard, L.; Leyssens, T. CrystEngComm 2013, 15, 79517958

Plenary Session: Bio-inspired Crystallization

Lecture Theatre

A Crystallisation Approach to Nanocomposite Crystals

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The production of crystalline materials with structures and properties resembling those of biominerals is a challenging synthetic goal that is relevant to a wide range of technologies, including the formation of nanomaterials, ceramics and biomaterials. A characteristic feature of biominerals is that they are invariably composite materials in which organic macromolecules are associated with the inorganic phase. Indeed, even incorporation levels of just a few weight percent leads to a significant enhancement of the mechanical properties. This talk will describe how this biogenic strategy can be employed to generate synthetic crystals with novel nanocomposite structures and properties. Occlusion-species ranging from micron-scale particles, to organic and inorganic nanoparticles, to small molecules have been incorporated within calcite single crystals using a simple one-pot method, where very high levels of occlusion can be achieved according to the particle surface chemistry and growth conditions. As examples, the incorporation of anionic block copolymer micelles results in composite crystals with structures and mechanical properties comparable to those of biominerals, and the incorporation process can be studied in real time using AFM. At an order of magnitude smaller, the occlusion of amino acids provides insight into the origin of the superior mechanical properties of biominerals. Our strategy has also been extended to the synthesis of nanocomposites comprising inorganic nanoparticles uniformly distributed throughout a single crystal matrix. Notably, exceptional levels of incorporation of gold nanoparticles within host calcite crystals – such that the nanoparticles are separated by just 4-5 nm – could be achieved by functionalising the nanoparticles with low-charge polymers and proteins. This surprising result can be attributed to the fact that these low-charge organics give the nanoparticles significant colloidal stability in the crystallisation solution, while also adsorbing strongly to the crystal surface. It also challenges current ideas about biomineralisation, where the role of low-charge proteins has been largely neglected. This methodology can potentially be applied to a huge number of nanoparticle/ host crystal systems, where its experimental simplicity makes it an attractive and general method for generating composite materials.

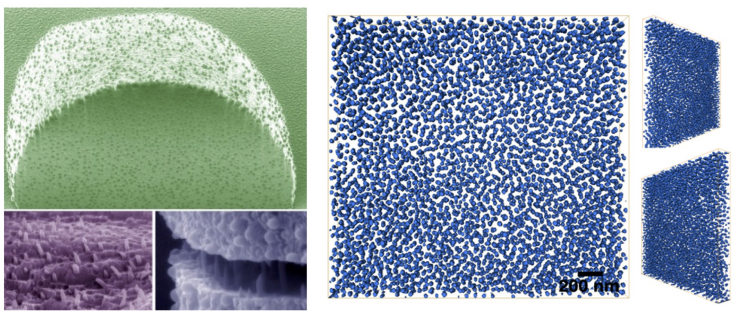

Figure 1: (Left) calcite single crystal containing latex particles, and after fracture, and (Right) electron tomograms of a calcite single crystal containing gold nanoparticles.

Invited contribution, sponsored by the Dutch Association for Crystal Growth

Shaping up bio-inspired functional materials

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Harnessing the basic principles that guide such crystallization processes is of fundamental scientific interest, but also promises a paradigm shift in the manufacturing of nano- and micromaterials. We recently demonstrated that the subtle balance between the diffusion of reactants and their reaction rates could lead to a wide range of microscopic shapes that could be further sculpted and hierarchically organized by rationally modulating the environmental conditions1-4. In this presentation we present new ways to steer the nucleation and growth of mineralizing microstructures and construct functional micromaterials. These results contribute to our understanding of fundamental crystallization processes in artificial and biomineralization processes and outline a new nano-fabrication strategy for functional self-organizing materials.

Figure 1: Hierarchically organized micro architectures.

References

[1] W. L. Noorduin, A. Grinthal, L. Mahadevan, J. Aizenberg, Science, 2013, 340, 832.
[2] C. N. Kaplan, W.L. Noorduin, L. Li, L. Folkertsma, J. Aizenberg, L. Mahadevan, Science, 2017, 355, 1395-1399.
[3] T. Holtus, L. Helmbrecht, H. C. Hendrikse, I. Baglai, S. Meuret, G. W. P. Adhyaksa, E. C. Garnett, W. L. Noorduin, Nature Chemistry, 2018, 10, 740.
[4] L. Li, A. J. Fijneman, J. A. Kaandorp, J. Aizenberg, W. L. Noorduin, Proceedings of the National Academy of Sciences, 2018, 115, 3575.

Invited contribution, sponsored by the Belgian Association for Crystal Growth

Do protein crystals and aggregates go with the flow?

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We will elaborate on the effect of flow on crystallization. Both theory and experiments have indicated that flow affects the nucleation rate, the size of the emerging phase and polymorphism. To enable detailed quantitative studies on the influence of shear flow on nucleation and growth, we have developed a new microfluidic setup that creates a controlled constant shear flow profile in a solution. The results indicate that shear rates promote nucleation and decrease solubility, not only in the supersaturated and metastable zones of the phase diagram, but also in the undersaturated zone. A monotonicly increasing nucleation rate was observed. With the unique shear rates that have been used in the present study, combined with the on-chip observation and crystallization, it is anticipated that the presented methodology can shed light on a variety of phase transitions that are influenced by flow. Our experimental results are complemented by kinetic Monte Carlo simulations. We focused on the dynamics of crystallization and the effect of impurities on step growth. For over 50 years, all discussions of impuritystep interaction have been framed in the context of the CabreraVermilyea (CV) model for step blocking. Our kinetic Monte Carlo simulations clearly falsify the CV model. Flows parallel to the crystal face and perpendicular to the step affect step growth in predictable ways depending on their direction: flows in the opposite direction of the growth raise the local supersaturation and enhance step velocity while those parallel the direction of step growth lower the local supersaturation and can even lead to dissolution of the crystal. Surprisingly, the combination of the two effects on an island causes spontaneous transport of the island in the opposite direction of the flow. We find strong, unexpected effects of flow parallel to the step face: effects strong enough to overcome step pinning by impurities.

Parallel Session: Bio-inspired Crystallization

Lecture Theatre

Understanding Kidney Stone Formation: A microfluidic approach

F. Ibis[1], P. Dhand[1], T. W. Yu[1], S. Suleymanli[1], D. Ganguly[1], R. Pleeging[2], U. Staufer[2], A. v. d. Heijden[1], H. Kramer[1], H. B. Eral[1]

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Nephrolithiasis can be seen as crystallization of salt and consequent aggregation in the presence of biologic complicity in kidney. The most common compound observed in kidney stones is considered to be calcium oxalate monohydrate (COM) crystals. Our aim is to improve the current understanding of the crystallization mechanism involved in kidney stones formation under controlled flow conditions. To this end, we start with a comparative solubility study of COM as a function of temperature and pH. We conducted evaporation, titration, inductively coupled plasma optical emission spectrometry (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS). Measurements of ICP-OES and ICP-MS show more consistent values with higher repeatability than evaporation and titration. We observe that COM solubility is a weak function of temperature. Furthermore, when the body temperature conditions are considered, it is seen that the solubility of COM at low pH is slightly higher than at high pH. Getting accurate solubility measurements of COM is initial and vital part of this project. Moreover, this knowledge will be used to evaluate of crystal formation in vitro models. Mimicking kidney stone formation with Lab on chip technology may provide unique insight for in vivo studies which reduce the time-scale drastically. We designed and 3D-printed different types of microfluidic devices for two essential aims. Firstly, the designed of collecting duct chip is used to induce in vitro crystallization. In experiments we are looking for COM formation originated from hypercalciuria. We mimic the condition of hypercalciuria which can happen because of high calcium content in urine. We evaluate whether the overlapping of results of simulation and experiments depended on crystal distribution and supersaturation ratio. Secondly, we generate micro droplets which can act as micro reactors to analyse induction time in the presence of potential inhibiting agents. We are still testing the conditions with different supersaturation ratios from 10 to 80 to determine the appropriate range required to evaluate the induction time.

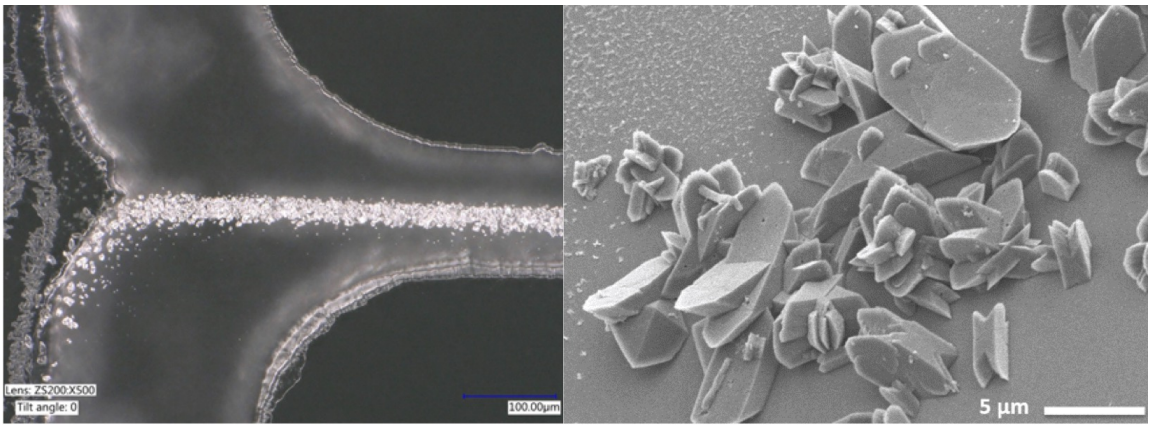

Figure 1: Formation of COM in Microfluidic device.

A Novel Platform for Continuous Protein Crystallisation

I. Rosbottom[1], **H. Yang**[1], **W. Chen**[1], **P. Pezculis**[1], **P. Ingua**[1], **X. Li**[1], **J.Y.Y. Heng**[1]

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Crystallisation of proteins could be a potentially cost effective and robust method to purify next generation of protein based biopharmaceutic therapies. However, the step from traditional small-scale high throughput screening methods (hanging drop, sitting drop etc.) of producing proteins, to crystallisers which can produce much higher yields of pure crystalline protein material, is still in its infancy. Here, we present a platform for continuous oscillatory flow crystallisation (COFC) (Figure 1) and its application for the crystallisation of lysozyme [1,2]. In addition, a workflow is developed from l screening experiments, to scaled up batch oscillatory flow crystallisation (BOFC) and COFC experiments, to identify the optimum conditions to produce highly crystalline lysozyme particles of desirable sizes and shapes. The optimum pH and precipitant solutions for lysozyme crystallisation have been well established from the literature and are used in this study. The initial lysozyme concentration, the amplitude and frequency of the oscillations are varied, whereby the set-up of the platform allows for the observation of their impact on the crystallisation kinetics and particle properties. The induction time for lysozyme is found to be inversely proportional to the initial protein concentration, with the same relationship found between the induction time and the frequency and amplitude of the oscillation. However, it is also observed that the decrease in induction time will have an impact on the crystal size and quality. This can be due to the high concentration resulting in many nuclei, which compete for solute molecules in solution, ultimately resulting in many smaller crystals with a wider crystal size distribution. In turn, the high shear environment from increased amplitude and frequency of the COFC can also damage the fragile protein crystals, resulting in the formation of more fine particles and an undesirable size distribution. Work around optimisation of the crystallisation parameters and crystalliser geometry using the GCrystal platform to find the optimum scale up conditions are also discussed. Further, the use of seeding and potential templating materials is also covered with a view to expanding the use of this crystallizer to less well characterized protein materials.

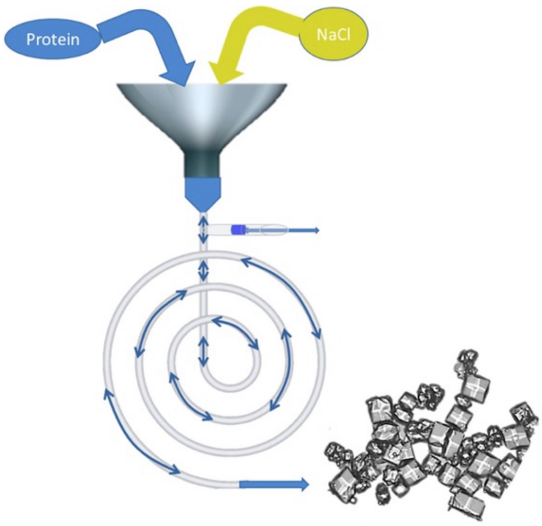

Figure 1: Schematic of the continuous oscillatory flow crystallisation platform

References

[1] H. Yang, W. Chen, P. Peczulis, J.Y.Y. Heng (2019): Development and Workflow of a Continuous Protein Crystallization Process: A Case of Lysozyme, Cryst. Grow. Des; 19, 983-991.

[2] H. Yang, P. Peczulis, P. Inguva, X. Li, J.Y.Y. Heng (2018): Continous Protein Crystallisation Platform and Process: Case of Lysozyme, Chem. Eng. Res. Des. 136, 529-53

Characterisation of the Effects on Ice Nucleation, Morphology and Growth upon Addition of Ice-active Compounds; a Biophysical Study

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Nature has evolved a series of adaptations to enable life to flourish in sub-zero climates. One such adaptation is the production of antifreeze proteins from polar fish species, which prevent the growth of ice crystals. Ice crystal growth is a major problem in cell/tissue cryopreservation, as well as for technological applications such as icing of aircraft wings. This work studies the field of synthetic macromolecular (polymer) mimics of antifreeze proteins by examining the effect of different compounds on ice crystal morphology and growth, molecularly as well as macroscopically, with the aim of elucidating mechanisms of action and enabling the production of more active, less toxic polymer mimics of biomacromolecular antifreezes. Two macroscopic effects investigated are ice recrystallization inhibition (IRI) activity and dynamic ice shaping (DIS). Microscopy, and for the first time, wide angle X-ray scattering (WAXS), were used. WAXS enabled the collection of more accurate and thorough results than the traditional microscopy methods. Microscopy also fails to give molecular insight and operate on long time scales, thus we used solid-state NMR to probe the ice dynamics in the presence of antifreeze proteins alongside potent synthetic mimics. We obtained molecular measurements of PVA demonstrating ice binding and established links between proteins and synthetic materials. These results have significance in basic cryo-science and to help develop new materials for extreme low temperature applications.

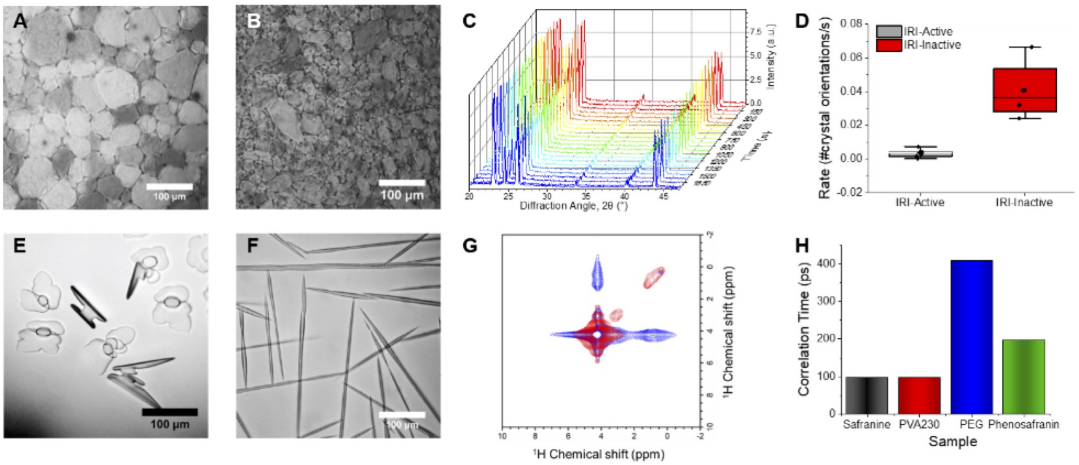

Figure 1: Figure 1 Examples of different macroscopic and molecular effects on ice crystals upon the addition of ice-active molecules. Microscopy analysis of A) Ice crystals formed in PBS control and B) Smaller ice crystals formed with addition of IRI-active PVA; C) Example waterfall plot of ice diffraction pattern over time and D) rates in change of ice crystal orientations obtained from analysis of waterfall plots for samples. Results from analysis of DIS of E) pure water and F) water with added IRI-active antifreeze (glyco)protein. Example solid-state NMR results of G) 2D EXSY of PVA binding to ice and H) Correlation times of IRI-active molecules (black and red) compared to their negative controls (blue and green).

References

[1] Gibson, M. I. Slowing the growth of ice with synthetic macromolecules: beyond antifreeze(glyco) proteins. Polym. Chem., 2010 1, 1141

[2] Voets, I. K. From ice-binding proteins to bio-inspired antifreeze materials. Soft Matter, 2017, 13, 4808–4823

[3] Biggs, C. I. et al. Polymer mimics of biomacromolecular antifreezes. Nat. Commun., 2017, 8, 1546

The hopper growth of NaCl crystals

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In nature, crystals generally are rarely found only in their equilibrium state; instead, many minerals and salts appear as clusters of interconnected crystalline regions known as hopper crystals[1-3]. . Although, such hopper crystals is common to many substances and minerals, such as bismuth, quartz, calcite, and halite (NaCl) but the mechanism of their formation had not been elucidated experimentally before. Here we investigate the growth of sodium chloride, the most abundant salt on the earth and present in various applications, by performing experiments at microscale, in confinement with micro volumes. In this way, we have been able to measure the supersaturation at the onset of nucleation as well as the morphology of the crystal and its speed of growth by direct visualization under the microscope. We show that sodium chloride crystals that grow very fast from a highly supersaturated solution form a peculiar form of hopper crystal consisting of a series of connected miniature versions of the original cubic crystal[1,3]. We report for the first time that the transition between cubic and hopper growth happens at a well-defined supersaturation of 1.45 which corresponds to the point where the growth speed of the cubic crystal reaches a maximum (6.51.8 m/s). Above this threshold, since cubic growth is limited by the incorporation of ions into the surface, the only way to incorporate more ions from the supersaturated solution is then to create new surfaces. The overall growth rate order of the hopper morphology is found to be 3, confirming that a new mechanism, controlled by surface integration of new molecules, induces the new mechanism of skeletal growth of cubic crystals in cascade. The results are in immediate importance for our understanding of salt nucleation and growth in general and for gaining a better control over the crystal structure. In addition, since the crystal morphology dictates the dissolution rate, it has a significant impact on various applications such as pharmacology and for the food industry. For the latter NaCl is the main seasoning ingredients on food industry and the control over the crystal structure is an important variable to consider as a strategy to reduce sodium reduction while maintaining salt intensity and saltiness perception in the food.

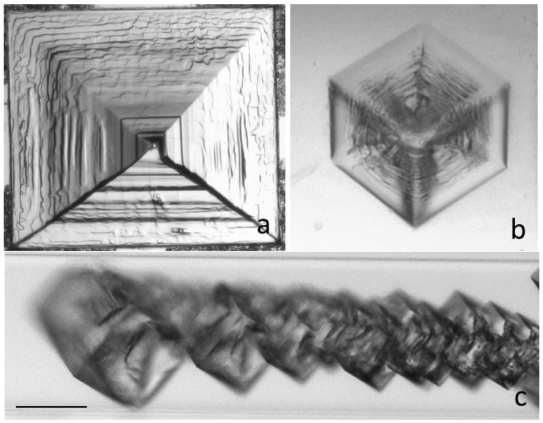

Figure 1: Different morphology of sodium chloride crystals as hopper growth: a) hollow pyramide b) hollow cube c) skeletal growth (1).

References

[1] J.Desarnaud; H.Derluyn; J.Carmeliet; D.Bonn;N. Shahidzadeh. J. Phys. Chem. Lett. 2018, 9 (11), pp 2961–2966

[2] A. Naillon; P. Joseph; M .Prat.; Phys. Rev. Lett , 2018, 120, 034502.

[3] J.Desarnaud , H.Derluyn, J. Carmeliet, D.Bonn, N.Shahidzadeh. J. Phys. Chem. Lett. 2014, 5, 890–895.

Jumping into Metastable 1:1 Urea-Succinic Acid Cocrystal Zones by Freeze-Drying

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Cocrystals formed by an active pharmaceutical ingredient (API) with a co-former can improve solubility, dissolution rate, stability [1-3]. Urea and succinic acid (SA) can form thermodynamically stable 2:1 urea and succinic acid (U-SA) cocrystal and metastable 1:1 U-SA cocrystal. By evaporation in aqueous solution, 2:1 cocrystals or mixtures always form [4,5], shown in the ternary phase diagram of 2:1 cocrystal in Figure 1, but 1:1 cocrystals do not appear due to the instability. By frozen and freeze-drying, the 1:1 U-SA cocrystals formed. The products of 1:1 cocrystal and mixtures with it obtained in freeze-drying revealed metastable zones related to 1:1 cocrystal, which split the 2:1 cocrystal + SA zone to five zones, (i) 1:1 cocrystal zone, (ii) 1:1 cocrystal + 2:1 cocrystal zone, (iii) 1:1 cocrystal + 2:1 cocrystal + SA zone, (iv) 1:1 cocrystal + SA zone, and (v) 2:1 cocrystal + SA zone. The formation of the 1:1 cocrystal indicated that the solution composition points in the phase diagram "jump" over the stable zone (2:1 cocrystal + SA zone) into the metastable zones (1:1 cocrystal zones). The crystallisation processes during the frozen and freeze-drying were complicated, and the formation of metastable 1:1 cocrystal should be due to high supersaturation during the nucleation, and it also determined by ratios between urea and succinic acid, concentrations, and frozen speeds. The establishing and understanding of the phase diagrams are essential to design and control the crystallisation processes.

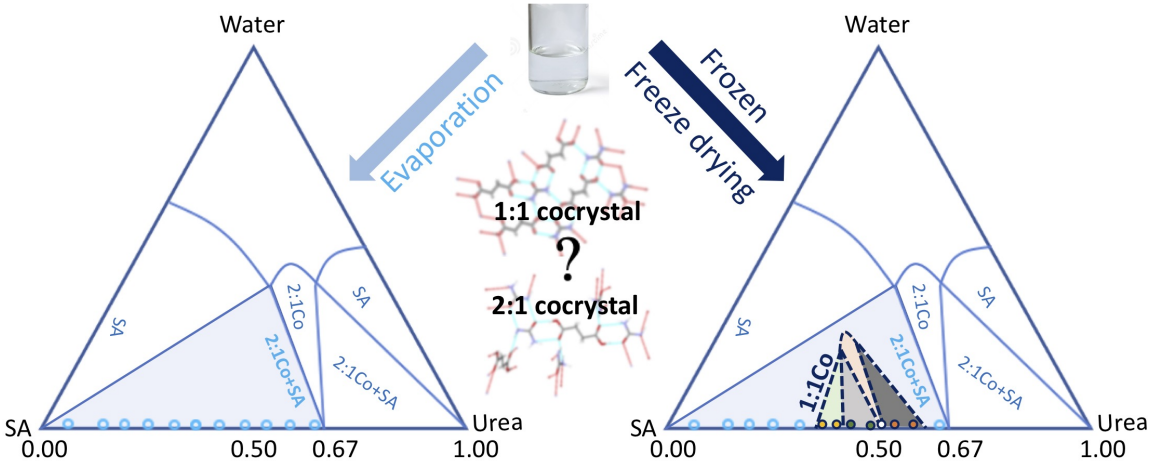

Figure 1: Schematic of 1:1 cocrystal and 2:1 cocrystal formation in ternary phase diagram with evaporation method or frozen and freeze-drying methods [6]. Co: cocrystal.

References

[1] Sebolt-Leopold, J. S., J. M. Nature 2006, 441
[2] Allu, S.; Bolla, G.; Tothadi, S.; Nangia, A., Cryst. Growth Des. 2017, 17, 4225
[3] Almarsson, Ö.; Zaworotko, M. J. Chem. Commun. 2004, 17, 1889
[4] Yao, G.-B.; Wang, L.; Sun, Y.-P.; Yi, J.-K.; Meng, L.; Zhao, H.-K., Chem. Eng. Data 2014, 59, 4081
[5] Alhalaweh, A.; George, S.; Bostrom, D.; Velaga, S. P., Cryst. Growth Des. 2010, 10, 4847
[6] Yu, Q.; Pu, J.; Qi, M.; Yang, H.,'Crystal Growth Design, 2019, 19, 1505

Influence of excipients on the stability of pharmaceutical cocrystals

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In pharmaceutical production processes, cocrystals are usually formulated with excipients, which may compete with the coformer for hydrogen bonding. Therefore, it is important to study the stability of cocrystals in the presence of excipients. In this study, six different excipients were selected to investigate their influence on the stability and formation of cocrystals of the model drug is chlorothiazide (CTZ), as we have reported a number of chlorothiazide cocrystals with a variety of coformers previously.[1] Isolated cocrystals of CTZ were first mixed with PVP and MCC, the two most common excipients and then milled and kept at 56% relative humidity (RH). Then two cocrystals were selected CTZ- Nicotinamide (Nia) and CTZ-Carbamazepine (Cbz) for further investigation with different excipients. The chosen excipients are hydroxypropyl cellulose (HPC), sodium taurocholate (NaTc), deoxycholic acid (DA) and alpha-lactose monohydrate (ALM). Powder mixtures of cocrystals and the respective excipients were compacted at 5:1, 3:1 and 1:1 (w/w) CTZ:PVP/MCC ratios. Most of the cocrystals were stable with 1:1 CTZ:PVP or MCC and after storage, all compacts showed the same structure. Surprisingly, the results suggested it is possible to form cocrystals in the presence of excipients, which would simplify the pharmaceutical process. Even with 1:1.5 CTZ:PVP or MCC cocrystals of 4,4'-bipyridine were formed by milling. Additionally, the powder X-ray diffraction analysis shows that, cocrystals of CTZ-Nia and CTZ-Cbz to some existent are stable in the presence of PVP, MCC, HPC and NaTc. However, new peaks appeared in the presence of DA and ALM. In the case of ALM the new peaks corresponded to the excipients, while DA was found to convert to a new polymorph via milling. In summary, this study showed that the influence of excipients on the cocrystals stability can depends on the coformer, how strongly they interact with each other and the nature of excipient.

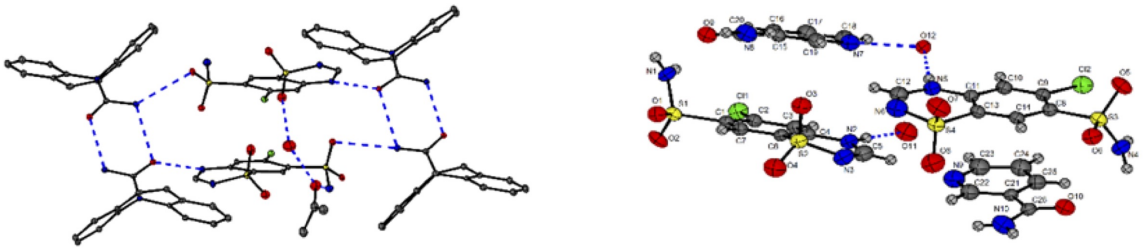

Figure 1: Hydrogen bonding in CTZ-Cbz left and CTZ-Nia right

References

[1] M. Aljohani, A.R. Pallipurath, P. McArdle, A. Erxleben, Cryst. Growth Des., 2017, 10, 1021

Influence of Impurities on the Solubility, Nucleation, Crystallization and Compressibility of Paracetamol

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Solution crystallization processes are widely treated as binary systems consisting of a solute and a solvent. For real systems, additional components such as additives and impurities are typically present in minute amounts. Such additional components may significantly impact crystallization processes even when present in very small amounts. , An understanding of the mechanistic role of additives and impurities is therefore essential to design and control crystallization processes. Impurity control is particularly important in pharmaceutical manufacturing, as such compounds can be toxic or may unfavourably affect the crystallization of the desired product. In the present work, the effect of two markedly different impurities 4-nitrophenol and 4'-chloroacetanilide on the solubility, nucleation and crystallization of paracetamol are described. In the first part of this work, the fundamentals are outlined and show that although each impurity led to a small increase in solubility of paracetamol, their effect as a nucleation inhibitor was much more pronounced. Induction time experiments were used in conjunction with the classical nucleation theory to show that the impurities did not affect the solid-liquid interfacial energy but instead significantly reduced the kinetic factor, overall resulting in reduced nucleation rates. In the second part of this work, the incorporation of 4'-chloroacetanilide into the solid phase of paracetamol was investigated. The presence of 4'-chloroacetanilide in the solid phase of paracetamol significantly increased the compressibility of paracetamol, resulting in improved processability properties of paracetamol. The compressibility efficiency of paracetamol could be controlled using the amount of incorporated 4'-chloroacetanilide. Therefore, an experimental design space was developed and utilized to select the most important process parameters for impurity incorporation. Intriguingly, the number of carbon atoms in the aliphatic chain of the alcohol solvent strongly correlated to the impurity incorporation efficiency. As a result, it was feasible to accurately control the compressibility and the amount of 4'-chloroacetanilide in the solid phase of paracetamol by simply choosing the required alcohol as the solvent for crystallization. Thus, the present work comprehensively shows how different impurities impact the key crystallization mechanisms and properties of a pharmaceutical product. Rational process control over the incorporation of impurities and additives allows for advanced manufacturing of products with tailored specifications.

References

[1] Sangwal, K., (2007): Additives and Crystallization Processes: From Fundamentals to Applications.

[2] Schmidt, C.; Jones, M. J.; Ulrich, J., (2013): The Influence of Additives and Impurities on Crystallization., Wiley-VCH Verlag GmbH Co. KGaA, 105-127.

[3] Singh, S., (2018): The last decade in regulation and control of impurities in pharmaceuticals. Trends Anal. Chem. 1, 101.

Revisiting the Solid-State landscape of Sildenafil: New insights from an old drug

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We have experimentally revisited the solid-state landcape of the drug Sildenafil and discovered new solvates, salts and cocrystals. The detailed examination of their crystal structures has allowed us to analyze three relevant phenomena in the field of crystal engineering such as the desolvate formation,[1] the hybrid salt-cocrystal continuum[2] and the competition between hydrogen bonding and π–interactions[3] in the solid state. In this talk, I will briefly describe them and discuss their impact concerning the search for new solid forms of APIs.

Figure 1: Solvates of Sildenafil.

References

[1] R. Barbas, M. Font-Bardia, R. Prohens, Crystal Growth Design, 2018, 18, 3740
[2] R. Barbas, M. Font-Bardia, A. Paradkar, C.A. Hunter, R. Prohens, Crystal Growth Design, 2018, 18, 7618
[3] R. Barbas, R. Prohens, M. Font-Bardia, A. Bauza, A. Frontera, CrystEngComm, 2018, 20, 4526

Plenary Award Session

BACG Young Investigator Award 2019

The role of active sites in heterogeneous ice nucleation

M. A. Holden[1,2,3,4], **T. F. Whale**[2], **J. M. Campbell**[1,5], **M. D. Tarn**[1,3], **D. O'Sullivan**[3], **R. D. Walshaw**[3], **B. J. Murray**[3], **F. C. Meldrum**[2], **H. K. Christenson**[1]

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Ice nucleation plays a key role in atmospheric cloud processes and can affect the Earth's radiative balance. The temperature at which ice forms homogeneously is typically below -33 ^{o}C, yet cloud ice is observed at much warmer temperatures owing to heterogeneous nucleants.[1] The ability of a range of substrates to act as ice nucleants is known due to decades of research, but the reason for this ability remains unclear, particularly with respects to the location, nature and number density of nucleation sites. One of the best studied atmospheric ice nucleants is K-feldspar. [2] Recently, some mechanistic insight has been gained from studying ice nucleation from vapour, [3] but our understanding of nucleation sites from the melt remains poor. Here we use high-speed video microscopy to investigate ice nucleation from the melt on K-feldspar surfaces, proving the existence of active sites.[4]

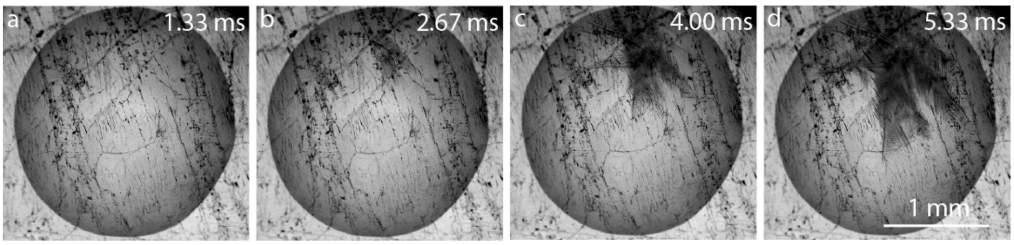

Figure 1: High speed video microscopy of ice growing in a liquid water droplet placed on the (010) face of K-feldspar.

Active site identification. By repeatedly freezing and thawing water droplets in contact with mineral surfaces, we find that nucleation occurs only at a few 'special' sites associated with micron-size surface pits. These sites are incredibly rare - in this case around 1 per 4 mm^2 - yet are exceptional at nucleating ice. This localised effectiveness is the salient factor in determining the freezing temperature of a water droplet. [4] There are a range of sites on the surface, where the most effective sites are the least common. This suggests that the best sites will comprise a statistically unlikely combination of several different interactions. These could be both chemical and topographical and will work in concert to create an active site. Whilst nucleation is site specific, we find that ice nucleation active sites from the melt are usually not the same as active sites from vapour. We suggest that the most likely reason for this is that nucleation from vapour can proceed by a condensation-freezing mechanism, where the most effective nucleation sites are not always the most effective condensation sites.

References

[1] Z. A. Kanji et al., Meteorological Monographs, 2017, 58, 1.1–1.33.
[2] J. D. Atkinson et al., Nature, 2013, 498, 355-358.
[3] A. Kiselev et al. Science, 2017, 355(6323), 367-371.
[4] M. A. Holden et al., Sci. Adv., 2019, 5(2), eaav4316.

BACG 2019 Annual Lecture

Mode of action of quinoline antimalarial drugs in red blood cells infected by Plasmodium falciparum, revealed in-vivo

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Malaria parasite resistance to current drug treatment highlights the need for identifying efficient targets to improve antimalarial therapies. Residing in a human red blood cell the parasite catabolizes hemoglobin in an organelle called the digestive vacuole. This digestion liberates large quantities of heme, which is toxic to the parasite. The heme is detoxified by sequestration into inert hemozoin crystals. To characterize this process in vivo we developed an approach using X-ray absorption and fluorescence nanometer scale imaging enabling measurement of atomic distribution in biological cells [1]. By this method we first characterized hemozoin nucleation [2] and growth[3] in Plasmodium-infected blood cells. Our measurements of hemozoin growth rate and discovery of considerable amounts of hemoglobin in the digestive vacuole suggested an assembly-line process of heme detoxification3 wherein the liberated heme molecules dimerize, and crystallize.[3] Thus hemozoin growth is vital for parasite survival. Quinoline antimalarials are believed to interfere with this crystallization process[4]. Molecular simulations predict that quinoline drugs cap hemozoin crystals preventing the liberated heme from docking onto the crystals.[5] To date, the growth inhibition studies have been done on synthetic hemozoin.[6] We have made an in-vivo study by mapping the distribution of a bromo-analogue of the chloroquine drug within parasitized red blood cells using X-ray imaging.[7] We observed that bromoquine capped biogenic hemozoin faces with a $10\pm5\%$ surface coverage. Moreover, the drug accumulated in the digestive vacuole reaching sub-millimolar concentration, 1000-fold more than that of the drug in the culture medium. Such an increase in concentration enhances the drug efficiency depriving heme from docking onto the hemozoin crystals. The bromoquine distribution in the digestive vacuole and at its membrane suggested that excess bromoquine complexes with the heme deprived from crystallization. This complex is driven towards the digestive vacuole membrane increasing the chances of membrane puncture and heme spillage into the parasitic interior.

References

[1] Kapishnikov S, Leiserowitz L,... Cloetens P, Pereiro E,... Als-Nielsen J. Sci. Rep. 7, 802 (2017).
[2] Kapishnikov S,... Als-Nielsen J, Leiserowitz L, PNAS, 109, 11184 (2012); Kapishnikov S, Shimoni E,..Schneider G N, Dzikowski R, Leiserowitz L, Elbaum [M, PNAS, 109, 11188 (2012).
[3] Kapishnikov S, Grolimund D,.... Als-Nielsen J, Leiserowitz L, Sci. Rep. 7, 7610 (2017).
[4] Sullivan DJ, Matile H, Ridley RG, Goldberg DE J. Biol. Chem. 273, 31103 (1998); Pagola S, Stephens WP, Bohle DS, Kosar AD, Madsen SK Nature 404, 307 (2000).
[5] Buller R, Peterson ML, Almarsson O, Leiserowitz L CGD 2, 553 (2002); Weissbuch I, Leiserowitz L Chem. Rev 108, 4899 (2008); Dubar F, et al ACS Chem. Biol. 6, 275 (2011).
[6] Solomonov, I, et al JACS 129, 2615 (2007); K. N. Olafson, et al PNAS 114, 7531 (2017); Fitzroy SM, et al Langmuir 33, 7529 (2017).
[7] Kapishnikov S,.... Pereiro E, Yang Y, Leiserowitz L, Als-Nielsen J, submitted for publication.

50^{th} Anniversary Dinner Talk

BACG – where did those fifty years go?

R. Davey[1]

IT

University of Manchester, UK.

In this pre-dinner talk I will attempt to reflect on the life of the Association from an historical, scientific and personal perspective.

Plenary Session: Engineering Crystallization

Lecture Theatre

On the Manipulation of the Size and Shape of Needle-like Crystals

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[2] Department of Electrical and Systems Engineering, University of Pennsylvania, Philadelphia 19104, United States

Crystallization from solution leads to a range of particle sizes and shapes, which are influenced by the solvent, the supersaturation, and the presence of additives, to name a few. The size and shape of crystals thus obtained impact various downstream processes, hence there is a lot of interest in developing processes and operating strategies to obtain equant shaped crystals with a narrow distribution. However, the majority of the crystallization literature deals with the manipulation of size, while little focus is given to the manipulation of shape, which can be attributed to the lack of commercially available size and shape monitoring tools. Recent advances in online size and shape monitoring [1] have provided a means to explore complex crystal size and shape modification processes. One such process, called the 3-stage process, involving a growth, a milling, and a dissolution stage operated cyclically, has shown promise in obtaining more equant-shaped particles with a narrow particle size and shape distribution (PSSD) starting from needle-like seed particles.[2] This process was developed first within a simulation framework and then subsequently tested experimentally [3] at predefined operating conditions.

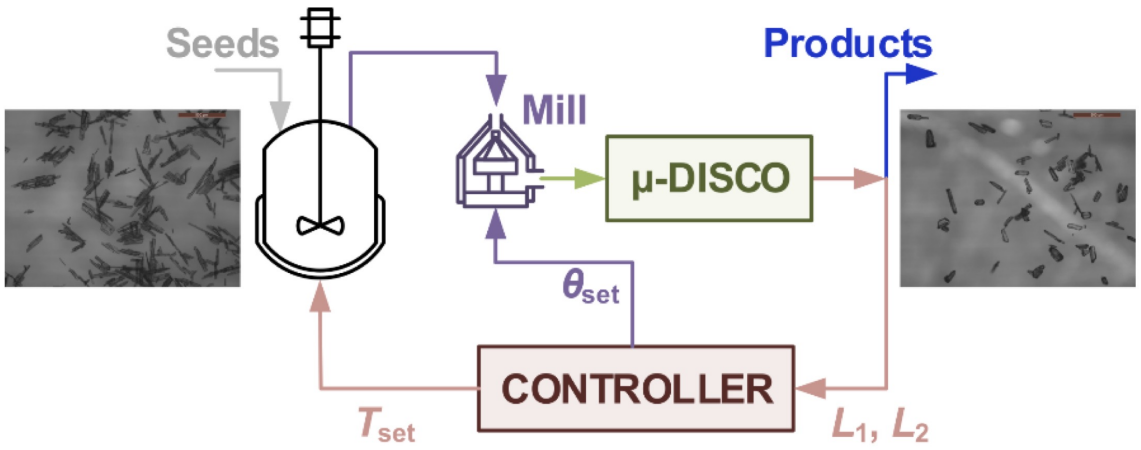

Figure 1: Schematic of the experimental setup. The solid phase is characterized online using the -DISCO. The two microscope images represent crystals at the beginning and at the end of the controlled process.

However, it is known that operating a process purely based on predefined operating strategies cannot guarantee consistent product quality over multiple runs, due to the presence of unmodeled phenomena and process disturbances. These undesirable effects can potentially be mitigated by employing feedback control. There are two main prerequisites for the successful application of feedback control to a process like the 3-stage process. First, the availability of a quantitative, online size and shape monitoring tool. Second, the availability of tailor-made feedback controllers for the individual stages of the process. The first point is addressed by the availability of a device like the μ-DISCO that is capable of providing statistically relevant PSSD data online.[1,4]

The second point is addressed by three control strategies that have been developed recently: a path following controller [5,6] to drive seed populations to predefined targets under growth-dominated conditions; a wet milling controller [7] to reduce the average length of the particles by subjecting them to breakage; and a particle volume controller to dissolve a certain fraction of the initial mass.[8] Dedicated experimental campaigns helped validating the robust performance and the generality of these algorithms. Addressing the aforementioned points enables operating the entire process in a controlled fashion. By defining a few targets on the process level, a needle-like seed population can be converted into a more equant-shaped population with a narrow PSSD repeatedly, irrespective of process disturbances. The employed controllers are designed such that they operate by solely relying on the online monitoring capabilities of the μ-DISCO, thereby eliminating the requirement of multidimensional models of the shape evolution of crystals. The studies performed in the last few years have provided great insights into crystallization processes. The availability of models is quite handy to understand, to design, and to optimize processes, but often these models lack predictive capabilities. Add to this, process models are highly compound specific and come at the cost of a lengthy experimental, model identification, and parameter estimation pipeline. Keeping these points in mind, a practical way forward would be to implement simple model-free feedback control strategies exploiting online monitoring, while explicitly addressing particle shape objectives.

References

[1] Rajagopalan, A. K.; Schneeberger, J.; Salvatori, F.; Bötschi, S.; Ochsenbein, D. R.; Oswald, M. R.; Pollefeys, M.; Mazzotti, M. A Comprehensive Shape Analysis Pipeline for Stereoscopic Measurements of Particulate Populations in Suspension. Powder Technol. 2017, 321, 479–493.

[2] Salvatori, F.; Mazzotti, M. Manipulation of Particle Morphology by Crystallization, Milling, and Heating Cycles - A Mathematical Modeling Approach. Ind. Eng. Chem. Res. 2017, 56 (32), 9188–9201.

[3] Salvatori, F.; Mazzotti, M. Manipulation of Particle Morphology by Crystallization, Milling, and Heating Cycles: Experimental Characterization. Ind. Eng. Chem. Res. 2018, 57 (45), 15522–15533.

[4] Bötschi, S.; Rajagopalan, A. K.; Morari, M.; Mazzotti, M. An Alternative Approach to Estimate Solute Concentration: Exploiting the Information Embedded in the Solid Phase. J. Phys. Chem. Lett. 2018, 9 (15), 4210–4214.

[5] Bötschi, S.; Rajagopalan, A. K.; Morari, M.; Mazzotti, M. Feedback Control for the Size and Shape Evolution of Needle-like Crystals in Suspension. I. Concepts and Simulation Studies. Cryst. Growth Des. 2018, 18 (8), 4470–4483.

[6] Rajagopalan, A. K.; Bötschi, S.; Morari, M.; Mazzotti, M. Feedback Control for the Size and Shape Evolution of Needle-like Crystals in Suspension. II. Cooling Crystallization Experiments. Cryst. Growth Des. 2018, 18 (10), 6185–6196.

[7] Rajagopalan, A. K.; Bötschi, S.; Morari, M.; Mazzotti, M. Feedback Control for the Size and Shape Evolution of Needle-like Crystals in Suspension. III. Wet Milling. Cryst. Growth Des. 2019, in press.

[8] Bötschi, S.; Rajagopalan, A. K.; Morari, M.; Mazzotti, M. Feedback Control for the Size and Shape Evolution of Needle-like Crystals in Suspension. IV. Modeling and Control of Dissolution. submitted for publication.

Design and optimization of isothermal and non-isothermal deracemization

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Solid state deracemization processes target the production of pure enantiomers from an initially enantiomerically impure mixture. For conglomerate forming enantiomers, such processes can be conducted in the presence of a liquid phase racemization reaction, leading to an enantiopure product, which is obtained quantitatively (i.e., all added solids are converted to the desired enantiomer). In its isothermal form (Viedma ripening[1]) the process is rationalized as an interplay of the racemization reaction, Ostwald ripening, agglomeration and breakage. State of the art models describing this process are based on population balance equations incorporating these phenomena. Such models have been used to explore the behaviour of the process operated both in batch[2] and continuous[3] operating modes. Non-isothermal variants (i.e., involving temperature cycling) represent an industrially attractive option and recently have been explored as well[4]. While these studies have been important to establish dependencies of the process behaviour on the kinetics of the different phenomena and its initial conditions, a study on how to optimize these processes in terms of their productivity is currently absent from the literature. To fill this gap, this work presents: i) intrinsically optimal ways to run batch campaigns of these processes, ii) a model-based optimization of operating parameters (initial enantiomeric excess, suspension density, milling intensity, shape of temperature profile and number of cycles) iii) how the optimal values of these parameters depend on the underlying kinetics of all phenomena. This is accomplished by introducing newly parametrized versions of dimensionless population balance models (isothermal, non-isothermal) together with an efficient numerical solution strategy based on the finite volume technique. The latter enables these complex models including all afore-mentioned mechanisms to be solved quickly, which, in turn, allows the posing and solving of optimization problems. Exemplarily, results regarding the optimal initial enantiomeric excess for an isothermal deracemization process with varying agglomeration and breakage kinetics are shown in Figure 1.

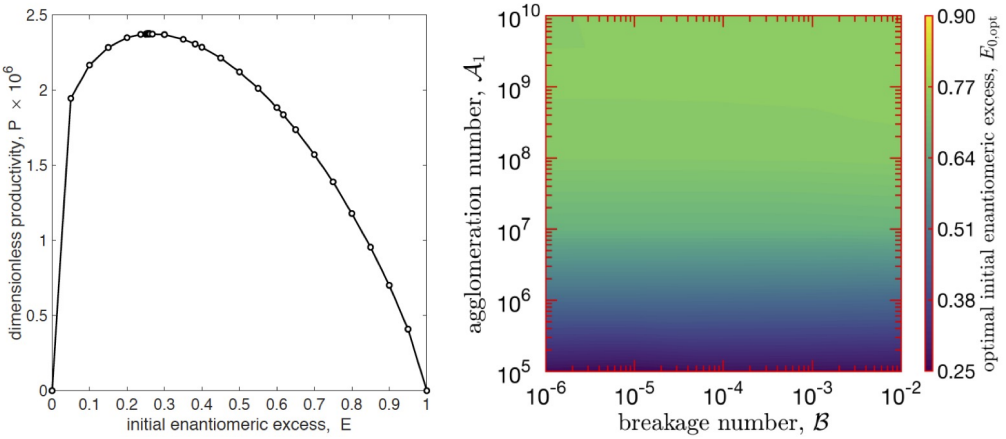

Figure 1: Isothermal deracemization process with optimal productivity: (left) Dependence of productivity on the initial solid state enantiomeric excess (E) for one set of kinetics (right) optimal initial E for different kinetics.

References

[1] Noorduin et al., Angew. Chem., Int. Ed., 2010, 49, 8435-8438,
[2] Iggland and Mazzotti, Cryst. Growth Des., 2011, 18, 4611-4622,
[3] Kollges and Vetter, Cryst. Growth Des., 2018, 18, 1686-1696,
[4] Bodak, Maggioni, and Mazzotti, Cryst. Growth Des., 2018, 18, 7122-7131.

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Modeling Support of Finite Pharmaceutical Crystal Growth

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[1] XtalPi Inc.

Given the complexity of the pharmaceutical solid-state landscape and challenges facing the pharmaceutical industry, an accelerated Drug Development greatly benefits from guidance provided by computational methods. Virtual polymorph screening through crystal structure prediction (CSP) is one of the most comprehensive and at the same time the most computationally intense theoretical approach to study drug polymorphism. In addition, it is important to perform calculations of properties of realistic finite crystals. This presentation will focus on computational support of such important tasks as decrease of pharmaceutical crystals agglomeration;[1] impurity purge via recrystallization;[2] as well as estimation of risk of kinetic hindering of stable forms.[3]

<table>
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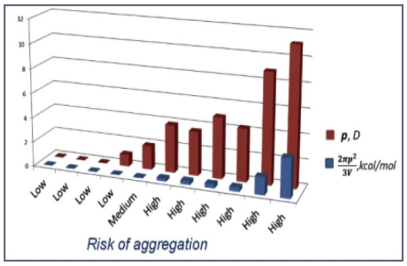
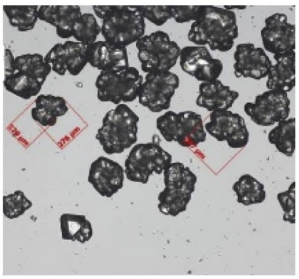
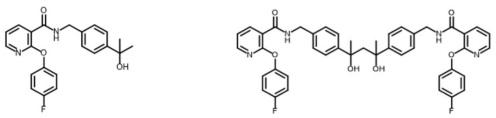
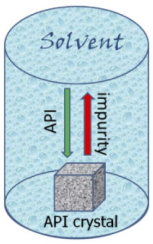
<tr><td> 
</td><td>  </td></tr>
<tr><td>API tertiary alcohol Impurity 1,3-diol impurity
 
$f = \left(P^{imp}_{solv,API\ cryst} - S^{API}_{cryst}\right)\rho_{solv}$</td><td> 

<table>
<tr><th>Solvent selected</th><th>Impurity purge,%</th></tr>
<tr><td>2-propanol</td><td>1.11</td></tr>
<tr><td>MTBE</td><td>0.46</td></tr>
<tr><td>ACN</td><td>1.12</td></tr>
<tr><td>MEK</td><td>1.02</td></tr>
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References

[1] Y.A. Abramov. Understanding the Risk of Agglomeration of Polar Pharmaceutical Crystals. Cryst. Growth Des., 2017, 17, 2873–2880.

[2] Y.A. Abramov. Rational Solvent Selection for Pharmaceutical Impurity Purge. Cryst. Growth Des. 2018, 18, 12081214.

[3] Y.A. Abramov, P. Zhang, M. Yang, Y. Liu. Molecular Perspective of Kinetic Hindering of Pharmaceutical Stable Forms Crystallization, 2019, to be submitted.

Parallel Session: Engineering Crystallization

Lecture Theatre

pH and Temperature Dependent Solubilities and Eutectic Points for the Continuous Chiral Resolution by Integration of Membrane and Crystallisation Technologies

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Amino acids, enzymes and cell receptors are chiral. Chiral molecules occur in left- and right-handed configurations that can be considered as mirror images (enantiomers), and that, like hands, cannot be superimposed onto each other. Despite their similarity, the biological activity of pharmaceutical enantiomers can be completely different. Therefore, most pharmaceuticals and pesticides, which usually act on enzymes and cell receptors, are chiral. The separation of these enantiomers in highly pure crystalline products from a complex multicomponent mixture is a challenge. Although continuous membrane technologies could potentially be used to achieve enantiomer enrichment, they cannot reach enantiomer purity levels close to 100%. The combination of membrane and crystallisation processes in continuous might be the solution to this problem. Starting from a racemic solution, the membrane system will provide sufficient enantiomer enrichment which, through crystallisation, will lead to enantiopurity. Here, the pre-enrichment step proposed combines chiral recognition by means of a chiral selector, in the feed solution, with a non-enantioselective membrane, in the filtration unit (Fig. 1). This combination will permit to maximise the yield and purity of the final enantiomeric product at the same time. The work presented will focus on the crystallisation studies of a racemic compound forming system for the determination of eutectic points and study the effect of pH and T on them. First, solubilities for DL-alanine and L-alanine in aqueous media are investigated over a pH range. Then, pseudo-binary phase diagrams permit the observation of nucleation and saturation within the pH range under study. This makes possible the exploration of the crystal morphology and eutectic points. Finally, the comparison with ternary phase diagrams enables the validation of the eutectic points previously explored. At this point, temperature and pH effects were found on solubility ternary phase diagrams. Temperature was observed to have an effect on the eutectic point, whereas pH was not. In addition, the crystallisation of pure L-alanine was validated with SC-XRD.

