Plenary Speakers

Building a Continuous Crystallization, Isolation, and Drying Capability at Pfizer

Dr Kevin Girard

Continuous processing of pharmaceuticals is a growing area of interest, with many companies engaged in the effort for both "flow chemistry" and continuous drug product manufacture. A critical missing link between these mor popular areas of study is continuous crystallization, isolation, and drying (CCID). Recognizing this essential need, Pfizer have begun developing a CCID capability to provide a critical bridge between synthetic steps as well as enable a "raws in, products out approach," creating a fully connected continuous processing chain from starting materials to drug products. The approach is based on several distinct pillars: Workflows, Equipment (Lab and Plant scale), PAT, Process Modeling and Control, and Nucleator Design. Each will be discussed in turn and within the context of Pfizer projects. Challenges in these pillars will be discussed, as well as several opportunities to enhance the capability of the kit. Finally, a modular CC skid for manufacturing in a kg/day scale plant will be presented, showing elements from all the pillars of the platform.

Self-organizing crystallization induced by evaporation

Prof Noushine Shahidzadeh

Salt crystallization by evaporation is widely used in industrial processes, but is also a natural phenomenon occurring frequently around us whenever salt solutions are present and the water evaporates. This can lead to very spectacular natural landscapes but is also a major cause of the weathering of artworks, buildings, soil solification and corrosion of outdoor electronics. I will discuss the dynamics of crystal growth during evaporation when salt creeping occurs and show the mechanism behind this self-amplifying process that leads to 'salt trees'. I will also show how by changing the wettability and/or the porosity of the surface in contact with the salt solution, self-organized crystallization with a fractal morphology spontaneously develops upon drying. I will discuss the importance of the ion advection and diffusion on the crystallization patterns that develop and relate our results to salt crystallization damage observed in our cultural heritage and for works of art.

Pharmaceutical Crystallization: BIG Lessons from Small Molecules (BACG Annual Lecture)

Dr Susan M Reutzel-Edens

Solid form screening to crystallize a molecule for the first time or in a suitable solid form that can be reliably delivered to patients is the first significant milestone along the path to transforming a molecule into a medicine. With challenges and continuous learning from the experience of crystallizing ever more complex molecules, what have we learned and where do we go from here? In this talk, big lessons – scientific and beyond – from the experience of crystallizing small molecules in early pharmaceutical development will be shared.

General role of amorphous aggregates in crystal nucleation

Prof Klaas Wynne

Nucleation of crystals from solution is traditionally described in the framework of classical nucleation theory. However, it has been challenged by observations of nanoscale and mesoscale metastable solute species in supersaturated solutions. In one case, these were found to be an intermediate in laser-induced crystal nucleation.[1] Here, we will show that a wide range of amino acids as well as di- and tripeptides in supersaturated aqueous solution form aggregates and investigate their role in laser-induced nucleation. Using light scattering, we demonstrate that these aggregates are far from monodisperse but have a wide range of sizes, while in situ Raman spectroscopy confirms their amorphous nature. Mass spectrometry is used to confirm that the solute molecules cluster over a very wide range of sizes. All but one of the samples investigated shows aggregate-assisted laser-induced nucleation. These results suggest a general role of amorphous aggregates in crystal nucleation and a universal role in laser-induced nucleation. The wide range of observed sizes of the aggregates is inconsistent with both classical and non-classical theories involving liquid–liquid phase separation, requiring a new theory of crystal nucleation.

1. Liao, Z. & Wynne, K. A Metastable Amorphous Intermediate Is Responsible for Laser-Induced Nucleation of Glycine. J. Am. Chem. Soc. 144, 6727–6733 (2022).

Investigating the mechanism and kinetics of the mechanochemical synthesis of multi-component systems

Dr Franziska Emmerling

Mechanochemistry is a promising and environmentally friendly approach for synthesizing (novel) multicomponent crystal systems. Various milling parameters, such as milling frequency, milling time, and ball diameter have been shown to influence the mechanisms and rates of product formation. Despite increasing interest in mechanochemistry, there is still limited understanding of the underlying reactivity and selectivity mechanisms.

Various analytical techniques have been developed to gain insight into the mechanochemical transformations, including powder X-ray diffraction, X-ray adsorption spectroscopy, NMR, Raman spectroscopy and thermography. Using these techniques, we have studied the formation of (polymorphic) cocrystals, organometallic compounds and salts, and elucidated the influence of milling parameters and reaction sequences on the formation mechanism and kinetics.

For example, our study of the mechanochemical chlorination reaction of hydantoin revealed that normalisation of the kinetic profiles to the volume of the grinding ball clearly showed that physical kinetics dominate the reaction rates in a ball-milling transformation. Attempts to interpret such kinetics in purely chemical terms risk misinterpretation of the results.

Our results suggest that time-resolved in situ investigation of milling reactions is a promising way to fine-tune and optimise mechanochemical processes.

Underground and above-ground mineralization of CO2 offers feasible CO2 management solutions

Mr Marco Mazzotti

CO2 mineralization into carbonates plays a key role in the underground storage of CO2 in basalts (e.g., in Iceland, carried out by Carbfix, https://www.carbfix.com/), and in the use and permanent storage of CO2 by carbonation of recycled concrete aggregates to make fresh construction materials (e.g., by the ETH spin off neustark, https://www.neustark.com/, as well as by other companies). Both are sustainable routes, that offer exciting opportunities and face big challenges, particularly in how fast they can be upscaled to help address the climate emergency. We are exploring the scientific, techno-economic, and systemic aspects of the two solutions by implementing and farther developing them within the project DemoUpCARMA (Demonstration and Upscaling of Carbon Dioxide Management Solutions for a net-zero Switzerland, http://demoupcarma.ethz.ch/en/home/). In its scope, biogenic CO2 (from a Swiss biogas upgrader) has been purified and liquified, transported (within Switzerland and to Iceland), used (for carbonation of recycled concrete), and permanently stored (in basalt and in concrete), thus realizing hundreds of tons of so called negative CO2 emissions.

Oral Abstracts

A1.1

Rapid, automated measurement of dynamic size distributions and size-dependent growth rates of crystal ensembles within microfluidic flow cells

Dr Ariel Yi Hui Chua[1], Mr Tan G. Y.[1], Dr Eunice W. Q. Yeap[2], Dr David M. Walker[2], Dr Joel M. Hawkins[3], Dr Saif A. Khan[1]

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In-process monitoring of crystal sizes and extraction of crystal growth kinetics during crystallization, enabled by process analytical technologies (PATs), is crucial for development of crystal size distribution (CSD) control strategies in pharmaceutical manufacturing. In this presentation, we demonstrate a well-based microfluidic flow cell platform for rapid and direct measurements of evolving crystal sizes and size-dependent growth rates within crystal ensembles exposed to well-defined flow fields. We present detailed growth measurements of two high aspect ratio model drugs - celecoxib and glycine, where growing crystal ensembles are trapped in pseudo-static fashion within wells in a microfluidic flow cell under controlled laminar shear fields and observed via polarized microscopy over sustained time intervals. Time-varying CSDs are extracted via a novel image segmentation-based length detection algorithm (ISLDA), which then allow rapid estimation of shear and size-dependent growth rates through a simple Eulerian-based optimization scheme. We also demonstrate discrimination between different regimes of crystal growth in the two model drugs. We envision the platform to be applicable both as a process development and analytics tool. The obtained growth kinetics data can be directly incorporated into computational fluid dynamics (CFD)-coupled population balance models (PBM) for improved accuracy in CSD prediction. The platform can also be retrofitted to crystallization vessels for rapid online measurements of evolving crystal sizes.

Capturing interface induced concentration enhancement in situ via surface plasmon resonance spectroscopy

Mr Ruairidh Mackay[1,2], Doctor King Hang Aaron Lau[3], Professor Jan Sefcik[1,2]

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Primary nucleation of crystals from solution typically proceeds heterogeneously at various interfaces present in crystallisation processes. Despite this, comprehensive understanding of the underlying mechanisms and means by which heterogeneous nucleation can be controlled have not yet been achieved. Recent studies found that glycine nucleation is significantly accelerated at hydrophobic interfaces, such as oil-solution and PTFE-solution interfaces. Subsequent molecular simulations indicated that glycine concentration enhancement within an interfacial layer of glycine solution was responsible for this effect, driven by dispersion (van der Walls) interactions and thus assisting heterogeneous nucleation. In this work, we are demonstrating for the first time the use of surface plasmon resonance (SPR) spectroscopy for in situ measurements of the interface induced concentration enhancement in solutions, with initial measurements being performed with aqueous glycine solutions in contact with a gold surface.

SPR spectra have two key figures of merit with which they can be interpreted: the critical angle of total internal reflection (which independently measures a bulk solution refractive index) and the SPR coupling angle (which characterises solution refractive index near the solid-liquid interface). By refractive index matching aqueous glycine solutions across a range of concentrations with reference solvents (methanol, ethanol and propanol) and their binary mixtures, we have developed a method to assess glycine concentration enhancement at a glycine solution-gold interface. We observe that the SPR coupling angle position for glycine solution was consistently shifted to higher values compared to what was expected for bulk glycine solutions. We propose that this indicates the presence of a 1 nanometre thick interfacial layer of highly concentrated glycine solution at the surface-liquid interface, consistent with the interfacial concentration enhancement effect due to dispersion interactions. This experimental evidence of interfacial concentration enhancement provides new insight into the role of interfacial interactions in heterogeneous nucleation mechanisms.

A1.3

Triggering the Growth of Magnesium Hydroxide Crystals in Stirred Tank Crystallizers using Sodium Hydroxide Solutions

Mr Salvatore Romano[1], Dr Silvio Trespi[2], Ph.D Ramona Achermann[2], Ph.D Giuseppe Battaglia[1], Dr Antonello Raponi[3], Prof. Daniele Marchisio[3], Prof. Marco Mazzotti[2], Prof. Giorgio Micale[1], Prof. Andrea Cipollina[1]

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Magnesium (Mg) has been listed by the European Commission as one of the 30 critical raw materials for its high supply risk and relevance to the European economy. Mg is extracted from magnesium-rich minerals that are mainly located in China. In this context, alternative sources are urgently sought to strengthen the domestic European supply.

Industrial or natural brines (or bitterns) have been identified as key candidates due to their high Mg concentration. Mg can be extracted from brines/bitterns in the form of Magnesium Hydroxide ($Mg(OH)_2$) via reactive crystallization by using an alkaline solution, namely sodium hydroxide (NaOH). The use of NaOH allows highly pure $Mg(OH)_2$ products to be synthesized. On the other hand, products were always characterized by nano-globular or flakes morphology. These characteristics do not comply with the flame retardant market that requires large hexagonal $Mg(OH)_2$ crystals.
The present work introduces an experimental campaign aiming at triggering $Mg(OH)_2$ crystal growth by controlling reactive crystallization operative conditions. The challenge is to favour the crystal growth and, at the same time, to limit the nucleation mechanisms. Relatively concentrated synthetic sodium hydroxide and magnesium chloride reactant solutions were employed and let to react in a stirred tank crystallizer fed in single and double modes. The influence of the reactant concentrations and flow rates was analysed. Precipitated particles were characterized by laser diffraction, dynamic light scattering and electron microscopy techniques.

Nano-flakes $Mg(OH)_2$ crystals with a mean size of 50÷70 nm were produced in single-feed configurations. Conversely, for the first time in the literature, grown well-defined $Mg(OH)_2$ hexagonal platelets characterized by a mean size of 300÷360 nm were successfully synthesized in double-feed mode, see attached Figure.

Results pave the road to the industrial production of $Mg(OH)_2$ hexagonal crystals recovered from brines/bitterns via NaOH solutions.

Facet Crystal Growth Rate Measurements of Beta-Form L-Glutamic Acid for Growth Kinetics Determination with Machine Learning

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Solid-form materials of such as pharmaceuticals, foods, agrochemicals etc. are mainly manufactured in crystalline form through crystallisation processes produce high purity products. Crystal size, shape and the corresponding surface chemistry play an important role in the downstream processes (e.g., filtration, drying, milling, blending, granulation and tableting) and also the delivery of the products to the patients. Controlling these crystal properties requires in-depth understanding of the face-based crystal growth under varying crystallisation environments, in particular quantifying the growth during crystallisation processes. This can provide face-based growth kinetics for morphological population balance modelling, hence crystal size/shape prediction and process control. Molecular modelling and molecular dynamics simulations are not readily available to accurately predict the face-based crystal growth under practical crystallisation conditions. Furthermore, the crystal images from a crystalliser are of low resolution and also may not be feasible to track the same crystal/s due to the motion and rotation of crystals under agitation. The single crystal growth measurement in a growthcell using high-resolution microscope becomes a feasible choice to achieve facet growth measurements.

In this study, the crystal growth rates of both capping and side faces of β-form L-glutamic acid were investigated. A crystal growthcell with temperature control by a cooling bath was setup to capture high quality β-form LGA crystal images using Keyence digital microscope. Manual, semi-automatic and full-automatic (with machining learning) tools were used to compare and assess their accuracies and efficiencies. The acquired images were then processed using the automatic tool to identify crystallographic faces and quantify their normal distances, hence the face-based growth rates of individual crystal faces (Fig. 1). The available growth data were used to compare with that from this study. Finally the growth mechanisms of both capping and side faces were obtained.

Kinetic Impurity Rejection and Form Control for GDC-4379 Drug Substance via Continuous Crystallization

Dr Andy Stumpf[1], Gary Morris[2], Umar Farid[2]
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In this presentation the development of a continuous crystallization process for GDC-4379 active pharmaceutical ingredient (API) will be discussed to overcome the shortcomings of the batch crystallization process. The batch process involved two back-to-back recrystallizations to purge impurities of the crude API and then deliver purified API as the desired hydrate form.

Study of the batch crystallization conditions, and the impurity contamination mechanism provided insight for the kinetic impurity rejection of a regioisomer, and guided the selection of residence time for a mixed suspension, mixed product removal (MSMPR) continuous crystallization. A form conversion map was acquired for the anhydrate/hydrate system to inform operating parameter selection for the continuous process to selectively crystallize the hydrate form of the API. Proof of concept for a continuous telescoped impurity rejection and form control crystallization was established and showed superior regioisomer rejection for flow (98%) vs. batch (32%).

Process Control and Design of the Continuous Crystallization of a Polymorphic Agrochemical

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Crystallization is an essential process of solids manufacturing and is left inadequately designed in several fields, including agrochemical manufacturing. Inadequately designed crystallization protocols can lead to particles with undesired physical or chemical characteristics, such as particle morphology, polymorphism, crystal size distribution/aspect ratio, manufacturability, and overall crystal quality.

In this work, we demonstrate the multi-objective process control and design of an agrochemical crystallization by i) controlling the produced polymorphic form via combined cooling and antisolvent crystallization, ii) controlling the final crystal size distribution (CSD) and resultant manufacturability with wet milling, and iii) designing the continuous crystallization for industrial manufacturing of the model system. Variations in combined cooling and antisolvent crystallization operating trajectory can have a dramatic impact on the generated polymorphic form (Kshirsagar et al., 2023). A polymorphic form design space was generated by a data-rich design of experiments (DoE) enabled by the inclusion of in-situ process analytical technology (PAT) tools. This design space allowed for informed crystallization operating trajectory design. Following the isolation of the singular polymorphic forms, concerns about manufacturability arose from the presence of a high aspect ratio (AR) morphology. High AR crystals are challenging to industrial processes in terms of poor mixing and filtration time, the inclusion of wet milling with specific crystallization operating trajectories improved both product CSD and AR regarding manufacturability (Eren et al., 2021). Using the polymorphic design space, wet milling, and targeted antisolvent and cooling crystallization operating trajectories, manufacturing in the presence of high AR morphology was greatly improved. Further applying this process control, design, and system information to the continuous crystallization of the model system reduces manufacturing time and variability during industrial manufacturing.

