CGOM15

BOOK OF ABSTRACTS

THE 15TH INTERNATIONAL WORKSHOP ON
CRYSTAL GROWTH OF ORGANIC MATERIALS

JULY 23-26, 2024 | PHUKET, THAILAND

DISCLAIMER

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WELCOME TO CGOM15

We are happy to welcome all participants to the 15th International Workshop on Crystal Growth of Organic Materials in Phuket, Thailand. This is the 15th meeting of CGOM, a biennial International meeting for those interested in the scientific and engineering aspects of crystallization, with previous meetings taking place in Belgium (2022), South Korea (2018), England (2016), Japan (2014), Republic of Ireland (2012), Singapore (2010), The Netherlands (2008), France (2006), Scotland (2003), England (1999), Germany (both 1994 and 1996), Scotland (1992) and Japan (1990). In this year's meeting we have a diverse set of international speakers and presenters from around the world, including Australia, Austria, Belgium. China, France, Germany, India, Italy, the Republic of Ireland, Japan, Korea, Singapore, Taiwan, the United Kingdom, the United States of America, and Thailand. We hope that we can maintain the high scientific quality and friendly atmosphere of these earlier editions of CGOM!

CGOM aims to cover all significant topics concerning crystallization of organic species including basic understanding of mechanism involved in crystallization such as nucleation and crystal growth, topics related to crystal structure and packing including polymorphism and multicomponent crystals, applications of crystallization for industrial uses such as its use in separation and purification operations and enantio-separations, as well as crystallizer design and optimization. We have Plenary Lectures from Professor Gérard Coquerel (University of Rouen) and Professor Hongxun Hao (Tianjin University) along with five eminent Invited Speakers (Dr. Doris Braun, Professor Jerry Heng, Professor Hiroshi Takiyama, Professor Woo-Sik Kim, and Professor Pramoch Rangsunvigit), four Tutorial Workshops, thirty-five Oral Presentations and thirty-three poster presentations.

We hope that all participants are inspired and motivated by the wide collection of research in crystallization that is being presented at CGOM, and that the meeting might provide a springboard for exchange of ideas and collaboration between the many groups who are attending. The meeting will provide an opportunity to engage with long-term friends and colleagues in the field but can also present an opportunity to create new friendships and bonds between researchers. In addition, the Organizing Committee sincerely hope that you have time to enjoy the natural beauty and charm of Phuket as well as its vibrant culture.

We hope all participants have a memorable and enjoyable time at CGOM15!

ADRIAN FLOOD · LEK WANTHA

on behalf of the Organizing Committee of CGOM15

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SCIENTIFIC PROGRAM

Tuesday 23rd, July 2024

12:00-20:00	Registration Desk Open
Tutorials and Workshop	
Session Chair: Lek Wantha	
13:30-14:30	O.08 - Thermodynamics of Crystals in Solution - ***Adrian Flood*** (Vidyasirimedhi Institute of Science and Technology, Thailand)
14:30-15:30	O.09 - Seeding - ***Jerry Heng*** (Imperial College London, UK)
15:30-15:55	Coffee Break
Session Chair: Adrian Flood	
15:55-16:55	O.10 - Process Analytical Technology (PAT) in Crystallization - ***Huaiyu Yang*** (Loughborough University, UK)
16:55-17:55	O.11 - Navigating the Complexities of Crystallisation with CrystalGrower - ***Nathan de Bruyn*** (CrystalGrower Ltd., UK)
18:00-20:00	**Welcome Reception** at Room Chom Talay

Wednesday 24th, July 2024

Session Chair: Lek Wantha	
08:40-08:50	Opening Ceremony
08:50-09:30	O.02 - Molecular Mechanism of Crystal Nucleation of Small Organic Molecules from Solution (Plenary Lecture) - ***Hongxun Hao*** (Tianjin University, China)
09:30-10:00	O.04 - BioCrystallisation (Invited Lecture) - ***Jerry Heng*** (Imperial College London, UK)
10:00-10:25	Coffee Break
Session Chair: Jerry Heng, Dhanang Edy Pratama	
10:25-10:45	O.12 - Growth "Self-Inhibition" of Irbesartan Desmotrope: Surface Intra-annular Tautomer Inter-conversion is the Culprit - ***Xiang Kang*** (Tianjin University, China)
10:45-11:05	O.13 - Symmetry-Breaking and Symmetry-Retaining Morphological Evolution of the Single Crystals of Cyclodextrin Metal-Organic Frameworks - ***Jiayin Zhang*** (Tianjin University, China)
11:05-11:25	O.14 - Deconstructing the Full 3D Facetted Growth Rates from the Temporal Capture of Crystal Growth through In-Situ Optical Microscopy - ***Cai Ma*** (University of Leeds, UK)
11:25-11:45	O.34 - Xylitol Nucleation in the Melt: Supercooling Rupture by Stirring - ***Denis Mangin*** (Université Lyon, France)
11:45-12:05	O.32 - Crystal Shape and Topography: Prediction and Optimisation with the CrystalGrower Model - ***Alvin Jenner Walisinghe*** (Curtin University, Australia)
12:05-12:25	O.33 - Integrating Docking-Based Screening Method for Impurities, within CrystalGrower Computational Workflow to Model and Control Crystal Growth for Advanced Process Design - ***Susi Cuccurullo*** (University of Manchester, UK)
12:25-14:00	Lunch Break, Exhibition & Poster Session
Session Chair: Koichi Igarashi, Cai Ma	
14:00-14:30	O.06 - How Does the Fluid Motion Affect the Crystallization? (Invited Lecture) - ***Woo-Sik Kim*** (Kyung Hee University, Korea)
14:30-14:50	O.28 - Digital Design of Intensified Crystallization Systems - ***Zoltan K. Nagy*** (Purdue University, USA)
14:50-15:10	O.31 - Numerical Simulation of Hydrodynamic and Particle Suspension Performance in a Novel Stirred Tank - ***Mingyu Chen*** (Tianjin University, China)
15:10-15:30	O.27 - Evaluation Models of Solvent Effect on the Dissolution and Crystallization Process of Aripiprazole - ***Xin Huang*** (Tianjin University, China)
15:30-15:50	O.29 - Shaping Crystals with Fundamental and Informatics Tools. Using Particle Informatics to Understand Growth Rates - ***Pietro Sacchi*** (The Cambridge Crystallographic Data Centre, UK)
15:50-16:15	Coffee Break
Session Chair: Huaiyu Yang, Hiroshi Takiyama	
16:15:16:35	O.30 - Stabilization and Coagulation of Colloidal Suspensions during Crystallization - ***Xiongtao Ji*** (Tianjin University, China)
16:35-16:55	O.36 - Growth of Organic Crystal Scintillators for High Energy Neutron Detection - ***Rajesh Paulraj*** (Sri Sivasubramaniya Nadar College of Engineering, India)
16:55-17:15	O.37 - 2D Elastic Organic Crystals with Thermomechanical/Acid Responses and Dual-Mode Optical Waveguides - ***Yang Ye*** (Tianjin University, China)
17:15-17:35	O.38 - Flexible Organic Crystal with Two-Dimensional Elastic Bending and Recoverable Plastic Twisting for Circularly Polarized Luminescence - ***Bo Jing*** (Tianjin University, China)
17:35-17:55	O.35 - The Synergy of Computation and Experiment in Solid-State R&D - ***Guangxu Sun*** (XtalPi)

Session Chair: Adrian Flood	
08:40-09:20	O.01 - Novel Processes for Chiral Symmetry Breaking (Plenary Lecture) - ***Gérard Coquerel*** (University of Rouen Normandy, France)
09:20-09:50	O.03 - Streamlining Pharmaceutical Molecule Cocrystallization (Invited Lecture) - ***Doris Braun*** (University of Innsbruck, Austria)
09:50-10:10	O.23 - Trimesic Acid as a Building Block for Ternary and Quaternary Cocrystals - ***Lamis Alaa Eldin Refat*** (University of Galway, Ireland)
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Session Chair: Kevin Roberts, Pui Shan Chow	
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10:55-11:15	O.40 - Structure Investigation of A Novel Organocobalt Complex of B12 Model - ***Jie Liu*** (University of Warwick, UK)
11:15-11:35	O.17 - Grain and Domain Microstructure in Long Chain N-Alkane and N-Alkanol Wax Crystals - ***Emily Wynne*** (University of Leeds, UK)
11:35-11:55	O.22 - Crystal Regeneration Post-Breakage: Effect of Solvent Selection, Multiple Breakage Sites, and Surface Growth Kinetics - ***Deniz Etit*** (Imperial College London, UK)
11:55-12:15	O.21 - Polytypism of Pharmaceutical Nanocrystals Investigated with 3D Electron Diffraction - ***Mauro Gemmi*** (Istituto Italiano di Tecnologia, Italy)
12:15-14:00	Lunch Break, Exhibition & Poster Session
Session Chair: Gérard Coquerel, Woo-Sik Kim	
14:00-14:30	O.05 - Operation Design of Reactive Crystallization for the Quality Improvement of Crystalline Particles (Invited Lecture) - ***Hiroshi Takiyama*** (Tokyo University of Agriculture and Technology, Japan)
14:30-14:50	O.15 - Improvement of Dissolution Rate and Tablet Performance of the Antiepileptic Drug Gabapentin Using a Multicomponent Crystal - ***Chenyang Zhao*** (Tianjin University, China)
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15:10-15:30	O.18 - New Insights into the Solubilization of Multicomponent Crystals: A Case Study of Pipemidic Acid - ***Chuanhua Wu*** (Tianjin University, China)
15:30-15:50	O.24 - Optimization in Expression and Crystallization of Cry Protein from Bacillus - ***Thuringiensis Zhichun Lin*** (Loughborough University, UK)
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16:55-17:15	O.20 - Kinetics of the Mechanically Induced Ibuprofen-Nicotinamide Co-Crystal Formation by In-Situ X-Ray Diffraction - ***Lucia Casali*** (BAM, Germany)
17:15-17:35	O.25 - Crystallisation of Molecuar Solids via Sublimation – An Uncommon Technique with Tremendous Potential - ***Ciaran O'Malley*** (University of Limerick, Ireland)
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Friday 26th, July 2024

Session Chair: Hongxun Hao, Doris Braun	
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09:30-09:50	O.42 - Preferential Crystallization Assisted by Supercritical CO2 - ***Joséphine de Meester*** (UCLouvain, Belgium)
09:50-10:10	O.44 - Green Technology for Salt Formation: Slurry Reactive Crystallization Studies for Papaverine HCl and 1:1 Haloperidol–Maleic Acid Salt - **Dhanang *Edy Pratama*** (National Central University, Taiwan)
10:10-10:30	O.46 - Preparation of Multifunctional Water Treatment Agents for Crystallization Scale Inhibition, Corrosion Inhibition and Sterilization - ***Jianxin Chen*** (Hebei University of Technology, China)
10.30-10.55	Coffee Break
Session Chair: Lek Wantha	
10:55-11:15	O.41 - Shifting Enzyme-Catalyzed Reaction Equilibrium - ***Camila Caro Garrido*** (UCLouvain, Belgium)
11:15-11:35	O.45 - Accelerating the Drying Process by Spherical Agglomeration: The Case of Benzoic Acid - ***Rosyid Shidiq Hidayatulloh*** (National Central University, Taiwan)
11:35-12:00	**Closing Remarks**

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ORAL PRESENTATION

+ PLENARY AND INVITED LECTURES

Novel Processes for Chiral Symmetry Breaking

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Abstract: Macroscopic chiral symmetry breaking refers to as the process in which a mixture of enantiomers departs from 50–50 symmetry to favor one chirality, resulting in either a scalemic mixture or a pure enantiomer. In this domain, crystallization offers various possibilities, from the classical Second Order Asymmetric Transformation (SOAT), Viedma ripening or Temperature Cycle-Induced Deracemization (TCID) to the famous Kondepudi experiment and then to so-called Preferential Enrichment. These processes, together with some variants, will be depicted in terms of Mechanisms, thermodynamic pathways, departure from equilibrium and operating conditions. Influential parameters on the final state will be reviewed as well as the impact of kinetics of the R ⇔ S equilibrium in solution on chiral symmetry breaking. How one can control the outcome of symmetry breaking is examined. Several open questions are detailed and different interpretations are discussed.

As the system departs more from equilibrium, the mechanical stress imposed on the system has to be softened in order to observe the spontaneous chiral symmetry breaking. Indeed, in Viedma ripening performed close to equilibrium, all sorts of abrasions, breakages, defects induced by shear forces, etc., are beneficial to the advancement of chiral symmetry breaking. In the Kondepudi experiment, the mechanical stress must be softer to avoid primary and secondary heteronucleation in the system. In the case of Preferential Enrichment (PE), the very large departure from equilibrium has to be associated with almost stagnant conditions. Indeed, for the latter case a simple magnetic stirrer is sufficient to return the solution to normal conditions of crystallization without macroscopic chiral symmetry breaking.

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Keywords: Static ad dynamic Recognition of molecular handedness, kinetics and thermodynamics.

Molecular Mechanism of Crystal Nucleation of Small Organic Molecules from Solution

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Abstract: As a key step and initial stage of crystallization, crystal nucleation determines the structure and morphology of crystal product, and thus affects the product quality and material performance. However, because of the complexity of flexible small molecules, the molecular mechanism of small flexible molecules nucleation is still not well understood, which affects the design and preparation of corresponding crystal products. Therefore, it is necessary to explore the crystal nucleation mechanism of flexible small molecules to achieve precise preparation of polymorphs. Tolbutamide and 5-nitrofurazone were used as model compounds to explore the molecular mechanism of nucleation from solution by using spectroscopic analysis and molecular simulation techniques. Firstly, the molecular conformation and inter/intra-molecular interactions in the different solutions were studied. It was found that multi conformations and different aggregates could exist in the solution, although the distribution of them might change with different operating conditions. Then, the molecular mechanism of nucleation of flexible small molecules was studied. By nucleation induction period experiments, spectral analysis, and molecular simulation, it was found that the same molecule could undergo different nucleation pathway under different conditions. Solvent-solute effect could affect the conformation and assembly of molecules, thus affecting the resulting polymorphs of crystals. The structural similarity between the molecular aggregates in solution and the final product, the solvent-solvent interaction, and the free energy of solvation all affect the nucleation process.

Keywords: Nucleation, conformation, organic molecules, aggregates.

Streamlining Pharmaceutical Molecule Cocrystallization

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Abstract: Developing drug products requires precise control over the physical properties of active pharmaceutical ingredients (APIs). Utilizing multi-component phase systems, like cocrystals, offers a means to enhance critical physicochemical properties of APIs, such as stability and solubility[1,2]. However, predicting which coformers will form cocrystals with a specific compound is challenging. Additionally, cocrystals can exhibit polymorphism, existing in different ratios of API:coformer, and may contain solvents (solvates) or water (hydrates). Both computational[3,4] and experimental techniques[5] have been developed to estimate cocrystal formation and synthesize cocrystals. However, there is limited consistency in the application of the proposed protocols, especially as numerous methods can be employed to produce cocrystals. Common approaches include solvent-based methods, neat and liquid-assisted grinding, as well as contact preparation, hot-melt extrusion, freeze-drying, spray drying techniques, etc., all of which have been used successfully. Consequently, the current state-of-the-art cocrystal discovery remains a time-consuming process. This talk aims to provide new insights into cocrystal screening and the solid form landscapes of cocrystals of model pharmaceuticals.

Metronidazole cocrystals were employed for evaluating commonly used virtual cocrystal screening methods, including assessments of molecular complementarity, multi-component hydrogen bond propensity, and molecular electrostatic potentials. This allowed for the identification of both the strengths and limitations inherent in the readily available virtual tools[6]. Carbamazepine, acetylsalicylic acid, and acetaminophen were selected as test compounds to assess crystal structure prediction (CSP) for cocrystal screening against a range of potential coformers, to ascertain the most stable cocrystal form, and to evaluate the feasibility of cocrystallization[4]. Finally, the cocrystal landscapes of dapsone[7] were systematically elucidated using state-of-the-art approaches. The combined experimental and computational screening led to the discovery of novel multicomponent solid-state forms and provided insights into their stability order.

Overall, the significance of employing a combination of computational and analytical techniques to gain a deeper understanding of cocrystal formation and cocrystal stability will be discussed, allowing finally to assess the potential of specific cocrystals for the use in pharmaceutical products.

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Keywords: Cocrystallization, solid-state forms, experimental and virtual cocrystal screening, crystal structure prediciton, stability.

BioCrystallisation

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Abstract: The purification of high molecular weight new modalities such as proteins and peptides, for their use in biopharmaceutical drug therapeutics, can still account for a significant proportion of the drug development cost. However, advances in the optimisation of crystallisation conditions have seen significant increase in the scalability of peptide/proteincrystallisation. Crystallisation remains an attractive isolation step for pharmaceutical products due to its unique ability to purify and control other properties such as particle size distribution, morphology, and polymorphism. In addition, crystallisation offers pharmacokinetic advantages such as better release control and higher bioavailability, and lower impurity loading. This talk will focus on my group's recent efforts to control nucleation and crystallisation of complex macromolecules such as proteins and homo-peptides; using 3D-nanotemplates for a range of model proteins (eg thaumatin, con A, catalase, etc) and the use of soft templates (eg amino acids) for insulin and the crystallisation behaviour of simple short-chain peptides. For peptides, the effects of chain length and thermodynamic properties (eg solubility) is determined to establish a rational design of the crystallisation conditions using glycine homopeptides as a model. The talk will also present results from our solubility studies for simple peptides in single and binary solvent mixtures, the effect of sequence and protection groups on solubility of peptides, and finally discussing their crystallisation behaviour in the absence and presence of templates. This talk will provide some insights into the challenges and opportunities in crystallisation as a purification unit process for proteins and peptides.

Keywords: Crystallization, nucleation, proteins, peptides.

Operation Design of Reactive Crystallization for the Quality Improvement of Crystalline Particles

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Abstract: Some organic crystals used in pharmaceuticals have complex external shapes, such as sea urchin-like. However, such crystals are avoided due to concerns about crystal quality, such as morphology, particle size distribution and purity. To improve the quality of crystalline particles, establishment of built-in quality method is needed. Seeding method is used as one of method to built-in quality for size distribution. The inner seeding method has an advantage because generates seed crystals without contamination within the crystallizer. One method of producing inner seed is to use modulation operation in the initial stage of crystallization operation[1,2]. Particularly the modulation operation with undersaturation may have the effect of disintegrating agglomeration by dissolving the sea urchin-like crystals. Furthermore, it has been reported that modulation operation with undersaturation is also effective in improving the external shape[1]. Therefore, the goal of this study is to investigate modulation operation with undersaturation and the use of inner seed to build-in quality. The conceptual diagram is shown in **Fig. 1**.

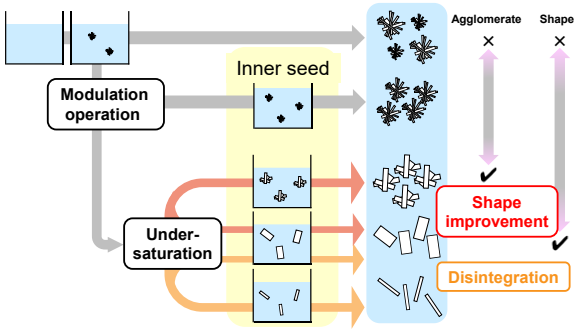

Fig. 1 Conceptual diagram of strategy for quality improvement.

The effect of modulation operation with undersaturation on the external shape was investigated. The reaction system was L-Aspartate sodium (L-AspNa) - HCl, the target was L-Aspartic acid (L-Asp). The modulation operation with undersaturation was performed by alternately adding L-AspNa solution or HCl solution at pump. The total amount of L-AspNa and HCl substance in all experiments was remained constant.

First, modulation operation was performed to produce inner seed, but the degree of agglomeration was worse than that of control experiment without producing inner seed. The dissolution of sea urchin-like crystals was observed using a growth cell[3] to investigate why disintegration did not occur.

The modulation operation was changed to increase the amount of inner seed, the percentage of product crystalline particles classified as high agglomeration was improved. When modulation operation by intermittent solution addition was also introduced to grow the inner seed, the generation of sea urchin-like crystals was suppressed.

It was found that the external shape of crystalline particles can be improved by modulation operation of producing inner seed, and the particle size distribution can be improved by devising a method of producing seed crystals.

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Keywords: Reactive crystallization, modulation operation, agglemeration.

How Does the Fluid Motion Affect the Crystallization?

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Abstract: The crystallization is frequently used for purification and crystalline materials processing in areas of pharmacuetical, food, and fine chemical industires. In the crystallization, the fluid motion gives an great influence not only on uniformity of concentration and temeprature but also on the nucleation and growth of crystal in the crystallizer. Particularly, fluid motions of Taylor vortex (TVF) and Batchelor vortex flows (BVF) induce the new phenomena in crystal nucleation, growth and agglomeration, which are not attainable by tranditional random fluid motion. TVF and BVF are periodic pair-wise toroidal circular fluid motions generated in the gap between two boundaries, of which one is rotated and the other is stationary. In polymorphic crystallization of SMZ, TVF induces a strong molecular alignment effect and so directly nucleates the stable form-I. In contrast, the randon turbulent eddy flow (TEF) first nucleates the metastable form-II of SMZ and then tranforms it to the stable form-I, as following Ostwald's Rule of Stage. In the cocrystallization of CAF and MA, similarly, the stable (1:1) cocrystal is directly nucleated in BVF, whereas the metastable (2:1) cocrystal is first generated and then shifted to the stable (1:1) cocrystal in TEF. In addition, the homo-chiral nucleation of $NaClO_3$ is induced in TVF, resulting in 100% chiral symmetry breaking at the induction point. Meanwhile, the chiral-mixture nucleation occurs in TEF, resulting in the no chiral symmetry breaking. The manss transfer in TVF is high, resulting in the fast phase transformation. So, the crystallization of GMP in TVF is 10~20 times higher productive than that in TEF. Also, the toroidal fluid motions of TVF and BVF are highly effective for the crystal agglomeration. So, they produced the spherical agglomerates of $(Ni/Mn/Co)(OH)_2$ with high tap density in the reaction crystallization. In this presentation, the new impact of the periodic fluid motion on the crystallization is addressed.

Keywords: Periodic fluid motion, taylor vortex, batchelor flow, polymorphic crystallization, agglomeration, chiral symmetry breaking.

Environmentally Friendly Gas Storage with Hydrate Technology

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Abstract: Hydrates offer a promising solution for natural gas storage and transportation, and carbon dioxide capture and storage, although their slow formation rate and high energy requirements have impeded commercialization efforts. To address these challenges, researchers have explored the use of promoters such as tetrahydrofuran (THF) and sodium dodecyl sulfate (SDS). While THF accelerates hydrate formation, SDS can lead to undesired foam formation.

This study investigates the efficacy of three amino acids—valine, methionine, and leucine—as promoters for methane hydrate formation. Our findings demonstrate that all three amino acids exhibit varying degrees of promotion, with some surpassing the performance of SDS. Optimal concentration levels of amino acids emerge as a critical factor for effective promotion. Importantly, the utilization of amino acids as promoters presents an eco-friendly approach devoid of foam formation, making them an appealing alternative to SDS.

Furthermore, this research sheds light on the morphology of the resulting hydrates, providing valuable insights for the advancement of hydrate formation systems. In conclusion, our results strongly indicate that amino acids hold significant potential as highly effective promoters for hydrate formation, potentially paving the way for the commercialization of this environmentally sustainable gas storage technology.

Thermodynamics of Crystals in Solution

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0.08

Abstract: Industrial crystallization from solution is a vital process in many industries including those involving minerals processing, petrochemicals, food products, consumer products, agricultural chemicals and pharmaceuticals, among others. The solubility of different solid species in a solution is vital information for the design of industrial crystallization units. The range of species involved is very wide, and the types of solid phases present in industrial process is also numerous, however a thermodynamic understanding of all potential systems can be achieved with a relatively small range of thermodynamic theory.