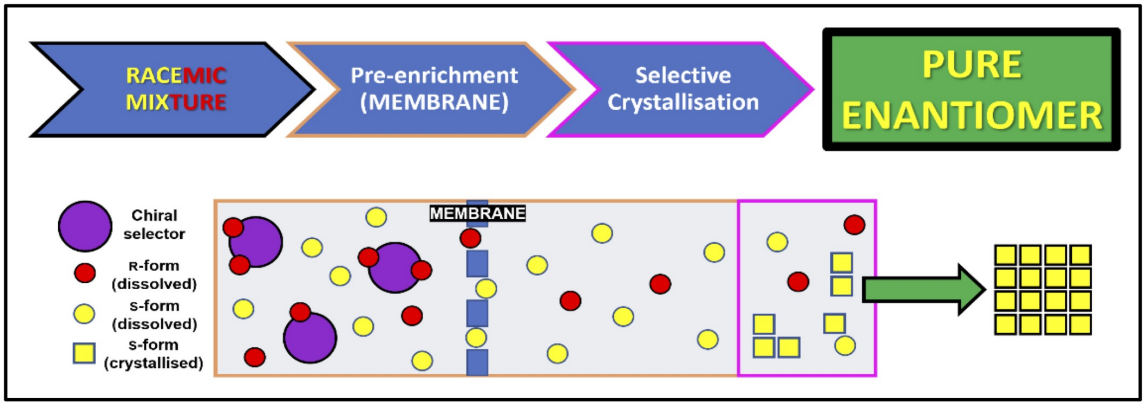

Figure 1: Figure 1 Continuous chiral resolution by integration of membrane and crystallisation technologies.

Serial Separation and Resolution in Eutectic Solutions

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As the majority of new pharmaceutical substances are chiral, pharmaceutical industry seeks access to a broad range of chiral resolution methods to separate enantiomers of such chiral compounds. An established method for the separation of conglomerates is preferential crystallization, were the most common application is preferential cooling crystallization. The aim of this work is to investigate the suitability of a new serial preferential cooling crystallization process configuration with continuous feed and recycle to separate racemic compound forming systems as well as conglomerate systems at the eutectic composition. As an example for the separation of racemic compound forming systems, mandelic acid (MA) in water is investigated. In the feed vessel, a saturated eutectic solution composition is equilibrated with a mixed suspension of the racemic and enantiopure compound crystals at a high temperature T1. At the start of the process a continuous flow of filtered solution from the feed vessel into the first crystallizer is started. The first crystallizer initially contains a suspension of saturated solution with a eutectic composition at a lower temperature T2 and seed crystals of the first product, in this case the racemic compound. When the feed enters the first crystallizer it is cooled and the racemic compound crystallizes, reducing the supersaturation for DL-MA. From the first crystallizer a continuous flow of filtered solution depleted of the excess of DL-MA is entering the second crystallizer. This crystallizer initially contains a suspension of saturated solution at the eutectic composition at T2 and seed crystals of enantiopure D-MA. The feed solution for this second crystallizer is supersaturated in respect to the D-MA crystalline phase, which is then crystallized, depleting the solution. The continuous flow of filtered and depleted solution leaving the second crystallizer is recycled to the feed vessel at the higher temperature T1. Raman spectroscopy showed to be a valuable method to both monitor the suspension density and solid enantiomeric excess in-situ in the second crystallizer. UV-Spectroscopy was used to monitor the total enantiomer concentration in both crystallizers during the process. Several experiments with residence times from 15 to 30 minutes and temperature differences T1-T2 = 2-5C were performed, at which none showed primary nucleation of the undesired product in the second crystallizer producing only enantiopure D-MA. However, in the first crystallizer, meant to crystallize the less valuable product, formation of D-MA eventually took place. This occurred earlier at larger temperature differences and shorter residence times. Up to around 67% of the D-MA available for crystallization did crystallize out in the second crystallizer. For the separation using a conglomerate forming system, asparagine monohydrate (ASN) in water was used in the same setup. A racemic composition was used for the solid excess in the feed tank and the process was run with a residence time of 30 minutes and a temperature difference of 5C. In the first crystallizer seed crystals of D-ASN were added and L-ASN seeds were used in the second crystallizer. During the experiments solid samples were taken regularly from both crystallizers and the solid enantiomeric excess was analysed for purity using HPLC. The results showed that L- and D-ASN with an enantiopurity higher than 99% were produced during the process. This process configuration presents a flexible and efficient option for the separation of conglomerate as well as racemic compound forming systems in the eutectic composition.

This research has received funding as part of the CORE project (October 2016 – September 2020) from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 722456 CORE ITN

Model-based analysis of solid-state deracemization via temperature cycles

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Solid-state deracemization is the transformation of a solid suspension of a conglomerate-forming substance initially consisting of crystals of both enantiomers D and L into a suspension containing crystals of only one of the two enantiomers, either D or L, where a racemization reaction occurs in solution. Among the solid-state deracemization techniques [1], that based on temperature cycles is a promising candidate for industrial applications due to the simplicity of the setup required[2]. The complexity of the process requires a mathematical model to understand the effect of initial conditions and operating parameters on the process outcome, i.e. to obtain the desired enantiomer. Extending our isothermal population balance based model of attrition-enhanced deracemisation [3], we have developed a non-isothermal model to simulate solid-state deracemization via temperature cycles [4]. The model describes the interplay of the phenomena present in the process (size-dependent solubility, crystal growth and dissolution, agglomeration, attrition and racemization) accounting for the dependence of their thermodynamic and kinetic parameters on the crystal size and on the temperature. By identifying the relevant variables and their corresponding characteristic values, we have also derived the nondimensional equations associated to the non-isothermal model. The nondimensional model allows to study the deracemization process in a quasi-universal manner, without the knowledge of the physical and chemical parameters, which are dependent on the specific system considered.

*R*esults. Using the PBE-model that we have introduced, we have simulated temperature cycles in batch crystallizers. The results of the simulations have been compared with the experimental data reported in the literature2, to qualitatively validate the model. The focus of this contribution is to investigate the effect of the initial conditions on the process. We observe how small deviations in the particle size distribution of the D and of the L enantiomer can alter the process outcome and performance. Moreover, this model aims at explaining the sensitivity to variations in the model parameters, such as the breakage rate, the agglomeration rate, etc. that is challenging to be experimentally investigated.

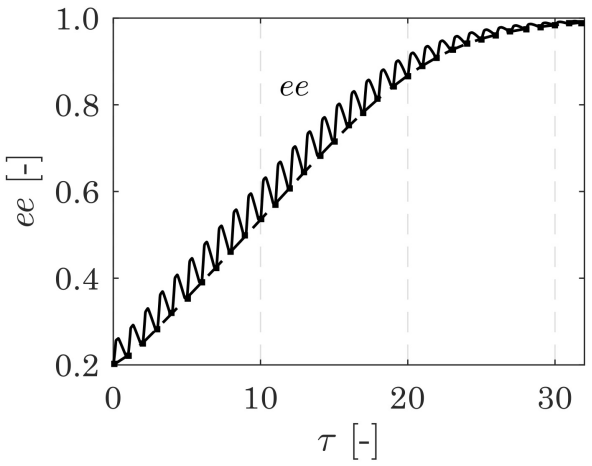

Figure 1: Evolution of the enantiomeric excess along the nondimensional time during deracemisation via temperature cycles: the overall monotonic increase of the enantiomeric excess is the typically observed trend.

References

[1] W. L. Noorduin, W. J. P van Enckevort, H. Meekes, B. Kaptein, R. M. Kellogg, J. C. Tully, J. M. McBride, E. Vlieg, Cryst. Angew. Chem., Int. Ed.., 2010, 18, 8435-8438

[2] F. Breveglieri, G. M. Maggioni, M. Mazzotti, Cryst. Growth Des., 2018, 18, 1873-1881

[3] M. Iggland and M. Mazzotti, Cryst. Growth Des., 2011, 18, 4611-4622

[4] B. Bodák, G.M. Maggioni, M. Mazzotti, Cryst. Growth Des., 2018, 18, 7122-7131.

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When crystals don't grow – the growth dead zone

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There is a region within the metastable zone near the solubility curve called the growth dead zone, within which a seed crystal is incapable of either growth or nucleation. On a practical level it is potentially problematic on two counts. It firstly prevents a crystallizing system from reaching equilibrium, reducing yields and compromising seeding processes often adopted commercially and secondly in a polymorphic system it may provide a long lived metastable state within which a second form may nucleate and grow. Such a crystallization gap was first described by Mullin [1] and its scientific status within the metastable zone was recently re-clarified by Threlfall and Coles.[2] In one sense, this growth behaviour has long been known for certain faces of the polar crystal -resorcinol3,4 and has subsequently been recognized in a significant number of other compounds. It sometimes seems to be an inherent feature of solution growth in others an impurity is an essential element for its appearance. But by now, the mechanisms underlying this particular, general zone of zero growth are too more phenomenological with relatively few structural examinations. In this contribution, we are thoroughly reviewing those previous works and report new kinetic cases of (R,S)-alanine, D-mannitol and benzophenone where the effects of solvent, temperature and additives are considered to explore the underlying causes of a dead zone in the context of crystal growth mechanisms, solvent adsorption and surface topology. We thus measured the crystal growth rate for these three new compounds at different supersaturations from in situ experiments using a growth cell and an inverted microscope. Confronting the existing and new data with crystal growth models, we identified that the dead zone cannot be uniquely attributed to a surface nucleation mechanism at lower supersaturations. However, the new data do confirm that temperature, solvent and additives have significant impact on the existence and extent of dead zone features which taken together suggest a mechanism of surface site blocking either in the form of solvent adsorption or self-poisoning. This is further supported by perusal of molecular packing arrangements which shows that the surfaces along the dead zone directions can be regarded as corrugated in two dimensions. A simple geometric approach was used to provide a pragmatic measure of the surface roughness, which reveals that faces with dead zones are significantly rougher than faces with no dead zones. A link appears to exist between those facets that exhibit such rugosity and their failure to grow at low supersaturations.

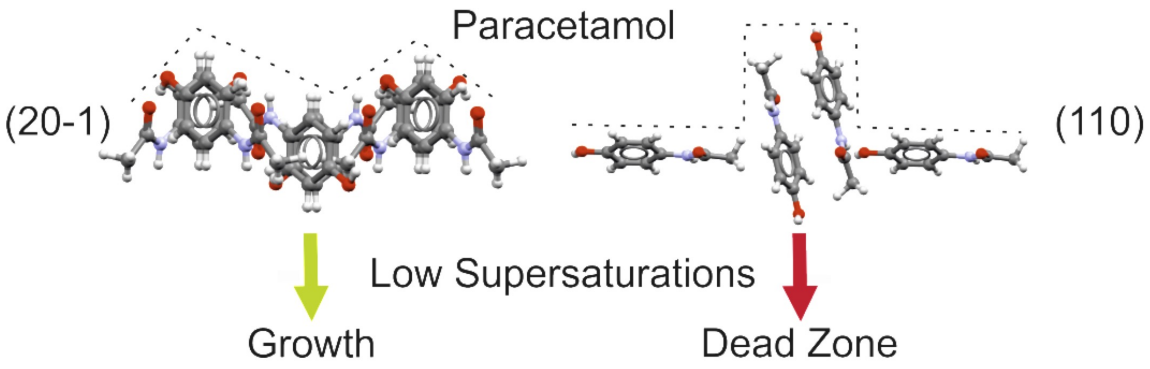

Figure 1: Dead zone related with Rugosity

References

[1] J. W. Mullin, Crystallization, 4th ed.; Butterworth-Heinemann: Oxford, U.K., 2001.

[2] T. L. Threlfall, S. J. Coles, A perspective on the growth-only zone, the secondary nucleation threshold and crystal size distribution in solution crystallisation, CrystEngComm. 2016, 18, 369-378.

[3] R. J. Davey, B. Milisavljevic, J. R. Bourne, Solvent interactions at crystal surfaces: the kinetic story of. alpha - resorcinol, J. Phys. Chem. 1988, 92, 2032-2036.

[4] A. F. Wells, Abnormal and modified crystal growth. Introductory paper, Discuss. Faraday Soc. 1949, 5, 197-201.

A Planar Aromatic Molecule that Cannot Crystallise: A Combined Computational and Experimental Study of 2nd Generation Sulflower

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The crystal structures of rigid planar polyaromatic molecules under ambient conditions have so far been shown to follow conventions documented by Desiraju and Gavezzotti in 1989, with competition between edge-face and face-face Van der Waals interactions determining crystal unit cell axes lengths and the angles between neighbouring molecules1. In this work, the newly synthesised molecule persulfurated coronene (PSC), in which the peripheral hydrogens of coronene have been substituted with sulfur atoms, has conclusively been shown to be unable to crystallise through differential scanning calorimetry and 3D TEM electron diffraction data. The calculated electrostatic potential (ESP) surface of the molecule shows a broadly homogeneous distribution of charge, preventing edge-face interactions such that only face-face interactions may take place. This is the first known example of a planar aromatic molecule that cannot crystallise, thereby conflicting with the established laws of crystallisation in such molecules.

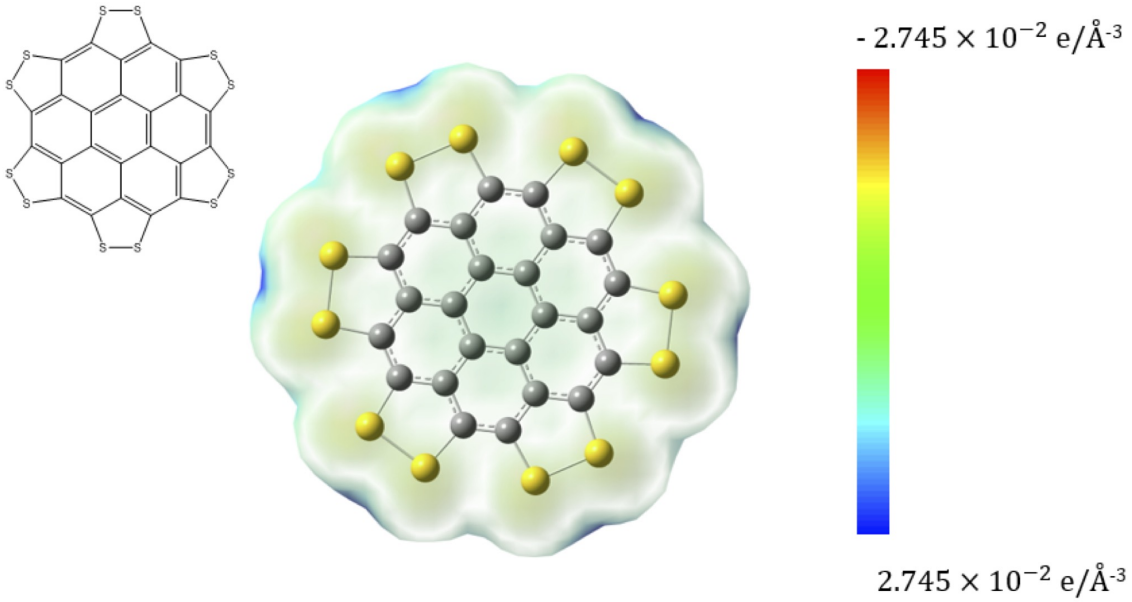

Figure 1: Electrostatic potential of persulfurated coronene.

References

[1] Desiraju GR, Gavezzotti A, IUCr. Crystal structures of polynuclear aromatic hydrocarbons. Classification, rationalization and prediction from molecular structure. Acta Crystallogr Sect B Struct Sci. 1989;45(5):473-482. doi:10.1107/S0108768189003794.

Conformational complexity limitations to the simulation of the nucleation of succinic acid polymorphs

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Succinic acid, despite being a structurally simple molecule (COOHCH2CH2COOH), presents a complex conformational landscape, which reflects on its polymorphs. Indeed, the only two polymorphs known until recently, namely α and β, present succinic acid molecules in a planar conformation, i.e. with its four carbon atoms laying on the same plane. Recently, a new conformational polymorph, γ, was serendipitously isolated; such polymorph contains molecules with a folded carbon skeleton. In a recent work [1], we show that γ is thermodynamically plausible, but labile. In addition, for a single molecule in water we identify 9 conformers, differentiated by the carbon skeleton arrangement and the relative orientation of the COOH groups with respect to the skeleton. Among such conformers the folded conformer building unit of γ is strongly dominant (70%). Hence, the most stable conformer in solution (folded) is not the building block of the most stable nucleating polymorph (β, planar). In our current work we aim at understanding the interplay between the conformation equilibration and the collective assembly processes that lead to nucleation. To tackle this problem, we employ molecular dynamics simulations (MD), Markov State Model (MSM), to evaluate the equilibrium distribution of conformers and their equilibration time, and metadynamics (MetaD), to enhance the fluctuations of relevant collective variables (CVs) and efficiently recover the rates of rare events. Firstly, we investigate the effect - if any - of increasing supersaturated solutions on the conformers distribution and equilibration. From MD simulations, we note that for increasing concentrations while the average local density raises, the conformers population shows no significant redistribution. The creation of denser clusters with MetaD also does not induce either conformer selection or ordering on a ns timescale. Hence, we infer that the local increase of density associated with the formation of clusters in solution does not favour any specific conformational rearrangement. Interestingly, the kinetics of the conformers equilibration becomes slower at higher concentrations, from 0.2ns for an isolated molecule to 0.65ns for highly supersaturated solutions. However, the rearrangement of the heavy atoms of the succinic acid skeleton is still a fast process. On the contrary, we observe that the rotation of the carboxylic hydrogen atoms takes place on significantly longer timescale, two order of magnitudes slower than conformers equilibration. The formation of hydrogen bonds (OH—O) that characterise succinic acid crystals might thus be a rate determining step for nucleation. Finally, we investigate solutions in which form nuclei of increasing size are introduced and restrained not to dissolve. The presence of an ordered cluster, containing exclusively a specific planar conformer, does not induce conformational selection. Interestingly, however, when the restrain on the cluster is lifted, the dissolution process takes place in two steps: firstly, the conformer population within the nucleus is equilibrated, and then the cluster is dissolved. Such mechanism is in agreement with the fast equilibration of conformers, but, it does not shed a light on the mechanism of conformational selection at play during the formation of ordered clusters. In conclusion, we observe a remarkable decoupling between clustering phenomena and conformer selection for succinic acid in water. This suggests that the nucleation mechanism cannot be classical: the fast conformational rearrangements appears to inhibit the creation and stepwise growth of a stable nucleus with a bulk structure compatible with that of macroscopically stable crystals.

References

[1] P. Lucaioli, E. Nauha, I. Gimondi, L. S. Price, R. Guo, L. Iuzzolino, I. Singh, M. Salvalaglio, S. L. Price, N. Blagden, CrystEngComm, 2018, 20(28), 3971–3977

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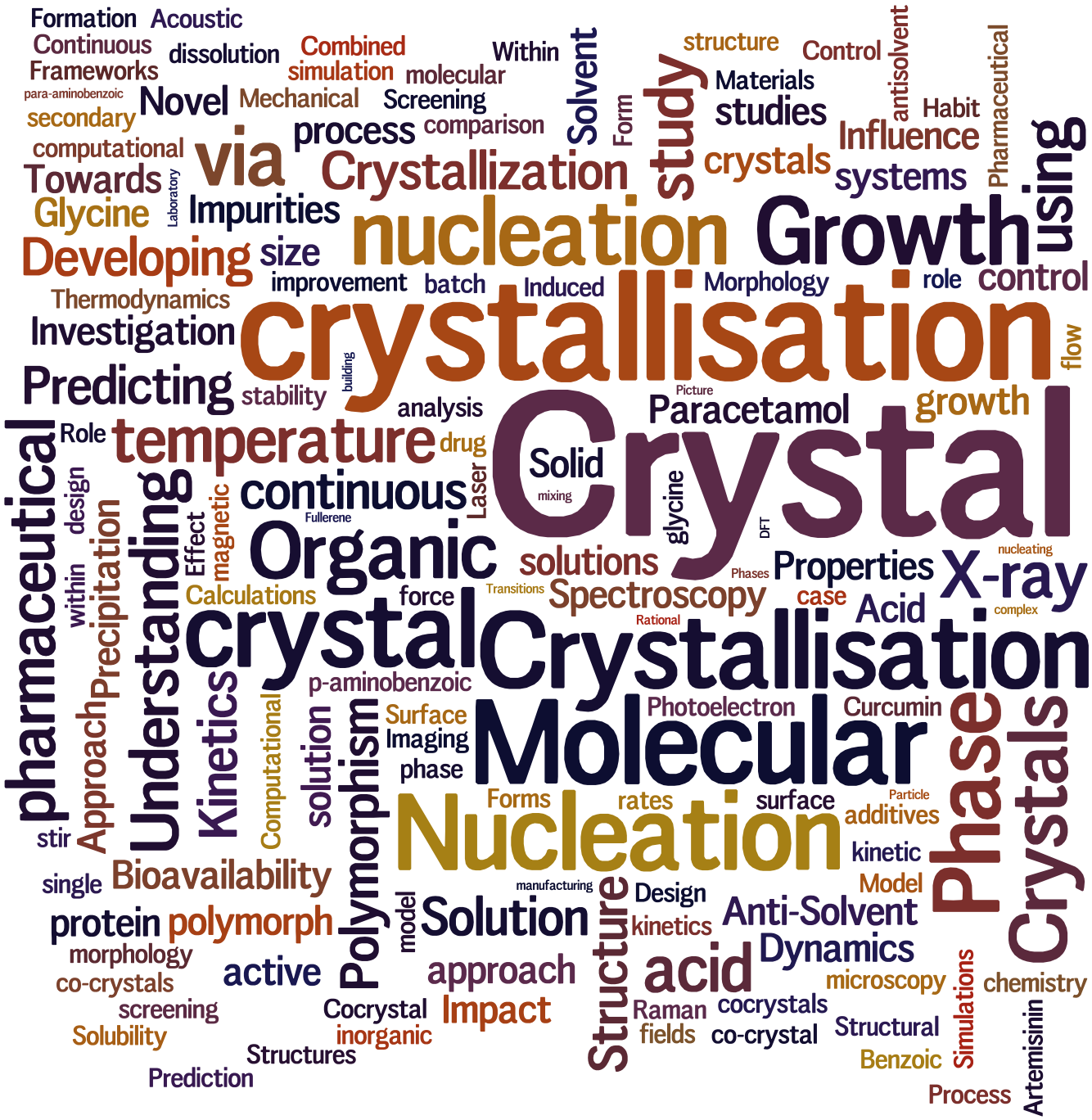

P001 Food Crystal Engineering at the University of Leeds

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Many food products such as salt, sugar and butter are crystalline and several complex food structures such as ice cream contains crystals. Crystal properties such as shape, size and polymorphism can have a dramatic effect on the properties of these food products in terms of stability, taste and texture as well as bioavailability. Therefore, tailoring crystal properties and controlling crystal nucleation and growth during food product manufacturing is essential to ensure the final product quality. The Crystal Engineering Approach utilises the understanding of the intermolecular interactions within a crystalline structure for the predictive, systematic design of crystals with specifically tailored properties as well as the crystallization processes necessary to achieve such crystals. Our group is applying this crystal engineering approach for: (1) better understanding the effect of crystal properties on the quality of complex food structures; (2) designing optimal manufacturing processes to control crystal nucleation and growth and obtained crystals with the desired properties; (3) developing novel control technologies and strategies to monitor crystallization processes. Few examples of our work include molecular modelling of flavonoid structures, foam stabilization using fat crystals and complex soft structure characterization using ultrasound, rheology and X-ray tomography. Figure 1 shows selected examples of the work currently being carried out in the group.

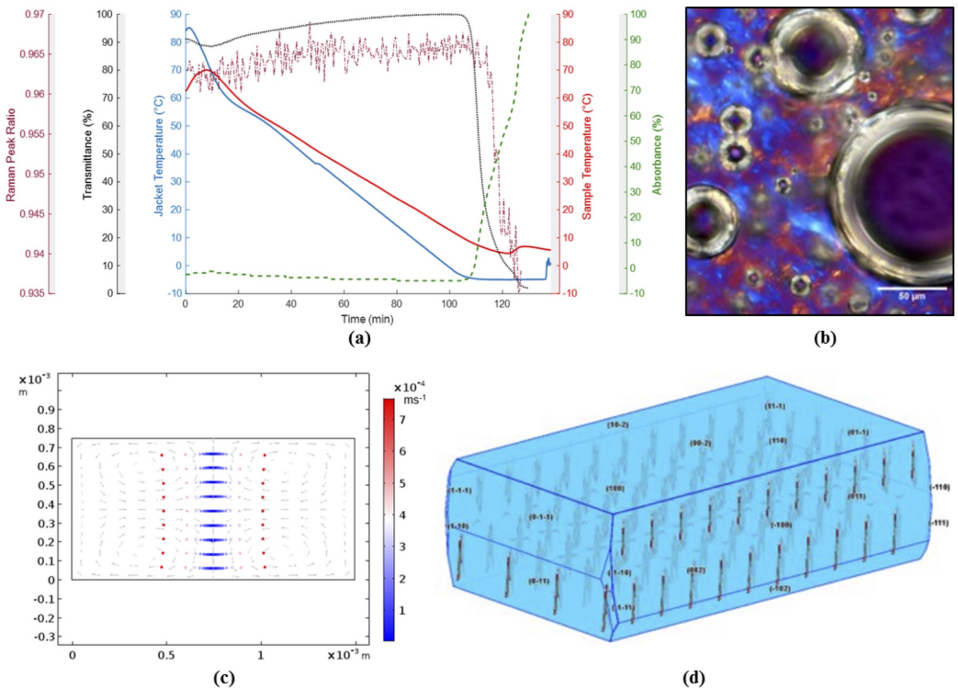

Figure 1: (a) Design, monitoring and control of crystallization processes; (b) Design of crystals for soft structures stabilization; (c) Fluid dynamic modelling of particle fractionation; (d) Molecular modelling of hydrate structures.

P002 pH and Temperature Dependent Solubilities and Eutectic Points for the Continuous Chiral Resolution by Integration of Membrane and Crystallisation Technologies

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This contribution is presented also as a talk. The abstract is reported in the talks section, Thursday 11th of July, Engineering Crystallization Parallel Session.

P003 In situ X-ray diffraction analysis of continuous segmented flow crystallisation at Diamond Light Source

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Continuous flow crystallisation is a growing field in the pharmaceutical industry, however thus far; the evaluation of crystallisation processes via in situ X-ray techniques has been limited [1]. The presented project aims to implement flow crystallisation and self-assembly methods compatible with beamlines on the Diamond synchrotron, extending applications in molecular materials discovery and self-assembly to crystallisation in a manufacturing context. Monitoring of continuous crystallisation processes by a range of synchrotron radiation techniques are being developed in a series of in situ experiments, using bespoke crystallisers optimised for operation on the beamlines at the Diamond Light Source (DLS). The first of these devices is the KRAIC-D (Kinetically Regulated Automated Input Crystalliser [2] at Diamond; Figure 1) segmented flow crystalliser, adapted for in-beam operation, and developed as a collaboration between Bath, Leeds and Diamond. The design of the KRAIC-D encompasses viewing windows, which facilitate X-ray penetration at set points along the length of the crystalliser. In the segmented flow employed in the KRAIC-D the solution passing a particular set point will always be at the same stage of the crystallisation process. Continuous crystallisation of the model system Carbamazepine (CBZ) in ethanol in the KRAIC-D platform on beamline I11 (high resolution powder diffraction) will be presented. The effect of introducing a controlled solid interface into the crystallisation process is investigated, where CBZ form III seeds are introduced in polymorphic purity at different seeding positions (pre- and post-nucleation) throughout the length of the KRAIC-D. The KRAIC-D design has recently been adapted to be compatible with the small molecule single crystal beamline I19; the updated design is the KRAIC-S. In situ studies have been used to successfully collect diffraction data on paracetamol single crystals grown in situ and tumbling in solution slugs, allowing full peak indexing to be achieved from a series of diffraction images. **References**

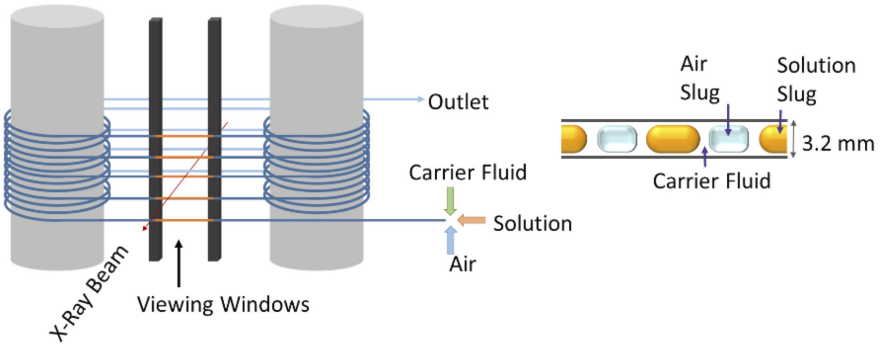

Figure 1: Schematic of KRAIC-D showing segmented flow and position of viewing windows

[1] Alison et al, Phys. Chem. Chem. Phys., 2003, 5, 4998-5000
[2] Robertson et al, Robertson, K., Flandrin, P.-B., Klapwijk, A. R. and Wilson, C. C., 2016. Design and Evaluation of a Mesoscale Segmented Flow Reactor (KRAIC). Crystal Growth and Design, 16 (8), pp. 4759-4764

P004 The uses and abuses of a database of computer generated crystal structures

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Since the start of the CPOSS (Control and Prediction of the Organic Solid State) project in 2003, we have been storing the CSP-generated crystal structures and associated properties. Our database of computed crystal structures [1] was set up in an eScience collaboration in 2005, and holds the metadata associated with all DMACRYS-minimized [2] computed crystal structures. This database is continuing to grow, with almost half a million crystal structures of over 200 different chemical compositions, many with different variations on the computational methods. The range of methods could include search structures with only rigid molecule energies, flexible molecule refinement, or include rigid body harmonic approximations to the room temperature free energy. One of the most exciting aspects of our work is when experimentalists have found a new polymorph of a compound we have studied by CSP.[3] Having the CSP-generated structures available in the database can aid with structure solution from powder diffraction or solid state NMR etc. New computational methods. As new methods, such as calculation of magnetic properties, have developed, we might want to revisit old searches and calculate these properties. Some properties can be stored, but the database is not currently able to accept new property types. With structures re-evaluated with respect to these new properties, the aim is to design experiments to target new forms. Risks. We know that most points on the landscape are not "predicted polymorphs", as many will not be free energy minima at room temperature.[4] We are still learning how changes in experimental conditions affect polymorphic outcome, through comparisons of CSP studies with extensive polymorph screens and targeted experiments. The unobserved low energy structures provide a stringent test of our understanding of crystallization kinetics.[5]

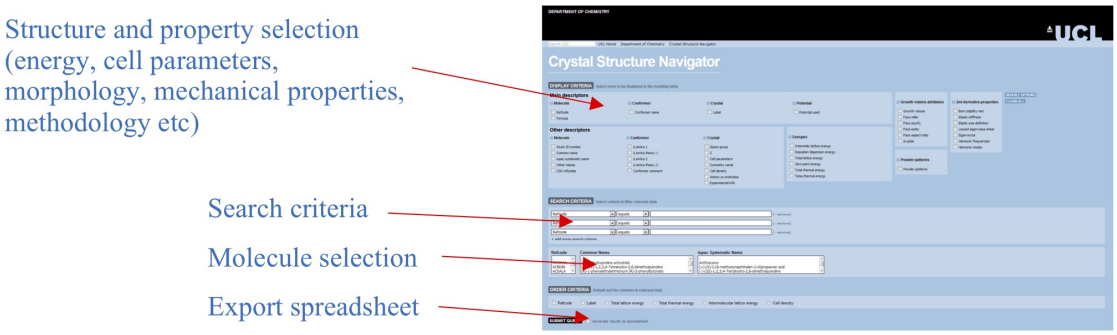

Figure 1: The Crystal Structure Navigator database search engine. New experimental structures.

References

[1] Roberts, L.; Blanshard, L. J.; van Dam, K. K.; Price, S. L.; Price, L. S.; Brown, I. In Providing an Effective Data Infrastructure for the Simulation of Complex Materials, Nottingham, 2006, National eScience Centre: Nottingham, pp 101-105.

[2] Price, S. L.; Leslie, M.; Welch, G. W. A.; Habgood, M.; Price, L. S.; Karamertzanis, P. G.; Day, G. M., Modelling Organic Crystal Structures using Distributed Multipole and Polarizability-Based Model Intermolecular Potentials. Physical Chemistry Chemical Physics 2010, 12, (30), 8478-8490.

[3] Askin, S.; Cockcroft, J. K.; Price, L. S.; Gonçalves, A. D.; Zhao, M.; Tocher, D. A.; Williams, G. R.; Gaisford, S.; Craig, D. Q. M., Olanzapine Form IV: Discovery of a New Polymorphic Form Enabled by Computed Crystal Energy Landscapes. Crystal Growth Design 2019, 10.1021/acs.cgd.8b01881.

[4] Price, S. L., Why don't we find more polymorphs? Acta Crystallographica Section B: Structural Science, Crystal Engineering and Materials 2013, 69, 313-328.

[5] Price, S. L., Is zeroth order crystal structure prediction (CSP_0) coming to maturity? What should we aim for in an ideal crystal structure prediction code? Faraday Discussions 2018, 211, 9-30.

P005 Bridging Molecular and Macroscopic Models of Solution Thermodynamics

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The equilibrium behaviour of natural aqueous solutions can be predicted using chemical thermodynamic models of solvent and solute activities. However, existing thermodynamic models of electrolyte solutions are semi-empirical [1-2]: (i) the values of parameters in the model equations are fitted to experimental measurements; (ii) key molecular level processes controlling the behaviour of aqueous electrolyte solutions (hydration and association of ions) are not treated explicitly. Major advances in the ability of these models to predict the properties of complex aqueous solutions, over wide ranges of solution conditions, are only likely when the molecular-level processes affecting solutes and solvent are explicitly described in the model. In this work we propose a strategy to reparametrize thermodynamic models using atomistic calculations: it uses information on the structure and dynamics of water molecules from ab initio molecular dynamics simulations of electrolyte solutions in numerical expressions which can subsequently calculate solute and solvent activities at a wide range of concentrations. For example, we will show that the effective hydration number parameter h in Zavitsas' model [3] can be obtained from the analysis of the hydrogen-bonding autocorrelation function of the water molecules surrounding the ions. The performance of the Zavitsas' and other models reparametrized using this approach is compared to experimental activity coefficients. Our approach represents a unique upscaling tool to bridge molecular simulations and macroscopic models of electrolyte solutions.

References

[1] R.H. Stokes and R. A. Robinson. Ionic Hydration and Activity in Electrolyte Solutions. J. Am. Chem. Soc. 1948, 70, 1870-1878

[2] H. W. Nesbitt. The Stokes and Robinson Hydration Theory: A Modification with Application to Concentrated Electrolyte Solutions. Journal of Solution Chemistry 1982, 11.

[3] A. A. Zavitsas. Aqueous solutions of calcium ions: hydration numbers and the effect of temperature. J Phys Chem B 2005, 109 (43), 20636-40.

P006 Understanding the dissolution behaviours of single co-crystals at molecular level using Non-contact Atomic force microscopy and Molecular dynamic simulations

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In recent years, pharmaceutical cocrystals have been studied extensively for enhancement of solubility and dissolution rates of poorly water soluble drugs. Understanding the dissolution mechanisms of pharmaceutical cocrystals is key for optimal product design. In this study, we used the combined techniques, atomic force microscopy [1,2] and molecular dynamics simulations [3], to understand the dissolution behaviour of cocrystals at molecular level. Single co-crystals of Flufenamic acid were successfully synthesised using the co-formers Nicotinamide and Theophylline. The surface morphology, dissolution rate, mechanisms of these single co-crystals and re-crystallisation on the surface were studied in distilled water in presence/absence of PEG, PVP, and PVPVA polymers. AFM results indicated that the dissolution and re-crystallisation of FFA and FFA-TP occurred in bulk solution whereas it recrystallized on the surface of FFA-NIC. The AFM results showed that PVPVA polymer was the best dissolution inhibitor followed by PVP then PEG for all single co-crystals. Molecular dynamics simulations were carried out to calculate binding energies, mean square displacement (MSD), radius of gyration evolution and radial distribution function between a polymer and cocrystal surface. Simulations revealed that PVP had coiled up, reducing its surface area considerably, suggesting least reactivity with the surfaces. The MSD results show that the mobility of PEG is the highest in the simulations, indicating low reactivity with the crystal surface. PVPVA was found to be the best dissolution inhibitor for the cocrystals, which is in good agreements with AFM experiments.

References

[1] H. M. Cuppen, W. S. Graswinckel, and H. Meekes. "Screw Dislocations on Polycenes: A Requirement for Crystallization." Crystal growth and Design, 2004: 1351-1357.

[2] Rimer JD, An Z, Zhu Z, Lee MH, Goldfarb DS, Wesson JA, Ward MD. "Crystal growth inhibitors for the prevention of L-cystine kidney stones through molecular design." Science, 2010: 337-341.

[3] Alexandra Nemkevich, H.-B. B. M. A. S. a. B. C., 2010. Molecular dynamics simulations of structure and dynamics of organic molecular crystals. Physical Chemistry Chemical Physics, pp. 14916-14929 .

P007 Developing Novel Multi-Component Crystal Forms of Artemisinin for Bioavailability Improvement

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Artemisinin, derived from the Asian plant Artemisia annua, is an active pharmaceutical ingredient used to treat multi-drug resistant strains of malaria and is also in early stages of development as an anti-cancer drug [1]. However, due to poor water solubility, low bioavailability of artemisinin after oral administration has led to inadequate treatments and high costs because of complicated chemical structure modification needed in the formulations. In recent years, Pharmaceutical cocrystals have drawn significant interests for its ability to enhance solubility and dissolution rate of poorly water-soluble drugs through supramolecular interactions between a drug and coformer [2]. In this project, a cocrystallisation approach will be used to synthesize novel Artemisinin cocrystals to overcome the absorption problems of Artemisinin caused by the intrinsic disadvantages of low solubility and dissolution rate. To develop novel Artemisinin cocrystals, both computational and experimental screening approaches have been used in the study. Computational screening based on molecular electrostatic potential surfaces is used to predict coformers which will have potential forming a cocrystal with Artemisinin [3]. Experimental Screening based on neat and liquid assisted grindings with four different solvents varying polarity is used to explore if coformers form a cocrystal with Artemisinin from the prediction of computational screening [4]. In this study, 86 coformers have been screened using the computational method. Among those, 30 coformers with highest probability of forming a cocrystal with Artemisinin have been screened using the experimental methods. From those, two coformers have been found to form cocrystals with Artemisinin. Structural determination of these two cocrystals will need to be done using solution methods to produce single crystals. Formulation development of the two cocrystals will be conducted in the future.

References

[1] S. Karki, T. Friscic, L. Fabian, W. Jones, CrystEngComm, 2010, 12, 4038
[2] N. Qiao, M. Li, W. Schlindwein, N. Malek, A. Davies, G. Trappitt, International Journal of Pharmaceuticals, 2011, 419, 1, 1
[3] D. Musumeci, C. A. Hunter, R. Prohens, S. Scuderia, J. F. McCabec, Chemical Science, 2011, 2, 883
[4] D. Hasa, E. Miniussi, W. Jones, Crystal Growth and Design, 2016, 16, 4582

P008 Computational studies of p-aminobenzoic acid self-association in solutions

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[2] Department of Chemical Engineering and Thomas Young Centre, University College London, London UK

p-Aminobenzoic acid (pABA) is known to exist in four different polymorphic forms, α,β, γ and δ. The α polymorph is the most accessible, as it can be crystallised from nearly all solvents and supersaturations, whereas polymorph β can be consistently obtained only by crystallisation from water or ethyl acetate at supersaturation below $\tilde{1}.35$ (higher supersaturations yield α form) [1, 2]. Here, in order to uncover polymorph selection effects in the early stages of nucleation, we investigate the impact of the solvent and supersaturation on the self-association of pABA in solution using molecular simulations. To meet the aim we perform molecular dynamics (MD) simulations of pABA in explicit solutions, and analyse its transient clusters distribution using graph-theory based clustering methods [3]. Our results indicate that $\pi - \pi$ stacked associates are favoured in all solvents and supersaturations. The thermodynamically preferred associate in water solutions at all supersaturations is a stacked dimer (Fig.1A); besides, larger stacked pABA entities, such as trimers and tetramers, are also favoured over pABA monomers. In ethanol and ethyl acetate the dominant specie is stacked trimer and larger clusters are more common than in water. Notably, carboxylic hydrogen bonded dimers, typically considered to be the main growth unit in solution, were observed only rarely. For instance, less than 1% of associated pABA molecules in water solutions were involved in carboxylic hydrogen bonding reaching fractions up to 10% in ethanol and ethyl acetate. While small molecular clusters (<5 molecules) dominate in all solvents, simulations in water revealed stable aggregates comprised of 20 to 40 pABA molecules (Fig.1B). These aggregates do not exhibit crystal-like structure, however, the stacking motif that is commonly observed in smaller associates is still maintained. Since no such clusters were observed in ethanol and ethyl acetate, it is not excluded that such aggregates might act as precursors for the nucleation of the β polymorph of pABA.

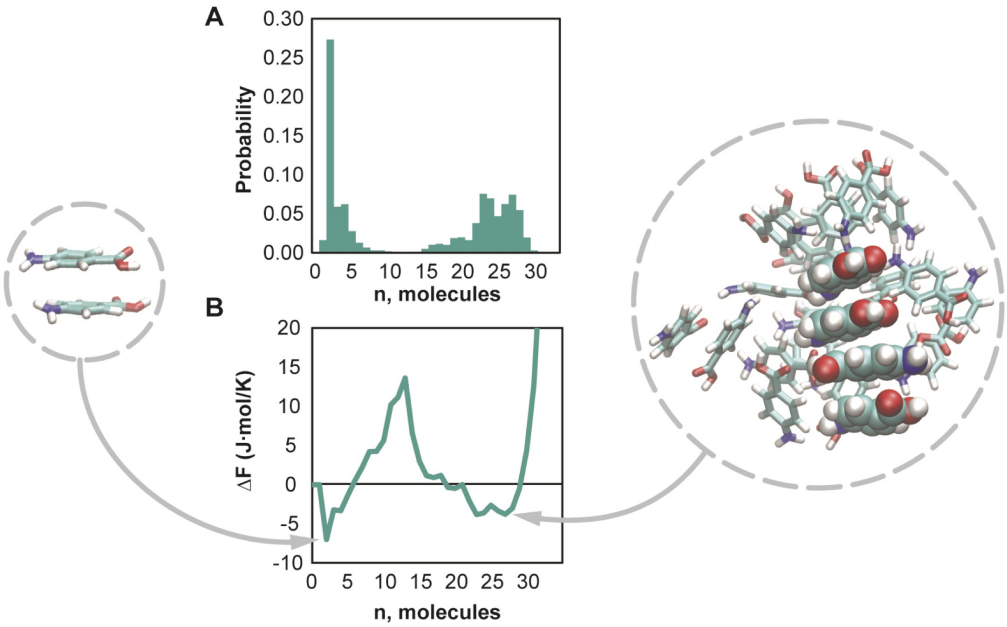

Figure 1: (a) (A) The probability distribution and (B) free energy profile of the pABA self-associate size in water at supersaturation 1.5. Examples of observed thermodynamically favoured structures are depicted next to the graphs. The stacked pABA molecule motif that is typically present in aggregates is shown as VdW spheres.

References

[1] S. Gracin, Å. C. Rasmuson, Crytal Growth Design, 2004, 4 (5), 1013
[2] A. J. Cruz-Cabeza, R. J. Davey, I. D. H. Oswald, M. R. Ward, I. J. Sugden, CrystEngComm, 2019, 21, 2034
[3] G. A. Tribello, F. Giberti, G. C. Sosso, M. Salvalaglio, M. Parrinello, J. Chem. Theory Comput., 2017, 13 (3), 1317

P009 Polymorphism in 4'-Hydroxyacetophenone: The full Picture from 0 K to Fusion

C. E. S. Bernardes[1], P. L. T. Melo[1], D. Yu. Ilin[2], V. A. Lukyanova[2], A. I. Druzhinina[2], M. E. M. d. Piedade[1]

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4'-Hydroxyacetophenone (HAP, Figure 1a) has, in the last decade, emerged in our group as an excellent model to investigate diverse aspects of polymorphism and crystallization. Two polymorphs and three hydrates have been identified up to now, and characterized from structural, stability domains, solid state transitions and crystallization points of view.[1-6] Solubility studies demonstrated that the two polymorphs (Form I, monoclinic, P21/c, Z' = 1 and Form II, orthorhombic, P212121, Z' = 2) are enantiotropically related by a solid-solid phase transition at 303 K, where packing, molecular conformation, and Z' simultaneously change. Reversible interconversion of both forms at that temperature only occurs, however, under slurry conditions. Indeed, due to high kinetic barriers [5], the Form II→Form I transition can only be detected in the solid state, if the sample is heated to temperatures significantly above 303 K (i.e. metastable zone widths of 30-60 K, depending on the heating rate) and the reverse process has never been observed. Capitalizing on this irreversible behaviour, we used adiabatic calorimetry and molecular dynamics (MD) simulations to investigate the thermal behaviour of both HAP polymorphs down to $\tilde{5}$ K. The adiabatic calorimetry experiments revealed the existence of a previously unknown fast and reversible enantiotropic phase transition, present in both polymorphs at $\tilde{7}$9 K (Figure 1b). The MD results showed no evidence of modifications in the crystal packing upon the transition (further confirmed by companion neutron diffraction analysis), [7] and also indicated that the observed thermal events are most likely related to the rotational freedom of the methyl group, which changes from a locked to a hindered-rotation regime. The full thermal behaviour and thermodynamic properties of both HAP polymorphs from 0 K to the fusion temperature will also be presented.

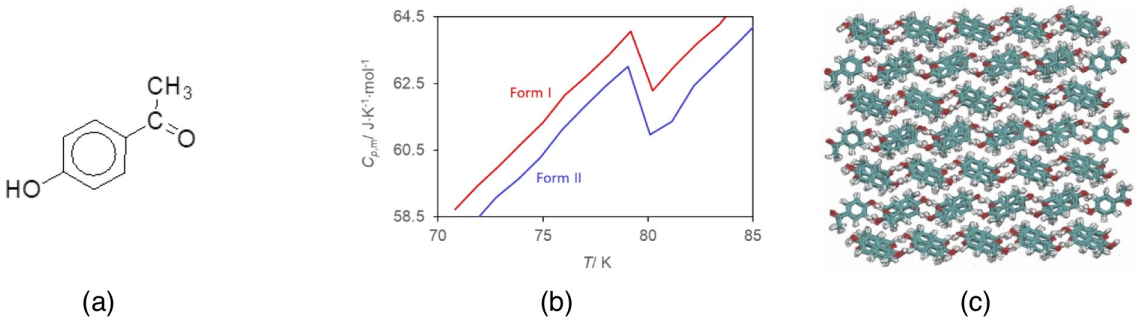

Figure 1: (a) 4'-hydroxyacetophenone (HAP); (b) Heat capacity curves obtained for forms I and II HAP by adiabatic calorimetry in the phase transition; (c) A snapshot from the MD simulations on Form I.

References

[1] C. E. S. Bernardes, M. F. M. Piedade, M. E. Minas da Piedade; Cryst. Growth Des. 2008, 8, 2419.
[2] C. E. S. Bernardes, M. F. M. Piedade, M. E. Minas da Piedade; Cryst. Growth Des. 2010, 10, 3070.
[3] C. E. S. Bernardes, M. E. Minas da Piedade; Cryst. Growth Des. 2012, 12, 2932.
[4] (a) C. E. S. Bernardes, M. L. S. Matos Lopes; J. R. Ascenso, M. E. Minas da Piedade; Cryst. Growth Des. 2014,14, 5436; (b) C. E. S. Bernardes, L. Ilharco, M. E. Minas da Piedade; J. Mol. Struct. 2014, 1078, 181.
[5] A. Joseph, C. E. S. Bernardes, A. I. Druzhinina, R. M. Varushchenko, T. Y. Nguyen, F. Emmerling, L. N. Yuan, V. Dupray, G. Coquerel, M. E. Minas da Piedade; Cryst. Growth Des. 2017, 17, 1918.
[6] M. Gutmann, C. E. S. Bernardes, M. E. Minas da Piedade, unpublished.

P010 Designing multi-component crystal forms of Praziquantel for Bioavailability improvement

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Praziquantel is an effective drug for the treatment of parasitic diseases caused by trematodes and cestodes[1]. However, the effectiveness of the drug has been limited by its low aqueous solubility. In comparison with many other strategies, such as cyclodextrin complexation and formulations of solid dispersions, crystallization approach has shown a huge potential for solubility improvement without affecting the original safety and therapeutic properties of the drug. The aim of the work is to discover novel cocrystals of Praziquantel for its solubility improvement. This will be achieved through combination of computational and experimental screening techniques. Computing screening method based molecular electrostatic potential surfaces will be used to determine the coformers which could potentially form cocrystals with Praziquantel [2]. Experimental screening will be carried out to confirm if the coformers can cocrystallise with the drug. The experimental methods include both neat and liquid assisted grinding techniques. Finally, the structures of novel Praziquantel cocrystals will be determined based single cocrystals from solvent crystallization techniques.

References

[1] EL-Arini, S.K. and Luenberger, H. Pharmaceutica Acta Helvetiae, 1998, 73(2), 89

[2] R. Musumeci, C. A. Hunter,R. Prohnes, S.Scuderia,J.F.McCabec, Chemical Science, 2011,2(5), 883

P011 The influence of tailor-made additives on the crystallisation of p-aminobenzoic acid

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Chemical additives are known to have a significant impact on the nucleation behaviour of crystal systems, but the fundamental knowledge of how they promote and/or inhibit crystallisation is not yet fully understood. This study focusses on the effect of introducing structurally similar additive molecules to the crystallisation behaviour of p-Aminobenzoic acid (pABA) in ethanol (EtOH). A classical drug screen was conducted on a number of appropriate candidate molecules to identify an additive which significantly impacted the crystallisation of pABA. Induction time and metastable zone width (MSZW) studies found that p-Nitrophenol (pNPL) had a significant accelerating effect on the nucleation of pABA, significantly reducing the time to crystallisation and the MSZW, respectively. The use of the KBHR approach [1,2] to assessing crystallisation kinetics, determined a mechanism change from instantaneous nucleation (IN) [3] to progressive nucleation (PN) upon the addition of pNPL to the pABA in EtOH solution. Growth was also found to be affected, leading to an increased aspect ratio of the needle-like morphology of pABA. Co-crystallisation studies were performed to determine how pNPL interacted with pABA. Differential Scanning Calorimetry (DSC) and x-ray diffraction (XRD) of a 1:1 mol sample prepared by dry grinding showed the presence of a pABA-pNPL co-crystal (Fig. 1). Molecular modelling corroborated these findings, with stronger pNPL-pABA molecular interaction energies when compared to pABA-pABA. The ability of a structurally-related additives to alter the mechanism by which a solute nucleates is of great importance, as systems that are required and/or desired to nucleate in a certain way could make use of additives to direct nucleation. Furthermore, the identification of new co-crystal is of great interest, as they can be used to modify the properties of solid phases, such as their solubility and bioavailability.

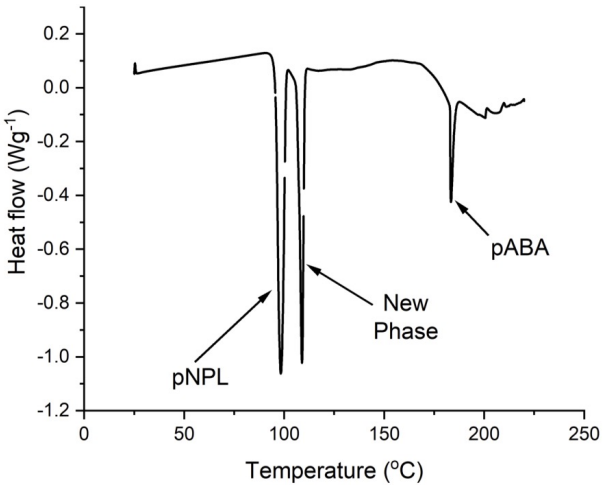

Figure 1: DSC performed on a sample of suspected pABA-pNPL co-crystal prepared by dry grinding, showing the emergence of a new phase.

References

[1] Kashchiev, D. Borissova, A. Hammond, R.B. Roberts, K.J. Effect of cooling rate on the critical undercooling for crystallization. Journal of Crystal Growth. 2010;312(5):698-704.
[2] Kashchiev, D. Borissova, A. Hammond, R.B. Roberts, K.J. Dependence of the Critical Undercooling for Crystallization on the Cooling Rate. The Journal of Physical Chemistry B. 2010;114(16):5441-6.
[3] Toroz, D. Rosbottom, I. Turner, T.D. Corzo, D.M.C. Hammond, R.B. Lai, X. et al. Towards an understanding of the nucleation of alpha-para amino benzoic acid from ethanolic solutions: a multi-scale approach. Faraday Discussions. 2015; 179(0):79-114.

P012 A comparison of solution nucleation kinetics of methyl stearate calculated from analytical and numerical solutions of the KBHR model

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Polythermal crystallisation is a well-studied route to determine key nucleation and growth parameters, however, it is widely accepted that expressions used to interpret data through this method lack a theoretical basis and do not allow for a deeper understanding of both nucleation and growth mechanisms. One such method that could overcome these limitations is the Kashchiev-Borissova-Hammond-Roberts (KBHR) model [1,2]. It makes use of the classical theory for stationary three-dimensional homogeneous (HON) and heterogeneous (HEN) nucleation and is based upon the Kolmogorov-Johnson-Mehl-Avrami (KJMA) formula, enabling a description of phase transformation kinetics. It permits the calculation of key kinetic parameters and also allows for the mechanism of nucleation, either progressive nucleation (PN) or instantaneous nucleation (IN), to be determined, through "the rule of three". Nevertheless, the current analytical solution to the KBHR model is subject to inequalities that limit its applicability to relatively low supersaturation crystallisation conditions. In this research an alternative and more rigorous numerical solution to the KBHR model, as implemented with gPROMS [3] software, is presented. This is illustrated through application to the nucleation of methyl stearate from kerosene solution. The data was collected within the limits of the inequalities, with the results for both the analytical and numerical solution to the KBHR model compared, providing information about the possibility for global implementation of KBHR.