Continuous Crystallization of Monoclonal Antibodies

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Monoclonal antibody (mAb) therapy is a very promising treatment for cancer and viral diseases due to their ability to recognize a particular infection. Despite of their broad usage from treatment of various diseases to measurement of hormone levels, their high cost remains due to the tedious purification processes by using ion-exchange chromatography making it difficult for the patients.

This work presents a methodological approach to develop a continuous crystallization system for mAbs to reduce the purification cost. Micro-scale scale experiments are done to investigate the crystallization behavior and to construct the phase diagram. Small-scale experiments are done to investigate the induction time and effects of process variables such as mixing. Crystallization of commercial mAbs were achieved by using salt within 45 minutes in 1.5 ml after constructing the phase diagrams via micro-well experiments where the induction time was around 12 hours. Then the process is scaled up to a continuous 2-stage MSMPR system with 25 ml volume for each MSMPR with pressure driven transfer. Pressure, temperature, inlet pH, salt concentration, and the liquid phase concentration along with the slurry density by using Raman spectroscopy are aimed to be monitored.

This process is designed to be integrated with tangential flow filters to discard the impurities that stay in the liquid phase. After the filtration and redissolution of the antibody crystals, off-line characterization tools such as HPLC are used to validate the use of crystallization in mAbs purification. Although continuous mAbs crystallization is very attractive due to being easily scalable and fast, the biggest challenge remains to be overcome is the low yield. Recent studies from this work are aimed to maximize the yield by conducting further experiments and developing the process model for process optimization.

Characterization of a Novel 7-Stage Continuous Crystallizer Cascade with Diaphragm-Driven Slurry Transfer

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The Mixed-Suspension-Mixed-Product-Removal (MSMPR) crystallizer is the most widely adopted among the continuous crystallization platforms. Specifically, the MSMPR is preferred for lower conversions, long residence times, and high slurry density while providing robust operation with intensive mechanical mixing that reduces settling. However, the slurry transfer in bench-scale MSMPR cascades (multiple MSMPRs connected in series) is challenging due to low withdrawal velocities, isokinetic withdrawal failure, and breakage of crystals when peristaltic pumps are employed. In this work, we present a novel continuous crystallizer with plug flow characteristics while alleviating all issues of bench-scale MSMPR cascades by enabling diaphragm-based slurry transfer. Specifically, the slurry transfer in the 7-tank MSMPR cascade is displaced vertically, by intervention of two inflating diaphragms, in the first and last stage. The novel crystallizer has a small footprint on the scale of similar benchtop flow synthesis systems and was characterized in terms of both homogeneous and heterogeneous phases handling capabilities (particles size 0-600 µm range and slurry densities up to 24%) supported by computational fluid dynamic (CFD) analysis. In addition, continuous antisolvent crystallization experiments have been conducted using glycine, azithromycin, and ketoconazole as model compounds. The results in this work represent the first proof-of-principle study for the novel crystallizer design, which addresses demands of the pharmaceutical manufacturing industry to provide novel slurry transfer mechanisms.

A3.1

Crystallisation in flow environments: smooth cooling gradients to in situ XRD analysis, a KRAICing series of crystallisers

Dr Karen Robertson[1]
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Flow technologies are often used where control over mixing and temperature environments is crucial. This has been highly successfully exploited for the intensification, optimisation and online analysis of chemical reactions which take place in the solution state. The direct link between reactor length and reaction time has enabled chemists to identify highly metastable species; analysing the composition of a continuous reaction stream at one location (reaction time) decouples experiment time with reaction time. Thus, species which are very short lived and cannot be isolated for offline analysis can be identified in situ.

Flow technologies for solid state production has had a surge of innovation in recent years through new technologies being developed to address the challenges of producing solids in flow. Here we exploit the inherent nature of flow technologies, which enabled the identification of short-lived transition states by flow chemists, to identify the crystal structure of growing crystals in an environment representative of both small and large-scale production. Many pharmaceutical crystallisation processes are performed through cooling, translation of a smooth temperature gradient to length scale in flow technologies is complex; traditional solutions employ discrete temperature zones with a buffer period in between. We will present the development of a flow crystalliser designed for a smooth cooling gradient over the length scale which can be used to rapidly identify the optimal cooling gradient for a given crystallisation.

The evolution of a series of flow crystallisers will be presented ranging from smooth gradient cooling crystallisation with rapid optimisation, through integrated flow synthesis and crystallisation to in situ analysis via Raman spectroscopy and both powder and single crystal X-ray diffraction. These crystallisers have been commissioned to control, monitor and understand crystallisation events including the promotion of unusual polymorphic forms and crystal habits, and elucidation of polymorphic stability.

A3.2

Mechanism and kinetics of salt recoveries by seeding membrane distillation crystallization

DI Stefanie Flatscher[1], Univ.- Prof. Dr.-Ing. Mark W. Hlawitschka[1]
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Membrane distillation (MD) coupled with crystallization presents a sustainable and continuous process for treating saline and wastewater while simultaneously recovering salt and water using renewable energy sources. However, further analysis is required to better understand critical details such as crystallization mechanisms, salt kinetics, seeding crystal types and sizes, and concentration to provide a physicochemical understanding. Seeding crystallization plays a vital role in preventing membrane surface crystallization and ensuring continuous operation by allowing crystal growth of seeds in the metastable region without requiring supersaturation levels. In this work, a pilot plant membrane distillation column, as well as the single effects of the processes, are studied in detail. At low temperatures and with saline solutions exceeding 10% initial salinity, the process achieves precipitation in the metastable region S = 1.002 ± 0.02 as the first salt reaches its solubility limit. The growing crystals can be continuously separated from the process by sedimentation. The crystal size ranges from 150 to 300 μm and were monitored by on- and offline detection. Varying operating parameters such as temperature, seeding concentration, and crystal growth revealed further insights into the separation of salts based on their solubility products, enabling the fractional crystallization of different salts. The investigations show that MDC is a relevant option for both water and salt recovery in wastewater treatment, as well as for complex solutions.

Effects of operating parameters on crystal properties of CaCO3 during an integrated CO2 capture and mineralization process

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Carbon mineralization in aqueous media is a promising technology for mitigating CO2 emissions and associated environmental impacts. An integrated CO2 capture and mineralization (ICM) process can produce calcium carbonate (CaCO3) particles for various applications. CO2 absorption in aqueous media and crystallization of CaCO3 are affected by several parameters, such as type of CO2 absorption promoters, CO2 supply method, reagents concentrations, additives, and temperature. This study investigates the effect of such parameters on the crystallization behavior of CaCO3. Amino acid glycine is selected as a CO2 absorption promotor due to its natural production source, non-toxic nature, stability against oxidation, low volatility, and high surface tension. Most importantly, it can absorb CO2 faster and has better desorption capacity compared to standard absorbents (monoethanolamine). Different amino acid concentrations, Ca2+ concentrations, and CO2 bubbling rates are investigated for their effects on mineralization efficiency and crystallization of produced CaCO3 particles. Next, the effects of a water-soluble polymer as a crystal growth modifier, temperature, and ultrasonication on CaCO3 crystal properties are investigated. We report that the concentration of CO2 absorption promoter glycine should be more than twice the Ca2+ concentration to achieve ca. 90% Ca2+ conversion to CaCO3. A very high concentration (> 0.5 M) of Ca2+ is unsuitable for forming CaCO3. Stable vaterite polymorph (spherical) of CaCO3 can be formed without crystal growth modifiers only at a specific CO2 bubbling rate. However, the addition of water-soluble polymers such as casein in small amounts (0.1–1 g/l) ensures the formation of spherical CaCO3 crystals at all experimental CO2 bubbling rates (0.1–0.9 l/min). Moreover, polymer addition produces well-dispersed porous spherical crystals of CaCO3 and does not interfere with the Ca2+ conversion when added in a small amount (0.1–0.4 g/l). The ICM process is simple, efficient, eco-friendly, and could be used for CO2/Ca2+ rich industrial waste valorization.

Highly-efficient production of desired solid forms of drugs with improved mechanical properties via an organic solvent-free sublimation process

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The pharmaceutical industry is required to constantly broaden its development areas and accelerate technical transformation because of the continued global rise in medicine consumption. However, the usage of organic solvents in pharmaceutical production results in up to 20 million tons annually of chemical waste, causing a serious environmental problem. Here, we proposed a solvent-free sustainable chemical technology, sublimation crystallization, for highly-efficient screening and preparation of pharmaceutical solid forms (i.e., polymorphs), which eliminates the wastes associated with solvent use from the source. By adjusting the parameters of sublimation crystallization, we have obtained multiple polymorphs of several important drugs including the anti-tuberculosis drug pyrazinamide (PZA) and the non-steroidal anti-inflammatory drug (NSAID) flufenamic acid (FFA) and mefenamic acid (MFA), particularly γ form of PZA and polymorphs Ⅳ and Ⅶ of FFA, which are difficult to produce from conventional solution crystallization methods. Mechanical property measurements from both powder and single crystals tests reveal that the γ form of PZA readily prepared by sublimation crystallization has the most excellent tabletability properties. In situ crystal growth observations indicate a direct vapor-to-crystal growth mechanism for the sublimation crystallization process consistent with conventional vapor phase deposition. Furthermore, the governing factors and growth mechanisms of sublimation and solution crystallization processes were analyzed and discussed, and it was found that the rate-limiting step of crystal growth is the surface-integration process in solution crystallization, whereas becomes the surface-diffusion process in sublimation crystallization. Overall, our developed sublimation crystallization provides a promising green technology for the development and production of (new) drugs, broadening the thinking behind the development of sustainable chemicals.

The Effect of Recirculation Rate on the Crystallization of REE Recovered using Antisolvent Crystallization in a Fluidised Bed Reactor

Mx Jacolien Sussens, Mr Jemitias Chivavava, Prof Alison Lewis
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Antisolvent crystallization is an alternative method for the recovery of rare earth elements from aqueous leach solution at high yield and good purity. The antisolvent is responsible for a large reduction in the solubility of the target salt, creating high supersaturations if uncontrolled. As a result, crystals with wide CSDs and unfavourable morphologies can form. These can be detrimental for metallurgical processing due to poor solid-liquid separation. Hydrodynamic control can greatly affect crystallization by influencing local supersaturation and mass transfer limitations. A fluidised bed reactor (FBR) allows for improved mass transfer through good mixing, no crystal-agitator collisions, and the ability to recover the product through gravity. The fluidisation velocity can be adjusted to control the hydrodynamics.

In this study the recovery of yttrium sulphate octahydrate (3 g/L), was investigated using ethanol as the antisolvent, at an aqueous-to-organic ratio of 0.9, in an unseeded FBR operated in batch mode. The fluidisation velocity was investigated by varying the recirculation rates (Qr); 20, 40, and 80 ml/min. Recirculation was done over a period of 5 hours, to obtain high yields. It has been found that an increase in Qr increased the vol. weighted mean D[4,3] size from 33 μm to 56 μm, respectively. The yields, however, decreased from 94 % to 81 %. More vigorous mixing at larger Qr allowed for the distribution of local supersaturations. This led to decreased nucleation rates, subsequently increasing the growth rate.

Secondary Nucleation Scale-Up for Stirred Vessels

Ms. Gina Kaysan[1], Dr. Andrew Cashmore[2,3], Dr. Mark Haw[2], Dr. Mei Lee[4], Dr. Cameron Brown[2], Dr. Matthias Kind[1], Dr. Jan Sefcik[2,3]
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Secondary nucleation is thought to be the dominant mechanism in industrial crystallization processes and is commonly used to achieve desirable critical quality attributes of crystalline products such as crystal size distributions. This is especially true in continuous crystallization, where efficient control of secondary nucleation is crucial for achieving and maintaining steady-state operation.

Here, the impact of fluid shear on secondary nucleation was evaluated across multiple scales using computational fluid dynamics (CFD) to characterize fluid flows in vessels. Rapid, small-scale experiments were employed in magnetically and overhead agitated vials with in-situ imaging for crystal counting and sizing to assess nucleation and crystal growth kinetics of α-glycine in aqueous solution under isothermal conditions. 100 and 700 mL sized stirred vessels were then used to investigate the scale-up strategy based on corresponding fluid shear rates.

Across all scales, experiments were carried out with seed addition and without additional seeding. Nucleation rates (primary and secondary) were assessed with a single seed crystal 'dropped in' and with a crystal held in place at a fixed location preventing any contact with the impeller. At small scale, the local shear rate at the surface of the crystal held in place was relatively high, showing a clear impact on the secondary nucleation rate which was significantly higher than for the seed dropped in or for unseeded systems. With increasing vessel volume and decreasing local shear rates at the surface of the seed crystal, secondary nucleation rates became similar to those for unseeded or seed dropped in systems.

This work has shown how the influence of fluid shear on the generation of secondary nuclei can be evaluated across multiple scales with well characterized flow regimes. It has been also described how CFD combined with intelligent experiment design can be used to develop a scale-up pathway for industrial crystallization processes.

The Scaling Up of Batch Crystallisation Processes: Small Changes, Big Impacts

Dr Amy Robertson[1]
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Crystallisation is a key unit operation in the manufacture of active pharmaceutical ingredients (APIs). Traditionally batch crystallisation processes are used, most frequently cooling or anti-solvent processes. These processes are required to deliver particles with the right purity, form, particle size, particle shape, bulk properties and in high yield. The scale up of such processes can often be problematic, with factors such as vessel design, additions, agitation, isolation and drying all having a potential impact on the particles and their properties.

A case study will be presented describing the impact of small changes to a crystallisation process on scale up and the resulting impact on the wet granulation stage of the drug product formulation process. The API was manufactured in three locations and equipment trains, in the subsequent wet granulation process varying amounts of water were required to produce the granules depending on the source of the API. A root cause investigation will be shared. This included characterisation of the API and the granules, investigation into the potential changes in the crystallisation process, the isolation process, the equipment train and the wet granulation process. The results from this investigation were combined with analysis of the crystal structure and computational fluid dynamics (CFD) modelling to understand the origin of the differences in scale up of the process at the three manufacturing sites, the fundamental impact on the crystal properties produced and their resulting performance in the wet granulation process.

Dynamic interplay of crystal growth, abrasion and shape in crystallization processes: modelling and experimental approaches

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Abrasion and growth are well-studied crystallization phenomena. However, their dynamic interaction is less well studied. The classical growth model for crystals is based on the assumption of faceted crystals. Growth is then modeled as displacement of crystal faces away from the center of mass. Abraded crystals have regions that cannot be described by the typical crystal faces. Thus, the classical growth model is not applicable. Therefore, we have developed and parameterized a model for Potash Alum that can describe the shape and size evolution of abraded single crystals by growth (Schiele, et al., 2021). We also combined the abrasion model of Gahn & Mersmann (1999) with the shape model of Reinhold, et al. (2015) for a corresponding model for high-dimensional description of abrasion on particle-scale. We then used both models to determine rates for a population balance model (PBM) for process simulations (Schiele, et al. 2023).

In this talk, we will first present our multiscale approach and the corresponding results of the process simulations (Schiele, et al. 2023). The simulations show how different crystal shape assumptions for secondary nuclei and seed crystals affect crystallization outcome in terms of crystallized mass. Accounting for the non-ideal shape of abrasion fragments leads to significantly (>40%) increased crystallized mass. Using seeds with fast growing faces or damaged (i.e. milled) seed material increased the crystallized mass even more. We thereby explain how growth and abrasion are both significantly affected by crystal shape AND both affect shape. We will further show yet unpublished experimental work corroborating the simulations. Samples from suspension are analyzed by means of micro-computed tomography and show size- and time-dependent shape of crystals in three dimensional images.