This short course presents an overview of the phase equilibria of crystals in solution including measurement techniques, types of phase diagram and thermodynamic modeling of solid-liquid phase equilibrium. The types of crystalline species considered will include free molecules, hydrates and solvates, cocrystals, salt forms, adducts such as clathrates, and solid solutions. Other characteristic thermodynamic properties of solid-liquid systems such as freezing point depression will also be covered. The course will focus on accurate thermodynamic models including analysis of both ideal and non-ideal systems.

Keywords: Crystallization, phase equilibrium, solid-liquid equilibrium, thermodynamic models.

Seeding

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0.09
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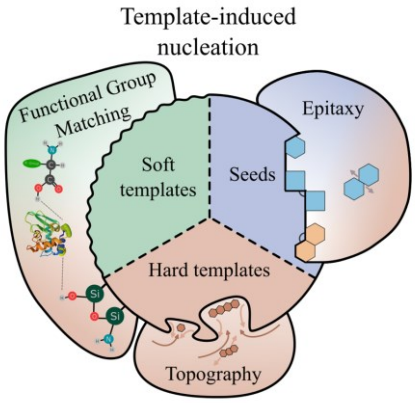
Abstract: The initial formation of crystalline nuclei remains the critical barrier to success and these approaches can be time consuming. Major efforts have been done to facilitate and control nucleation by controlling factors such as concentration, temperature, pH, precipitants, additives, and detergents. The use of external stimuli, such as an electric or magnetic field, ultrasonication, microgravity, etc has also been explore. Amongst these approaches, seeding represents a critical step in optimising crystallisation process. Seeding, in its most basic form, refers to the addition of crystals of the desired solute, generated from previous crystallisation experiments, into a supersaturated, but metastable, solution. The seeding method involves utilising either macromolecular crystalline seeds, dissolved additives (soft templates), or undissolved additives (hard templates). The underlying principles of these methods primarily rely on three fundamental mechanisms: functional group matching, epitaxy, and topographical effects, all of which are extensively discussed in this chapter. By controlling the supersaturation and the mass of crystal seeds added, one can prevent excessive primary or secondary nucleation and promote growth of the seeds. Such a process has been used ubiquitously for small molecules, as it allows for enhanced control of the crystallisation process. The size distribution of the seeds can be controlled via sieving or equivalent methods to ensure that seeds are as monodisperse as possible, which in turn allows for further control over the final size of the crystals grown in the seeded experiment. In this lecture on seeding, aspects of crystal nucleation, yield, understand the importance of seeding, seed quality, cross-seeding and crystallisation methods employed will be discussed.



Keywords: Nucleation, crystallisation, CNT, seeding, yield.

Process Analytical Technology (PAT) in Crystallization

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Abstract: Process Analytical Technology (PAT) has been defined by the United States Food and Drug Administration (FDA) to design, analyze, and control pharmaceutical manufacturing processes by measuring critical process parameters (CPP) that impact critical quality attributes (CQA). PAT plays a important role in crystallisation processes, which is a critical purification process in pharmaceutical manufacturing.

This comprehensive tutorial will delve into the role of Process Analytical Technology (PAT) in deepening our understanding of complex crystallisation processes. We will explore a range of analytical techniques including focused beam reflectance measurement (FBRM), particle video microscopy (PVM), and in-situ infrared (IR) and Raman spectroscopy. FBRM can be employed to estimate particle size distribution, providing insights into the growth dynamics of crystals. PVM offers a visual observation of the solution conditions, allowing for real-time monitoring of crystal formation and behavior. In-situ IR and Raman spectroscopy can be utilized to measure concentrations within the solution, helping to determine the supersaturation levels and the presence of impurities.

The tutorial will include some case studies demonstrating how these analytical tools are applied in various systems. We will examine the crystallization processes of small organic molecules in both homogeneous environments and complex scenarios involving oiling out and liquid-liquid phase separation systems. Additionally, we will explore the crystallization of protein molecules, highlighting specific challenges and observations unique to biological substances.

We will also discuss the limitations of these PAT tools. This includes potential issues with sensitivity, resolution, and the interpretability of data in complex mixtures, as well as the practical aspects of integrating these technologies into existing pharmaceutical manufacturing processes. Finally, Finally, we will look ahead to the future developments and potential advancements in PAT tools. This tutorial aims to help researchers and practitioners to effectively employ PAT in enhancing product quality and consistency in pharmaceutical crystallisation development.

Keywords: Crystallization, PAT, FBRM, PVM, in-situ IR, Raman.

Navigating the Complexities of Crystallisation with Crystal*Grower*

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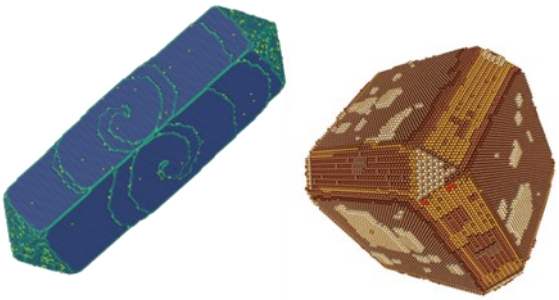
Abstract: Crystallisation, a fundamental yet intricate process, plays a crucial role in material science and industry. Despite its significance, understanding the multifaceted dynamics of crystallisation remains a challenge due to the myriad of parameters influencing the process. Small changes, such as altering the solvent, can drastically affect various factors including the free energy between building units, supersaturation levels, diffusion rates, and thermodynamic properties. Grasping these interconnections is essential for advancing in the field.

The CrystalGrower Workshop is designed to demystify the complexities of crystallisation through a hands-on, problem-solving approach. Utilizing the CrystalGrower software, participants will explore the journey of crystallisation from the foundational concepts of individual building units to the practical implications of growing crystals for industrial applications. This workshop aims to equip attendees with a deep understanding of crystallisation processes and the proficiency to employ CrystalGrower in addressing real-world challenges.1–3

Participants will engage in a series of tutorials covering a broad spectrum of topics, including:

- Defining and manipulating building units.
- Analysing the impact of various interactions on crystallisation.
- Investigating solvent effects on crystal growth.
- Conducting morphology mapping to predict crystal shapes.
- Understanding the relationship between growth rates, thermodynamics, and crystal morphology.
- Applying seed engineering techniques to control crystallisation outcomes.

By the conclusion of this workshop, attendees will have acquired the knowledge and skills necessary to navigate the complexities of crystallisation, leveraging CrystalGrower to innovate and solve problems. This workshop is suited for researchers, academicians, and professionals seeking to enhance their expertise in crystallisation science and its applications.



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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.

P. R. Spackman, A. J. Walisinghe, M. W. Anderson and J. D. Gale, Chem. Sci., 2023, 14, 7192–7207.

Keywords: Cocrystallization, solid-state forms, experimental and virtual cocrystal screening, crystal structure prediciton, stability.

Growth "Self-Inhibition" of Irbesartan Desmotrope: Surface Intra-Annular Tautomer Inter-conversion is the Culprit

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0.12

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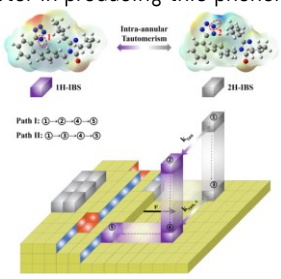
Abstract: The phenomenon of growth self-inhibition of tautomeric crystals was discovered recently when coexisting minor tautomer(s) function as native inhibitors, even in a highly supersaturated condition. This discovery opens up new opportunities to tailor diverse crystalline materials for superior properties such as electronic, magnetic, and/or optical properties, and thus is crucial for crystal engineering. More importantly, it provides valuable insights for the production of tautomeric drug molecules that have been prescribed for HIV, epilepsy, COVID-19, schizophrenia, cancer (e.g., skin, lung, and pancreatic), and other diseases that impact millions of people worldwide. In this contribution, we generalize this phenomenon to the desmotropes (or tautomeric polymorphs) of irbesartan drug that shows intra-annular tautomerism. Our results unveil the dynamic inter-conversion between tautomers on the surface is the essential factor in producing this phenomenon.



Scheme 1

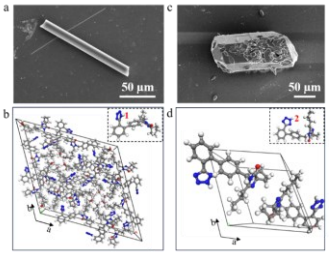


Figure 1

Irbesartan (IBS) is an active pharmaceutical ingredient in Avapro and Avalide used to treat hypertension acting as Angiotensin II receptor inhibitors. Hypertension is responsible for more than 10 million people of deaths worldwide each year and has a high prevalence of over 30%, especially in the elderly. Irbesartan is known to exist in two desmotropes (form A and form B) that involve an intramolecular proton transfer on the tetrazole ring in two crystal structures, leading to changes in the overall molecular conformation and supramolecular interactions, ultimately resulting in tautomeric polymorphism. Herein, we observed growth self-inhibition of tautomeric form B in highly supersaturated IBS aqueous solutions wherein the predominant species is anionic form, and the 1H-tautomer is insignificant. In stark contrast, the growth self-inhibition phenomenon is absent in 2-propanol solution in which the intra-annular tautomerism of IBS is more prevalent (with 14% 2H-tautomer). This result suggests the tautomeric exchange in solution is not a sufficient condition for producing growth cessation, and the surface intra-annular tautomer inter-conversion (2H-IBS to 1H-IBS tautomer) is the culprit.

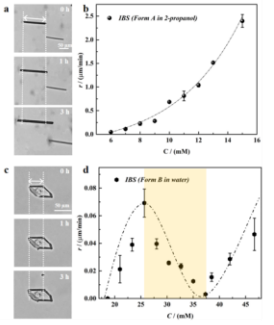


Figure 2

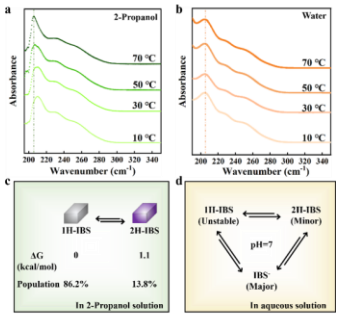


Figure 3

We believe our findings will captivate a diverse audience, given that tautomerism is a ubiquitous characteristic of many organic crystalline materials widely used in applications spanning from pharmaceuticals to energy harvesting technologies.

Keywords: Crystal growth, tautomer, self-inhibition, surface.

Symmetry-Breaking and Symmetry-Retaining Morphological Evolution of the Single Crystals of Cyclodextrin Metal-Organic Frameworks

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0.13

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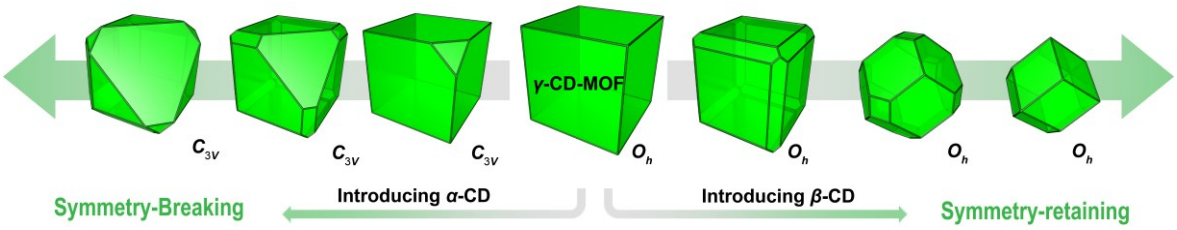
Abstract: The morphological symmetry-retaining and symmetry-breaking of single crystals of the γ-cyclodextrin metal-organic framework have been achieved via introducing lower symmetric β-cyclodextrins and α-cyclodextrins, respectively. β-cyclodextrins led to a morphological evolution with retained symmetry from cubic to rhombic dodecahedra, while α-cyclodextrins resulted in the original cubic crystal missing a vertex angle presenting symmetry-breaking behavior. The crystal structures of rhombic dodecahedra and angle-deficient crystals were confirmed through X-ray crystallography, and the mechanism underlying the morphological transformation evolution was further analyzed. Our work not only provides a rare case realizing two different paths of morpho-logical evolution in one system, but also encourages future efforts towards the evolution of artificial crystal systems in a natural way.



Keywords: Crystal engineering, morphological evolution, symmetry breaking, metal-organic frameworks.

Deconstructing the Full 3D Facetted Growth Rates from the Temporal Capture of Crystal Growth Through In-Situ Optical Microscopy

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0.14

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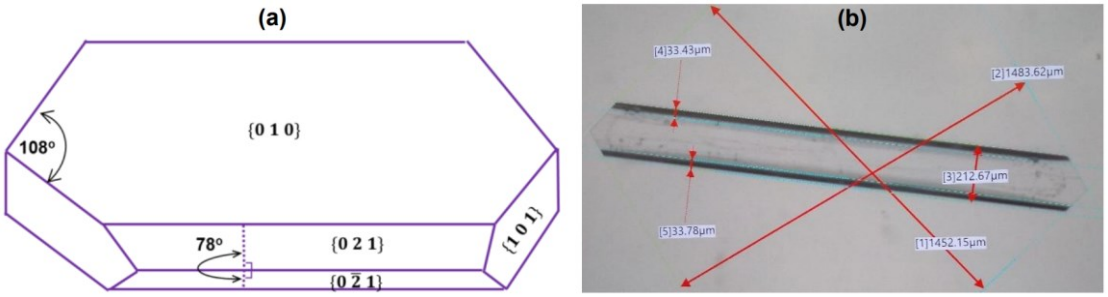
Abstract: Crystal shape and size are of critical importance in digital design of particle manufacture and formulation processes. The use of morphological population balance (MPB) models can predict and control the evolution of crystal size and shape in crystallisers, presenting a determinant factor in crystallisation process digital design. However, crystal facet growth kinetics forms the key input for MPB modelling. Imaging systems were previously used to investigate the growth kinetic mechanisms of L-glutamic acid (LGA) crystallising from solution mainly in 1D and 2D. The facet growth rate of beta-form LGA (β -LGA) crystals in {010} face direction could not be found in literature as it is the slowest of the three faces (Figure 1).

Figure 1. (a) Schematic of β-LGA crystal morphology with some face-to-face angles; (b) Measurements of three faces of a β-LGA crystal from an in-situ image and also the shadow thickness of face {021}



A morphologically-based approach is used for the in-situ characterisation of 3D crystal growth rates from the solution phase. Crystal images of single β-LGA crystals are captured in-situ during growth using transmission optical microscopy at a relative supersaturation of 1.05. Analysis of the crystal growth rates for both the {101} capping and {021} prismatic faces through image processing are consistent with those determined using reflection light mode. The growth rate in the {010} face direction is, for the first time, estimated based upon the shadow widths of the {021} prismatic faces and found typically to be about half that of the {021} prismatic faces with the surface area of the {010} face also about half that of the {021} facet. Analysis of the 3D shape during growth reveals the initial needle-like crystal morphology develops to become more tabular (associated with a Zingg factor evolving from 2.9 ~ 1.7 (> 1)) (Figure 2). Calculations of the crystal volume are used to estimate the change in solution supersaturation, offering an alternative way to determine this value from visual observations.

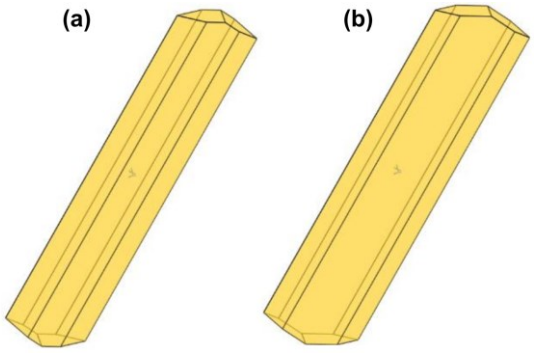


Figure 2. Morphology change of β-LGA crystal during growth at two different times: (a) 0 min; (b) 1135 min with corresponding Fz = (a) 2.9 and (b) 1.7.

Acknowledgements: This study is financially supported by EPSRC UK through the Shape4PPD project (EP/W003678/1) in collaboration with AstraZeneca, Cambridge Crystallographic Data Centre, Infineum, Keyence, Pfizer, Roche, Syngenta, Imperial College London, Universities of Hertfordshire and Strathclyde

Keywords: L-glutamic acid, crystal image, facet growth rate measurement, crystal image analysis, 3D crystal evolution.

Improvement of Dissolution Rate and Tablet Performance of the Antiepileptic Drug Gabapentin Using a Multicomponent Crystal Strategy

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0.15

Abstract: Pharmaceutical materials are considered to be a critical part of contemporary drug manufacturing, processing and formulation. Utilizing the current understanding of the topology of interactions, intermolecular interactions can be purposefully altered to produce new solid forms with better functional properties. Tablets are the predominant dosage form due to their physical and chemical stability, high productivity and low manufacturing cost. Gabapentin (GBP) is a neurotransmitter gamma-aminobutyric acid analog used in the treatment of partial seizures. Cocrystals are homogeneous crystal solids containing pharmaceutically acceptable coformers and active pharmaceutical ingredients (APIs). Pharmacologically acceptable para-aminobenzoic acid (PABA) was selected to form a 1:1 cocrystal with GBP, and the cocrystal tablets formed were successful in slowing down the dissolution rate of the original drug and reducing the intrinsic dissolution rate. Therefore, it is believed that GBP-PABA holds great promise for the development of slow-release formulations. At the same time, GBP exhibits poor compaction behavior, which increases the possibility of capping or delamination during compression. The incorporation of water molecules into the multicomponent crystals gives them different molecular conformations as well as multiple packing arrangements. All powder samples were then subjected to CTC (Compressibility, Tabletability, Compressibility) analysis to determine the behavior of bulk powder deformation. Based on the crystal structure analysis, GBP-H_2O showed quite good compressibility properties due to the slip planes, which allowed us to explore how molecular packing could be tuned at the molecular level to improve tabletting properties. Therefore, the link established in this work between crystal topology, mechanical properties and their tabletting performance is an indispensable step towards the ultimate goal of precise performance design of tablet products.

Keywords: Gabapentin, multicomponent crystals, structural analysis, in vitro dissolution, tabletability.

Composite Crystals of Antihypertensive Agents Prepared by Simultaneous Crystallization

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0.16

Abstract: Particle engineering through crystallization is a widely employed technique in pharmaceuticals, addressing intricate demands by incorporating minute polymer quantities. This strategic approach allows precise control over bioavailability, crystal stability, and drug release kinetics. The innovative concept of polymer-directed crystallization aims to unify crystals of distinct drug entities within a single tablet, offering enhanced manufacturability, stability, and cost reduction. The process initiates crystal genesis via atypical pathways, guided by the physical adsorption of polymer chains. The study focuses on antihypertensive agents, an angiotensin II receptor blocker and a calcium channel blocker, demonstrating the formation of composite drug crystals with unique morphologies. Various analytical techniques, including optical microscopy, scanning electron microscopy, birefringence analysis, differential scanning calorimetry, powder X-ray diffraction, and proton nuclear magnetic resonance, confirm the success of this approach in fabricating complex crystals. A single particle has submicron crystallites of two drugs originated by ordered nucleation processes. This innovative strategy holds promise for streamlined formulation, improved processability, and improved stability, thereby revolutionizing the landscape of pharmaceutical crystallization techniques.

Keywords: Reverse antisolvent crystallization, composites, amlodipine, valsartan, nucleation control.

Grain and Domain Microstructure in Long Chain *N*-Alkane and *N*-Alkanol Wax Crystals

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0.17

Abstract: Waxes encompass a rich variety of technologically as well as biologically important solids. Paraffin waxes, among the simplest waxes, are used in many products, from lubricants to coatings. Waxes also serve key biological functions such as in the layers on plant leaves that restrict water loss, to inhibit plant dehydration. Many such natural waxes are complex chemical mixtures of hydrocarbon chain lengths and functional groups. Despite comprising in large part simple linear chain hydrocarbon structures, that arrange in side-by-side chain packing, waxes support a great deal of crystalline structural variety due to diverse ordering and disordering possibilities. Subsequently, determining the degree of (dis)ordered crystal structure of these organic materials at the fundamental length scale of a few chain repeats (nanometer-scale) is crucial across a number of sectors for understanding properties such as density and hardness, as well as underpinning understanding of how water and agrochemical active ingredients interact with plant crops.

Here, we reveal the microscopic structure of replica leaf wax models based on the dominant wax types found in the *Schefflera elegantissima* plant, namely $C_{31}H_{64}$, $C_{30}H_{61}OH$, and their binary mixtures. Using transmission electron microscopy, atomic force microscopy, and scanning electron diffraction (SED) measurements, we first assess the unit cell space group symmetries for both the *n*-alkanes and *n*-alkanols. These descriptions offer a context for interpreting experimental evidence of grain microstructure as well as disorder in mis-aligned chain ends producing nematic phases. SED at low electron fluence enables visualisation of the grain microstructure in $C_{31}H_{64}$, a feature conspicuously absent in $C_{30}H_{61}OH$.

In $C_{31}H_{64}$ grain microstructure contains domains of highly ordered chain lamellae, co-existing with nematic phases (disordered chain-ends) as well as dynamical disorder. These observations suggest the unit cell descriptions serve as guideposts only for the 'endmember' structural motifs in what is otherwise a complex, nanoscale landscape. $C_{30}H_{61}OH$ does not exhibit domains of lamellar ordering, and binary mixtures from 0-50% of $C_{30}H_{61}OH$ show a loss of grain structure due to more nematic chain packing with increasing alcohol content, suggesting a partial but limited solid solution behaviour. These results provide a guide for understanding underpinning microstructural features that might control layer flexibility and permeability (to water) in leaf waxes. More broadly, this work could be extended to look at systems such as wax-tuned, lipid crystallization pathways in oil in water emulsions, for food applications, and applied to pharmaceutically relevant formulations with layered structures or containing long chain polymer systems (solid dispersions).

Keywords: Crystallization, electron microscopy, structure identification.