References

[1] Kashchiev, D., Borissova, A., Hammond, R. B. Roberts, K. J. Effect of cooling rate on the critical undercooling for crystallization. Journal of Crystal Growth 312, 698–704 (2010).
[2] Kashchiev, D., Borissova, A., Hammond, R. B. Roberts, K. J. Dependence of the critical undercooling for crystallization on the cooling rate. Journal of Physical Chemistry B 114, 5441–5446 (2010).
[3] Process Systems Enterprise Limited. PSE. (2018). Available at: https://www.psenterprise.com/.

P013 Isothermal by design: An accelerated approach to the prediction of the crystallisability of slowly nucleating systems

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A route to the accelerated nucleation of -para-aminobenzoic acid (pABA) in ethanol:water (EtOH:H_2O) mixed solvent solutions, using antisolvent crystallisation, is presented, accessing solution supersaturations (S) unachievable through conventional crystallisation routes. An 'isothermal by design' (IbD) approach is adopted, whereby the exothermic enthalpy of mixing associated with antisolvent addition is offset by the control of the temperature of the antisolvent added. Induction times (τ) are found to be reduced by over three orders of magnitude using this methodology, consistent with the use of this approach as a nucleation acceleration technique. A comparison of values and reproducibility of τ between those determined from the IbD methodology and by experiments where the enthalpy of mixing was not taken into account, demonstrate how effective the IbD route is to obtain more accurate and useful kinetic information. Calculation of the nucleation kinetic parameters for a range of solution concentrations, compositions and supersaturations reveal that effective interfacial tensions (γ_{eff}) varies from 8.4 to 2.3 mJ m^{-2} from solutions in H_2O solvent and EtOH solvent, respectively, in line with the trend in solubility. The critical nucleus radius (r*) is calculated to decrease from 1.98 nm to 0.40 nm associated with a decrease in the number of molecules in the critical nucleus (i*) from 196 to 2 molecules. A change in nucleation mechanism from heterogeneous nucleation (HEN) to homogeneous nucleation (HON) is observed to take place at S≈ 1.5.

P014 Another 120year-old Solid-state Puzzle involving Acetaldehyde Phenylhydrazone. Why did Fischer and Causse not agree?

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At last year's bacg meeting, Hugo Meekes presented on acetaldehyde phenylhydrazone (APH). The same structure melted at vastly different temperatures. The reason was that the crystal, dependent on the acidity of the medium from which it had been crystallised, fuses to different melts [1]. This is the antithesis of Polymorphism, for which different crystal structures fuse to the same melt. In 1896, Emil Fischer [2] asserted that acetaldehyde reacted with phenylhydrazine to give only APH. Causse stated simultaneously [3] that APH cannot be obtained, only the cage product from further reaction. Both Fischer and Causse were right and both were wrong. Both products are formed and undoubtedly both experimenters has both sorts of products in their hands. The confusion arose because APH when prepared in acid solution typically melts at 60^{o}C in neutral solution at 80oC and in alkaline solution at 100^{o}C. We have found that the cage compound has 3 polymorphs of melting point about 60^{o}C, 80^{o}C and 103^{o}C. Given that the early investigators were so dependent on melting points for identification, the possibility for confusion is apparent. What is remarkable is that Causse should have been able to identify to identify the cage compound with so few tools at his disposal. In trying to understand the conversion from phenylhydrazone to cage compounds, we reacted benzaldehyde with phenyl hydrazine which gives only benzaldehyde phenylhydrazone, whilst formaldehyde gives only cage compounds. Propionaldehyde gives an unexpected hydrated propionaldehyde phenylhydrazone. The reactions are exceedingly erratic and what we have been unable so far to find is a reliable route to the acetaldehyde cage compound, although XS acetaldehyde, sodium thiosulfate or borax is sometimes effective. The commonest products are orange-red tars although dark green esmeraldine-like compounds are sometimes formed. We have also been unable so far to produce mixed substituent cage compounds which may give some insight as to the mechanism.

References

[1] Bernardes, C. et al CGD, 2019, 19, 907
[2] Fischer, E., Ber, 1896,29, 795:1897, 30, 1240.
[3] Causse, H., Bull. Soc. Chim. Fr., 1897, 17, 234, 342; Comptes rendues, 122, 197, 940, 1274.

P015 Is the Metastable Zone Width of Magnesium Sulfate >12^{o}C, ∼6^{o}C or >1^{o}C?

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We have been investigating the seeding of Magnesium sulfate solutions for over 6 years, seeking to establish seeding factors and mechanism, largely by Design of Experiment studies. Other than the much enhanced crystallisation by magnetic as opposed to overhead stirring, presumably due to the generation of nascent surfaces [1], no seed preparation, presentation, size, mass or surface area or solution or process variation has any effect. This must raise questions as about the accepted wisdom of seeding processes. Even a momentary dipping of a crystal in solution is just as effective as quantities of loose seeds. On the other hand there are vast differences between different set sets of experiments. We had examined in detail 16 potential seeding factors, but had overlooked two key ones, ageing and cycle history. New solutions in new vessels cycled slowly had MZW>12^{o}C, cycled quickly 6^{o}C: re-used solutions or solutions in re-used vessels had MZW 2-7^{o}C cycled slowly but as little as 0.1^{o}C cycled rapidly. All these measurements refer to heating and cooling rates at the events of 1^{o}C per hour. The reason for the difference with cycle time was hydration change. Metastable hexahydrate crystallises even when seeded with stable hydrate (Ostwald's Rule of Stages). But during slow ramps it converts to heptahydrate with a higher dissolution point. The ageing effect might be related to retention of crystals, to solution structure, or to templating of surfaces. We favour the latter explanation, since overheating had no effect. The reason why the misbehaviour of magnesium sulfate has not previously been noticed in many, many studies is presumably that larger vessels with inevitable slow cycle times and aged solutions have been used

References

[1] Rousseau, J. Cryst Growth, 1972.

P016 Developing classical models of piezoelectric biological crystals

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Advances in piezotronics and piezo-phototronics have led to improved materials for devices [1]. Atomistic simulations at the quantum level, in particular DFT calculations, have played a key role in guiding experiments. Illustrations of this simulation-led design are the reverse growth of two ZnO crystals back to back which leads to considerable increase of the piezoelectric properties [2]; and the size effect on mechanical and piezoelectric properties of nanowires [3]. Recently, the piezoelectric properties of biological molecules such as synthetic polypeptides or amino acid crystals have attracted a lot of attention for their potential use in biopiezoelectric generators. DFT calculations show the high piezoelectric coefficients of amino acid crystals originate from an efficient packing of the molecules along certain crystallographic planes and directions [4]. Calculations combined with experiments help measure the variation of the piezoelectric constants in collagen building blocks, such as the collagen-like alanine-hydroxyproline-glycine trimer peptide, as the crystal symmetry is lowered and the molecule size increases. The piezoelectricity of collagen building blocks can be easily tuned, e.g., addition of an hydroxyl group doubles the piezoelectric constants [5]. Thus, first principles calculations can guide experimental crystal growth, device fabrication and electrical testing. Despite the success of the building block approach, DFT is limited to crystal structures with few hundreds of atoms in the unit cell. Extrapolation may work to some extent for fibrils that carry and scale up the dipole moments of their building blocks but fails for the complex charge balance in globular proteins. Large bio/macromolecules can contain on order of ten thousand atoms and inclusion of solvent, surfactants and ions make it even more challenging to model with a QM approach. Classical forcefields have been successfully used to study, predict, understand many biological systems, and even guide experiment and biological re-engineering. However, they were initially parameterised for liquid phase proteins, not protein (or amino acid) crystals. In this work, we aim to devise an accurate, fast and intuitive classical model to estimate elastic and piezoelectric constants of amino acid and peptide crystals. Early tests on amino acid crystals yield poor results with standard force fields and a completely new parametrisation may be required. Conversely, protein crystals with bound water molecules and ions may be predicted with relatively few adjustments of the standard and polarisable force fields.

References

[1] Y. Zhang, Y. S. Leng, M. Willatzen, and B. L. Huang, MRS Bull., 2018, 43, 928.
[2] R. Baraki, N. Novak, T. Fromling, T. Granzow, and J. Rodel, Appl. Phys. Lett., 2014, 105, 4.
[3] H. D. Espinosa, R. A. Bernal, and M. Minary-Jolandan, Adv. Mater., 2012, 24, 4656.
[4] S. Guerin, A. Stapleton, D. Chovan, R. Mouras, M. Gleeson, C. McKeown, M. R. Noor, C. Silien, F. M. F. Rhen, A. L. Kholkin, N. Liu, T. Soulimane, S. A. M. Tofail, and D. Thompson, Nature Materials, 2018, 17, 180.
[5] S. Guerin, T. A. M. Syed, and D. Thompson, Nanoscale, 2018, 10, 9653.

P017 Passive Acoustic Emission for Crystallization

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Passive acoustic emission (PAE) which has been applied successfully for monitoring a wide variety of solids elaboration processes (e.g. particle size in granulation, end-point detection in drying, granulation etc. [3]-[9]) has recently been evaluated in the field of industrial crystallization [1, 2]. At Bayer the technology has been evaluated and has been realized successfully for seed treatment end-point detection (BaySTEP®, https://youtu.be/psSBmE912Pg) in production. Figure 1 shows a typical acoustic burst for this technique. In this work the technology has been tested in lab scale for the detection of nucleation events during crystallization. For a real system (cooling crystallization) nucleation events could be detected qualitatively at different cooling rates. Thereby, an easy to measure variable, the average sound level (ASL) has been used and the detection of nucleation events has been validated with a standard in-line sensor (Focused Beam Reflection Measurement). Summarizing, the non-invasive, low cost and easy maintenance technique has shown first promising results in the laboratory and will be tested in large scale crystallizers soon.

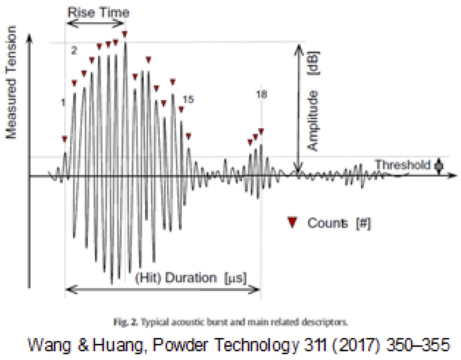

Figure 1: Typical acoustic burst during crystallization process.

References

[1] Wang Huang, Powder Technology, 2017, 311, 350–355
[2] Gherras et al., IJoP, 2012, 439, 109-119
[3] Wang et al., Powder Technology, 2016, 301, 70–77
[4] E.M. Hansuld et al., Powder Technol., 2012, 219, 111–117
[5] Jayakumar, C.K. et al. J. Mater. Process. Technol., 2005, 159, 48–61
[6] D. Daniher et al., Powder Technol., 2008, 181, 130–136
[7] E.M. Hansuld et al., Int. J. Pharm, 2009, 378, 37–44
[8] M. Whitaker et al., Int. J. Pharm., 2000, 205, 79–91
[9] J.T.T. Leskinen et al., Chem. Eng. J., 2010, 164, 268–274

P018 Oxcarbazepine Form III: Observation of Twisted Habit in Crystals of an Elusive Pharmaceutical Polymorph

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Crystals exhibiting twisted habit have been observed at the nanoscale, mesoscale, and macroscale and pose challenges with respect to structural characterisation because of their lack of long-range translational symmetry [1]. Crystal structure prediction (CSP) investigations of an active pharmaceutical ingredient's lattice energy landscape are a potent tool for assisting experimentalists in identifying and characterising novel polymorphic forms that are thermodynamically feasible, including ones that crystallise with twisted morphologies [2-4]. Oxcarbazepine (OXCBZ) is a pharmaceutical used for the treatment of epileptic seizures and three polymorphic forms have been reported, two of which (form I and form II) crystallise in the monoclinic space groups P21/c and P21 respectively [5]. OXCBZ form III was originally prepared by slow evaporation from methanol solutions containing polymer additives but structure determination was not possible because of the small size and poor quality of the crystals produced. Herein, we present robust protocols for the crystallisation of OXCBZ III from both solution and the vapour phase. Our efforts combined CSP studies of OXCBZ with physical vapour deposition and solution-based polymorph screening experiments. Needle-like and fibre-like crystals of form III exhibiting variable twisted habit were serendipitously obtained through vapour deposition of OXCBZ onto metallic substrates. By performing scanning electron and atomic force microscopy investigations we have managed to gain insight into the mechanism of formation and growth of the twisted OXCBZ III crystals over the course of the deposition process.

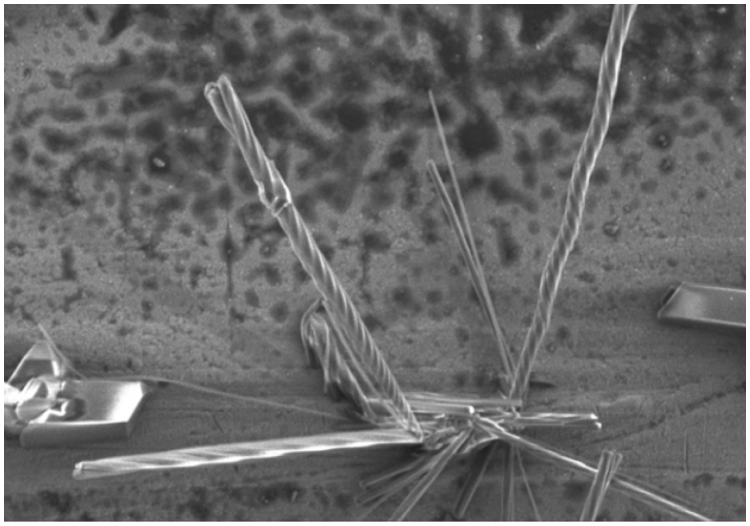

Figure 1: (SEM micrograph showing twisted crystals of OXCBZ form III grown via physical vapour deposition.

References

[1] A.G. Shtukenberg, Y.O. Punin, A. Gujral, B. Kahr, Angew. Chem. Int. Ed., 2014, 53, 672 – 699
[2] S.L. Price, Phys. Chem. Chem. Phys., 2008, 10, 1996-2009
[3] J.B. Arlin, L.S. Price, S.L. Price, A.J. Florence, Chem. Commun., 2011, 47, 7074–7076
[4] A.G. Shtukenberg, Q. Zhu, D.J. Carter, L. Vogt, J. Hoja, E. Schneider, H. Song, B. Pokroy, I. Polishchuk, A. Tkachenko, A.R. Oganov, A.L. Rohl, M.E. Tuckerman, B. Kahr, Chem. Sci., 2017, 8, 4926-4940
[5] K.M. Lutker, A.J. Matzger, J. Pharm. Sci., 2010, 99, 794-803

P019 Disappearing conglomerates

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As the majority of active pharmaceutical ingredients are chiral, resolution methods to separate their enantiomers are of great importance for the pharmaceutical industry [1]. Preferential crystallisation, second order asymmetric transformation (SOAT) and deracemization are different processes for obtaining pure enantiomers; [2] however, these methods all have in common the need for a stable conglomerate forming system. The system discussed in this work is an atropisomer couple of enantiomers understood to be a conglomerate forming system [3]. Indeed, in the CSD, 2'-(phenylmethoxy)-[1,1'-Binaphthalen]-2-ol] (Binol- OBn) is reported with the space group P212121 (refcode UBULUB, CCDC 1443741) and the binary phase diagram with its two enantiomers possessing a 'stable' conglomerate has been established. However, upon crystallisation in our laboratory a stable racemic compound appeared. This new racemic compound was characterized by means of: Differential Scanning Calorimetry, IR spectroscopy, Second Harmonic Generation and single crystal X-ray diffraction.

Discussion. The conglomerate melts about 30 degrees lower than the newly identified racemic compound. With such a large difference in melting points, one can wonder how the conglomerate could have ever been observed. The complexity of the racemic compound structure with three molecules with different conformations in the asymmetric unit might explain this rare case. Moreover, a fast racemization is observed in the molten state. The structure of the racemic compound will be compared to that of the enantiomer. The following open question should now be carefully considered: how to predict the threat that such a case would occur in an industrial setting, while using a conglomerate forming system?

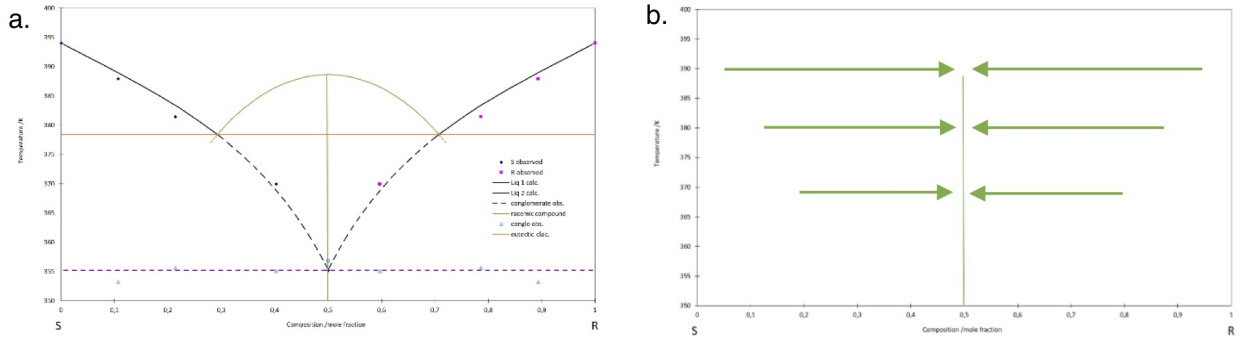

Figure 1: Revisited binary system between enantiomers of 2'-(phenylmethoxy)-[1,1'-Binaphthalen]-2-ol], a) without considering racemization, b) considering racemization in the molten state.

References

[1] Brooks, W. H.; Guida, W. C.; Daniel, K. G. The Significance of Chirality in Drug Design and Development. Curr. Top. Med. Chem. 2011, 11 (7), 760–770.
[2] Novel Optical Resolution Technologies; Sakai, K., Hirayama, N., Tamura, R., Eds.; Topics in Current Chemistry; Springer-Verlag: Berlin Heidelberg, 2007.
[3] Maria, T. M. R.; Marins, F. A.; Costa, J. B. S.; Silva, M. R.; Carrilho, R. M. B.; Monteiro, C. J. P.; Pereira, M. M.; Eusebio, M. E. S. Thermochim. Acta 2017, 648, 32–43.

P020 Investigation of the Crystallisation of Phase Change Materials

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The phenomenon of crystallisation has impeded a substantial number of chemical processes from pharmaceuticals, semiconductors, food products, and phase change materials. Therefore, an elaborate understanding of the area is required to manipulate the rate and conformation of the crystal growth. Hereby, the initial nucleus morphology must be researched to uncover its effect on the crystal. Only when the nucleation process is fathomed, will it be possible to modify the surroundings of the material to attain the desired crystallisation. Crystallisation, the process of the crystal formation and growth, exposes the ordered solid form of a material. The phenomenon of crystallisation has impeded a substantial number of chemical processes from pharmaceuticals, semiconductors, food products, and phase change materials. All the areas listed require a high calibre of understanding of crystallisation and, more significantly, the method of controlling it. [1] Although the crystal growth determines many characteristics, the nucleation plays a crucial role in the crystallisation. Nucleation, the initial cluster formation in the crystal, has been proven to very difficult to control as it is initiated by a variety of factors like impurities, temperature fluctuations, surfaces and pH. Overall, this stems how vital a thorough knowledge of crystallisation is to a large range of scientific disciplines. [2]

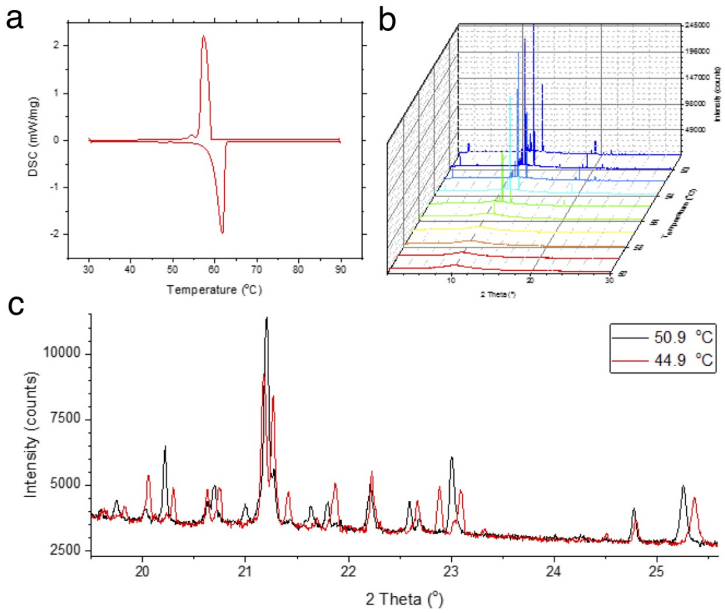

Figure 1: The DSC (a), temperature-controlled (b) and comparison (c) powder XRD of CrodaTherm 60

Phase Change Materials An essential focus of crystallisation is in the physical transformation of solid-liquid phase change materials. Here, the energy storage credentials of phase change materials is hindered via the ordering of the crystalline solid. Down to the effect of crystallisation has on the density and uniformity of the solid material; it would hinder the heat transfer, energy storage density and transformational volume change. This impedes the application it has on all its use in areas including food, buildings and textiles.[3] Croda Europe Ltd produces a range of organic non-paraffin phase change materials, each under the name of CrodaTherm^{TM} followed by a number corresponding to its melting point. Thus, thermo-analytical techniques such as powder x-ray diffraction, differential scanning calorimetry and confocal Raman spectroscopy are useful tool in analysing each CrodaTherm^{TM}.

References

[1] F. Artusio and R. Pisano, International Journal of Pharmaceutics, 2018, 547, 190-208.
[2] U. V. Shah, C. Amberg, Y. Diao, Z. Q. Yang and J. Y. Y. Heng, Curr. Opin. Chem. Eng., 2015, 8, 69-75
[3] M. K. Rathod and J. Banerjee, Renew. Sust. Energ. Rev., 2013, 18, 246-258

P021 Crystal Growth of L-Cystine, atomic force microscopy and simulation

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L-Cystine ($C_6H_{10}O_4N_2S_2$) is an amino acid. At normal pH, L-cystine crystallizes as hexagonal plates expressing 0001 face. The accumulation of L-cystine crystal in the body results in highly recurring kidney stone. In this work, in-situ atomic force microscopy (AFM) combined with computer simulation was used to study the growth of L-cystine. There are six molecules in the unit cell that has a space group P6122. The growth of L-cystine crystal is predominantly via screw dislocations in [0001] direction. The screw axis is expressed as a pinwheel of minor steps that rotate clockwise around the c-axis by 60^o. The anisotropy of the bonding in the unit cell results in six interlaced layers that resemble a stacked island. The height of each stack is 5.6 nm corresponding to the c unit cell length in the hexagonal crystal and the height of each step is 0.8-0.9 nm which equates the length of a molecules in the unit cell; c/6. Near the core, different patterns of growth were observed that are attributed to change in the supersaturation. Moreover, at high supersaturation, a finger-like structure was observed on both the terraces and near the core. The molecular imposter; L-cystine dimethyl ester (LCDME) was added to study their effect on L-cystine growth. There was a major change in the crystal morphology from hexagonal plates to tetragonal needles that is only crystallized under very basic solution; pH>8. In addition, different facets exhibit different pattern under AFM. *CrystalGrower* [1] is a Monte-Carlo simulation program developed by Manchester group(1) that is used to simulate these features. Both morphologies were simulated successfully as well as the finger-like structure on terraces.

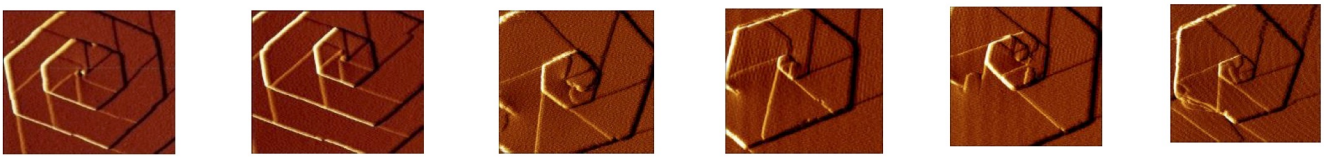

Figure 1: Different patterns of growth at spiral core

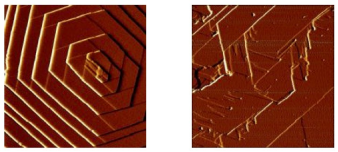

Figure 2: Finger-like structure at the screw core and on terraces

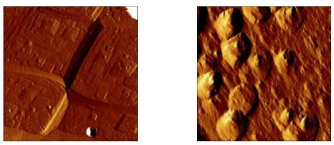

Figure 3: AFM images of (001) and (101) facets

Figure 4: Simulated morphologies; a) hexagonal plates, b) tetragonal needles and c) finger-like structure

References

[1] Predicting crystal growth via a unified kinetic three-dimensional partition model Michael W. Anderson, James T. Gebbie-Rayet, Adam R. Hill, Nani Farida, Martin P. Attfield, Pablo Cubillas, Vladislav A. Blatov, Davide M. Proserpio, Duncan Akporiaye, Bjørnar Arstad Julian D. Gale Nature, 2017, 544, 456-459.

P022 Developing a method to determine the flux of material arriving and leaving a crystal at equilibrium

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It is often said that a crystal in a saturated solution neither grows nor dissolves, however, this is an equilibrium so there must be some flux between the crystal and the solution. The question is how could this be measured. The aim of this work was to develop a method to make this measurement, as a prelude to investigating the effect of ultrasound on the rate of molecular exchange between the surface layer of a growing crystal and the surrounding slightly supersaturated solution. The challenge of labelling the molecules in the crystal as distinct to those in the surrounding solution can be overcome by taking an isotopically labelled material where the atoms in the label are not labile and do not play a critical part in intermolecular hydrogen bonds thus 2H labelled samples were considered unsuitable. Therefore, a ^{15}N $^{13}C_2$ labelled paracetamol was selected as the model compound. The next challenge was to develop an experimental methodology in order to control both the saturation of the surrounding solution and the ultrasonic intensity, which the crystal is exposed. Starting from a paracetamol solution saturated at 20°C, slight temperature decreases in the order of 0.20C, were made to achieve different saturation values. The ultrasonic field was quantified using a needle hydrophone for intensity measurement and by varying the percentage of the power of the ultrasonic bath. In addition, the mass and morphological changes to the crystal before and after ultrasonic intervention were measured (Figure 1). The final component in the process was to establish a method to quantify the amount of labelled material leaving the crystal. The extent and rate of molecular transfer from the crystal into the solution as a function of relative supersaturation and ultrasonic field intensity were measured using complementary techniques NMR and LC-MS. This enables assessment of the range of conditions under which crystal growth is accompanied by loss from the surface by dissolution and estimation of the relative magnitude of the flux in each direction.

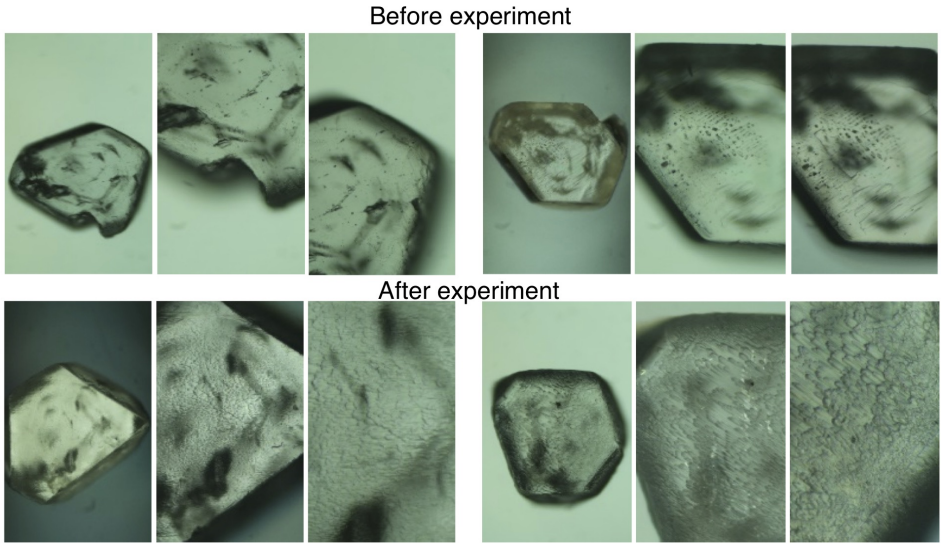

Figure 1: Two crystal faces of an isotopic paracetamol crystal before and after ultrasonic intervention (carried out at 50% power and 20°C) .

References

Thai T. H. Nguyen et al. Crystals 2017, 7, 294.

P023 Conundrum of glycine nucleation revisited: to stir or not to stir?

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Glycine is the smallest amino acid and it has three polymorphs: α, β and γ under ambient conditions. All three polymorphs can be crystallised from aqueous solution in the absence of additives or cosolvents under suitable conditions. However, it is widely reported that α is predominantly obtained in conventional cooling crystallisation, although γ is the stable form under ambient conditions. The understanding of glycine nucleation from aqueous solutions is limited, although various theories have been proposed [1]. Key challenges are obtaining reliable data on nucleation kinetics and corresponding solid forms [2] and decoupling the effects of primary and secondary nucleation, and crystal growth kinetics in the competitive crystallisation of multiple polymorphs. In this work, we investigate effects of agitation, temperature and glycine concentration on polymorph formation of glycine from aqueous solution [3]. The crystallisation of two polymorphs of glycine (α and γ) was investigated over a wide range of glycine concentrations. We performed controlled cooling (without agitation) from 90^{o}C down to 0^{o}C. The samples were then kept isothermal at 0^{o}C for 3h to monitor crystal formation, with or without agitation. The effect of agitation was investigated under isothermal conditions with different stirring rates using a magnetic stirring bar. Polymorphs were identified using FTIR and powder XRD. Figure 1 shows that stirring has a dramatic effect on polymorphic outcome and promotes the fast formation of after the final temperature was reached, as expected. Surprisingly, γ was predominantly obtained in the absence of agitation at higher concentrations and lower temperatures. This may be due to two possible effects: enhancement of α nucleation by fluid shear (as we recently demonstrated in Couette cell and capillary flow [4]) or secondary nucleation of α triggered by agitation in the presence of γ crystals nucleated spontaneously.

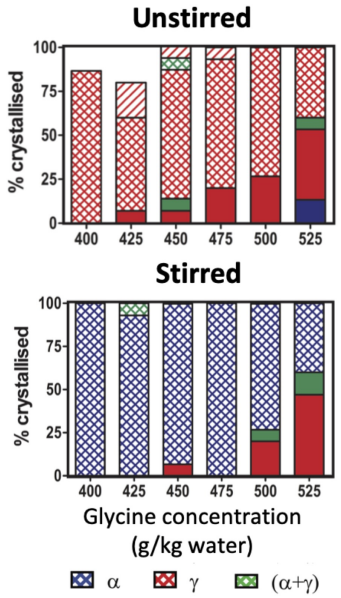

Figure 1: Crystallisation of glycine solutions under (a) quiescent conditions with stirring bar present, and (b) stirring at 1600 rpm. For each concentration, the percentage was calculated over 15 vials.

References

[1] C.S.Towler et al., J. Am. Chem. Soc. 2004, 126 13347; S. Chattopadhyay et al., Cryst. Growth Des. 2005, 5, 523; A. Jawor-Baczynska. et al., Cryst. Growth Des. 2013, 13, 470; A. Jawor-Baczynska et al., Faraday Discuss. 2013, 167, 425.
[2] K. Renuka Devi, K.J. Srinivasan, Cryst. Growth 2014, 401, 227; L. J. Little et al., Cryst. Growth Des. 2015,15, 5345; J. Chem. Phys. 2017, 147, 144505.
[3] M.J. Vesga et al., CrystEngComm 2019, 21, 2234.
[4] C.P. Forsyth et al., Cryst. Growth Des. 2015, 15, 94; C. Forsyth et al., Cryst. Growth Des. 2016, 16, 136.

P024 Spectroscopic and computational study of association of 2-chloro-4-nitrobenzoic acid in solution

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2-chloro-4-nitrobenzoic acid (2C4NBA) has been disclosed for the treatment of immuno-deficiency diseases, e.g., the HIV infection, and has been reported to form two polymorphs I (Z'=1, one conformer) and II (Z'=4, both conformers) as well as several solvates [1,2]. In the evaporation crystallization no clear explanation for formation of either I or II could be established, so study of molecular association was performed to try to rationalise the crystallization outcome and explore crystallization control possibilities. IR spectra of 2C4NBA at various concentrations in different solvents suggested that the equilibrium between dimers and monomers can be observed in the least polar solvents – toluene, o-xylene, chloroform and dichloromethane. The presence of more than one peak in carbonyl stretching region for each species was explained by the presence of both conformers among monomers and more than one of their combinations among dimers. In other solvents (alcohols, DMSO, ethers, ACN, nitromethane) there were 2-3 peaks, but their position, position difference and the absence of characteristic variation of intensity ratio with concentration suggested that these peaks should correspond to associates with solvent molecules. Also NMR measurements at various concentrations confirmed that among the studied solvents the equilibrium between dimers and monomers can be observed in particularly toluene and chloroform. However, in other solvents (DMSO, MeOH, THF, acetone, and ACN) NMR appeared to be more informative than the IR measurements, as in fact two different association processes could be identified one having high association constant (K_{ass} = 1̃600) where chemical shift saturation was reached for 1̃0-30 mM solution and the other one having low association constant (K_{ass} = 0̃.1-0.3) thus starting to affect the chemical shift only above 10-30 mM. Association Gibbs energy calculations in solvent continuum in Gaussian 09 suggested that in most of the solvents the most stable associates would be hydrogen bonded dimers. The exception from this is alcohols where hydrogen bonded dimers are not stable, but several $\pi - \pi$ stacked dimers are stable instead. Nevertheless, this is not consistent with the experimental observations, although also in the calculations hydrogen bonded dimers were the most stable species in the least polar solvents. Preliminary results from the MD simulations confirmed the observations in spectroscopic measurements, as hydrogen bonded dimers were present only in the least polar solvents, while in polar solvents association with solvent molecules occurred, and some $\pi - \pi$ stacking dimers were also present.

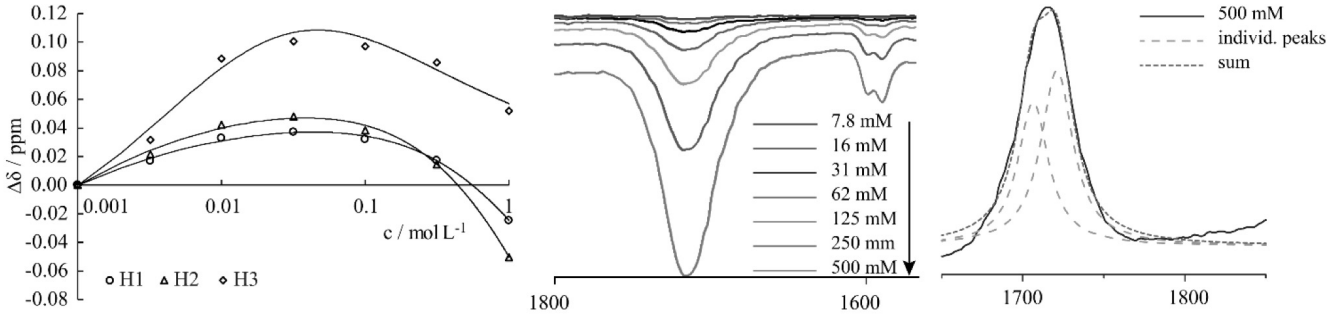

Figure 1: Spectroscopic characterisation of 2C4NBA association in DMSO solution. On the left: change of 1H NMR shifts by increasing the concentration, in the middle: carboxylic stretching band in IR spectra at different concentrations, and on the right: deconvolution of the carboxylic stretching band in IR spectra.

References

[1] I. Barsky, J. Bernstein, P.W. Stephens, K.H. Stone, New J. Chem. 2008, 32, 1747-1753

[2] S. Aitipamula, P.S. Chow, R.B.H. Tan, CrystEngComm 2011, 13, 1037-1045

P025 The role of structural complexity during the early nucleation stages of MOF building units in solution

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Porous materials, such as Metal-Organic Frameworks (MOFs), have great potential in a broad range of applications from carbon capture and storage to industrial separations, catalysis and drug delivery [1]. Interactions between metal clusters and organic linkers result to the large surface area and porosity of MOFs. Nevertheless, their synthesis is not thoroughly understood; hence it usually proceeds by implementing trial-and-error practices. This work provides a mechanistic and systematic way to treat the early stages of nucleation that is the rate-limiting step in MOF synthesis. Nucleation spontaneously follows the assembly of three isomer half secondary building units (half-SBUs) [2]. In our work we choose MIL-101(Cr), a MOF with several potential applications, which has been studied extensively in the literature. We investigate the early stages of MIL-101(Cr) nucleation using Molecular Dynamics with Well-Tempered Metadynamics [3] on two collective variables (CVs). The chosen CVs correspond to the smallest values in the sets of distances between the metal centres and the terminal carboxylic carbons of organic linkers with the metal centres. These CVs let us explore the configurational landscape of interactions between all possible pairs of the MIL-101(Cr) half-SBU isomers forming units that are likely to be incorporated in the crystal lattice. The role of composition of the parent phase is assessed through an extensive sampling of SBU isomers, consisting of multi-microsecond simulations of half-SBU couples in solution. Simulations were performed in water and DMF, both in absence and presence of ions (Na^+, F^-), with a classical force field validated at a higher order of theory in order to allow thorough sampling of the dimerization free energy landscapes. We compute a total of 60 free energy surfaces projected on the 2 CVs. A remarkable ensemble of 300 different SBU conformational isomers emerge from this work. We classify SBUs between structures that resemble units present in the experimentally obtained crystal lattice as well as potential defects. Free energy estimates for different SBU isomers forming through interactions between initially detached half-SBUs are obtained from this analysis. This enables us to compute the equilibrium distribution of species in various conditions with respect to the initial fraction of half-SBU isomers and to the solution composition. Ultimately, in this work we understand how ionic species promote crystal-like SBUs over defects providing a molecular-level understanding for the experimental observation that ions favour crystallinity [4,5]. In DMF, SBU conformers are appreciably more stable and compact in comparison with water. Additionally, the initial distribution of half-SBUs is correlated with the likelihood to incorporate defects during the early nucleation stages. We further verify these findings by performing large scale molecular dynamics simulations of half-SBU nucleation in explicit solvent.

References

[1] Li, J. R.; Sculley, J.; Zhou, H. C., Chem. Rev., 2012, 112 (2), 869-932.
[2] Cantu, D. C.; McGrail, B. P.; Glezakou, V. A., Chem. Mater., 2014, 26 (22), 6401-6409.
[3] Barducci, A.; Bussi, G.; Parrinello, M. , Phys. Rev. Lett., 2008, 100 (2), 020603.
[4] Whitehead, G. F.; Cross, B.; Carthy, L.; Milway, V. A.; Rath, H.; Fernandez, A.; Heath, S. L.; Muryn, C. A.; Pritchard, R. G.; Teat, S. J.; Timco, G. Winpenny, R. E., Chem. Commun., 2013, 49 (65), 7195-7197.
[5] Kollias, L.; Cantu, D. C.; Tubbs, M. A.; Rousseau, R.; Glezakou, V.-A.; Salvalaglio, M., J. Am. Chem. Soc., 2019, 141 (14), 6073 – 6081.

P026 Elastic Properties of Solid Forms from First Principles

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The elastic properties of a crystal contain extensive information about the response of a material to applied stress and strain and influence key properties such as hardness, powder flexibility, and tabletability. Different polymorphs and solid forms of an active pharmaceutical ingredient (API) can exhibit markedly different elastic and mechanical properties, and therefore understanding the mechanical properties of different solid forms would greatly aid pharmaceutical solid-form development. However, experimentally characterising elastic properties is challenging and time-consuming. In recent years, computational methods, particularly dispersion-inclusive density-functional theory (DFT+D), have been maturing for studying the stability and properties of molecular crystals.[1, 2] This opens up the possibility of calculating elastic properties (Figure 1), even of postulated solid forms. In this contribution, DFT+D methods have been used to calculate the elastic properties of a series of archetypal APIs, including paracetamol forms I and II, aspirin form I, and piroxicam. The elastic properties will be compared to experimental data, existing calculated results, and the density-functional tight-binding semi-empirical method, which is computationally orders of magnitudes faster than DFT+D. This benchmark work will serve as a bridge towards studying plastic behaviour and eventually mechanochemistry based on first-principles methods.

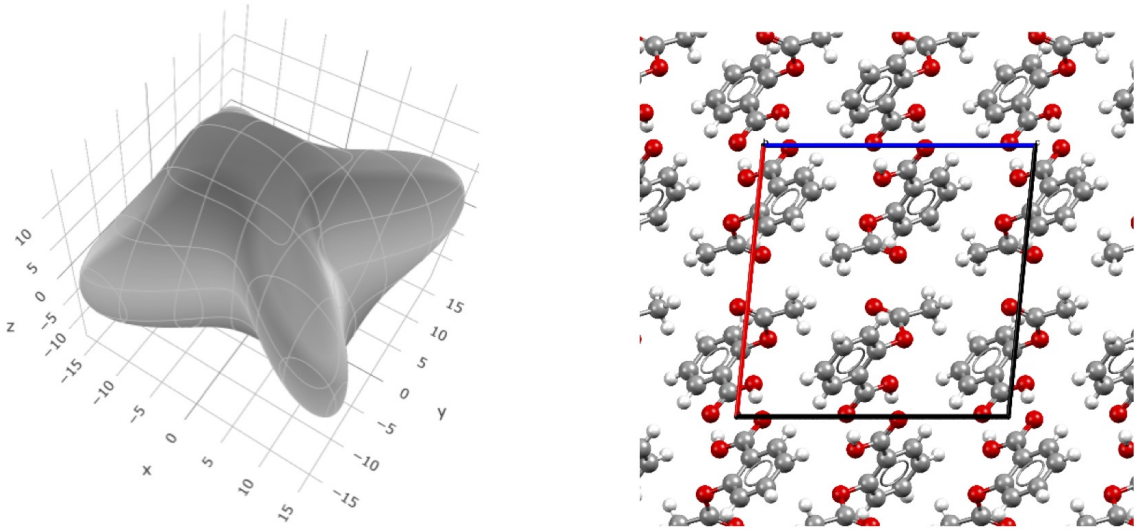

Figure 1: A spherical plot of Young's modulus of aspirin I determined by using DFT-calculated elastic constants. The x and y axes are parallel to the a and b lattice vectors respectively, with the z axis perpendicular to x and y.

References

[1] A. M. Reilly and A. Tkatchenko, Understanding the role of vibrations, exact exchange, and many-body van der Waals interactions in the cohesive properties of molecular crystals, J. Chem. Phys., 2013, 139, 024705.

[2] A. M. Reilly and A. Tkatchenko, Role of Dispersion Interactions in the Polymorphism and Entropic Stabilization of the Aspirin Crystal, Phys. Rev. Lett., 2014, 113, 055701.

P027 Nucleation Kinetics of Benzoic Acids from Solution – The Impact of Molecular packing and Conformation

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The precise molecular mechanisms that control the process of nucleation from solution remain subject to much debate and speculation [1,2]. Recently, we showed that in the case of para-substituted benzoic acids nucleating from a range of solvents that the nucleation kinetics are controlled by the attachment of molecules to the growing nuclei via aromatic ring stacking interactions [1]. Here, we turn our attention to the additional impact of conformational flexibility in determining the nucleation rate (Fig. 1). We present new data in which we compare our existing results with new measurements on an alkyl and alkoxy benzoic acid. Firstly, the potential energy surfaces are calculated in order to assess the flexibility of the molecules in solution. Subsequently, the CSD together with Mogul geometry searches are implemented to explore how the important torsions are populated in known crystal structures. By examining and exploring this statistical and energetic scope of torsional freedom in these molecules, we are able to draw conclusions about how conformation can be an important rate determining factor and molecular feature in this stochastic nucleation process.

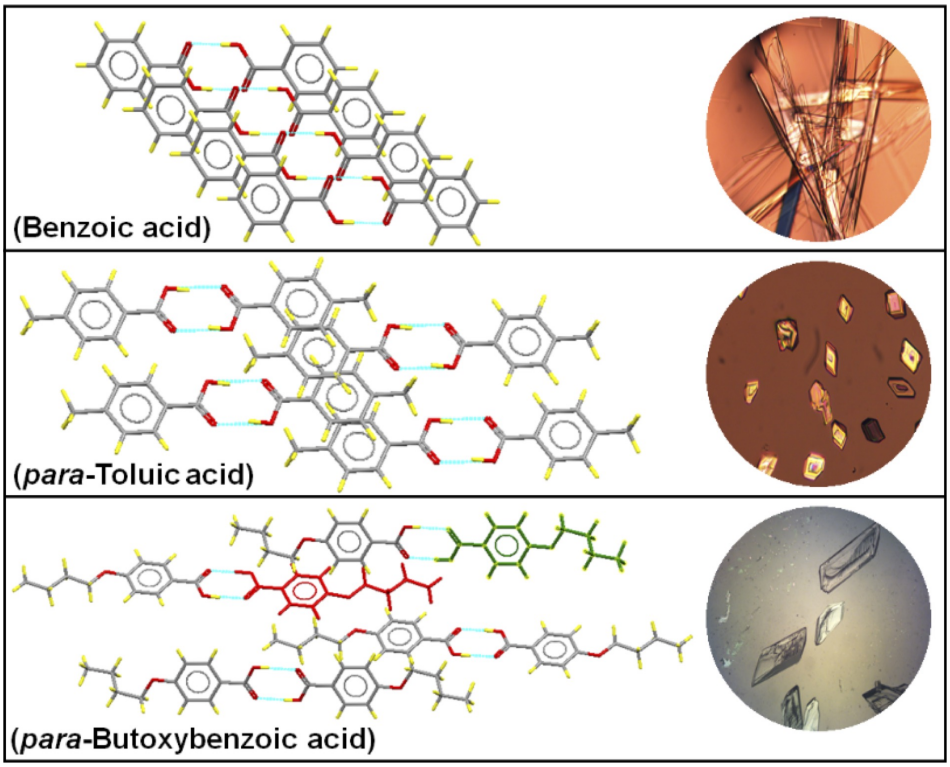

Figure 1: Geometries of stacked dimers in the crystal structures and optical micrographs

References

[1] A. J. Cruz-Cabeza, R. J. Davey, S. B. Salim Sachithananthan, R. Smith, S. K. Tang, T. Vetter, Y. Xiao, Chem. Commun., 2017, 53, 7905-7908.
[2] Y. Xiao, S. K. Tang, H. Hao, R. J. Davey, T. Vetter, Cryst. Growth Des., 2017, 17, 28522863.

P028 A simulation study of the coupled plug flow crystallizers for the separation of the conglomerate forming enantiomers

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Crystallization is an attractive means to separate the conglomerate forming racemic mixtures since typically the chiral crystal structure is highly selective towards preferred enantiomer while no reagents other than solvent are needed. Pharmaceutical industry is on the verge of a paradigm shift from batch to continuous crystallization processes. This shift is necessary to cope with increased molecular size complexity, quality purity specifications and sustainability demands of future manufacturing processes. In this work, a simulation study is carried out for a recently proposed coupled plug flow crystallizers (PFC) (which can be approximated by continuous oscillatory baffled crystallizer (COBC) in an industrial setup) for the separation of conglomerate forming enantiomers [1]. A schematic of the crystallizer configuration is shown in Figure 1(a). This configuration consists of two PFCs coupled through solid free liquid phase exchange while cooling crystallization is carried out. Each of these PFCs are continuously fed with saturated racemic solution containing homochiral seeds which promotes growth of the preferred enantiomers. The liquid phase which is rich in counter enantiomer for a given PFC is exchanged between the PFCs to compensate the depletion of the concentration of the preferred enantiomers in that PFC to some extent. A population balance based model of the process is developed and simulation studies are carried out for L/D-threonine – water system for which the kinetic parameters are obtained from literature [2]. The two key process parameters for this configuration is the location and the amount of liquid phase exchange (calculated as a fraction of the fresh feed). The effect of these parameters on the productivity is shown in Figure 1(b). As can be seen, the productivity increases monotonically as the exchange fraction is increased. This finding is expected as higher the exchange rate, higher the compensation of the depleted enantiomer in the solution phase. In contrast, the productivity goes through a maximum value when the exchange location is varied. It is argued that the optimum location should neither be too close to the inlet so that there is not enough time for the fresh feed to crystallize, nor too far away from the inlet so that the exchange liquid does not spend enough time in the crystallizer. The performance of this configuration is also compared with other existing coupled crystallizer configurations.

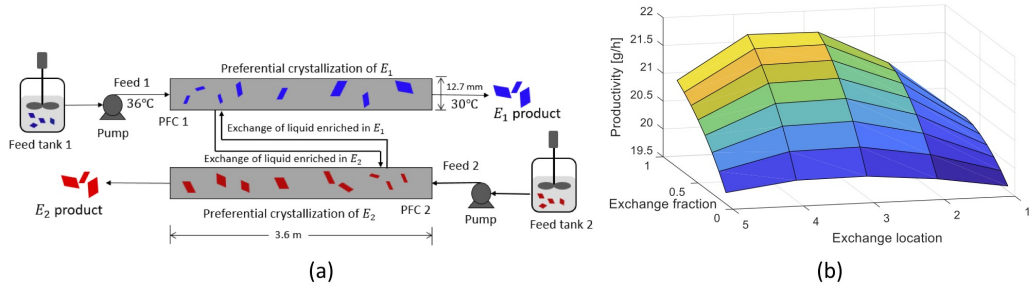

Figure 1: (a) A schematic showing the configuration of the coupled PFC with the liquid phase exchange. (b) For a PFC with six equal segments, the effect of exchange location and exchange fraction on the productivity (purity 99%) is shown. Productivity increases as exchange fraction increases while for exchange location there is an optimum position which is the after the segment 3 in this case.

References

[1] A. Majumder, Processes 6, (2018).
[2] M. P. Elsner, G. Ziomek, and A. Seidel-Morgenstern, Chem. Eng. Sci. 62, 4760 (2007).

P029 Practical application of Crystallisation Theory to optimise established small molecule pharmaceutical manufacturing processes

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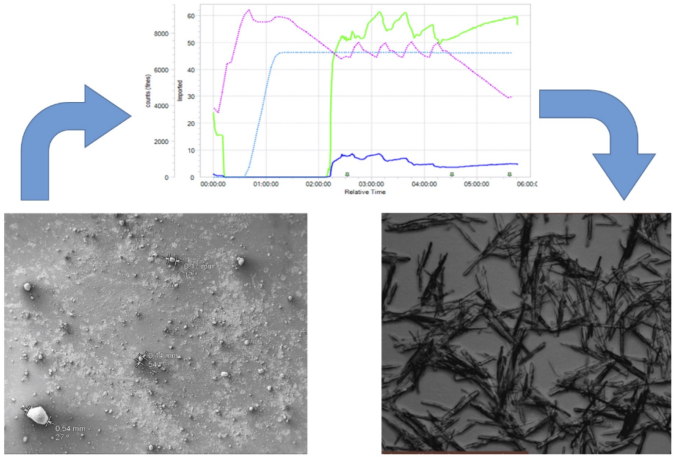
In recent years, significant progress has been made in the control of crystallisation processes, leading to improvements in different aspects of crystalline product quality [1]. One factor which has promoted crystallisation process control is the advent and application of process analytical technology (PAT). For many commercial molecules, these advancements have led to improvements in manufacturing robustness, including isolation and drying performance. In the pharmaceutical industry today, there are many well-established commercial products which possess crystallisation steps, many of which were developed prior to recent developments and present-day knowledge of crystallisation and particle engineering theory, resulting in suboptimal particle properties and deficiencies in manufacturing robustness. These commercial processes represent a challenge to chemists, whereby any improvements to the crystallisation process must realise a meaningful benefit, while respecting the regulatory boundaries. Here, a case study is presented detailing the significant improvements achieved in a legacy small molecule crystallisation process for a key pharmaceutical intermediate. Utilising in-line Process Analytical Technologies such as FBRM [2], key information about the crystallisation design space, primary/secondary nucleation behaviour and metastable zone widths was established. Following this, an optimal set of parameters was identified through a series of laboratory experiments, with the ultimate outcome of a significant improvement in particle properties and a subsequent successful scale up from lab to plant resulting in much improved batch processing times and expedited production of the active pharmaceutical ingredient.



References

[1] Z. Gao, S. Rohani, J. Gong, J. Wang, Engineering, 2017, 3, 343-353.