Digital design framework for pharmaceutical crystallization processes – A case study for continuous cooling crystallization of Diphenhydramine hydrochloride

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Model-based design and optimization have shown potential for a) promoting process intensification, b) reducing the resource-intensive nature of process design, c) increasing process understanding, and d) addressing the challenges associated with continuous crystallization, such as fouling and particle agglomeration. However, a prerequisite for implementing the above strategies is the availability of an accurate and reliable model capturing the essential dynamics of the crystallization process for a given system. Although applications of model-based design are being well studied for continuous crystallization systems, a unified framework for building a reliable model for a given system is still an open subject. Only a few studies have focused on developing frameworks for parameter estimation and model development procedures for continuous crystallization processes with experimental validation. In this work, we address this gap by developing a digital design framework for building a digital twin for the continuous crystallization process of a model compound, diphenhydramine hydrochloride. The integrated experimental and simulation-based framework includes thermodynamic operating space investigation followed by kinetic parameter estimation using population balance modeling. To minimize the overall resource consumption during the process development phase, systematic experiments were designed to first estimate the parameters using the batch crystallization setup, and then the translation of these parameters to continuous crystallization systems (multi-stage MSMPR) was studied. Furthermore, a new kinetic parameter uncertainty analysis-based approach is presented comparing experimental uncertainties and model prediction uncertainties to justify the robustness of parameter estimation procedure. Finally, the validated digital twin of the process was used in a multi-objective process optimization framework to control the final product crystal size distribution.

Evaluation of Methods for Particle Characterisation from In-Situ Sensors

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In-situ measurements of particle characteristics offer several advantages over ex-situ: higher sample rates and no sample extraction. However, there are difficulties – sample presentation is more challenging. For process modelling and control, these measurements are generally analysed to yield Particle Size Distribution (PSD). Many algorithms are available for this. Combinations of analysis and sensor could have preferred operating conditions (e.g. optimally measures high concentration samples). Figuring out which combinations to apply, and when, is a challenge.

This work seeks to address this challenge by providing a framework for evaluating in-situ methods. Analysis results are tied back to a trusted independent, usually offline, measurement of particle size. In-situ and independent PSDs are quantitatively compared by Integral Absolute Error of Cumulative Density Function (IAE of CDF). Two sensors are considered: FBRM giving Chord Length Distribution (CLD), and PVM giving microscope images (see Fig 1A-C). We consider both deep learning (DL) and classical (not DL) approaches for both images and CLD. Measurements from each sensor are taken for standard polystyrene microspheres of different sizes and concentrations. These are analysed using the two techniques to develop a map of error against particle size and concentration (Fig 1E): evaluating the combination of sensor and analysis. This process is repeated for a mixture of non-standard polystyrene spheres and ellipsoids, and lactose particles.

Results show little effect of concentration on DL image analysis and a stronger impact on classical image analysis. Size is much more impactful on image analysis results. Small particles can be difficult to identify and have fewer pixels to their size resulting in larger variance; larger particles are less likely to fall entirely within the field of view and large sample numbers are therefore difficult to obtain. Preliminary CLD analysis evaluations show little dependence on concentration, with a slight preference for higher concentrations.

Model Predictive Control of Supersaturation and Crystal Size During Batch Cooling Crystallisation of Hexamine from Ethanol Solution

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Batch cooling crystallisation is used to produce a range of fine chemicals. These often require a certain crystal size distribution (CSD) to give desired properties that affect product performance and downstream operations. Process control schemes for achieving this CSD are mostly measurement-based, where supersaturation is held within a specific range to control nucleation and growth. Many model-based control methods are heavily empirical, but shifting the focus to a mechanistic model would reduce the overall time required to experimentally quantify a system's crystallisation behaviour for a broad range of operating conditions.

The main aim of this research is to develop a model predictive control (MPC) strategy built upon a mechanistic crystallisation process model, using 1D population balance equations (PBEs) that can accurately predict the CSD evolution with time. A model describing the hexamine-ethanol system was built, using kinetic parameters available from literature, in gPROMS Formulated Products software (Siemens-PSE). The model was coupled with a control algorithm in PharmaMV software (Perceptive Engineering) to create a digital twin used to train a series of model controllers.

After using the digital twin to simulate supersaturation control in a theoretical 0.5L crystalliser, the MPC strategy was validated using a real 0.5L jacketed vessel. The effects of supersaturation set-point, seed size/loading and the presence of impurities on the controller performance have been assessed. The MPC strategy was further adapted to control the product crystal size through manipulation of the supersaturation profile. This strategy was also tested in-silico and validated using the 0.5L crystalliser, where supersaturation profiles were determined to achieve different target sizes within a range of 20μm.

This MPC strategy provides a basis that could be adapted for industrial crystallisation systems through increasing complexity of the digital twin, such as by introducing 2D PBEs or direct quantification of the impurity concentration's effect on growth rate.

Application of Deep Learning to Support Industrial Crystallization Process Development

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The measurement, control, and analysis of crystallization outcomes in-situ and real-time are critical to optimizing the performance of industrial crystallization processes. By combining high-resolution in-process image acquisition with intuitive image analysis algorithms and trends, important events such as nucleation, breakage, agglomeration, morphology change, or formation of immiscible phases can be easily identified. This study focuses on developing AI-enabled image analysis workflow to support traditional process analytical technologies (PAT) to increase versatility when compared to common tools such as focused beam reflectance measurement (FBRM). Image analysis algorithms introduce new capabilities to monitor process changes by measuring and interpreting changes to size, shape, and particle counts, directly from image sequences, thereby reducing the delays and complexity of doing offline analysis or manual image analysis.

A deep learning-based image analysis technique was used to address the needs of crystallization process development. Metler Toledo's EasyViewer¬—an in-situ PAT tool based on high-resolution microscope images and verifiable image analysis—is used to record and collect images during crystallization experiments. The images were used to train a deep learning algorithm, convolutional neural network (CNN), or ConvNet. The CNN architecture, Resnet-101 were re-trained on crystal images collected using the Easyviewer PAT tool and validated for single and multi-classification tasks. The images were labeled (or annotated) by crystallization experts (human annotators) through the use of image annotation tools to distinguish particles, droplets, or bubbles in every image. The model inference showed >97% accuracy on the unseen test datasets. This approach shows superior performance to classical image analysis and traditional standalone PAT tools for analyzing high aspect ratio crystals and high-density slurries during crystallization process development.

New Salts and Cocrystals of Pymetrozine with Improvements on Solubility and Humidity Stability: Experimental and Theoretical Study

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Pymetrozine (PMZ) is a highly effective non-biocidal pesticide that offers excellent control against piercing and sucking mouthparts pests. However, its low water solubility and poor humidity stability are disappointing drawbacks. In conditions where the relative humidity (RH) exceeds 70%, PMZ spontaneously converts to its dihydrate, leading to the undesirable formation, decomposition, and dissociation of hydrates during processing, storage, and transportation, which can seriously affect the product's quality.

To improve PMZ's solubility and humidity stability, new multicomponent crystals were developed based on the connotation of crystal engineering. Seven single crystals of PMZ's new multicomponent solids, including three cocrystals and four salts, were obtained. The detailed structure and molecular interactions in these new crystals were clarified using single-crystal X-ray diffraction and Hirshfeld surface analysis.

Thermogravimetric analysis, differential scanning calorimetry, and Fourier-transform infrared spectroscopy were used to characterize the thermodynamic properties and spectral data. Through dynamic vapor sorption and equilibrium solubility measurement, it was found that these multicomponent crystals exhibited better humidity stability and higher water solubility than PMZ. Moreover, the insecticidal activity of PMZ was preserved during the formation of cocrystals/salts. We conducted atoms-in-molecules (AIM) analysis and molecular electrostatic potential surfaces (MEPs) analysis to evaluate the strength of hydrogen bonds and reveal the origins of salt/cocrystal formation. This allowed us to rationalize and explain the variations and origins of these physicochemical properties on an atomic scale.

In conclusion, new multicomponent crystalline forms of PMZ were successfully obtained, which prevent the parent compound from undergoing hydrating transformation. These crystals offer improved stability and solubility properties, potentially enhancing the effectiveness of PMZ in controlling pests.

Levofloxacin and Quercetin drug-GRAS co-crystal: solid-state characterization, solubility and dissolution rate investigation of a novel biologically-active system.

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Co-crystallization, a crystal engineering tool, provides alternative routes to the synthesis of new solid materials and/or to the enhancement of the properties of active molecules for pharmaceutical or nutraceutical applications. The basic idea is that the solid-state association of an active ingredient with a molecular component belonging to the GRAS family (generally recognized as safe) may allow to explore new ways to enhance and/or alter, in a synergistic way, the overall performance of the final product. Nowadays, bioactive compounds isolated from different plants, fruits or vegetables have gained interest in the crystal engineering community due to their beneficial effects on human health; hence, they are considered promising candidates for co-crystallization with active pharmaceutical ingredients. Following this trend, for this work, the flavonoid quercetin (QUE) was chosen as a co-former, being flavonoids a large group of naturally occurring bioactive compounds present in various plant species, playing an important role in the protection against pathogenic microorganisms, such as bacteria, fungi or viruses. The antibacterial API Levofloxacin (LEVO), selected here to be crystallized with quercetin, belongs to the fluoroquinolone class, and it has a broad spectrum of activity against gram-positive and gram-negative bacteria. In this work, the potential multi-target activity of a LEVO-QUE co-crystal was investigated. The antibacterial performance of the co-crystal was investigated and compared with that of the separate components as well as of their physical mixture. Solubility data and dissolution rate experiments were performed for a better understanding of the antibacterial test results. In situ Raman spectroscopy and the Crystal16 platform tools were applied to obtain some preliminary information on the system under investigation.

Novel series of Ivosidenib-Polymer cocrystals

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Pharmaceutical salts are a ubiquitous front-line approach to improve the inherent low aqueous solubility of increasingly complex small molecules where an ionisable group is present. Within pharmaceuticals, cocrystals have been increasingly investigated and found wider regulatory acceptance in the prior two decades and their formation can provide a viable alternative to improve aqueous solubility and tune solid form properties of non-ionisable active molecules.

We argue that cocrystallisation utilising polymers (common drug product excipients) instead of traditional small molecule coformers can generate cocrystals with a unique opportunity that can combine aspects of the drug substance and formulation development workflows of a drug product.

We present the case of a commercial molecule, Ivosidenib, a complex chiral drug substance used in the treatment of relapsed or refractory acute myeloid leukemia (R/R AML). The solid form landscape is complex with multiple hydrates, solvates and anhydrates. Of these, a series of alcohols forming isostructural solvates was identified. The instability of these solvates makes developability challenging and we have studied the substitution of the solvent for less labile entities such as polyethylene glycol (PEG) in the system.

We present the single crystal structures and complete solid-state characterisation of a series of Ivosidenib-PEG cocrystals to understand the interaction within the lattice. Whereas linear polymers have been crystallised with simple model systems (carbamazepine , diflunisal), our work demonstrates a solution crystallisation preparation at scale on a more complex molecule such as Ivosidenib. We suggest that small molecules forming a high number of solvates could be good candidates to evaluate for potential cocrystallisation with polymer materials.

Co-crystal screening of novel solid forms and determination of the relationship between crystal structure and particle properties.

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The nutraceuticals research area is an evergrowing field due to the potential health benefits and therapeutic effects associated with this class of compounds, such as pain killers, digestion aiders, and prevention of certain types of cancer.[1] Natural polyphenols are undoubtedly the largest class of nutraceuticals and are commonly found in fruits, vegetable and barks of medicinal plants.[2] As a result, they are interesting candidates for the treatment of various symptoms and diseases such as inflammation and for antiaging purposes in cosmetic formulations.[3] However, nutraceuticals display poor aqueous solubility due to their large molecular size and their lipophilicity and so their use in pharmaceutical applications is still limited.[4] Crystal engineering was proven to be an effective and robust method of tailoring the physicochemical properties of solid materials. In particular, the formation of a salt or a co-crystal can dramatically increase the dissolution rate and bioavailability of a specific molecule, without changing its biological activity. [5]

The aim of the presented work is to discover novel solid-state forms of selected nutraceutical compounds (e.g., curcumin, quercetin) and to study the relationship between the crystallographic properties of each solid form and the physical and chemical properties of the resulting particles (e.g., solubility, thermal stability, wettability).[6] The novel materials are characterized with PXRD, Raman spectroscopy, FTIR, DSC and TGA Analysis. The computational analysis is performed with Material Studio 2022 and Mercury software.

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Taking Cues from Elementary Chemical Kinetics: Absolute Rate Theory of Homogeneous Crystal Nucleation from Solution

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Taking cues from elementary chemical reaction kinetics, a mathematically simple yet quantitative rate theory for organic crystal nucleation from solution has been developed. Its focus is explicit modelling of local phase behaviour in solutions prior to nucleation, through interactions between solvated solute molecules. Solving the resulting system of rate equations for solute aggregation into pre-nucleation assemblies leads to an overall rate equation that is mathematically very simple yet reproduces the supersaturation-dependence of organic crystal nucleation rates quantitatively. Most importantly it contains only a single a priori unknown rate parameter, which is easily determined by standard nucleation rate measurements. Within this framework, the temperature-dependence of experimental crystal nucleation rates is consistent with an Arrhenius-like activation energy. The activation energy is straightforward to determine from standard polythermal nucleation rate measurements. The results of analysing experimental nucleation rate data of more than 20 different solute/solvent combinations highlight the importance of interactions between solvated solute molecules and of desolvation in influencing the activation barrier. While the new rate equation retains an exponential free energy activation term, the interpretation of its pre-exponential terms is fundamentally different from that in classical nucleation theory. The quantitative agreement between calculated rates and experimental data for such a wide range of systems demonstrates that homogeneous nucleation rates from solution can be analysed and predicted within the framework of absolute rate and transition state theory that has been established in the chemical sciences for almost 100 years.

Classical and non-classical nucleation mechanisms of insulin crystals

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Nucleation represents a first-order phase transition by which molecules pass from a wholly disordered state to an ordered one [1]. Introduced by Volmer and Weber in 1926, the Classical Nucleation Theory (CNT) describes nucleation as a process involving the formation of a critical nucleus and its subsequent growth [2]. Nonetheless, some of the CNT suppositions have been questioned and even contradicted over the past two decades. The non-classical approaches typically describe nucleation as a multi-step process, where metastable intermediate states are involved [3]–[5].

This work aims to explore classical and non-classical mechanisms of protein nucleation. For this purpose, shear-induced crystallization experiments were performed in the presence of variable precipitant solution concentration. The study involves the rheological characterization of insulin solutions by rotational rheometry to investigate crystallization and/or aggregation. Moreover, the analysis of the protein behaviour in solution is done by DLS to characterize the oligomeric distribution over time.

The results can be divided in three main parts: (I) Crystal formation in accordance with the CNT mechanism, where the nuclei are formed and grow until reaching a detectable size (crystal). The rheological characterization reveals a transition from shear-thinning to Newtonian responses. (II) A multi-step nucleation mechanism (non-classical CNT) governs the crystallization process as crystal appearance seems to require the presence of initially formed aggregates. The rheology is dominated by shear-thinning responses. (III) Aggregate formation with shear viscosity values ranging more than six orders of magnitude (shear-thinning response). Preliminary DLS measurements indicate that the precipitant solution concentration clearly impacts the distribution of the different insulin oligomeric forms, which are mostly hexameric. A slow decay of the first-order correlation function is verified for conditions promoting aggregation. Further experiments are still necessary to draw reliable conclusions in terms of the connection between rheological characterization and analysis of the insulin behaviour in solution.