New Insights into the Solubilization of Multicomponent Crystals: A Case Study of Pipemidic Acid

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0.18

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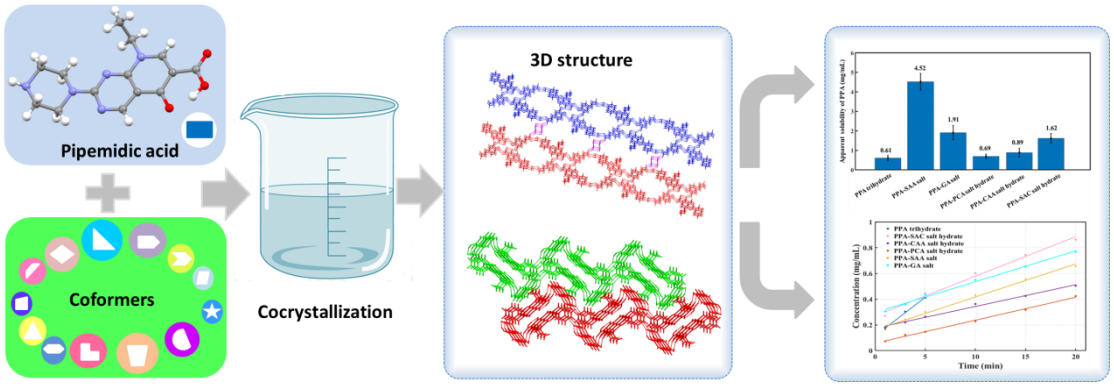
Abstract: Multicomponent crystals have been proven to be an effective strategy for tuning the dissolution property of pharmaceuticals. As one of the most prominent medications of the second generation of quinolones with broad-spectrum antibacterial activity, the therapeutic effect of pipemidic acid (PPA) has been seriously underestimated due to its low solubility, short half-life, poor efficacy and numerous side effects. In response to these issues, some new multicomponent crystals of PPA were successfully synthesized based on crystals screening using salicylic acid (SAA), gentian acid (GA), protocatechuic acid (PCA), caffeic acid (CAA) and saccharin (SAC) as coformers, and fully characterizations on the crystal structures, morphology, solubility, stability, etc., were performed. Single crystal structure analysis (SCXRD) combined with solid-state carbon nuclear magnetic resonance spectra (ssNMR) confirmed that proton transfer occurred between PPA and the five coformers at room temperature, resulting in the formation of salts. Differential scanning calorimetry (DSC) analysis and variable temperature single crystal structure analysis (VT-SCXRD) confirmed the existence of interconverting polymorphism in the PPA-GA system. The solubility and the *in vitro* dissolution test of the multicomponent crystals shows that all the multicomponent crystals exhibit advantages such as increased solubility and decelerated intrinsic dissolution rate, compared with the pure PPA crystals, which can lead to the release of the multicomponent crystals at a slower rate, thus improving bioavailability. In additionally, all multicomponent crystals exhibited excellent stability over 8 weeks at accelerated storage conditions (40 °C and 75% RH). Further exploration of the solubilization mechanism of multi-component crystals was conducted using molecular simulation techniques, and the results indicate that the solubilizing effect is caused by the lower lattice energy and full exposure of hydrophilic groups. Hirshfeld Surface (HS) analysis showed that compared with PPA trihydrate, the contribution of the strong interactions in the multicomponent crystal structure to maintain the crystal structure tended to be weakened, indicating that the multicomponent crystal may increase the apparent solubility of PPA. Moreover, unlike cyclic supramolecular synthons in other multicomponent crystals from structure point, the synthons in PPA-SAA salts are chain-like, which may be one of the main reasons for the most significant increase in its apparent solubility. In summary, this work demonstrates that multicomponent crystals can offer a promising potential to slow the release rate and enhance the solubility for these defective pharmaceuticals.



Keywords: Multicomponent crystals, solubilization, intrinsic dissolution rate, structure characteristics, molecular dynamic simulation.

Influence of Solvent Selection on the Crystallisability and Polymorphic Selectivity Associated with the Formation of the "Disappeared" Form I Polymorph of Ritonavir

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Abstract: The comparative crystallisability and polymorphic selectivity of Ritonavir, a novel protease inhibitor for the treatment of acquired immune-deficiency syndrome, as a function of solvent selection is examined through an integrated and self-consistent experimental and computational molecular modelling study. Recrystallisation at high supersaturation by rapid cooling at 283.15 K is found to produce the metastable "disappeared" polymorphic form I (Fig. 1(a)) from acetone, ethyl acetate, acetonitrile and toluene solutions in contrast to ethanol which produces the stable form II. Concomitant crystallisation of the other known solid forms are not found under these conditions. Isothermal crystallisation studies using turbidometric detection based upon classical nucleation theory reveal that, for an equal induction time, the required driving force needed to initiate solution nucleation decreases with solubility in the order of ethanol, acetone, acetonitrile, ethyl acetate and toluene consistent with the calculated solute solvation free energies. Molecular dynamics simulations of the molecular and intermolecular chemistry reveal the presence of conformational interplay between intramolecular and the intermolecular interactions within the solution phase (Fig. 1(b)). These encompass the solvent-dependant formation of intramolecular O–H .... O hydrogen bonding (Fig. 1(c)) between the hydroxyl and carbamate groups coupled with differing conformations of the hydroxyl's shielding phenyl groups. These preferences and their relative propensities as a function of solvent selection may play a key rate-limiting role in the crystallisation behaviour by not only inhibiting to different degrees the nucleation process but also restricting the assembly of the optimal intermolecular hydrogen bonding network needed for the formation of the stable Form II polymorph.

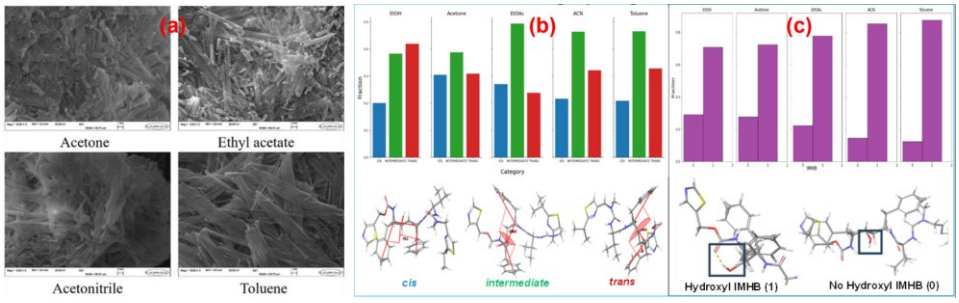

Figure 1. (a) SEM micrographs of ritonavir crystals produced in different solvents; (b) Histogram of observed ritonavir phenyl conformations via MD simulations for each solvent and example depictions of conformers in cis, intermediate, and trans conformations; (c) Histogram of intramolecular hydrogen bonding (IMHB) observed for O-H group via MD simulation and structural depiction of O-H group forming an IMHB with carbamate oxygen and free O-H group without IMHB.

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Keywords: Solvent selection, disappeared polymorphic form, crystallisability, nucleation kinetics, Ritonavir, intra- and inter-molecular interactions, conformational polymorphism, molecular dynamics.

Kinetics of the Mechanically Induced Ibuprofen-Nicotinamide Co-Crystal Formation by In-Situ X-Ray Diffraction

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

Among the APIs in the WHO Model List of Essential Medicines, ibuprofen is an analgesic drug with a market size estimated at around 45,000 MT, and to grow at an annual rate of 2%. As its poor aqueous solubility, bioavailability and thermal stability affect its therapeutic efficacy, several strategies have been developed over the decades to overcome these issues, and co-crystallisation has been one of the most effective. In particular, the cocrystal of ibuprofen with nicotinamide is noteworthy, since it presents a 7.5 times higher water solubility than ibuprofen itself, along with an increased thermal stability.

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

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

By taking as a benchmark system the co-crystal ibuprofen-nicotinamide, we proved the efficacy of the synergistic effects of TRIS-XRD and analytical kinetic modelling in investigating the mechanochemical behaviour, and for the specific case study we demonstrated that the co-crystal formation likely occurs via the mechanically induced melting of ibuprofen.

With the rules of this chemistry becoming increasingly clear, we believe that the new reaction pathways of mechanochemistry will soon represent not a limit anymore, but an asset, that may lead to lot of opportunities for the pharmaceutical industry.

Keywords: Mechanochemistry, kinetics, in-situ PXRD, co-crystals, ibuprofen, nicotinamide.

Polytypism of Pharmaceutical Nanocrystals Investigated with 3D Electron Diffraction

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Abstract: Polytypism is a key properties for drug development. Its control is mandatory both for the safety and the effectiveness of a pharmaceutical compound. The polytipism characteriztion becomes incresingly difficult as soon as the crystal size of the compound falls below the limit for single crystal x-ray diffraction to be performed, usually few tens of nanometers. In those cases the alternative would be x-ray powder diffraction, which can be very challenging espacially if the as synthesized powder contains more than one crystal phase. 3D electron diffraction (3D ED or MicroED) is a novel approach which allows to collect signle crystal diffraction data on grains as small as few hundres of nanometers. In this way we can unambigously identify all the phases present in a powder sample and the 3D ED data can be used for both the structure solution and refinement of unknown organic crystals. Thanks to specific data collection protocols which increase the speed of a diffraction experiment and to a new generation very sensitive single electron detectors, it is nowadays possible to perform 3D ED experiments also on samples that are both beam and vacuum sensitive, a standard condition for pharmaceuticals. In this contribution we will illustrate the state of the art of 3D ED and we will show how its application to the problem of polytypism in phamaceuticals has allowed the solution of long lasting crystallographic problems. Succesful selected examples will be: the crystal structure determination of orthocetamol and delta polymorph of indometacine; the structure solution of the last unknown polymorph of olanzpine, the form III; the structure determination of two new polymorphs of oxyresveratrol, a natural compound, one hydrated and one dehydrated. This reserch has been carried out in the frame of the ITN NanED project founded by European Union's Horizon 2020 program (grant. n. 956099).

Keywords: Crystallization, polytipism, electron diffraction.

Crystal Regeneration Post-Breakage: Effect of Solvent Selection, Multiple Breakage Sites, and Surface Growth Kinetics

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Abstract: Post-breakage crystal growth has been understudied, and often implemented into crystallisation process models indifferent from regular growth. In a recent study on the breakage of paracetamol (PCM) crystals in ethanol, a novel crystal regeneration phenomenon was published [1]. When the breakage exposed their internal cleavage plane (ICP) (020), the PCM crystals predominantly grew from their ICP, and regenerated into their original shape. Regenerative growth rate from the ICP was around 2-3 times higher than the growth parallel to ICP, whereas the two directions grew at the same rate after the completion of regeneration. This work presents the effect of solvent choice and multiple ICP breakage sites on regeneration and estimates regeneration kinetics towards improved process modelling. Firstly, by single-crystal regrowth experiments via evaporative crystallisation, PCM regeneration was monitored in acetone and THF, and compared with ethanol. Among all the studied solvents, the growth from the ICP was circa 2-3 times faster than the growth parallel to it during regeneration, which is followed by similar growth rates after the regeneration. Then, by 'cross-solvent' experiments, crystal regeneration was conducted via growing broken crystals in a solvent different from which they were initially produced. The crystals featured a more balanced regenerative growth in this case, characterised by relatively faster growth from the ICP that is accompanied by considerable growth of other surfaces, ultimately reaching their equilibrium shape in the final solvent. Simultaneous regeneration of multiple surfaces was demonstrated via growing single PCM crystals with 2 parallel ICP fractures in ethanol. This resulted in 4-5 times higher growth rate for the growth perpendicular to the ICP compared to the parallel direction during regeneration. The doubled regenerative growth rate in this case indicated that regenerating facets do not inhibit each other by competition. Finally, crystal regeneration kinetics was studied via isothermal crystallisation of single PCM crystals in ethanol, within a supersaturation range of 1.03-1.30. This yielded the empirical equation $r\ (mm/h) = 2.56\times(\Delta C)^{1.41}$ for the growth rate of the ICP (020) during regeneration at 25°C, describing the dependence of regeneration on absolute supersaturation. Kinetic studies are currently expanded to multiple temperatures, to quantify the activation energy of regeneration. The study reports new findings on post-breakage crystal growth to enhance crystallisation processes by improved crystal size, shape, and growth rate estimations, that can be benefited to optimise industrial processes.

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Keywords: Crystal breakage, regeneration, solvent-solute interactions, crystal growth kinetics.

Trimesic Acid as a Building Block for Ternary and Quaternary Cocrystals

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Abstract: Higher-order cocrystals are not only interesting compounds with enhanced properties and functions, but also continue to present the intellectual challenge of their rational synthesis[1]. Design strategies of ternary cocrystals include the use of a ditopic, unsymmetric coformer that can form two distinct synthons or H bonds of different strength, or the combination of complementary intermolecular interactions. More recently, quaternary and even five- and six-component cocrystals have been obtained by applying the structural inequivalence/shape-size mimicry strategies[2]. In continuation of our previous work on cocrystals of the 2,4-diaminopyrimidines trimethoprim (tmp) and pyrimethamine (pyr)[3], we have used trimesic acid (H_3tma) to design ternary and quaternary cocrystals containing different combinations of tmp, pyr, 4,4'-bipyridine (bipy), 1,2 di(4 pyridyl)ethylene (ebipy), 1,3 di(4-pyridyl)propane (pbipy), and phenylpyridine (phpy) coformers. First we investigated if the stoichiometry of binary H_3tma-diaminopyrimidine cocrystals can be controlled. 1:1 cocrystals of H_3tma with tmp and pyr crystallized from equimolar mixtures in methanol and we were also able to obtain 2:1 and 3:1 cocrystals of pyr and H_3tma. Since the structures of the binary 1:1 and 2:1 cocrystals have carboxyl groups that do not participate in H bonding with pyr or tmp, the pyridine coformers were used to attempt to construct three-component cocrystals. Three new ternary molecular ionic cocrystals were obtained from solution crystallization experiments with mixtures containing H_3tma, a pyridine coformer, tmp or pyr in equimolar ratio. Two more ternary cocrystals were obtained in the presence of 2,4-diamino-6-hydroxypyrimidine. We also investigated the possibility of crystallizing three-component cocrystals that contain both 2,4-diaminopyrimidines. Pyr and tmp are not coformers of choice for shape-size/packing mimicry and the presence of various (self-complementary) H bond donor and acceptor sites is not conducive to selective higher order cocrystal formation. Nevertheless, we were able to crystallize two forms of the ternary cocrystals in different molar ratios from methanol. Finally, we were able to isolate two quaternary cocrystals, one containing $Htma^{2-}$, $Htmp^{+}$ and two different pyridine coformers and one containing $Htma^{2-}$, bipy and both 2,4-diaminopyrimidines. In summary, a range of three- and four-component cocrystals were successfully isolated through carefully balancing the intermolecular interactions and the relative solubilities of the coformers and potential combinations of binary systems. This study provides a more predictive approach towards identifying higher-order cocrystals.

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Keywords: Crystal engineering, trimesic acid, ternary cocrystals, quaternary cocrystals.

Optimization in Expression and Crystallization of Cry Protein from Bacillus Thuringiensis

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Abstract: The phenomenon of intracellular crystallization has attracted considerable interest due to its implications in protein structure determination and biopharmaceutical applications. The intricate architecture of cellular compartments, coupled with the densely packed molecular environment, provides a conducive milieu for the spontaneous crystallization of certain proteins that are traditionally challenging to crystallize in vitro. Recombinant Cry protein also demonstrates the potential as a protein delivery platform[1]. In this research, we devised a optimized approach for cultivating bacillus thuringiensis to facilitate the expression and intracellular crystallization of Cry protein. Examination via scanning electron microscopy (SEM) revealed the presence of classic bipyramidal and a new type of polyhedral shape crystal. Further analysis utilizing High-resolution transmission electron microscopy (TEM) and synchrotron radiation confirmed the presence of diffraction patterns consistent with crystalline structures. Following spore extraction[2] and alkaline dissolution, the cry proteins were subjected to a rigorous screening hanging drop process[3] to identify optimal re-crystallization conditions, encompassing a range of pH values and solvent compositions. The results provide insights into the mechanisms governing intracellular protein crystallization and offer useful methods for the direct purification of biopharmaceuticals in downstream processes.

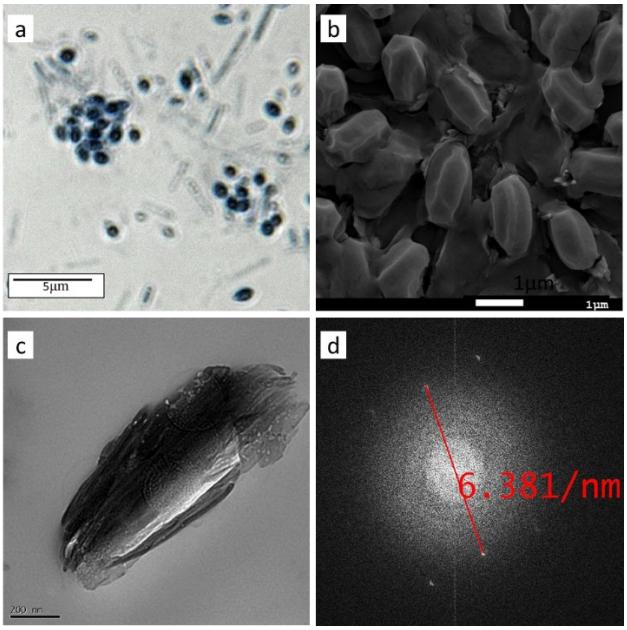

Figure 1. (a) Cry protein crystals under microscope. (b) SEM figure of Cry protein crystals. (c) Cryo-TEM of bipyramidal crystal. (d) Fourier transform of high-resolution TEM figure.

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Keywords: Protein expression, hanging drop crystallization, intracellular crystallization.

Crystallisation of Molecuar Solids via Sublimation – An Uncommon Technique with Tremendous Potential

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Abstract: Crystallisation by evaporation remains by far the most dominant method to produce organic molecular crystals. However crystals produced in this method are limited from persistent solvate formation, conformer solubility in their respective solution, generation of undesirable organic solvent waste and long crystallisation timescales.

Sublimation is defined as the direct transition of a solid to a vapour without passing through a liquid phase. It is estimated that two-thirds of all organic compounds are sublimable and while the use of sublimation has gained increasing attention recently, the use is still in its infancy with a sparse number of reports in the last number of years. Sublimation as a technique for crystal growth offers several advantages over traditional solvent based techniques, being a solvent free 'green' alternative, offering good polymorph, morphology and orientation control by adjustment of the crystallisation driving force and scalable to industrial operation.

In my work we have investigated sublimation as a novel tool for the crystallisation of organic compounds. Using the NSAID, Diflunisal, as a focus we developed a facile method to prepare multicomponent pharmaceutical crystals from the gas phase that were previously unavailable by other methods. We were able to show the ability to obtain morphology control of these systems by using tailor made additives in less than 5% w/w quantities to produce dramatic changes compared to effects observed in the solution phase. Using pyrimethamine as a model compound we were then able to expand this study to confirm the viability of the sublimation method to produce ternary and higher order multicomponent crystals.

This method has now been adapted for the production of biomolecular piezoelectric sensors. The piezoelectric effect is the property of crystalline materials to generate an electrical potential upon the application of mechanical stress and find use in industrial and consumer products including medical devices and energy harvesters. What has been missing to date in the effort to accelerate the uptake of biomolecular crystals as high-performance commercial piezoelectrics, is a technique for growing polycrystalline assemblies in a repeatable manner with minimal cross-sample variation. We control the self-assembly of a number of amino acids by subliming them onto copper substrates and are made into simple three-layer disc-shaped actuators. The solvent-free crystallisation technique results in polycrystalline films with uniformly orientated crystals, and a resulting consistent and repeatable piezoelectric response that exceeds that of single crystals.

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Keywords: Sublimation, crystal growth, morphology control, multicomponent crystallisation, piezoelectric sensors.

Polymorphism of Aspirin: Nucleation Control and Separation of Form-I and Form-II Polymorphs through Solution Crystallization Process

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Abstract: Polymorphism plays an important role in the crystallization of various pharmaceutical materials. It infulences important properties of the drug materials, such as dissolution rate, thermal and mechanical stability, shelf-life etc., which greatly affect the bioavailability of the drug materials and their industrial processing. Acetylsalicylic acid, commonly known as aspirin, is a therapeutic pharmacological substance being used widely. The stable Form-I and the preferred metastable Form-II polymorphs of aspirin have close similarities in terms of their structural and energetical aspects. Hence, the isolation of preferential polymorphic Form-II of aspirin is always a challenging issue in the pharmaceutical industry. In addition, the occurrence of liquid-liquid phase separation (LLPS) or oiling-out and the cross-nucleation of Form-I over Form-II are the bottleneck issues during the solution crystallization process. These issues have been successfully overcome through a novel swift cooling crystallization process from a water-acetonitrile mixed solvent medium and by a template-assisted crystallization method. Through antisolvent crystallization, Form-I and Form-II have been separated effectively. Morphological analysis of the grown polymorphs was carried out through in-situ observation, their internal structure was ascertained through powder and single-crystal X-ray structural refinement, and thermal stability by differential scanning calorimetry analyses. Results will be presented.

Keywords: Crystallization, polymorphism, nucleation control, mixed solvents, x-ray diffraction analysis.

Evaluation Models of Solvent Effect on the Dissolution and Crystallization Process of Aripiprazole

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Abstract: Hydrate of APIs has received a lot of attentions as it can broaden the options for final dosage forms and can also enrich the methods for developing new crystal forms. In this work, aripiprazole whose solubility in water is quite low was used as model compound to investigate the mechanism of hydration and low solubility. Based on single crystal structures of Form H1 and anhydrous Form III, molecular surface electrostatic potential (MSEP) was calculated to localize strong intermolecular interaction sites. The conformational energies and cohesive energies of Form III and Form H1 were calculated and their stabilities were compared. The energy calculation results show that the relative stability of Form III and Form H1 can be determined by the cohesive energy. Furthermore, the insolubility mechanism of Form III in water was explored based on the synthetic analysis of the crystal structure, crystal energy, and molecular dynamics simulation results. It was found that the overall decrease in polarity caused by the formation of APZ diamide dimer structure and the strong binding effect on APZ molecule clusters due to strong hydrogen bonds and van der Waals interactions lead to the water insolubility of Form III. Finally, a dandelion-sowing mechanism for the solid-phase transformation process (hydration process) of Form III to Form H1 in water was explored by suspension crystallization experiments and molecular dynamics simulations. The core step of the mechanism lies in the detachment of APZ molecules or small molecular clusters from the surfaces of Form III molecular clusters induced by external input energy, like the detachment of dandelion pappi from blowballs blown by the wind.

Keywords: Aripiprazole, water-insoluble, energy analysis, dandelion-sowing, hydration mechanism.

Digital Design of Intensified Crystallization Systems

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Abstract: Crystallization is a key operation in many industries, used for tailoring the purity and particle properties during the manufacturing of pharmaceutical, fine chemical, energetic and other products. The advent of process analytical technologies (PAT) more than two decades ago has brought the applications of advanced control in crystallization processes in the realm of possibility. The presentation will review key challenges and recent developments in the measurement, modeling, and control of crystallization processes. The role of mathematical modeling, model-based digital design, and advanced feedback control concepts in improving the performance of batch processes, as well as enabling technologies in the paradigm shift from batch to ontinuous manufacturing will be corroborated.

The use of modern crystallization systems that are based on oscillatory flow platforms will also be illustrated as integrated unit operations to enable process intensification through better control of the crystallization mechanisms. The model-based quality-by-control (QbC) framework will be illustrated for the design of spherical crystallization systems, and novel processes that increase overall manufacturability and efficiency of the manufacturing process will be demonstrated via various industrial case studies. The integrated design and control of continuous crystallization-filtration-drying process will be presented using an innovative integrated and modular continuous reactor-crystallizer-filter-dryer platform that provides the link between reaction systems and secondary manufacturing and enables fully integrated manufacturing processes. Several innovative software tools will be presented that enable to rapid adoption and application of modern digital design approaches in crystallization process development. The novel digital design approaches for optimization and comparative techno-economic analysis of batch and continuous crystallization systems will be illustrated.

Keywords: Crystallization digital design, spherical crystallizer, integrated crystallization-filtration-drying, continuous crystallization.

Shaping Crystals with Fundamental and Informatics Tools. Using Particle Informatics to Understand Growth Rates

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Abstract: The shape and size distribution of organic crystalline products can have a profound impact on a material's attributes. Properties such as powder tabletability, flowability, filterability and dissolution profile, can all be affected by crystal morphology.

Crystal morphology can be influenced by several environmental variables, therefore the ability to predict the effect of different solvents, supersaturations, temperatures, and possible growth modifiers on crystal morphology would enable a reduction of the effort required for process development.

Non-mechanistic models for morphology prediction based on geometry (BFDH) or energetics (attachment energy model) have the advantage of being inexpensive and easy to implement, but they lack the ability to consider the effect of environmental variables[1].

Morphology predictions obtained with mechanistic models are often considered more accurate, as they have the capability of assessing the effect of several environmental variables. Crystal growth, however, is a complicated process, and the accurate description and modelling of relevant physico-chemical processes is often non-trivial[2,3].

In this contribution, we present our recent progress in developing a model for morphology prediction of compounds of pharmaceutical interest based on the concept of *Particle Informatics*[4]. Our approach takes advantage of data from over one million and a quarter experimental crystal structures deposited in the Cambridge Structural Database (CSD) to combine a mechanistic model for crystal growth with a description of surface interactions that will allow for the estimation of the effect of environmental variables on crystal morphology.