[2] https://www.mt.com/us/en/home/library/videos/automated-reactors/Lasentec-FBRM-Method-of-Measurement.html

P030 The nucleation mechanism of diesel fuels within fractionation driven crystallisation

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The formation of n-alkane waxes in solution during cold weather is a recurrent problem in the automotive industry. In diesel fuels, crystallisation of long chains n-alkanes can result in the formation of large flat plate-like crystals leading to flow impairment, blockage of filters and engine fuel starvation. Clearly the unwanted formation of these waxes and their associated problems can cause significant issues for the manufacturer and end-users. Current wax mitigation strategies involve the development of chemical additives to control or inhibit the nucleation and growth of crystals so that they no longer form large deposits or block filters. However, the variable nature of fuel composition, specifically the fractionation of the n-alkanes, results in a complex challenge for the additive provider to meet operational needs [1]. This project aims to further develop knowledge in this area and study the effect of fractionation on fuel nucleation kinetics in the presence and absence of additives using a model fuel from a homologous series of n-alkanes. Here we present the results from an experimental study on the nucleation kinetics and solubility behaviour of 7 alkanes ranging from C_16H_34 to C_22H_46 in toluene. Analysis of the experimental polythermal data making use of the analytically derived KBHR approach [2–4] reveals, that in all odd and most even alkanes studied, bar C18 and C16, the preferred nucleation mechanism for single n-alkane solutions is instantaneous. i.e. all the nuclei are formed at once at a certain level of supersaturation, to further grow. Furthermore, the influence of chain length on solubility was observed between odd and even alkanes in toluene. By analysing the nucleation and solubility behaviour within the set of n-alkanes tested, suggestions of the factors controlling wax crystallisation in fuel systems are presented and discussed from first thermodynamic principles.

References

[1] A. R. Gerson, K. J. Roberts and J. N. Sherwood, An instrument for the examination of nucleation from solution and its application to the study of precipitation from diesel fuels and solutions of n-alkanes, Powder Technol., 1991, 65, 243–249.
[2] D. Kashchiev, A. Borissova, R. B. Hammond and K. J. Roberts, Effect of cooling rate on the critical undercooling for crystallization, J. Cryst. Growth, 2010, 312, 698–704.
[3] D. Kashchiev, A. Borissova, R. B. Hammond and K. J. Roberts, Dependence of the Critical Undercooling for Crystallization on the Cooling Rate, J. Phys. Chem B, 2010, 114, 5441–5446.
[4] D. M. Camacho Corzo, A. Borissova, R. B. Hammond, D. Kashchiev, K. J. Roberts, K. Lewtas and I. More, Nucleation mechanism and kinetics from the analysis of polythermal crystallisation data: Methyl stearate from kerosene solutions, CrystEngComm, 2014, 16, 974–991.

P031 Kinetic Monte Carlo Simulations of Crystal Growth: Application to Structures with Zeolitic Frameworks

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In the widespread industrial applications of zeolites, properties such as morphology, crystal size, defects and pore length are of high significance. These properties are of particular consequence for zeolite catalysts, where they play a role in determining catalytic activity, diffusional properties and rates of catalyst deactivation through coking. Consequentially, there is considerable motivation for improved understanding of how the crystals grow, and for development of methods to model growth and predict morphology in these materials. With these aims in mind, this work explores the application of CrystalGrower software to materials with zeolitic frameworks. CrystalGrower offers a new tool for modelling the growth of crystalline materials through three-dimensional partitioning of structures and re-construction of crystals using kinetic Monte Carlo simulations.[1] The challenge of how to address structural partitioning of zeolitic structures is addressed by using an interface with the software ToposPro, which generates natural tilings for any zeolite crystal structure.[2]

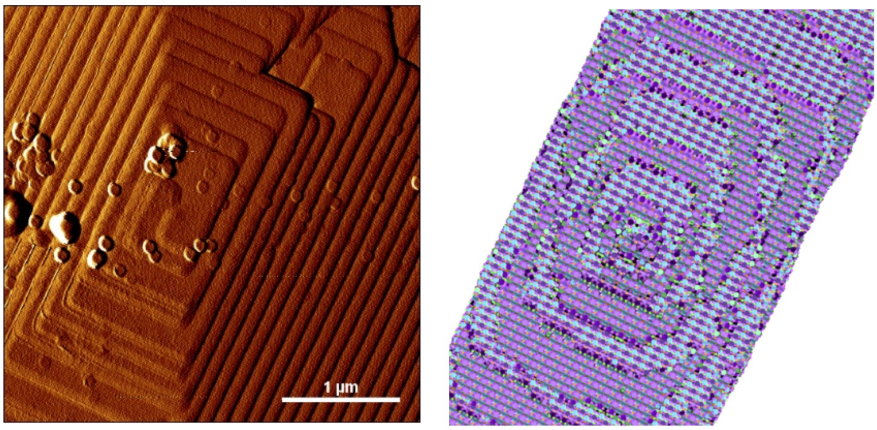

Figure 1: a) AFM imaging of spiral growth on silicalite-1 (010) surface b) Spiral growth on silicalite-1 simulated by CrystalGrower

Through comparison with AFM and SEM images, simulated crystals can be fitted to experimental observations of morphologies and surface fine structures. In the case of zeolites, such observations indicate that crystal growth can occur through both layer-by-layer growth and spiral growth. Both of these growth mechanisms can be modelled using CrystalGrower. In certain materials, modelling reveals an inhomogeneous 3-D distribution of co-ordinatively unsaturated tiles, often mapping out an hourglass shape. This provides an alternative explanation for the so called 'hourglass effect' observed in silicalite-1.[3]

References

[1] M. W. Anderson, J. T. Gebbie-Rayet, A. R. Hill, N. Farida, M. P. Attfield, P. Cubillas, V. A. Blatov, D. M. Proserpio, D. Akporiaye, B. Arstad and J. D. Gale, Nature, 2017, 544, 456–459.
[2] V. A. Blatov, A. P. Shevchenko and D. M. Proserpio, Cryst. Growth Des., 2014, 14, 3576–3586.
[3] M. B. J. Roeffaers, R. Ameloot, M. Baruah, H. Uji-i, M. Bulut, G. De Cremer, U. Müller, P. A. Jacobs, J. Hofkens, B. F. Sels and D. E. De Vos, J. Am. Chem. Soc., 2008, 130, 5763–5772.

P032 Development of nanoparticle tracking in high magnetic fields to probe pharmaceutical crystallisation

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The pharmaceutical industry is plagued by polymorphism, the ability of certain molecular species to crystallise into different molecular arrangements. As different polymorphs impart differing properties to the pharmaceutical, including solubility and stability, polymorph control is integral to pharmaceutical efficacy [1]. A notable instance of failure to control polymorphism was the appearance of a new polymorph of ritonavir, an AIDS treatment, which rendered the product unmanufacturable [2]. Recently, polymorph control via the application of a strong magnetic field (1 T) during crystallisation has been demonstrated for coronene, resulting in the discovery of a new polymorph [3]. This finding has immediate application in the pharmaceutical industry as polymorph discovery has the potential to unearth new, more efficacious polymorphs. Our group has also demonstrated polymorph control for carbamazepine, an anti-epileptic pharmaceutical [4]. What remains puzzling is the mechanism by which the magnetic field causes polymorph transition. The contribution from k_BT is much larger than even a strong magnetic field for single molecules and so they are not likely to be influenced in that way5. Aggregates of molecules in the form of prenucleation clusters (PNCs) [6], however, have the potential for sufficient interaction with a magnetic field to begin to compete with thermal fluctuations [5]. It is thought that the magnetic field influence on PNCs affects the kinetics of crystallisation, shown not only by polymorph control, but by changing the temperature at which crystallisation occurs when cooling [4]. PNCs are nanoscale, thermodynamically-stable assemblies of concentrated solute within a solution which are distinct from crystallites and are involved in crystallisation6. PNCs have been the subject of study in the crystallisation of organic materials [7–9] including olanzapine [10], a pharmaceutical. The discovery and characterisation of PNCs of crystals which experience magnetic field effects would help determine the mechanism of polymorph control in a magnetic field. We have developed a technique based on light-sheet microscopy to perform Nanoparticle Tracking Analysis (NTA) to determine size and concentration of PNCs during the crystallisation process. We will describe the technique and its advantages in characterising PNCs. We will also show our discovery of prenucleation clusters for coronene, carbamazepine, and flufenamic acid, all of which show polymorph modification behaviour within a strong magnetic field [4].

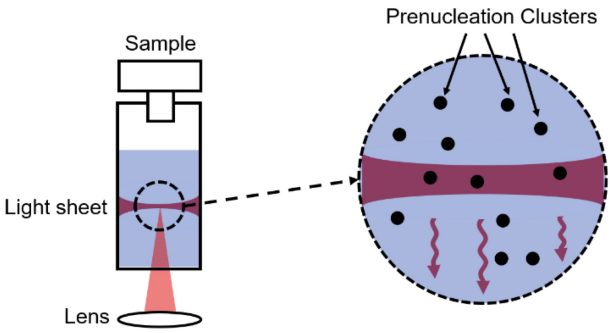

Figure 1: Light sheet microscopy has been used to analyse prenucleation clusters in-situ to determine size distribution and concentration.

References

[1] Higashi, K.; Ueda, K.; Moribe, K. Recent Progress of Structural Study of Polymorphic Pharmaceutical Drugs. Adv. Drug Deliv. Rev. 2016, 117, 71–85. https://doi.org/10.1016/j.addr.2016.12.001.
[2] Bauer, J.; Spanton, S.; Henry, R.; Quick, J.; Dziki, W.; Porter, W.; Morris, J. Ritonavir: An Extraordinary Example of Conformational Polymorphism. Pharm. Res. 2001, 18 (6), 859–866. https://doi.org/10.1023/A:1011052932607.
[3] Potticary, J.; Terry, L. R.; Bell, C.; Papanikolopoulos, A. N.; Christianen, P. C. M.; Engelkamp, H.; Collins, A. M.; Fontanesi, C.; Kociok-Köhn, G.; Crampin, S.; et al. An Unforeseen Polymorph of Coronene by the Application of Magnetic Fields during Crystal Growth. Nat. Commun. 2016, 7. https://doi.org/10.1038/ncomms11555.
[4] Potticary, J.; Hall, C.; Guo, R.; Hoffmann, W. H.; Gersen, H.; Price, S. L.; Hall, S. R. Manuscript Submitted. 2019.
[5] Potticary, J.; Terry, L. R.; Bell, C.; Collins, A. M.; Fontanesi, C.; Kociok-Köhn, G.; Crampin, S.; Da Como, E.; Hall, S. R. Control of Polymorphism in Coronene by the Application of Magnetic Fields.
[6] Gebauer, D.; Kellermeier, M.; Gale, J. D.; Bergström, L.; Cölfen, H. Pre-Nucleation Clusters as Solute Precursors in Crystallisation. Chem. Soc. Rev. 2014, 43 (7), 2348–2371. https://doi.org/10.1039/C3CS60451A.

[7] Salvalaglio, M.; Giberti, F.; Parrinello, M. 1,3,5-Tris(4-Bromophenyl)Benzene Prenucleation Clusters from Meta-Dynamics. Acta Crystallogr. Sect. C Struct. Chem. 2014, C70 (2), 132–136. https://doi.org/10.1107/S2053229613026946.
[8] Kellermeier, M.; Rosenberg, R.; Moise, A.; Anders, U.; Przybylski, M.; Cölfen, H. Amino Acids Form Prenucleation Clusters: ESI-MS as a Fast Detection Method in Comparison to Analytical Ultracentrifugation. Faraday Discuss. 2012, 159, 23–45. https://doi.org/10.1039/c2fd20060k.
[9] Sleutel, M.; Van Driessche, A. E. S. Role of Clusters in Nonclassical Nucleation and Growth of Protein Crystals. Proc. Natl. Acad. Sci. 2014, 111 (5), E546–E553. https://doi.org/10.1073/pnas.1309320111.
[10] Warzecha, M.; Safari, M. S.; Florence, A. J.; Vekilov, P. G. Mesoscopic Solute-Rich Clusters in Olanzapine Solutions. Cryst. Growth Des. 2017, 17, 6668–6676. https://doi.org/10.1021/acs.cgd.7b01299.

P033 Structural Characterisation of Organic Salts by Combined X-ray Raman Scattering, X-ray Photoelectron Spectroscopy and Excited-State DFT Calculations

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Active pharmaceutical ingredients in salt form can provide favourable biopharmaceutical and physicochemical properties, such as physical and chemical stability, and increased solubility [1]. Predictive modelling of organic salt crystallisation from solution requires knowledge of speciation in solutions, as structural and electronic properties impact on the crystal structure and morphology of the final product. Core-level X-ray Absorption Spectroscopy (XAS) has recently been used to probe the properties of organic ions in solution through the Near-Edge X-ray Absorption Fine-Structure (NEXAFS) region, which is highly sensitive to hydrogen bonding and protonation and hence changes in solvation structure [2]. However, currently available vacuum instruments for soft XAS studies of solutions rely on the use of microjets and similar liquid sample dosing technologies, which are prone to nozzle blockage by spontaneous crystallisation of concentrated solutions. Moreover, expansion into vacuum precludes the high degree of temperature control required for nucleation and crystallisation studies. The use of X-ray Raman Scattering (XRS) for the detection of the near-edge fine-structure spectra has allowed us to work around these limitations, as the hard X-rays (photon energy 10 keV) can be used in complex environments at ambient pressure. We obtained C and N K-edge fine-structure spectra of aqueous solutions of the neutral imidazole species (pH 10) and imidazolium hydrochloride salt (pH 3). The spectra confirm that the near-edge fine-structure in low momentum transfer XRS agrees well with previously obtained NEXAFS data [3]. Two π^* N 1s transitions of the non-equivalent nitrogen moieties in imidazole are observed, whereas the imidazolium cation exhibits an N K-edge fine-structure with a single π^* resonance due to equivalence of the nitrogen moieties in the ion. The XRS results are consistent with observations for the N and C 1s binding energies of imidazole and imidazolium in aqueous solution measured using Near Ambient Pressure X-ray Photoelectron Spectroscopy (NAP-XPS). Time-dependent density functional theory (TD-DFT) calculations were performed for several solvation structures, including implicit and explicit solvation models. They reproduce the peak positions and intensities of the K-edge fine-structure features for both neutral imidazole and the cationic imidazolium species. In summary, we have demonstrated that soft K-edge measurement via XRS permits characterisation of organic solutes in solution at ambient pressure. TD-DFT calculations model the observed changes successfully and provide an understanding of the effect of solute-solvent interactions.

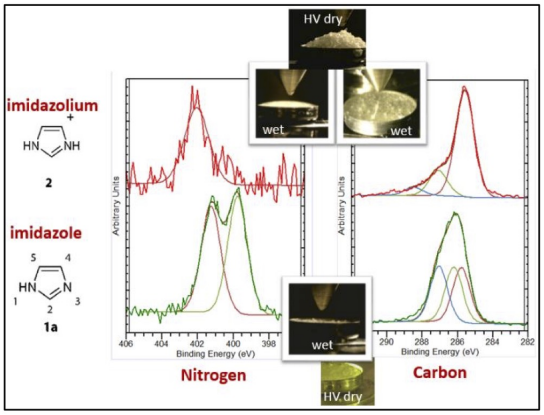

Figure 1: Binding energy for nitrogen (l) and carbon (r) measured at 11 mbar with water vapour

References

[1] P.H. Stahl, C.G. Wermuth, Int. Union of Pure Applied Chem., VHCA, 2011.
[2] J. S. Stevens, S. J. Byard S. L. M. Schroeder, Cryst. Growth Des., 2010, 10, 1435–1442
[3] L. H. Al-Madhagi et al., CrystEngComm 2018, 20, 6871–6884

P034 Crystallisation of Glycine from Binary Solvent under Acoustic Levitation

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Surfaces play an important role in crystallization, as the interaction of the solute molecules with a surface alters the energetics and kinetics of nucleation1. Acoustic levitation of microdroplets in gaseous media is a very attractive novel approach to study the nucleation of organic molecules without the presence of foreign surfaces such as container walls or impurities2. In this work, we studied the crystallisation of the simplest amino acid, glycine from either pure aqueous solution or a binary solvent mixture while the microdroplets evaporated under acoustic levitation. High speed video microscopy was used to monitor droplets in environmentally controlled chamber in order to extract the evaporation profiles and induction times. The product crystals were analysed using Raman spectroscopy and Scanning Electron Microscopy (SEM).

References

[1] J. W. Mullin, Crystallization, Butterworth-Heinemann, Oxford, Boston, 4th ed., 2001.
[2] E. Welter and B. Neidhart, Fresenius. J. Anal. Chem., 1997, 357, 345–350.

P035 Unconventional ultra scale-down techniques for active pharmaceutical ingredient filtration and size reduction

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The use of scale down devices for early-stage process development enables early availability of experimental data, indicative of large-scale processes. In this work, an automated ultra scale-down (USD) filtration and a shear device which when used together allow the study of the recovery of active pharmaceutical ingredients (API) of different crystal particle size distributions at 10s of milligram-scale. For an early understanding of the process interactions based on a simple DoE design, a pressure difference of 70 kPa was observed to be significant for the filtration process when the 5 m filter pore size is used. At all other conditions investigated, the outcomes of the USD filtration were compared with established laboratory-scale filters operating at 10-fold scale based on total working mass. Good comparability was obtained for samples with narrow PSD, while samples with larger PSD had reduced predictive capability. API of narrower PSD was achieved by using a USD shear device and applied mechanical force. For the shear stressed crystals using USD shear device, crystals were found to be robust to shear stress with a small amount of fines produced, and the impact of fines on filtration was not remarkable. Mechanically size reduced crystals produced a substantial amount of fines, which resulted in a considerable reduction of the filtrate flux and approximately ten-fold rise in specific cake resistance when compared with shear stressed crystals. In general, the PSD of the crystals were found to be critical to determining the filtration conditions such as pressure difference and filter pore size. As concluded in this study, PSD is directly related to filter pore size and inversely related to the pressure difference, as would be expected. The implementation of the automated USD filtration platform enables rapid-process understanding and reduces cost and time due to a reduced amount of materials. The data obtained shows similar process trends and are primarily indicative of process performance at a larger scale.

P036 Developing process understanding for continuous manufacturing of Lamivudine (Epivir®) Stable Form I

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This study aims to develop a workflow based continuous crystallisation [1] with specific interests in process automation and platform miniaturisation for an early stage accelerated process development. The workflow presented in this study focuses on establishing a robust knowledge database of the compound specifics from literature survey[1,2] and small-scale screening. An existing solvent screening platform was used to evaluate the solubility profiles, supersaturation, and transformation of Lamivudine from form II to I in binary mixtures of solvent-antisolvent pairs. The set-up consists of a temperature-controlled waterbath housing a magnetic stirrer for the continuous stirring of the reactor vials. A webcam was positioned to continuously monitor crystals present in the vials, and all the PATs measurements were acquired via a LabVIEW graphic user interface (GUI). In parallel, a novel miniaturised platform was developed to specifically screen for crystal shapes and sizes as influenced by solvent mixtures/antisolvent pairs. The modular miniaturised platform was controlled via a dedicated LabVIEW GUI which processed the images captured by a camera fixed on the platform. Initial solubility and supersaturation screening of two solvent systems namely, DMF/Acetone, and water/acetonitrile showed DMF/Acetone pair as the potential solvent pairs suitable for antisolvent crystallisation of Lamivudine form I. A maximum possible supersaturation of 3.5 and predicted yield of 75% is achievable. The water/acetonitrile system resulted in achievable supersaturation of 1.5 and projected yield of 32%. The modular miniaturised screening platform was tested, and the GUI which integrated the camera, pumps, and other pieces worked as planned. Improvement work is underway to fine-tune the acquired images for better resolution and precise image counts. Overall, the workflow provides a systematic approach to developing process understanding for a commercial product such as Lamivudine that has not been extensively investigated and reported for continuous manufacturing. Part of the short-term future work includes screening more potential solvent pairs, process translation to small-scale stirred tank crystalliser and optimisation of the miniaturised platform for morphology screening.

References

[1] Brown, C. J. et al. Enabling precision manufacturing of active pharmaceutical ingredients: workflow for seeded cooling continuous crystallisations. Mol. Syst. Des. Eng. 3, 518–549 (2018).

[2] Jozwiakowski, M. J., Nguyen, N. A. T., Sisco, J. M. Spancake, C. W. Solubility behavior of lamivudine crystal forms in recrystallization solvents. J. Pharm. Sci. 85, 193–199 (1996).

P037 A Flexible Lattice Dynamics Approach for Free Energy Calculations within Crystal Structure Prediction studies

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A plethora of organic molecules exhibit polymorphism, which refers to the ability of chemical compounds to pack into different crystal structures. This phenomenon is of significant importance both to industry and academia since physical properties, such as solubility, bioavailability and mechanical strength may vary tremendously between polymorphs. Crystal structure prediction (CSP) is the area of research that seeks to determine all polymorphs for a given compound based on minimal information, such as the chemical connectivity diagram [1]. From a thermodynamic standpoint, polymorphs can be identified as minima on the free energy (FE) landscape, with the most stable form corresponding to the global minimum. The recent advances of CSP have been highlighted in the last blind test, organised by Cambridge Crystallographic Data Centre [2]. It is worth noting that only 7 out of 25 groups participated in the last blind have incorporated FE calculations within their workflow, while the remaining groups used only lattice energy for their predictions, thus neglecting temperature and pressure effects. The most successful methodology involved lattice dynamics (LD) theory for the evaluation of vibrational free energies utilizing either dispersion corrected periodic density functional theory [3,4] or force field methods, based on distributed multipoles expansion [5,6,7]. The former method can provide very accurate results at a high computational cost, whereas the latter provides a good trade-off between accuracy and efficiency but cannot account for internal modes arising from intramolecular vibrations. A limitation of both methods is that they rely on the construction of supercells, which further increases computational demands and results in some ambiguity in the generation of dispersion curves. In this work, we present a recently-developed methodology [8] for performing flexible lattice dynamics calculations, which is suitable for conducting FE calculations for a large number (>100) of structures generated in CSP studies. This methodology is based on LD theory within the harmonic approximation, with intramolecular interactions quantified by isolated quantum mechanical calculations [9]. The intermolecular interactions are partitioned into electrostatics and repulsion/dispersion interactions and are modelled using ab-initio distributed multipoles and a semi empirical potential, respectively. We apply this methodology to tetracyanoethylene (C_6N_4), a small planar molecule for evaluating the free energy of predicted structures in a temperature range between 0 and 400K.

References

[1] Pantelides, C. C.; Adjiman, C. S.; Kazantsev, A. V. General Computational Algorithms for Ab Initio Crystal Structure Prediction for Organic Molecules. In Prediction and Calculation of Crystal Structures Methods and Applications. Topics in Current Chemistry; Atahan-Evrenk, S.; Aspuru-Guzik, A., Eds.; Springer, 2014; Vol. 345, pp. 25–58.

[2] Reilly, A. M.; Cooper, R. I.; Adjiman, C. S.; Bhattacharya, S.; Boese, A. D.; Brandenburg, J. G.; Bygrave, P. J.; Bylsma, R.; Campbell, J. E.; Car, R.; et al. Report on the Sixth Blind Test of Organic Crystal Structure Prediction Methods. Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater. 2016, 72, 439–459.

[3] Hoja, J.; Ko, H.-Y.; Neumann, M. A.; Car, R.; DiStasio, R. A.; Tkatchenko, A. Reliable and Practical Computational Prediction of Molecular Crystal Polymorphs. 2018, 1–9.

[4] Brandenburg, J. G.; Grimme, S. Organic Crystal Polymorphism: A Benchmark for Dispersion-Corrected Mean-Field Electronic Structure Methods. Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater. 2016, 72, 502–513.

[5] Nyman, J.; Day, G. M. Static and Lattice Vibrational Energy Differences between Polymorphs. CrystEngComm 2015, 17, 5154–5165.

[6] Price, S. L.; Leslie, M.; Welch, G. W. A.; Habgood, M.; Price, L. S.; Karamertzanis, P. G.; Day, G. M. Modelling Organic Crystal Structures Using Distributed Multipole and Polarizability-Based Model Intermolecular Potentials. Phys. Chem. Chem. Phys. 2010, 12, 8466.

[7] Stone, A. J. Distributed Multipole Analysis, or How to Describe a Molecular Charge Distribution. Chem. Phys. Lett. 1981, 83, 233–239.

[8] Vasileiadis, M. Calculation of the Free Energy of Crystalline Solids, Imperial College London, 2013.

[9] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenb, D. J. al. Gaussian 09, 2009.

P038 Towards a computational approach at finite-temperature polymorph screening

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Computational Crystal Structure Prediction methods are becoming increasingly accurate at pre- dicting the energetically most favoured crystal packing, even if they usually grossly overestimate the number of possible polymorphs, especially for what concerns organic crystals [1, 2]. The purpose of this work is to refine the CSP results by including finite temperature effects and reduce the number of predicted polymorph structures in organic systems. In fact, at finite tem- perature, structures corresponding to local potential energy minima are expected merge into a smaller number of states or become unstable and melt [2]. In order to identify these structures, classical molecular dynamics simulations at finite temperature are performed on CSP-generated crystal structures. Unstable structures are easily removed by checking if molecules exhibit a random inter-molecular orientation. A distance matrix and cluster analysis is then performed on the remaining structures to group those with similar packing and molecular conformation. Finally, metadynamics [3] simulations are performed on the most representative structures to estimate their metastability and generate a temperature-dependent ranking. After developing a program that can automatically transfer and adapt the CSP results to classical MD inputs, we performed this analysis on two molecules: urea, a small rigid molecule and succinic acid, a small molecule that exhibits conformational polymorphism [4].

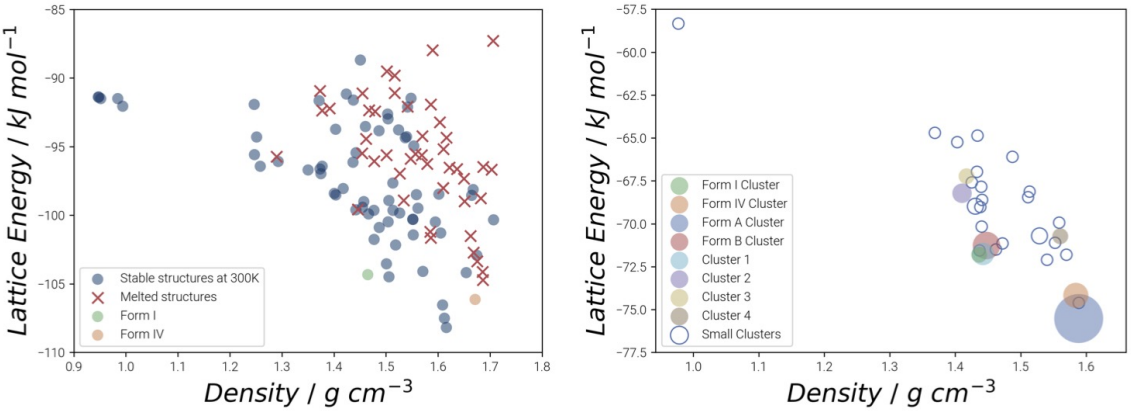

Figure 1: On the left, the lattice energy vs density plot of the urea set of crystals with the structures that melt during the equilibration shown with a red cross. On the right, the coarsened crystal energy landscape obtained after the cluster analysis. Over 70% of the initial geometries are discarded based on this analysis.

References

[1] D.A. Bardwell, C.S. Adjiman, Y.A. Arnautova, E. Bartashevich, S.X.M. Boerrigter, et al., Acta Crystallographica Section B: Structural Science 67(6), 535-551 (2011).
[2] S.L. Price, Acta Crystallographica Section B: Structural Science, Crystal Engineering and Materials, 69(4), 313-328 (2013).
[3] A. Barducci, G. Bussi, M. Parrinello, Phys.Rev. Lett., 100, 020603 (2008).
[4] P. Lucaioli, E. Nauha, I. Gimondi, L. S. Price, R. Guo, L. Iuzzolino, I. Singh, M. Salvalaglio, S. L. Price and N. Blagden, CrystEngComm, 20, 39713977 (2018).

P039 Stacking Disorder by Design: Factors Governing the Polytypism of Silver Iodide upon Precipitation and Formation from the Superionic Phase

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Materials with zinc blende/wurtzite- type structures display stacking disorder consisting of varying fractions of cubic and hexagonal stacking sequences that are interlaced in a complex way (Figure 1).[1,2,3] This is not a simple physical mixture of the two polymorphs; instead the extent of stacking disorder is dependent on a number of factors including starting materials, the route by which the material was made[1] and so-called memory effects resulting from the thermal history of the sample.[2,3]

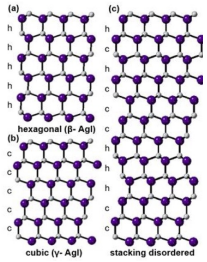

Figure 1: Crystal structures of AgI along [100] in (a) hexagonal, (b) cubic and (c) stacking disordered AgI.

Silver iodide (AgI). AgI is used for a wide range of applications from photocatalysis and antimicrobial coatings to photography and ice nucleation. By fitting powder X-ray diffraction patterns with MCDIFFaX, we show that AgI displays a strong tendency to form stacking-disordered materials. Its polytypism is determined by the silver cation to iodide molar ratio during precipitation (Figures 2(a) and (b)).[4] Under iodide-rich conditions, fully hexagonal β-AgI is obtained whereas a maximal percentage of cubic stacking of 81% is obtained at a 1:2 molar ratio in the silver cation-rich regime. These findings are explained on the basis of a concentration-dependent competition between kinetically and thermodynamically-favoured adsorption processes. Furthermore, the previously reported memory effects, observed upon transforming hexagonal and cubic AgI to the high-temperature superionic phase and back, are now followed in a quantitative fashion. We propose that the memory effects originate from excess ions at the surfaces of AgI crystals that stabilise the pyroelectricity of AgI associated with hexagonal stacking. The ability to 'design' the polytypism of AgI by tuning the precipitation conditions provides the first example where the stacking disorder of a material can be controlled in a continuous fashion. Future work will determine if this design principle can be applied to other materials.[4]

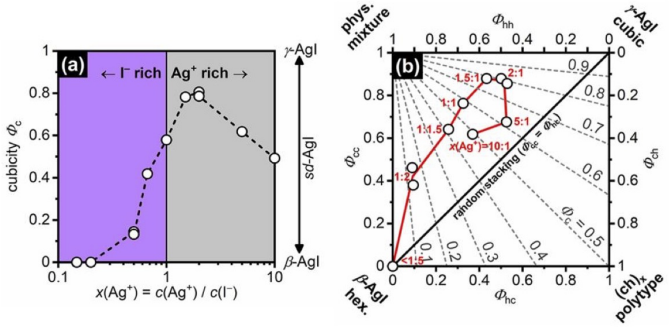

Figure 2: (a) Silver molar fraction against cubicity (determined by MCDIFFaX) (b) A stackogram showing stacking probabilities for AgI samples along with associated molar fractions of silver.[4]

References

[1] T. L. Malkin, B. J. Murray, C. G. Salzmann, V. Molinero, S. J. Pickering, T. F. Whale, Phys. Chem. Chem. Phys., 2015, 17, 60-76

[2] C. G. Salzmann, B. J. Murray and J. J. Shephard, Diam. Rel. Mater., 2015, 59, 69-72

[3] C. G. Salzmann, P. G. Radaelli, B. Slater, J. L. Finney, Phys. Chem. Chem. Phys., 2011, 13, 18468-18480 [4] R. L. Smith,

[4] M. Rosillo-Lopez, M. Vickers, C. G. Salzmann, Cryst. Growth Des., 2019, 19 (4) 2131-2138.

P040 Synthesis and Intercalation of Fullerene into Metal Organic Frameworks

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The evolution of superconducting transition temperature may be seen to evolve with lattice spacing in the fullerene C60 when doped with alkali metals of increasing size, up to temperatures as high as 30K in Cs doped C60. In 2005, Hamel published on the effect of incorporating these fullerene atoms into metal organic frameworks to increase lattice spacing and enhance the overlap of wave functions, supporting electronic transport within the lattice without hybridisation of fullerene bands with the MOF [1]. To explore the possibility of incorporation of C60 into isoreticular frameworks, IRMOF-0, IRMOF-1, and Zn4(FMA)32 have been constructed from solvothermal methods (figure 1), and encapsulation of the fullerene molecule explored before and after the fabrication of MOFs. Potential doping mechanisms of fullerene with potassium are also investigated to induce superconductivity in these structures of various pore diameters.

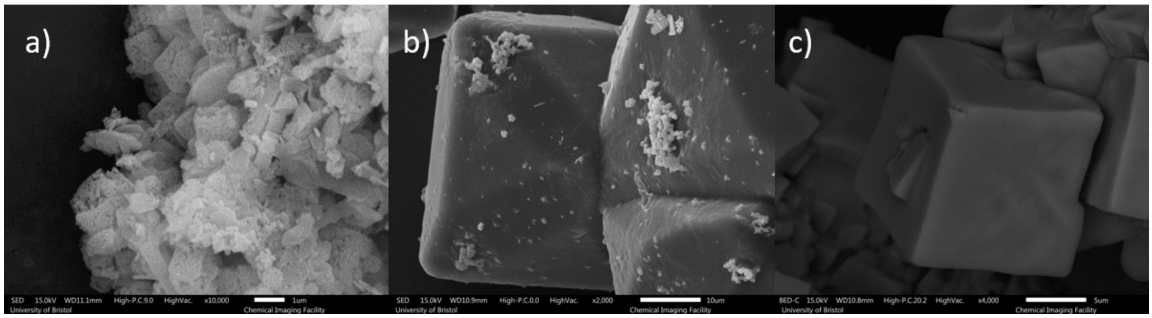

Figure 1: SEM images of various MOFs synthesised via solvothermal methods.a) IRMOF-1, b) IRMOF-0, c) Zn4(FMA)3.

References

[1] S. Hamel, V. Timoshevskii, M. Cote PRL, 2005, 95, 146403
[2] M. Xue et al, Inorg. Chem. 2009, 48, 4649–4651

P041 Impact of face-specific surface chemistry on dissolution rates for single faceted crystals

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In-vitro tablet dissolution tests are routinely carried out in the pharmaceutical industry to guide the solid dosage form development and to assess product performance and batch-to-batch quality. In some cases in-vitro dissolution behaviour is indicative of in-vivo dissolution and bioavailability. However, understanding of the underlying process of faceted single particle dissolution remains largely empirical. The development of a dissolution model which is both accurate and mechanistic is highly desirable for accurate predictions of dissolution rates. Existing models generally assume that the particles are spherical with a constant surface area and a singular, undifferentiated interface with the solution medium. These models largely fail to predict the dissolution rates of faceted crystals accurately as they do not incorporate face-specific factors such as surface areas and relative intermolecular binding energies of molecules at the crystal surfaces [1]. In this study, the VisualHabit software [2] is used to predict the crystal habit of RS-ibuprofen, as illustrated in Figure 1, and quantify the strength of intermolecular binding interactions. The ratio of the binding energy (EB) for face (011) and face (002) is used to predict the relative dissolution rate in vacuum. The predicted ratio of dissolution rates is close to the ratio of experimentally determined dissolution rates of face (011) and (002). The wetting interactions (Es) between ibuprofen molecules on faces (011) and (002) with an ethanol probe molecule have been investigated by the grid-search method. Face (011) shows stronger interactions with ethanol molecule compared to face (002) suggesting that ethanol is more likely to bind to the face (011). To incorporate the effect of in-equivalent wetting of the faces, the binding energies of the faces (011) and (002) are normalised by their respective surface ES. This improves the agreement between the predicted and measured relative dissolution rates of face (011) to (002). This modelling approach is also applied to the Furosemide-water system as a test case. The experimental data of dissolution rates of faces (001), (010) and (101), see Figure 2, is taken from Ref. [3]. The results of modelling suggest that face (101) is expected to dissolve faster than faces (010) and (001) and this is validated by experimentally determined dissolution rates of these individual faces. The outcomes of this study suggest that incorporation of modelling approach used here into the dissolution models could be useful to make better dissolution rate predictions.

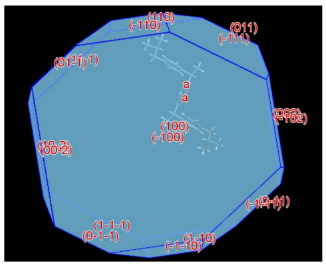

Figure 1: Top view of the ibuprofen crystal showing faces (100), (002) and (011)

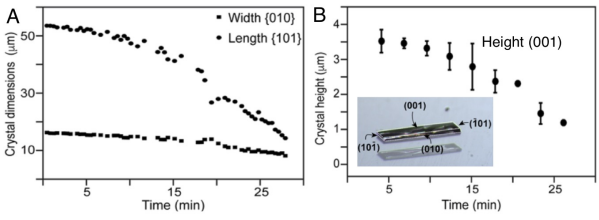

Figure 2: Furosemide experimental dissolution rates of (A) faces (101), (010) and (B) face (001). From Ref [3]

References

[1] L. P. De Almeida, S. Simões, P. Brito, A. Portugal, M. Figueiredo, J. Pharm. Sci., 1997, 86 (6), 726
[2] G. Clydesdale, K. J. Roberts, R. Docherty, J. Cryst. Growth, 1996, 166(1–4), 78
[3] M. Adobes-Vidal, F. M. Maddar, D. Momotenko, L. P. Hughes, S. A. C. Wren, L. N. Poloni, M. D. Ward, P. R. Unwin, Cryst. Growth Des., 2016, 16(8), 4421

P042 Insights on the amorphous and crystal phases of a plastic crystal: Levoglucosan

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In plastic crystals, the mass centers of the molecules form a regular crystalline lattice but the molecules are dynamically disordered with respect to the orientational degrees of freedom [1]. The phase diagram of levoglucosan (a plastic crystal, fig. 1a) presents particular landscapes: On heating two crystalline phases are observed, one orientationally ordered (ORC), stable at room temperature, which is transformed in an orientationally disordered crystal (ODIC), a plastic crystal. On cooling it is extremely difficult to form the structural glass from the isotropic liquid, but it is easy to form the orientational glass (OG) from the ODIC phase. The stability of the OG and ODIC phases allowed the study of the orientational glass transition, O-G to ODIC, by differential scanning calorimetry (DSC) and thermally stimulated depolarization currents (TSDC) with the determination of the respective dynamic fragility. Two new polymorphs of levoglucosan, not previously described in the literature, were found. These crystalline ORC forms are converted into an ODIC phase by heating, as happens with the most stable polymorph (as received). The three ORCs show ORC $\rightarrow$ ODIC transitions that differ greatly in temperature, enthalpy, and entropy of transition. In his context we could consider four levoglucosan polymorphs, three ORCs and one ODIC. In addition, TSDC technique was also used to study the secondary relaxations in the levoglucosan orientational glass, and it was possible to identify a β-type mobility (Johari-Goldstein) in addition to fast relaxations.

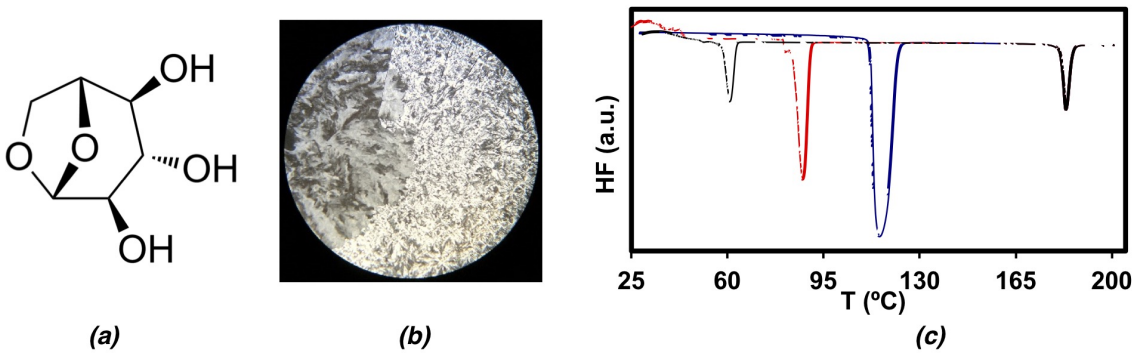

Figure 1: Levoglucosan: (a) molecular structure; (b) Hot Stage Microscopy image; (c) DSC thermogram

References

[1] J. N. Sherwood, The Plastically crystalline state: Orientationally disordered crystals, Wiley (1979)

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P043 Machine Learning Approach for Predicting Crystal Morphology from Molecular Structure

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The crystal morphology strongly influences the end-product quality, functionality as well as downstream processing in any industrial crystallisation process. Additionally, the presence of impurities, nucleation events, solvent effects and the solid form play crucial roles on the resulting crystal shapes. Investigation of these issues with respect to a prior prediction can have significant impact on the downstream manufacturability. Existing methods to calculate morphologies requires information of crystal structure. The present work aims to develop a database guided machine learning method to predict morphology of small organic compounds in the absence of crystal structure. The method uses 2D and 3D molecular descriptors to estimate the unit cell dimensions from the molecular structure. The unit cell dimensions extracted from the method are collated with the BFDH morphology data sets extracted from Cambridge Structural Database (CSD). Whilst the method estimates the unit cell dimensions with a reasonable accuracy in a range of molecules, further improvements are necessary for molecules which crystallise with more than one molecule in the asymmetric unit. The workflow for morphology prediction is presented in Figure 1.

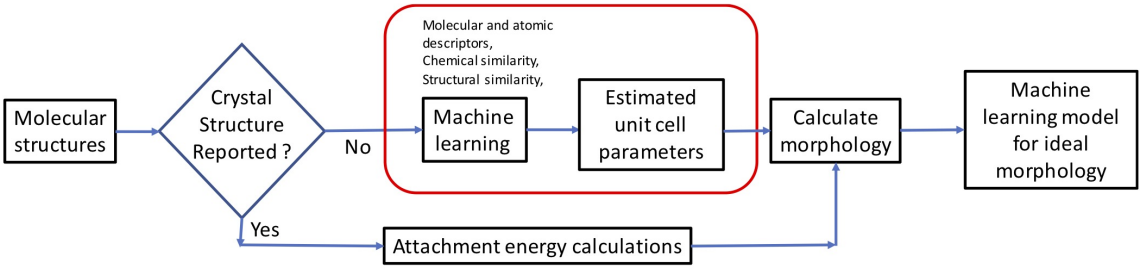

Figure 1: The workflow for morphology prediction.

References

[1] Docherty, R., Clydesdale, G., Roberts, K. J., Bennema, P. (1991). Application of bravais-friedel-donnay-harker, attachment energy and using models to predicting and understanding the morphology of molecular crystals. Journal of Physics D: Applied Physics, 24(2), 89–99.
[2] Pidcock, E., Motherwell, W. D. S. (2003). A new model of crystal packing. Chemical Communications (Cambridge, England), (24), 3028–3029.

P044 Crystal engineering of multicomponent solids: Novel cocrystals of an anti-tuberculosis drug, isoniazid, with 1,3,5-triazine-based coformers

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Crystal engineering strategies offers a paradigm for the facile design and synthesis of multicomponent crystals using self-assembly of complementary molecular solids. Recently, co-crystals, multicomponent crystals of active pharmaceutical ingredient (API) and co-former(s), are actively being explored due to their ability to fine tune biopharmaceutical properties of APIs. [1] In this poster contribution, we present discovery of two novel co-crystals of an anti-tuberculosis drug, isoniazid (INA), [2] with 1,3,5-triazine-based (cyanuric acid, CYA and melamine, MEL) coformers in the context of crystal engineering and their potential in modulating the physicochemical properties of API (Figure 1).

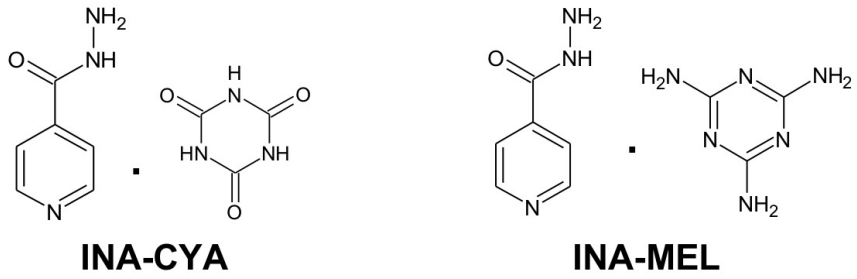

Figure 1: Figure 1. Chemical structures of cocrystal components.

Results and discussion Screening for cocrystal formation have been performed using mechanical activation i.e. neat and liquid assisted grinding and the resulted materials were characterised by thermal (DSC, TGA) and powder X-ray diffraction (PXRD). The suitable qualities of crystals INA and INA-CYA have been generated using ethanol via solution crystallisation method and crystal structures were determined using single crystal X-ray diffraction. The crystal structure analyses confirm that INA-CYA has crystallised in orthorhombic P212121 space group and is a 1:1 stoichiometric cocrystal. The solid state packing suggests formation heterosynthons. Conclusions Crystal engineering based cocrystallisation presents promising approach for the production and fine tuning of solid-state of pharmaceutical cocrystals. We successfully prepared two novel cocrystals of an anti-tuberculosis drug, isoniazid with two coformers, cyanuric acid and melamine, respectively. Further studies include evaluation of their biopharmaceutical properties.

References

[1] S. Aitipamula, V. R. Vangala, J. Ind. Inst. Sci. 2017, 97, 227.
[2] B. Swapna, D. Maddileti, A. Nangia, Cryst. Growth Des., 2014, 14, 5991.

P045 Modelling diffusive mixing in continuous antisolvent crystallisation

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Recently, there has been a significant rise of research into the development of continuous crystallisation processes within the pharmaceutical industry. The driving force behind this increased interest is the numerous advantages that continuous processes offer over the more traditional batch methods with regards to the manufacture of pharmaceuticals. Continuous crystallisation offers better control and monitoring of process parameters via online process analytical technologies, therefore leading to less variation in final product quality. One such parameter is the supersaturation profile during the crystallisation process. This has a significant impact on the resulting crystalline product and therefore a better fundamental understanding of how mixing effects local supersaturation, would be beneficial in the control and optimisation of mixing controlled crystallisation processes.[1] This research focuses on the control of mixing in continuous anti-solvent crystallisation processes at the microscale, where diffusion plays a vital role in the mixing process. Figure 1 shows an example of diffusion controlled mixing in a microfluidic device. To investigate diffusive mixing in anti-solvent crystallisation, we implemented a Maxwell-Stefan approach [2] for modelling a ternary system in order to determine local supersaturation profiles in a microfluidic device. This was achieved using a finite volume PDE solver for python 3.7, namely FiPy. A model system of aqueous glycine solution with isopropanol/water as the antisolvent was investigated in order to compare our results to a previously published case study [3] Design of experiment approach was employed to determine the effect of various parameters on the diffusive mixing. The parameters considered were initial compositions of the solution and antisolvent, ratio of anti-solvent to solution and the channel width. Parametric sensitivity analysis was performed to determine how variation of the diffusion coefficients impacted diffusive fluxes and local supersaturation profiles

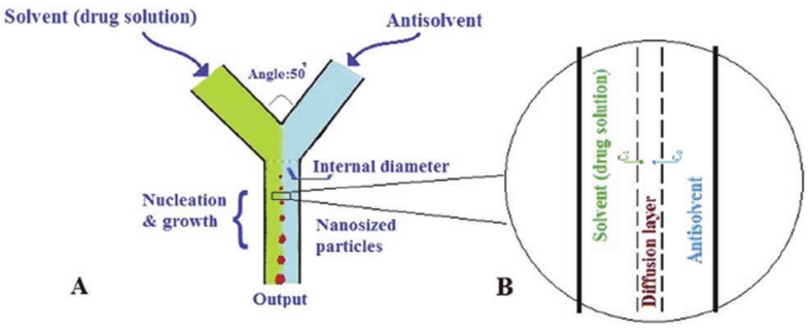

Figure 1: Diffusion controlled mixing in an anti-solvent crystallisation process, within a microfluidic device.1

References

[1] Aghajani, M.; Shahverdi, A. R.; Rezayat, S. M.; Amini, M. A.; Amani, A. Preparation and Optimization of Acetaminophen Nanosuspension through Nanoprecipitation Using Microfluidic Devices: An Artificial Neural Networks Study. Pharm. Dev. Technol. 2013, 18 (3), 609–618. https://doi.org/10.3109/10837450.2011.649854.
[2] Krishna, R. Uphill Diffusion in Multicomponent Mixtures. Chem. Soc. Rev. 2015, 44 (10), 2812–2836. https://doi.org/10.1039/c4cs00440j.
[3] Bhamidi, V.; Lee, S. H.; He, G.; Chow, P. S.; Tan, R. B. H.; Zukoski, C. F.; Kenis, P. J. A. Antisolvent Crystallization and Polymorph Screening of Glycine in Microfluidic Channels Using Hydrodynamic Focusing. Cryst. Growth Des. 2015, 15 (7), 3299–3306. https://doi.org/10.1021/acs.cgd.5b00420.

P046 Towards Rational Control of Crystal Morphology

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The morphology of a crystal plays a vital role in defining the mechanical and physicochemical properties of materials including; surface charge, reactivity, bulk density, mechanical strength and filtration properties. Understanding the impact of external crystallisation conditions like supersaturation, temperature, solubility, including solvents and additives interactions with the growing surface is necessary to achieve controlled morphology as slight changes in these can cause dramatic modifications to the crystal habit. Despite numerous reports in the literature, controlling crystal morphology remains a challenge and in practice mainly occurs by trial and error. In this work, a combination of computational and experimental techniques is utilised to develop a rational approach for the designed creation of desired crystal morphologies. The objective is to obtain a complete set of crystal morphologies under known growth conditions to direct the molecular modelling studies. The growth of benzamide with benzoic acid as the additive was selected as the test case due to the well-known morphological changes in this case.[1] The solubility of benzamide in several pure solvents and at different temperatures was initially measured gravimetrically. Controlled crystallisation at known supersaturations with differing levels of additive were undertaken. In this work, the solubility of benzamide was observed to increase with the addition of benzoic acid. Results also indicated that benzoic acid had effect on the nucleation and crystal growth rates. SEM analysis was used to compare the morphology of crystals of benzamide grown in the presence of benzoic acid (Figure 1), while PXRD was used to confirm the crystal phase present. As expected, the morphology develops a more block-like shape. Subsequent studies will utilise single crystal diffraction and computational modelling to characterise the morphology and changes observed.

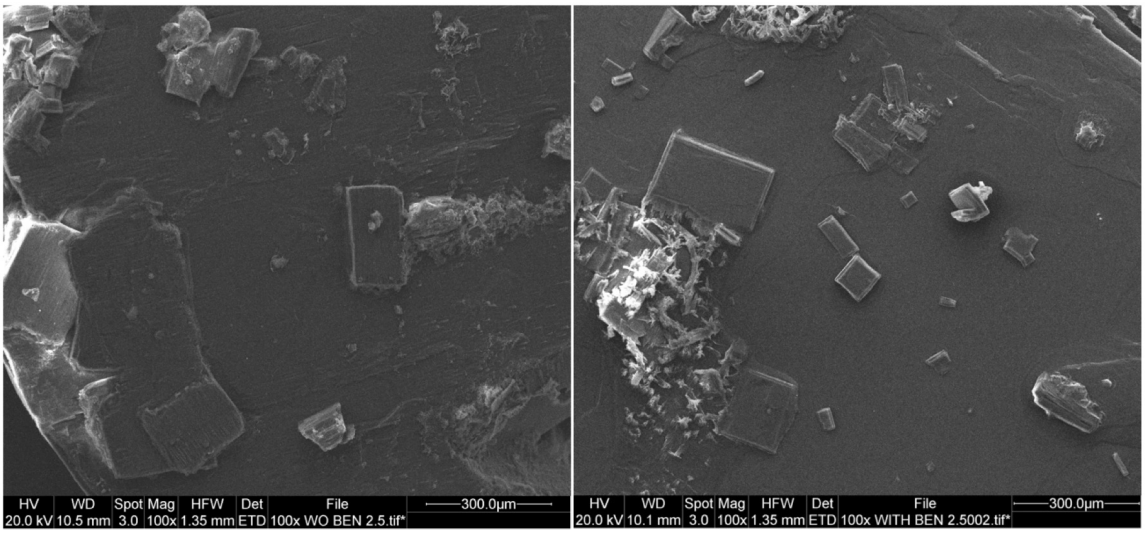

Figure 1: Images of benzamide crystals grown (left) without benzoic acid and (right) with 0.002g of benzoic acid at magnification of 100x.

References

[1] Z. Berkovitch-Yellin, L. Addadi, M. Idelson, M. Lahav and L. Leiserowitz, Angew. Chem. Suppl., 1982, 1336–1345.