C1.3

On the kinetics of stochastic ice nucleation from aqueous solutions

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The freezing of aqueous solutions is of great importance to many fields, but the kinetics of its first step, stochastic ice nucleation, is not well understood. Relevant studies in the literature typically assess the freezing behavior of micrometer-sized droplets due to their relevance to cloud microphysics. It is unclear, however, whether the findings of these contributions can be generalized and extended to larger volumes, such as those often used to freeze biopharmaceuticals. This is because the volume affects both process conditions, such as attainable cooling rates and heat transfer in general, and the inherent nature of nucleation: in large volumes, heterogeneous nucleation promoted by the presence of surfaces dominates, while in micrometre-sized droplets homogeneous nucleation is commonly considered dominant.

To accurately capture how the stochastic nature of nucleation manifests itself in larger volumes, we measured a total of about 6,000 freezing events in vials with a fill volume of 1 mL from solutions of ten different compositions. We build on earlier work where we developed and validated the methodology to measure ice nucleation temperatures under tightly-controlled conditions at mid-throughput, and where we showed how to estimate the parameters in the kinetic rate expression and their uncertainty (cf. 10.1016/j.ces.2023.118531).

The statistical analysis revealed that the kinetics of stochastic ice nucleation is independent of solute type and concentration: we estimated the kinetic parameters for all solution compositions, and we found that a single set of parameters was able to quantitatively describe the nucleation from all solutions. This is true whether the driving force for nucleation is expressed in its rate expression as a function of water activity or of temperature. While the former expression is used more frequently in the literature, the latter is significantly less computationally demanding and hence is considered the method of choice for pharmaceutical applications.

Prediction of API solubility: an overview of the recent developments of the SAFT-gamma Mie approach

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The prediction of the solid-liquid equilibrium solubility of active pharmaceutical ingredients (APIs) is a significant challenge which is of importance in pharmaceutical applications and solvent selection. The SAFT-gamma Mie group-contribution equation of state [1] has been recently extended to model the phase behavior and solubility of mefenamic acid, a nonsteroidal anti-inflammatory drug, in a range of solvents [2]. The SAFT-gamma Mie approach has also been applied to the prediction of aspirin solubility, octanol-water partition coefficients for a range of APIs, and pH-solubility profiles of aqueous buffered solutions of ibuprofen and ketoprofen [3].

Literature data for the vapor pressure, single-phase density, saturation density, vaporization enthalpy, bubble temperature, dew temperature, and bubble pressure are used to characterize the new group interactions. Solubility data are used to characterize the new group-group interactions only if there are no other experimental data available. The transferability and predictive accuracy of the new models are assessed by comparing the theoretical predictions with the experimental solubility data. Our comparison includes water, alkanes, alcohols, ketones, esters, and aromatic compounds as families of solvents. The approach is also applied to the solubility prediction in mixed solvents. A very good agreement with the experimental data is obtained for the considered systems.

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Heterogeneous crystallization on the surface of formulation additive

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In many cases, the processability or bioavailability of crystalline active substances is difficult due to the unique needle-like habit of crystals or the inadequate particle size or particle size distribution of the product. Although these properties can be influenced by crystallization, it is not always possible to achieve optimal physical properties. Crystallization with formulation additives can improve crystal properties, such as product flowability, the width of particle size distribution, or even crystal structure, beyond the effect of simple process parameters. Heterogeneous nucleation with additives can promote or inhibit nucleation and crystal growth, and thus improve product properties, through the strength and lifetime of the additive-active pharmaceutical ingredient interactions. The aim of our work is the development of an additive-assisted heteroepitaxial crystallization to improve the processability of a poorly flowable Form B polymorph of famotidine. Following the selection of promising drug-additive combinations at a small scale (10 ml), experimental design-based batch experiments were conducted to investigate significant process parameters where crystallization on the surface of the excipient also occurs on a lab scale (150 ml crystallizer). Processes were quantified by production and accurately analyzed the physical properties of the products (polymorphism, crystal shape, size, and flowability). A neural network-based image evaluation method was developed to identify the particle size distribution of products with variable habit and an offline Raman spectroscopy method to quantify the exact drug-additive compositions. A crystalline product with good flowability and a significant production improvement (28%→65%) compared to the system without additives was obtained, with no change in the crystal structure (Form B).

Deracemization of Conglomerates via Temperature Cycling and Cooling

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Since the biological activity of a chiral molecule depends on its handedness[1], there is an increasing effort to distribute drug products in their enantiopure form. Among available separation processes, those based on crystallization enable the isolation of the pure crystals of the desired enantiomer in an effective manner[2].

Deracemization by temperature cycling, where a racemic suspension slightly enriched in one enantiomer turns into pure enantiomer via cyclic growth-dissolution steps, has been shown to be effective for several conglomerates[3]. This process enables full deracemization but with limited yield dependent on the initial suspension mass and performing deracemization at higher temperatures is beneficial due to the faster racemization reaction. At the end of the process, the solution, still containing large amounts of solutes due to the high solubility, is either discarded or recycled to be used for another deracemization process.

In this work, we propose a new process that is based on the integration of temperature cycles into cooling crystallization-induced deracemization[4] and hence termed deracemization by temperature cycling and cooling. Building on earlier work, we determine the important process parameters by performing parametric analysis using the population balance model of a batch system[5]. Then, we experimentally show successful deracemization of the conglomerate-forming chiral model compound N-(2-methylbenzylidene)-phenylglycine amide (NMPA). We show how different process conditions such as initial enantiomeric excess and predefined thermal evolution can affect process productivity. The process proposed here, not only allows full deracemization of the initial seed mass suspended in the solution, but also depletes supersaturation by cooling, hence increasing the process yield.

Towards protein crystallization as a tool for bio-separation: study of insulin crystallization in a meso OFR-SPC

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Introduction
Protein therapeutics have become an important segment of biopharma due to their increasing use to treat diseases. While chromatography has been the main bio-separation method, the future of the industry relies on its ability to develop more cost-effective and scalable separation techniques. Crystallization allows to separate, purify and stabilize in a single step. Despite its huge potential, barriers to the industrial adoption of crystallization as a bio-separation method remain. This is namely due to the complexity of the occurring phenomena and the unavailability of generalized crystallization strategies in the case of proteins.

The present work aims to develop a unique platform for protein crystallization based on oscillatory flow technology (1). The target system is insulin, where the influence of protein concentration and the role of acetone on nucleation kinetics and on crystal size distribution (CSD) are assessed. For this, batch crystallization trials were carried out in a meso oscillatory flow reactor provided with smooth periodic constrictions (OFR-SPC) (Figure 1) and monitored by turbidity. The collected suspensions were characterized by optical microscopy to evaluate CSD (Feret diameter).

Results and Discussion
The results show the high reproducibility of the process and the significant contribution of both protein concentration and acetone to nucleation kinetics and CSD. As the initial insulin concentration increases, the induction time (up to 10-fold) and average insulin crystal size decrease. The presence of acetone allowed for a faster nucleation event (10 to 20-fold) and a narrower CSD. However, larger crystals were obtained when compared to the crystallization trials without acetone. The insulin crystals show a rhombohedral morphology for all the tested conditions.

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How polymer templates influence the crystallisation rate of pharmaceutical materials

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The crystallisation rate of two pharmaceutical systems was experimentally investigated through induction time and metastable zone width determinations in the presence of heterogeneous polymer templates.

We collaborated to establish a molecular dynamics model that describes the interaction between an active pharmaceutical ingredient (API) and extrinsic particle (polymer).

Combining experiment and computation led to the correlation of physical and chemical descriptors from the molecular dynamics model with the rate and extent of crystallisation in the presence of a diverse set of polymers. In doing so, we have built knowledge of important intermolecular interactions between API and polymer that can be applied to influence difficult to crystallise compounds, or on the contrary the stabilisation of amorphous solid dispersions.

Key deliverables from this project include a computational model and experimental protocol that accurately account for the crystal, solvent, and polymer combination.

Applying the chemical and physical aspects of heteronuclei that correlate with crystallisation tendency, we permit experimental screen design on novel systems that we may wish to crystallise for the first time. Conversely, we might support the goal of stabilising the amorphous state using polymers in a drug product, for the purpose of increased kinetic solubility through supersaturation to positively influence bioavailability.

Integrated Filtration and Washing modelling of Active Pharmaceutical Ingredients and Impurities

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There is an increasing interest in the application of continuous processing technologies in pharmaceutical manufacturing to control crystal properties and deliver consistent particulate products. The focus of the work is to combine filtration and washing operations commonly used in active pharmaceutical ingredient (API) purification and isolation by combining predicted and experimental data generated during upstream crystallization process.

A Carman-Kozeny filtration model is integrated with a custom diffusion with axial dispersion washing model. This model assumes no solid phase dissolution or precipitation. To mimic dispersion washing, a single stage continuous stirred-tank reactor approach was used. For model validation, experimental data measured from the lab scale using the AWL CFD25 semi-continuous isolation unit and the Biotage filtration unit were used. To validate the cake and filtrate composition during filtration and washing stages, HPLC quantitative method was used.

Mefenamic acid and paracetamol were selected as representative test compounds. Three different crystallization solvents were used for mefenamic acid and for paracetamol, with relative structurally-related impurities derived from synthesis. The objective of the models was to:

- Identify the product purity reached with a fixed wash ratio.
Optimize process conditions to minimize impurity content in the isolated cake.

- The model provides detailed evolution of species concentration during washing in the liquid phase. The washing of the wet filtered cake is then simulated to predict: washing efficiency and to generate washing curves, cake and filtrate composition, and residual cake moisture content and composition.

Model validation was used to estimate cake properties (specific cake resistance, cake composition after washing, washing curve). The data was generated via small-scale batch pressure filter experiments. As a precursor to optimization, a Global Systems Analysis was conducted to explore the design space and critical process parameters. The findings from this were translated to a final model to simulate the optimal point.

C3.2

Temperature correction of spectra to achieve isothermal local model performance for monitoring and control of cooling crystallisation

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The role of changing temperature is intrinsic to cooling crystallisation. If spectroscopic methods are deployed for monitoring and control of such processes, then the effects of temperature changes upon spectra are inherently unavoidable. Removal of temperature effects from spectra may be achieved via loading space standardisation (LSS), which transforms spectra so that they appear as though they were all acquired at a single temperature. This then enables the construction of global calibration models with a performance comparable to the analogous isothermal local model.

A recommended structured approach to removal of temperature effects from spectra via LSS is proposed. The model requirements are at the forefront of all decision-making in the workflow, which avoids potentially unnecessarily expending effort in applying an advanced algorithm. Prior to embarking on removing the effects of temperature from spectra, the potential gains that may be achieved in the absence of temperature effects are established. Application of the workflow is demonstrated with a dataset for monitoring solute concentration of ibuprofen (IBU) in EtOH/H_2O by ultraviolet spectrometry. For population balance modelling requirements, the error in the predicted concentration should be below 10 g/kg solvent. Global and isothermal local partial least squares (PLS) models were constructed with root mean square error of predictions (RMSEP) of 24.2 and 5.7 g/kg solvent, respectively. As this indicated that pursuing removal of temperature effects would be worthwhile, an LSS model was constructed to transform the dataset such that all spectra appear as though they were acquired at a single temperature. The global PLS model constructed from the LSS-transformed spectra (RMSEP of 7.9 g/kg solvent) satisfies the monitoring requirements. Investing in the advanced chemometric effort to implement LSS was necessary in this example and illustrates how process modelling and control may be improved accordingly.

A Computationally Efficient Framework for Solving Population Balances in Crystallization Using Adaptive High-resolution Finite Volume Method

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The application of quality-by-control (QbC) approach to batch crystallization in drug manufacturing has gained attention in recent years since it provides insights into the process dynamics and offers suggestions for achieving desired product properties. However, the QbC approach requires a high-fidelity model that is amenable to rapid process design and control. Population balance equations are chosen to represent complex crystallization mechanisms and various numerical solutions have been proposed to solve this. The high-resolution finite volume method (HRFVM) is a popular numerical method used to solve population balances in crystallization processes. The success of any numerical technique depends upon the tradeoff between model structure complexity, numerical accuracy, and computational expense. HRFVM provides better flexibility in terms of its application to various crystallization mechanisms such as agglomeration, breakage, and dissolution. However, it results in model uncertainty due to the numerical diffusion, unless a larger mesh size is implemented at the expense of computational time. These challenges were addressed before in several studies through hardware implementation for acceleration, using hybrid numerical structure, and applying moving-mesh algorithms. Yet, there are limited studies focusing on feasible numerical frameworks for industrial application.

This work proposes a robust framework that discusses the first-time implementation of HRFVM in crystallization with the optimal moving-mesh algorithm that improves numerical accuracy. A parallel computing structure is also introduced in this work to improve computational efficiency. The benefits of the proposed framework are demonstrated using an industrial case study using batch cooling crystallization of a pharmaceutical compound.

Mesoscale clusters in the crystallization of amino acids

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Nucleation is the initial step in the formation of crystals, and it is known to greatly influence the physicochemical properties of crystalline products. However, the underlying phenomena on the mesoscale that govern nucleation remain difficult to conceptualize despite numerous mechanisms proposed in the literature. The lack of suitable tools to investigate this phenomenon is typically attributed to its very short characteristic times and to the small size of the species involved. The formation of crystal nuclei from precursors at the colloidal scale, termed mesoscale clusters, has been proposed for several species, among which biomolecules and various organic molecules. [https://doi.org/10.1073/pnas.1309320111-https://doi.org/10.1016/j.colsurfa.2019.123633]

Mesoscale (or submicron) species of variable nature have been observed in solution and understanding their behavior is key to shed light on the mechanisms by which crystals form, grow and dissolve. If involved in the crystallization phenomena, they could serve as building blocks for crystal formation and play a relevant role in determining crystal size, shape, and polymorphism. In-depth knowledge of the mechanism of crystal nucleation can help to optimize the crystallization process and to improve the yield and purity of the final product. Understanding the behavior and evolution of mesoscale clusters can also provide insights into the kinetics and thermodynamics of crystal growth, as well as those of crystal dissolution, which plays a vital role in determining the bioavailability of drugs.

Using a custom polarized laser microscopy setup developed in our group, the concentration of mesoscale species and information on their structure through optical isotropy and anisotropy can be obtained. With this tool, we investigate the properties of model compounds relevant for the study of nucleation and for the pharmaceutical industry in undersaturated, saturated and supersaturated conditions, to characterize the nature of mesoscale clusters in solution and to gain experimental insight into the mechanisms of primary and secondary nucleation. [https://doi.org/10.1021/acs.cgd.2c00577-https://doi.org/10.1021/acs.cgd.1c01193]

Tackling Intermolecular Interactions and Transient Liquid Phases in Protein Crystallization using Molecular Rotors

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In protein solutions, the interplay between short-range attraction and long-range molecular repulsion leads to a complex phase behavior with the formation of transient dense liquid phases, equilibrium clusters, and kinetically arrested states. The role of liquid-liquid phase separation (LLPS) in crystal nucleation is still debated, and the high viscosity of dense phases is known to be a parameter limiting nucleation within the dense phase.

We propose a methodology based on fluorescence lifetime imaging microscopy (FLIM) to characterize protein interactions in solution and study the role of LLPS in crystal nucleation mechanisms. As phase transition implies local changes in solution structure, we propose to use environment-sensitive fluorophores, molecular rotors, which fluorescence lifetime correlates with local viscosity or free volume available in its immediate vicinity. We have studied the relation between protein-protein interactions and fluorescence lifetime in lysozyme solutions using Sulforhodamine-B (SRh-B). Fluorescence lifetime evolution showed a nonmonotonic trend at constant protein concentration (Fig.1A), with the increase of sodium chloride concentration. Preliminary SAXS analyses revealed changes in solutions structure factors near the minima of lifetime curves. We argue that the observed tendency is related to the transition from a repulsive to an attractive interaction regime.