With the aid of a few selected case studies, we will present our model at its current stage and some of the successes and challenges we have encountered along the way.

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Keywords: Crystal shape modelling, particle informatics, crystal morphology, crystal growth.

Stabilization and Coagulation of Colloidal Suspensions During Crystallization

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Abstract: In colloidal suspension, the disordered colloidal particles could be rearranged under the artificial control, which show great potential in some areas like nanomaterials, energy and biomedicine. However, colloidal suspension could be catastrophic for the phase separation process like crystallization. Due to the high viscosity, colloidal suspension would be a great burden on the equipment, which cause the clogging in pipeline and difficulty in stirring. In addition, due to the collapse of the colloidal suspension, impurities and solvents trapped significantly affect the purity of the final product. Hence, understanding the motion and interaction of particles are crucial and instructive to control the colloid suspension during crystallization. Due to the special thermodynamic properties of cefradine, the mutation of supersaturation usually led to the explosive nucleation, resulting in the formation of large amounts of nanocrystals as the colloidal particles. Via surface analysis of nanocrystal and molecular simulation, the electric double layer on ionized crystal surface was revealed. Then, DLVO model was further derived to analyze interaction between particles. Combining dynamic light scattering, zeta potential measurements and rheology, the stability of colloidal suspension and motion behavior of particles was understood during the whole crystallization process. The developed knowledge based on the suspension can form a basis for further optimization of purification and crystallization for cefradine.

Keywords: Crystallization, colloid suspension, particle behavior, surface interaction.

Numerical Simulation of Hydrodynamic and Particle Suspension Performance in a Novel Stirred Tank

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0.31

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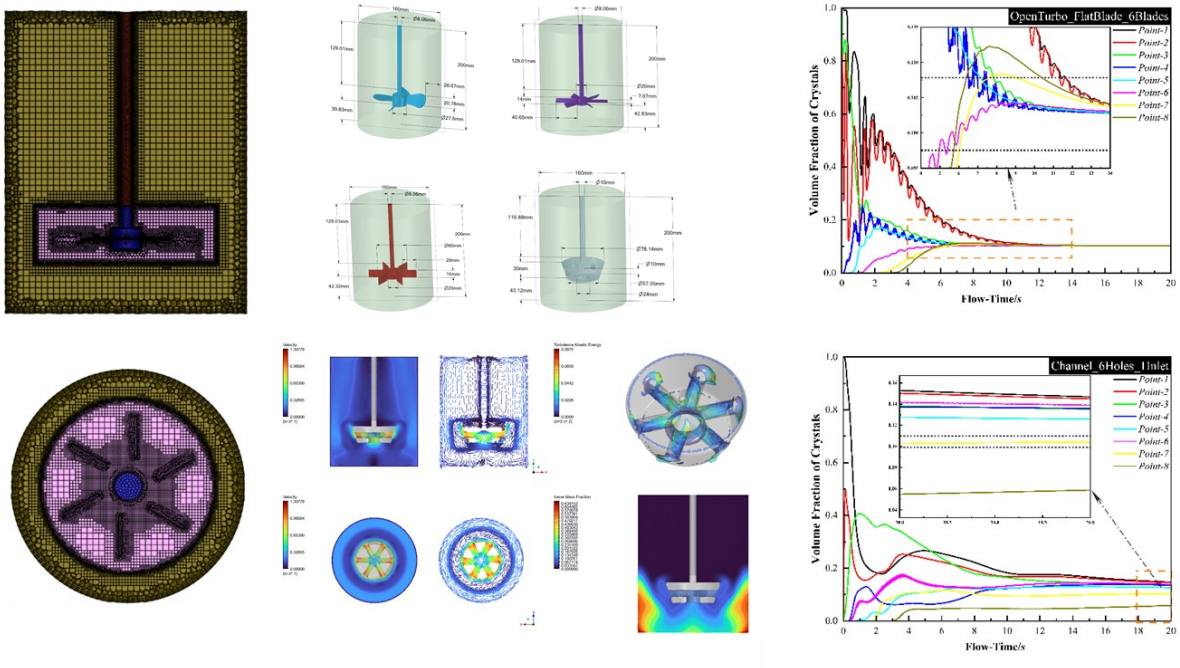
Abstract: Crystallization poses a significant challenge in achieving uniform mixing due to its nature as a multiphase flow system. In industrial crystallization, stirrers are commonly used to enhance mixing and improve heat and mass transfer by converting mechanical energy into kinetic energy through the rotation of impellers. There has been a longstanding effort to enhance the performance of stirred tank crystallizers. This study presents a new channel-type stirred tank design that is optimized for crystallization. The study employs computational fluid dynamics(CFD) and the Euler-Euler two-fluid model to analyse the solid-liquid flow and particle suspension performance of this novel stirrer, leading to structural optimization. Compared to conventional stirrers like open turbine, rushton turbine, and paddle-type tanks, the channel-type stirred tank is an axial-flow stirrer that excels in particle suspension while minimizing fluid shear force near the impeller. This reduces mechanical collisions and subsequent crystal breakage, leading to less secondary nucleation. Additionally, the innovative impeller design offers flexibility in adjusting the vessel's flow pattern. The insights from this research will inform the design and optimization of crystallization stirred tanks.



Keywords: Crystallizer, CFD, hydrodynamics, particle suspension performance, channel-type impeller.

Crystal Shape and Topography: Prediction and Optimisation with the CrystalGrower Model

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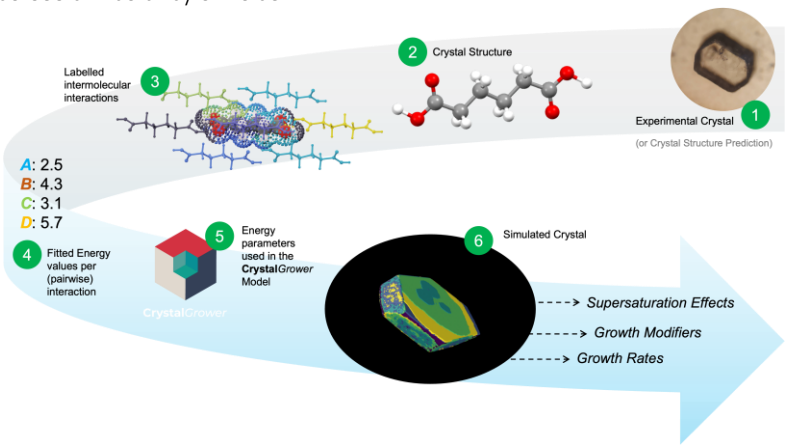
0.32

Abstract: Particle or crystal shape engineering represents a fundamental aspect of any industry that produces or handles solid matter, including fields such as pharmaceuticals, agrochemicals, energy, and electronics. Numerous important physical properties, such as mechanical strength, dissolution/sublimation rates, agglomeration, and compressibility are influenced by the crystal shape. Therefore, understanding the effects of intermolecular interactions on the shape and size of a crystal becomes crucial in determining how these physical properties can be controlled.

The CrystalGrower software developed by Anderson et al.[1,2] provides a generalised Monte Carlo (MC) model for crystal growth, introducing an improved 3D approach based on the MONTY approach by Meekes and co-workers[3]. The model can be utilised to simultaneously model both the crystal shape and surface features. Those which are automatically generated and governed by the input (free) energy parameters for specified intermolecular interactions within a nearest neighbour model, obtained from a crystal structure.

The general workflow for CrystalGrower to date has involved fitting of the nearest neighbour interaction energy parameters to an experimentally observed crystal shape and information from atomic force microscopy. In this work, a powerful new automated protocol will be presented that rapidly predicts the free energies of interaction for use within such a MC model for a wide range of molecular crystalline solids and solvents, thereby removing a major bottleneck to the study of new materials[4]. Furthermore, it will be shown how global search algorithms can also be utilised along with a robust shape descriptor and a reference (experimental) crystal shape to optimise the aforementioned interaction energies. In combination, the above methods create a powerful tool that can aid crystal shape engineering across a wide array of fields.



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Keywords: Crystal growth, molecular crystals, crystal shape, shape optimisaiton.

Integrating Docking-Based Screening Method for Impurities, within Crystal*Grower* Computational Workflow to Model and Control Crystal Growth for Advanced Process Design

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0.33

Abstract: The latest augmentation to the CrystalGrower simulation tool[1] is designed to extrapolate the distinct grown and ungrown sites of various crystal structures. CrystalGrower has established its proficiency in predicting the morphology and habits of any crystal structure, allowing for the modelling of these features by manipulating physichal-chemical parameters such as temperature, supersaturation, and individual molecular interaction energy. The presented computational approach aims to refine the characteristics of a crystal structure, ultimately contributing to an optimized formulation that aligns with the functionality of the final product.

The recent enhancement to this computational software integrates a module for detailed interrogation of specific sites within molecular architectures. Additionally, it enables a comprehensive docking analysis determining the effects of a spectrum of impurities on the crystallization pathway under study. The adopted docking strategy evaluates the affinity expressed in energy of various small molecules selected to poison the targeted site, thereby providing in-depth insights into their potential impact on the dynamics of crystallization. An interesting feature of this upgrade is the capacity to dock individual sites with a broad library of molecules, facilitating the systematic screening of numerous compatible candidates to discern those with the optimal fit, thereby elucidating potential binding interactions. Such analysis is central in predicting the most favourable poisonable sites where specific small molecules may adversely alter the crystalline desired morphology, potentially impacting the desired crystal shape. The predictive power of the docking method offers a strategic asset in the early detection of potential crystallization inhibitors, thereby improving the efficiency and dependability of the crystallization process across various application.

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Xylitol Nucleation in the Melt: Supercooling Rupture by Stirring

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0.34

Abstract: Xylitol is a promising phase change material (PCM) for heat storage, thanks to its high energy density and its melting temperature of 93°C. However, it has a high and persistent supercooling and a very low crystal growth rate, making it hard to crystallize.

In this work, xylitol primary nucleation was first studied in a rheometer and in two differerent crystallizers with bubbling agitation and mechanical agitation by a propeller, respectively. The results showed that primary nucleation was impossible to activate by shearing or stirring in a melt cooled down to 60°C within reasonable time. This is in contradiction with crystallizations observed in literature. A particular attention was paid to unintentional seeding by xylitol dust present in the laboratory. When no precautions were taken, crystallization took place, but with highly non-reproducible induction times. Crystallization was then likely initiated by secondary nucleation, from unintentional seeding, suggesting that the results observed in literature might have been affected by this phenomenon.

A second series of experiments dealed with the study of the secondary nucleation induced by (intentional) seeding. A parametric study of the effects of both temperature and stirring intensity, involving around 100 experiments, was performed in the two different crystallizers. A formulation of the measured induction times was proposed to distinguish secondary nucleation from crystal growth. The estimated secondary nucleation kinetics was found to strongly vary with temperature beyond a metastable zone limit and only slighly vary with stirring intensity. This goes in favor of a kinetics which likely obeyed a thermally activated mechanism, suggesting a mechanism of *surface* secondary nucleation in the xylitol melt. Finally, a first model for the surface secondary nucleation in supercooled Xylitol, emphasizing on the influence of xylitol viscosity, was proposed.

Secondary surface nucleation clearly appeared to be a very promising mechanism to trigger Xylitol crystallization. Coupling bubbling and seeding could then answer to the difficulties encounded to control xylitol crystallization and allow using xilitol as an efficient PCM.

Keywords: Melt crystallization, secondary nucleation, seeding, unintentional seeding, sugar alcohols.

The Synergy of Computation and Experiment in Pharmaceutical R&D

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0.35

Abstract: Computational modeling and machine learning are becoming increasingly important to the process of pharmaceutical drug discovery. Using computational modeling and machine learning, XtalPi has developed a series of methods to guide and enhance the experimental workflow for drug development:

- Virtual salt, cocrystal, and solvate screening are used to predict likely salt, cocrystals, or solvates and recommend corresponding solvents. Virtual screening can be used to reduce the number of screening experiments and increase the likelihood of obtaining the desired result.
- Crystal structure prediction (CSP) predicts all possible polymorphs of a compound and ranks them by thermodynamic stability. The CSP energy landscape can reveal if the most stable polymorph has been discovered yet and predict structures complement XRPD, SC-XRD, and MicroED experiments.
- AI-enhanced crystallization (Xtal2) is a machine learning model used to recommend crystallization strategies based on API structural information, constructed from more than 100,000 virtual data and 10,000 real data. With the help of Xtal2 and automated crystallization, intelligently designed experiments can stay active around the clock.
- Morphology prediction calculations reveal how variables like solvents and incorporated additives affect the external shape of crystals. These calculations reveal if needle-like morphologies can be avoided by crystallization, or if engineering solutions, like milling, must be implemented.

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Keywords: Crystallization, virtual screening, crystal structure prediction, morphology prediction.

Growth of Organic Crystal Scintillators for Neutron-Gamma Discrimination

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0.36

Abstract: Organic scintillators in the form of solid, machinable plastic material have long been an inexpensive source of radiation detection material. Plastic scintillator is a scintillating material in which the primary fluorescent emitter (fluor) is suspended in a solid polymer matrix called the base. They are characterized by the presence of a benzene ring structure in the constituent molecule, are more durable than liquid scintillators, and can be molded into any shape. We have grown and fabricated various crystal and plastic scintillators such as trans-stilbene (TSB), triphenyl benzene, styrene, and vinyl toluene-based plastic scintillators by conventional crystal growth and thermal polymerization reactions, respectively. The good quality defect-free single crystal of TSB was grown successfully in the modified VBT. The cone angle of the ampoule plays an important role in the growth process. The radioluminescence spectrum exhibits a broad emission band between 365 and 450 nm, peaking at 387 nm. The scintillation lifetime of 6 ns of the synthesized sample makes its utilization in fast timing measurements. The FOM is calculated to be 1.6, which is adequate for fast neutron detection. Radioluminescence, decay time, and the light yield are measured for all the crystals. The changes that occurred in the light yield are evaluated for the various radiation sources irradiations. Pulse shape discrimination is an important technique for high-energy neutron detection in the presence of gamma radiation background by utilizing the difference in the shapes of the scintillation pulses excited by neutrons (recoil protons) and γ -rays in organic scintillators. Emission wavelength in the visible region for plastic scintillators and efficient pulse shape discrimination for organic crystal scintillators are obtained.

Keywords: Crystallization, bridgeman method, scintillators, radaition detection.

2D Elastic Organic Crystals with Thermomechanical/Acid Responses and Dual-Mode Optical Waveguides

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0.37

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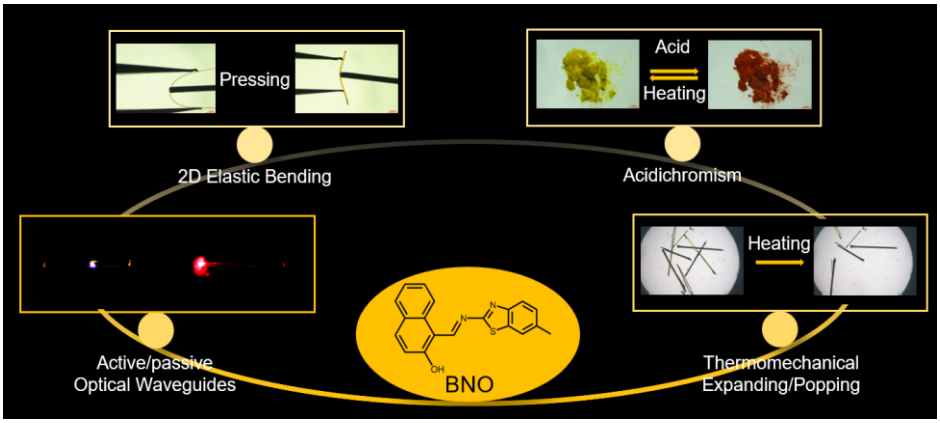
Abstract: Achieving the combination of multiple external stimuli responses and mechanical flexibility has become the current emerging research in the field of crystalline materials. We synthesized and prepared two polymorphs of 1-[(E)-[(6-methyl-1,3-benzothiazol-2-yl) imino] methyl] naphthalen-2-ol (BNO), form-I with excellent two-dimensional mechanical elasticity, the unique herringbone stacking along two crystal faces providing the structural basis. Two types of thermomechanical responses (mild and drastic) of form-I were examined. The analysis of the single crystal structures indicates that the variations of π-π stacking distance inside the molecular columns and herringbone stacking angle are the source of the thermomechanical responses. Further, the lattice energies at different temperatures were calculated to analyze the thermomechanical responses from the thermodynamic point of view, and the second thermomechanical response during the cooling process was successfully predicted. The acid-stimuli response of the crystals was successfully realized through molecular design, and the crystalline to amorphous transition caused by acid treatment was observed. The fluorescence switch was achieved through acid and heat treatments. Finally, the active/passive dual-mode optical waveguides of the two forms were explored, demonstrating their potential applications in optoelectronic devices. This study provides a new perspective on the study of thermomechanical responsive crystals and an important reference for the development of multi-stimuli responsive materials.

Graphical abstract:



Keywords: Polymorphism, flexible crystal, stimuli-responsive material, optical waveguides.

Flexible Organic Crystal with Two-Dimensional Elastic Bending and Recoverable Plastic Twisting for Circularly Polarized Luminescence

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Abstract: Flexible organic crystals could relax internal stress through molecular reconfiguration under external stimuli, manifesting as bending, twisting, and curling while maintaining macroscopic morphological integrity. This remarkable nature of crystal brings light to solving the brittleness bottleneck of optoelectronic functional materials based on molecular crystals. Over the past five years, numerous photoluminescent organic single crystals with elasticity and plasticity based on π-conjugated planar molecules have been designed, developed, and explored their multifunctional applications. Among them, circularly polarized luminescence has aroused great interest due to its high optical sensitivity and resolution. Creating innovative chiral materials with circularly polarized luminescence has become a cutting-edge field in the research of chiral science. However, only one case of one-dimensional elastic small-molecular-weight organic crystals with circularly polarized luminescence has been reported to our knowledge[1].

In this regard, integrating multidimensional flexibility and circularly polarized luminescence into one organic single crystal requires considerations of 1) The flexibility of organic crystal originates from the molecular sliding/rotating cooperatively controlled by intermolecular interactions and packing structures. Flexible molecular conformation may be beneficial for the mechanical reconfiguration process in different directions of organic crystals, which may realize multidimensional flexibility. 2) Photoluminescence in the solid state is required, which aggregation-induced emission molecules can satisfy well. 3) Chirality, including molecular chirality, structural chirality, or macroscopic chirality, will probably induce the production of circularly polarized luminescence. We proposed a molecular design strategy of flexible Schiff base compounds with chirality via introducing a nonplanar 1,2,3,4-tetrahydronaphthalene and chiral center[2]. The single crystals obtained through evaporation crystallization and sublimation crystallization realized multidimensional flexibility at room temperature and liquid nitrogen temperature, including two-dimensional elastic bending and recoverable plastic twisting. It is the first time to endow multidimensional flexible organic molecular single crystals with circularly polarized luminescence, highlighting the potential talent of the application under complicated surroundings. In contrast to the widespread use of π-conjugated planar rigid molecules, this contribution put forward an approach based on nonplanar flexible molecules to manufacture photoluminescent flexible crystals, which broadens the horizons for future development of flexible functional crystal materials.

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Keywords: Crystallization, organic crystal, multidimensional flexibility, circularly polarized luminescence.

Organic Crystals with Response to Multiple Stimuli: Mechanical Bending, Acid-Induced Bending and Heating-Induced Jumping

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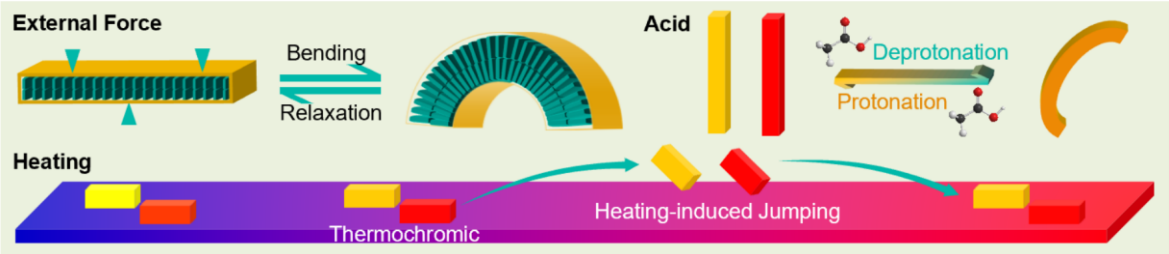
0.39

Abstract: Stimuli-responsive molecular crystals can effectively convert external stimuli of force, light, heat, solvent, acid etc. into various macroscopic motions such as bending, twisting, and jumping, so that they are attracting extensive attentions as smart materials, such as molecular machines, actuators, and sensors. However, crystals are generally prone to rupture, which may limit the stimuli-induced mechanical motions and further applications. Moreover, it is extremely challenging to effectively fabricate multiple stimuli-responsive flexible crystalline materials. The development of 3rd generation of crystal engineering concepts provides an effective strategy for designing and fabricating flexible multifunctional organic crystals. Herein, two polymorphs (Form I and Form II) of a Schiff base compound (2-hydroxy-4-dimethylamino-benzene-2-chlorine-4-benzonitrile) were succesfully fabricated, which could respond to multiple stimuli (external force, acid, heat). Further investigation revealed that Form I and Form II are amenable to elastic deformation, but they have different elastic deformability. Single crystal structure analysis (SCXRD) combined with energy framework analysis hypothesized that the π-stacking columns and interlocked crisscrossed molecular packing in Form I and Form II provide a "structural buffer" during crystal deformation. However, Form I has better elasticity due to fairly isotropic interactions. What is more, both polymorphs exhibit reversible bending driven by volatile acid vapor, due to the reversible protonation reaction of imines with formic acid. Finally, both polymorphs would undergo jumping upon heating. Differential scanning calorimetry (DSC) analysis and variable temperature single crystal structure analysis (VT-SCXRD) confirmed thermosalient effect induced by the sudden release of accumulated stress caused by anisotropic distortion upon heating. The excellent multiple stimuli-responsive performances of this material reveal the possibility of developing multifunctional smart organic crystals for the application such as flexible smart drives, flexible sensors, etc. Through the rational modification of molecular structures and substituents, more flexible organic crystals with multiply mechanical responses could be developed.



Keywords: Crystalline material, elastic crystal, functional crystal, multiple stimuli response.

Structure Investigation of a Novel Organocobalt Complex of B_{12} Model

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Abstract: We investigated the organocobalt complexes of B_{12} models as cobalt-based catalysts, which are extensively used in radical polymerization[1]. The cobaloxime complexes possessing an O-BF_2-O moiety were prepared (Fig. 1a). During crystallization experiments, apart from the crystals of (H_2O)Co-(dimethylglyoximeBF$_2$)$_2$ (**1**, Fig. 1b) were obtained, a new one-dimensional cobalt-based coordination polymer [Co-(dimethylglyoximeBF$_2$)$_2$]n (**2**, Fig. 1c) was discovered for the first time. Detailed characterizations via crystal structure determination from single crystal X-ray diffraction data at 100 K have been discussed. The crystal structure of **2** reveals that oxygen atoms bridge cobalt atoms, leading to an unusual coordination of polymer **2**. The ligand units of O-BF_2-O moiety in complex **2** orient above and down the main equatorial plane, adopting an extended chair conformation[2], and face the adjacent molecular neighbor's dimethylglyoxime (dmg) moiety planes. The shorter bond length of Co-O in **2** (1.942~1.963Å) results in the enhancement of the intramolecular interactions between the two closest molecular groups of O-Co-(dmgBF2)2 compared with the bond length of Co-O (2.275 Å) in **1**, consequently **2** displays a better thermostability than **1**. The application of this cobalt-based coordination polymer on free radical polymerization will be investigated in future studies.