P047 Bio-separation via protein crystallisation: A case study of crystallisation from lysozyme-thaumatin model binary protein mixture

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Recent progress of advanced biotechnology has enhanced the development of commercial biopharmaceutical products. Over 246 approved biotechnology drugs had been developed with cumulative revenues reaching $140 billion [1]. A cost effective and reliable downstream route becomes a major industrial challenge in therapeutic protein manufacture to meet the increasing market demands. Crystallisation of proteins as downstream separation and isolation steps is considered to be more efficient and cost-effective compared to conventional purification techniques such as chromatography [2, 3]. Additionally, crystalline proteins have a higher purity and stability which can benefit formulation, storage, and drug delivery steps [3]. In this work, we report a demonstration of selective crystallisation of target protein from binary protein mixtures validated by using lysozyme and thaumatin as the model proteins. Lysozyme-thaumatin mixtures with a wide composition range were crystallised using hanging-drop vapour-diffusion (HDVD) crystallisation method and the experiments were monitored under optical microscope for 1-2 weeks. Both model proteins can be crystallised out by addition of the same precipitant. Protein crystals of these two model proteins were distinguishable from their crystal shapes. Phase diagrams were constructed based on the observations. Unsaturated region with no crystal formation, target region with only single type of protein crystals (lysozyme crystals only or thaumatin crystals only) and mixture region in which a mixture of both types of protein were determined to show the operation windows of selective crystallisation of target protein from the mixtures. These regions were time-dependent and were related to the protein mixture compositions. And we also discovered that the difference in lysozyme and thaumatin crystallisation kinetics played a key role in this study. To conclude, this work demonstrates that protein crystallisation is not only applicable to high-purity protein solution but also a feasible approach to separate a target protein from a complex mixture environment. And selective crystallisation of target protein from mixtures was achievable by manipulating crystallisation operation conditions such as mixture composition, precipitant concentration, and operation time.

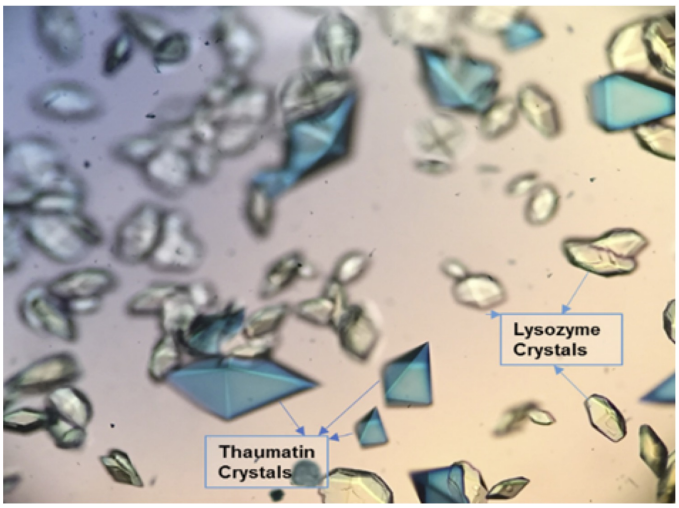

Figure 1: Representative crystal image from lysozyme-thaumatin mixture. Izit crystal dye (Hampton Research) was added to the solution to label the protein crystals.

References

[1] A.L. Demain, Industrial Biotechnology, 2007. 3(3): p. 269-283.
[2] U.V. Shah, C. Amberg, Y. Diao, Z. Yang, J.Y.Y. Heng, Current Opinion in Chemical Engineering, 2015. 8: p. 69-75.
[3] S.K. Basu, C.P. Govardhan, C.W. Jung, A.L. Margolin, Expert opinion on biological therapy, 2004. 4(3): p. 301-317.

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P048 Crystallization for novel polymorphs of organic molecular crystals in magnetic fields – can it be predicted?

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Since the most stable polymorph of coronene was discovered by crystallization in a magnetic field[1] we have been trying to develop a theory to predict whether a novel polymorph could be found by this unconventional crystallisation experiment. We have developed a method of calculating the diamagnetic susceptibility tensor (ξ) of an organic crystal by adaption of the routines in CASTEP [2] for calculating solid state NMR properties. This approach is too time-consuming and expensive in computing resources to be applied to the many thermodynamically competitive structures that are often produced by crystal structure prediction studies. The result from tensor addition for the calculation of crystal from the molecular ones (calculated in the crystalline conformation), agrees well with the calculated directly from more costly periodic PBE method for the known polymorphs of benzene, pyridine, anthracene, acridine, coronene and pharmaceuticals, such as carbamazepine, flufenamic acid, diclofenac and chalcones. The anisotropy of the diamagnetic susceptibility tensor of a crystal can be very dependent on the crystal packing. However, the change in the relative thermodynamics of polymorphs from being oriented in a large magnetic field is small. Hence a thermodynamic model suggests that the relative stability ranking of two structures can only be changed by a large magnetic field if they are very close in energy and have very different magnetic susceptibility anisotropies. The MagnaPharm project (EU Horizon 2020 736899) is trying to understand the effect of magnetic fields on polymorph outcome.

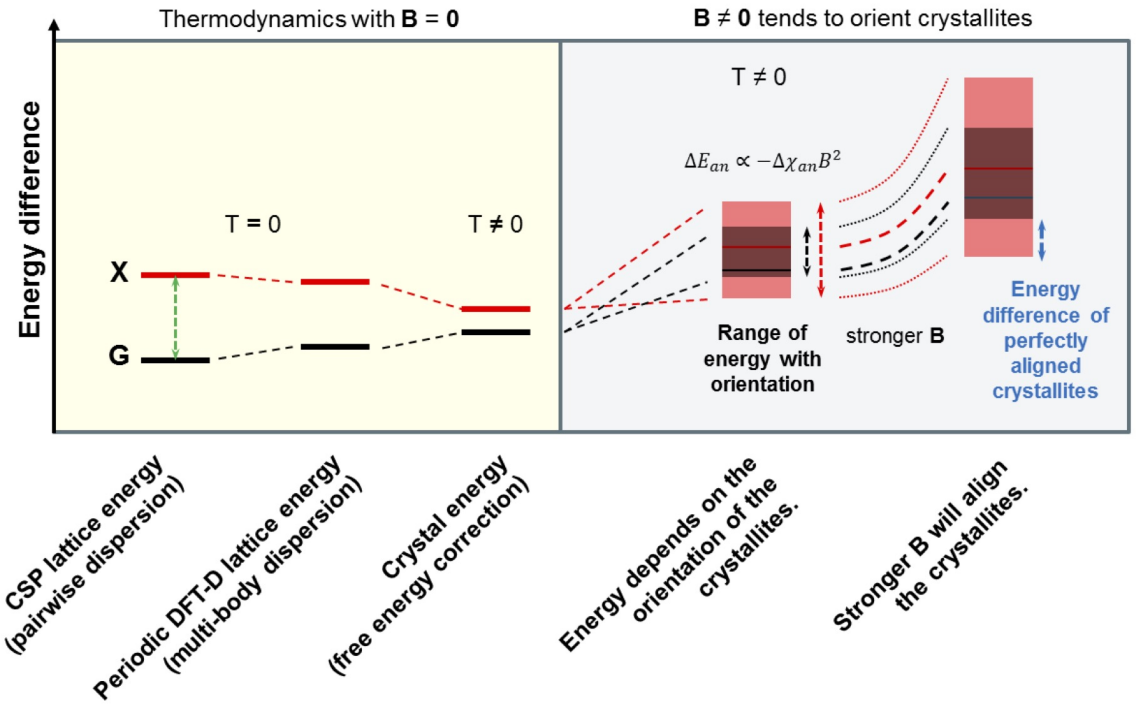

Figure 1: The induction time measurement of Glycine homopeptides at 278.15K

References

[1] Potticary, J.; Terry, L. R.; Bell, C.; Papanikolopoulos, A. N.; Christianen, P. C. M.; Engelkamp, H.; Collins, A. M.; Fontanesi, C.; Kociok-Kohn, G.; Crampin, S.; Da Como, E.; Hall, S. R., An unforeseen polymorph of coronene by the application of magnetic fields during crystal growth. Nature Communications 2016, 7, 11555.

[2] Clark, S. J.; Segall, M. D.; Pickard, C. J.; Hasnip, P. J.; Probert, M. J.; Refson, K.; Payne, M. C., First principles methods using CASTEP. Zeitschrift fur Kristallographie 2005, 220 (5-6), 567-570.

P049 Bioavailability improvement of Artemisinin through cocrystal approach: in vivo and in vitro studies

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Malaria, caused by the protozoal parasites of the genus Plasmodium, is a potentially life-threatening disease which causes more than 200 million clinical cases and 450,000 deaths annually. Artemisinin is the preferred treatment for malaria, which is both effective and well tolerated in patients, however, has the problem of low bioavailability after oral administration due to its low solubility, leading to inadequate treatments and high costs because of complicated chemical structure modification of artemisinin. Although many potent derivatives of artemisinin with better bioavailability have been found, they are all associated with toxicity, metabolic instability and short half-life. A substantial amount of research is ongoing in order to develop methods that can overcome issues related to the solubility and dissolution rates of drugs. In recent years, pharmaceutical cocrystals have attracted remarkable interests for enhancing solubility and dissolution rate of poorly water soluble drugs. A pharmaceutical cocrystal is formed by combining an active pharmaceutical ingredient (API) with an inactive coformer through a specific stoichiometric composition. The aim of this work was to improve the bioavailability of Artemisinin through cocrystal approach. The API, Artemisinin, was formulated with pharmaceutically accepted coformers to obtain two artemisinin cocrystals. The performance of the artemisinin drug and its two cocrystal based formulations have been investigated through in-vitro studies such as dissolution and permeability tests. The anti-malarial activity of drug alone and two cocrystals was tested against Plasmodium berghei infection in female BALB/c mice in a 4-day Peter's test. The in-vivo study results have shown a significant improved parasite clearance in cocrystal formulations as compared to the artemisinin drug alone. The artemisinin concentrations in serum samples were tested using LC-MS/MS and the results showed higher artemisinin concentration in serum for both cocrystal formulations, as compared to the artemisinin drug alone. Through the study artemisinin cocrystal formulations would open new opportunities for development of novel anti-malarial medicines.

References

[1] N.Qiao, M. Li, W. Schlindwein, N. Malek, A. Davies, G. Trappitt. Int. J. Pharm. 2011,419, 1-11.
[2] S. Karki, T. Friscic, L.Fabian and W.Jones. CrystEngComm. 2010 Aug 31; 12: (4038-4041)
[3] M.Guo, K.Wang, N.Qiao, V.Yardley and M.Li. Mol. Pharmaceutics, 2018 15(9), pp 4257-4272

P050 Understanding and mitigating the consequence of undesired crystallization taking place during washing of active pharmaceutical

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Washing is a key step in pharmaceutical isolation to remove the unwanted crystallization solvent (mother liquor) from the Active Pharmaceutical Ingredient (API) filter cake. The mother liquor is typically replaced with a miscible solvent in which the API has lower solubility, to prevent any product loss, and lower boiling point to allow for easy removal during drying. However, precipitation of API and the associated impurities of synthesis in the mother liquor may occur during washing and can affect the purity of the isolated product. In addition, formation of crystal bridges in the cake leads to agglomeration, which affects the particle size distribution and powder flow properties.[1] An anti-solvent screening methodology is developed to quantitatively analyse the propensity for precipitation of paracetamol and its impurities during the washing process. Aim of this work was to validate the notion that the precipitation of API and its impurities occurs during the washing process. This analysis was conducted on paracetamol crystalized from three different solvents; ethanol, isopropanol and isoamyl alcohol. Three different wash solvents were evaluated; heptane, acetonitrile and isopropyl acetate. The solubility of paracetamol in different binary wash solutions was measured to support the wash solvent selection. A map of wash solution composition boundaries for the systems investigated was developed to depict where anti-solvent phenomena will take place. For some crystallization and wash solvent systems investigated, as much as 90% of paracetamol and over 10% of impurities present in the paracetamol saturated mother liquor was found to precipitate out. Similar level of uncontrolled crystallization during washing in a pharmaceutical process can have drastic effect on final product purity. The use of n-heptane as wash solvent always resulted in precipitation of both paracetamol and related impurities, for any given crystallization solvent. n-Heptane used to wash paracetamol crystallized from ethanol was found to produce the highest amount of precipitation. This is consistent with the largest difference in solubility of paracetamol between the crystallization and wash solvents. By using a mixture of heptane and ethanol as the initial wash solvent this effect could be minimized preventing precipitation of the API and its impurities. Use of acetonitrile as a wash solvent does not result in any precipitation of the API or impurity. However, the high solubility paracetamol in acetonitrile, would result in dissolution of API during the washing process. Wash solvents with high solubility should therefore be used cautiously to prevent any reduction in yield. Also the presence of a wash solvent in which the API has appreciable solubility in a deliquored / damp cake can lead to the formation of crystal bridges, in between particles, during drying and will result in agglomeration. X-Ray Powder Diffraction (XRPD) analysis was carried out on the paracetamol deposited API crystallizing out, this showed the presence of metastable form 1 (monoclinic) form. Therefore, no change in polymorphism was encountered due to this unwanted precipitation of API in the system investigated. Future research involves deliberately wetting the API cake with selected wash solvent and controlling the rate of washing to aid both displacement and dilution washing mechanism.

References

[1] Ottoboni, S., Price, C., Steven, C., Meehan, E., Barton, A., Firth, P., Mitchell, P., Tahir, F., 2018. Development of a novel continuous filtration unit for pharmaceutical process development and manufacturing. J Pharm Sci, 1.

P051 Probing the Role of Solute – Solvent Interactions on Nucleation

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Crystallisation is the crucial final process in pharmaceutical manufacturing for the separation and isolation of purified material. Presently, the exact role of solvent on nucleation remains elusive.[1] Thus, there is an increasing trend in using computational modelling to elucidate the role of solvent. Predictions of the ease of nucleation have been shown, based on atomic models of solute and solvent interactions, and correlated with available experimental data.[2-6] We recently predicted that isonicotinamide nucleates fastest from chloroform and slowest from acetic acid among a range of seven solvents with differing hydrogen bonding abilities based on computed solute – solvent interaction energies.[6] To advance the understanding of the role of solvent on INA nucleation at a molecular level, we have employed molecular dynamics to probe the influence of different solvents on the pre-nucleation behaviour of isonicotinamide. Different patterns of pre-nucleation clusters were observed, depending on the solvent. As the number of isonicotinamide molecules in the simulations was increased, larger clusters were observed in the simulation timescale. Similarly to the results of our 1:1 isonicotinamide – solvent models,[6] larger clusters were inhibited in solvents exhibiting strong solute – solvent interaction energies. In addition, the potential for a chiral solvent to be used for enantioselective crystallisation of chiral solutes has been examined. This advances the work of Tulashie et al. where using chiral solvents allowed for enantioselective crystallisation of mandelic acid.[7] Using ethyl-L-lactate as the chiral solvent, we can predict the enantioselective crystallisation of a single enantiomer of several chiral solutes based on the magnitude of solute – solvent interactions.

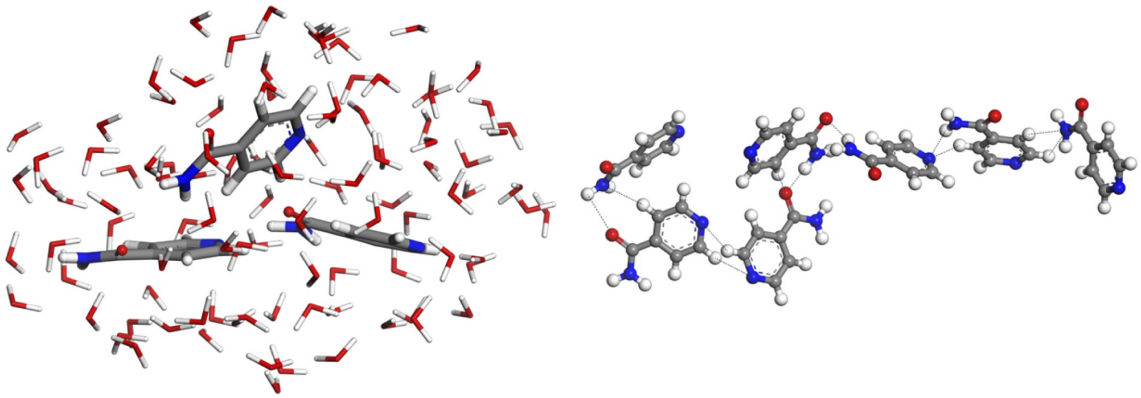

Figure 1: Solvation of an INA trimer (left) and a heptamer cluster formed in dichloromethane (right).

References

[1] R. J. Davey, S. L. Schroeder, J. H. ter Horst, Angew. Chem. Ind. Ed., 2013, 52, 2166
[2] H. Yang, M. Svard, J. Zeglinski, Å. C. Rasmuson, Cryst. Growth Des,. 2014, 14, 3890.
[3] D. Khamar, J. Zeglinski, D. Mealey, Å. C. Rasmuson, J. Am. Chem. Soc., 2014, 136, 11664.
[4] D. Mealey, J. Zeglinski, D. Khamar, Å. C. Rasmuson, Faraday Discuss., 2015, 179, 309.
[5] J. Zeglinski, M. Kuhs, D. Kamar, A. Hegarty, R. Devi Krishanraj, Å. C. Rasmuson Chem. Eur. J., 2018, 24, 4916.
[6] M .B. Lynch, S. E. Lawrence, M. Nolan, J. Phys. Chem. A, 2018, 122, 3301-3312.
[7] S. K. Tulashie, H. Lorenz, A. Seidel-Morgenstern, Cryst. Growth Des. 2009, 9, 2387.

P052 Enhanced Crystallisation of Isonicotinamide Under Strong Non-Uniform DC Electric Fields

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An electric field is reported to have an influence on protein nucleation, growth and crystal quality. To prevent the electrolysis of water relatively weak electric fields are used. Stronger fields can be used in isolator solvents such as dioxane using small organic compounds that resist electrolysis. It has been found that strong inhomogeneous electric fields result in peculiar particle mobility behaviour in suspensions. [1] In this contribution we build on this and investigate the effect of a strong electric field on the crystallization behaviour of small non-polar organic molecule systems from a supersaturated solution. A crystallisation study of isonicotinamide in 1,4-dioxane in the presence and absence of a strong electrostatic field has been conducted. A potential difference of 9 kV applied between two copper electrodes at 1 cm distance immersed in a supersaturation solution promoted nucleation. In addition, isonicotinamide crystals were consistently first detected at the anode. In the presence of the field higher cloud points and smaller induction times were measured. The difference with respect to spontaneous nucleation was more pronounced at lower supersaturation ratios. Nucleation rates, quantitatively determined from nucleation probability measurements, showed a significant effect of the applied field on nucleation kinetics. The mechanism of the enhancement of the nucleation due to the electric field is still unclear, although electromigration seems to be involved. Crystallisation induced at a specific electrode suggests that temporal and spatial control of crystallisation can be achieved by the use of electric fields.

References

[1] Li, W. W., Radacsi, N., Kramer, H. J. M., van der Heijden, A. E. D. M. ter Horst, J. H. Angew. Chemie Int. Ed. 1–5 (2016). doi:10.1002/anie.201609832

P053 Model based design of experiment for precision kinetic parameter estimation in an unseeded batch cooling crystallisation

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Crystallisation is an important separation and purification unit operation in the food and pharmaceutical industries. The process objective is to achieve tightly defined crystalline product specifications in terms of size, shape and purity. The approach adopted here is to design optimal and robust operating strategies based on first-principles models of crystallisers, but often this requires a large number of experiments to gather data for kinetic parameter estimation1. The objective of this work is to obtain maximum information with a reduced number of experiments which is also called D-Optimal Design [1], by using optimized batch cooling temperature profiles and sampling points. The system studied was paracetamol in a 4:1 w/w solvent mixture of water in propanol. A dynamic mathematical model was developed by combining the population balance, mass balance and heat transfer equations; power law based primary nucleation and growth kinetics were considered. The objective of the optimization problem was to maximize the determinant of the Fisher Information Matrix (FIM), which consists of first-order sensitivity coefficients of parameters to outputs at different sampling times. To simplify the optimization problem, the batch temperature profile was discretized into six intervals and four particle size sampling points and ten fixed concentration sampling points. The MATLAB global optimization genetic algorithm was used to solve this optimization problem. A validation crystallisation experiment was set up with focused beam reflectance method (FBRM) probe and UV/vis probe for concentration measurements. The chord length distribution (CLD) measured by FBRM was converted to crystallisation size distribution (CSD) using software developed by ICT-CMAC project. Comparison of the parameter estimation from a linear cooling and random sampling experiment, and one with the optimized operating conditions, showing higher precision with smaller confidence domain in the latter case.

References

[1] Maheshwari, Vaibhav, Gade Pandu Rangaiah, and Lakshminarayanan Samavedham. Industrial Engineering Chemistry Research 52.24 (2013): 8289-8304.

P054 Carrier Particle Mediated Stabilization and Isolation of API Nanoparticles

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One of the greatest challenges in the pharmaceutical industry is to enhance the bioavailability of poorly water- soluble active pharmaceutical ingredients (APIs). It has been estimated that almost 90% of new APIs suffer the problem of poor water solubility[1]. Thus, the bioavailability of these APIs is limited due to their poor solubility and dissolution rate. API solubility, dissolution rate, and gastrointestinal permeability are the key determinants of oral bioavailability. For APIs that exhibit poor water solubility, enhancing the dissolution rate and/or solubility in the gastrointestinal system can often improve their bioavailability. Nanoparticle (NP) formulation strategies can address these problems. The greater surface to volume ratio of nanoparticles (NPs) can result in an improvement in dissolution and bioavailability as well as enhanced permeability. Among the different techniques to form nanosuspensions, liquid antisolvent precipitation is fast, easy and cost-efficient. However, isolation of the resulting NPs to the dried state is a major challenge, due to agglomeration and Ostwald ripening resulting from the high surface energy of the NPs. In this work, montmorillonite clay particles (MMT), as received and/or with a slight surface modification with protamine sulphate salt (PA)(a cationic protein), have been employed as carriers to stabilize and isolate NPs of four different APIs (with different zeta potential) directly from suspension into dried state without the use of any API-specific soluble stabilizers (Figure 1)[2]. Process parameters were optimized to generate the NPs of valsartan, carbamazepine, curcumin and clozapine in suspension via the antisolvent precipitation method. Analysis of these nanosuspensions revealed that particles smaller than 170 nm were obtained in each case. A panel of carrier particles was screened to identify the best carrier-API combination for stabilization and isolation of the respective API. From these screening procedures, MMT was identified as the most promising carrier. The dissolution rate of dried NP-carrier composites was comparable with those of the stabilized nanoparticles in suspension. The dissolution rates of these nanoparticles from their respective MMT/PA-MMT nanocomposites were shown to be influenced by parameters such as zeta potential of nanoparticles, degree of PA functionalization and API loading on the carrier particle system. API nanoparticles with zeta potentials more negative than ca. -20 mV required the MMT surface to be modified with protamine (PA) in order to preserve the dissolution rate at higher API loadings. The optimal loading of PA on MMT was consistently around 4 mg/g, limiting nanoparticle aggregation and thus maintaining the enhanced dissolution rate of these API nanoparticles at higher loadings from the dried state. API nanoparticles with zeta potentials less negative than ca. -20 mV did not require the MMT modification with PA in order to maintain the enhanced dissolution rate at high API loadings.

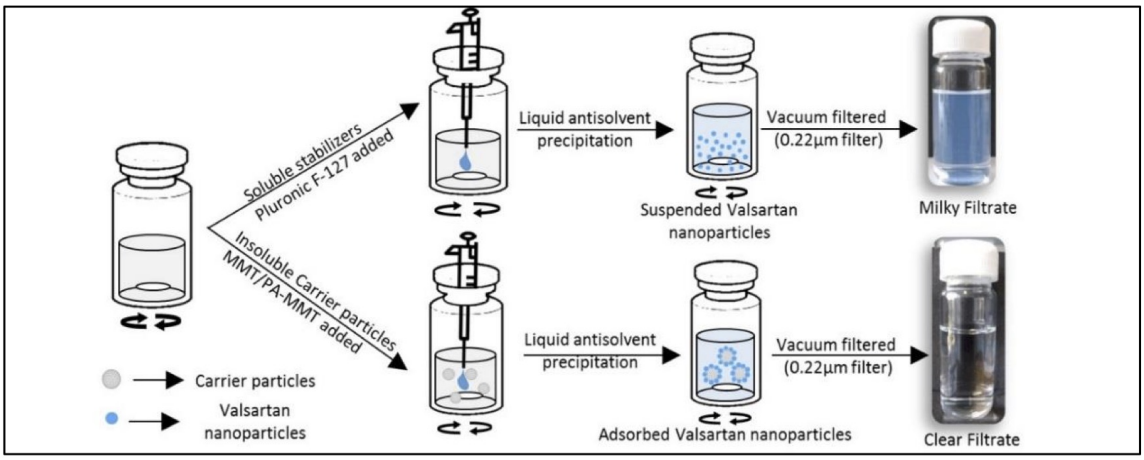

Figure 1: A schematic of the production and isolation of valsartan nanoparticles in the presence of (i) Pluronic® F-127 (upper path), and (ii) MMT or PA-MMT carrier particles (lower path).

References

[1] T. Loftsson, M.E. Brewster, J. Pharm. Pharmacol. 62 (2010) 1607–1621.
[2] A. Kumar, P. Davern, B.K. Hodnett, S.P. Hudson, Colloids Surfaces B Biointerfaces 175 (2019) 554–563.

P055 The effect of inorganic ions on Li_2CO_3 crystal growth

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Demand for Li has risen from 200 metric tons in 1994 to over 40,000 metric tons in 2008, due to the surge in electric cars and other Li-powered battery systems [1]. Sixty-six percent of global Li resources are found in high salinity aqueous solutions (brines) trapped within the Earth's surface or found as lakes [2]. Therefore, effective Li extraction from this medium is a critical technological goal. One extraction method currently used is the precipitation of Li_2CO_3. However, at present there is little information about the influence of inorganic ions present in brines on the precipitation and growth of Li_2CO_3. Therefore, in this study we explore how different inorganic ions in solution compete and interact with Li_2CO_3 using experiments and computational simulations. Crystals of Li_2CO_3 were grown using the method of Taborga et al. [3], with the addition of monovalent (NaCl, KCl) or divalent salts ($CaCl_2$, $MgCl_2$, Na_2SO_4) at ionic strengths of 1 or 0.1. Experiments were run for 60 minutes in stirred glass batch reactors that were sealed from the atmosphere and heated to at 80^oC using a water bath. After the experiments the precipitate was extracted using gravity filtration and dried in a desiccator for 24 hours. Phase identification was conducted using Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy and X-ray diffraction. The morphology of the samples was imaged using a scanning electron microscope (SEM). Changes in morphology were correlated with surface complexation information, gained from attenuated total reflectance (ATR)-FTIR. Finally, the crystal morphology and surface complexation analysis were directly compared with expected crystal equilibrium morphologies derived from surface energies calculated using density function theory (DFT) implemented using the Vienna ab-initio simulations package (VASP). The analyses showed that Mg^{2+} can effectively outcompete Li^+ for the carbonate anion, as only a hydrated $MgCO_3$ phase was found after these experiments. Similarly, Ca^{2+} also competed directly for carbonate, producing calcite ($CaCO_3$) in the most concentrated experiment and a mixture of calcite and Li_2CO_3 in the presence of lower $CaCl_2$ concentrations. Monoclinic Li_2CO_3 (zabuyelite) was the only precipitate formed in the other experiments. Evidence of growth via a precursor phase was observed in the experiments as hollow cores within crystals in the presence of sulphate, and empty centres of crystal clusters arranged into rosette shapes. ATR-IR analysis of the Li_2CO_3 crystals in the sulphate experiments and the computational simulations demonstrated that this anion can interact directly with the growing surfaces of Li_2CO_3 crystals. In contrast, Na^+, K^+ and Cl^- are only expected for interact with Li_2CO_3 in a solvent-mediated fashion. This is consistent with solvent-mediated ion pair formation in solution between monovalent monoatomic cations and CO_3^{2-} [4]. Evidence from in situ Raman analysis of Li-carbonate solutions also conducted in this study indicates that Li^+ and CO_3^{2-} can form ion pairs in solution, which are also expected to be solvent mediated due to the strong interactions between Li^+ and water molecules [5].

References

[1] Blomgren J. Electrochem. Soc, 2017 16, A5019.
[2] Gruben et al. J. Ind. Ecol. 2011 15, 760.
[3] Taborga et al. J. Cryst. Growth 2017 460, 5.
[4] Rudolph et al. Dalton Trans. 2008 900-908.
[5] Ichieda et al. J. Phys. Chem. A. 2003 107, 7597.

P056 Second Harmonic Generation Microscopy (SHG-M) to Monitor Phase Transitions in Disordered Organic Crystals

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Among nonlinear optical effects, Second Harmonic Generation (SHG) is an extremely sensitive and rapid technique to detect absence of inversion centers in crystalline structures. [1] In addition, while combined with microscopy (SHG-M), it permits (i) to monitor temperature-induced phase transitions; (ii) to detect non-centrosymmetric zones inside heterogeneous materials. Therefore, as an analytical tool, SHG-M covers a large domain of applications, in complement with other classical techniques (e.g. XRPD, DSC, optical microscopy). While non-centrosymmetric structures are not the most popular among crystalline materials (i.e. 24.1% of the structures reported in the Cambridge Structural Database) [2], they are preponderant in many industrial applications (e.g. production of pharmaceuticals and optoelectronic devices); thus, their studies correspond to important issues. The present work illustrates the use of SHG-M in selected monophasic and multiphasic sample studies. Particularly, reinvestigation of Phenanthrene and Adamantane (Figure 1) phase transitions by means of SHG and/or Third Harmonic Generation (THG).

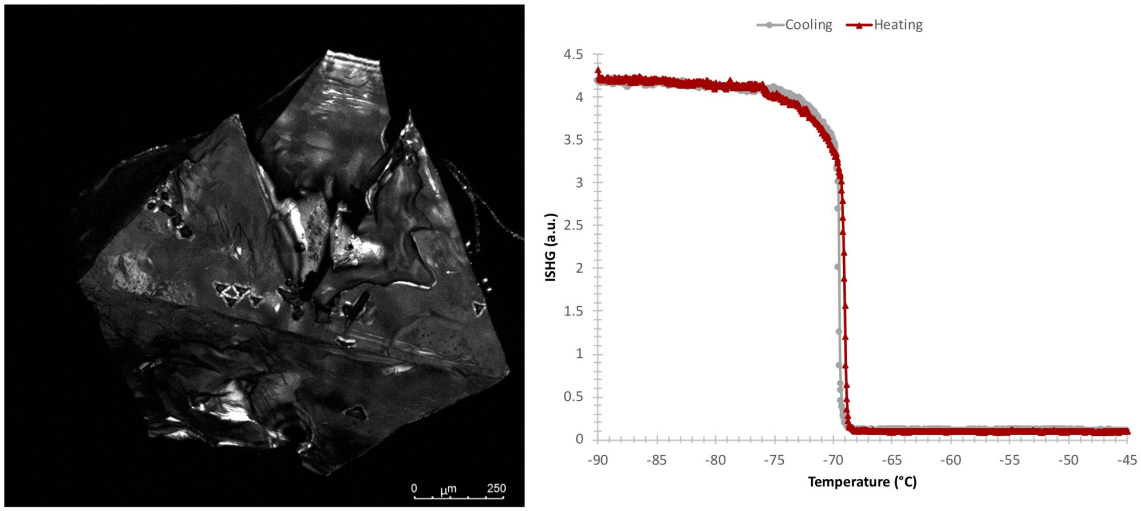

Figure 1: Adamantane crystal image obtained by THG microscopy (left) and SHG signal evolution upon heating and cooling (right). Phase transition temperature was determined at -69.5C and -69.0C for cooling and heating, respectively. Acknowledgments This work has been funded by Region Normandie and the European Regional Development Fund (FEDER-FSE Normandie 2014-2020) through the project SCAMPI

References

[1] F. Simon, V. Dupray, and G. coquerel, "Relevance of the Second Harmonic Generation to Characterize Crystalline Samples," Chem. Eng. Technol., vol. 38, no. 6, pp. 971–983, 2015.

[2] F. H. Allen and W. Motherwell, "Applications of the Cambridge Structural Database in organic chemistry and crystal chemistry," Acta Crystallographica Section B, 2002.

P057 Solvent Dynamics and Thermodynamics at the Crystal-Solution Interface of Ibuprofen

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Active pharmaceutical ingredients (APIs) are often manufactured as crystalline solids. The solid form of a drug provides several advantages in the isolation, handling and storage of the material, such as higher purity, improved flow, and higher chemical and physical stability [1]. In the process and product design of the API manufacture, the choice of the solvent for the crystallisation step is by far the most critical decision. The morphology of solution-grown crystals is found to be affected by the solvent due to specific surface-solvent interactions, which can alter the relative growth rate of the morphologically dominant crystal faces. Factors such as solubility, formation of hydrogen bonds, strong non-bonded interactions can play a role in determining the growth mechanism at the crystal surface. Solvent-specific crystal shape prediction has been achieved for several systems [2,3], however the development of a universal and systematic crystal shape prediction model still presents outstanding challenges [4]. Here we lay the groundwork of systematically accounting for the effects of specific surface-solvent interactions on the morphology of solution-grown crystals. Our efforts are focused on the investigation of the solvent behaviour as a function of the distance from the morphologically dominant crystal faces of ibuprofen. We obtain information on the thermodynamics and dynamics of solvent molecules at the crystal-solution interface. We account for the free energy difference between a molecule adsorbed on the crystal surface compared to bulk solution, as well as the exchange rate of an adsorbed solvent molecule with a molecule from the bulk solution or a subsequent solvent layer. In this work the 002, 011, 110, 100 polar and 100 apolar ibuprofen crystal faces are considered in 9 solvents – water, 1-butanol, toluene, cyclohexanone, cyclohexane, acetonitrile, trichloromethane, methanol and ethyl acetate. This work is carried out with the aid of molecular dynamics (MD) simulations. The investigation of the solution structure reveals that the arrangement of solvent molecules in the solution and the stability of the absorbed state vary greatly depending on their interaction with the crystal face. While for some surface/solvent combinations an adsorbed state is practically non-existent, in other cases specific interactions promote a stable adsorbed state and can furthermore induce a structuring effect in the solution. Long-range effects are observed in the case of surface-induced stacking of solvent molecules, which propagates beyond the solvent molecules in direct contact with the crystal surface. In such cases the rate of exchange of solvent molecules between adsorbed layers is remarkably slow, with characteristic exchange times up to three orders of magnitude slower than in the cases in which long- range layering is not observed. In the context of crystal growth our findings have important consequences. Mass transport driven processes such as rough growth can be significantly affected by the solution structure, particularly for cases where we observe solvent layering. Furthermore, under the assumption that the lifetime of the adsorbed state of a solvent molecule is correlated with the vacation of a kink site, the solvent kinetics at the surface/solution interface may significantly impact the growth rate of specific crystal faces and hence contribute to the definition of solvent effects on the growth shape of crystals.

References

[1] N. Variankaval, A. Cote, AIChe Journal, 2008, 54(7),1682
[2] M. Salvalaglio, T. Vetter, M. Mazzotti, M. Parinello, Angewandte Chemie Int Edition, 2013, 52(50), 13369
[3] J. Li, M. Doherty, Crystal Growth and Design,2017, 17(2), 659
[4] E. Elts, M. Greiner, H. Briesen, Crystals, 2017, 7, 288

P058 Deep Eutomic Solvents – Crystallisation Via Self-Destruction

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A new deep eutectic solvent (DES) system, in which one of the components is inherently volatile, has been discovered. Using phenol as the volatile component allows for the suppression of melting point for many pharmaceutical compounds, resulting in the ability for crystallisation from a deep eutectic at room temperature. This new class of material is known as a deep eutomic solvent (DXS) [1]. The extensive hydrogen bonding within these systems opens the opportunity for the control of crystal polymorphism. To demonstrate this, we have shown that by altering the ratio of the DXS used for crystallisation in paracetamol, we can repeatedly differentiate as the whether the ubiquitous form I or the high temperature form II emerges spontaneously at room temperature (Figure 1). The use of a DXS for crystallisation also introduces a system where a highly concentrated solution of pharmaceutical exits at room temperature. For systems with low solubility in organic solvents, this may be very useful for numerous applications. Both caffeine and theobromine show increased available concentrations of two orders of magnitude in DXS form. The ability to add multiple compounds into such mixtures then allows the ability for the creation of new co-crystals, unobtainable from solvent systems due to low solubility. A systematic search of ternary eutomic systems has shown that co-crystalline growth in the manner is applicable, highlighted by the ability to easily produce difficult to synthesize urea-2-nitrophenol co-crystals [2].

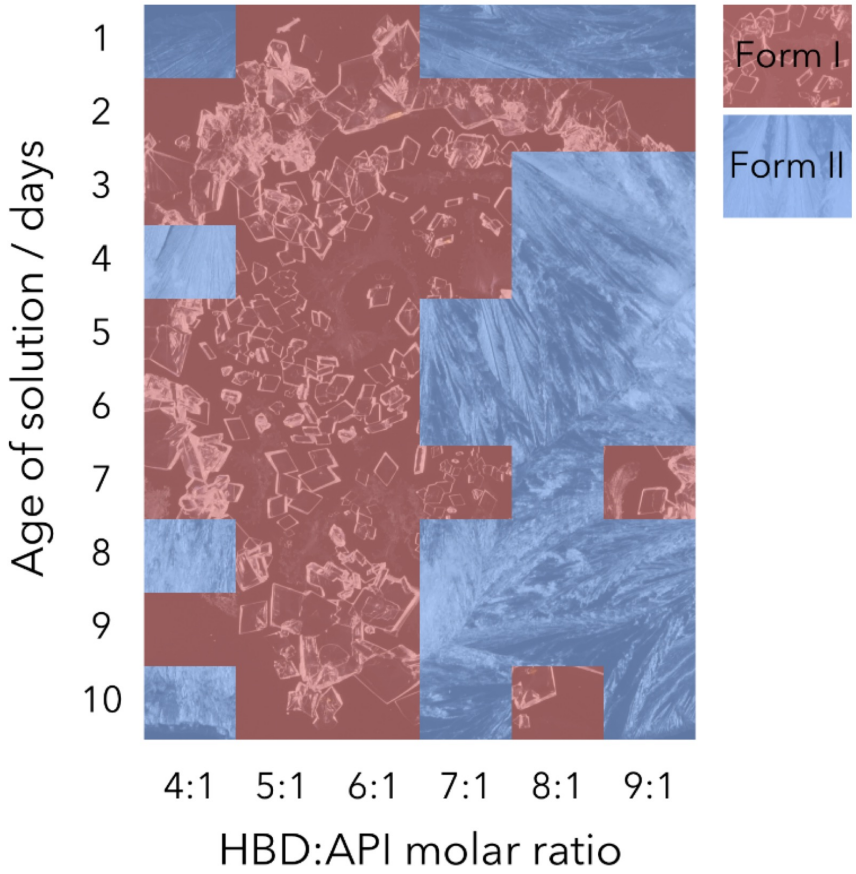

Figure 1: The form of paracetamol grown by evaporating DXSs different of molar ratios. Phenol acts as the hydrogen bond donor (HBD) and paracetamol and the hydrogen bond accepter (HBA). The experiment was run each day for a total of 10 days.

References

[1] J. Potticary, C. L. Hall, V. Hamilton, J. F. McCabe, S. R. Hall, arXiv:1902.08376, 2019.
[2] Patent Applied for: GB1902284.7.

P059 Towards Digital Design of Crystals: Predicting Solubility via Absolute Chemical Potentials for Solid, Solution and Gas Phases

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Currently, more than 90% of small molecule drugs are delivered in crystalline form. Solubility of these crystalline molecules plays a crucial role in drug design as it directly affects the bioavailability of a drug. Also, the supersaturation at a given temperature and solute concentration (as determined from the solubility) is crucial in all efforts to predict nucleation and growth rates [1]. The thermodynamic definition of solubility is, the concentration of the solute in the solvent which makes its (solute) chemical potential equal in both the phases (solid solution). Solubility prediction using atomistic simulations is a challenging task. The solubility prediction of NaCl took nearly a decade of research efforts. The solubility prediction of polyatomic molecules is an ongoing challenge and we have developed a new approach that employs independent predictions of absolute chemical potentials in the solid (μ_{xtal}) and solution (μ_{soln}) phases without having a common starting reference system. For the solid phase we apply the Einstein crystal method in its unaltered form although we have extended it differently from some of the previous works [2] to compute the absolute free energy of the molecular crystal (solid). In order to compute the absolute chemical potential in the solution phase, we have developed a new gas phase reference system to compute the absolute chemical potential of an isolated polyatomic gas molecule (μ_{gas}); to which we add the solvation free energy of the molecule at a given solute concentration to give the absolute chemical potential in the solution phase. We leverage and demonstrate the computational tools developed so far to predict the solid-vapor equilibrium curve for succinic acid (our model compound), i.e., predict its sublimation vapor pressure as a function of temperature. We find excellent agreement between our predicted results and experiments in the literature. Thus, having tested our methodology we are currently applying it to the solubility problem.

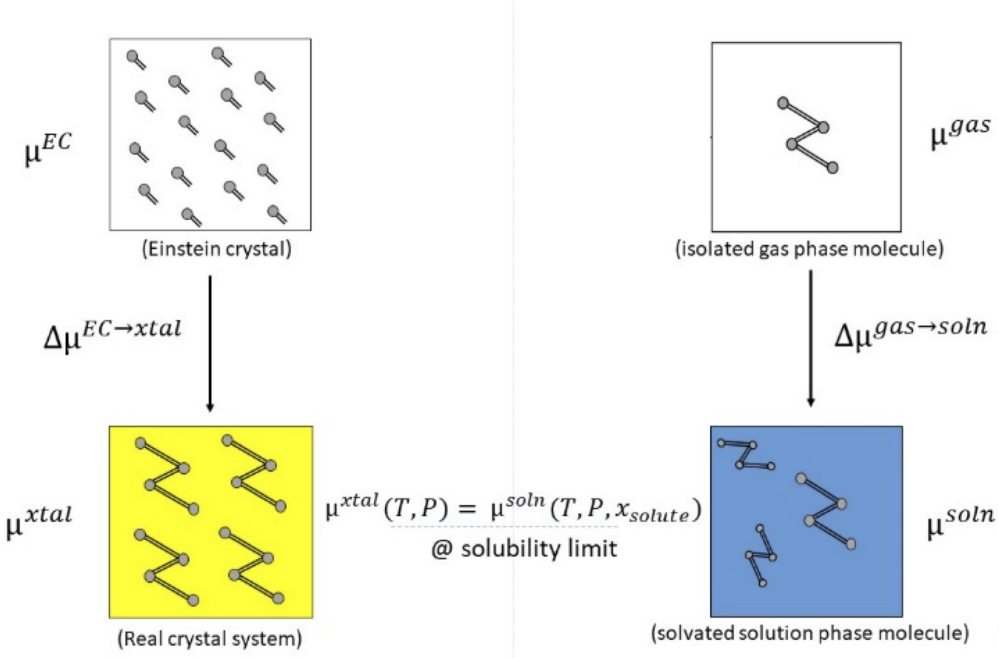

Figure 1: The solubility prediction route

References

[1] Nils ER Zimmermann, Bart Vorselaars, Jorge R Espinosa, David Quigley, William R Smith, Eduardo Sanz, Carlos Vega, and Baron Peters. NaCl nucleation from brine in seeded simulations: Sources of uncertainty in rate estimates, The Journal of Chemical Physics, 2018, 148(22), 222838-222846

[2] Lunna Li, Tim Totton, and Daan Frenkel. Computational methodology for solubility prediction: Application to the sparingly soluble solutes, The Journal of Chemical Physics, 2017, 146(21), 214110-214124

P060 Sulfur Precipitate Formation and Sedimentation

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The abstract is redacted for confidentiality reasons.

P061 Investigation of solid-liquid phase diagrams for sulfamethazine co-crystals

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Introduction. Co-crystals are crystalline molecular complexes consisting of two or more neutral components that are solid at room temperature. Pharmaceutical industry holds interest in co-crystals because of their ability to alter the physicochemical properties of the Active Pharmaceutical Ingredient (API) without affecting its chemical structure and properties. A lot of research so far has been focused on finding new co-crystals and their formation. There are only a few studies in literature that focus on their physical properties or how these depend on the coformer. Not much work has been performed on the manufacturing of co-crystals. A complete and detailed phase diagram aids the development of a crystallization process for manufacturing co-crystals as it highlights the regions/zones where the different solid phases are stable. The important aspects to study about co-crystals and phase diagrams include understanding the co-crystal dissolution behaviour, solubility, the size of the region in the ternary phase diagram where the co-crystal is the stable solid phase and co-crystal stability.

Objectives. The main objectives of this work are to study the effect of temperature, solvent and coformer on the solid-liquid phase diagram. 1:1 sulfamethazine (SMT)-salicylic acid (SA) was chosen as the model system. Ternary phase diagrams for this system were constructed in three solvent systems-methanol, acetonitrile and 7:3 (v/v) dimethylsulfoxide-methanol mixture, at three temperatures. To gain a deeper understanding of the phase diagrams, the ternary phase diagrams for the same API i.e SMT were constructed with another coformer (CoF). The dissolution behaviour and the relationship between the size of the region in the ternary phase diagram where the co-crystal is the stable solid phase were studied. Some process experiments were carried out to determine possible yield and volumetric productivity.

Results and Discussion. The 1:1 SMT-SA co-crystal shows congruent dissolution in acetonitrile and incongruent dissolution in the other two solvent systems. The SMT-CoF system showed incongruent dissolution in the two solvents. The solvent is shown to have a strong impact on the appearance of the ternary phase diagrams and causes a system to show congruent or incongruent dissolution. Temperature does not show a significant effect in the temperature range (20 °C) studied. Using the solubility data for the SMT-SA co-crystal in acetonitrile, the Gibbs energy associated with the co-crystal formation were estimated, which range between -5.7 to -7.7 kJ/mol. The negative values depict the thermodynamic stability of the co-crystal over the pure components. It was seen that the solubility ratio between the two co-crystal components could not predict with absolute confidence the dissolution behaviour of a co-crystal. The size of the region where the co-crystal is the stable solid phase is inversely proportional to the solubility ratio of coformer and API. In all solvents, pure co-crystal can be synthesized by slurry conversion co-crystallization irrespective if a system is congruent or incongruent.

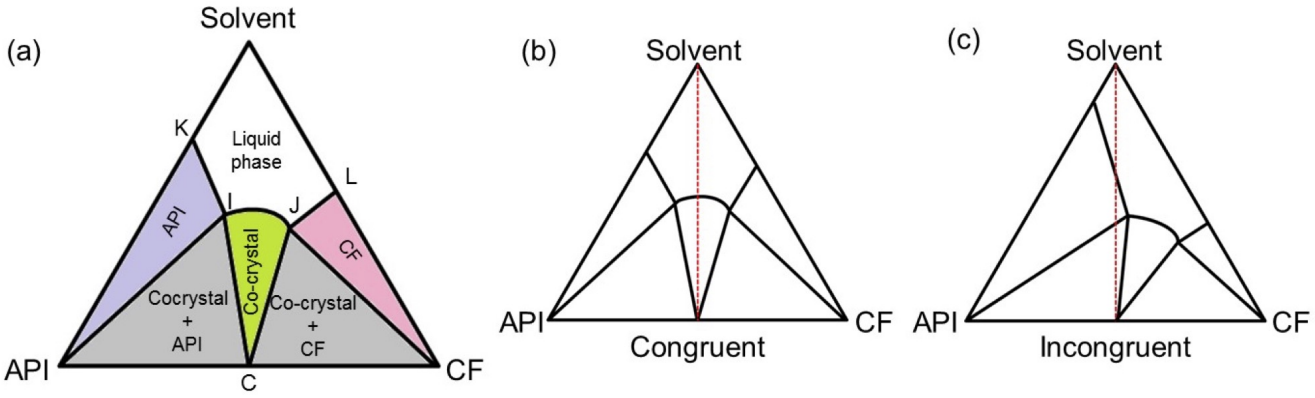

Figure 1: A typical ternary phase diagram for a co-crystal depicting various stability regions (a), a symmetric ternary phase diagram showing congruent dissolution (b), and an asymmetric ternary phase disgram showing incongruent dissolution (c).

P062 Understanding solute-solvent interactions in non-classical nucleation

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Introduction For many years crystallization through classical mechanism was the basis of crystal science. With increasing interest in nanoparticles, evidence was found where classical mechanism was challenged by non-classical mechanism due to its shortcomings. In classical mechanism, the primary building blocks are atoms and molecules i.e. growth of a single crystal is atoms/molecules mediated. On the other hand non-classical mechanism defines growth of single crystal through assembly of particles in the nanometre range. Using salicylamide as a solute, kinetics of these nanoparticles/nanoclusters has been studied in different organic solvents. Solute-solvent interactions were experimentally studied by IR experiments and modelled using molecular dynamics (Figure1). In undersaturated solutions, the size of the clusters range to hundreds of nanometres and in saturated and supersaturated solutions, up to micrometre. Overall, the size of the clusters increases gradually with increase in solute concentration but at higher mole fractions a step-wise increase in size of clusters was observed. At all times, a change in this trend for different solvents was observed above and below the saturation concentration. However, the trends tends to have correlation to the trends obtained through IR spectroscopy and modelling.

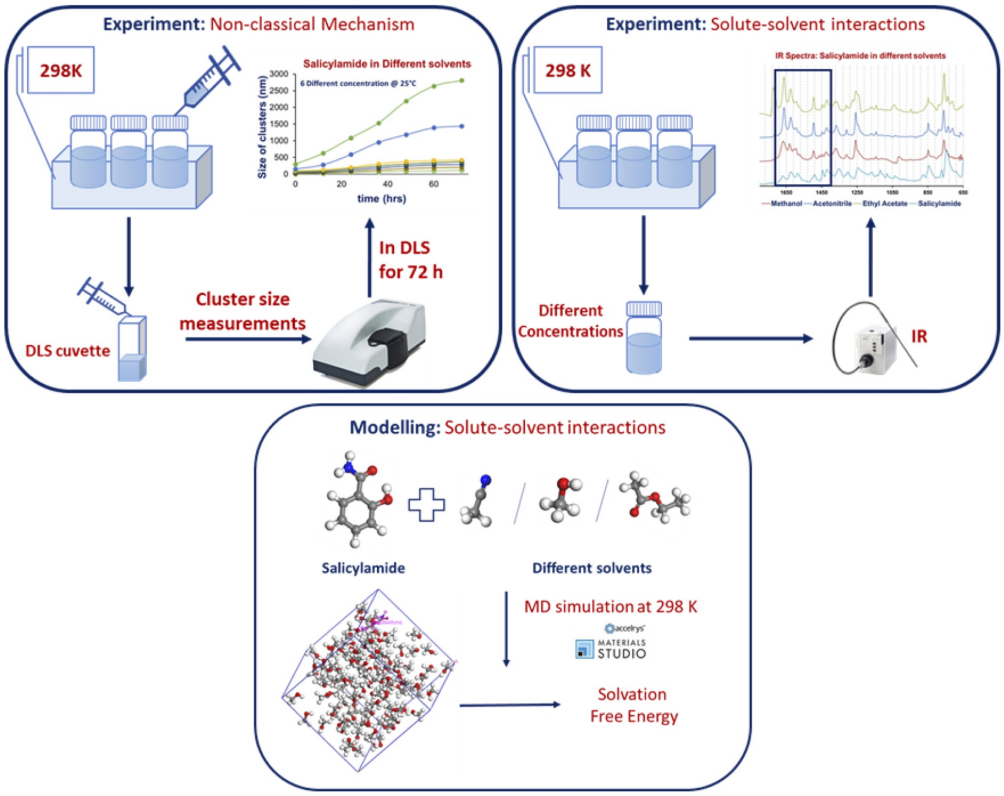

Figure 1: Summary of experimental work Results and discussion Depending on the concentration and solvent, a trend in these nanoclusters was observed.

References

1. M. Niederbergera and H. Cölfen, Phys. Chem. Chem. Phys., 2006, 8, 3271.

P063 Screening Polymorphism in 4-HOC_6H_4COR Compounds

M. F. M. Piedade[1,2], **R. G. Simões**[1], **C. S. D. Lopes**[1], **C. E. S. Bernardes**[1], **M. E. M. d. Piedadea**[1]

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Polymorphism, the ability of a molecule to crystallize in more than one solid structure, is a phenomenon commonly observed in many organic compounds. Different packing arrangements are often accompanied by changes in the physical and chemical properties of the solid (e.g. color, melting point, solubility, etc.), and this represents a major challenge for the industrial production of organic materials with highly reproducible properties. Systematic studies of polymorphism using families of organic crystals where the different building blocks are structurally related molecules are particularly interesting to understand how the interplay of molecular size, shape and types of interaction may affect the packing architecture and the relative stability of crystal forms. One such family is the one with 4-HOC_6H_4COR backbone, that has H-bond donor (OH) and acceptor (C(O)R) substituents separated by a phenyl ring, since they have been shown to be prone to polymorphism, both due to changes in their molecular conformation (such in the case of HAP) [1] or through adjustments in their packing architecture (as in HBA and HVP), [2, 3] and can provide information on how the length of the R side chain impacts on the observed crystallization patterns and crystal structures. In this work the thermodynamic properties (e.g. enthalpies of fusion and sublimation) of different 4-HOC6H4COR compounds (Figure 1), and their dependence on the packing architectures, were analyzed as a function of the length of the side chain.

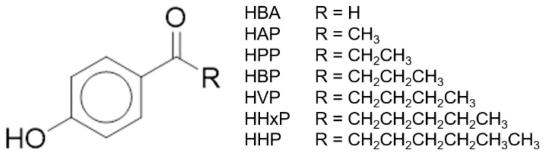

Figure 1: 4-HOC_6H_4COR compounds studied in this work

References

[1] Bernardes, C. E. S.; Piedade, M. F. M.; Minas da Piedade, M. E. Cryst. Growth Des. 2008, 8, 2419-2430.
[2] Lopes, C. S. D.; Bernardes, C. E. S.; Piedade, M. F. M.; Diogo, H. P.; Minas da Piedade, M. E. Eur. Phys. J. Sp. Top. 2017, 226, 849-855.
[3] Simões, R. G.; Bernardes, C. E. S.; Minas da Piedade, M. E. Cryst. Growth Des. 2013, 13, 2803-2814.