We have analogously characterized the dense liquid phase formed upon lysozyme LLPS. Results show higher fluorescence lifetime and intensity inside the protein-rich droplets (Fig.1B), indicating a more restricted environment for the rotor. The difference in lifetime between 1.90 ns in the bulk solution and 2.06 ns inside the droplets corresponds to a change in local viscosity by a factor of 1.4. Rotor-protein interactions have additionally been studied using X-ray Crystallography and found to be non-specific. Therefore, we suggest that molecular rotors' fluorescence lifetime can be used as an indicative of protein interactions and thus FLIM is a promising tool for characterizing transient phases in nucleation studies.

Modular microfluidic platform for solubility measurement, nucleation statistics and polymorph screening of active pharmaceutical ingredients.

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Drug efficacy strongly relies on the solid state of the active pharmaceutical ingredient. Classical solid-state screening methods involve different solvent compositions and supersaturations. Moreover, the statistical approach needed to address the stochasticity of nucleation make this approach costly in material consumption. One answer is the use of microfluidics to generate hundreds of droplets (nano or micrometric volume) which are as many crystallisers in which the nucleation conditions can be varied and repeated.[1 3] This communication presents a newly developed modular microfluidic platform that provides a universal and flexible plug-and-play tool for crystallisation studies without use of surfactants. By dissolving a powder, our set-up generates saturated solutions that can be used for solubility measurements or distributed in microdroplets for crystallization studies.[4]

Here, we describe solubility measurements performed on different forms, stable and metastable, of pharmaceutical molecules (Irbesartan, Rimonabant and Aripiprazole) in organic and aqueous solvents. In addition, we provide nucleation statistics obtained for Sulfathiazole in water and in acetonitrile. Reporting polymorph screening on Sulfathiazole and statistics for nucleated forms, we find that the cooling rate influences both nucleation and polymorphism results, reflecting the competition between thermodynamics and kinetics. Three unknown forms were discovered. We also demonstrate the limitations of microfluidics for crystallisation by cooling: reducing the crystalliser volume considerably increases nucleation induction time.

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Heterogeneous nucleation of urea from aqueous solution: a combined experimental and simulation approach

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Control of nucleation rate and polymorphism is a major challenge for developing better crystallisation processes. Nucleation is likely to be heterogeneous, and occur at solution-container or solution-impurity interfaces. Previous work showed that contact with PTFE and tridecane significantly increase the nucleation rate of glycine from solution (1,2). This was attributed to an interfacial concentration enhancement, observed using fully atomistic molecular dynamics simulations (2,3).

Following these studies, we aim to develop a new approach to control nucleation rate and polymorphic outcomes, based on tunable surface interactions. Crystal nucleation at solid interfaces will be investigated using both molecular dynamics simulations and small-scale, high-throughput experiments, with urea-water as a model system.

Simulations of urea aqueous solutions at interfaces including PTFE and graphite will be presented. Previous work identified the most suitable urea force field considering both crystal and solution properties (4), Lennard-Jones walls are used for simulating the interfaces (3). Preliminary results in Figure 1 show that Lennard-Jones interactions induce a concentration enhancement of urea near the interface, indicating that dispersion interactions cause these interfacial effects. The simulations will be used to make predictions of how various interfaces affect nucleation, which will be validated against the experimental results.

Experimental results of heterogeneous induction times at control interfaces (glass vial surface and air), PTFE (coated stirrer bars) and diamond surfaces will be presented. As shown in Figure 2, PTFE significantly increases the nucleation rate in aqueous urea solutions whereas diamond does not have an affect.

Future simulation work will investigate heterogeneous nucleation by probing the effect of various interfaces, including those studied experimentally, on crystal 'nuclei' seeds at the interface. Our studies will lead to an increased understanding of how different interfaces impact nucleation, which will enable design of nucleants to enhance heterogeneous nucleation or design of process equipment to prevent fouling.

Green Synthesis of Magnolol Multicomponent Crystals for Improved Natural Antibiotics and Customizable Release Profiles

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Green and eco-friendly antibiotic is one of the challenges facing the global pharmaceutical industry. Antibiotics are widely consumed in clinic, livestock and agriculture, increasing annually. Non-biodegradable antibiotics cause widespread and persistent pollution of ecosystems, setting off microbial resistance storms. Developing new antibiotics is the main strategy to solve resistance, and natural products are the important sources of drugs. However, the common poor physiochemical properties of natural products prevent it from clinic. Additionally, it is difficult and challenged to customize release and antibacterial activity of antibiotics without loading materials, but crystal engineering is a potential powerful tool to overcome these challenges.

Magnolol is a natural antibiotic, but poor physicochemical properties result in low bioavailability. In this work, the building blocks of multicomponent materials were manipulated by designing different isomers to achieve precise tuning of release profiles with good gradients and improved antibacterial activity. Three novel multicomponent crystalline solids were synthesized from magnolol and isomeric coformers by mechanochemistry. It was found that the multicomponent crystals achieved the customizable release profile of magnolol by manipulating the substituent positions of the isomers and complexation. Antibacterial activity test showed that bioactivity on two bacteria was significantly improved by designed multicomponent crystals. In addition, the variable statistical analysis indicated that the coformers controlled the dissolution behavior and further stabilized the improvement. This contributes to the efficient use of antibiotics and seeks to customize therapy for the needs of specific individuals.

In conclusion, the properties of magnolol multicomponent crystals can be manipulated through the predesign of building blocks. Crystal engineering provides an efficient strategy to control the release of drugs and meet individual biological differences and various treatment needs.

Understanding the crystallization of complex mixtures of triglycerides: towards rational design of confectionary products with improved sustainability

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Chocolate is a popular confectionary and its supply is increasing, with sales in Europe in 2020 estimated to be worth £46 billion, growing at an average annual rate of around 2.2%. In recent years, confectionary companies have put increasing effort in developing novel recipes to improve the nutritional profile of chocolate and to counteract the increasing price of cocoa butter and address sustainability issues related to some chocolate ingredients. One of this these strategies is the use of cocoa butter equivalents (CBE), which are mixtures of triglycerides from multiple sources (e.g., sunflower oil, mango kernel, sal) that resemble cocoa butter in both physical and chemical properties. Despite being widely used, the crystallization behaviour of many CBEs is still poorly understood. The aim of this work was to develop a fundamental understanding, at the molecular level, of the crystallization behaviour of selected CBEs, and compare it with that of cocoa butter. In order to do so, chromatography was used to determine the composition of CBEs, in terms of fatty acids and triglycerides while the thermodynamic and kinetics of crystallization were studied using polarized microscopy, differential calorimetry and several, unique synchrotron X-ray scattering setups (the multi-capillary holder at Diamond Light Source in the United Kingdom, the combined DSC/SAXS at Elettra Sincrotrone Trieste in Italy and the combined SAXS/rheometry at ESRF in France). The combination of these techniques enabled the determination of crystal properties that affect the sensorial perception of chocolate: namely the type of crystals formed (e.g., polymorphism), their thermal stability and their size and shape distributions. Furthermore, the kinetics of crystallization as a function of CBE composition and the effect of shear were evaluated. The presented multi-technique investigation is the key for a rational design of new chocolate recipes and manufacturing processes.

Separation Strategies for Tailored Molecular Weight Fractionation: The Inherent Complexity of Lignins Polydispersity During Fractional Precipitation

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The constantly growing global energy demand, the negative effects of increasing greenhouse gas emissions, and the finite nature of fossil raw materials calls for alternative sources, which are low cost and renewable. Lignocellulosic biomass (LCB) is a suitable raw material for carbon-neutral materials [1].

LCB can be pretreated by (acetone) organosolv pulping for fractionation into cellulose, hemicellulose and lignin. The latter is an amorphous polymer widely available from various resources. Efficient processes for lignin precipitation from organosolv pulping liquors ("LigniSep") have been developed earlier [2]. However, current technical lignins' are hardly industrially utilized due to their complex heterogeneous nature. Tailored narrow lignin fractions could e.g. be used in functional additives for polymer formulations or in pharmaceutical applications benefiting from lignins' antibacterial/antioxidant properties.

Stepwise decreasing the acetone concentration in a lignin-acetone-water solution allows to precipitate lignin fractions of different molecular weight distribution [1]. In this regard, understanding the solution and solid-state properties of lignin (fractions) as an amorphous "pseudo-component" is of crucial importance. This includes its solubility and phase behavior as well as its thermal properties. In particular, its molecular weight distribution affects lignins' solubility behavior and subsequently its functionality.

Therefore, fundamental studies on precipitation and simultaneous fractionation of lignins into various molecular weight "classes" are of high interest from an industrial point of view. In this contribution, we investigate the solubility behavior of a typical lignin and its fractions obtained from beech wood and aim to visualize the phase separation during the fractionation via dilution and evaporation in pseudo-ternary phase diagrams. The results provide a better understanding of the fractionation strategies and form the basis to design a scalable process for continuous lignin fractionation.

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Impact of additive concentration on stabilization and carrier particle mediated isolation of dalcetrapib nanoparticles

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Anti-solvent precipitation was employed to generate nanoparticles of active pharmaceutical ingredients (APIs) in a fast, cost and energy efficient way to solve the well reported problem of poor solubility and slow dissolution rates in aqueous media of many drugs in the pharmaceutical developmental pipeline. Surfactant and polymeric additives are frequently used to stabilize the nanoparticles. However, the stabilizing effect of additives at much lower concentrations is not often reported. To increase their shelf life, particles are dried to solid state via traditional methods such as freeze-drying or spray drying or by using carrier particle mediated filtration.

Carrier particle mediated filtration involves the attachment of the precipitated drug particles to the surface of carrier particles followed by filtration. This study probes the impact of lower concentrations of additives on the resultant particle size distribution and carrier particle mediated isolation of dalcetrapib (DCP), Fig 1. Using mixture of sodium docusate (DOSS) and polyvinyl alcohol (PVA) at 0.03 mg/ml concentration, the DCP nanosuspension was stable for up to 1 hour whereas higher concentrations of 0.5 mg/mL and 1 mg/mL respectively resulted in an unstable suspension after 30 minutes. Table 1 shows how higher additive concentration in the nanosuspension also negatively impacted the carrier particle mediated isolation and loading efficiency.

The isolated DCP nanocomposite powder at 20% and 30% loading underwent nearly 100 % of dissolution within 30 min which is much faster than 'as received' DCP, Fig 2. This can be attributed to the retention of the nano particle size during filtration and drying.

Thus, low concentration of additives can produce narrow particle size distributions with longer stability and results in a better isolation efficiency during a liquid antisolvent precipitation production process followed by carrier particle mediated isolation to dryness.

Crystallization of Ni-Co-Mn-Li in Battery Recycling Applications

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Our economies and technologies shift from carbon based to electrical energy. To meet the needs of this paradigm shift, industrial crystallization technology must likewise transition and be adapted to meet these needs. Crystallization plays a key role in production of raw material for modern batteries, and also as part of the process for recycling of batteries. Hatch is working in this space and has completed research resulting in patented technology using crystallization.

In the production of such battery grade materials, the removal of impurities is essential to meet Battery Grade specifications. Our presentation will provide insight into methods crystallization methods to provide an effective separation of impurities.

The homogeneous distribution coefficient would be used as a mathematical way to describe the effectiveness of crystallization as a purification process.

Hatch has investigated different crystallization systems in the Ni-Co-Mn-Li-SO4 system and the distribution of impurities such as Ca, Mg within the resulting macro-component phases. Experimental work has been carried out to better understand the dependencies of the homogeneous distribution coefficient to external factors such as pulp density, cooling rates, crystal size distribution and morphology. This provides opportunities to achieve higher crystal purity by manipulating crystallization parameters.

Crystal size, chemical assay balance, and structure are investigated at different temperatures with SEM and QEMscan imaging to understand the morphology of the impurities. Predictive chemical thermodynamic models (OLI, UNIQUAC, Pitzer) are evaluated with experimental data to examine the way that non-ideality is related to operating conditions, e.g. temperature, for different battery metal ions.

Examples will be presented of the tracking particle size analyzer by Mettler Toledo in an Ni-Mn-Co-Li-SO4.

Thermodynamic data are compared with experimental data at equilibrium conditions.

D3.2

Controlling reaction equilibrium and crystal formation using membrane-assisted antisolvent crystallization

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Antisolvent crystallization is extensively used to form organic compounds, especially to purify reactions. This operation requires exhausting downstream processing to fine-tune crystal properties. Instead, membranes could be used to produce in one step a narrow crystal size distribution (CSD) saving raw material, and energy. This work investigated the role of membrane-assisted antisolvent crystallization (MAAC) in shifting forward the reaction equilibrium while controlling crystal formation. MAAC encompasses the membrane's ability to both control antisolvent mass transfer and provide high mixing, which correlates directly with the supersaturation rate. The optimized operation of MAAC is reflected in the stability of the mass transfer coefficient, no membrane wetting by the crystallizing solution, and controlled transport of the antisolvent. A specific combination of the operating conditions, such as flow rate, antisolvent composition, temperature, or gravity resistance plays a key role in tailoring the induction times. Besides, fine-tuning the properties of the membrane, such as its porosity, thickness, and hydrophobicity is advantageous to control crystal formation. The thinner the membrane, the more hydrophobic or the more porous it was, the higher the antisolvent transmembrane flux, the lower the induction time, and the smaller the resulting crystals. This work demonstrated that indeed MAAC is capable of intensifying crystallization processes by providing a one-step narrow CSD, up to four times better than batch or drop-by-drop crystallization, and helping purify challenging reactions for the development of organic compounds.

Understanding washing behavior and optimizing its efficiency during continuous particle isolation in a modular Vacuum Screw Filter (CVSF)

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Approximately 90 % of all active pharmaceutical ingredients (APIs) are obtained in crystalline form, thus particle generation and isolation are crucial to the production process. However, there is still a lack of equipment for the isolation of continuously produced particles in small quantities (<1 t/a). The patented modular Continuous Vacuum Screw Filter (CVSF) enables full continuous product isolation by combining the unit operations of filtration, washing, and drying in one apparatus in a unique flexible fashion [1]. An example setup of the CVSF is given in Figure 1. The CVSF consists of two main parts: a variable number of tubular modules connected by flanges and a PTFE screw. Each module is specifically designed to perform one of the unit operations: filtration, washing, or drying, while the PTFE screw enables axial transport of the suspension/ particles. The setup is designed for high flexibility and adaptability. Thus different material systems with various challenges regarding filtration, washing and drying can be processed. [2-3]

Washing is a very critical process step, which is mainly responsible for maintaining the particle size distribution. By effectively displacing the mother liquor, possible secondary processes such as agglomeration can be prevented. In previous studies, only the entering and exiting particle size distributions (PSDs) were compared and the resulting product residual moisture was evaluated to assess the washing efficiency. Unfortunately, due to the nozzles used, the wash ratio was very high. For a more sustainable process, a significant reduction in the wash ratio is necessary. Color tracers were used to better understand the processes taking place within the CVSF and to evaluate the washing efficiency of the nozzles. Also with the reduced wash ratio long term operation over 24 h was possible with constant high-quality dried particles leaving the CVSF.