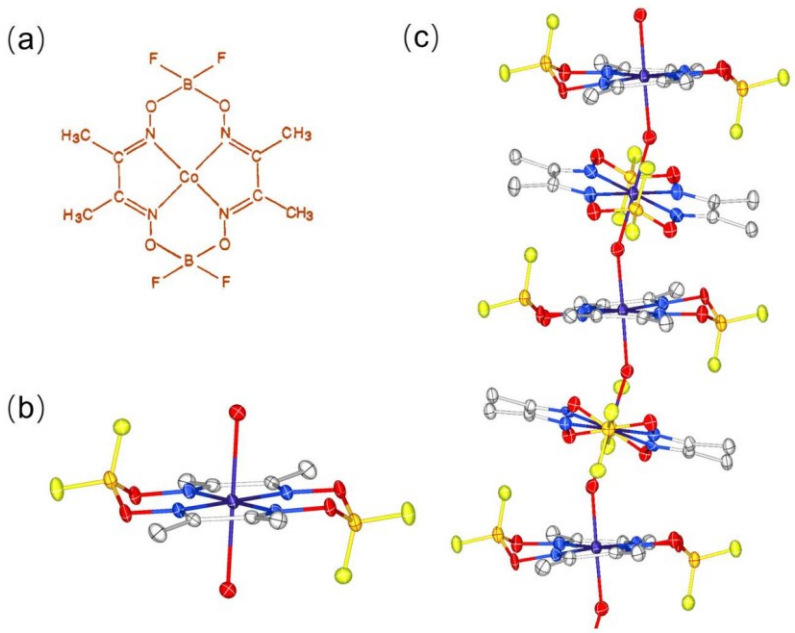

Figure 1. (a) Chemical structure of Co-(dmgBF$_2$)$_2$; (b) Crystal structure of complex **1**. The hydrogen atoms are not included in the ORTEP drawing for clarity, thermal ellipsoids are drawn at 50% probability; (c) Crystal structure of complex **2**, The hydrogen atoms are not included in the ORTEP drawing for clarity, tthermal ellipsoids are drawn at 50% probability

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Keywords: Organocobalt, complex, crystallization.

Shifting Enzyme-Catalyzed Reaction Equilibrium

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Abstract: Enantiomerically pure chiral amines are valuable intermediates for the synthesis of pharmaceutical compounds. The existing production of chiral amines frequently requires a multi-step process, involving expensive homogeneous catalysts and substantial energy consumption for purification. Biocatalytic pathways are nowadays known as potentially more sustainable alternatives. Indeed, transaminases (TA) are enzymes able to synthesize chiral amines from ketones and donor amines in mild conditions with excellent enantioselectivity. Nonetheless, the thermodynamic equilibrium of these reactions strongly favors the reactants[1,2]. Here, we develop a novel methodology, combining an enantioselective biocatalyzed reaction and a controlled crystallization purification process, displacing the reaction towards the synthesis of the chiral amine of interest: (R)-2-fluoro-α-methylbenzylamine ((R)-2-FMBA). In our process, an enantioselective transaminase enzyme is immobilized on a membrane, facilitating the reaction between 2-fluoroacetophenone (2-FAP) and isopropylamine (IPA), into acetone and (R)-2-FMBA, as illustrated in Figure 1A. A crystallization agent (CA), 3,3-diphenylpropionic acid (3,3-DPPA), forms two salts in the system: a product salt with the chiral amine (R)-2-FMBA:3,3-DPPA and a donor salt with the donor amine IPA:3,3-DPPA. The crystallization of the product salt and therefore, the continuous removal of the chiral amine from the solution, drive the equilibrium toward the transamination. Since the donor salt is more soluble than the product salt in the reaction medium, the reactant consumption also led to the solubilization of IPA:3,3-DPPA, continuously feeding the solution in the reactant.

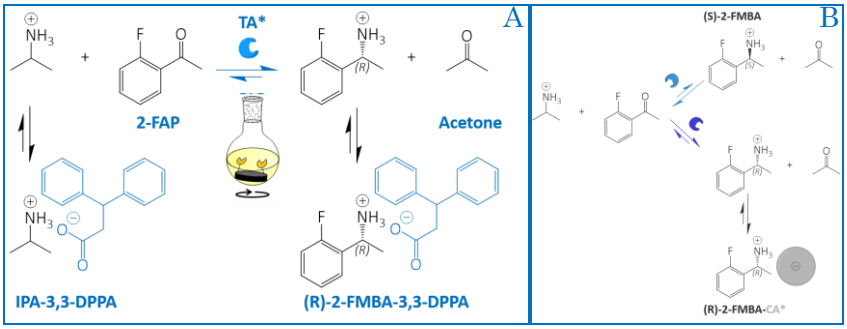

Figure 1. A: Shifted amine transaminase-catalyzed reaction by crystallization. B: Application of the deracemization process.

A further application of the system is the development of a deracemization process with two enantioselective transaminases and a chiral crystallization agent (CA*), by diastereoisomeric salt formation. With an appropriate chiral crystallizing agent targeting (R)-2-fluoro-α-methylbenzylamine and both of the (R)- and (S)-enantioselective transaminase, it is interesting to form a selective salt with the chiral amine of interest and recycle acetone and (S)-2-fluoro-α-methylbenzylamine into the desired diastereoisomeric salt, as illustrated in Figure 1B.

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Keywords: Chiral amine, transaminase, enzyme immobilization, enantioselective catalysis, salt crystallization, deracemization, crystallization agent.

Preferential Crystallization Assisted by Supercritical CO_2

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0.42

Abstract: Preferential crystallization is a kinetic separation technique limited to chiral molecules that crystallize as conglomerates. The technique relies on a difference in crystallization rates of enantiomers in the presence of enantiopure seeding.[1-3] Here, we are the first to employ supercritical carbon dioxide (SC-CO_2) to assist preferential crystallization. We do so, focusing on the nefiracetam-mandelic acid cocrystal system (Fig. 1), previously resolved by classical preferential crystallization[3].

The increased interest in SC-CO_2 reflects a growing interest in replacing conventional organic solvents known for their environmental drawbacks. SC-CO_2 presents an appealing alternative, given its environmentally friendly properties, including non-toxicity, non-flammability, chemical inertness, and recyclability through pressure reduction.[4,5] As research on SC-CO_2 expands, our study aims to contribute to the understanding of its potential in chiral resolution. While prior investigations have successfully utilized SC-CO_2 for resolution through diastereoisomeric formation[6-9], we here, are the first to showcase its potential in preferential crystallization.

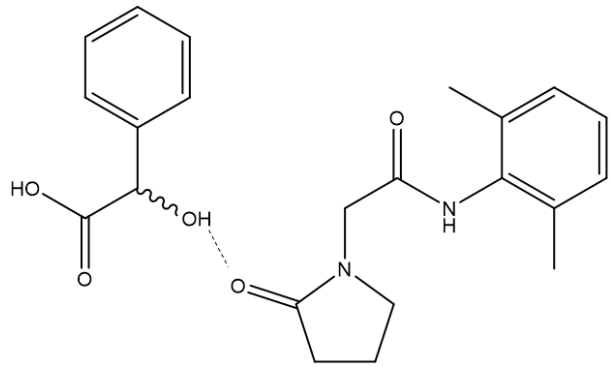

Figure 1. Nefiracetam-mandelic acid cocrystal system

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Keywords: Chirality, preferential crystallization, supercritical CO_2.

Crystalline Perfection and Thermoelectric Property Investigation of Melt-Grown Sb, Se Co-Doped Bi_2Te_3 Single Crystals

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0.43

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Abstract: Thermoelectric (TE) materials have found uses in various industries. Due to its extraordinary thermoelectric capabilities, bismuth telluride (Bi_2Te_3) stands out among these materials as a well-known and thoroughly investigated thermoelectric material. Bi_2Te_3, a thermoelectric material known for its exceptional performance at low temperatures, is used in Peltier coolers and refrigeration devices that operate under similar conditions. This research focuses on generating Bi_2Te_3 single crystals utilizing a highly efficient Melt-growth process. Powder XRD is used to determine the crystal structure and lattice properties. The crystalline quality of the samples is determined by High Resolution-XRD, which confirms a layered structure. Raman spectroscopy reveals three distinct peaks typical of bulk Bi_2Te_3. In addition, particle size analysis is performed to ascertain the precise crystallite size of the materials. The present work emphasizes the study of the Thermoelectric properties of Sb and Se-doped Bi_2Te_3 single crystals in the 10-400 K temperature range. The thermoelectric performance shows significant enhancement as the Seebeck coefficient increases to 253μV/K in $Bi_2Te_{2.7}Se_{0.3}$ and 211μV/K in $(Bi_{0.98}Sb_{0.02})_2Te_{2.7}Se_{0.3}$ which is equivalent to required value for Thermoelectric modules getting used in present cooler applications. Comparatively, the electrical conductivity rises by a factor of 3 for $Bi_2Te_{2.7}Se_{0.3}$ and 2.5 times for $(Bi_{0.98}Sb_{0.02})_2Te_{2.7}Se_{0.3}$ crystals at 400 K, in contrast to Bi_2Te_3. Moreover, the power factor experiences a remarkable 30-fold and 20-fold improvement for $Bi_2Te_{2.7}Se_{0.3}$ and $(Bi_{0.98}Sb_{0.02})_2Te_{2.7}Se_{0.3}$, respectively. Furthermore, the figure of merit values exhibits a significant enhancement by 28.5 times for $Bi_2Te_{2.7}Se_{0.3}$ and 14 times for $(Bi_{0.98}Sb_{0.02})_2Te_{2.7}Se_{0.3}$, compared to pristine Bi_2Te_3. The overall result implies a significant enhancement in the thermoelectric parameters of melt-grown Bi_2Te_3 single-crystal material.

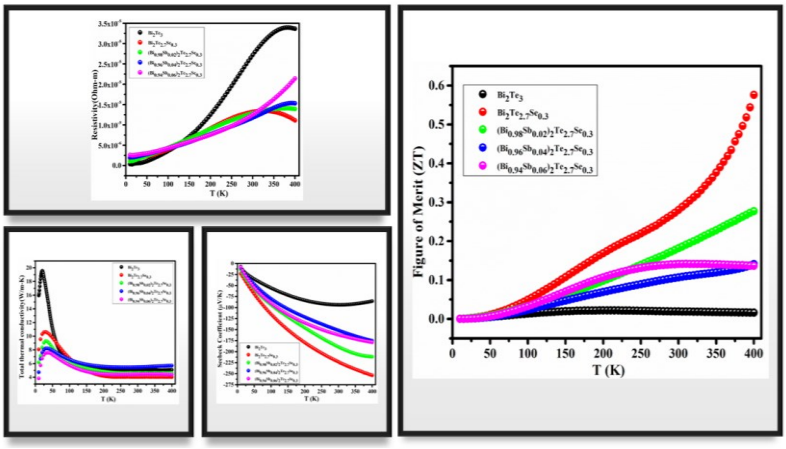

Figure 1. Electrical resistivity, thermal conductivity, Seebeck coefficient and ZT images of (a) Bi_2Te_3, (b) $Bi_2Te_{2.7}Se_{0.3}$, (c) $(Bi_{0.98}Sb_{0.02})_2Te_{2.7}Se_{0.3}$, (d) $(Bi_{0.96}Sb_{0.04})_2Te_{2.7}Se_{0.3}$, and (e) $(Bi_{0.94}Sb_{0.06})_2Te_{2.7}Se_{0.3}$ melt grown single crystal samples

Table 1. Seebeck Coefficient(S), Electrical conductivity (σ), thermal conductivity (κ), Power factor (PF), and figure of merit(ZT) for the prepared sample at 400K

Crystal	Seebeck (S μV/K)	Conductivity (σ x10^5 Sm^{-1})	Thermal conductivity (κ $Wm^{-1}K^{-1}$)	Power factor (μ$Wm^{-1}K^{-2}$)	ZT
Bi_2Te_3	- 78.74	0.29	5.08	194	0.02
$Bi_2Te_{2.7}Se_{0.3}$	-253.70	0.90	4.02	5800	0.57
$(Bi_{0.98}Sb_{0.02})_2Te_{2.7}Se_{0.3}$	-211.39	0.72	4.62	3210	0.28
$(Bi_{0.96}Sb_{0.04})_2Te_{2.7}Se_{0.3}$	-175.36	0.65	5.70	2010	0.14
$(Bi_{0.94}Sb_{0.06})_2Te_{2.7}Se_{0.3}$	-178.79	0.40	4.37	1490	0.14

Keywords: Single crystal, particle size analysis, crystalline perfection, melt-growth.

Green Technology for Salt Formation: Slurry Reactive Crystallization Studies for Papaverine HCl and 1:1 Haloperidol–Maleic Acid Salt

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0.44

Abstract: Papaverine HCl was successfully suspended by slurry reactive crystallization with the use of isopropyl lcohol (IPA) at 25°C, a solid-to-liquid ratio of 0.19 g/mL, an aging time of 8 h, a yield of 82.0 w/w%, crystal sizes of 200–400 μm, and the value for enthalpy of fusion of 154.5 J/g. The poor solubility of papaverine in IPA and better solubility of papaverine HCl in water-containing IPA had made the homogeneous nucleation of papaverine HCl dominate. Crystal size and crystallinity of papaverine HCl were time and temperature dependent. However, the 1:1 haloperidol–maleic acid salt was also successfully suspended and generated by slurry reactive crystallization with the use of water at 25°C, a solid-to-liquid ratio of 0.18 g/mL, an aging time of 8 h, a yield of 82.0 w/w%, crystal sizes of 500–1000 μm, and the value for enthalpy of fusion of 84.9 J/g. The poor solubility of haloperidol and 1:1 haloperidol–maleic acid salt in water had made the heterogeneous nucleation of 1:1 haloperidol–maleic acid salt dominate. Crystal size and crystallinity of 1:1 haloperidol–maleic acid salt became less sensitive to time and temperature. Comparing with grinding, solution reactive crystallization by cooling, and solution recrystallization by cooling, slurry reactive crystallization was a simple, robust, straightforward, low-constant-temperature, low-solvent-volume, and environmentally benign process giving comparable yield, particle size distribution, and crystallinity. Moreover, the use of a poor solvent in the slurry reactive crystallization enabled the recycling of the mother liquor without any significant loss in yield and crystallinity up to three cycles.

Keywords: Slurry, crystallization, reaction, salt, recycle.

Accelerating the Drying Process by Spherical Agglomeration: The Case of Benzoic Acid

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0.45

Abstract: Spherical agglomeration is a well-known process intensification method that offers several advantages, including material and energy savings associated with the reduction of processing steps and improvement in compressibility, packability, and flowability of the solid products. However, the energy-saving potential of spherical agglomeration is still underexplored in the context of energy conservation and carbon reduction in filtration and drying processes. By using benzoic acid, a common food preservative and precursor for industrial synthesis, as a model system, its fine crystals and spherical agglomerates were prepared separately, and the resulting drying behavior was evaluated. It was found that the round granules produced by spherical agglomeration could not only reduce the initial moisture content of the filter cake and shorten the drying time but also enhance the overall drying rate, having distinct drying curves and internal mechanisms compared to the ones of fine crystals by recrystallization. Notably, by comparison against the fine crystals of benzoic acid, spherical agglomerates had 3.4 times less specific cake resistance, 24% faster drying rate, and 71% reduction in the energy consumption for drying. In addition, the effect of different operating parameters (filter cake washing, amount and type of bridging liquid used, and mass of benzoic acid being handled per batch) on the drying behavior was investigated as well. It was revealed that filter cake washing and changes in the bridging liquid volume had a minimal impact on the drying behavior of benzoic acid round granules, while the choice of bridging liquid type and the mass of material being handled per batch showed significant differences in the drying behavior. Upon drying, the drying temperatures could influence both the drying behavior and the total energy consumption. These findings may serve as a platform for optimization in a bulk solid filtration and drying processes.

Keywords: Spherical agglomeration, benzoic acid, drying process.

Preparation of Multifunctional Water Treatment Agents for Crystallization Scale Inhibition, Corrosion Inhibition and Sterilization

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0.46

Abstract: Crystallization scaling, corrosion and microbial growth in equipment piping are serious problems that industrial circulating cooling water systems have to face. The addition of water treatment agents is considered to be the most effective and convenient way to solve this problem. Polyaspartic acid (PASP) and polyepoxysuccinic acid (PESA) have been widely studied as green water treatment agents due to their non-toxic, biodegradable and environmentally friendly features. In this paper, PASP and PESA are used as raw materials and modified monomers containing amino groups are used for ring-opening or copolymerization to synthesize four kinds of multifunctional water treatment agents, so that they have the properties of scale inhibition, corrosion inhibition and sterilization at the same time, and they are studied in detail.

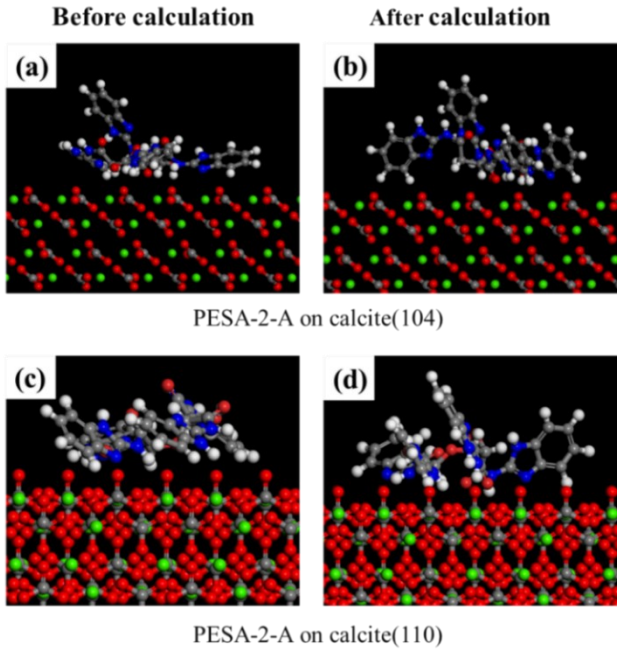

Figure 1 Molecular dynamics simulation calculation of PESA-2-A and calcite. (a, c) is before the interaction and (b, d) is after the interaction

Keywords: Crystallization fouling, circulating cooling water, multifunction water treatment reagent, scale inhibition and dispersion, corrosion inhibition, germicide and algicide.

POSTER PRESENTATION

Altering the Substrate Preference of a Quorum Quenching Lactonase Using Rational Design

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P.01

Abstract: Many bacteria, including Gram-negative pathogenic strains like *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* use *N*-acyl L-homoserine lactones (AHLs) with varying acyl carbon chain lengths as their signaling molecule. This signal accumulates with increasing cell density as the bacteria populate an environment, and at a threshold concentration bind to cytoplasmic transcription factors in the cell to coordinate changes in gene expression on the community level. This phenomenon is known as quorum sensing and controls behaviors including virulence, antibiotic resistance, and biofilm formation. Lactonases are esterases that hydrolyze the lactone rings in AHL communication signals, rendering them ineffective for quorum sensing. Lactonases are thus known as quorum quenching enzymes and can be used to turn off virulence and biofilm formation and modulate antibiotic resistance and susceptibility profiles.

As different bacteria respond to AHLs with different acyl chain lengths, the substrate preference of lactonases may be used to specifically target the communication of certain bacterial species. Previous characterization of naturally occurring enzymes revealed that most lactonases have broad specificity and prefer longer acyl chain lengths. Here, we aimed to generate lactonase variants with increased specificity for short chain substrates, both for application as well as for understanding how enzymes might exclude longer/larger substrates from smaller ones.

We focused on GcL, a thermostable broad-spectrum lactonase from *Parageobacillus caldoxylosilyticus*. Analysis of crystal structures of GcL revealed key amino acid positions interacting with the AHL acyl tail that we subjected to saturation mutagenesis. Libraries were screened for mutants with altered substrate preference, preferring short-chain AHLs vs. long-chain AHLs. We combined several favorable mutations and generated mutants that have up to 200-fold shift in preference for short-chain substrates. Crystal structures of these mutants showed that these changes in substrate specificity arise from a reshaping of the active site binding cleft and altered active site loop configuration for alternative substrate binding conformation. This data illuminates our understanding of the molecular determinants involved in the substrate preference of these enzymes and will serve as a platform to create more specific quorum quenchers to study microbial communication and determine the application potential of specific interference in quorum sensing.

Keywords: Lactonases, enzyme mechanism, cocrystalisation, substrate soaking, SAXS.

Effect of Temperature and Time on Crystal Growth and Phase Transition of MIL-101(Cr) for CO_2/CH_4 Separation

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P.02

Abstract: Metal-organic framework, MIL-101(Cr), was synthesized through the hydrothermal method using chromium (III) chloride hexahydrate ($CrCl_3{\cdot}6H_2O$) without HF at different temperatures (463-493 K) and times (1-24 hr). The resulting materials were characterized through Powder X-Ray Diffraction (PXRD), Field Emission Scanning Electron Microscope (FE-SEM) analysis, and surface area measurement utilizing N_2 adsorption/desorption at 77 K. The MIL-101(Cr) was synthesized successfully in a shot crystallization time of 4 hr at 493 K. However, when the crystallization temperature was reduced to 463 K, the crystal growth rate of MIL-101(Cr) decreased. Because the phase transition took place to produce MIL-53(Cr) rather than MIL-101(Cr). The crystallization time has to be increased to more than 4 hr at low temperatures to successfully synthesize MIL-101(Cr). We can draw a map of the phase transition between MIL-101(Cr) and MIL-53(Cr) on temperature and time axes from this finding. Furthermore, synthesized materials were used to separate CO_2 and CH_4 gas mixtures at 273 and 298 K up to 1 bar. A high CO_2/CH_4 selectivity of 60 can be obtained in synthesized MIL-101(Cr) which is promoted as a candidate sorbent.

Keywords: Crystallization, crystal growth rate, phase transition, metal-organic framework, MIL-101, MIL-53.

Crystallization-Induced Diastereomeric Transformation of Chiral Primary Amine Using Homogeneous Ir-based Racemization Catalyst

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P.03

Abstract: Chiral amines are an important structural component in pharmaceutical molecules and natural products, and there is always a demand for access to enantiomerically pure forms.Although primary amines, in particular, are often susceptible to oxidation and require careful handling, the deracemization of primary amines by crystallization except for amino acids, remains challenge because the racemization reactions that can be realized simultaneously with conglomerate or diastereomer forming conditions are not studied.

In this study, we achieved crystallization-induced diastereomeric transformation (CIDT), which is one of deracemization processes by crystallization, of a chiral primary amine, 4-cyano-1-aminoindane (**1**), using an Ir-based racemization catalyst (Figure 1). We have previously reported that **1** forms a diastereomeric solid solution with di-*p*-toluoyl-L-tartaric acid **2**. Its resolution was achieved by combining crystallization and enantioselective dissolution based on the phase diagram study[1]. Here, we introduced (pentamethylcyclopentadienyl) iridium(III) diiodide dimer as a racemization catalyst, and successfully carried out CIDT of **1**·L-**2** in the solid phase up to 60% in a single crystallization. Interestingly, this composition is close to the solid solution limit of the diastereomers, suggesting a connection between the driving force of crystallization-based deracemization and the thermodynamic equilibrium state[2]. In this presentation, the phase diagrams and chiral resolution by crystallizations will be discussed in detail.