Acknowledgements This work was supported by Fundação para a Ciência e a Tecnologia (Portugal) through projects FCT UID/MULTI/00612/2013 and LISBOA-01-0145-FEDER-028401, and post doctoral and doctoral grants awarded to R. G. Simões (SFRH/BPD/118771/2016) C. E. S. Bernardes (SFRH/BPD/101505/2014) and C. S. D. Lopes (SFRH/BD/128794/2017), respectively. We also acknowledge COST Action CM1402.

P064 Assessment of Secondary Nucleation Kinetics of Alpha-Glycine

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Crystallisation is a highly efficient purification process commonly used within the pharmaceutical industry to ensure product quality during active pharmaceutical ingredient manufacture. Many industrial pharmaceutical processes induce secondary nucleation by seeding to enhance control over a process resulting in a more uniform particle size and properties improving the downstream processability. Many questions are still left unanswered regarding the fundamental mechanisms which are significant to a secondary nucleation process and therefore full control and scalability has yet to be achieved. Secondary nucleation rates of glycine (α) were determined at a range of different experimental supersaturations, following a comprehensive workflow previously developed at the University of Strathclyde [1]. This method involves the use of a well characterised single crystal seed at small laboratory scales. The metastable zone width and induction times were firstly measured to determine the onset of primary nucleation under known, controlled conditions and in-turn provided the operating window for crystal seeding. Seeds were then grown, characterised and selected before adding them to vials at specific supersaturations selected in order to limit the onset of stochastic, primary nucleation and then secondary nucleation rates were calculated.

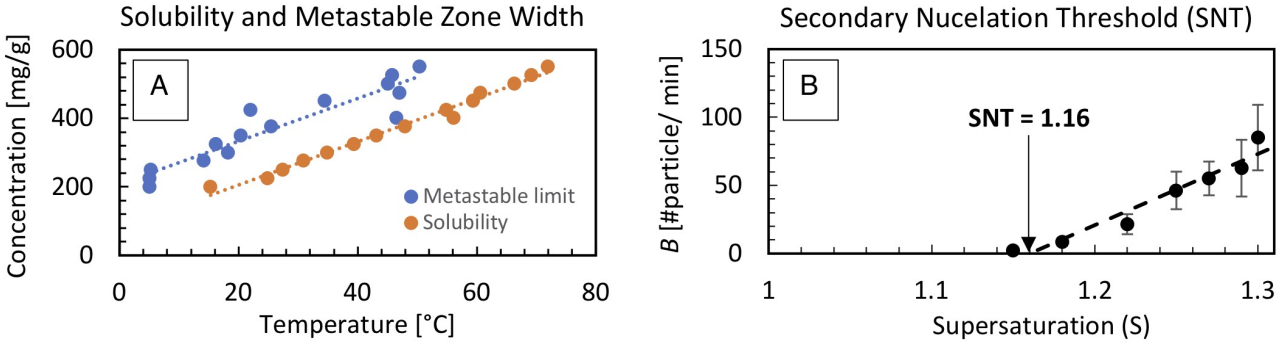

Figure 1: (A) displays the metastable zone width, which is the area between the solubility and metastable limit. The metastable zone width has an average width of 20 ± 5^{o}C therefore providing a large operating window for supersaturation selection. Within this region, 5 different levels of supersaturation were selected and the induction times recorded using the Crystal 16®. It was noticed that as S was reduced the time taken for the onset of primary nucleation increased and the total number of vials nucleating decreased. Finally, as shown in figure 1 (B) the rate of secondary nucleation was determined and seen to increase with supersaturation. The SNT was found at S=1.16.

References

[1] Briuglia, M.L.; Sefcik, J.; ter Horst, J.H. Measuring secondary nucleation through single crystal seeding. Cryst Growth Des. 2019, 421, 421–429.

P065 Crystal growth rates of six active pharmaceutical ingredients in methanol

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Several experimental techniques can be used to investigate crystal growth rates and fundamental mechanisms of crystal growth, e.g. growth cells, rotating disc (RD) or isothermal seeded desupersaturation (ISD) experiments [1]. The agreement of results is often a challenge due to the different fluid dynamics. In this study, the crystal growth of six different active pharmaceutical ingredients, Acetaminophen (AAP), Carbamazepine (CBMZ), Piracetam (PCM), Phenylbutazone (PBZ), Fenofibrate (FF) and Risperidone (RIS), in methanol is studied by two growth experimental methods, RD and ISD. RD experiments were conducted in a 250 mL crystallizer at 288 K and supersaturation of (S-1)=0.1 and at 200 rpm. ISD experiments were carried out in 250 mL jacketed crystalliser within 288-303 K at 275 rpm, and at supersaturations (S-1) below 0.4. In-situ IR and FBRM were used to monitor the desupersaturation and the number of crystals and their size distribution. For each API, the experimental desupersaturation data were modelled individually using the power law empirical equation, and the Burton Cabrera Frank (BCF) and Birth and Spread (B+S) mechanistic models. Examples of the growth rates obtained by ISD and RD methodologies are illustrated in Figure 1, where a good agreement can be observed. Activation energies (27-47 kJ/mol) and growth exponents estimated from power law equation suggest surface integration controlled growth, as confirmed by a separated mass transfer analysis. The relative order of growth rates has been rationalized on a basis of the influence on growth of some fundamental physicochemical properties, namely solubility, solid-liquid interfacial energies, mass transfer coefficients, diffusivities, molecular volumes and lattice energies. Instead of a prominent effect of one of these properties, they are all at play simultaneously, making the rationalization of the growth rates observed more challenging than when the growth rates of one API in different solvents is studied. Different steric effects induced by distinct molecular volumes, different solid surface properties, and inter and intramolecular interactions with different functional groups eventually define the rank of growth rates observed.

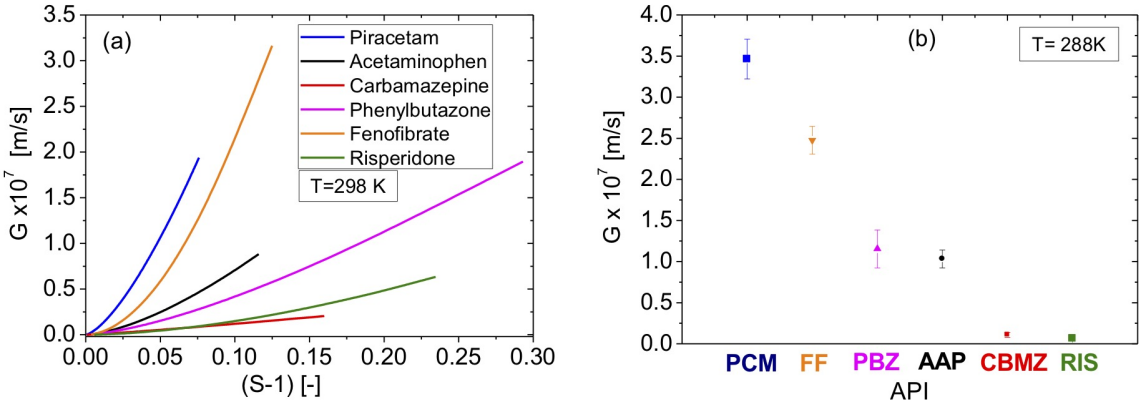

Figure 1: (a) Estimated growth rates vs. supersaturation at 298 K by isothermal seeded desupersaturation experiments. (b) Average crystal growth rate in terms of length of the six APIs seed crystals grown using the rotating disk method at growth temperature of 288 K at supersaturation (S-1) of 0.1.

References

[1] Mullin, J. W. (John W. Crystallization; Butterworth-Heinemann, 2001.

P066 Real-Time Imaging of Nucleation and Crystal Growth during Continuous Anti-Solvent Crystallisation: X-ray Phase Contrast Imaging in a Concentric Flow Device

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Microscopic imaging of mixing, nucleation and pre-nucleation stages of organic molecule crystallisation in organic solvents presents formidable challenges to conventional microscopy techniques, due to the low absorption, scattering or refraction contrast between the organic phases. We have now demonstrated that synchrotron-based X-ray Phase Contrast Imaging (XPCI) and X-ray Grating Interferometry (XGI) are excellent techniques to achieve sufficient phase boundary contrast to visualise processes in the early stages of crystallisation. We performed XPCI and XGI to monitor the mixing zone of a continuous anti-solvent crystalliser, [1] to probe the dynamic phase separation processes in the initial stages of crystallisation, to gain a better understanding of nucleation and growth from solution.[2] Real-time visualisation of the mixing process has been achieved with approximately 1 μm resolution. We are able to visualise the boundaries in the mixing zone between solution and anti-solvent, and we can detect microscopic metastable phases as well as crystal growth. XPCI [3] in particular is powerful for studies of organic systems, as it facilitates much better contrast than conventional absorption X-ray radiographic imaging under in situ conditions. We compare and contrast nucleation phenomena for two crystallising systems, namely, glycine and lovastatin. Studies were carried out using different solvent/anti-solvent systems and using different flow rate ratios. While glycine nucleates as expected from the mixing zone, lovastatin forms heterogeneous prenucleation phases on the walls of the outer reactor walls (Fig 1), from which crystallisation of needle shaped crystals takes place.

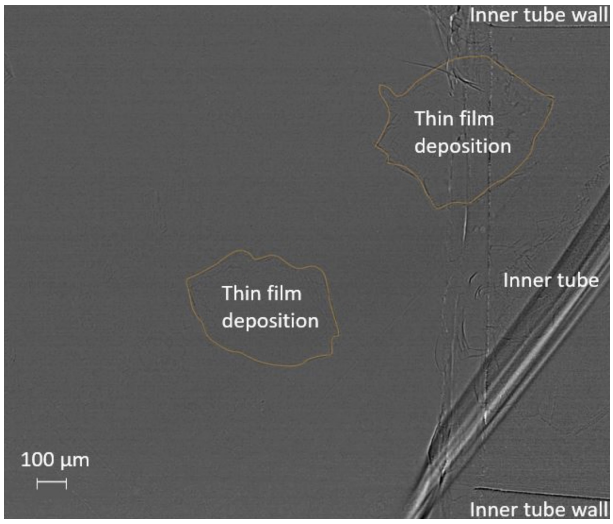

Figure 1: Thin film deposition.

References

[1] V. Svoboda, P. MacFhionnghaile, J. McGinty, L. E. Connor, I. D. H. Oswald and J. Sefcik, Crystal Growth Design, 2017, 17, 1902-1909. [2] R. J. Davey, S. L. M. Schroeder and J. H. ter Horst, Angewandte Chemie International Edition, 2013, 52, 2166-2179. [3] C. Rau, M. Storm, S. Marathe, A. J. Bodey, S. Cipiccia, D. Batey, X. Shi, M.-C. Zdora and I. Zanette, AIP Conference Proceedings, 2019, 2054, 030012.

P067 Reducing risk in drug development through Crystal Structure Prediction

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The ability to computationally predict crystal structures of drug-like small molecules would reduce risk and improve efficiency during drug development by guiding and complementing experimental screens for low energy crystal forms. Recent advances in computational algorithms and hardware have enabled high accuracy crystal structure prediction (CSP) methods to assist in pharmaceutical decision making for molecules with few low energy crystal forms or large energy gaps between forms. However, the computational demand of CSP increases exponentially with the number of degrees of freedom in a molecular system, thus challenging the ability of CSP methods to accurately and efficiently predict crystal structures for more complex, pharmaceutically-relevant molecular systems within timescales suitable for drug development. Through tight coupling of algorithmic and technological innovation, we have developed a cloud-based CSP platform that harnesses the high accuracy of customized force fields and the scalability of cloud-computing in order to predict crystal forms of complex systems, and further characterize their stabilities at physically relevant temperatures, within reasonable timescales (Figure 1). We demonstrate the strength of our CSP method coupled with finite temperature analysis on compounds with multiple low energy crystal forms, including Molecule XXIII from the 2016 CSP Blind Challenge. To the best of our knowledge, our findings are the first predictions for Molecule XXIII that correctly explain the experimentally observed stabilities between its five known crystal structures. Such ambient temperature predictions can guide and accelerate the selection of stable crystal forms of small molecule drug candidates for further development.

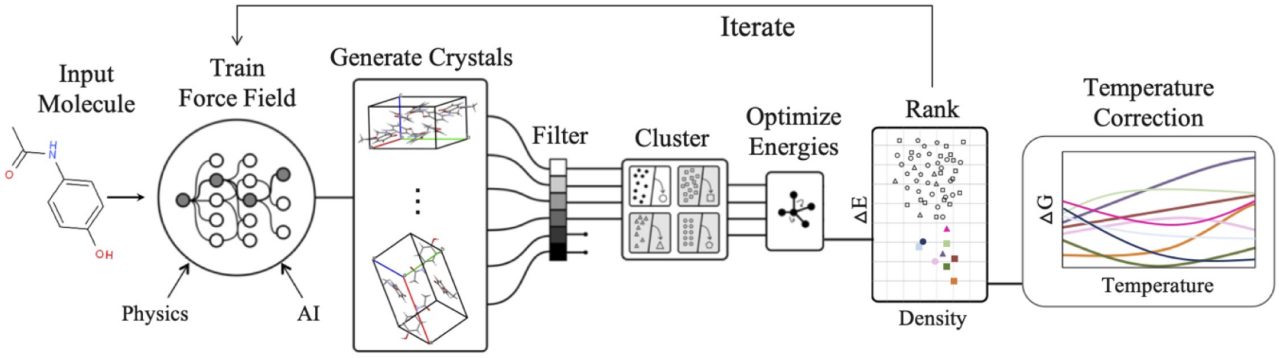

Figure 1: Overview of Crystal Structure Prediction at XtalPi with Finite Temperature Correction.

P068 Manipulating co-crystal size and morphology using a combination of temperature cycling and additives

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Crystal shape and particle size distribution can affect the properties of solid-state materials such as product dissolution rate and bioavailability as well as downstream processing and secondary manufacturing. In particular, needle-like crystals can pose problems due to poor flowability, filterability fines formation. This work describes methods to control and modify shape and particle size distribution of a co-crystal system. Benzoic acid (BZA) and Isonicotinamide (INA) in a 1:1 stoichiometric ratio in ethanol form a co-crystal with a needle-like morphology. Temperature cycling has long been known to increase particle size and avoid the formation of fines. As a general approach, a high number of cycles is often used to induce a large crystal shape modification. In this study, a relatively small number of deep temperature cycles are used in which a high amount of solid is dissolved in each cycle to generate significant crystal shape variation. For the BZA-INA co-crystal system a few deep temperature cycles on a 3 ml scale is enough to increase the average crystal size from less than 10 up to around 500 micron. A second approach uses the additive addition to modify the habit of the crystals. A series of structurally related additives were selected and tested in the process. During cooling crystallization crystal shape was successfully changed from needle-like to more equant crystals, upon the addition of 8% w/w additive. A combination of both methods resulted in excellent crystal shape with a substantial lower aspect ratio and an average size of around 200 microns using just 0.7% w/w of additives.

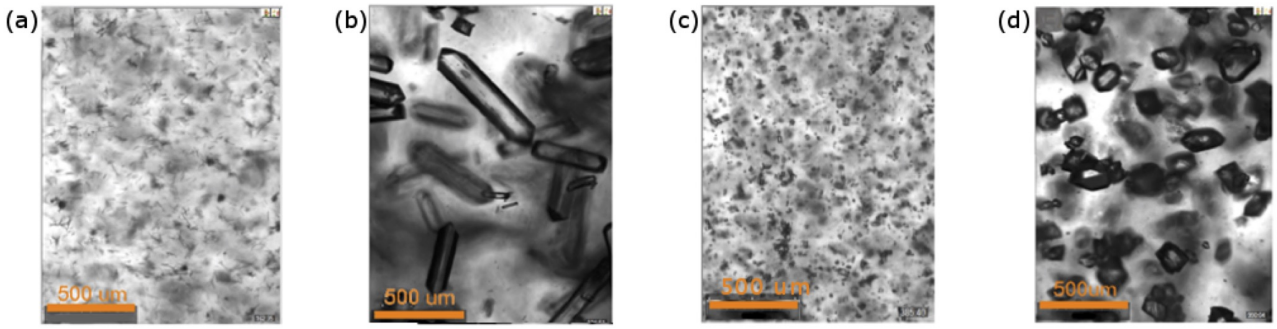

Figure 1: Co-crystal material after (a) cooling crystallization, (b) eight deep temperature cycles, (c) crystallization in the presence of an additive and (d) additive addition and eight temperature cycles.

P069 An Approach to Accurately Determine Anti-Solvent Phase Diagrams

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Obtaining reliable solubility data is one of the fundamental requirements towards crystallisation process design, optimization and control. Generally for anti-solvent phase diagrams, gravimetric methods at specific temperatures are primarily used. Although effective, these methods can take days at a time to acquire data and slight inconsistencies in sample preparation or temperature variances can cause large discrepancies thereby reducing the accuracy. Here we present a convenient clear point temperature based method to establish reliable anti-solvent solubility data, showing its effectiveness on four model compounds. The clear point denotes the temperature at which a suspension of a sample with a known overall composition turns into a clear solution upon slow heating. This composition is then taken as the saturation composition at the clear point temperature. First, the solubilities in the pure solvents and anti-solvents are determined. From these, samples at a number of concentrations at specific anti-solvent fractions are measured, obtaining a series of clear point temperatures at these specific anti-solvent fractions. Finally, a model combining the anti-solvent fraction, solubility and temperature allows the construction of an anti-solvent phase diagram. For Lovastatin, at small anti-solvent fractions an increase in the solubility is observed compared to that in pure solvent. A sharp decrease of the solubility is only observed at an anti-solvent fraction above 10 w%. Unlike Lovastatin, the other model compounds all show a sharp drop in solubility even at low anti-solvent fractions, with the solubility reduced by 50% at just 10 w% anti-solvent. All phase diagrams produced represent typical anti-solvent phase diagrams found in literature. Despite the temperature as an additional parameter, reliable solubility data are obtained much quicker, reducing the time to design and optimise process systems.

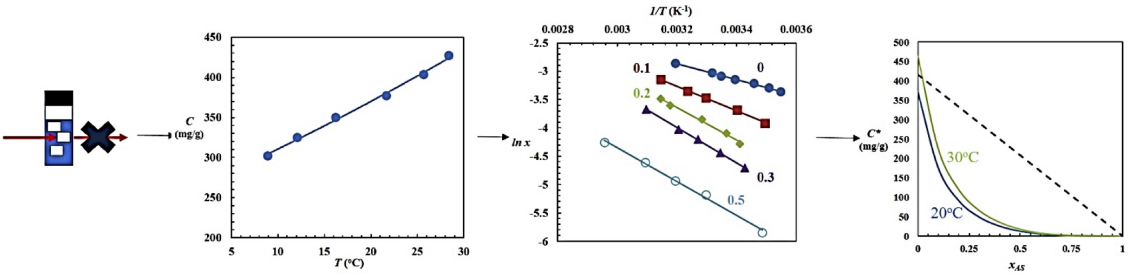

Figure 1: Schematic of the method to establish anti-solvent phase diagram of NaBrO3 in water-ethanol solutions. From left to right: Clear point temperature measurement using the transmission of light through a vial, with the light blocked due to the presence of solid particles. Van't Hoff plots at different water-ethanol mixtures (numbers denoting the specific mass fraction of ethanol present in each solution). The anti-solvent phase diagram for $NaBrO_3$ in water at 20 C and 30 C determined using the fitted model, along with a dilution line for the anti-solvent crystallisation by mixing a 400 mg/g solution with anti-solvent.

P070 Close Contacts and the Crystallisability of Small Molecule Organic Materials

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The prediction of which crystal polymorph will crystallise from a supersaturated solution is a significant challenge for the physico-chemical sciences. Here, we examine the crystal packing and cluster energies of four polymorphic crystalline materials, carbamazepine (CBZ), d-mannitol (DMAN), p-aminobenzoic acid (pABA) and paracetomal (PARA) and relate it to the crystallisability of these different polymorphs. For CBZ and DMAN, there are two polymorphs relatively accessible from traditional crystallisation methods, forms II and III for CBZ and forms β and δ for DMAN. Both forms II and form III of CBZ contain an NH...O H-bonding homodimer, with the differences in the packing are the dispersive forces between the ring structures. Similarly, the two forms of DMAN examined also contain very similar H-bonding interactions, with weaker interactions being the difference between the two packing structures. Further to this, the calculated cluster energies of these two forms finds that the metastable form is most stable at the smallest cluster sizes, with the thermodynamically stable form becoming more stable at higher cluster sizes, consistent with experimental data which suggests that the metastable form crystallises at higher supersaturations, in comparison to the stable form. This is consistent with previous studies. In contrast, the α and β forms of PABA have very different packing structures, as do form I and II of PARA. For the clusters examined, α-PABA and form I of PARA are always calculated to be more stable than their counterpart polymorphs, due to the strong short contacts found in their crystal structures. In turn, it is experimentally observed that these polymorphs dominate traditional solution crystallisation experiments of these two materials.

Summary. The results shown here suggest that if the packing of two polymorphs is similar, it is likely that the pre-nucleation clusters found in solution could resemble either polymorph, and as such small differences in the crystallisation conditions can bring out either polymorph. In contrast, if the packing structures are found to be very different and one polymorph contains particularly strong short contacts, it is perhaps likely that the pre-nucleation clusters are dominated by these contacts and set off a chain reaction of self-assembly into this polymorph, dominating the crystallisation from solution. In these cases, it may be suitable to explore non-traditional methods of crystallisation, such as anti-solvent or drowning out to explore a greater phase space of the material to access the difficult to crystallise polymorph.

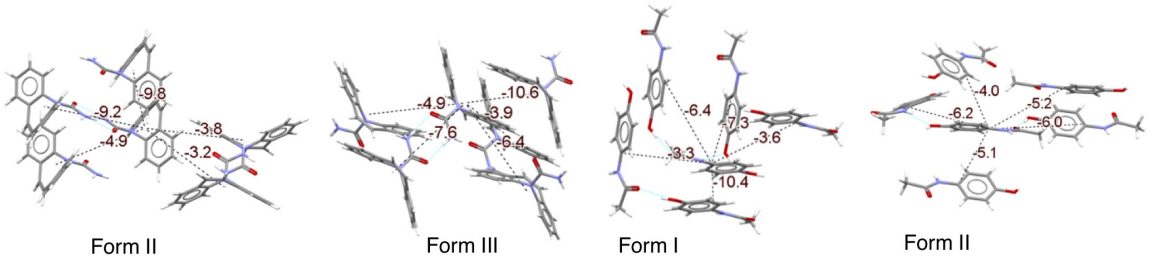

Figure 1: Comparison of the packing of polymorphs of CBZ and PARA, where the intermolecular energies of CBZ are found to be similar but the energies of PARA are found to be significantly different

References

[1] Parambil, J. V.; Poornachary, S. K.; Tan, R. B. H.; Heng, J. Y. Y., CrystEngComm 2014, 16, 4927-4930
[2] Cornel, J.; Kidambi, P.; Mazzotti, M., Ind. Eng. Chem. Res. 2010, 49, 5854-5862
[3] Gracin, S.; Rasmuson, A. C., Crystal Growth Design 2004, 4, 1013-1023
[4] Nicoud, L.; Licordari, F.; Myerson, A. S., CrystEngComm 2019, 21, 2105-2118
[5] R B Hammond, K Pencheva and K J Roberts, Journal of Physical Chemistry B, 2005, 109, 19550-19552

P071 Molecular Dynamics Simulations of the Solution Chemistry of Benzoic and p-Aminobenzoic Acid

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The plethora of arrangements that molecules can adopt in crystalline structures results in multiple crystal structures (polymorphs) of the same material. The differing physical properties that these polymorphs display, such as solubility, morphology and stability, results in significant importance in controlling the polymorphic form during crystallisation, especially in the case of active pharmaceutical ingredient (API) crystallisation. The choice of solvent in has been shown to impact upon the polymorphic form crystallised, and one theory is that solute pre-ordering in solution can drive the crystallisation of polymorphs that have structures which are analogous to the solute pre-ordering. Here, molecular dynamics simulations are used to probe the solute interactions of benzoic acid in hexane and ethanol, where previous experimental infa-red (IR) studies of benzoic acid/hexane have identified the presence of OH...O hydrogen bonds in solution. The detection of the interactions uses a novel and flexible expression (DANAI expression) which can be modified to be applied to a range of intermolecular interactions [1]. The simulations suggested that the vast majority of the benzoic acid molecules are forming OH...O interactions. Further examination of these interactions confirmed the presence of dimers and trimers of benzoic acid molecules, which are associated through OH...O hydrogen bonds. These structures are used to predict IR spectra using density functional theory, which are found to be in good agreement with the experimental data. Further to this, the interactions of p-aminobenzoic acid (pABA) in ethanol, acetonitrile and water are also examined. The molecular structure of pABA is identical to benzoic acid, except with a hydrogen in the para position being replaced by an amino group. The addition of this amino group is found to greatly impact upon the intermolecular interactions found in the simulations. These results are then related to experimental data on the kinetic barrier to nucleation of α-pABA [2] and experimental observation that the β-polymorph can only be reliably crystallised from water [3].

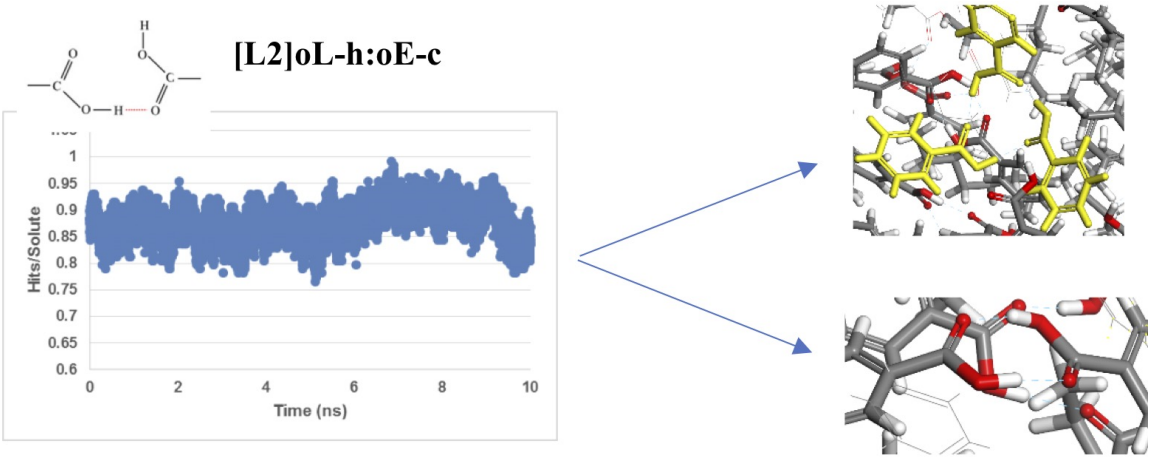

Figure 1: Propensity of OH...O single H-bonding interactions between benzoic acid molecules in 0.8 M hexane solutions, along with the molecular structures of the dimers and trimers. The DANAI expression to detect the interactions is also shown

References

[1] Yong, C.; Todorov, I., DL_ANALYSER Notation for Atomic Interactions (DANAI): A Natural Annotation System for Molecular Interactions, Using Ethanoic Acid Liquid as a Test Case. Molecules 2018, 23, (1), 36.

[2] Turner, T. D.; Corzo, D. M. C.; Toroz, D.; Curtis, A.; Dos Santos, M. M.; Hammond, R. B.; Lai, X.; Roberts, K. J., The influence of solution environment on the nucleation kinetics and crystallisability of para-aminobenzoic acid. Physical Chemistry Chemical Physics 2016, 18, (39), 27507-27520.

[3] Black, J. F. B.; Davey, R. J.; Gowers, R. J.; Yeoh, A., Ostwald's rule and enantiotropy: polymorph appearance in the crystallisation of p-aminobenzoic acid. CrystEngComm 2015, 17, (28), 5139-5142.

P072 Impact of Polyvinylpyrrolidone (PVP) on the Polymorphism of Succinic Acid formed via Monodisperse Droplet Evaporation

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Particle structure, whether it is an amorphous form or one of multiple crystalline polymorphs, directly impacts the performance of crystalline products with applications in the food product and pharmaceutical industry. Based on the structure, the final product can have different behaviour ranging from varied solubility and bioavailability to surface functionality. Additionally, morphology can impact surface properties or downstream processing ability. The formation of amorphous structures is often achieved by forming particles using the addition of a polymer excipients to the system. Sometimes, however, these polymer additives can impact the resulting polymorphism of the small molecule of interest when the amount of polymer present is below the amount needed to form a fully amorphous particle. Previous work has shown that monodisperse droplet evaporation can be a valuable experimental method to study polymorphism of small molecule systems at room temperature [1], whereas spray drying typically takes place at notably elevated temperature. Succinic acid is known to crystallize into two polymorphs, α and β, and those polymorphs have entantiotropic behaviour with the β polymorph being stable at room temperature, while the polymorph is stable above the transition temperature of ĩ37 ^{o}C. The polymorph is typically formed at atmospheric conditions. In this work, we report the ability to form particles containing the polymorph at atmospheric conditions. The particles are generated through monodispersed droplet evaporation using a vibrating orifice aerosol generator (VOAG). The resulting polymorphs are determine d using powder X-ray diffraction (pXRD), and are quantified through comparison to standardized pXRD peak intensities. Results for particles formed from methanol, ethanol and isopropanol are shown in Figure 1. Through evaporation from isopropanol or ethanol the metastable alpha polymorph of succinic acid is not present; however, it is formed with the addition of low loadings of polyvinylpyrrolidone (PVP). The amount of alpha polymorph formed with a small PVP loading (< 5%) is greater for ethanol solutions compared to isopropanol solutions. However, both solutions reach an equivalent maximum amount of alpha present at levels of PVP > 10 wt%. We explain the polymorphic behaviour based on PVP's inhibition of solute nucleation, allowing the droplet to achieve higher levels of supersaturation before the crystals form. This inhibition reaches a maximum due to thermodynamic limitations. Further, through evaporation from methanol solutions, the alpha polymorph is dominant, and increasing the amount of PVP in the solution slowly decreases the amount of alpha present. This behaviour is explained based on the hydrogen bonding donating capability of methanol relative to ethanol and isopropanol. Further, the addition of PVP reduces the impact of that hydrogen bond donating ability due to it being a hydrogen bond acceptor. Finally, we discuss the resulting particle morphologies as a function of PVP fraction, as well as the potential of this work to extend to more general methods to understand polymorph formation.

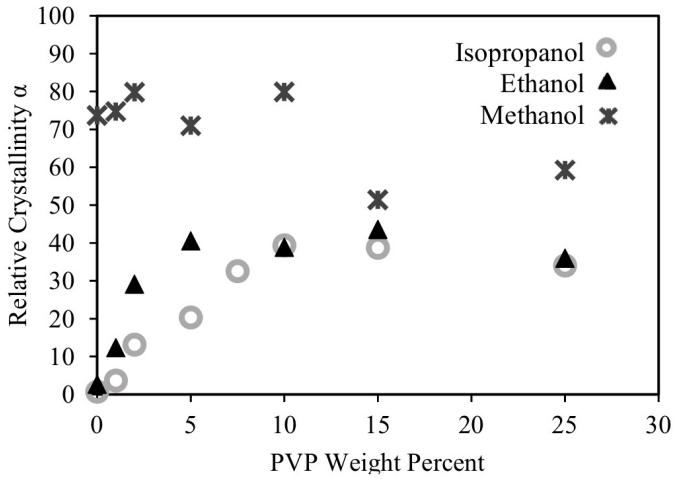

Figure 1: Percentage of polymorph present as a function of PVP weight percent in the particles formed via evaporation from methanol, ethanol and isopropanol.

References

[1] D. I. Trauffer, A. K. Maassel, R. C. Snyder, Crystal Growth Design, 2016, 16, 1917-1922.

P073 Paracetamol Habit Modification by Impurities

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The presence of impurities during crystallisation can affect final crystal attributes other than chemical purity. For example, metacetamol, a regioisomer of paracetamol, has been reported to modify the morphology of the API, leading to the isolation of columnar crystals in place of crystals with an equant habit. Small scale recrystallisation of pure paracetamol from 2-propanol was found here to produce small, relatively equant crystals. In the presence of increasing amounts of metacetamol or acetanilide (des-hydroxyl analogue) paracetamol nucleated at the same initial supersaturation contains increasing concentrations of the impurities. Microscopic inspection of the crystals shows the crystals elongate along one face to produce lath-shaped crystals, seemingly as a function of the impurity concentration. Quantification of this using Malvern Morphologi G3 methods confirms this observation for the bulk material. By means of the impurity concentration increases, the aspect ratio D50 decreases. X-ray powder diffraction of crystals contaminated with metacetamol revealed that this impurity is capable of slightly modifying the paracetamol unit cell. An elongation of one vertex and increase in cell volume accommodates the intruding impurity molecule into the crystal lattice. This observation is supported by examination of the Tamman relationship for this binary system, which indicates a partial solid miscibility of 6.7 $\pm$ 2.1% metacetamol in paracetamol. It is proposed that this solid-state interaction makes metacetamol more difficult to purge than acetanilide, and leads to the higher impurity concentrations after crystallisation.

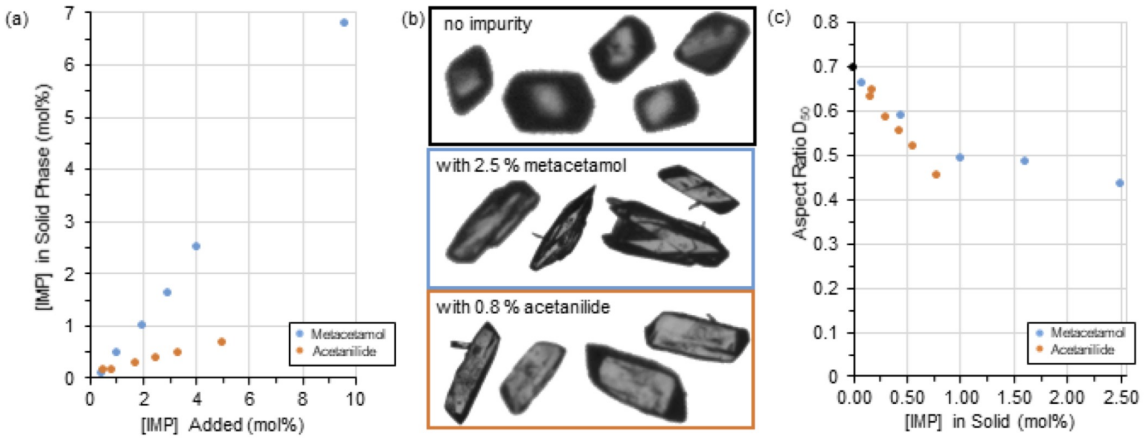

Figure 1: (a) Increasing the starting concentration of impurity linearly increases the concentration of impurity in the isolated solid phase. Metacetamol is more readily incorporated into the paracetamol cry stals. (b) Representative Morphologi images of particles bearing the D50 aspect ratio of the sample indicated, not to scale (c) Aspect ratio D50 as a function of bulk crystal impurity concentration.

P074 Investigating co-crystal robustness through integrated wet milling processes

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Crystallization with an integrated wet milling setup is increasingly employed to achieve a relatively homogenous Crystal Size Distribution (CSD) by reducing crystal size and increasing aspect ratio [1]–[3]. A CSD towards smaller sizes improves drug bioavailability for Oral Solid Dosage (OSD) or pulmonary drug delivery formulations [4], [5]. Wet milling enables CSD control of systems with complex kinetics such as fast growth or slow nucleation [6]. Additionally, wet milling can induce nucleation by mechanisms of contact secondary nucleation and macro abrasion by creating a large degree of attrition and mass fracture [7]. Co-crystals are reformed Active Pharmaceutical Ingredients (API) with improved physicochemical properties (solubility, bioavailability, tabletability, stability, etc) whilst retaining the fundamental activity of the API(s) [8][9]. Co-crystal systems are multicomponent systems that are constructed by intermolecular interactions as hydrogen bonding, - stacking, or Van Der Waal forces. [9] Co-crystals offer prime intellectual property opportunities by extending life cycles of older APIs [10]. This work is the first study undertaken to investigate the impact of wet milling processes on crystallinity disintegration of non-covalently bound co-crystals. The robustness of three co-crystal systems is showcased for maintaining co-crystallinity through the intensive shear forces generated under an integrated wet-milling setup on batch cooling co-crystallization of 1:1 and 3:2 p- Toluenesulfonamide/Triphenylphosphine Oxide (TSSA/TPPO) and slurry conversion of 1:1 Sulfamethazine-Salicylic acid (SMT-SA) co-crystal systems. Furthermore, the influence of grinding tools (coarse, medium, and fine) and grinding intensity with a multi-stacked rotor-stator wet milling setup (5000, 15000, and 25000 rpm) have been demonstrated on a 3:2 TSSA/TPPO system to investigate their impact on CSD.

References

[1] D. Wilson et al., "Particle engineering of needle shaped crystals by wet milling and temperature cycling: Optimisation for roller compaction," Powder Technol., vol. 339, pp. 641–650, 2018.

[2] D. Kumar et al., "Comparison of wet milling and dry milling routes for ibuprofen pharmaceutical crystals and their impact on pharmaceutical and biopharmaceutical properties," Powder Technol., vol. 330, pp. 228–238, 2018.

[3] B. Ahmed, C. J. Brown, T. McGlone, D. L. Bowering, J. Sefcik, and A. J. Florence, "Engineering of Acetaminophen Particle Attributes Using a Wet Milling Crystallisation Platform," Int. J. Pharm., vol. 554, no. October 2018, pp. 201–211, 2018.

[4] D. Xia et al., "Effect of crystal size on the in vitro dissolution and oral absorption of nitrendipine in rats," Pharm. Res., vol. 27, no. 9, pp. 1965–1976, 2010.

[5] J. I. Jinno et al., "Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs," J. Control. Release, vol. 111, no. 1–2, pp. 56–64, 2006.

[6] Y. Yang et al., "Application of feedback control and in situ milling to improve particle size and shape in the crystallization of a slow growing needle-like active pharmaceutical ingredient," Int. J. Pharm., vol. 533, no. 1, pp. 49–61, 2017.

[7] J. Wiencek, Handbook of Industrial Crystallization, no. October. 2002.

[8] S. Kumar and A. Nanda, "Pharmaceutical Cocrystals : An Overview," Indian J. Pharm. Sci., vol. 79, no. 6, pp. 858–871, 2017.

[9] N. Qiao, M. Li, W. Schlindwein, N. Malek, A. Davies, and G. Trappitt, "Pharmaceutical cocrystals: An overview," Int. J. Pharm., vol. 419, no. 1–2, pp. 1–11, 2011.

[10] A. V Yadav, A. S. Shete, A. P. Dabke, P. V Kulkarni, and S. S. Sakhare, "Co-crystals: a novel approach to modify physicochemical properties of active pharmaceutical ingredients.," Indian J. Pharm. Sci., vol. 71, no. 4, pp. 359–70, Jul. 2009.

P075 A Combined Theoretical and Experimental Investigation into the High Throughput Screening of Cocrystal Coformers

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The CrystalPredictor [1-3] and CrystalOptimizer4 codes have been used to explore the space of crystal structures successfully in several crystal structure prediction (CSP) investigations in recent years, including in the series of blind tests organised by the Cambridge Crystallographic Data Centre [4] and in the prediction of the crystal structures of pharmaceutically-relevant molecules [5-7]. Recent advances in CrystalPredictor [8], have allowed for orders of magnitude increases in the efficiency of the global search stage, whilst the capacity of CrystalOptimizer to reuse quantum mechanical calculations for the same molecule using LAM databases, allows for Quantum Mechanical (QM) accuracy in conformation, intramolecular energy and molecular electrostatics, at forcefield cost. Exploiting these advances, we present a high throughput co-crystallisation study into 4 Active Pharmaceutical Ingredients (API's), combined with 10 coformers, selected from the GRAS list. Having performed a standard, neat, CSP study on each of the molecules, assessing the energy of potential cocrystals of the API and any of the coformers becomes an almost trivial task, through the judicious use of LAM databases. Comparing the energies of the cocrystals, versus the combined single crystal energies, allows the user to make informed decisions on which coformer to crystallise the API with, in order to target specific physical properties. Combined with the theoretical predictions, experimental co-crystallisation experiments were performed between the API's and each of the coformers; comparisons will be made to assess the accuracy, as well as demonstrate the capacity for the technique to be taken up into standard pharmaceutical development workflows.

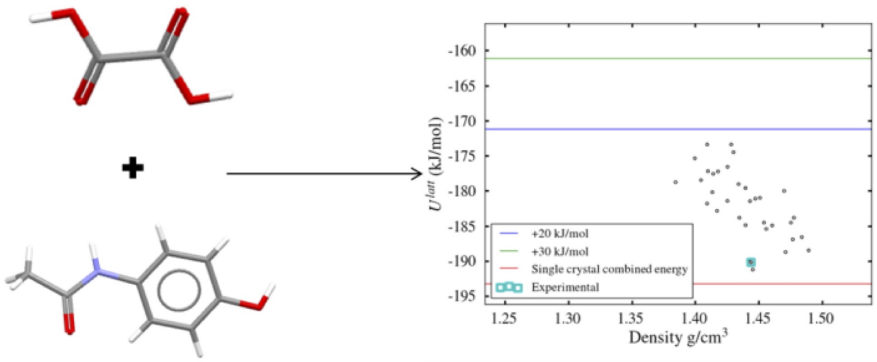

Figure 1: CSP landscape of Paracetamol and oxalic acid.

References

[1] M. Habgood, I. J. Sugden, A. V. Kazantsev, C. S. Adjiman, and C. C. Pantelides, J Chem Theory Comput, 2015, 11, 1957 (2015).
[2] I. Sugden, C. S. Adjiman, and C. C. Pantelides, Acta Crystallogr B, 2016, 72, 864
[3] I. Sugden, C. S. Adjiman, and C. C. Pantelides, Acta Crystallogr B, 2019, 75, 423
[4] A. V. Kazantsev, P. G. Karamertzanis, C. S. Adjiman, and C. C. Pantelides, J Chem Theory Comput, 2011, 7, 1998
[5] A. M. Reilly, et al., Acta Crystallogr B, 2016, 72, 439
[6] D. E. Braun, T. Gelbrich, K. Wurst, and U. J. Griesser, Cryst Growth Des, 2016, 16, 3480
[7] D. E. Braun, V. Kahlenberg, and U. J. Griesser, Cryst Growth Des, 2017, 17, 4347
[8] S. L. Price, D. E. Braun, and S. M. Reutzel-Edens, Chem Commun, 2016, 52, 7065

P076 Crystallisation characteristics of para-aminobenzoic acid in ethanol: Effect of process conditions and crystalliser scale size

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Batch cooling crystallisation is a widely used unit operation in the pharmaceutical as well as in the fine chemical industries for the isolation and purification of active ingredients. The crystalliser design and selection of its operating conditions are vital for the production of high value organic crystalline solids with the required physical properties, such as narrow, unimodal crystal size distribution, morphology, high purity and yield. These particles characteristics have a large impact on the final product properties (such as solubility and bioavailability) and the operation of downstream processing units such as filters and driers. The optimal design and control of a crystallisation process require a thorough understanding of the underlying mechanisms involved in the crystallisation process and the effect of operating conditions on the product crystal properties. This abstract summarizes the findings of an investigation on the crystallisation characteristics of para-aminobenzoic acid (pABA) in ethanol in agitated crystallisers as functions of operating conditions and scale sizes. The experimental data provides a basis for the estimation of nucleation and growth kinetics and validation of crystallisation process models. The unseeded batch cooling crystallisation of pABA from ethanol was carried out in 0.5 and 5 L jacketed glass crystallisers agitated using a retreat curved impeller. The solution temperature was controlled using Huber thermostatic bath operated through a LabVIEW software. Solution concentration was monitored throughout the crystallisation process using ATR UV-Vis spectroscopy and onset of nucleation was monitored via a turbidimetric technique. A calibration model was developed for on-line prediction of pABA concentration from measured UV-Vis absorbance spectra. The crystal size and shape measurements were carried out using Malvern Morphologi G3. In the 0.5 L crystalliser, the cooling rate was varied from 0.3 to 0.7 oC/min and agitation rates from 100 to 250 rpm. Whereas in the 5 L crystalliser, the investigations focused on varying agitation rate from 100 to 170 rpm at a constant cooling rate of 0.5^{o}C/min. The agitation rates were scaled from corresponding rates in the geometrically similar 0.5 L crystalliser using the constant specific power scale-up rule. The supersaturation profiles obtained from on-line measurements of analyte concentration in both the scale sizes reveal that the supersaturation increases up to a peak level depending on the cooling and agitation rates as the solution temperature decreases. This is followed by a rapid desupersaturation due to the consumption of solute resulting from primary nucleation and subsequent growth of the freshly generated solids. It was found through the analysis of data using the KBHR approach [1] that the nucleation process was dominated by instantaneous nucleation mechanism. This suggests that all nuclei appeared at the same instance of time. The meta-stable zone width (MSZW) was found to increase with increasing cooling rate and decrease with increasing impeller speed. As for the effect of crystalliser scale size, the MSZW was much wider in 5 L compared to that in the 0.5 L. For all experimental conditions investigated in both the crystallisers, needle-like alpha form of pABA was obtained as confirmed by the Morphologi G3 images (see Figure 1). In addition, crystal shape characterised by the aspect ratio was reasonably consistent across the experimental conditions and crystalliser scale sizes. However, the mean crystal size in the 0.5 L was significantly lower than that in 5.0 L. It appears that in order to achieve comparable product crystal sizes between the two crystallisers scaling up of the cooling rate in combination with the agitation rate scale up will be necessary.

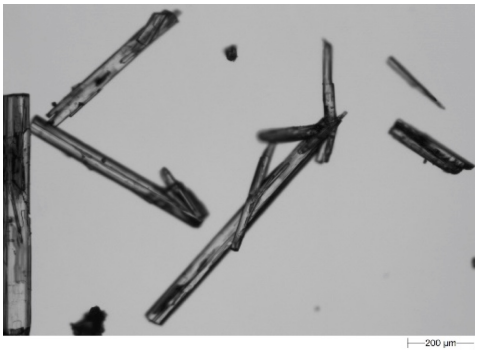

Figure 1: Images of α-pABA crystals.

References

[1] D. Kashchiev, A. Borissova, R. B. Hammond, K. J. Roberts, J. Cryst. Growth, 2010, 312(5), 698-704.

P077 The Removal of Surface Contaminants from Organic Crystals by Anti-Solvent Surface Treatment

B. Tayler-Barrett[1], **A. A. Moldovan**[1], **S. Chang**[2], **E. Willneff**[1,3], **E. Shotton**[2], **S. L.M. Schroeder**[1,2]

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Given the surface sensitivity of XPS, surface cleanliness is of paramount importance. Typical methods for removing contamination, for example, argon sputtering, heating or the use of ozone cleaning is destructive to organic crystals. We have developed an anti-solvent surface treatment method for the non-destructive removal of surface contaminant. Optimization of the cleaning protocol was performed initially by using atomic force microscopy (AFM), in which ultra-pure water, ethanol, methanol, isopropyl alcohol, and dichloromethane (DCM), as well as saturated solutions of all solvents, were examined. In the case of paracetamol crystals, the solvent that provided the best cleaning results was DCM. With the polar solvents all significantly altering the surface topology of the crystals. The optimized cleaning protocol was then taken forward for NAP-XPS experiments at the NSLS-II 23-ID-2 CDX-II beamline. Spectra were acquired before and after cleaning on the same facet of a crystal at 3 mbar water vapor pressure. Paracetamol C1s XPS spectra have a distinctive carbonyl shoulder at 287.7 eV binding energy, which was used to calibrate the energy positions and normalize the spectra intensities. Elemental analysis showed a 14% reduction in total C after cleaning. The total amount of paracetamol, as determined from the carbonyl shoulder, remained unchanged. No chlorine was detected in the survey spectra suggesting that there was no residual DCM solvent at the surface.

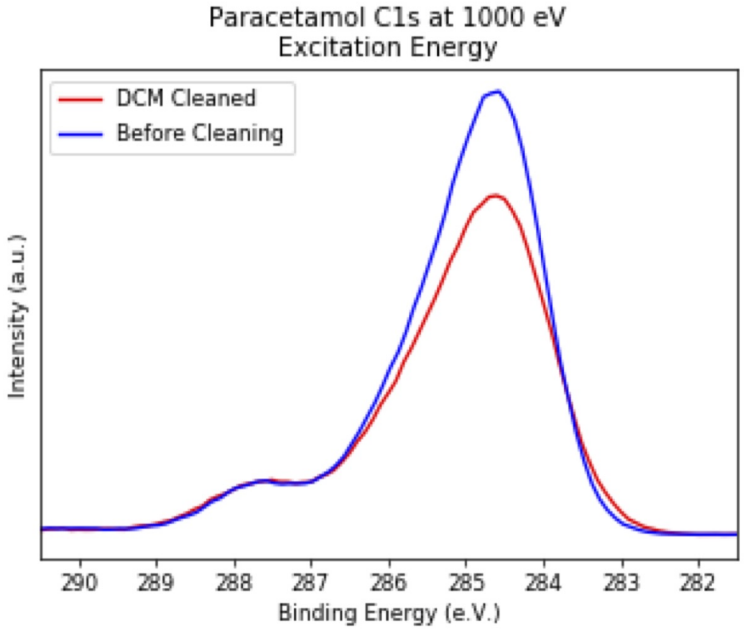

Figure 1: C1s high-resolution specta of paracetamol obtained at 1000 eV excitation energy.

P078 Selective protein crystallisation with hard templates

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Protein-based biologics including monoclonal antibodies are high-value pharmaceutical compounds, whose purification is mainly achieved with chromatography.[1-2] In comparison, crystallisation is much more attractive in terms of cost and scalability and protein crystallisation has been shown feasible at large scale.[3] Over the past few years, our research group has developed a strategy for the selective crystallisation of proteins through the use of hard templates.[1–6] A range of hard templates with different pore size, surface chemistry, particle size and shape have been developed and their effectiveness has been demonstrated for a range of proteins such as concanavalin A, ferritin, lysozyme and trypsin. The investigation of the underlying mechanism suggests that selectivity can be achieved by developing hard templates with a narrow pore size distribution and then matching the pore size of the hard template with the hydrodynamic diameter of the target protein. A methodology has been developed to determine the effectiveness of a hard template on promoting protein crystallisation. The nucleant investigated was rod-like SBA-15, which had high loading capacities of the model proteins (i.e. lysozyme and thaumatin). It was found that rod-like SBA-15 required repeated loading of proteins as the pre-treatment for the crystallisation study in order to de-couple the effect of sorption on crystallisation. The protein-saturated SBA-15 significantly reduced the meta-stable zone width and always induced earlier crystallisation as compared to unseeded sample in the nucleation zone (Figure 1). Otherwise, the sorption of protein would lower the protein concentration, hinder the crystallisation process and lead to the wrong judgement about the effectiveness of the nucleant. Therefore, the proposed methodology for using such nucleant is to include the pre-treatment (protein-loading) as a necessary step and is applicable to heterogeneous protein crystallisation in general.[4-7]

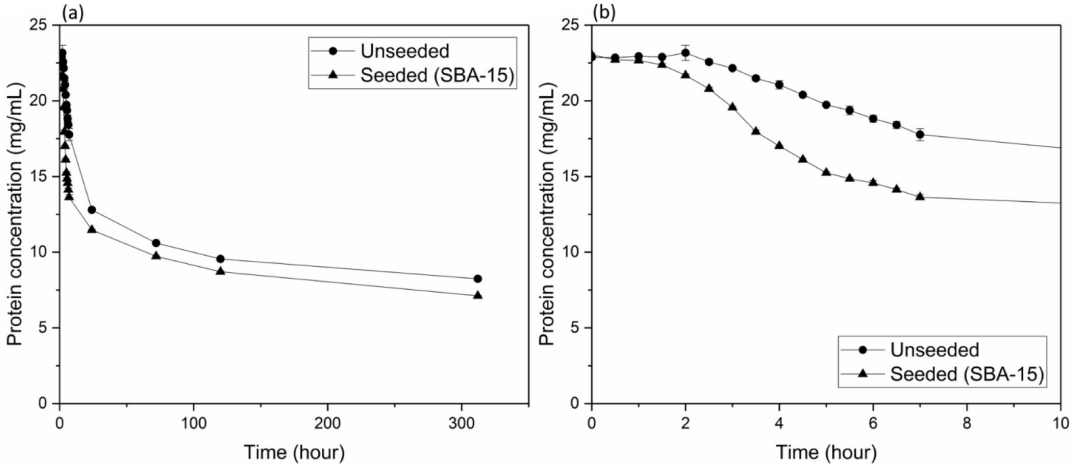

Figure 1: Protein concentration over time of rod-like SBA-15.