Design and Characterization of Electrochemical pH-shift Crystallization Processes

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Biobased platform chemicals, such as carboxylic, amino, or benzoic acids, represent promising alternatives to established petrochemicals. Representatively, the biotechnological production of succinic acid has already been implemented on an industrial scale with up to 30kt/a [1]. However, the downstream processing of the aqueous fermentation broths is responsible for a large part of the total production costs. To neutralize the produced succinic acid in the fermentation calcium hydroxide is added. In the subsequent downstream process, the acid salt must be protonated again with sulfuric acid, for example, to obtain and crystallize the target protonated acid product. The use of these pH-adjusting agents creates neutral salts (e.g. calcium sulfate) in the process that cause additional costs for disposal or further treatment.

Electrochemical downstream processes offer the possibility of avoiding waste salt production altogether [2-4]. The developed electrochemical pH-shift crystallization uses water electrolysis to increase the hydroxonium ion concentration at the anode through the oxidation of water, resulting in a decrease in the pH. Thereby, the proportion of protonated acid is increased, which leads to the crystallization of the protonated form of succinic acid.

This work presents the latest experimental results and methods in the study of electrochemical pH shift crystallization processes. The experiments were carried out in a specifically developed prototype with an electrode surface of 100 cm². Based on preliminary work, quasi-continuous crystallization processes were planned and carried out over several hours in the laboratory. Using optical methods, the fluid dynamics of the three-phase (gas-liquid-solid) electrochemical separation apparatus were investigated in more detail, and the apparatus was characterized. In addition, a measuring cell for inline detection and measurement of particles was developed. With the help of these investigations, additional insides as well as a deeper understanding of the underlying phenomena/mechanisms were generated.

How do you select a form for progression from a complex landscape?

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The most thermodynamically stable form is favoured for drug development but it is not always easy to differentiate between the stability of two forms; especially when their free energies are too close together. Polymorphism, salts, hydrates, solvates and multiple molecular conformational degrees of freedom create significant barriers to crystallisation. Together, we will confront the complexity of a solid form landscape in modern drugs and link industrial practices with crystallisation science. A deep dive into a complex landscape is discussed and the following questions addressed: How do we choose between two polymorphic forms with similar Gibbs free energies? How do we isolate a stable form with an enantiotropic relationship and a transition at room temperature? How can we tackle chemical entities that favour the formation of transient forms in solution? Challenges behind the science can drive us in a particular direction but we must also consider industrial practicalities (robustness, volume efficiency and minimisation of cycle times). We can anticipate that the complexity of solid form landscapes will only increase. Here we cover the utilisation of crystal structure prediction and high-pressure crystallography and discuss how embracing these technological advances can help us to understand complicated solid form landscapes for the design and development of a commercially viable crystallisation process.

Liquid-liquid phase separation of highly aqueous soluble crystal forms – the case of thiamine chloride salts

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Liquid-liquid phase separation, also known as oiling-out, is a phenomenon that often poses challenges to industrial crystallisation processes. The reported reasons for its appearance are varied, from excessive initial solute concentration and supersaturation, to structure-specific factors like high molecular weight and differences in solvent polarity. Although oiling-out has already been advantageously used to target the crystallisation of desired crystal forms and spherical particle agglomerates, for example, it is mostly considered a risky strategy. The major issues that arise are product impurity, uncontrolled batch behaviour, and scale-up inconsistency.[1]

In this work, we report the occurrence of liquid-liquid phase separation in the crystallisation of thiamine salts (vitamin B1, 2-[3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium-5-yl]ethanol chloride salts, $C_{12}H_{17}ClN_4OS$ and $C_{12}H_{17}ClN_4OS \cdot HCl$). These salts show a significant difference in solubility between aqueous and organic solvents. This characteristic may have caused the selective partitioning of solute molecules in the solvent mixtures, which might translate into poor miscibility and processability problems (e.g. fouling, precipitation of amorphous solids, and differences in the metastable zone width). Ternary phase diagrams were used to quantify this phenomenon for the system studied. Experiments were performed in ethanol:water and acetone:water mixtures, at different temperatures. Ethanol:water appeared to be a better solvent to crystallise thiamine Cl HCl as no evidence of liquid-liquid phase separation was observed – as opposed to the acetone:water solvent system (see attached figure). The thiamine Cl salt, in turn, showed major issues of oiling-out in both solvent mixtures. The phase diagrams were used to map the oiling out domains and, consequently, identify safe crystallisation conditions and strategies to scale-up.

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Crystal or Amorphous? Impact of Chemical and Crystal Structure on Formation Rate

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Modifying the physical properties of solid phases is a key objective in many fields of science and technology. This can cover both different crystalline and amorphous forms of a given compound. Understanding the relationships between structural and experimental factors controlling the selective growth of a desired phase is key objective to creating reproducible formation methods. The stability of an amorphous phase with respect to crystallisation has been classified as one of three classes [1]:
(1) crystallisation on cooling of melt
(2) crystallisation on heating of melt
(3) metastable amorphous phase (no crystallisation on heat or cool)

While many materials have been classified in these groupings based on thermal analysis and relationships with thermodynamic parameters have been investigated [2], it is still not clear what the balance between thermodynamic and kinetic factors is for the classification of materials and subsequent behaviour.

This presentation will present our recent studies on a set of structurally related benzylanilides (Figure 1), of which 7 are class 1, 3 class 2 and 7 class 3. The Cl, Br and I systems form isostructural sets allowing behaviour to be related to the chemical changes. Across the systems, a balance between thermodynamic factors and structural factors is observed with different hydrogen bonding patterns present in the class I and III systems. The role of different intermolecular interactions to influence the kinetic factors is investigated through diffraction, spectroscopic studies with computational studies.

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Studying Ultra-Small Silver Nanoparticle Formation by Coupling Ultra-Fast Mixing and in-situ UV-Vis and SAXS

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In this study, ultrasmall silver nanoparticles (Ag NPs) (<3nm) have been synthesized with strict control over their morphology and size distributions. To achieve this, we have developed an OSTEMER based microfluidic reactor [2] with sub-millisecond mixing times (tm~200µs) and coupled it with UV-Visible Spectroscopy and Small Angle X-Ray Scattering (SAXS) to track the evolution of Ag NPs at high spatiotemporal resolutions. Experiments involved reducing AgNO3 by triethylsilane (TES) in oleylamine (OY) and hexane media at 40°C. Pair Distribution Function (PDF) analysis of in-situ HE-XRD data confirmed that the NPs have an icosahedral structure. Time resolved UV-Vis measurements were used to determine induction times and reaction rates for Ag particle formation, yielding an indirect relationship with [TES] and a direct relationship with [OY].

Ex-situ SAXS measurements determined that the NPs are monodisperse, quasi-spherical particles with an average size of 2.86nm, remaining constant independent of [TES], temperature, and [nominal Ag], but decreasing to 2.2nm as a function of [OY]. Further preliminary in-situ SAXS analyses determined the existence of Pre-Nucleation Clusters (PNCs), whose size was slightly smaller to that of the final NP, and was also found to be dependent on [OY], starting from 2.46nm and decreasing to 1.85nm in the presence of a large excess of OY. These findings are inconsistent with the model depicted by classical nucleation theory (CNT), and suggest that the nucleation events (transition of Ag(+) complexes to reduced Ag(0) particles) are confined within the PNCs and dependent on the coordination of Ag and OY. Time-resolved in-situ SAXS and XAS experiments are underway to understand the transition from PNC to NP and the role of the surfactant herein. Our study provides valuable insights into the synthesis of ultrasmall metallic nanoparticles and highlights the importance of in-situ studies at various length and time scales to understand nucleation kinetics and mechanisms.

Identification and characterisation of mesoscale clusters in ethanolic solutions of flufenamic acid

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The nucleation and prenucleation stages of crystallisation play a crucial role in determining the characteristics of the resulting crystal. The molecular mechanisms underlying these early stages of crystallisation remain unknown. The objective of this research is to investigate the effects of two critical sample treatment parameters, filtration and thermal pre-treatment, on the properties of mesoscale clusters in ethanolic flufenamic acid (FFA) solutions, as well as their subsequent role in the nucleation process. Dynamic light scattering, nanoparticle tracking analysis, and liquid-phase transmission electron microscopy (LPTEM) were used to accomplish this. Initial investigations of unfiltered samples at various concentrations revealed the presence of mesoscale clusters even when the samples were undersaturated. Furthermore, solution concentration and ageing time have no effect on cluster sizes. To see how closely mesoscale clusters resemble particles, nanoparticles of FFA in the same size range were prepared and filtered to compare their behaviour. Clusters, in contrast to FFA nanoparticles, occupy a very small volume fraction, as evidenced by the lack of change in concentration, and are extremely fragile, breaking under filtration pressure. Despite no change in solute concentration following filtration, the mesoscale cluster peak vanished from the size distribution and did not reform even after 72 hours of incubation at two temperatures, indicating a significant kinetic barrier to reformation. The well-known phenomenon of electron beam-induced nucleation in highly undersaturated solutions was used in LPTEM experiments to investigate the effect of solution history on the FFA nucleation pathway. High-temporospatial imaging of samples incubated at various temperatures and times revealed that FFA molecules in solution take a very distinct route to nucleation. A freshly prepared FFA solution took a classical path with no intermediates, whereas a sample incubated at 40 °C for 24 hours took a non-classical path through unknown intermediates with spherical morphology to form the final hexagonal crystal.

Deep-learning based in-situ image monitoring crystal polymorph and size distribution: modeling and validation

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In-situ monitoring and closed-lope control of the solution crystallization process are the modernization trends for pharmaceutical development, in which the critical process parameters (CPPs) as well as the product critical quality attributes (CQAs) can be regulated and guaranteed during the manufacturing process. In this study, an in-situ image monitoring methodology based on the state-of-the-art deep-learning model was developed to track the CQAs such as polymorph ratio, two-dimensional crystal size, and shape in a solvent-mediated polymorphic transformation (SMPT) process. Coupled with the multidimensional process information, a 2D population balance model (PBM) was built to provide a cross-validation for the results of the in-situ image-based CQAs analysis. The training framework of the image analysis model Mask-RCNN contains mask annotation, progressive annotation, training and data mining procedures, and the results showed high accuracy for in-situ crystal image segmentation and polymorphic classification in the SMPT process. To validate the SMPT process kinetics and in-situ image analysis accuracy, a 2D-PBM was solved using a high-resolution finite volume method (HR-FVM) which could provide a high dimensional particle size distribution. Through the cross-validation between the process image analysis and the 2D-PBM, the kinetics of the crystal nucleation, growth and the SMPT process were determined and the parameters of the 2D-PBM were fitted using experimental supersaturation, initial volume particle size distribution, shape, and number density information. The 2D-PBM simulation results support the accuracy of image analysis in terms of polymorphism and 2D crystal size distribution (CSD). This work aims to integrate the crystal polymorphism and 2D-CSD information in the SMPT process using intelligent microscopic image analysis and to cross-validate the multidimensional CPPs by solving the numerical solution of the 2D-PBM.

Using a morphological population balance to develop a model-driven QBD approach for crystallisation processes

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The bulk powder properties of pharmaceutical APIs impacts their downstream performance and it is determined by both the size and the morphology. Therefore, understanding the process, by means of appropriate morphological population balances, emerges as a powerful tool to achieve reconciliation of particle properties with other process KPIs (yield, purity etc.).

In this presentation, UCB's roadmap for the development of a model driven QBD approach for crystallisation processes, is described, in the context of a therapeutic project. This trip includes the development of a strategy of the calibration of a morphological population balance, in the context of process-specific considerations related with the solubility curve, nucleation and attrition. Based on this, a model-driven QbD approach for crystallisation process design was created. The analysis conducted to determine the relevant sweet-spot regions and operating windows was quite informative, regarding the process robustness. It provided useful conclusions on the nucleation control and seeding strategies required for the development of crystallisation processes reconciling particle properties (size, morphology, span) simultaneously, while ensuring process yield and cycle time.

The results are quite revealing. Even for growth dominated processes, reconciling all the particle properties requires very high seed loadings, as the control space is really tight. Otherwise, the system will move out of this tight space, leading to sub-optimum product quality control. Considering the high seed loading, undesired for process industrialisation, it becomes evident that a transition to control nucleation strategies is key for the development of crystallisations, tightly controlling particle properties.

This is a pioneering study, demonstrating, for the first time, a systematic calibration strategy for morphological population balances. Furthermore, it describes a workflow for the utilisation of such a population balance, for the development of model-driven QbD approaches, which can inform the process design and control strategies. Finally, interesting conclusions for future research directions are extracted.

Two Dimensional Population Balance Model of a Cooling Crystallization Process for Particle Morphology Control

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Needle-shaped particles are typically undesirable, as they exhibit poor flowability, low bulk density, and increased cohesiveness. Optimization of crystallization process parameters can be leveraged to generate lower aspect ratio particles with better powder properties. As there are many crystallization process parameters that can impact particle morphology, the application of population balance modeling (PBM) to guide the experimental work helps conserve resources. Two dimensional (2D PBM) provides the capability to model two size dimensions with individual nucleation and growth kinetics. Herein, we present how 2D PBM was utilized to guide lab experiments to successfully reduce the particle aspect ratio in a cooling crystallization process which originally generated long needles.

Major and minor axis size quantiles from four crystallization experiments were utilized to construct the 2D PBM. Despite numerous parameter estimations, a good fit to the size data was not achieved. However, by utilizing aspect ratio to describe the particles in lieu of particle size quantiles, a 2D PBM was constructed that provided a good match to the experimental data. Predictions of the impact of various crystallization process parameters on particle aspect ratio identified conditions that successfully generated particles with a greatly reduced aspect ratio of ~3 (Figure 1b).

Although fitting the aspect ratio enabled the construction of a 2D PBM which successfully guided experimental conditions to control particle morphology, this approach is still limited in that PSD of the particles cannot be predicted. By revising the model to account for different growth mechanisms at different degrees of supersaturation, a significantly improved fit to the size quantiles was obtained, thus providing a 2D PBM capable of predicting both PSD and particle morphology.

Impact of a multistage cyclic crystallization process on the size and shape of plate-like crystals

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The particle size and shape distribution of a crystalline powder governs critical product attributes such as filterability and flowability. Powders containing needle- or plate-like particles tend to have poor downstream processability compared to more equant particles [https://doi.org/10.1007/s11095-007-9511-1]. As various active pharmaceutical ingredients crystallize in elongated shapes, strategies to manipulate the crystal shape in a desired fashion are of interest for the pharmaceutical industry. Various techniques to manipulate the shape of needle-like crystals have been previously investigated [https://doi.org/10.1016/j.compchemeng.2019.106581]. Whilst plate-like crystals pose similar difficulties as needles, a lack of adequate characterization techniques has hindered investigations into designing shape manipulation techniques. However, recently an imaging technique has been developed to accurately characterize platelets using three characteristic lengths [https://doi.org/10.1021/acs.iecr.0c04662, https://doi.org/10.1002/smtd.202201018].

This work leverages these advances to study the effectiveness of a cyclic three-stage process, incorporating growth, wet milling, and dissolution steps. In this study, experiments are complemented by simulations. A 3D morphological population balance equation model is used to gain a deeper understanding of the underlying phenomena and to help design the experimental campaign. An experimental factorial study is conducted in which the overall number of cycles, the intensity of the milling operation, and the amount of mass dissolved per cycle is varied. The experimental results are used to inform the model parameters. A process optimization is conducted with the goal of manipulating the size and shape of plate-like particles with the refined model that incorporates kinetic parameters obtained from the experiments. The operating strategy obtained from the process optimization is subsequently used to perform a three-stage cyclic process experiment.

The downstream processability of all product powders is compared to demonstrate that a measurable improvement has been achieved.

This work presents a complete scheme for the design and optimization of an advanced crystallization process to obtain an improved product for plate-like crystals.