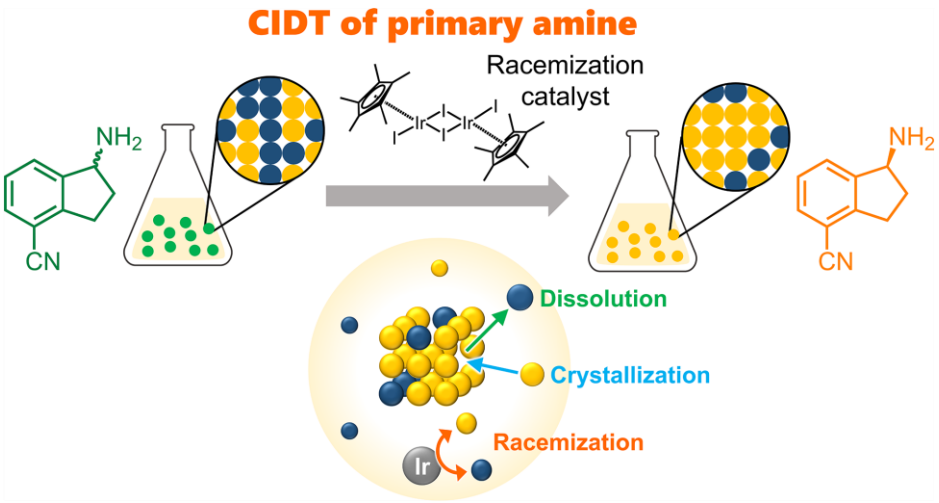

Figure 1. CIDT of salt of 4-cyano-1-aminoindane and di-*p*-toluoyl-L-tartaric acid with Ir catalyst

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Keywords: Chiral resolution, deracemization, solid solution, homogeneous catalyst.

Influence of the Crystallisation Solution Environment on the Structural Pathway from Solute Solvation to the Polymorphic Forms of Tolfenamic Acid

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P.04

Abstract: The influence of the solution environment on the solution crystallisation of the conformational polymorphic forms I and II of tolfenamic acid is assessed through integrations of multi-scale (molecular, cluster and crystallographic) modelling with polymorphic screening using polythermal crystallisation as a function of solvent selection. Solid-state analysis reveals the contrasting crystal chemistry with the strongest synthon involving hydrogen bonding synthons and $\pi - \pi$ van der Waals interactions for forms I and II, respectively. Analysis of the molecular conformational energies reveals the molecular structures for forms I and II to be very close which is matched by their calculated lattice energies, consistent with the observed enantiotropic relationship between the two forms with form I being more stable under ambient conditions than the more close-packed form II. Crystallisation as a function of both solute concentration and solution cooling rate reveals form II to be mostly more preferred than form I. The higher stability of the form II conformer together with its easier conformational adjustment during the formation of form II crystals, is consistent with its greater crystallisability compared to the more stable form I. Solute concentration analysis of the relative stabilities of the two forms as a function of their sizes reveals that smaller cluster sizes, i.e. high supersaturations, are required to stabilise the crystal structure for form I with respect to form II. Polymorphic screening as a function of solvent confirms the predicted poor crystallisability of form I whose crystallisation is preferred at higher solute concentrations and lower cooling rates in polar solvents but less so in toluene, the latter being consistent with $\pi - \pi$ solute/solvent interactions promoting hydrogen bonded synthon at the expense of $\pi - \pi$ solute interactions. Modelling work correlates well with the observed crystallisation behaviour, highlighting the importance of understanding solvent selection and solution state structure at the molecular-scale level in the direction of the polymorphic outcomes, confirmed by the higher crystallisability of metastable form II.

Acknowledgements: Y. L. acknowledges funding support from China Scholarship Council for a visiting scholarship at University of Leeds. This work was also supported by Innovate UK through D-DAP Project (TS/T011262/1) and KTP with CCDC (KTP 12057). This work also builds upon software developments in collaboration with Drs R Hammond and J Pickering at Leeds funded through UK AMSCI ADDoPT (Grant No. 14060) and UK EPSRC Synthonic Engineering Programs (EP/I028293/1).

Keywords: Conformational analysis, intrinsic synthon chemistry, molecular modelling, molecular cluster, polymorphic form, molecular solvation, tolfenamic acid.

Highly Crystalline Poly-3-Hexylthiophene Particles Prepared from Pickering Emulsions Stabilized by Alkylamine Functionalized Graphene Quantum Dots

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P.05

Abstract: Pickering emulsions are solid-stabilized emulsions that have received much attention for their high emulsion stability and ability to form functional emulsions compared to existing emulsions. The stability of Pickering emulsions is related to the detachment energy at the interface and depends on the geometry and wettability of the particle-type emulsifier. Therefore, surface property control of the particle is essential. Graphene quantum dots (GQDs) were functionalized with octylamine (C8), dodecylamine (C12) and hexadecylamine (C16), and the stability of the oil-in-water Pickering emulsions was compared according to the changed surface properties. The detachment energy was calculated based on the structure and wettability of the pickering emulsifier. Among the three GQDs, C12-GQDs, which had the highest detachment energy at the CHCl3-water interface, formed the most stable Pickering emulsions due to the appropriate balance between the water-oil phases. Crystalline poly-3-hexylthiopene nanoparticles (P3HT NPs) were synthesized from the Pickering emulsions with C12-GQDs. Pickering emulsions formed with C12-GQDs not only have improved stability, but can also synthesize higher crystalllinity P3HT NPs due to the lower solvent evaporation rate.

Keywords: Graphene quantum dots, amphiphilicity, pickering emulsion, solvent barrier properties, P3HT nanoparticle.

Surface Lattice Matching Induced by Inorganic-Derived Zero-Dimensional Perovskite for High-Efficiency and Stable All-Inorganic Perovskite Solar Cells

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P.06

Abstract: Inverted $CsPbI_3$ perovskite solar cells (PSCs), derived from inorganic materials, are promising for next-generation photovoltaic applications due to their inherent thermal and photo-stability and their compatibility with tandem configurations. However, their performance and stability are currently inferior to n-i-p structures, mainly due to issues with energetic alignment and a high density of interfacial defects. In this study, we introduce an inorganic zero-dimensional Cs_4PbBr_6, known for its effective lattice strain retention and stable structure, as a surface anchoring layer with $CsPbI_3$. This Cs_4PbBr_6 perovskite layer enhances the electron-selective junction, promoting efficient charge extraction and significantly reducing non-radiative recombination. Consequently, $CsPbI_3$ PSCs incorporating Cs_4PbBr_6 achieve a record power conversion efficiency (PCE) of 21.03% from a single unit cell and 17.39% from a 64 cm^2 module. Furthermore, these devices demonstrate remarkable stability, retaining 92.48% of their initial efficiency after 1000 hours under simultaneous 1-sun illumination and damp heat conditions (85°C, 85% relative humidity).

Keywords: Perovskite, lattice strain retention.

A Novel Polymorph Search of Pharmaceutical Crystals in Microgravity - Crystallization Phenomena of Indomethacin in Indomethacin-Acemetacin-EtOH/H_2O System

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P.07

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Abstract: An important aspect of pharmaceuticals is bioavailability, which is a measure of how well a drug product reaches and acts in the systemic circulation of the blood. Bioavailability is affected by the solubility of the drug, improving solubility is an important factor in medicine. One way to improve solubility is to destabilize the crystal structure, and controlling the crystalline polymorph is important. Crystal polymorph is a phenomena the crystal structure of the same compound differs, and it is estimated to be present in about 80% of pharmaceuticals[1]. Addition of impurities, adjustment of stirring speed, and control of supersaturation are examples of polymorph control. In recent years, crystallization experiments have been conducted under microgravity conditions on the International Space Station (ISS) in order to create innovative pharmaceuticals. Gravity has a negative impact on the reproducibility of nucleation and growth by inducing two-dimensional nucleation through density-difference convection and particle sedimentation phenomena that depend on the solution concentration[2]. Experiments on the ISS are attracting attention as a new experimental system because microgravity experiments can be conducted for long periods of time, approximately 30 days. On the other hands, Indomethacin (IMC) has been used in many pharmaceutical preparations as an anti-inflammatory and anti-pyretic drug. IMC is reported to show a complicated polymorphism that consists of have true polymorphs and a wide range of solvate forms, which are collectively named β-form. Among the true polymorphs, only two, which are referred to as the most stable γ form and metastable α-form, are regularly produced and are potentially the most useful forms. The thermodynamic stability of the two polymorphs of IMC at atmospheric temperature and pressure is in the order of α-form < γ-form.

In this study, above indomethacin (IMC) was used as the crystallization target material, and acemetacin (ACM), converted to IMC in vivo after human administration, was used as the impurity, ethanol (EtOH) as solvent, and water (H_2O) as antisolvent. IMC was crystallized by the counter diffusion method, that is a concentration gradient is formed in the capillary by contacting the solution inside and outside the capillary through the agarose gel. The capillary is filled with IMC-ACM-EtOH solution, and a sealing compound is attached to one end of the capillary and a gel tube filled with agarose to the opposite end. The capillary and H_2O are loaded into a polyethylene terephthalate container and placed in a thermostatic chamber. With the capillary in the thermostatic chamber, the sample is crystallized on the ISS for about 30 days using the High Quality Protein Crystallization Service provided by the Japan Manned Space Systems Corporation (JAMSS). The same sample was also crystallized on the ground for the same number of days. The crystals obtained from each gravity environment were measured by Raman microscopy.

The experimental results suggested that the difference of gravity environment affects the polymorphism of IMC, and that the effects of ACM added on the crystallization phenomena of IMC polymorphs are varied by the gravity environment.

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Keywords: Crystallization, microgravity, polymorph.

Mechanisms of Photomechanical Response, Reversible Photochromic and Mechanochromic Luminescence based on Polymorphic-Modulated Acylhydrazone Crystals

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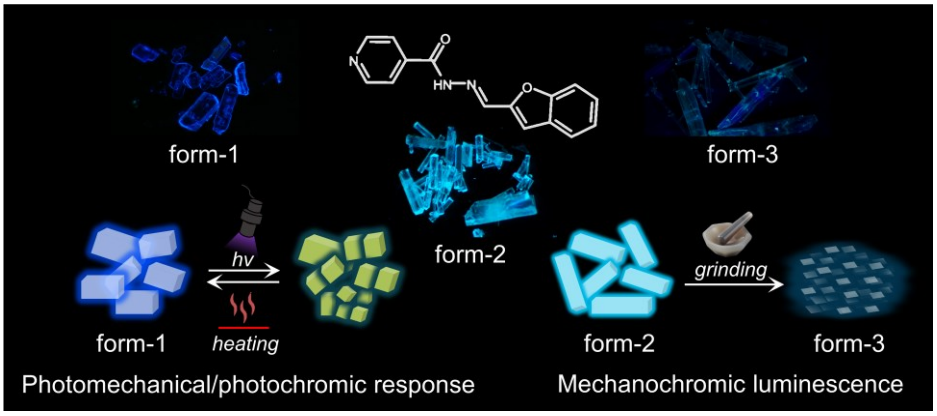
P.08

Abstract:

Stimuli-responsive crystalline materials have received much attention for being potential candidates of smart materials. However, the occurrence of polymorphism-driven responses in crystalline materials remains interesting but rare. Herein, three polymorphs of an acylhydrazone derivative, N'-[(E)-(1-benzofuran-2-yl) methylidene] pyridine-4-carbohydrazide (BFMP) were prepared. Form-1 undergoes a photomechanical response via *E*→*Z* photoisomerization under UV irradiation, accompanied by a decrease in fluorescence intensity and a change from colorless to yellow. Two types of *Z*→*E* thermal isomerization mechanisms with significant differences in conversion rate were observed at different temperatures in form-1. The solid-melt-solid transition has a faster conversion rate compared to the solid-solid transition due to freedom from lattice confinement. Conversely, no photoisomerization occurs in form-2 and form-3. The transition from form-2 to form-3 can be achieved under grinding, coupled with a significant decrease in fluorescence intensity. The similar molecular stacking pattern of form-2 and form-3 provides a structural basis for the grinding-induced crystalline transition behavior. Additionally, this study extends the application of acylhydrazone derivatives to repeatable optical printing scenarios.

Graphical abstract:



Keywords: Polymorphism, fluorescence, photoisomerization, stimuli-responsive crystal.

Molecular Recognition and Assembly of Cocrystal and Its Performance

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Abstract: Cocrystal is defined as a single crystalline structure at room temperature composed of two or more components in a certain stoichiometric ratio with no proton transfer between components acting on non-colvent bonds, such as hydrogen bonding, van der Waals interactions, halogen bonding, π··π stacking, etc., through specific molecular recognition processes. Cuttentlly, cocrystals or cocrystallization has been widely used in the fields of pharmaceutialc industry, fine chemical industry, functional materials, energetic materials, and substance separation and purification to btain cocrystal products with better quality and performance,by fully utilizing the synergistic effect between each components. However, the molecular recognition and self-assembly mechanism of the cocrystal formation process has not yet been revealed from a scientific perspective, which severely limits the development and application of cocrystallization technology. Under the above background, the molecular recognition and assembly evolution mechanism of cocrystals formation are systematically investigated in detail through the combination of experimental verification, theoretical analysis and molecular simulation, from the molecular and supramolecular view of points. The conformational search and topological analysis of coformers shows that hydrogen bonding or halogen bonding plays a dominant role in the cocrystallization process, and the coformers will referentially match into the non-covalent interaction topological optimal forms rather than the energy optimal forms. And on this basis, the "multimers - double equilibrium" self-assembly evolution path in the cocrystal formation process was proposed. Moreover, guided by the above theories, suitable cocrystal coformers were screened to address the issues of poor solubility and low dissolution rate of poorly soluble drugs. Drug cocrystals with a 2.8-fold and 74-fold increase in solubility and dissolution ratewere successfully synthesized. Additionally, some multi-responsive and functional cocrystals with rotation, rolling, torsion and flexibility were successfully designed and developed using the manipulation of cocrystal coformers and crystal forms, to solve the problem of single deformation mode in azo-materials. These researches indicate that the cocrystallization strategy is an effective solution tomanipulate material properties.

Keywords: Cocrystallization/cocrystals, molecular recognition mechanism, self-assembly evolution, performance manipulation.

Fracture Induced Surface Charges in Piezoelectric Pharmaceutical Crystals

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P.10

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Abstract: Surface chemistry plays a crucial role in controlling physiochemical properties of molecular crystals. In case of pharmaceutical crystals one of the common surface phenomena is generation of surface charges during processing which is normally attributed to triboelectricity. Apart from this, there are other sources of surface charge in pharmaceutical crystals. For example, noncentrosymmetric molecular crystals under uniform mechanical stress produce surface charges which is called piezoelectricity (Fig. 1a). Some of our recent findings intrigued us to investigate the formation of surface charge by mechanical fracture in the vast domain of pharmaceutical crystals. Herein, we report emergence of mechanical fracture induced surface charge in pharmaceutical piezoelectric crystals (Fig. 1b). With the help of Cambridge Structural Database, we searched for noncentrosymmetric (NCS) as well as centrosymmetric (CS) pharmaceutical crystals. Fracture tests were performed on several crystals under stereomicroscope. It was found that some of the NCS crystals show self-attraction behaviour followed by recombination of the crystal shards. We further continued our investigation on levofloxacin hemihydrate (LH) crystals and compared it with nalidixic acid (NA) crystals (Fig. 1c). We observed a high attraction behaviour in LH crystals but no attraction or actuation was found in NA crystals (Fig. 1d & e). Kelvin probe force microscopy (KPFM) was performed to establish the generation of the high surface potential on fractured surfaces of LH crystals (Fig. 1f). Further, flowability, compactibility and tabletability studies were performed for these crystals to establish the effect of surface charges. In this work, we show fracture induced surface charges in pharmaceutical piezoelectric crystals and the effect on bulk properties during processing and manufacturing of pharmaceutical solids

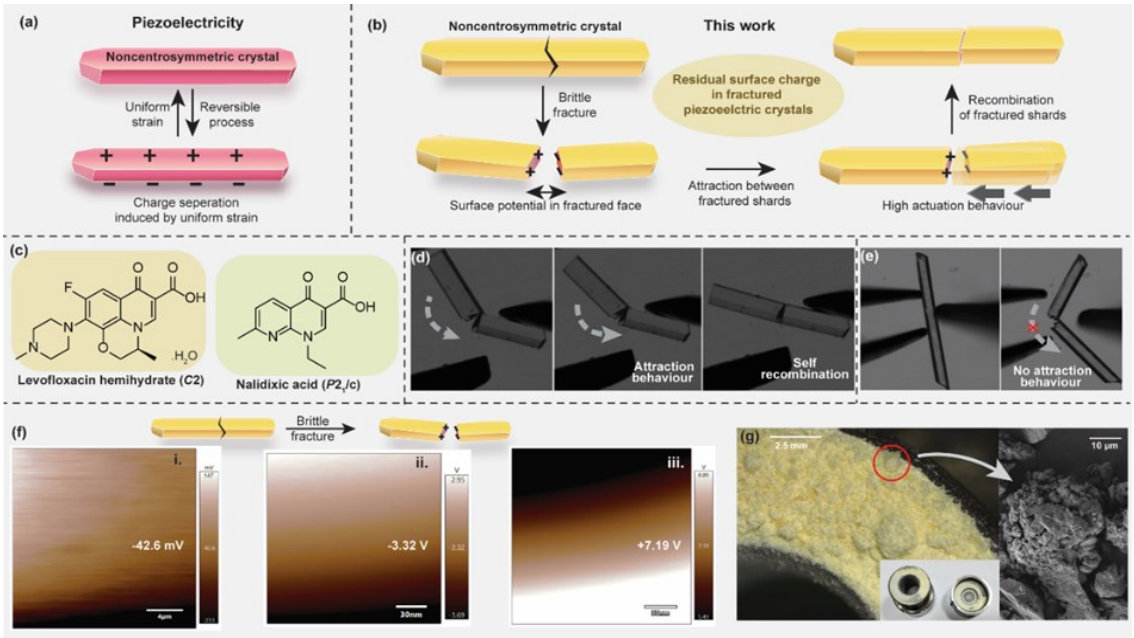

Figure 1. Illustration of (a) piezoelectricity & (b) fracture induced surface charges in piezoelectric crystals. (c) Molecular structure of levofloxacin hemihydrate (NCS) & nalidixic acid (CS) crystal. (d) Attraction behaviour in fractured LH crystal and (e) absence of attraction behaviour in NA crystal. (f) Kelvin probe force microscopy (KPFM) imaging of pristine and opposite fractured faces of LH crystal. (g) Optical image (left) showing generation of agglomerates after ball-mill, SEM image of an agglomerate (right).

Keywords: API crystals, piezoelectricity, surface charges, tabletability.

Relating Surfactant Crystal Properties to Pickering Emulsion Stability

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Abstract: Pickering emulsions, stabilized by surfactant crystals, are found in many everyday products such as cosmetics, food, and pharmaceuticals. Fat crystals (mono-, di-, and triglycerides) are known to stabilize water-in-oil (w/o) emulsions through adsorption at the oil/water interface (Pickering stabilization) and/or by forming a network of crystals within the continuous phase.[1-3] The relative contribution of these stabilization modes depends on the crystallization behavior and properties of the fat crystals, as well as the composition of the oil phase and the emulsification process conditions.

To understand the relationship between fat crystal properties and their role in stabilizing Pickering emulsions, we examined two different emulsion systems. The first system involved a w/o emulsion prepared using medium-chain triglycerides (MCT) oil as the continuous phase, with pure monoglyceride or triglyceride as the solid surfactant. The second system consisted of propylene glycol (PG) dispersed in mineral oil, with mono- and diglycerides (MDG) serving as the stabilizer. The microstructure of the emulsions was analyzed using polarized light microscopy, confocal fluorescence microscopy, and small-angle X-ray scattering.

In the case of the w/o emulsion, the needle-like monoglyceride crystals formed an interfacial layer around individual water droplets and created a network of crystals within the continuous phase. This dual structure prevented inter-droplet contact and coalescence. Conversely, the triglyceride crystallized with a spherulitic morphology exclusively in the continuous phase. These findings support the idea that the combination of Pickering stabilization and network stabilization contributes to the long-term stability of emulsions.

For the PG/mineral oil system, the temperature at which emulsification was carried out affected the emulsion's microstructure and stability under accelerated testing conditions. When the MDG solution in mineral oil was cooled, plate-like crystals (L_α polymorph) initially formed at 53 °C, followed by the crystallization of spherulites (β polymorph) at 40 °C. There, MDG acted as a dual function stabilizer where plate-like crystals act as Pickering particles as they formed a close-fitting shell around the PG droplets, whereas those with a spherulitic morphology primarily formed a network in the bulk oil phase. When emulsification was carried out pre or post crystallization of both the polymorphs formed at 55 or 35 °C respectively, relatively more stable emulsions were formed. However, when emulsification occurred at 45 °C (post crystallization of L_α but pre crystallization of β polymorph), unstable emulsion was formed. Microscope images indicated that the network formed was less continuous where large plate-like crystals were predominant in the bulk phase under this condition, whereas continuous network with plate-like crystals with smaller sizes could be observed for the other two emulsions. This suggested that processing conditions affected properties of MDG crystals and emulsion microstructure, which in turn affected the kinetic stability of the PG/oil emulsions.

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Keywords: Pickering emulsion, multiphase system, surfactant, fat crystals, morphology.

Influence of Water Content on Polymorphic Crystallization of Dihydrosphingomyelin

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Abstract: Dihydrosphingomyelin (DHSM), a type of phospholipid, is an important compound as a raw material for liposomes used in drug delivery systems for anticancer agents. Therefore, pharmaceutical-grade quality is required, but more research needs to be conducted on its crystal characteristics and polymorphism. By investigating the factors affecting the crystal characteristics and polymorphism of DHSM, this study could contribute to developing more effective drug delivery systems and enhance the quality of pharmaceutical-grade DHSM.

DHSM (90 mg) was dissolved in various mixed solvents (3 mL). Crystallization was performed by cooling from 65°C to 5°C at 5°C/h. During cooling, the time and temperature at which crystals appeared were recorded using a camera and a thermocouple. Precipitated crystals were recovered, and X-ray diffraction (XRD) analysis was performed to examine polymorphism. The moisture content in the crystals was measured using the Karl Fischer method.

Crystals obtained in various solvents could be classified into three types of crystals with different peak positions: Types I, II, and III. Type I tended to precipitate at lower crystallization temperatures, while Type III tended to precipitate at higher temperatures. Next, DHSM solutions, including trace amounts of water (10 μL), were prepared using a mixed solvent of THF/methanol=94:6, and crystallization was performed. Samples with added trace amounts of water showed higher crystallization temperatures than those without(Fig. 1). XRD analysis revealed that the sample with added trace amounts of water precipitated highly crystalline Type III crystals. In contrast, the sample without water addition precipitated Type I crystals(Fig. 2). It is considered that the addition of trace amounts of water increased the temperature at which crystals precipitate, affecting crystallinity and polymorphism. Based on these results, similar experiments were conducted by varying the water content from 2 μL to 20 μL, confirming the precipitation of Type I crystals and a decrease in crystallinity in samples with lower water content. Therefore, an appropriate water content was required to precipitate highly crystalline Type III crystals. This study found that DHSM exists in addition to commercially available crystals in two other polymorphic forms (Types II and III). Additionally, trace amounts of water were identified as significant factors in the precipitation of Type III crystals.

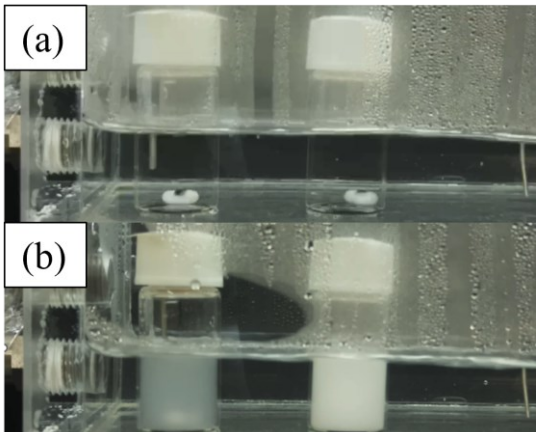

Figure 1. Cooling process (a) before cooling, (b) at 43.72 °C. (Right) No water added, (left) 10 μL of water added

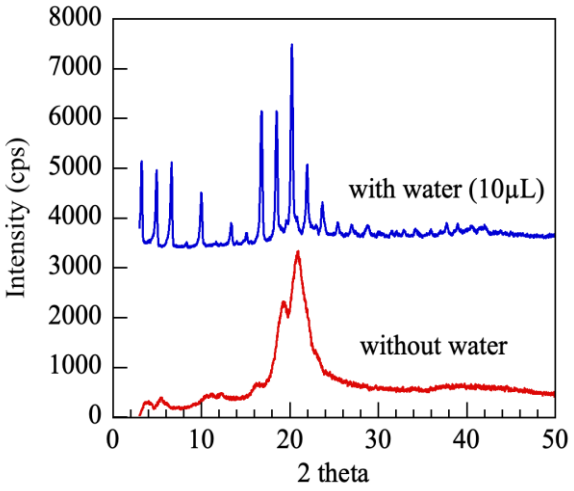

Figure 2. XRD patterns of DHSM obtained by adding water.