References

[1] D. J. Newman, G. M. Cragg. Natural Products as Sources of New Drugs over the 30 Years from 1981 to 2010. Journal of Natural Products. 2012, 311–335.
[2] A. A. Shukla, B. Hubbard, T. Tressel, S. Guhan, D. Low. Downstream Processing of Monoclonal Antibodies - Application of Platform Approaches. J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci. 2007, 28–39.
[3] D. Hekmat. Large-Scale Crystallization of Proteins for Purification and Formulation. Bioprocess and biosystems engineering. 2015, 1209–1231.
[4] A. McPherson, P. Shlichta. Heterogeneous and Epitaxial Nucleation of Protein Crystals on Mineral Surfaces. Science (80-.). 1988, 239 (4838), 385–387.
[5] N. E. Chayen, E. Saridakis, R. El-Bahar, Y. Nemirovsky. Porous Silicon: An Effective Nucleation-Inducing Material for Protein Crystallization. J. Mol. Biol. 2001, 312 (4), 591–595.
[6] U. V. Shah, C. Amberg, Y. Diao, Z, Yang, J. Y. Y. Heng. Heterogeneous Nucleants for Crystallogenesis and Bioseparation. Curr. Opin. Chem. Eng. 2015, 8, 69–75.
[7] Y. W. Chen, C. H. Lee, Y. L. Wang, T. L. Li, H. C. Chang. Nanodiamonds as Nucleating Agents for Protein Crystallization. Langmuir 2017, 33 (26), 6521–6527.

P079 The Interfacial Interactions between Faceted Organic Crystals

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In this work, we have probed the interactions between specific organic crystal surfaces using Molecular Mechanics and Atomic Force Microscopy. This has allowed us to identify the impact of surface chemistry onto inter-particulate interactions. The compatibility between the active pharmaceutical ingredient (API) and the excipients used plays a critical role in the final drug product performance. The cohesive (API-API) and adhesive (API-Excipient) balance (CAB) between an API-excipient can be used to describe the likelihood of two powders sticking together. The ability to pre-screen API-Excipient compatibility in-silico would allow formulators to make a more informed decision on the experimental studies to be carried out, thus reducing the development time and resources required to get a molecule from discovery to product. However, as with any computational model, this must be validated with experimental data. For the in-silico approach, a molecular mechanics (MM) framework has been developed to calculate the interfacial interactions between faceted organic crystals. The Surface-Surface Interaction Model (SSIM) is designed to calculate the interaction energy between two slabs at an atomistic scale. By focusing on facet-specific interactions both computationally and experimentally, energetics associated with the surface chemistry can be identified. A surface compatibility ranking system has been used, allowing relative comparisons to be made between adhesive and cohesive forces, as seen in Figure 1a). Atomic force microscopy (AFM) is being used to measure the adhesive force between defined crystal planes of paracetamol (Figure 1b). These faceted surfaces will also be measured against a range of excipients (α-L-Glutamic Acid and β-D-Mannitol). AFM studies [1] have been previously carried out using colloidal probes and coated cantilevers, however, there is a lack of fully faceted organic crystal adhesion data. This work has significant applications within pharmaceutical research by offering a piece of the puzzle that has always been difficult to probe. The impact of surface chemistry based on facet-specific termination has been tested both computationally and experimentally.

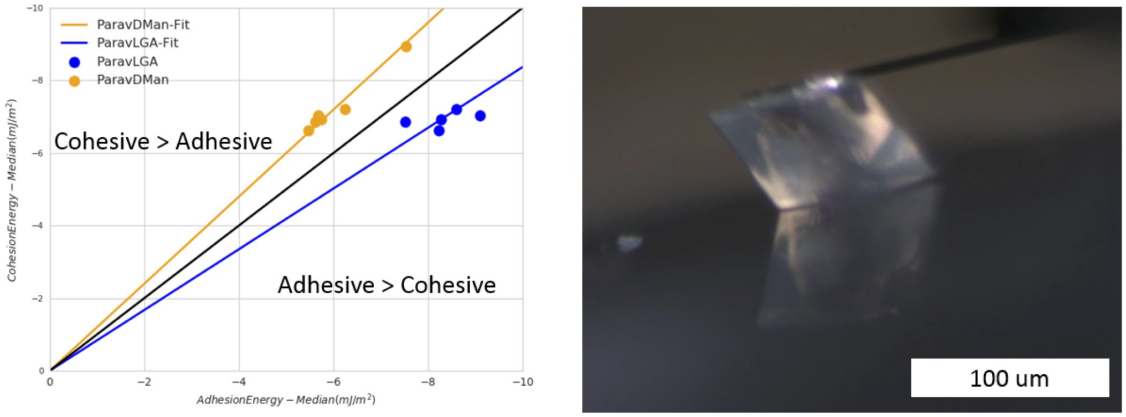

Figure 1: A) Cohesive/Adhesive plot of paracetamol against α-L-Glutamic Acid, and β-D-Mannitol predicting the adhesive nature of the powders based on their surface chemistry. Calculated using SSIM. B) Side view of paracetamol probe crystal making contact with paracetamol surface.

References

1. Jones, M. D. Buckton, G. (2016). Int. J. Pharm. 509, 419-430.

P080 The acid-soap structure of stearic acid system and the phase transition as function of temperature

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Carboxylic soaps are the salts of neutralised neutral fatty acids by alkali such as sodium hydroxide and potassium hydroxide, etc, and they can form acid-soaps with the fatty acids with fixed ratios. Studies regarding acid/soap ratio and binary/ternary phase diagrams were published including simulation of the interaction between palmitic acid and sodium palmitate was reported by Lynch et al..[1] However, the morphology of the acid-soaps' crystals is still unclear, especially in solid state. And this is quite important as acid-soaps' crystals are introduced into personal care and cosmetics products as gelator to amend the physical properties.[2]

The DSC measurements were carried out to construct the phase diagram of the acid-soap system. By repeating the DSC experiment, the results fit well with the published phase diagrams. Based on the phase diagram of fatty acid-soap system, the authors suggested that the acid-soap has 5 acid/soap ratios, 1:1, 1:2, 2:1, 3:2, 4:1, and this conclusion was wildly accepted [3]. The SAXS/XRD was used to determine the crystal structure of acid-soaps and the results showed unexpected phenomenon – only two kinds acid-soap, 2:1 and 1:1, were observed in both SAXS and XRD results. The SEM was done to observed to morphology of the crystals. Fibre-like soap crystals and plate-like acid-soap crystals were observed. Once the soap ratio exceeds 50%, the excess soap forms fibre-like crystals.

Previous studies on the acid-soaps indicated that 5 kinds of acid-soaps were detected by DSC and this conclusion is wildly accepted. By combining the phase diagram with SAXS and XRD results, we suggested that only two kind acid-soaps formed in acid/soap system. Combining the 3rd order in XRD and the 1st order in SAXS, two kinds acid-soap structure can be observed.

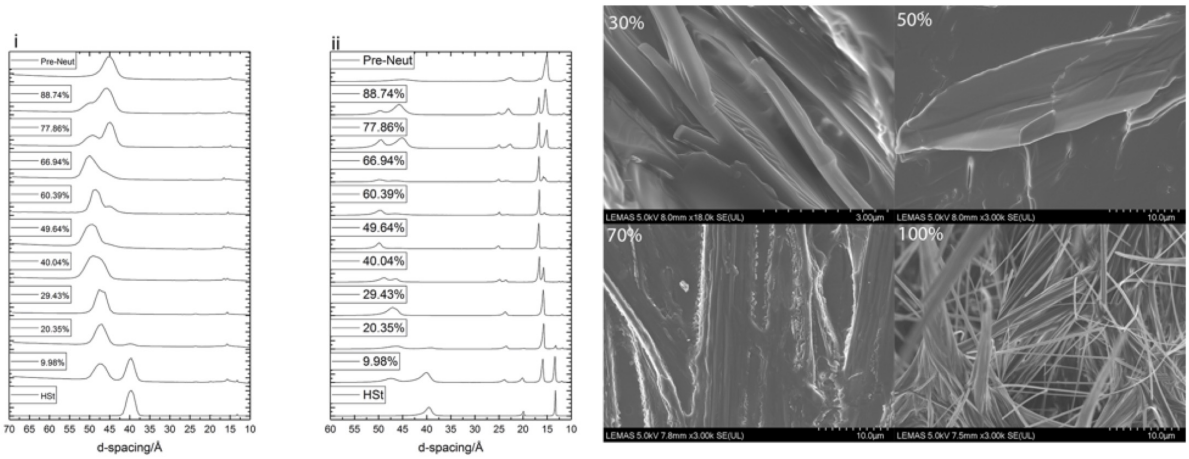

Figure 1: i. SAXS results of acid-soaps with different neutralisation ratio. ii. XRD results of the acid-soaps with different neutralisation ratio. The 30%, 50%, 70% and 100% are the soap ratio in the acid/soap mixtures. Soap (100%) formed fibre-like crystals. The fibre-like crystals can also be observed in 70% sample and some small plate-like crystals deposited on the surface. In 30% and 50% samples, only plate-like crystals were observed.

References

[1] Lynch, M. L.; Wireko, F.; Tarek, M.; Klein, M., Intermolecular interactions and the structure of fatty acid soap crystals. The Journal of Physical Chemistry B 2001, 105 (2), 552-561.
[2] Zhu, S.; Heppenstall-Butler, M.; Butler, M.; Pudney, P.; Ferdinando, D.; Mutch, K., Acid soap and phase behavior of stearic acid and triethanolamine stearate. The Journal of Physical Chemistry B 2005, 109 (23), 11753-11761.
[3] Kralchevsky, P. A.; Danov, K. D.; Pishmanova, C. I.; Kralchevska, S. D.; Christov, N. C.; Ananthapadmanabhan, K. P.; Lips, A., Effect of the precipitation of neutral-soap, acid-soap, and alkanoic acid crystallites on the bulk pH and surface tension of soap solutions. Langmuir 2007, 23 (7), 3538-3553.

P081 Electrochemically Controlled Precipitation of Amorphous Calcium Carbonate Within Nanopipettes

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Calcium carbonate ($CaCO_3$) is one of the most well-studied and abundant materials on Earth. Its formation is often observed to proceed via an amorphous calcium carbonate (ACC) phase, before forming more stable crystalline polymorphs such as vaterite and calcite. ACC plays a central role for allowing morphological control in biogenic calcite formation [1], providing a metastable localised concentrated source of ions even in solutions of low equilibrium supersaturation. Despite its importance, ACC has proved difficult to study, in part due to its rapid formation at moderate supersaturations [2], and its thermodynamic instability with respect to all other polymorphs [3]. However, ACC can be stabilised under confinement conditions [4], such as those of a nanopipette. Through electrochemical mixing in a nanopipette, achieved by applying a bias to a two quasi-reference counter electrode system, we can repeatedly and reversibly precipitate single nanoparticles of ACC under confinement conditions, using AC and DC ion currents to provide microsecond-resolved measurement of the nucleation and growth rate [5]. From this technique, we have been able to demonstrate that the growth rate of ACC has an exponential dependence on pH, and that the absolute rates are fast compared to the step growth of the bulk crystal.

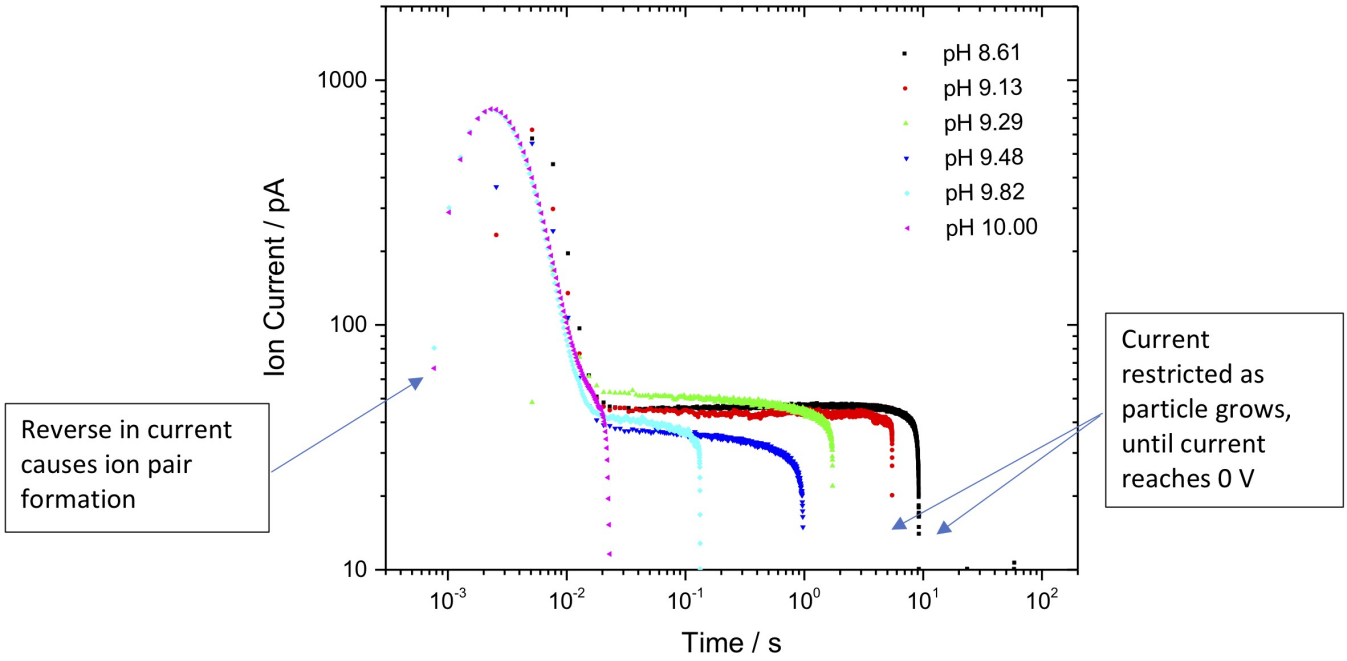

Figure 1: Variation in ion current upon switching voltage from E = 0.2 V to E = -0.025 V at different $[CO_3^{2-}]$

References

[1] P. U. P. A. Gilbert, T. Z. Forbes, A. Navrotsky, C. E. Killian and A. V. Radha, Proc. Natl. Acad. Sci., 2010, 107, 16438–16443.
[2] D. Gebauer, A. Völkel and H. Cölfen, Science (80-.)., 2008, 322, 1819–1822.
[3] D. J. Tobler, J. D. Rodriguez Blanco, H. O. Sørensen, S. L. S. Stipp and K. Dideriksen, Cryst. Growth Des., 2016, 16, 4500–4508.
[4] E. Loste, R. J. Park, J. Warren and F. C. Meldrum, Adv. Funct. Mater., 2004, 14, 1211–1220.
[5] D. Perry, A. S. Parker, A. Page and P. R. Unwin, ChemElectroChem, 2016, 3, 2212–2220.

P082 Molecular modelling and experimental study of the crystal structure, morphology and surface chemistry of quercetin and its hydrates

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Quercetin is a naturally occurring flavonoid found in many fruits and vegetables, and widely used in the nutraceutical and food industry due to its vast range of health benefits. [1] Quercetin can exist as an anhydrous, monohydrate and dihydrate crystal form. Hydrates are particularly important in the pharmaceutical industry as they can exhibit different physiochemical properties, like solubility, stability, morphology and surface chemistry. [2] Understanding these properties and selecting the most appropriate crystal form in terms of thermodynamic and kinetic stability is of critical importance for several industrial applications. In this work, Habit 98, a synthonic modelling tool, was used to explore three different hydrated crystalline structures of quercetin: the anhydrous, monohydrate and dihydrate forms, for which the bulk intrinsic and surface extrinsic synthons (intermolecular interactions) were examined. The role of water molecules within the three hydrated structures was studied to understand how it affects the packing and conformation energetics of quercetin crystals. This knowledge was used to predict physiochemical properties such as relative stability, and to better understand the mechanisms of nucleation and growth during the crystallization process. The attachment energy model was utilized to predict the crystal morphology of each form, as shown in Figure 1, and explore their surface chemistry. Understanding the surface chemistry of anisotropic crystals is essential to predict the material's behaviour during crystallization and downstream manufacturing operations (e.g. filtration, granulation and handling). [3] The modelling calculations were then compared to experimental work involving Dynamic Vapour Sorption (DVS) experiments, DSC/TGA and dehydration experiments by slurrying in solvents, to study the relative stability of the different crystal forms of quercetin. Furthermore, Inverse Gas Chromatography (IGC) and disk contact angle measurements were performed to experimentally study the surface chemistry of the quercetin forms, and assess the reliability of the modelling work. This work shows how synthonic modelling can be used as a predicting tool to better understand the relationship between crystal properties and product quality, leading to a more efficient product formulation and faster development.

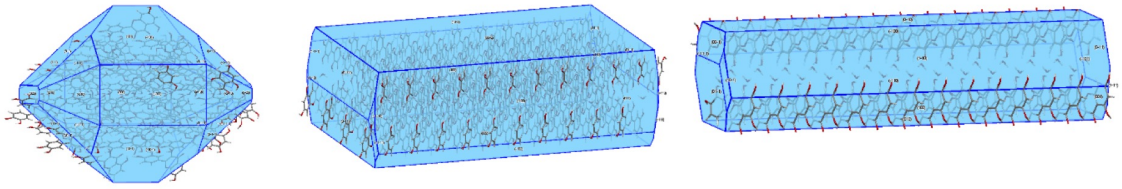

Figure 1: Morphology of quercetin anhydrous (a), monohydrate (b), and dihydrate (c), as predicted by the Attachment Energy model.

References

[1] M. Rossi, L.F. Rickles, W.A. Halpin, Bioorg. Chem. 14 (1986) 55–69.
[2] A.M. Healy, Z.A. Worku, D. Kumar, A.M. Madi, Adv. Drug Deliv. Rev. 117 (2017) 25–46.
[3] R. Ho, J.Y.Y. Heng, KONA Powder Part. J. 30 (2012) 164–180.

P083 Thermodynamic polymorph selection in enantiotropic systems using a Novel Semi-batch supersaturation control implementation

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Concentration Feedback Control (CFC) strategy, also designated as "Supersaturation Control (SSC)", a closed-loop advanced control approach based on PAT tools generally combined with chemometrics determinations, has been extensively employed in polymorphic control at both laboratory and industrial scales. Based on the process characteristics, the feedback control method is predominantly beneficial for polymorph selection crystallization, which can be operated by designing a target concentration profile in the phase diagram according to the solubility and nucleation metastable zone of desired crystal form However, for enantiotropic polymorph system it is difficult to obtain pure form by conventional batch cooing SSC operation because of the transition temperature point on solubility curves between the two different forms, hence, temperature dependency of polymorphs stability. This often makes difficult to produce consistently one or the other form with good yield in batch crystallization process. Due to the constant temperature operation, continuous tank crystallizers could overcome this problem, but the scale of production often does not justify their application. Moreover, the batch crystallizer produces narrower size distribution and larger crystals than. In this work, we propose a semi-batch

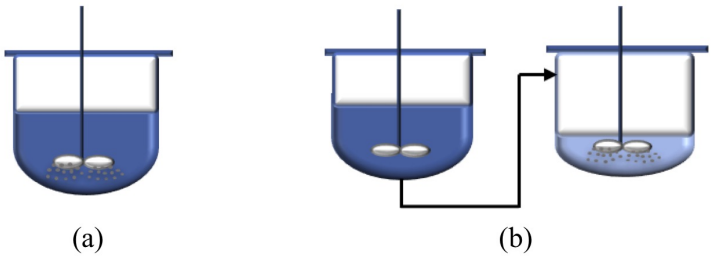

Figure 1: Schematic diagram of different SSC procedures: (a) batch SSC; (b) semi-batch SSC

supersaturation control for enantiotropic polymorphic cooling crystallization processes, where high temperature, highly concentrated solution is fed into the low temperature slurry. The crystallizer temperature is fixed, and supersaturation feedback control is applied by manipulating the flow rate of the feeding stream. In this case, polymorph selection can easily be achieved by fixing the temperature and concentration (supersaturation) setpoint such way that the system is supersaturated only for the desired polymorph. The system is presented through the case study of para-amino benzoic acid (PABA) crystallization from ethanol, which has two known polymorphs and transition temperature of 13.8 C, as determined by Hao et al (Hao et al., 2012). The α form of PABA (α-PABA) is more stable than β form (β-PABA) above 13.8 C, hence, the operation window for β-PABA is under 13.8 C. Moreover, it is particularly difficult to obtain β-PABA in solution crystallization as β-PABA easily undergoes phase transformation to α-PABA in most solvents (Davey et al., 2012; Garg and Sarkar, 2016). In the work, we demonstrate that β-PABA can consistently be produced in semi-batch configuration without yield limitations by the transition temperature. Figure 2 shows the PVM image sequence of PABA polymorphic selective crystallization in batch and semi-batch experiments. The results show that the batch cooling crystallization was failed to obtain pure β-PABA crystals even though conduct the initial temperature under the transition temperature. The semi-batch SSC however was able to produce pure β-PABA, with yield equivalent to the batch experiment. During the process, no α-PABA impurity was detected and large β-PABA crystals were obtained as shown in Fig. 2c. In addition to polymorph selection, the nucleation was also suppressed, hence, large crystals were produced with narrow distribution. Our work suggests that in enantiotropic systems efficient, thermodynamic polymorph selection can be achieved with a simple controlled charging of the crystallizer.

References

[1] Z. K. Nagy, R. D. Braatz, Annu. Rev. Chem. Biomol. Eng. 2012, 3, 55–75
[2] E. Simone, A. N. Saleemi, N. Tonnon, Z. K. Nagy, Cryst. Growth Des. 2014-14, 1839-1850.
[3] A. Saleemi, C. Rielly, Z. K. Nagy, Cryst. Growth Des. 2012, 12, 1792–807.
[4] J. Cornel, C. Lindenberg, M. Mazzotti, Cryst. Growth Des. 2009, 9 (1), 243–252.
[5] N. C. S. Kee, R. B. H. Tan, R. D. Braatz, Ind. Eng. Chem. Res. 2011, 50, 1488-1495.
[6] H. Hao, M. Barrett, Y. Hu, Org. Process Res. Dev. 2012, 16, 35-41.

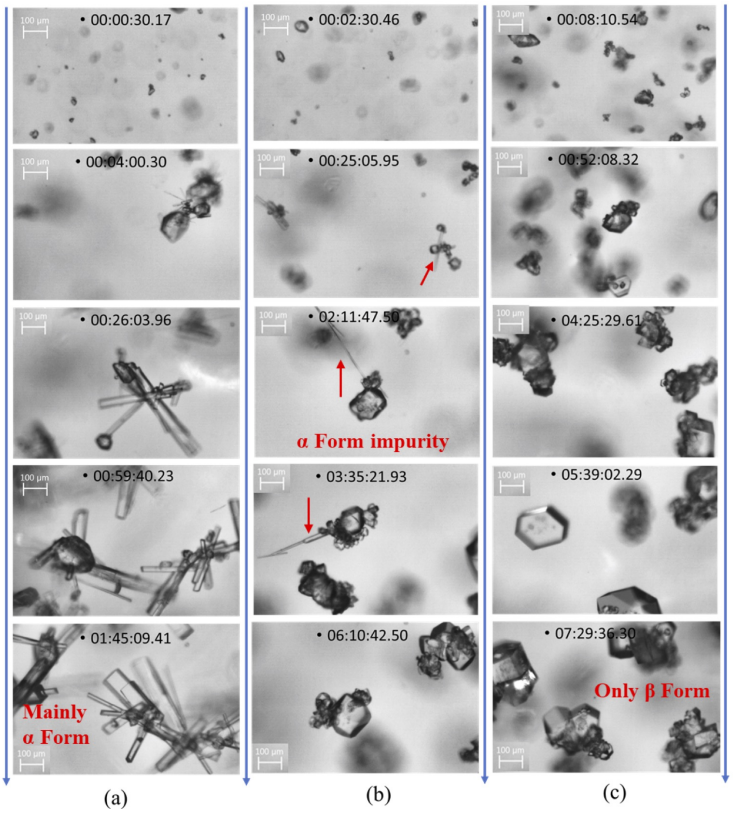

Figure 2: PVM images in representative time moments in (a): batch SSC 1 from 22^{o}C to 0 ^{o}C; (b): batch SSC 2 from 14^{o}C to 0^{o}C; (c): semi-batch SSC with feeding temperature 22^{o}C.

[7] R. J. Davey, J. Black, R. Gowers, Cryst. Eng. Comm. 2015, 17, 5139-5142.
[8] Q. Su, R. D. Braatz, M. Chiu, AIChE J. 2017. 63, 5007–5018.
[9] T. Vetter, C. L. Burcham, M. F. Doherty, Chemi. Eng. Sci. 2014. 106, 167-180.
[10] T.C. Lai, J. Cornevin, S. Ferguson, N. Li, B.L. Trout, A.S. Myerson, Cryst. Growth Des. 2015. 15 (7), 3374–3382

P084 Solvent-Mediated Morphology Selection of the Active Pharmaceutical Ingredient Isoniazid: Experimental and Simulation Studies

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Crystallization experiments reveal the isoniazid (INH) crystals present needle-like morphology in water, and rod-like shape in alcohols (Fig. 1). The Constant Chemical Potential Molecular Dynamics simulation (CMD) method in which an external force is applied to keep the concentration near the crystal surface constant while the rest of the solution acts as a molecular reservoir (Fig. 1) to provide a steady crystal growth condition [1-3] was carried to reveal the solvents role in INH morphology selection. The CMD scheme was implemented in a private version of Plumed-2 code patched with Gromacs-5.1.4.

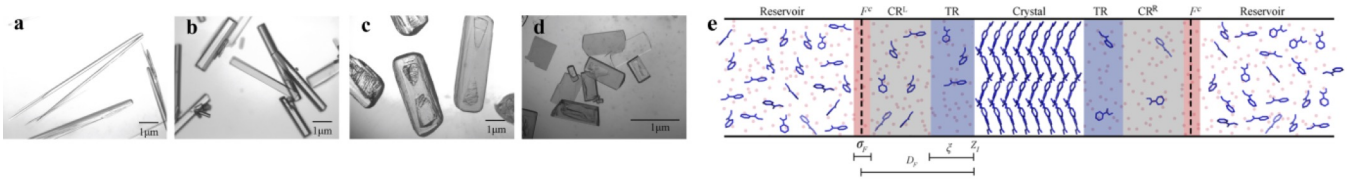

Figure 1: INH crystals grown in (a) water, (b) MET, (c) ETH, (d) IPA and (e) a schematic of the simulation box.

By comparing the predicted INH morphology to experimentally observed (Fig.2a-b), the fast growing (110) and the slow growing (002) surfaces which determine the aspect ratio of INH crystals were selected to simulate the growth rate of INH in the solvents. The number of crystalline INH molecules (N) newly deposited on the growing surfaces was plotted as a function of simulation time. Fig.2c shows the (110) surface growth follows a decreasing trend as methanol, ethanol, and isopropanol. Moreover, the continuous growth rate profiles of (110) surface suggest a rough growth mechanism of this surface, the relative growth rate decreases from methanol, ethanol and isopropanol. From Fig. 2b, it is evident that (002) surface grows much slower than the (110) surface in all three solvents. Besides, it is most likely that the (002) surface growth rate increases from methanol to ethanol and isopropanol. All the simulated growth profiles of the (002) surface suggest two clearly noticeable steps, which suggest that (002) surface follows a stepwise growth mechanism. The relative growth rate increases from methanol to ethanol and isopropanol.

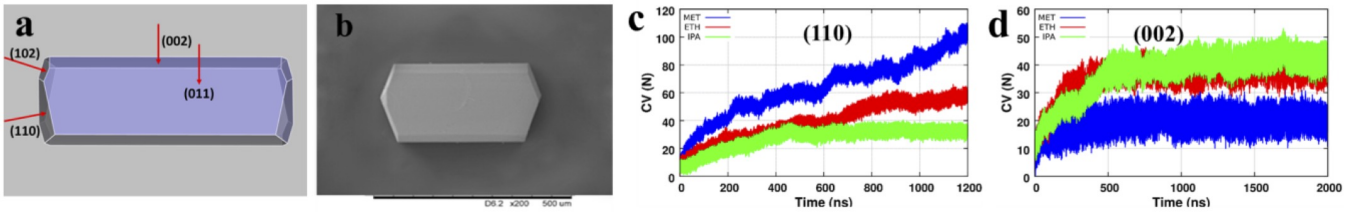

Figure 2: (a) Predicted (AE model) and (b) experimental INH morphology in isopropanol. Growth profiles of (c) (110) and (d) (002) surfaces in methanol (MET), ethanol (ETH) and isopropanol (IPA) obtained from simulations.

References

[1] C. Perego, M. Salvalaglio, M. Parrinello, J. Chem. Phys. 2015, 142, 144113.
[2] M. Salvalaglio, T. Vetter, M. Parrinello, J. Am. Chem. Soc. 2012, 134, 17221-17233.
[3] T. Karmakar, P.M. Piaggi, M. Parrinello, J. Chem. Theory Comput. 2018, 14, 2678-2683.

P085 Interfacial Supersaturation as the Driving Force for Heterogeneous Nucleation at Liquid-Liquid Interfaces

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This contribution is presented also as a talk. The abstract is reported in the talks section, Tuesday 9th of July, Crystal Nucleation and Growth Parallel Session.

P086 CrystalGrower: Understanding the Fundamentals of Molecular Crystal Growth in the Example of Paracetamol

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In this study, the authors look at predicting crystal growth of paracetamol form 1 using CrystalGrower software. [1] The study is a top down approach using the AFM data and face indexing to then simulate results to achieve an understanding of the free energies of crystallisation to then give a probability of growth. The software allows the user to manipulate the crystal shape and surface topology based on the intermolecular interactions and the many free energies of crystallisation $_{cryst}$ for individual crystallisation processes. To do this the closest and strongest interactions are chosen and given values. The simulation will then run the crystal growth based on probability of growth and dissolution using the Monte Carlo technique.2 These values depend on the interactions between growth units and solvent. Paracetamol has 11 main interactions ranging from hydrogen bonds to Van der Waals, and each interaction has a different $_{cryst}$ that can affect the shape of the crystal. To see how each interaction effects the shape, and interaction map was developed using CrystalMaker, by giving each different interaction its own colour which then shows the directions of each interaction and how it effects each facet separately. This method gives an insight into how each interaction affects the morphology as well as surface topology and provides an understanding of how the crystal grows.

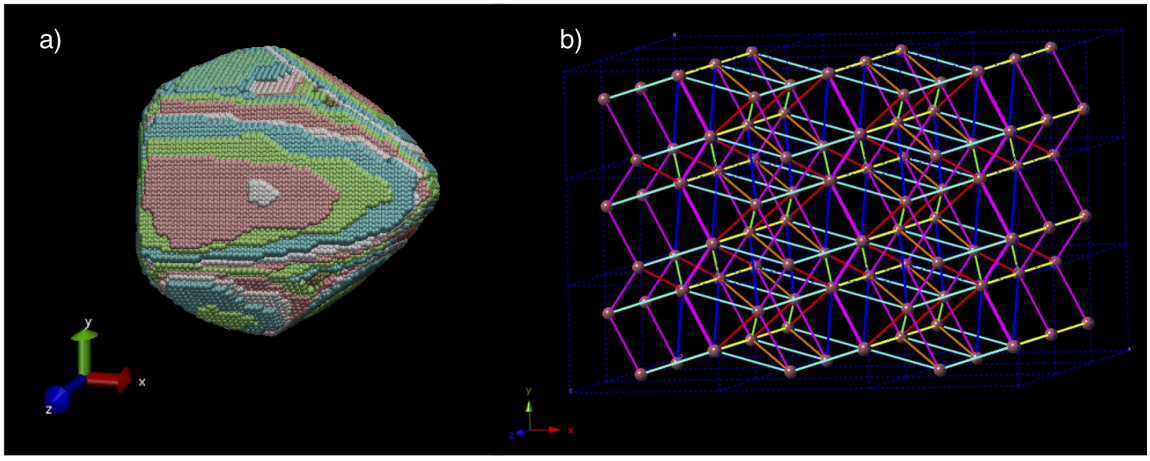

Figure 1: a) Simulated crystal growth of paracetamol form 1, b) Interaction network map of paracetamol.

References

[1] M.W. Anderson, J.T. Gebbie-Rayet, A.R. Hill, N. Farida, M.P. Attfield, P. Cubillas, V.A. Blatov, D.M. Proserpio, D. Akporiaye, B. Arstad J.D. Gale, Nature, 2017, 544, 456-459.
[2]H. M. Cuppen, G. M. Day, P. Verwer and H. Meekes, Cryst. Growth Des., 2004, 4, 1341–1349.

P087 Model comparison for studying secondary nucleation by attrition

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Secondary nucleation is ubiquitous in nature and of fundamental importance for crystallization processes[1]. Attrition is the mechanism through which fragments form after a collision of a crystal with a stirrer. Those fragments, if small enough, can be considered secondary nuclei. In this contribution, two population balance equation (PBE) models to simulate secondary nucleation processes have been derived. The traditional approach, developed by Mersmann [2], describes secondary nucleation as attrition fragments formed through collisions, and their rate of formation is the secondary nucleation rate, which is included in the population balance model as a boundary condition at zero crystal size. In the alternative approach, the formation of attrition fragments is described in the model as a breakage contribution [3], while the growth rate is accounting for size dependent solubility [4]. Conversely to the traditional model, this formulation takes into account the size distribution of attrition fragments and their evolution due to growth. In both models, the number of parameters to estimate has been minimized by using expressions, where physical and mechanical properties of the system, together with operative conditions, have been employed. In particular, for the breakage frequency and the attrition daughter distribution, a physical model [3,5] has been further developed and adapted to PBE. For the secondary nucleation rate, a new expression has been derived and then compared with standard ones [2]. The two models lead to very similar results, even though they describe the same phenomenon with two fundamentally different approaches. This gives the great flexibility of describing secondary nucleation by attrition as an integro-differential term in the PBE, in the case of breakage, or, alternatively, as a boundary condition. The choice between the two approaches is usually dictated by the other phenomena in the model and, in general, by the model framework.

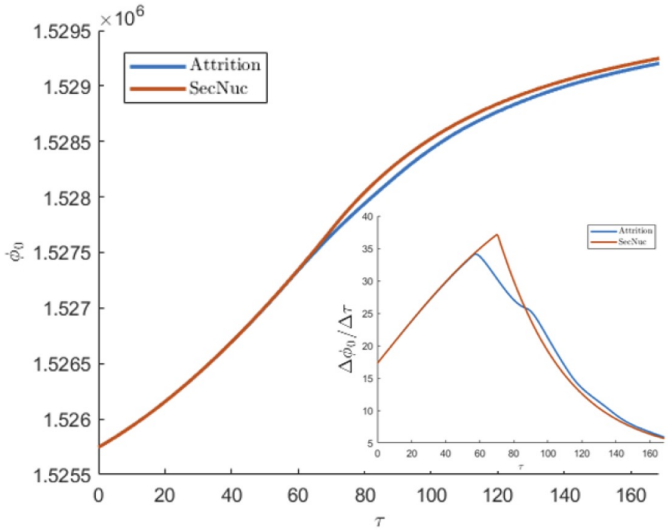

Figure 1: Results of an isothermal de- supersaturation experiment. The profile of the zeroth moment corresponds to the formation of attrition fragments. The variation of the zeroth moment represents the secondary nucleation rate. The results look different, because supersaturation acts differently in the two models. In the model with attrition, it influences the size dependent growth, while in second model it influences the effective number of nuclei formed.

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References

[1] Agrawal, S. G., Paterson, A. H. J. (2015). Chemical Engineering Communications, 202(5), 698–706.
[2] Iggland, M., Mazzotti, M. (2011). Crystal Growth and Design, 11(10), 4611–4622.
[3] Gahn, C., Mersmann, A. (1999). Chemical Engineering Science, 54(9), 1273–1282.
[4] Mersmann, A. (Ed.). (2001). Crystallization technology handbook. CRC Press.
[5] Bermingham, S. K. (2003). A design procedure and predictive models for solution crystallisation processes. T.U. Delft.

P088 Sublimation crystallisation and polymorph stability

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In the case that an organic compound exhibits crystalline polymorphism, it is often necessary to know, which of the polymorphs is the most stable one, in particular for pharmaceuticals. Polymorph stability can be obtained through computational methods, but often experimental proof is required as well. Whereas computational methods may suffer from approximated interaction potentials, experimental values have their own shortcomings and depend on the purity of the sample -unknown impurities are well-known triggers for polymorphism-, its propensity to decompose during measurement or a sheer impossibility to experimentally obtain a certain polymorph that has been found in silico. Presently the most used method by far in the literature to determine polymorph stability is a few differential scanning calorimetry runs. Although, the speed of DSC measurements can definitely be considered as an advantage, the precision and accuracy of the results have suffered with respect to adiabatic calorimetry. Using examples from pyrazinamide and benfluorex [1], it will be shown that solid-solid phase equilibrium temperatures can be hard to observe by DSC. Although the absence of solid-solid transitions can be due to activation barriers that are too high to overcome in the solid state, it is often the case that DSC measurements are just too fast for the experimental question at hand. Another approach to obtain polymorph stabilities as a function of temperature is sublimation crystallisation under a temperature gradient, although whether or not it is possible to observe transition temperatures depends to a large extent on the vapor pressure of the molecular compound. As an example, the formation of two polymorphic crystals of carbamazepine under a gradient has been shown in Figure 1. Although the sharp boundary in Figure 1 for carbamazepine is the preferred outcome, sublimation experiments are not often this clear-cut. [2] In the case of pyrazinamide polymorphs alpha and gamma were found both in a range of temperatures. Therefore, sublimation measurements at specific temperatures were carried out and the preferential growth of single crystals of one of the polymorphs was used to determine the equilibrium temperature between them. This temperature can then be used with enthalpy data from the DSC and specific volumes of the two polymorphs from X-ray diffraction to draw up a pressure-temperature phase diagram of the system. It will be shown that redundancy in such pressure-temperature phase diagrams and thermodynamic requirements can be used to confirm and improve data analysis.

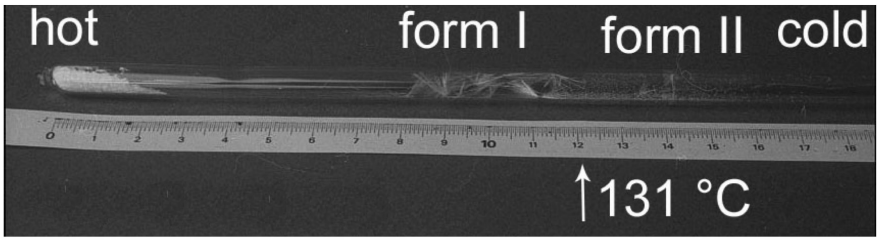

Figure 1: Sublimation under a temperature gradient of carbamazepine.

References

[1] M. Barrio, E. Maccaroni, I.B. Rietveld, L. Malpezzi, N. Masciocchi, R. Ceolin, J.-Ll. Tamarit, J. Pharm. Sci. 2012, 101, 1073.
[2] M.-A. Perrin, M. Bauer, M. Barrio, J.-Ll. Tamarit, R. Ceolin, I.B. Rietveld, J. Pharm. Sci. 2013, 102, 2311.

P089 Polymorphic control of carbamazepine using batch and continuous supercritical CO_2 antisolvent methods

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About 40% of drugs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble. Polymorphism, purity and crystal size distribution are key control objectives of pharmaceutical crystallisation processes directly impacting the drug product quality including solubility and rheological behaviour during downstream processing. Particularly, controlling polymorphism in the transition from batch to continuous crystallization represents a major obstacle for the pharmaceutical industry. Supercritical CO_2-antisolvent methodologies have attracted interest due to their potential to control the crystalline form of pharmaceutical substances. Supercritical antisolvent crystallization provides a unique environment for different molecular recognition events to occur which may induce the formation of particular (stable and metastable) polymorphic forms in the micron and nanosized range that are not reproduced by other techniques.[1] This work provides a detailed study of how specific additives, combined with operating parameters, control the polymorphism of Carbamazepine (CBZ) in supercritical media in batch and continuous processes.[2-4] A Design of Experiments (DoE) approach was performed to confirm the impact of batch and continuous (nano-spray drying) CO_2 antisolvent processing parameters (e.g. temperature, pressure and CO2 flow rate) and the type of additive used (e.g. sodium stearate, sodium dodecyl sulfate) on the polymorphic form and particle size of CBZ. This novel methodology provides control over the final polymorphic form of CBZ obtained by (1) templating the desired polymorphic form when supercritical CO_2 supersaturates the CBZ-additive methanol solution in the spray drying nozzle and (2) avoiding/minimizing the occurrence of any possible polymorphic transformation by immediately spray drying the supercritical antisolvent induced suspension into a fine dried powder.

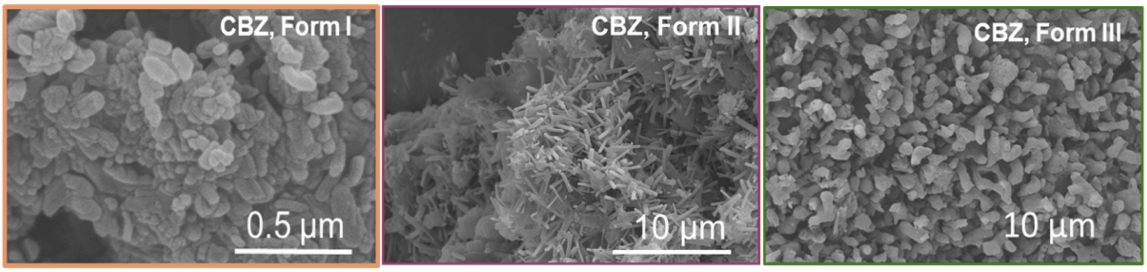

Figure 1: Scanning electron microscopy (SEM) images of distinct polymorphic forms (I, II and III) of carbamazepine (CBZ) nanoparticles produced by supercritical CO_2-assisted spray drying.

References

[1] M. A. Rodrigues, J. M. Tiago, L. Padrela, H. A. Matos, T. G. Nunes, L. Pinheiro, A. J. Almeida, E. G. de Azevedo, Pharm. Res., 2014, 31, 3136–3149

[2] L. Padrela, J. Zeglinski, K. M. Ryan, Cryst. Growth Des., 2017, 17, 4544-4553

[3] L. Padrela, B. Castro-Dominguez, A. Ziaee, B. Long, K. M. Ryan, G. Walker, E. J. O'Reilly, CrystEngComm, 2019, 21, 2845-2848

[4] B. Long, K. M. Ryan, L. Padrela, Cryst. Growth Des., 2019, Accepted

P090 Predicting Curcumin Polymorphism for Liquid Antisolvent Precipitation using In-Situ Raman Spectroscopy

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Controlling polymorphism of an Active Pharmaceutical Ingredient (API) remains an area of active research amongst the scientific community. Therefore, the objective of this work was to employ in-situ raman spectroscopy for prediction of the polymorphic outcome beforehand for liquid antisolvent (LAS) precipitation of curcumin. Curcumin (Cur), a poorly water-soluble ingredient found in turmeric, possesses anti-oxidant, anti-inflammatory, anti-cancer, and analgesic properties. It exists in three polymorphic forms [1]. In this study, LAS precipitation of curcumin was carried out from ethanol (EtOH) and acetonitrile (ACN) in semi-batch mode. Water was used as an antisolvent. The effect of different additives and mixing conditions (ultrasound) was also studied. It was observed that curcumin precipitated as the metastable form (Form 3) from ethanol, while the stable form (Form 1) precipitated from acetonitrile. This was found to hold irrespective of the initial supersaturation, additives or ultrasound. The Raman spectra of organic solutions of curcumin (Fig. 1) in acetonitrile and ethanol highlights the effect of solvent on solute-solvent and solute-solute interactions present in solution. The presence of curcumin rich clusters could be observed in ethanol which were absent in acetonitrile. The peak around 1532 cm^{-1} in ethanolic curcumin solution showed that the keto-enol functional group on the inter-ring chain of curcumin molecules was directly involved in the formation of curcumin clusters. The presence or absence of these keto-enol stretching vibrations in solvent was found to be dictating the polymorphic outcome. In ethanol, interaction of the solvent with curcumin was found to facilitate the formation of curcumin clusters as seen by the stretching and bending vibrations of the keto-enol group (1532 cm^{-1}). Such keto-enol vibrations are also present in the crystal structure of the metastable form (Form 3). Thus, during LAS from ethanol, these curcumin clusters provided a pathway for the crystallization of the metastable form, Form 3. On the other hand, acetonitrile was found to interact more with the hydroxyl moieties attached to the phenyl groups at the ends of the curcumin molecule (O-H...N interaction). Increased phenolic interaction of curcumin with acetonitrile could be observed as a shoulder band present at 1592 cm^{-1}. One can also observe the absence of the keto-enol vibrations of curcumin in acetonitrile (also absent in Form 1). Therefore, the addition of water during LAS led to the precipitation of Form 1. Similar observations were also made during LAS from acetone and methanol where LAS from methanol resulted in Form 3 and Form 1 resulted from acetone. Thus, in this study, we report the role of existing curcumin rich clusters in solvent which drive the final polymorphic outcome. Though reports exist in literature where researchers have reported alteration of the polymorphic outcome of curcumin using ultrasound and additives [2,3], no study shows a possible way of predicting the polymorphic outcome of curcumin beforehand. Therefore, this study emphasizes the importance of in-situ techniques in gaining control over polymorphism for better quality control.

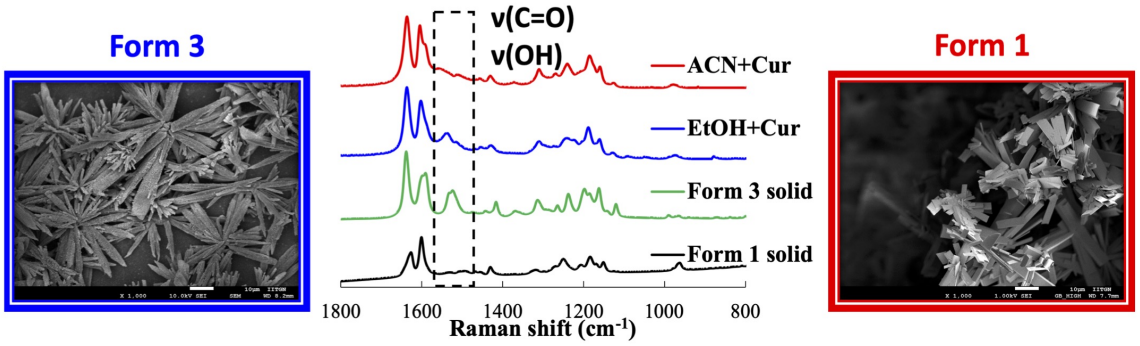

Figure 1: Raman spectra of curcumin dissolved in acetonitrile (red), and ethanol (blue). SEM images corresponding to different polymorphic forms of curcumin obtained after LAS have also been shown.

References

[1] P. Sanphui, N. R. Goud, U. B. R. Khandavilli, S. Bhanot, and A. Nangia, Chem. Commun., 2011, 47, 5013–5015.
[2] A. A. Thorat and S. V. Dalvi, CrystEngComm, 2014, 16, 11102–11114.
[3] A. A. Thorat and S. V. Dalvi, Ultrason. Sonochem., 2016, 30, 35–43.

P091 Role of racemisation kinetic in the deracemisation process via temperature cycles

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Solid-state deracemisation via temperature cycles is an emerging technique for enantiomers purification. By applying a periodic temperature profile to a suspension of a solid mixture of a conglomerate forming compound in its saturated solution, it is possible to isolate the desired enantiopure crystals. The phenomena responsible for deracemisation are dissolution and growth, promoted by the temperature variation, agglomeration and breakage in suspension, but also by the racemisation reaction in solution [1]. Since the desired enantiomer grows preferentially, its concentration in solution decreases faster than the one of the counter enantiomer. The racemisation reaction converts the counter enantiomer in excess in solution into the desired one, thus restoring its solution concentration. In this work, the racemisation occurs thanks to an acid/base reaction, but, depending on the compound reactivity, the reaction can be spontaneous, catalysed by enzymes, or by the light.

Racemisation and deracemisation rate. The racemisation reaction has been characterised experimentally by optical rotation measurements and it was shown that the reaction rate varies with the base concentration and with temperature, according to the Arrhenius law. The measurements performed in two different solvent systems were compared to analyse how the solvent chemical physical properties affect the reaction rate. We, hence, investigated experimentally the effect of the rate of racemisation on the deracemisation rate, finding that a faster racemisation rate, obtained by increasing the catalyst concentration, promotes a faster deracemisation process. When the solvent is varied, the impact of the reaction rate cannot be easily decoupled from the one of the other phenomena, since all the kinetics are affected, i.e. growth, dissolution, and racemisation. These results highlight that the solvent system can have an important effect on the process, since the deracemisation rate is determined by all the kinetics together. Therefore, preliminary information on the rate-limiting step of the process can promote the choice of the right solvent to perform deracemisation via temperature cycles successfully.

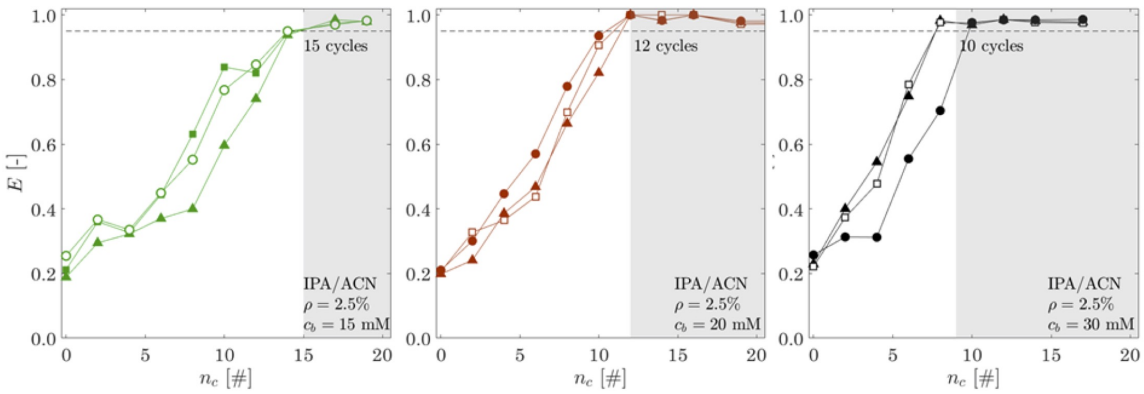

Figure 1: Evolution of the enantiomeric excess in function of the number of cycles, during deracemisation via temperature cycles, with increasing catalyst concentration for left to right.

References

[1] F. Breveglieri, M. Mazzotti, Cryst Growth Des., 2019, doi:10.1021/acs.cgd.9b00410.

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P092 Effects of Structurally-Related Impurities on the Nucleation and Crystal Growth of Curcumin

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Separate studies of nucleation and seeded crystal growth of Curcumin (CUR) have been performed in Propan-2-ol in the presence of structurally related impurities Demethoxycurcumin (DMC) and Bisdemethoxycurcumin (BDMC) [1]. Molar masses were in excess of 350g mol^{-1}, making both nucleation and crystal growth slow and necessitating the use of high supersaturations (in the range 3.6 to 4.9 in nucleation and 2.0-2.2 for seeded isothermal desupersaturation). The impurities to Curcumin molar ratios explored were in the range 1-10mol%. Nucleation was examined using the multi-vial technique (vol. 20ml) and crystal growth (vol. 150ml) was examined using Uv-Visible and FBRM probes to follow desupersaturation and particle numbers. The presence of impurities inhibited nucleation and growth to similar extents but the mechanism of inhibition was different for each. For nucleation there was a modest change in measured solid-liquid interfacial energy (γ_{sl}) when impurities were present but the pre-exponential factor was significantly lowered when the impurities were present. The γ_{sl} calculated from the Birth and Spread model for crystal growth increased by a factor of 2.5 when measured in the presence of impurities. DFT and Metadynamic molecular modelling reveal that the 1:1 bonding between CUR and an impurity molecule is stronger than between two CUR molecules. The absence of methoxyl groups in the impurities increases the charge on the adjacent hydroxyl groups generating stronger CUR-impurity interactions (Figure 1). In the case of nucleation, the decreased pre-exponential factor is associated with the generation of a significant number of pre-critical size nuclei containing one or more impurity molecules which subsequently fail to progress across the critical free energy barrier, ultimately slowing the rate of nucleation. In the case of crystal growth, the same strong CUR-impurity interaction leads to a surface layer of impurity on the growing CUR surface which ultimately stops growth. Growth can only resume via 3-D nucleation as indicated by a discontinuity in the needle growth observed in the presence of impurities and consistent with a value of γ_{sl} characteristic of 3-D nucleation [2]. A common feature for nucleation and growth is the strong CUR-impurity interaction which inhibits nucleation by incorporation into pre-nucleation clusters preventing their progress to fully mature crystals and by adsorption onto growing CUR surfaces stopping their growth and forcing 3-D nucleation as a route to restart growth.

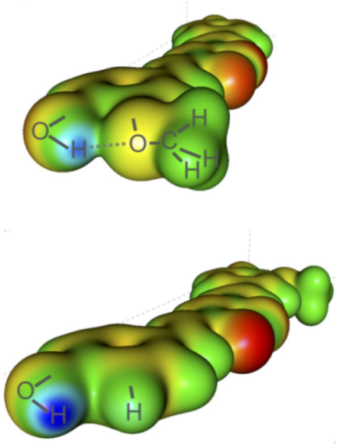

Figure 1: Electrostatic potential isosurface of CUR (top) and DMC (bottom) (blue - positive, red - negative, yellow - weakly-negative, green - neutral potential.