Recovery of metals from Lithium-ion battery recycling through simultaneous precipitation of hydroxide metal salts

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Lithium-ion batteries (LIB) are widely applied to electronics and electric vehicles. Limited mineral extraction coupled with the criticality of some raw materials in the EU and the surge in the production of batteries due to the energy transition has attracted interest in the recycling and recovery of metals from LIB. State-of-the-art recycling relies on hydro-/pyrometallurgy and a series of solvent extractions each followed by crystallization. This work investigates the simultaneous recovery of the major components – lithium, cobalt, nickel, and manganese – from a LIB recycling leachate in a single precipitation step. The goal is to use crystallization from the multicomponent solution to avoid a series of solvent extraction currently implemented. We use thermodynamic simulations (OLI Studio Stream Analyzer) to study the behaviour of metallic systems in the precipitation of hydroxides using NaOH as a precipitant agent. Results show that cobalt and nickel can be recovered in a simultaneous crystallization process, followed by fractional precipitation of manganese hydroxide, with recovery rates higher than 99% using hydroxide/metal molar ratios higher than 5. No lithium precipitation is expected, nonetheless the presence of lithium influences the amount of precipitant agent required to reach similar recovery levels, requiring 3.8 times the dose of NaOH than systems containing only Co, Ni, and Mn. The product was characterized using XRD, SEM and microscopy. The remaining solution was characterized through ICP-OES. Experimental results have shown good agreement with the simulations, with the removal of 99.9% of Co, Ni and Mn. The solids formed display distinct phases without any defined characteristic morphology. The following steps involve investigating the influence of the multicomponent solution on the kinetic parameters and the interaction between different metal salts under simultaneous precipitation.

Keywords: LIB recycle, hydroxides, simultaneous crystallization, multicomponent systems, thermodynamic simulation.

Recovery of Spent Lithium-Ion Batteries Using a Novel Reactive Crystallization Process

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Lithium Ion Batteries (LIBs) are widely used for energy storage in portable devices, electric vehicles, and storage due to their high specific energy density, high rated voltage, and low self-discharge rate. With their increased consumption, recycling and disposal of LIBs pose a significant challenge for human health and the environment as they contain a high percentage of heavy metals and toxic electrolytes. In recent years, much effort has been made to recover spent lithium cobalt oxide (LCO), $LiCoO_2$, present in the cathode material using hydrometallurgical, pyrometallurgical, mechanical, and mechano-chemical processes. However, these processes can be energy intensive and have a complex framework of downstream processing. In the present study, a novel solvothermal method is proposed for the reactive crystallization of an intermediate novel precursor material (PM1), $[Li(C_2O_4)]_2[Co_5(OH)_8]$. The layered structure of PM1, similar to LCO, enables less energy-intensive calcination of PM1 at T = 300-350˚C for LCO recovery. The PM1 was synthesized by a reaction of metal oxalates in a pH range (8-10) with 1:1 cobalt and lithium oxalate in an aqueous medium at T = 100˚C. Powder X-ray diffraction indicates this new synthetic route is successful in synthesizing PM1 with high phase purity for the synthesis of LCO at a significantly lower temperature. However, the presence of excess cobalt in the PM1 lattice leads to the production of LCO and cobalt oxide (II, III) mixture (CO_3O_4) upon calcination. Thus, the separation of CO_3O_4 particles from the mixture is conducted to complete this low energy high recovery cathode recycling process. Furthermore, the method has been demonstrated to be extendable to NMC chemistries using an analogous intermediate PM2. In this study, a novel process utilizing these crystalline intermediates and associated plant designs is developed and compared with industrial processes to demonstrate their economic and industrial feasibility for lithium-ion battery recycling.

Continuous precipitation of terephthalic acid in a back-to-monomer recycling process for PET

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Alkaline hydrolysis is a promising approach to back-to-monomer recycling (BMR) of previously non-recyclable polyethylene terephthalate (PET)-containing materials. In this process, the PET is selectively depolymerized into its monomers ethylene glycol and terephthalic acid (TA). The intermediate product is disodium terephthalate, which reacts in aqueous solution by adding acids to form recycled r-TA. The low solubility of TA in water leads to the direct precipitation of the acid in crystalline form. In order to cope with the global quantities of plastic waste, recycling processes must be developed that can process these quantities efficiently, e.g. with the advantages of a continuous mode of operation.

Focusing on monomer recovery in downstream processing, this contribution presents the conversion of the batch wise TA precipitation into a continuous process. The experiments were carried out in a stirred 1.5 L glass reactor with reactant from depolymerized PET/PE multilayer flakes. Varying different process parameters such as residence time, precipitation temperature and acidification agent, their influence on purity and crystal size distribution of the obtained r-TA is shown. PET can contain colored impurities as well as isophthalic acid (IA), a structural isomer of TA that influences polymer properties. It can be shown that these impurities accumulate only in the start-up phase of the continuous precipitation and shortly reach a stationary concentration. This is in accordance with a constant particle size after 7-8 times volume exchange of the crystallizer. This stationary state is characterized by a significantly reduced proportion of fine crystals and a dendritic crystal growth, which subsequently leads to a shortening of the filtration time in comparison to batch precipitation. Overall, the results show a great potential of continuous precipitation in the stirred tank for BMR and a beneficial TA recovery.

"The Big Man" The Early Career of Professor John Sherwood (1955-1985) together with some Reflections upon his Wider Community Impact

Dr Kevin Roberts

Understanding, characterising and defining the crystal growth of organic and molecular crystals and, in particular, the pivotal inter-relationship between their growth conditions, defect types generated and resulting properties owes so very much to the seminal work, spanning 6 decades, of Professor John N Sherwood of the University of Strathclyde who died at the age of 87 on 4th December 2020. He produced a wide body research work encompassing fundamental crystal and crystallisation science right through to its practical applications, though a number of key areas notably: the growth or large, perfect and pure single crystals; plastic crystals and their mechanical behaviour; crystal characterisation using synchrotron radiation; industrial crystallisation processes; and non-linear optic materials. His academic research career, as an independent researcher, was carried out exclusively within the Department of Pure and Applied Chemistry at the University of Strathclyde in Glasgow, Scotland, UK.

In this talk, building upon his PhD work at the Universities of Durham and Glasgow, I will try to describe some of his early research work, spanning the period 1955-1985, on the purification and growth of organic materials and his quest to develop characterisation methods and preparative approaches for the production of large, nearly perfect and highly pure single crystals of these complex molecular solids. Within this perspective, seeking to understand the role of crystal lattice defects on the physical chemical properties of organic materials was central to his research.
I will also highlight his wider community impact. Within the UK research council he championed synchrotron radiation science promoting the case for the ESRF at Grenoble and, ultimately, the Diamond light source. He was a founder member of the British Association for Crystal Growth (BACG) and the international groups initiating the ICCOSS and CGOM conference series and the journal Molecular Crystals Liquid Crystals. At the BACG, as its chair, he led its re-vitalisation enhancing its inclusivity and scientific diversity, and promoting emerging talent. At the University of Strathclyde, he was an excellent mentor to both students and colleagues and held many senior academic offices including his election by his peers as the university's Vice-Principal.
John Sherwood was, without doubt, a giant within the crystal growth and organic and molecular materials and solid-state chemistry fields and his presence will be greatly missed by the community to which he made such a vibrant contribution.

Remembering Prof John Sherwood

Dr Radoljub Ristic

I worked with Prof John Sherwood for almost eleven years. He was a wonderful man, full of joy and love for all of us around him in his huge and internationally one of the most prestigious research groups in crystal growth and characterisation. He was not only the center of all activities in the group, but also he had an extraordinary breadth of interests with a keen eye and appreciation for novel and imaginative science of crystal growth.

Needless to say about his great contributions and impacts that he had made in both national and international crystal growth communities. In spite of all the great work he had done, he had such humility and such love of sharing: a fresh mind, always working on something original. He will be sorely missed by us all. His insights helped shape our modern understanding of the nature of crystallisation. What is quite remarkable is that he was still so passionate, curious, and enthusiastic even at the last stage of his life. He represented what I aspire to be.

In this short presentation, I shall try to revive my memories on our joint work on some of the most challenging aspects of crystal growth fundamentals at the time, his leading role in it, as well as the impact of the experience gained on my further career.

Piezoelectric Biomolecules for Lead-Free, Reliable, Eco-Friendly Electronics

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Billions of crystalline piezoelectric sensors are produced every year, improving the efficiency of many current and emerging technologies. By interconverting electrical and mechanical energy they enable medical device, infrastructure, automotive and aerospace industries, but with a huge environmental cost. The majority of piezoelectric sensors contain poled polycrystalline Lead Zirconium Titanate (PZT), the fabrication of which requires toxic lead oxide. Prominent lead-free alternatives are heavily processed, and rely on expensive, non-renewable materials such as Niobium.

Biological materials such as amino acids and peptide crystals have emerged as exciting new piezoelectrics. Biomolecular-crystal assemblies can be grown at room temperature with no by-products, and do not require an external electric field to induce piezoelectricity, unlike PZT and other piezoceramics. Currently no research is focused on developing these crystals as reliable, solid-state sensors to integrate into conventional electronic devices, due to their high water solubility, uncontrolled growth, variable piezoelectric response, and difficulty in making electrical contact.

Our research is taking on the challenge of developing biomolecular crystals as organic, low-cost, high-performance sensors, to out-perform and phase-out inorganic device components with dramatically reduced environmental impact. In this talk we will discuss our methodologies for the design, growth, and engineering of these novel piezoelectric materials under three pillars:
• An ambitious computational workflow to enable the design of super-piezoelectric crystalline assemblies by combining high-throughput quantum mechanical calculations with machine learning algorithms.
• A new method of growing polycrystalline biomolecules, allowing for easy, efficient creation of macroscopic piezoelectric structures.
• Establishing effective electromechanical testing procedures to characterise fully insulated and contacted biomolecular device components.

Crystal Structure and Solid-State Behavior of Derivatives of Praziquantel

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Praziquantel (PZQ) is a medicine which is widely used to treat the parasitic worm infection schistosomiasis. PZQ is currently marketed as a racemic mixture although only the R-enantiomer possesses the desired pharmaceutical action. Because PZQ crystallizes as a racemic compound, crystallization-enhanced resolution methods cannot be applied directly. Nevertheless, a Praziquantel chemical derivative that crystallizes as a conglomerate was identified and successfully deracemized by Valenti et al.[1]

The percentage of racemic mixtures of enantiomers crystallizing as conglomerates is estimated to be in the range of 5 to 20%, but large fluctuations from one series of molecules to another have been reported. Despite progress in the understanding of the solid-state behavior of chiral molecules, it is still impossible to predict whether a conglomerate or a racemic compound will crystallize. This study aims at identifying new scientific principles for conglomerate formation with the goal of understanding the causes of this spontaneous symmetry breaking.

Numerous enantiopure and racemic Praziquantel chemical derivatives were synthesized. Second Harmonic Generation, binary phase diagram analysis and single-crystal structure determination were used to identify conglomerate or racemic compound behavior.

Herein, we report that although no other conglomerate system could be identified among the 35 derivatives, the difference in melting temperature of the enantiopure and racemic mixture shows that the relative racemic compound stability does vary substantially. While some similar derivatives show similarities in their solid-state behavior many others show substantially different hydrogen bonding patterns. Interestingly, one system shows a very rare crystallization behavior with no less than three enantiotropic polymorphs of the racemic compound. Moreover, the reported conglomerate-forming system was found to crystallize in a slightly more stable racemic compound at elevated temperature.

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Mechanical Motion and Modulation of Thermal-Actuation Properties in a Robust Organic Molecular Crystal Actuator

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Dynamic molecular crystals with multiple functions are attractive and valuable for their enormous potential in the application of single crystal materials. Here, we report a smart dynamic crystal, 6-Chloronicotinic acid, which responds to heat stimulus by bending, splitting-to-self-healing and jumping, induced thermally by a reversible single-crystal-to-single-crystal phase transition. This phase transition proceeds by a well-organized migration of habit plane in a shearing deformation manner, which is reproducible after more than twenty times phase transition cycles. The temperature function introduced externally can realize a reversible migration of phase interface and also acts as jump switch. Importantly, the phase transition process can be controlled. The migration of the phase interface can be interrupted, thus to maintain a stable state of two-phase coexistence, and even the phase interface can be reversible migration through the regulation of the variation of temperature.

About 15% crystals perform a remarkable splitting-to-self-healing which is temperature independent. The heterogeneity of phase transition along the thickness direction accounts for the splitting and under self-driven force, the splitting crystals usually heal into a whole. We believe that similar molecular stacking patterns are beneficial for the self-healing behaviors. Apart from a remarkable response to heat stimulus, both forms of this crystal materials are mechanically compliant in two dimensions and can be twist and shaped to suit the required application.

Most importantly, it presents great prospect to be attractive lightweight actuators. Utilization of shearing deformation led by reversable phase transition of 6-CNA single crystal can generate a pushing force which is > 10000 times gravitational force of the crystal, thus to make 6-CNA as an actuator to drive the reversible movement of glass plate. The reproducibility of SCSC and soft nature of single crystal further broaden its applicability prospects. This contribution provides an avenue for designing dynamic crystals for multistimuli-responsive actuating properties.

Maximizing similarity: using correlation coefficients to calibrate kinetic parameters in PBMs

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Population Balance models (PBMs) have been successfully employed for decades to simulate, optimize, and control particulate processes. It has proven to be one of the most powerful techniques when modeling the dynamics of particle systems. In constructing PBMs, identifying kinetic parameters is one of the most challenging steps since it demands expertise in mathematics, computational science, engineering, and modeling compatible experimental data. Nowadays, solubility, in-process concentration, and seed and product particle size distributions (PSD) are the generally applied inputs of model-based kinetics identification. In-situ solid-phase process analytical technology (sPAT, including the Mettler's ParticleTrack and the Blaze systems) is becoming standard in pharmaceutical process design, as it is suitable for observing and tracking crystallization events. However, despite being successful in process monitoring and indirect process control, these are not generally applied for quantitative characterization. A reason behind is the nonlinear characteristics: sPAT signal (e.g., relative particle number and size) does not change linearly with the particle number, and a saturation effect happens beyond a sufficiently high solid load.

This study introduces a new approach to applying sPAT measurements for kinetic parameter estimation. Instead of relating the sPAT signal directly with the simulated crystal number and size, these two values' correlation coefficients are observed and applied as a member of the objective function. This way, not the direct agreement but the "maximal similarity" is to be reached when the kinetic parameters are calibrated.

The approach is compared to two alternative model calibration modes in-silico: (i) the "ordinary case" when the parameter identification is executed using concentration data and PSD values are available; (ii) a "naive case" when the sPAT data is compared directly, neglecting its nonlinear characteristics. Experimental evaluation is realized through the case study of aspirin crystallization from ethanol, tracked with a Blaze900 system, giving reasonable global agreement with literature data.

Machine Learning Nucleation Collective Variables using Graph Neural Networks

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In this work, a framework is developed to approximate complex nucleation collective variables. A size-transferable approximation of physics-inspired collective variables is constructed by training a graph-neural network architecture on labelled simulation data. The resulting model exhibits a high degree of accuracy and excellent cost-to-system-size scaling. This degree of size-transferability enables the biasing of nucleation simulations at previously inaccessible scales. Further, this provides a possible answer to the "chicken-and-egg" problem inherent in the creation of data-driven collective variables, by allowing data to be collected at small system sizes that are accessible by traditional means. Deploying these models in, previously, prohibitively large systems, opens up new possibilities for studying the effects of saturation and finite sizes.