Keywords: Phosholipid, polymorphs, crystallinity.

Symmetry Breaking and Chirality: A Journey Through Molecular Crystals

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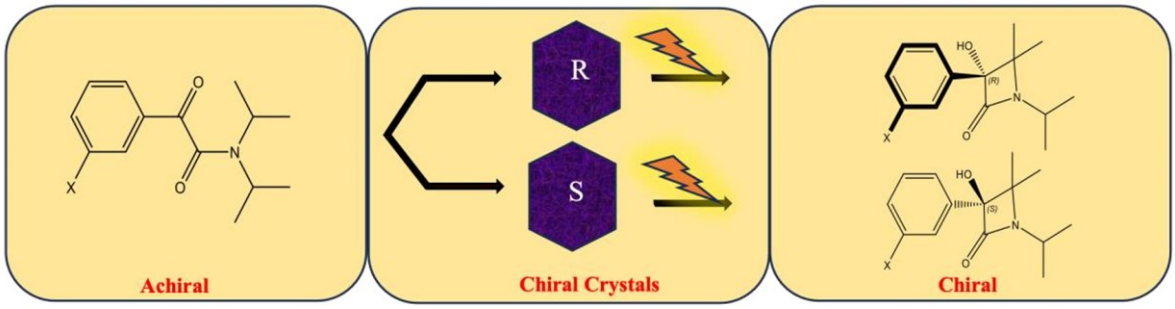
P.13

Abstract: Chirality has become increasingly significant across a spectrum of disciplines, such as chemistry, materials science, biology, and the pharmaceutical industry[1]. Chiral crystals have garnered significant attention due to their potential applications in enantioselective catalysis, chiral sensing devices, and as fundamental components for innovative functional materials. The study of chiral symmetry breaking in molecular crystals presents an engaging interdisciplinary research area[2]. Under non-equilibrium conditions, the symmetric state becomes unstable and the spontaneous emergence of a non-zero enantiomeric excess arises from an achiral state through a chiral symmetry breaking transition[3]. This study focuses on a series of achiral X-oxoamide molecules that crystallize as chiral crystals, exhibiting an uncommon similarity in their crystal structure. Utilizing UV light, we can freeze the chirality in the solid-state and fix the stereo genic centres into a preferred configuration, which enables the separation of enantiomers. This transition from the supramolecular chirality to molecular chirality is significant, as it enhances the ability to control and manipulate chiral properties of materials at a molecular level. Characterization techniques such as X-ray diffraction, HPLC, spectroscopy, and computational modelling are employed to investigate chiral symmetry breaking. These methods offer insights into the three-dimensional arrangement of molecules within the crystal lattice, elucidating the origins of chirality and the critical intermolecular interactions, including hydrogen bonding, van der Waals forces, and electrostatic interactions. These interactions play a pivotal role in the stability and properties of molecular crystals. By comprehending the intricate relationships between molecular structure, intermolecular interactions, and crystal symmetry, we can unravel the mechanisms underlying chirality emergence and pave the way for designing advanced materials with tailored chirality and desired properties.



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3. J.PhotoChem.Rev.,2006,183–196.

Keywords: Chirality, crystallization, chiral symmetry breaking, photoirradiation.

Influence of Ultrasound on Crystal Nucleation, Morphology and Crystallization of Maltol Polymorphs I and II From Aqueous Solution

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Abstract: The influence of ultrasound on the nucleation control and separation of stable Form-I and metastable Form-II polymorphs of maltol from aqueous solution was studied. This study involved varying ultrasound parameters such as power (ranging from 75W to 225W), pulse rate (from 10% to 50%), and insonation time (2, 4, 6 minutes) at room temperature and at different supersaturation levels. In addition to the expected effects of supersaturation on induction time, nucleation, and morphology of the maltol polymorphs, ultrasound was found to have a significant influence on nucleation control and separation of the polymorphs. The results revealed that ultrasound promotes the nucleation of maltol polymorphs with shorter induction times by creating nucleation hot spots through cavitation effect, and improves the quality of the crystals. Notably, under specific conditions, ultrasound induced the nucleation of the rare metastable Form-II polymorph of maltol in aqueous solution, while without ultrasound, only the stable Form-I polymorph was obtained. The morphology of the nucleated polymorphs was observed using in-situ optical microscopy, and their structure was confirmed through powder X-ray diffraction (PXRD) and single crystal X-ray diffraction (SCXRD) analyses. Furthermore, the thermal stability of the grown stable Form-I and metastable Form-II polymorphs of maltol was studied using differential scanning calorimetry (DSC).

Keywords: Ultrasonication, nucleation, polymorphism, morphology, crystallization, separation.

Effect of Methanol on the Solubility and Nucleation Point of Papain

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Abstract: The solubility is important information for enhancing the industrial crystallization design and the enzyme crystallization as well. In this work, the solubility of crystalline papain was measured by the gravimetric method. An excess amount of papain powder was dissolved in the buffer solution (pH5) and buffer solution with methanol ratio (10mL:0mL, 10:1, 10:2, 10:3, 10:5.2, 10:8.4, 10:20) with controlling the different temperatures (20, 10, 0, and -8°C) to observe the saturated point. The saturated solution was filtrated and monitored by refractometer (Reflective Index) each range of hours. The concentrations of the saturated solution were measured by evaporation to dryness.

The studying of the supersaturated points of this papain was performed in two methods. First testing as conducted the experiment by step cooling the saturated solution to the temperature of 3, 0, -3, -4, -6 and -8°C until crystal nucleation. Second as performed the experiment by dropping-wise (0.2mL/20min) of methanol into the saturated papain solution until reaching cloud point (nucleation point) with observing by Dinoe-camera, Focus Beam Reflectance Measurement (FBRM) and Easy-viewer camera. The weigh fraction of usage methanol at the cloud points were calculated and plotted in phase-diagram. The activity of redissolution papain was determined by Ruth's methodology.

This papain powder was found out the result that the solubility was raised with increasing temperature and decreased while increasing the ratio of methanol. Even though, there were trend of difference.

From 1st experimental of supersaturation studying resulted that the saturation of papain (zero methanol, from saturation at 20°C) to reached supersaturated point at about -3°C and it had taken time for 3days. Crystal shape is likely to needle. From the 2nd experiment conducted by dropping-wise of methanol was found out nucleation points at higher fraction of methanol than solublity at 20°C and 0°C. Therefore, phase-diagram of saturation curve and supersaturation by using methanol. The activity numbers were stable after using methanol.

Keywords: Papain, saturation, supersaturation, crystallization, activity.

Effect of Ethanol on the Crystallization of the Polymorphs of DL-Methionine

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P.16

Abstract: DL-methionine plays a crucial role in maintaining health and is utilized in various fields such as pharmaceuticals, dietary supplements, animal feed, and chemical synthesis. When crystallized, DL-methionine can exist in three forms: α, which is metastable, β, which is stable, and γ, the most stable form. Typically, α and β forms nucleate simultaneously during crystallization, eventually transforming into the γ form. In this study, an antisolvent crystallization process was conducted to induce nucleation, focusing specifically on obtaining a pure α form of the crystal in order to estimate its nucleation rate. Raman spectroscopy and microscopy were employed to identify the crystal polymorph, while the solubility of DL-methionine in each antisolvent fraction was measured to determine the supersaturation ratio. Additionally, the nucleation rate of the α form was assessed using Focus Beam Reflectance Measurement (FBRM). The relationship between the solubility of DL-methionine and the quantity of ethanol added as an antisolvent was performed, an increase in the volume fraction of ethanol (x) in the mother solution was resulted in the solubility decreased, as refer to the higher driving force (supersaturation ratio (S)). Nucleation rate (J) of the α form was increasing with increasing the volume fraction of ethanol. Furthermore, the transformation of polymorph(s) was also carried out as an offline-Raman. Therefore, this research delved to understanding the solubility, the nucleation and transformation stage, and nucleation rate of pure α form of DL-methionine.

Keywords: Polymorph, nucleation, solubility, transformation, antisolvent.

Growth Rate Measurements with Agglomerate Analysis of Beta-Form L-Glutamic Acid Crystals from Crystallisers Using Machine Learning-Based Image Processing

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P.17

Abstract: In-process crystal images captured from a batch cooling crystalliser using in situ camera imaging systems generally are of low resolution with blurred and overlapping crystals due to the translation and rotation of the crystals in the slurry within the crystalliser under continuous agitation. A machine learning-based approach is developed and utilised for the characterisation of crystal growth rates as a function of supersaturation, together with the variations of agglomerates. The Segment Anything from MetaAI is used to segment the captured video images with a set of training data being curated for the classification of single crystals, agglomerates, etc. using a crystal labeller. A machine learning-based software is developed to automatically categorise single crystals with their sizes (length and width) and agglomerates. From this, the variation of the agglomerates as a function of crystallisation conditions is examined and furthermore, the crystal growth in two dimensions is obtained from the identified single crystals. For statistically analysis of growth data, a time window is used to generate 2D growth rate, then the kinetic mechanisms.

Acknowledgements: This study is financially supported by EPSRC UK through the Shape4PPD project (EP/W003678/1) in collaboration with AstraZeneca, Cambridge Crystallographic Data Centre, Infineum, Keyence, Pfizer, Roche, Syngenta, Imperial College London, Universities of Hertfordshire and Strathclyde.

Keywords: in-Process crystal Image, growth rate measurement, crystal image analysis, machine learning, L-glutamic acid.

Optimal Precursor Recovery from Spent Lithium-Ion Batteries Using Population Balanced Equation (PBE) Integrated with Impurity Classifier

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P.18

Abstract: The co-precipitation of leachate from spent lithium-ion batteries (LIBs) allows for the direct regeneration of precursor without selective metal precipitation. However, in the presence of impurity ions in leachate, the selection of operating condition including temperature, reagent concentration is crucial for achieving high purity and recovery rates. Therefore, this study reveals the optimal operation strategies to produce impurity-free precursor using a population balanced equation (PBE) with impurity classifier model. Using the thermodynamic equilibrium model of the leachate, the infeasible operation domain, which produce impurity solid, is firstly revealed, and surrogate modeling of highly nonlinear infeasble domain is conducted using deep neural network (DNN). By integrating DNN with PBE of co-precipitation, bayesian optimization was conducted to optimize the operating condition to minimize both operation time and particle size while satisfying 100% purity of precursor. Proposed optimization is conduced on both unseeded batch and semi-batch system for comparison its performance. Optimization results shows that selection of seim-batch can sustain high nucleation and particle growth rate, and results reduction of opertion time by 23.3% but increase of particle size by 54.75% compared with the batch system. This PBE model-based optimization provides comprehensive operational guidelines for batch and semi-batch co-precipitation, facilitating the production of high-purity precursor materials from spent LIBs while reducing both operating time and maximum particle size.

Keywords: Spent lithium-ion batteries, co-precipitation, population balance eqation, optimization, precursor-resynthesis, surrogate model.

Mechanism of the Enrichment Process of Enantiomeric Excess in Temperature Cycling-Induced Deracemization

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P.19

Abstract

Deracemization, a resolution technique to convert a racemate into a pure enantiomer via racemization and crystallization, has been actively explored. However, most reports utilize batch crystallizer, and continuous deracemization which is adaptable to continuous manufacturing was strongly demanded.

In this study, we validated semicontinuous temperature-cycle-induced deracemization (TCID) utilizing a batch-type crystallizer and the amplification of the enentiomeric excess (*ee*) of the crystalline phase. As a model compound, the axially chiral naphthamide derivative **1** shown in Figure 1 was used. We explored deracemization by repeating collection of the enantiopure crystals and feeding of the racemic suspension using a peristaltic pump. Additionally, we examined optimal operating conditions by varying the suspension density that represent the amount of crystals in the suspension. Furthermore, the enrichment process of *ee* was clarified by tracking the change in *ee* of the crystalline phase during the crystallization-dissolution cycle.

In semicontinuous deracemization, an amplification of *ee* in the crystalline phase was observed with increasing temperature cycles at all suspension densities. A temporal decrease in *ee* after the feeding of the suspension and the addition of racemic suspension was observed. However, the *ee* of the crystals was recovered through temperature cycles. Repeated collection of the enantiopure crystals and feeding of the racemic suspension successfully led to the semicontinuous TCID using a batch-type crystallizer. In terms of process productivity, the condition with a suspension density of 3.2×10^{-2} kg·kg^{-1} gave the highest productivity (Figure 2). Furthermore, the direction of enrichment was never reversed once enriched, consistently leading to the same chirality. At lower suspension densities, the enrichment proceeds with fewer cycles but results in lower amount of crystals obtained. On the other hand, at higher suspension densities, more crystals can be obtained at once, but more cycles are required for enrichment. Therefore, it is thought that this balance results in the highest productivity under conditions with a moderate suspension density. The productivity of the semicontinuous deracemization exceeded that of the batch-type[1].

Focusing on the change in *ee* during tempareture cycle, it was found that the enrichment proceeded in the heating lamp and cooling lamp resulted in the racemization of the solid phase, as shown in Figure 3. The higher *ee* at the start of the temperature cycle resulted in the efficient enrichemnt in a following cycle. In the presentation, we will discuss the details of experimental conditions, particle size distribution, and enrichment behaviour during the single temperature cycles.

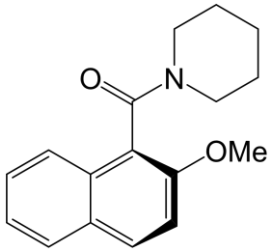

Figure 1. Naphthamide derivative **1**.

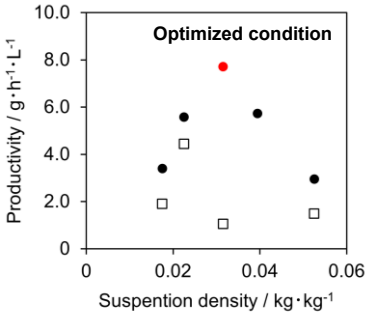

Figure 2. Process productivity and the ratio of dissolution to the solid during temperature cycle for (●) continuous operation and (□) batch operation.

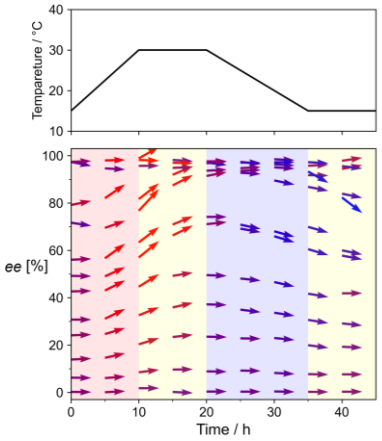

Figure 3. Evolution of the *ee* at varied initial *ee*. Arrows in red indicate *ee* enrichment and arrows in blue indicate *ee* reduction. In addition, the red background of the graph represents temperature increase, yellow represents temperature stability and blue represents temperature decrease

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Keywords: Crystallization, chiral resolution, deracemization.

In-Situ Measurement of Asymmetric Crystal Growth of α-Form L-Glutamic Acid

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P.20

Abstract: It has always been a problem about how to obtain crystal 3D shape and size during their growth. An appoarch of solving this problem is presented. A simulated crystal mesh is created and tuned until it prefectly match a real crystal photo in 2D captured during crystal growth. The mesh is generated with the known crystal habit and faces, simulated as a projector of the microsope, and takes all refraction inside the crystal into account. The mesh aims at creating a exactly same view as how the crystal should look like under microscopy systems. The parameters of the mesh (facet distances, refractive index, etc.) are tuned manually until it matches the crystal in the real image, and can then be collected to get crystal 3D shape and size. The feasibility of this approach has been tested using images captured during the asymmetric growth of a single alpha form L-glutamic acid crystal. The mesh matching shows very promising results, and the measured crystal size has been used for growth rate analysis on different faces of the crystal. The method proposed can be further optimized using automatic methods with the help of machine learning techniques in the future.

Acknowledgements: This study is financially supported by EPSRC UK through the Shape4PPD project (EP/W003678/1) in collaboration with AstraZeneca, Cambridge Crystallographic Data Centre, Infineum, Keyence, Pfizer, Roche, Syngenta, Imperial College London, Universities of Hertfordshire and Strathclyde. One of the authors (C. J.) would like to thank the EPSRC UK for the Doctoral Training Partnership award (EP/W524372/1) which is sponsored by Syngenta in collaboration with Neil George, Jennifer Webb and Raphael Stone.

Keywords: Crystallization, growth rate measurement, crystal 3D shape and size.

From Crystal Structures to Surfaces with Particle Informatics and CSD-Particle

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P.21

Abstract: In the pharmaceutical, fine chemical and agrochemicals industries, understanding particles' chemical and mechanical properties is key. By performing particle shape and surface analyses, crystallisation scientists, formulators, computational materials scientists and particle scientists can anticipate manufacturing issues including sticking, wettability, and tabletability.

In this contribution, I will provide an overview of CSD-Particle[1] – our new suite of software, drawing on the data from 1.3M crystal structures held in the Cambridge Structural Database (CSD) – that provides researchers with visual displays of surface chemistry, charge and topology, as well as numerical descriptors that can then be used to guide manufacturing decisions, eliminating potential bottlenecks before they occur.

References

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Keywords: Surface analysis, particle informatics, surface chemistry, crystal structure, CSD.

Regulation on Performance of Organic Crystals Based on Noncovalent Interactions

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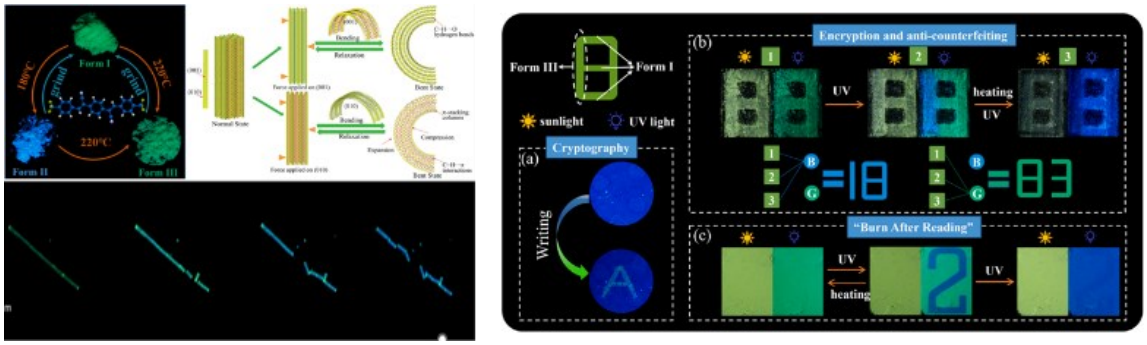
P.22

Abstract: Noncovalent interactions (hydrogen bonds, halogen bonds, van der waals bond, etc.) often plays a dominant role in the regulation of crystal structure, which further influences their physicochemical properties such as solubility and bioavailability. However, for crystalline materials, this change in structure would also have a significant effect on their performance, endowing a better mechanic flexibility or wonderful stimulus response. In this report, we would like to give a introduce to our recent work that related to the noncovalent-regulated property of crystalline materials. The effect of crystal structure, noncovalent bonds, supramolecular clusters, together with the molecular arrangement on the materials' performances were fully analyzed and summarized, based on the various of characteristic and molecular simulation. Furthermore, the potential application of these materials will also be discussed.



Keywords: Crystallization, noncovalent bonds regulation, crystalline materials, crystal structure, elasticity, stimulus response.

Photo/Mechanical/Acidic Multi-Stimuli Responses and Information Encryption Design of Acylhydrazone Derivative

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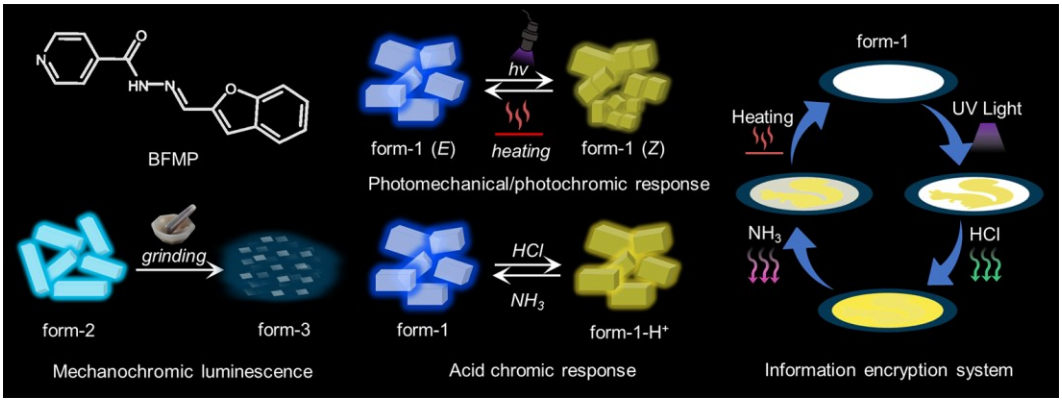
Abstract: Stimuli-responsive crystalline materials have received much attention for being potential candidates of smart materials. However, the occurrence of polymorphism-driven stimuli responses in crystalline materials remains interesting but rare. Herein, three polymorphs of an acylhydrazone derivative, N'-[(E)-(1-benzofuran-2-yl) methylidene] pyridine -4-carbohydrazide (BFMP) were prepared. Form-1 undergoes a photomechanical response via E→Z photoisomerization under UV irradiation, accompanied by a decrease in fluorescence intensity and a change from colorless to yellow. Two types of Z→E thermal isomerization mechanisms with significant differences in conversion rate were observed at different temperatures in form-1. The solid-melt-solid transition has a faster conversion rate compared to the solid-solid transition due to freedom from lattice confinement. The transition from form-2 to form-3 can be achieved under grinding, coupled with a significant decrease in fluorescence intensity. The similar molecular stacking pattern of form-2 and form-3 provides a structural basis for the grinding-induced crystalline transition behavior. In addition, the presence of the pyridine moiety imparts an acid chromic property. The combination of photochromism and acid chromism explores the possible applications of acylhydrazone derivatives in information encryption.

Graphical abstract:



Keywords: Polymorphism, fluorescence, photoisomerization, stimuli-responsive crystal, acid chromism.

Mechanistic Study on the Structure–Property Relationship of Flexible Organic Crystals

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P.24

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Abstract: Flexible crystals have attracted extensive attention for their potential as smart materials, such as flexible field-effect transistors, wearable devices and flexible displayers. However, developing flexible materials with specific properties still remains challenging because the design standards for flexible organic crystals are still not well established. Herein, two Schiff-based molecules, together with their polymorphs were reported and investigated in detail, which exhibit different photophysical behaviors and mechanical properties. It was found that, due to the distinguished molecular stacking arrangements, they exhibit diverse fluorescence properties. MN-I exhibits orange emission at 590 nm, while MN-II shows yellow emission at 579 nm. MO-I shows bright yellow-green fluorescence at 538 nm, while the emission spectrum of MO-II cannot be measured due to the presence of photochromism caused by its distorted molecular conformation. Furthermore, MN-I exhibits better elasticity than MN-II, while MO-I and MO-II are plastic and brittle, respectively. Detailed crystallographic analyses and energy framework calculations were performed to reveal the mechanisms, which suggest that the differences in the strength of intermolecular interactions and the diverse types of intermolecular interactions caused by the differences in molecular conformation lead to flexible properties.