References

[1] C. Heffernan, M. Ukrainczyk, R.K.Gamidi, B.K. Hodnett and A.C. Rasmuson, OPRD, 2017, 21, 821-826.
[2] C. Heffernan, M. Ukrainczyk, J. Zeglinski, B.K. Hodnett and A.C. Rasmuson, Crystal Growth Design, 2018, 18, 4715-4723

P093 Crystallization of peptides: Case of glycine homopeptides

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A compound containing 2-50 amino acids linked in a chain is called a peptide. Despite their relatively small size, peptides still can fold and pack into complex spatial structures. Peptides have the potential for treatment of a range of diseases. However, producing large amounts of stable and pure peptide material is still a significant challenge, one that could be met by using crystallisation as a purification step. In this work, the induction time and metastable zone of glycine homopeptides of increasing chain lengths are measured to provide insight into their nucleation and growth mechanisms, with respect to how the crystallisability of these materials can be improved to satisfy the needs of peptide manufacturers. The solubility of glycine homopeptides (Gly-Gly, Gly-Gly-Gly, Gly-Gly-Gly-Gly, Gly-Gly-Gly-Gly-Gly) were measured using UV vis absorption at 190-260nm wavelength. [1] The result shows that solubility will decrease with the increase of the glycine residues and increase with the temperature increasing. Based on this thermodynamic research, the crystallisation process (cooling crystallisation and anti-solvent crystallisation) of glycine homopeptides were researched in order to select the suitable crystallisation method. The induction time at different supersaturation level (Figure 1) and the metastable zone of glycine homopeptides at different cooling rate were measured. It shows that the nucleation becomes more and more difficult with the increase of the glycine residues and the metastable zone became larger when the cooling rate became higher. In the next step, the effect of pH, solvents, supersaturation will be considered to find more suitable crystallisation methods and conditions.

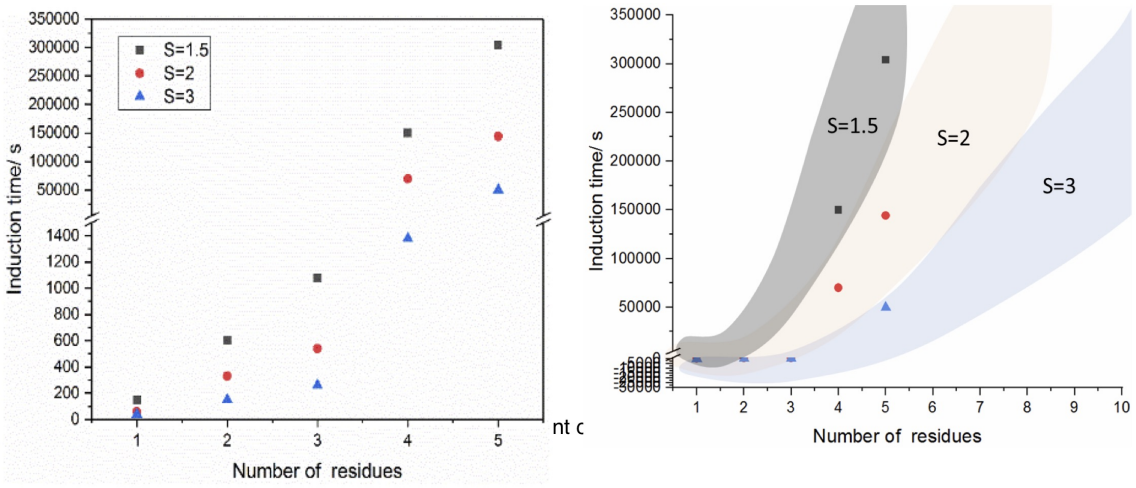

Figure 1: The induction time measurement of Glycine homopeptides at 278.15K

References

[1] N. J. Anthis, G. M. Clore, Protein Science, 2013, 22 (6), 851-858.

P094 Crystal Growth Kinetics of Salicylamide Investigated Under Different Process Conditions

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Experimental Approach This research focuses on improving knowledge of the crystal growth process and kinetics of salicylamide by investigating the growth of single crystals in a non-stirred growth cuvette (CV) and on a rotating disk (RD). The impact of organic solvent, supersaturation, and temperature on the crystal growth process were also examined. In the CV the crystal growth rates were measured for a seed crystal manually inserted into the cuvette which contained a stagnant supersaturated solution. In the RD 32 seed crystals were attached to a disk that was rotated in a supersaturated solution. Crystals were allowed to grow for up to 1 hour in a controlled temperature. Micrographs of each crystal were captured using an optical light microscope either at intervals throughout or else before and after the growth period depending on method. The crystal growth rates in the length and width direction were precisely measured in-situ for each individual crystal; and growth rates were also extracted for a specific crystal facet i.e. (200). The solvents investigated were acetone, acetonitrile, ethyl acetate and methanol (AC, MeCN, EA or MeOH). The supersaturations (S-1) used were in the range of 0.01-0.12 to prevent nucleation. RD further examined the effect of temperature on the growth of salicylamide in MeCN by using three growth temperatures (10, 15 and 20^{o}C). Results Experiments revealed that salicylamide crystals grown in different solvents, at different supersaturations and also within each solvent receive different shapes. The average crystal growth rate of the (200) face of individual seed crystals is similar for both the CV and RD methods as it follows the order MeOH>MeCN$\geq$AC>EA at supersaturation (S-1) of 0.06 and 0.03 respectively. This (200) surface of salicylamide crystals was examined by SEM, it is more systematic and structured when grown in MeOH than in EA. In addition it was deduced that EA could adsorb more strongly on the faces, the increased size of which, can explain both the shape change and slower growth rates. In each solvent, the average growth rates increase with increasing supersaturation. Increasing temperature by 10^{o}C led to a fourfold increase in salicylamide growth rates under certain conditions. The crystal growth rates of salicylamide's (200) facet obtained via RD resulted in 20 times faster growth rates than when grown using the CV as compared in Figure 1. Different rotation speeds were tested in the range of 50-350 rpm for the RD, and 200 rpm was found to be sufficient to essentially eliminate the film mass transfer resistance and thus growth is expected to be controlled by the surface integration step. Whereas the CV experiments occur in a stagnant solution and so are significantly influenced by the volume diffusion resistance. The RD method combined aspects of observing crystals both individually and as a group under the one study to give both a fundamental examination of the growth of a specific crystal yet also have overall growth rates of the larger crystal population. This combined with its controlled hydrodynamic conditions that produce growth rates which were controlled by rate of surface integration make the rotating disk crystal growth method relevant to both fundamental and industrial knowledge.

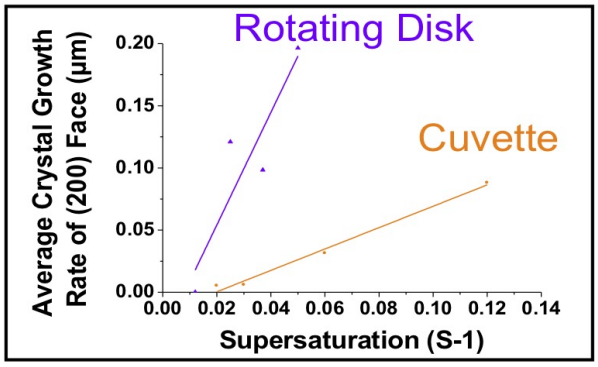

Figure 1: Average crystal growth rate (μm/s) of the (200) face of salicylamide seed crystals grown in MeCN with respect to supersaturation at 15^{o}C by the two crystal growth methods, CV and RD.

P095 Estimating crystal growth kinetics of inorganic salts in volatile and complex electrolyte systems: The case study of ammonium bicarbonate in aqueous ammonia solutions

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The need for the abatement of greenhouse gases emissions in the energy sector has recently led to the development of ammonia-based CO2 capture absorption technologies that exploit continuous crystallization of ammonium bicarbonate to decrease the overall energy penalty of the capture process [1]. The knowledge of the crystallization and dissolution kinetics of this compound is therefore key to the design, process synthesis and optimization of the relevant crystallization equipment [2]. In this work, we estimate the macroscopic crystal growth and dissolution rates of ammonium bicarbonate in aqueous ammonia solutions as a function of the solution supersaturation in a range of process conditions of industrial relevance. The electrolytic and reactive nature of the mixtures requires the computation of the driving force for crystallization using an activity-based speciation model [3]. The model parameters have been estimated based on experimental speciation data obtained by applying tailored multivariate data analyses on the measured ATR-FTIR spectra of the solutions [4]. Moreover, the volatility of CO_2(aq) and NH_3(aq) requires to operate the system under its vapor pressure in order to avoid the depletion of the solute in the liquid phase. For this reason, a sealed crystallizer equipped with custom-made connections for the on-line monitoring tools such as FBRM and ATR-FTIR probes has been used during the experiments. In addition to estimating the crystallization kinetics, it has been found that the speciation in solution and the supersaturation can affect the relative growth of the ammonium bicarbonate crystal facets, thus leading to different crystal habits. Finally, this work provides a sound thermodynamic framework that allows for the exploitation of kinetics models to design industrial applications in which the crystallization and the dissolution of ammonium bicarbonate is of concern.

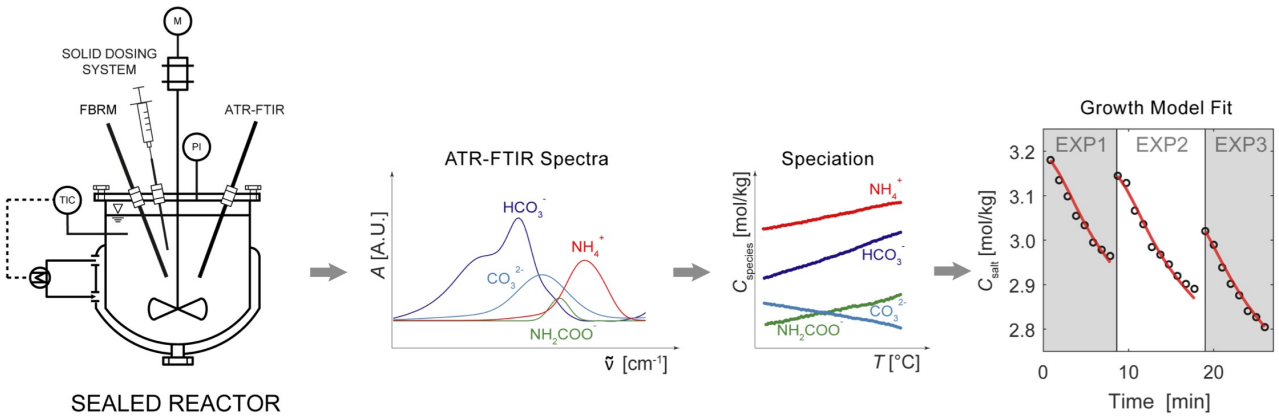

Figure 1: Graphic representation of the experimental and theoretical frameworks used to estimate the crystallization and dissolution kinetics of ammonium bicarbonate in aqueous ammonia solutions.

References

[1] D. Sutter, M. Gazzani and M. Mazzotti, Faraday Discuss., 2016, 192, 59-83.
[2] F. Milella, M. Gazzani, D. Sutter and M. Mazzotti, Ind. Eng. Chem. Res., 2018, 57, 11712-11727.
[3] K. Thomsen and P. Rasmussen, Chem. Eng. Sci., 1999, 54, 1787-1802.
[4] F. Milella and M. Mazzotti, React. Chem. Eng., 2019.

P096 The Effect of Graphene on the Crystallisation of Glycine

M. Boyes[1], A. Alieva[1], V. Nagyte[1], J. Tong[1], M. Melle[2], T. Vetter[3], C. Casiragh[1]

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The crystallisation of organic molecules from solution is a vital part of numerous processes in many industries like the chemical, pharmaceutical and food1. The ability to control the polymorphic outcome of a crystal has been an active area of research for many years and can still cause a problem for crystal engineers as it makes the design of solids or drugs complicated and expensive [2,3]. Graphene, a single layer of graphite, shows unique properties that can be exploited for several applications [4]. However, graphene-templated crystallisation has not yet been attempted, despite the attractive properties of this advanced material, which include tunability of its surface properties via covalent functionalisation [5] and ease of solution processability [6]. Graphene with different surface properties and produced in different ways has been tested for the crystallisation of glycine using micro-droplets. The polymorphic outcome has been studied by Raman spectroscopy as this technique was able to detect even trace amounts of different polymorphs, well below that of the sensitivity of X-Ray Diffraction. Our results show that graphene does affect the polymorphic outcome of glycine, but this strongly depends on the surface properties of graphene, in agreement with molecular dynamic simulations [7].

References

[1] E. J. W. P. Schmelzer, Nucleation Theory and Applications, 2005.
[2] E. K. Rideal, Nature, 1949, 164, 303-305.
[3] G. R. Desiraju, J. Am. Chem. Soc., 2013, 135, 9952-9967.
[4] K. S. Novolselov, V. L. Fal'ko, L. Colombo, P. R. Gellert, M. G. Schwab and K. Kim, Nature, 2012, 490, 192-200.
[5] D. C. Elias, R. R. Nair, T. M. G. Mohiuddin, S. V Morozov, P. Blake, M. P. Halsall, A. C. Ferrari, D. W. Boukhvalov, M. I. Katsnelson, A. K. Geim and K. S. Novoselov, Science, 2009, 323, 610–3.
[6] Y. Hernandez, V. Nicolosi, M. Lotya, F. M. Blighe, Z. Sun, S. De, I. T. McGovern, B. Holland, M. Byrne, Y. K. Gun'Ko, J. J. Boland, P. Niraj, G. Duesberg, S. Krishnamurthy, R. Goodhue, J. Hutchison, V. Scardaci, A. C. Ferrari and J. N. Coleman, Nat. Nanotechnol., 2008, 3, 563–568.
[7] M. Boyes, A. Alieva, V. Nagyte, J. Tong, M. Melle, T. Vetter, C. Casiraghi, submitted.

P097 Influence of Laser Polarization on Glycine Polymorphism in Non-Photochemical Laser Induced Nucleation

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Non-photochemical laser induced nucleation (NPLIN) of glycine in the presence of polarized light was investigated to shed light on the underlying mechanisms responsible for the thermodynamic phase transition. The investigation focused on how the nucleation process can be affected by laser polarization, number of pulses, peak wavelength, supersaturation and impurity content of the solution. The impact of these parameters was studied using large number of samples (greater than 100) to generate a statistically significant data. Glycine samples were exposed to nanosecond laser pulses in a beam with unfocussed Gaussian spatial profiles and moderate intensities (220 MW/cm^2) in order to avoid laser triggered-photochemical reactions. Hence, nucleation is triggered solely by the interaction between the laser light and the supersaturated solutions. The study aims at providing a deeper insight into the mechanisms underlying the laser-assisted nucleation, especially the controversial optical Kerr effect, where the laser polarization is expected to induce the formation of a particular crystal polymorph.1 This is achieved by varying the polarization state of the laser photons and the number of pulses for glycine supersaturations ranging from 1.5 to 1.7. The results showed no clear evidence of selective control of polymorphism by switching the polarization of the laser beam.2 However, the polymorph formed by the laser pulse is different from that induced by crash cooling. When compared to crash cooling, it was observed that laser pulses exhibit a stronger impact on the nucleation kinetics, reducing the induction time from days to hours. It was also noticed that the nucleation probability is not significantly affected by the number of laser pulses used in the experiment. In most cases, a single pulse is sufficient to trigger NPLIN in comparison to previously reported studies utilizing order of hundred pulses.[1,2] Irradiation by multiple infrared light pulses is not desirable as it may lead to a significant temperature rise in the solution and a decrease in the supersaturation. Since the nucleation rate and the type of polymorph are strongly dependent on the degree of supersaturation, temperature stability is imperative for the reliability of the investigation. Furthermore, filtration of samples showed a drastic decrease in nucleation probability suggesting that the presence of molecular clusters or solid nanoparticles could play a dominant role in the light-induced nucleation. Hence, we conclude that selection of glycine polymorph through laser polarization is not possible within our experimental parameters. We are investigating other possible mechanism such as formation of cavitation bubbles either by impurity heating or non-linear laser solute/solvent interactions.

References

[1] Garetz, B. A., Matic, J. Myerson, A.S. (2002). Polarization switching of crystal structure in the nonphotochemical light induced nucleation of supersaturated aqueous glycine solutions. Physical Review Letters, 175501-1

[2] Liu, Y., van den Berg, M. H. Alexander, A. J. (2017). Supersaturation dependence of glycine polymorphism using laser-induced nucleation, sonocrystallization and nucleation by mechanical shock. Phys.Chem.Chem.Phys., 19386

P098 Magnetically Induced Co-Crystalline Phase Manipulation via an Evaporatively Driven Growth Process and Structural Analysis via Electron Diffraction of a new Organic TCNQ-PAH Charge Transfer Complex

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A new polyaromatic organic charge transfer complex has been created and its structure solved using 3D electron diffraction via TEM. Polyaromatic hydrocarbons are of interest owing to their ability to sustain ring currents over their hybridized pi-electron system, which in turn offers an avenue for magnetic flux coupling during crystallization [1]. To this end, we hope to create a new subset of TCNQ-donor co-crystals and extend this work by crystalizing and characterising the field effects upon subsequent halogenated derivatives of both species.

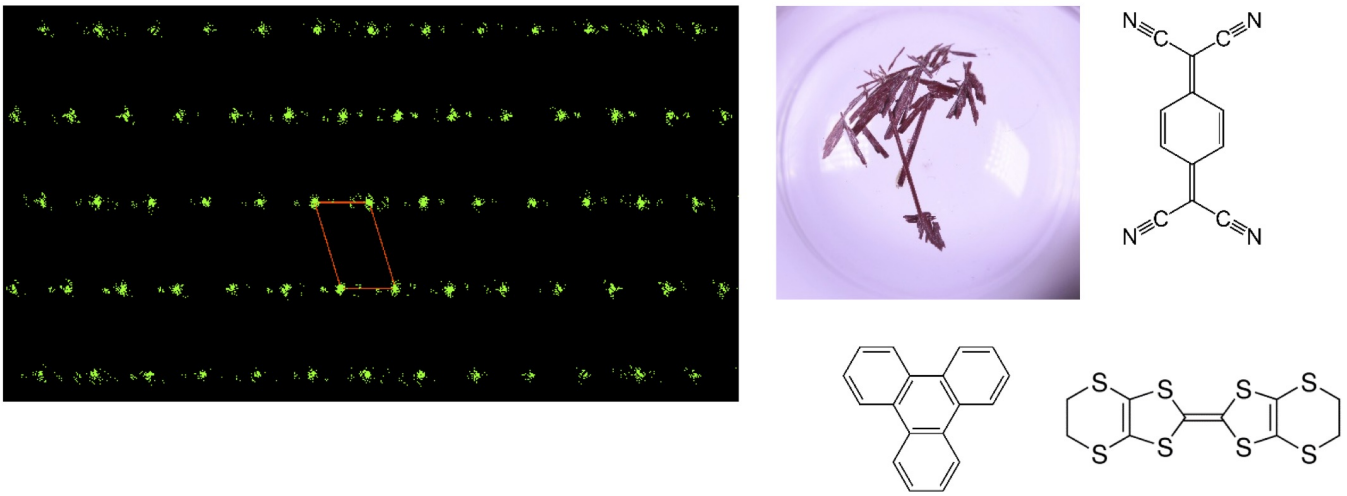

Figure 1: From left to right: Electron diffraction pattern of TCNQ-Triphenylene co-Crystal viewed down c*, Optical image of TCNQ-Triphenylene, TCNQ, Triphenylene and Bis(ethylenedithio)tetrathiafulvalene chemical structures.

References

[1] Jason Potticary et al. "An unforeseen polymorph of coronene by the application of mag-netic fields during crystal growth". In: Nature Communications 7.May (2016),

P099 Model-driven Control for Continuous Crystallisation of -lactose monohydrate

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The focus of this research is around the use of model development in order to optimally control the progression of lactose crystallisation from water. To optimise the crystallisation process with respect to a given parameter such as yield or particle size, it is first necessary to build a comprehensive model that depicts the crystallisation process while incorporating process conditions. Once the model has been used for optimisation, a control system can be implemented in order to maintain the system within this optimal trajectory. It is therefore key to have a model which is capable of depicting all the different parameters of crystallisation accurately. The building of such a model requires gaining kinetic data for the parallel mechanisms of crystallisation that can be within a system at one time. In this research the use of sequential parameter estimation is in the format described by Perez-Calvo, Kadam and Kramer [1]. Within this method the different parameters are assessed by manipulating the process conditions in order to limit the presence of some parameters while highlighting the dominant parameter being investigated. This allowed for individual parameters to be assessed and therefore allow for the more integrated parameters that cannot be assessed individually, such as agglomeration, to be defined following the exclusion of the effects of previously defined parameters. The model itself is built upon small batch experiments in this manner with the resulting data set being inputted within gPROMS in a corresponding flowsheet of the experimental set-up as depicted within Figure 1. The parameter estimation capabilities of gPROMS can be utilised to define the parameter based upon the experimental results of the batch systems. The gathering of this kinetic data allows for the complete crystallisation system to be defined. With a definitive model in place, optimisation of the system can then be applied within the gPROMS software. With an optimal profile having been identified this allows for optimum control to be implemented which is of clear importance to the pharmaceutical industry.

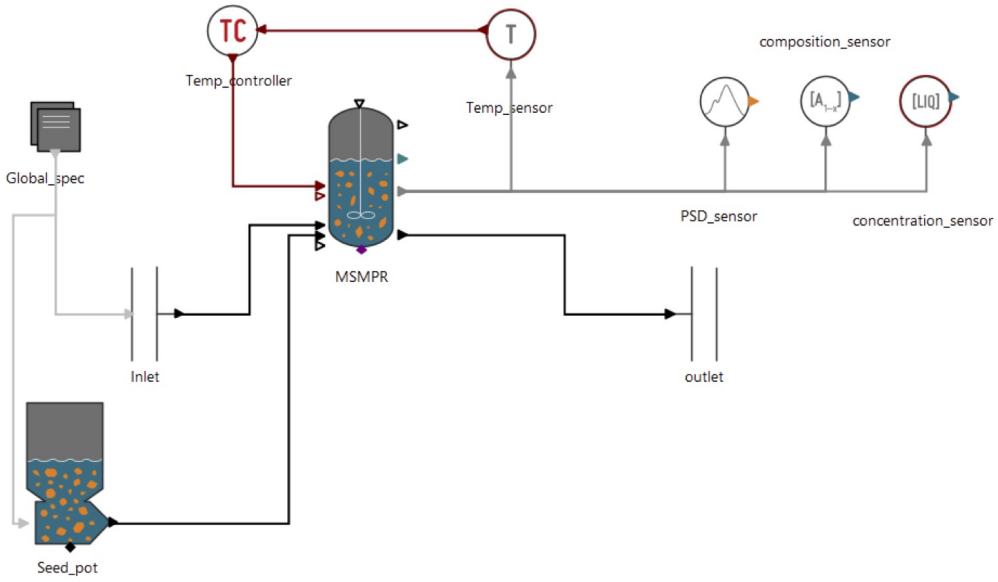

Figure 1: This is a process diagram of the batch experimental set-up within gPROMS.

References

[1] J.-F. Perez-Calvo, S. S. Kadam, and H. J. M. Kramer, "Determination of kinetics in batch cooling crystallization processes-A sequential parameter estimation approach," AIChE J., vol. 62, no. 11, pp. 3992–4012, Nov. 2016.

P100 On the role of secondary nucleation in temperature cycling-induced deracemization

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Crystallization techniques are currently regarded as the most effective methods for chiral resolution. Among those, temperature cycling-induced deracemization is gaining the spotlight due to the possibility of achieving full conversion of the counter enantiomer and complete recovery of the target species in the solid-state only by using temperature sweeps. This process involves partial dissolution and re-crystallization of a chiral suspension of conglomerate crystals (racemic mixture of enantiopure crystals) via thermal oscillations in the presence of a solute racemization reaction [1,2]. Although growth/dissolution are deemed as the driving deracemization mechanisms in process models, secondary nucleation was observed when running the thermal cycles under intensified operating conditions of fast heating and cooling [3]. Thus, in order to shed light on the role of secondary nucleation in the deracemization scheme, a parametric study was performed on the operating parameters that mainly affect secondary nucleation such as agitation rate, supersaturation, and suspension density. The system featured 3-hydroxy-2-isopropyl-3-phenyl-1-isoindolinone conglomerate crystals in a solution of toluene and catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). By inspecting the particle size along with the chiral enrichment trend it is apparent how the occurrence of secondary nucleation strictly correlates with the deracemization process. Moreover, the initial enantiomeric excess is greatly responsible for the chiral bias that drives the deracemization as shown in Figure 1a. In fact, 77% of the total crystallizing mass comprises of the target molecule when 41% initial enantiomeric excess was employed (red curves), whilst only 4% difference in the crystallization rate of the two chiral populations is attained with 0.5% initial excess (orange curves). Furthermore, in all experiments secondary nucleation governed the crystallization phase as suggested by the increasing trend of specific surface area in Figure 1b.

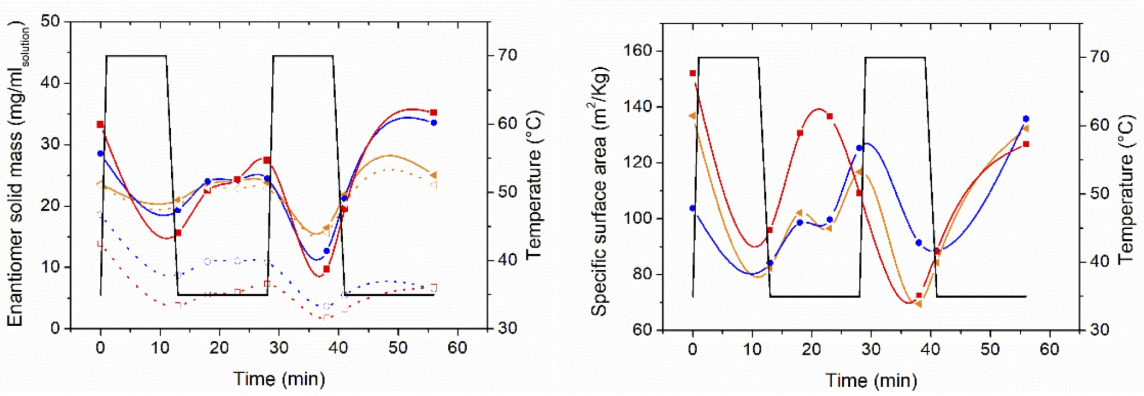

Figure 1: (a) Mass evolution of the target enantiomer (solid lines) and the counter enantiomer (dotted lines) during two temperature cycles in experiments featuring different initial enantiomeric excesses: 0.5% (orange curves), 21% (blue curves) and 41% (red curves). (b) Specific surface area trend over the application of two thermal sweeps for the same experiments.

References

[1] C. Viedma, P. Cintas, Chem Commun. 2011, 47, 12786-8.
[2] K. Suwannasang, A. E. Flood, C. Rougeot, G. Coquerel, Cryst. Growth Des, 2013, 13, 34983504.
[3] F. Cameli, C. Xiouras, and G. D. Stefanidis. CrystEngComm, 2018, 20, 2897-2901.

P101 Mechanism and Kinetics of Solid State Grown Cocrystal of Caffeine-Oxalic Acid

M. Anim-Addo[1], B. Alsirawan[2], A. Paradka[2], P. Shelle[3], D. Banna[3], X. Lai[1]

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[2] School of Pharmacy, University of Bradford
[3] Centre for Atmospheric Science, University of Manchester

Cocrystal of caffeine-oxalic acid can be prepared by heating the mixed powders of caffeine (CA) and oxalic acid (OX) without solvent. Our in-situ microscopic observations showed that the growing front of needle-like single co-crystals are not in contact with the caffeine and oxalic acid particles, and hence is evident that this solid-solid reaction of the cocrystal formation is through the gas phase. In order for the growth kinetics via gas phase, the vapour pressures for the solids of pure caffeine, pure oxalic acid and their cocrystal were measured using Knudsen Effusion Mass Spectrometry (KEMS) technique. Growth rates of the needle-like single cocrystal and the bulk powder cocrystals were measured as a function of temperature using microscope and powder XRD respectively. The chemical potential difference between the saturated vapours of caffeine and oxalic acid the equilibrium vapour of the caffeine and oxalic acid cocrystal are calculated based on the KEMS results, and is then related to crystal growth rates to establish the kinetic model via gas phase.

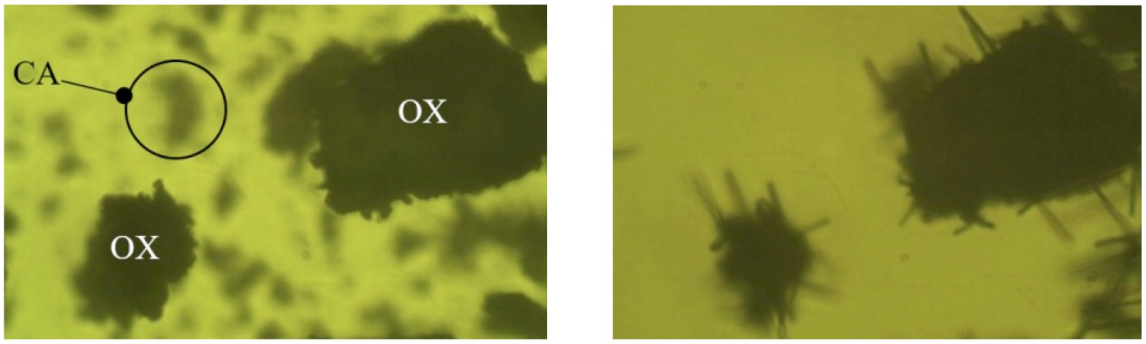

Figure 1: Microscopic images tracking the growth of caffeine-oxalic acid cocrystal (left): pure finer caffeine and the large oxalic acid particles placed together on hot stage at 120C; (right): the needle-like co-crystals began from the surface of oxalic acid solids and the front of the growing cocrystal proceeded without contact with the oxalic acid or caffeine particles.

P102 Hydrogen bond polarization overcomes unfavourable packing in the most stable high Z' polymorph of Pterostilbene

L. Bofill[1], **D. d. Sande**[1], **R. Barbas**[2], **R. Prohens**[1,2]

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The polymorphic landscape of the nutraceutical pterostilbene [1] has been analyzed by solving the crystal structure of forms II and III from PXRD data.[2] Polarization effects [3] in the previously know form I crystal structure have been observed and the structural features of the most stable high Z polymorph have been discussed in relation to the relative stability between the polymorphs of this important natural product.

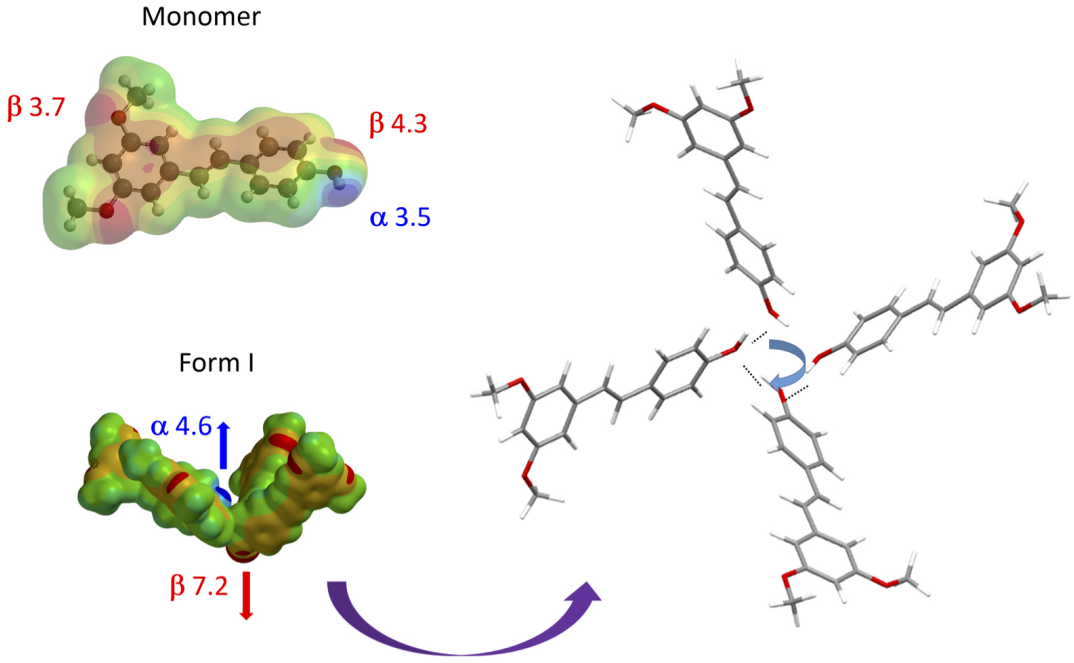

Figure 1: (Left) MEPS of the monomer and the tetramer of Pterostilbene. H-bond parameters of the terminal groups are shown and red and blue arrows show the direction of acceptor and donor hydrogen bonding respectively. (Right) Helicoidal arrangement of Pterostilbene form I.

References

[1] Bethune, S. J.; Schultheiss, N.; Henck, J. Cryst. Growth Des. 2011, 11, 2817– 2823.
[2] Bofill, L.; de Sande, D.; Barbas, R. and Prohens, R. Cryst. Growth Des., 2019, 19, 2552–2556.
[3] Henkel, S.; Misuraca, M. C.; Troselj, P.; Davidson, J.; Hunter, C. A. Chem. Sci., 2018, 9, 88– 99.

P103 Recovery of high-pressure solid forms to ambient pressures

M. R. Ward[1], **I. D. H. Oswald**[1]

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This contribution is presented also as a talk. The abstract is reported in the talks section, Tuesday 9th of July, Characterising, predicting and Controlling Polymorphism Parallel Session.

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Reabetswe	Zwane	Dublin City University	Ireland

Useful Information

Registration

The BACG registration desk will be open on Tuesday 9^{th} July at 8.15 am in the lobby inside the Rooms on Regent's Park. Delegates will be provided with name badges, lanyards, WiFi password, poster voting form, Crystal in Art voting form and conference materials. The registration desk will be staffed each day during conference hours. Please do come along and see anyone on the registration desk to request any information.

Language

The official language of the conference is English.

Weather

June is a good month for weather in London with temperatures generally ranging between 16 – 23^{o}C (64-80 F). However, this is the is the UK so please do be prepared for rain and much cooler temperatures. Pack an umbrella and a jacket.

Security

Please kindly wear your name badge and lanyards during the conference hours so people are aware that you a conference participant.

Poster Sessions, voting, and prizes

The poster sessions will be held on Tuesday 9th and Wednesday 10th July. The main poster session will be on Tuesday evening following the conclusion of the afternoon session. Drinks and canapes will be provided including birthday cake to celebrate the 50^{th} anniversary of the BACG.

There are five poster prizes which have been kindly sponsored by CGD, the Buckley Trust, and XtalPi Inc. The prizes are: 1^{st} Prize is £100, 2^{nd} Prize is £75 and 3^{rd} Prize is £50. In addition to the top three overall posters there will be a fourth poster prize of £100 dedicated to novel experimental techniques, and a fifth poster prize of £100 dedicated to modelling contributions.

Each delegate is allowed two votes for their preferred poster. You will be given a voting form during registration. Votes will be collected in a ballot box at the registration desk. Poster prize winners will be announced at the conference dinner on Wednesday evening. Good luck!

The posters can be displayed throughout the duration of the conference. All materials required to display your poster will be provided and can be collected from the registration desk. Please display your poster on the poster board allocated with your number. Posters must be taken down at lunchtime on Thursday 11th July.

Crystals in Art and voting

There are three Crystals in Art prizes which have been kindly sponsored by CGD. The prizes are: 1^{st} Prize is £100, 2^{nd} Prize is £75 and 3^{rd} Prize is £50.

Each delegate will vote for the Art submission they think should be recognised with a prize. You will be given a voting form during registration. Each delegate is allowed two votes. Votes will be collected in a dedicated ballot box at the registration desk. Crystals in Art prize winners will be announced at the conference dinner on Wednesday evening. Good luck!

The art work can be displayed throughout the duration of the conference. All materials required to display your work will be provided and can be collected from the registration desk. Please display your art work on the crystals in art poster board. Please make sure your art work is provided with a clear label including your name and art work title. Art work must be taken down at lunchtime on Thursday 11^{th} July.

Eating

London has an overwhelming choice of places to eat. The nearest "pub with grub" is The Windsor Castle, which backs onto the conference centre. There are a variety of eating places nearby in Baker Street, past 221B (which is between 239 and 241 for reasons that may elude Watson). However a walk through Regents Park (café serves breakfast) can take you to the diverse eateries of Camden (Greek, Argentian, Japanese, ...) and Drummond Street (Indian).

Exercise

Do explore Regents Park, which is right in front of the venue, and use it as a pleasanter route than walking along the Marylebone/Euston Road. The Rose Garden is particularly good at this time of year.

Travel

TFL can help with route planning around London on `https://tfl.gov.uk/plan-a-journey/`. Payments for underground or buses can be made with contactless cards on boarding a bus (flat fare), and entering and leaving underground or overground rail stations.

Conference Dinner

The conference dinner is organised at The Royal Society, 6-9 Carlton House Terrace, London SW1Y 5AG.

Online information on the venue can be found on:
`https://royalsociety.org/about-us/contact-us/carlton-house-terrace-london/`.

It starts with a reception with some light canapes at 6.30 pm in The City of London Rooms which overlook The Mall, with the meal at 7.00 pm. There will be a speech at the dinner after the main course. This will be followed by a prize giving ceremony after dessert over tea, coffee and petit fours. You will need your BACG conference badge to pass through the reception area.

Please allow at least 40 minutes for your journey, and consider allowing longer to enjoy the surrounding area. The official Transport for London fastest estimate from the conference venue is taking the 139 bus from Park Road/London Business School to Trafalgar Square and then walking is 35 minutes. Alternatives would be the underground from Baker Street to Piccadilly Circus and a short walk down Lower Regents Street. Going to Green Park allows a pleasant stroll through the parks via Buckingham Place, or to Oxford Street a chance to do some shopping as walking down Regents Street, but don't get lost in Hamleys toy shop.

Directions to the Rooms on Regent's Park

27 Sussex Place, Regent's Park

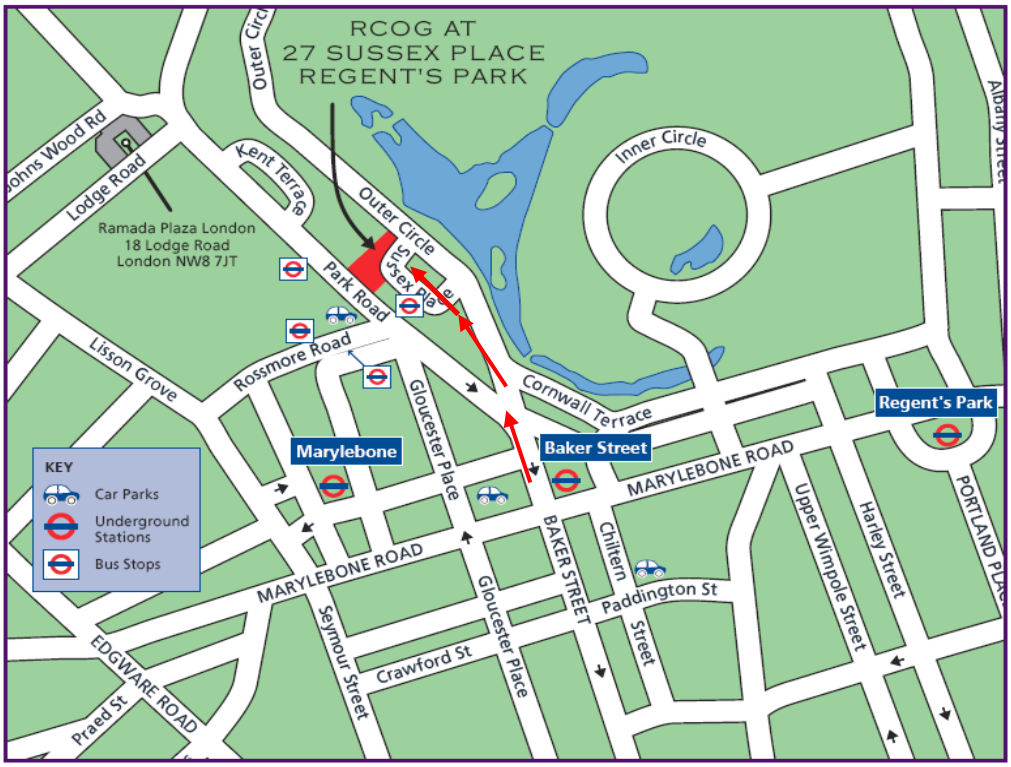
London

NW1 4RG

Tel: 0207 772 6-200
www.rcog.org.uk

- **By Train:** Marylebone mainline rail station is only a ten-minute walk Paddington, Euston; King's Cross-and St Pancras are also close by.
- **By Tube:** The nearest Underground station is Baker Street (served by the Hammersmith & City, Bakerloo, Circle, Jubilee and Metropolitan lines). ***Exit*** Transport for London ***Lost Property*** office.
- **By Bus:** The area is also well served by a number of different buses, including the numbers: 13, 82, 113, 139, 189 and 274.
- **By Car:** Car parking facilities are available at the NCP Park Road (24-hour) and on the Regent's Park Outer Circle (short-stay metered parking). For directions and route planner please see http://www.theaa.com/travelwatch/planner_main.jsp
- **NCP** Park Road information: www.londontown.com/LondonInformation/Travel/Park_Road_NCP/5341/

- → **From Baker Street Tube, walk down to the Outer Circle of Regent's Park, continue until you pass the London Business School (huge white building) and look out for the distinguish glass cones (see above picture)**



Underground station
Bus stop
Cycle hire
Cycle parking
Car parking
Disabled car parking
Information
Accessible toilets
Public toilets
Children's toilets and drinking fountain
Children's play area
Deckchair hire (seasonal)
Café
Seasonal Café
Restaurant
Drinking fountain
Viewing point
Road open to motor traffic and cyclists
Shared use pedestrian cycle way
Park features
Public access sites (opening periods vary)
Non public access sites
Jubilee Greenway
Cycling Permitted

WALKING DISTANCE (MINUTES) 5

SPORT & LEISURE

A wide range of sports are available in The Regent's Park and Primrose Hill including; tennis/netball courts, an athletics track, trim trail, cricket pitches and nets, softball, football and rugby pitches. In addition, there are four children's playgrounds and boating on the main lake.

THE HUB is a multi-sport venue for a host of community and sporting activities and is available for hire.

The Hub opens seven days a week at 8.30am and closes at 5.00pm during winter. Closing times vary during summer (9.00pm latest).

T: 0300 061 2323
E: thehub@royalparks.org.uk
www.royalparks.org.uk/parks/the-regents-park/things-to-see-and-do/the-hub-sports-facility

THE REGENT'S PARK TENNIS CENTRE provides high quality tennis facilities and is accredited by the Lawn Tennis Association. Coaching courses available for children and for adults. Floodlit courts and a padel court are available.

Three tennis courts at York Bridge are also marked out for netball. Four netball courts are available.

The café offers a selection of hot and cold food. Licensed for alcohol.

T: +44 (0)207 486 4216
E: regentspark@willtowin.co.uk
www.willtowin.co.uk

EATING & DRINKING

ESPRESSO BAR
Open daily from 8.00am, closing times vary seasonally.
T: +44 (0)20 935 5729

THE REGENT'S BAR & KITCHEN
Open daily, from 8.00am, closing times vary seasonally.
In winter the café closes at 4.00pm.
In summer closing times vary, the latest being 8.00pm between May and August.
T: +44 (0)20 7935 5729
E: regentspark@benugo.com
www.benugo.com/restaurants/the-regents-bar-kitchen

THE BOATHOUSE CAFE
Boats for hire for adults and children.
Open daily, from 9.00am. Closing times vary by month, between 4.00pm and 8.00pm seasonally.
T: +44 (0)20 7724 4069

THE BROAD WALK CAFE
Open daily from 8.00am.
Closing times vary seasonally.

THE HUB CAFE
Open daily, from 9.00am
(Monday's from 10.30am). In winter the café closes at 4.00pm. In summer closing times vary, the latest being 8.00pm between May and August.

QUEEN MARY'S GARDENS

Queen Mary's Gardens was originally used as a plant nursery while the park was under development as a residential estate. It was then laid out by Marnock and Burton as the Gardens of the Royal Botanic Society of London until disbanded in 1932 and much of the original structure remains.

Roses are not the only treasure of the Gardens. The Delphinium border has full National Collection status. The Mediterranean Borders are well established, and the Begonia Garden is twice yearly planted with seasonal bedding. Shrubberies are strategically designed and located to add a sense of mystery and privacy to the Gardens.

THE ROYAL PARKS ARE

Bushy Park
The Green Park
Greenwich Park
Hyde Park
Kensington Gardens
The Regent's Park & Primrose Hill
Richmond Park
St James's Park
Brompton Cemetery
Grosvenor Square
Victoria Tower Gardens

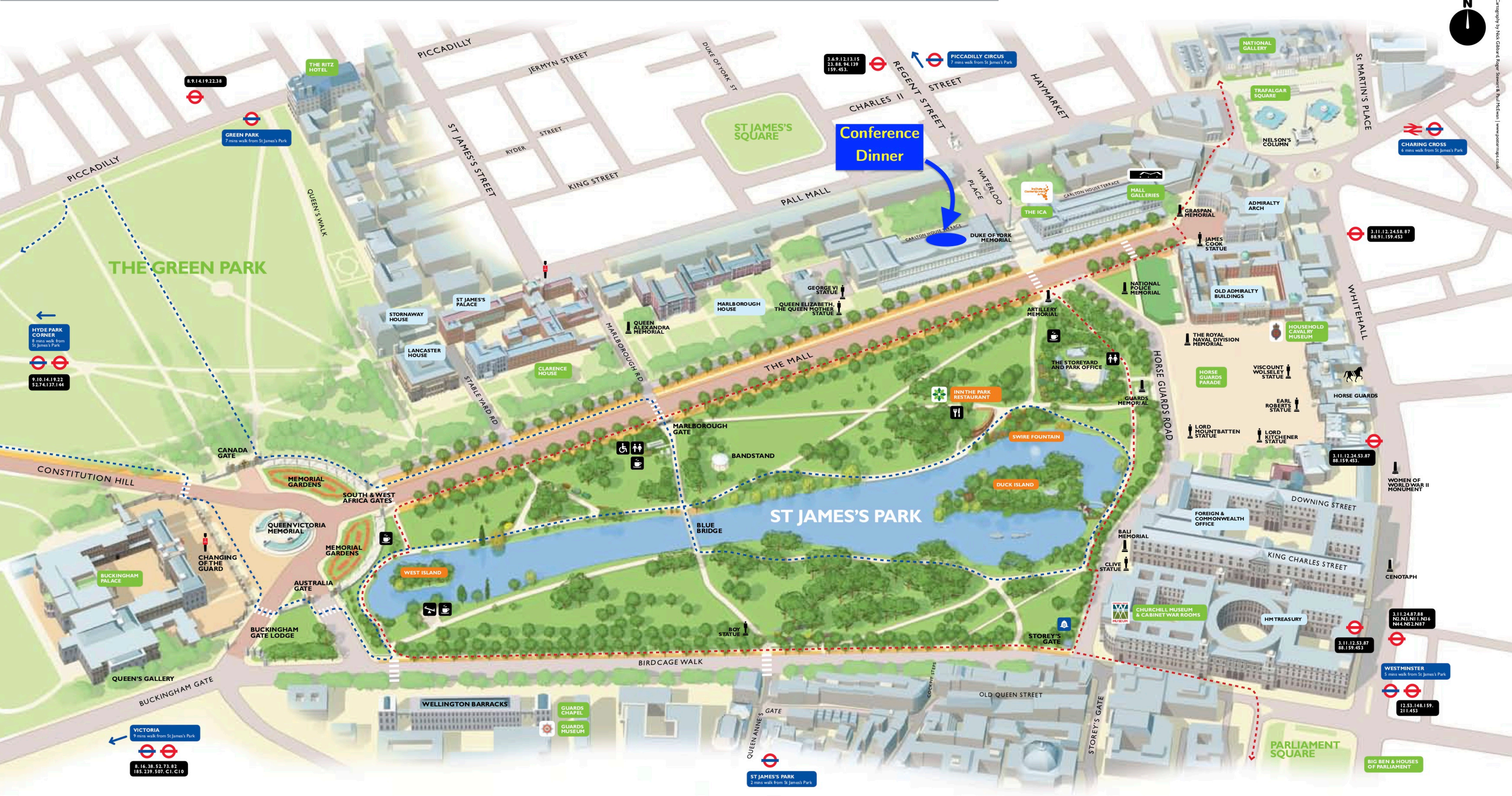
PARK MANAGEMENT
Nick Biddle
The Storeyard, Inner Circle, Regent's Park, London NW1 4NR
T: 0300 061 2300
E: regents@royalparks.org.uk

CONTACTING POLICE

T: 999 for emergencies.
T: 101 for other calls.
You can also report a crime online at www.online.met.police.uk

The park is open from 5.00am to dusk all year round. The following park roads are closed between midnight and 7.00am: Outer & Inner Circle, Park Square East & West, York Gate, Hanover Gate, Macclesfield Bridge, Chester Road.

THE ROYAL PARKS
www.royalparks.org.uk



Register for Royal Parks updates
www.royalparks.org.uk/registerstjames

Underground Station
Bus Stop
Railway Station
Pedestrian Crossing
Police Station
Horse Guards
Guards
Statue
Memorial
Disabled toilets
Public Toilets
Kiosk
Children's Play Area
Restaurant
Jubilee Walkway
Diana Princess of Wales Memorial Walk
Public access sites (opening periods vary)
Non public access sites
Park features

WALKING DISTANCE (MINUTES) 1 2

A BRIEF HISTORY OF ST JAMES'S PARK

1531	Acquired by Henry VIII and Court of St James established
1603	Park laid out for James I with menagerie and duck decoys
1660	Park relandscaped for Charles II in formal French style
1663	Horseguards constructed
1667	Exotic birds introduced, including pelicans
1703	Buckingham House developed which later became the official Royal residence
1827	John Nash appointed to carry out present landscape in informal style for George IV
1905	Queen Victoria Memorial Garden created

FAMOUS LANDMARKS

BUCKINGHAM PALACE has served as the official London residence of Britain's sovereigns since 1837. Changing of the Guard takes place at 11:30am every day in the summer, and alternate days in the winter.

CLARENCE HOUSE was designed by John Nash and built between 1825 and 1827 for the Duke of Clarence, later William IV. It was the London home to the late Queen Elizabeth, The Queen Mother.

QUEEN VICTORIA MEMORIAL is a 25 metre (82ft) high edifice by the sculptor Thomas Brock and the architect Aston Webb. The whole edifice and statues are of white marble, of which a generous 2,300 tons were used.

ST JAMES'S PALACE was built by Henry VIII alongside his newly acquired deer park in 1532. It is still the official Royal Court.

ICA GALLERIES are home to the best new art and culture from Britain and around the world.

MALL GALLERIES is central London's focal point for new figurative art by living British artists.

HORSE GUARDS PARADE is the park's ceremonial parade ground and is the scene of Trooping the Colour on the Queen's official birthday in June. The Lifeguard change takes place here at 11:00am daily and 10:00am on Sundays.

ST JAMES'S PARK LAKE is the centrepiece of the park's romantic landscape. It is the home to the park's collection of waterfowl including the famous pelicans.

DUCK ISLAND is a nature reserve for the park's bird collection. It also houses the water treatment facilities and pumps for the lake and fountain.

INN THE PARK RESTAURANT is where you can feast on the best of British food using the freshest seasonal produce from small independent producers.

THE CHURCHILL MUSEUM & CABINET WAR ROOMS are dedicated to the life of the 'greatest Briton'. The secret underground headquarters were the nerve centre of Britain's war effort.

THE GUARDS MUSEUM contains a wealth of information and artefacts relating to the five regiments of Foot Guards.

THE ROYAL PARKS OF LONDON

PARK MANAGEMENT

Mr Mark Wasilewski

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METROPOLITAN POLICE

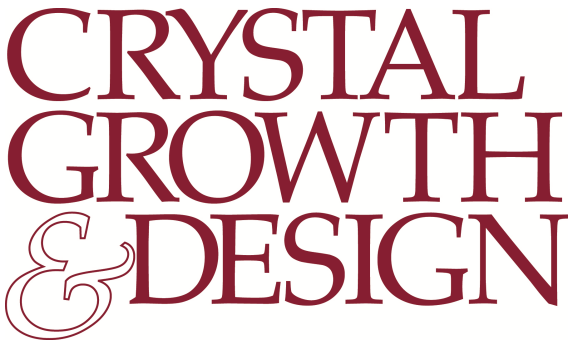
Storey's Gate Lodge, St James's Park
London SW1A 2BJ

T: 999 for emergencies.
T: +44 (0) 20 7706 7272 for non-emergencies within the park.

The park is open from 5am until midnight.

THE ROYAL PARKS

www.royalparks.org.uk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