Keywords: Schiff-based, flexible crystals, structure–property relationship.

Integrating 2D Elasticity and Elastoplasticity into a Multi-Stimuli-Responsive Crystal Through Phase Transitions

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P.25

Abstract: Practical applications of flexible crystals are often limited due to their monotonous property. In this study, multi-stimuli-responsive crystals of isonicotinamide (INA), which astoundingly respond to all mechanical force, heat and humidity, are reported. Moreover, conversion of mechanical property from two-dimensional (2D) elasticity to elastoplasticity in one single crystal is implemented through phase transitions. Temperature and humidity are both the triggers of phase transformations accompanying crystal elongation, deformation and displacement, which endows INA crystals with temperature/humidity-reliant dynamic properties. Interestingly, the heat/humidity-induced dynamic motions can be controlled by coating silicone grease onto crystal surfaces. Our work explores the structure properties of multi-stimuli-responsive crystals of INA integrated with different mechanical properties, which is important for the design of flexible materials with manifold properties.

Keywords: 2D elasticity, multi-stimuli-responsive crystal, phase transition, dynamic property, elastoplasticity.

Fabrication of 2D ZIF-8 Nanosheets and Their Application as Fillers in Mixed Matrix Membranes with Various Pebax Polymers

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P.26

Abstract: Extensive research has been studied to improve gas separation in mixed-matrix membranes (MMMs) using engineered zeolitic imidazole frameworks (ZIF-8). 2D ZIF-8 can separate gas species more effectively than 3D ZIF-8 due to its morphology and pore aperture. Moreoever, the choice of polymer among Pebax (Polyether block amide) grades significantly affects filler dispersion and gas separation performance. Pebax-2533, characterized by a higher polyether content and longer polyamide chains, demonstrates high permeability but low selectivity compared to Pebax-1657. In this study, we synthesized 2D ZIF-8 nanosheets and dispersed them into two types of Pebax (Pebax-1657 and Pebax-2533) with different content. Pebax-1657/2D ZIF-8 MMM exhibited superior separation performance over Pebax-2533/2D ZIF-8 MMM due to the highly ordered and well-dispersed nanosheets within the Pebax-1657.

Keywords: Gas separation, ixed-matrix membrane, 2D ZIF-8, pebax.

Advanced Synthesis and Characterization of Mesoporous Transition Metal Oxides Using Spray Pyrolysis and Sol-Gel Method

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P.27

Abstract: Transition metal oxides such as Al_2O_3, TiO_2, SiO_2, and ZrO_2 are extensively employed as catalyst supports because of their excellent stability and favorable interactions with catalysts. However, their broader industrial application is constrained by challenges like limited surface area and production difficulties. This study introduces an innovative synthesis strategy combining spray pyrolysis and sol-gel method to effectively prepare these transition metal oxides. This method offers advantages such as uniformly dispersed particles, high mass production, spherical morphology, and controllable pore structures. The synthesis of γ-Alumina via ultrasonic spray pyrolysis yielded a spherical morphology with an excellent specific surface area (377.06 m^2/g) compared to commercial Alumina (Alfa Aesar, 182m^2/g). Additionally, when these metal oxides were mixed, they maintained a high surface area and stability. The product materials were analyzed using X-ray diffraction (XRD), scanning electron microscopy (SEM/EDX) and Brunauer-Emmett-Teller (BET) surface area measurements.

Keywords: Spray pyrolysis, spherical morphology, mesoporous transtition metal, sol-gel.

Crystal Engineering in Oligorylene Molecules for Optimized Crystal Packing and Influence on Their Charge Transport Properties

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Abstract: Crystal engineering involves designing and synthesizing organic materials with specific, predictable crystal structures[1,2]. This field is vital for developing new functional organic materials with desired properties, primarily through manipulating directional intermolecular interactions like hydrogen and halogen bonds. However, in organic compounds without functional groups, less directional interactions such as steric hindrance, dipolar, and quadrupolar dispersion interactions determine the crystal structure. These weak interactions collectively influence crystal packing in the absence of stronger forces.

To understand the combined effect of these weak interactions on crystal structures, π-conjugated systems such as polycyclic aromatic hydrocarbons (PAHs) are particularly useful due to their low conformational freedom. We explored crystal engineering in novel PAHs from the rylene family, focusing on steric factors from bulky substitutions.

We designed and synthesized six oligorylene molecules, substituting them with bulky side groups to influence crystal packing through steric effects. X-ray diffraction studies revealed that these oligorylene derivatives have planar molecular structures and adopt herringbone-stack type packing. The degree of steric hindrance from substitutions altered the crystal packing, consequently changing the intermolecular interactions and electronic coupling between neighboring molecules. Crystal structures were analyzed using Hirshfeld surfaces to identify intermolecular contacts. The analysis identified TMP as the optimized molecular structure with balanced intermolecular interactions. The OFET of perylene-based TMP showed a mobility of 0.05 $cm^2V^{-1}s^{-1}$. Notably, no polymorphs were observed in these novel oligorylene molecules.

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Keywords: Crystal engineering, crystals, steric hinderance, x-ray diffractions, oligorylenes, polymorphism, organic semiconductors.

Preparation of Adsorbent Powder for Radioactive Cesium by Crystallization Technique

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P.29

Abstract:

1. Introduction

A large amount of radioactive caesium was released from the Fukushima nuclear accident. The removal of radiocesium is extremely important due to concerns about the effects of radioactive cesium on the human body. Cobalt ferrocyanide is an effective adsorbent for the removal of radioactive cesium in environmental water samples such as seawater and river water. Cobalt ferrocyanide can be obtained by continuous crystallisation.

In this study the details of the preparation of this powder adsorbent, its application and comparison with other powder adsorbents were investigated.

2. Results and Discussion

Cobalt ferrocyanide was obtained by continuous crystallisation by mixing cobalt chloride solution and potassium ferrocyanide solution in the reactor (static mixer, lenge 20 mm, Ø 23 mm.)(Fig. 1) . In the crystallisation of cobalt ferrocyanide, $Co[CoFe(CN)_6]$ was presipitated when the concentrations of $K_4[Fe(CN)_6]$ and $CoCl_2$ were constant, on the other hand, $K_2[CoFe(CN)_6]$ was presinitated in the concentration of $CoCl_2$ was low[1]. The mean particle sizes of $Co[CoFe(CN)_6]$ was 6.9 μm and $K_2[CoFe(CN)_6]$ was 11 μm, respectively (Fi.2). Both of the two adsorbents adsorbed radioactive cesium from simulated river water and simulated water well.

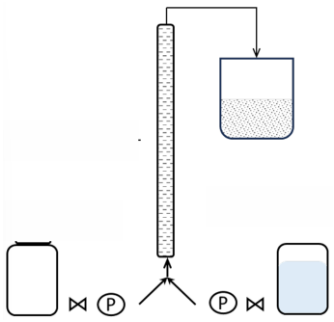

Figure1. Continous crystallisation

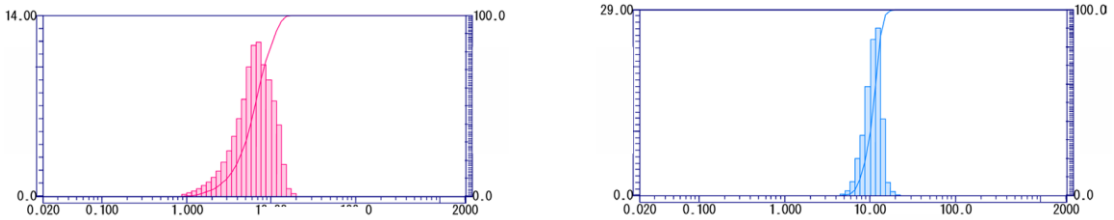

Figure 2. Particle size of $K_2[CoFe(CN)_6]$ and $Co[CoFe(CN)_6]$

Furthermore. the results of a water flow test using a spring-loaded filter pri-coated with $K_2[CoFe(CN)_6]$ are also reported.adorption isotherms of radioactive cerium are reported qre were investigated.

3. Conclusions

$K_2[CoFe(CN)_6]$ is effective to remove of radioactive cesium from environmetal waters such as sea water and river water, and this study contributes to SDGs NO.7(CLEAN WATER AND SANITATION, Ensure availability and sustainable management of water and sanitation for all).

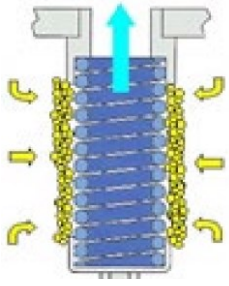

Figure 3. Pre-corting

References

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Keywords: Crystallization, cobalt ferrocyanide, radioactive cesium.

Rapid and Sustainable Production of Nano and Micro Medicine Crystals via Freeze-Dissolving Technology

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P.30

Abstract: Modern pharmaceutical manufacturing emphasizes the need for sustainable technologies. A novel application of freeze-dissolving technology has been demonstrated in the producing nano and micro-sized crystals of a model organic medicine compound, metronidazole. This process involves creating frozen spherical particles by introducing a good solution containing dissolved metronidazole into liquid nitrogen. Then the frozen spherical particles were added to anti-solvents to dissolve these frozen solvent templates, at temperatures below the frozen point of good solvent but above the melting point of anti-solvent. During this process, pre-formed metronidazole micro and nano particles within the frozen template remained after the frozen solvent dissolved. For traditional freeze-drying method, the frozen particles in a vacuumed freeze dryer with sublimation of the frozen solvent, and nano or micro particles of metronidazole will be collected. The new freeze-dissolving technology can save 99% both energy and time compared to the traditional freeze-drying method, demonstrating a significantly more efficient and sustainable pharmaceutical manufacturing approach.

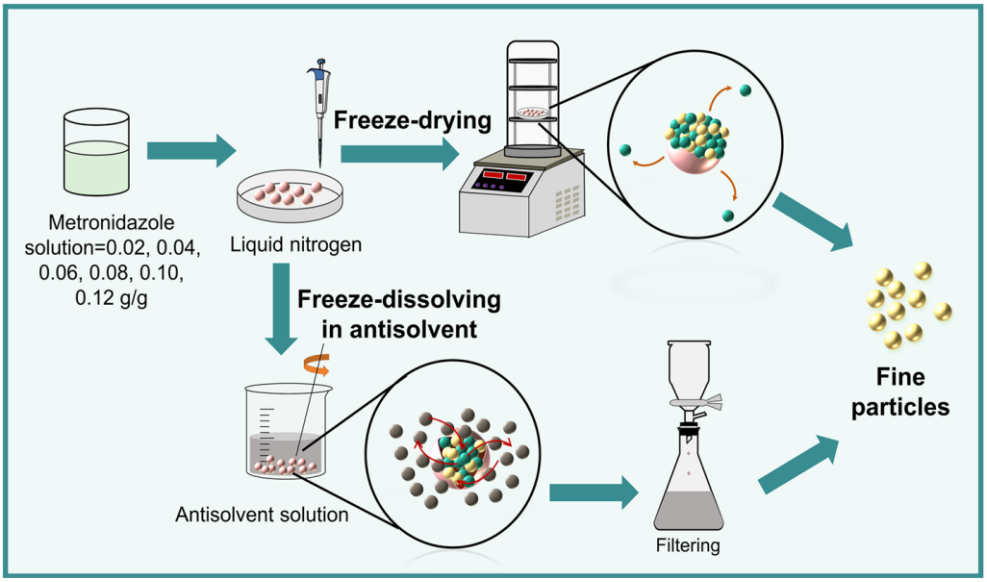

Figure 1. Freeze dissolving technology vs Freeze drying technology

Keywords: Fine particle, freeze-dissolving, metronidazole, nano and micro crystal, sustainable.

Production of Submicron API Particles by Membrane Crystallization

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P.31
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Abstract: Generating stable suspensions of particles in the submicron size range remains a significant hurdle in the fine chemicals and pharmaceutical sectors. For long-acting injectable medications, submicron-sized active pharmaceutical ingredient (API) particles are essential to achieve the desired pharmacokinetic profile and inflammatory response. Presently, mechanical milling stands as the preferred method for producing fine crystalline particles. However, this approach is energy-intensive, challenging to scale, and often negatively impacts particle properties, such as crystallinity, leading to wide particle size distributions and inconsistent batch-to-batch reproducibility. Crystallization from solution presents a potential avenue for directly and cost-effectively producing micron to nano-sized particles. Nevertheless, traditional batch crystallization processes struggle to yield such particles due to difficulties in suppressing secondary nucleation and growth.

In this study, we explored the potential of employing a reverse antisolvent membrane crystallization process[1,2] to generate submicron particles of fenofibrate, a poorly water-soluble active pharmaceutical ingredient (API) selected as the model compound. In this method, the API solution within the hollow fibers (tube-side) permeates through numerous micrometer-sized pores on the membrane wall and comes into contact with the anti-solvent on the shell side. By precisely regulating micromixing on the shell side and shear stress at the membrane surface, it becomes possible to finely adjust the properties of the API particles.

For this proof-of-concept investigation, we utilized a 3M™ Liqui-Cel™ hollow fiber membrane contactor alongside a custom-made hollow fiber membrane module. Across two distinct crystallizer modules, we delved into the influence of operational parameters such as flow mode and rates, antisolvent-to-solvent ratio, and solute concentration on the size of the active pharmaceutical ingredient (API) particles. The particle size exhibited variations dependent on the design of the membrane module, solute concentration, antisolvent-to-solvent ratio, and flow rates. Although initially producing submicron-sized API particles, their size gradually increased over the operational period in both membrane crystallizer modules. This increase is attributed to declining crystallization efficiency owing to fouling and encrustation of the membrane module. Preliminary efforts were made to address the fouling and blockage issues, and the outcomes of these experiments will be elaborated upon in this presentation.

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Keywords: Membrane crystallization, submicron particles, nucleation, antisolvent crystallization.

Crystallization of Carbonate by $CO_2/O_2/N_2$ Fine Bubble Injection into Concentrated Seawater Discharged from Salt Manufacturing Process

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P.32

Abstract: During the salt manufacturing process in Japan, NaCl is manufactured by evaporative crystallization after concentrating seawater through electric dialysis membranes, and the concentrated seawater and boiler exhaust gas are discharged. To build up an efficient salt manufacturing process that is adaptable to a carbon neutral society, the development of not only the recovery and upgrading method of Ca and Mg dissolved in concentrated seawater discharged from salt manufacturing process but also the utilization method of CO2 in boiler exhaust gases is desired. The reactive crystallization technique of carbonate using the bubble feeding of $CO_2/O_2/N_2$ with an exhaust gas composition is effective for a separation/recovery method of the dissolved Ca^{2+} and Mg^{2+} in the concentrated seawater and capture/utilization method of CO_2, because the solubility of carbonate is lower than the solubility of hydroxide in the solution at a pH range below 10.0. Especially, dolomite ($CaMg(CO_3)_2$), which is double salt of calcium carbonate ($CaCO_3$) and magnesium carbonate, has numerous applications as the manufacture of refractories, as neutralizer of soil acidity in agriculture, as mineral supplement for food and drug, etc.. $CaMg(CO_3)_2$ has crystal structure derived from that of calcite ($CaCO_3$) by ordered replacement Ca^{2+} in calcite by Mg^{2+}. To improve the functionality of crystal for the better $CaMg(CO_3)_2$ utilization, it is essential to gain access to the Mg/Ca ratio of 1.0 and to reduce the particle size in the crystallization process. Generally, high concentrations of Ca^{2+}, Mg^{2+} and CO_3^{2-} are necessary for the production of $CaMg(CO_3)_2$ with a Mg/Ca ratio of 1.0, because the Mg/Ca ratio increases with increasing the supersolubility product in the bulk solution[1]. In this study, the micron-scale bubble formation technique that enables the generation of regions with a higher ion concentration around the minute gas-liquid interfaces was applied to the reactive crystallization of $CaMg(CO_3)_2$. In the regions near the minute gas-liquid interfaces, Ca^{2+} and Mg^{2+} accumulate because of the negative electric charge on the fine bubble surface, and the concentration of CO_3^{2-} increases because of the acceleration of CO_2 mass transfer caused by minimizing the bubble diameter; hence, the fine particles of $CaMg(CO_3)_2$ with a high Mg/Ca ratio can be expected to crystallize.

At a reaction temperature of 298 K and reaction pH of 6.8, $CO_2/O_2/N_2$ bubbles with an average diameter (d_{bbl}) of 40 - 2000 μm were continuously supplied to actual seawater bittern discharged from salt manufacturing process and $CaMg(CO_3)_2$ was crystallized within the reaction time (t_r) of 90 min. Fine bubbles with a d_{bbl} of 40 μm were generated using a selfsupporting bubble generator by the shear of the impeller and a negative pressure owing to high-rotation[2]. For comparison, the bubbles with a d_{bbl} of 200, 300, 800 or 2000 μm were obtained using a dispersing-type generator. Fig. 1 shows the time changes in the molar concentration ($C_{dolomite}$) and Mg/Ca ratio of $CaMg(CO_3)_2$ produced at different dbbl values. $C_{dolomite}$ and Mg/Ca ratio increased with a decrease in d_{bbl} at all t_r values. Additionally, SEM observation results revealed the spherical particles with an average size of about 2 μm were observed at a d_{bbl} of 40 μm, whereas the agglomerated particles with a size of almost 20 μm were obtained at a d_{bbl} of 2000 μm. Consequently, $CO_2/O_2/N_2$ fine bubble injection is effective for the high-yield crystallization of $CaMg(CO_3)_2$ with a Mg/Ca ratio of 1.0 and downsizing of $CaMg(CO_3)_2$ particles owing to the acceleration of crystal nucleation caused by the local increase in the supersaturation around the minute gas-liquid interfaces.

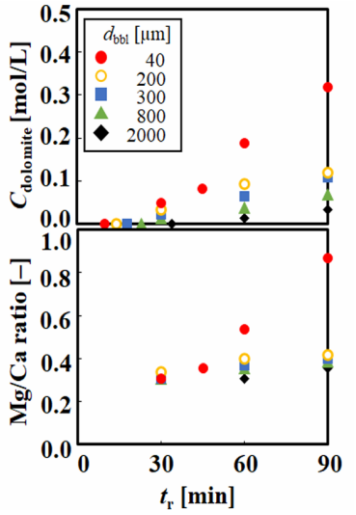

Figure 1. Time changes in $C_{dolomite}$ and Mg/Ca ratio

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Keywords: Carbon capture and utilization, carbonation process, reactive crystallization, fine bubbles.

Encapsulation of Papain by Antisolvent Precipitation

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Abstract: Papain, known for its medicinal benefits, including anti-inflammatory, antibacterial, and antioxi-dant effects, holds promise in various medical applications, including digestion and cancer therapy. Despite its efficacy, papain's susceptibility to chemical instability limits its use, especially in high temperatures and acidic conditions. To address this issue, acetylated starch, capable of controlling drug release, is utilized for papain encapsulation. Encapsulation was achieved through a stepwise antisolvent precipitation method, exploring different starch concentrations, starch solution vol-umes, and surfactant types and concentrations. Higher starch concentrations generally improved encapsulation efficiency and loading capacity, but excessive concentrations led to decreased per-formance due to starch aggregation, while starch solution volume primarily influenced loading capacity. Employing surfactants aided in dispersing particles to prevent aggregation during en-capsulation. However, higher surfactant concentrations, particularly Tween 80, improved en-capsulation efficiency and loading capacity but reduced papain activity. The optimal conditions achieved were a starch concentration of 30 mg/ml, a starch volume of 7 ml, and a 3% v/v Tween 80 concentration, yielding an encapsulation efficiency of 97.31 ± 1.24% and a loading capacity of 12.34 ± 0.26%, while retaining approximately 50% of papain activity. Confirmatory analyses via fluo-rescent spectra and FTIR confirmed successful papain entrapment within acetylated starch with a lower degree of substitution.

Keywords: Polymorph, nucleation, solubility, transformation, antisolvent.

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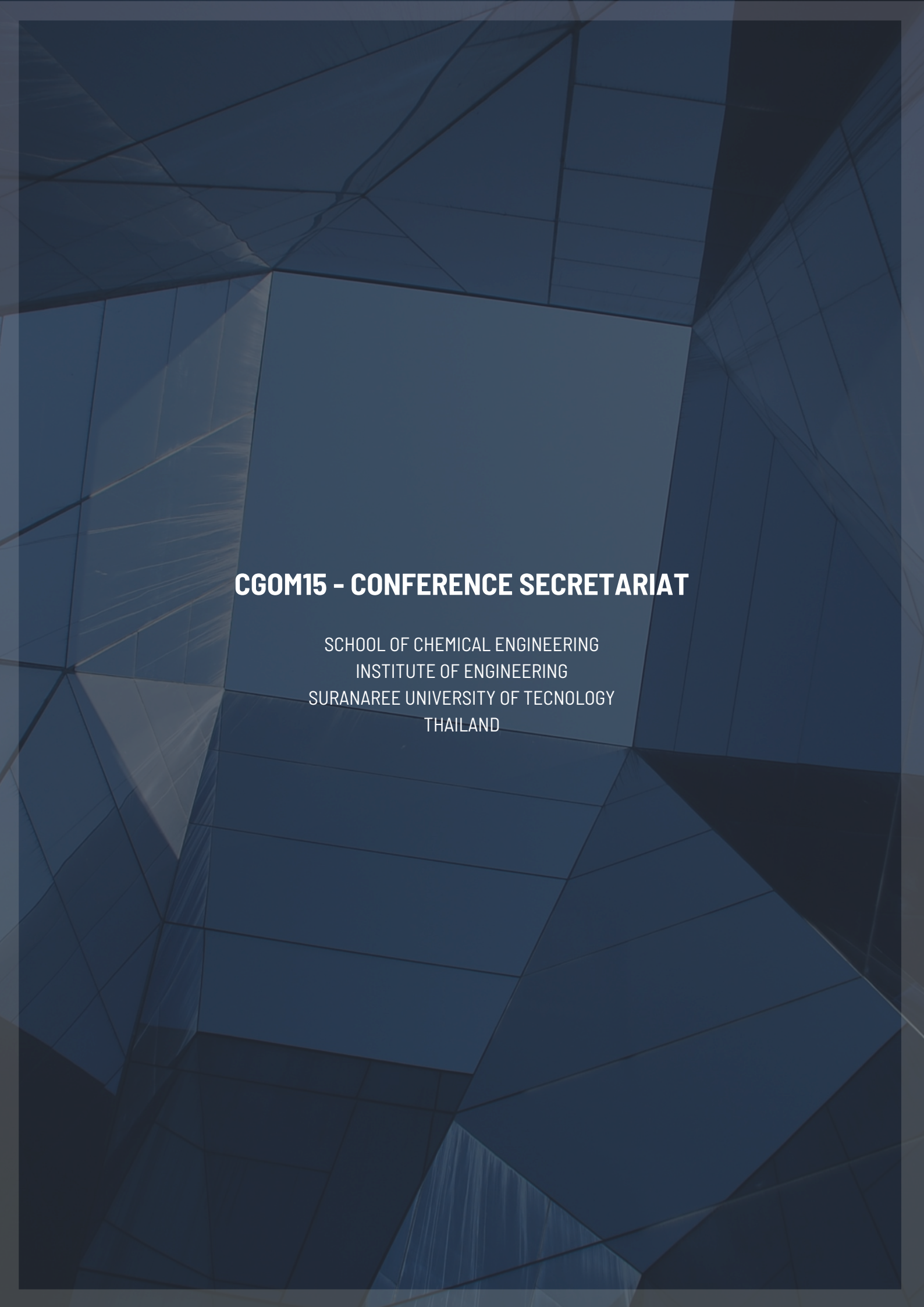

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