The method is demonstrated on a system of colloidal particles and a metal melt. Finally, an approach is shown to translate this framework to systems possessing a significant degree of conformational flexibility to, in the future, enable the simulation of unseeded nucleation of flexible organic molecules.

Machine learning for multivariate parameter identification of first-principle model: the Mg(OH)2 test case

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Reactive crystallization processes involve different phenomena, touching all scales. Supersaturation is generated at the micro-scale as a consequence of chemical reactions. The increasing supersaturation level triggers directly primary nucleation and molecular growth (molecular processes) and indirectly irreversible agglomeration (secondary process). All these phenomena can be modelled once a functional form (kernel) is assumed and the relative fitting parameters are properly tuned (eight in this contribution). The most widespread methodology is to perform a multivariate optimization routine that finds the optimal parameters set by comparing the model predictions with the desired experimental target (i.e., characteristic lengths from Number Size Distributions). An initial point (or a swarm of initial points) is randomly picked and a local minimum is found through an optimization method (conjugate gradient, for instance). However, an eight-parameter function reveals a huge amount of local minima that in turn makes the optimization problem strongly dependent on the initial candidate. In this contribution, the authors want to propose an innovative, quick-responsive procedure providing a data-driven model. At first, a simplified 1D model, describing a T-mixer (Figure 1), was run to generate the initial data-set. The model, solving ordinary differential equations, associates parameters set and operative conditions (i.e., reactants initial concentrations) to the corresponding diameters. A deep learning neural network (DLNN) was trained using the aforementioned data-set switching the input-output order (Figure 2): diameters and concentrations were given as input and the parameters set as output. Therefore, experimental diameters at five concentrations were given to the trained DLNN and the predicted parameters mean set was tested with the 1D model. The resulting set was able to reproduce the experimental data used to infer parameters and predict the diameters in a Y-mixer. Moreover, the uncertainty on parameters was quantified and reported in Figure 3.

Using sub-millisecond microfluidic mixers coupled to time-resolved in-situ photonics to study ultra-fast gold nanoparticles formation kinetics

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The comprehension of crystal nucleation pathways is at the forefront of cutting-edge research, impacting a vast range of natural and industrial processes. Understanding the mechanisms and actors involved in the process is essential for achieving optimal process control. We report a microfluidic platform achieving controllable sub-millisecond homogeneous reagent mixing (~ 200 μs) for the study of reactive crystallization. The platform can operate within mixing time frames below system characteristic times, providing a unique opportunity to track and separate phase nucleation and early growth stages, enabling the study of reactive crystallization in unprecedented detail. The mixer is coupled to a continuous microreactor, which channel length can be approximated to a given reaction time when operated in continuous mode and steady state. As a result, the system can be statically interrogated, eliminating technique-dependent probing time constraints and local inhomogeneities caused by mixing issues.

We have studied the synthesis of monodisperse ultra-small gold nanoparticles (NPs) by coupling our platform with SAXS, UV-Vis, and X-ray absorption spectroscopy (XAS). Our study focuses on the kinetics of Au(0) NP formation from Au(III) precursors complexed with oleylamine in organic media, using triisopropylsilane as a reducing agent. Through in-situ time-resolved SAXS experiments, we have been able to observe the existence of Au(III)/Au(I) prenucleation clusters, and the formation of a transient A(I) lamellar phase under certain conditions, before the onset of Au(0) formation.

On-chip UV-Vis measurements, in combination with time-resolved synchrotron XAS, have enabled us to investigate the kinetics of NPs formation. Taking advantage of the highly resolved time information, we have been able to propose and model two different reaction pathways associated with the presence (autocatalytic reaction) or absence (classical first-order reaction) of the Au(I) lamellar phase. In both cases, non-classical pathways lead to the formation of NPs.

Filler surface induced heterogeneous nucleation of polymer crystals

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Filler surface induced heterogeneous nucleation of polymer crystals
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Switching from non-degradable to compostable plastics can help to reduce global plastic pollution. However, to use compostable plastics in food packaging films, properties including mechanical strength and gas barrier must be optimised. These properties depend on the crystallinity and microstructure of the plastic film, which can be modified by adding filler particles, which act as nucleants for polymer crystallisation [1]. In order to select appropriate fillers, it is necessary to understand the polymer-filler interface.

We use a modified Kremer-Grest polymer model [2] to study crystal nucleation of 20-bead chains. Filler surfaces are modelled using a Lennard-Jones 9-3 potential. The system is cooled from the melt using an NPT ensemble, and the crystal fraction is estimated from straightening of chain segments. Polymer nucleation was observed to occur at the surfaces. Interestingly, this polymer model does not crystallise in simulations without the surfaces. The dependence of crystallisation on the surface-polymer interaction strength, the polymer chain stiffness, and cooling rate will be presented and rationalised in terms of free energy changes. The addition of plasticiser and its effect on nucleation and growth will also be explored. This work provides insight into how filler surfaces can be used to control polymer crystal nucleation and growth, leading to the design of compostable plastics with desired properties.

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Investigating the effect of heat exchanger roughness and surface energy on scaling during eutectic freeze crystallization.

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Scaling of heat exchanger (HX) surfaces by ice and salt is currently one of the major setbacks in the industrial implementation of eutectic freeze crystallization (EFC). Hence, the scaling process has been extensively studied, mainly in batch systems, focusing on vertical growth rates of ice scale from the HX surface. In this study, the differential interference contrast (DIC) technique is used to investigate the formation of the initial ice scale layer on the HX material, in-situ and in real-time. This technique allowed the observation of the differences in the scaling mechanism on the primary-SS316, roughned-SS316 and polytetrafluoroethylene (PTFE) coated SS316 HX plates in a continuous EFC process. Previous studies have shown that HX surfaces with lower surface energy delay the onset of freezing, thereby reducing the probability of scaling through heterogeneous nucleation, growth and/or adhesion. The PTFE-coated-SS316 was found to increase the scaling induction times 2.79-fold at a coolant temperature of -15°C, compared to that of the primary-SS316. However, at -20°C and -25°C, the scaling induction times on both surfaces were comparable for all three surfaces, which indicated that the benefit of using a low surface free energy material counteracted at fast cooling rates. It was also found that the scaling induction times were shorter when using a rough-SS316 HX plate, compared to the primary-SS316 and PTFE coated-SS316, because of the larger surface area available for heat transfer. The scaling rates were slowest when using the PTFE coated-SS316. This was attributed to the low nucleation rates observed on this HX plate. It can therefore be concluded that operating with a crystallizer with a HX wall constructed from a material with a smooth surface of low surface free energy can reduce the probability for scaling by increasing the induction time and reducing the rate of scaling.

G1.4

Assembling of the masses: the crystallisation of larger, more flexible pharmaceuticals

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The pharmaceutical landscape is ever broadening, and some of the current trajectories of interest are moving towards larger, more flexible molecules. New modalities at Novartis include larger peptides/proteins and inorganic complexes for radioligand therapy.

X-ray crystallography remains the gold standard to determine absolute structure, understand crystal packing and subsequently exploit structure-property relationships for improving solubility, morphology and melting point. A general rule of thumb in the crystallisation of molecules for X-ray diffraction is that the larger and more flexible a molecule is, the longer it takes to crystallise. With crystallisation as a crucial step in the drug pipeline, how do we attempt to tackle new modalities?

At Novartis, we have a database of every crystallisation trial performed in the small molecule X-ray department of the analytical group in NIBR (Novartis Institute for Biomedical Research) since 2011. The solvents used, experiment type and experiment outcomes were mostly conducted and logged (~90%) by the same scientist, assuring a reasonable control on the subjectivity of the records. Efforts were made to clean the data in the past and to use them for machine learning to guide solvent choice [1]. In the current study we combine the analysis of these data for trends in crystallisation with bespoke crystallisation techniques to enhance our success for stubborn-to-crystallise new modalities. Techniques such as crystallisation in gels, microfluidics and sitting drop / hanging drop usually used in protein crystallisation were some of the crystallisation methods employed.

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Integrated continuous crystallization and isolation using a carousel filter dryer

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As continuous manufacturing continues to gain interest in the pharmaceutical industry to enhance sustainability and efficiency with reduced variability due to batch-batch differences, the question now arises of how to integrate multiple steps from flow chemistry through crystallization to product isolation. Relatively well established and robust process analytical technology combined with automation tools provide a pathway to controlled continuous operation in a truly autonomous manner in the crystallization stage, but limitations remain in relation to the final isolation of the product. The AWL CCF 20 carousel filter dryer is one of only a handful of tools available which is providing a real opportunity to fill this gap.

In this work, a carousel filtration system with 5 ports (AWL CCF 20) was used to continuously isolate pure crystalline material. To optimize a process and evaluate the carousel, a model system of paracetamol in ethanol was firstly selected and spiked with a known quantity of impurity. The carousel was then run in automatic mode, and the product from each individual port was collected. HPLC analysis of each sample was then used to check the impurity concentration, enabling observation of the consistency between ports. Finally, the carousel filter dryer was combined into an automated, continuous crystallization platform with in-process control, monitored using a series of process analytical technology tools for continuous isolation.

Continuous isolation of dry, pure crystalline product is the final step which needs to be addressed in the realization of a fully integrated continuous manufacturing platform prior to drug product formulation. This work has shown that the development of novel technology such as the continuous carousel filter dryer discussed here, provides the possibility to quickly screen isolation conditions, and facilitates the development of integrated continuous crystallization and isolation procedures to recover pure crystalline material with desired properties.

Towards autonomous continuous slug flow crystallization for small-scale applications

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Crystallization is an important purification step producing active pharmaceutical ingredients (APIs). Despite the rising trend towards continuous API production, downstream processing is still a bottleneck. Here, continuous crystallization is a promising strategy for process intensification, offering various advantages compared to the established batch processes.

The Slug Flow Crystallizer (SFC) is a promising apparatus concept aiming to fulfill the high-quality demands. It is a tubular crystallizer characterized by a segmented three-phase flow. A second fluid, mostly air, segments the process medium containing particles. These so formed process medium segments (slugs) are transported through the SFC tubing and crystallization takes place. The segmentation results in interfaces that induce internal vortices during transport, enhancing the liquid phase mixing and ensuring the particle suspension. Further, the segmentation results in a plug-flow-like flow profile under laminar conditions, preventing back-mixing and resulting in a narrow residence time distribution of the solid and liquid phase. However, the experimental data is limited to the investigated chemical systems and operating conditions, but the transferability for the use of aqueous solutions containing amino acids or APIs as solutes is desired. The selection of suitable material systems has been made on the basis of an experimental strategy [1], but the description of the complex process parameter interactions has only been possible by experiments so far.

To obtain an autonomous process control of a continuous SFC achieving precise narrow particle size distribution and high process yield while preventing fouling of the apparatus, a physics-based population balance model for the prediction of particle size distribution is developed. This incorporates the characteristic hydrodynamics in the SFC, the energy balance, and the crystallization phenomena occurring inside SFC using a mechanistic approach. This model allows the prediction of the crystallization behavior in the SFC, which is the first step to a model-predictive control of SFC.

Purification of High-Value Natural Substances from Complex Multicomponent Extracts - Towards an efficient and more sustainable process

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Nature is the source and inspiration for a large number of the nowadays-available pharmaceuticals. A prominent example is Artemisinin (ARTE), a secondary metabolite of the Artemisia annua plant, which is used for the production of the most potent antimalarials.

Extraction of the target component from raw plant material mostly results in multicomponent mixtures containing several often-unidentified substances. Hence, purification of the target substance as the final production step is challenging. Conventional production of ARTE from the plant starts with extraction using petroleum ether or hexane. After extraction, at least five unit operations, such as solvent exchange, chromatography, and crystallization follow to obtain pure ARTE [1]. Within the purification process, solvents like chloroform and acetonitrile are involved, making the overall process complicated and not very sustainable. Our approach towards a more efficient and sustainable purification process is to reduce a) the number of unit operations and b) the amount of harmful solvents.

As extraction solvent, toluene is used. It ensures higher extraction yield and productivity compared to conventional extraction solvents and was successfully applied in continuous extraction [3]. A combination of adsorptive pre-purification and final crystallization without solvent exchange is currently under investigation. The first step was to screen for a suitable adsorbent. Three easy accessible adsorbents were studied in detail with three differently purified extracts as result. The acquisition of fundamental thermodynamic and kinetic crystallization-related data of ARTE within the remaining impurity profiles of the extract solutions is of crucial importance prior to development of a crystallization step. It was already observed that the co-extracted substances can enhance the solubility or suppress nucleation and growth of ARTE dramatically. The latest results of this investigation will be presented in this contribution.

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Automated In-line Sampling and Analysis of Crystal Slurries in Industrial Processes

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This paper presents a fully automated in-line sampling and dilution system for characterization of crystals in industrial crystal slurries. The performance of the measurement system is successfully demonstrated in a phosphoric acid production plant for the characterization of gypsum crystals in the product solution of phosphoric acid. For every ton of produced phosphoric acid the process produces at least 2.3 tons of gypsum (calcium sulfate dihydrate) byproduct, which must be separated from the product solution. The separation efficiency of gypsum crystals limits the production capacity. The morphological properties of crystals greatly affect the fluid dynamical and mechanical properties of a gypsum crystal slurry. The online monitoring of crystal morphology is essential for maintaining the runnability of the separation process. However, the online analysis of crystal morphology is not possible from dense crystal slurries. Thus, we have developed an inline sampling and dilution system to produce online information on crystal morphology and size distribution.

The developed system operates fully automatically on 24/7 basis collecting slurry samples, diluting the samples and analyzing them with a process microscope equipped with image analysis software. The 100 ml samples of slurry are collected every 5 minutes from a phosphoric acid product tank utilizing a suction line equipped with level sensor, automated valve and vacuum pump. Samples are diluted in 1:60 ratio and analyzed automatically in a flow-through cell with a process microscope. This paper presents the operation principle of measurement system, experiences at phosphoric acid production plant and shows some interesting results of the measurement campaign.

Systematic design and optimization of multistage antisolvent continuous crystallization processes

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A model-based optimization methodology was developed to systematically optimize the design features and operating conditions of multistage antisolvent continuous MSMPR (mixed-suspension mixed-product removal) crystallizers. The antisolvent crystallization of ibuprofen in ethanol (solvent) and water (antisolvent) is used as a case study. A first-principle mathematical model which involves the population balance equations, primary and secondary nucleation and growth was developed to achieve the intended objectives. Model parameters were obtained from the literature. Several key performance criteria and critical quality attributes were considered in the optimization framework which includes yield, mean particle size and coefficient of variation. The vector of the decision variables comprised the antisolvent flowrates at different stages, feed flowrate, volume of crystallizers and seeding policies, which includes seed loading and seed particle size distribution. Several performance and quality constraints were set to facilitate downstream processing such as filtration and drying. In addition, constraints on the supersaturation level were applied to control the nucleation and the population of crystals to achieve a narrower span of the final product. The constraints used here were aiming to give an optimised operating window, which avoids some pitfalls of practical operation, such as blockage during interstage line transfers (too high a solids content) or fouling of vessels or probes (too high a supersaturation). The number of stages was also optimized to achieve the targeted key performance indicators at lower capital and operating costs.

Correlating Particle Informatics with Surface Wetting Measurements

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Particle properties are important. Formulated product industries such as pharmaceuticals, agrochemicals, and dyes expend significant effort in mitigating manufacturing bottlenecks and improving product performance. Particle characteristics impact processes such as flow, compaction, and cohesivity. Shape, size, roughness, and hydrophilicity/hydrophobicity are typical properties of interest in understanding downstream behaviour [1].

Particles are susceptible to solvent deposition that can cause capillary bridges, reducing flowability or impacting the likelihood of agglomerates forming and affecting blend homogeneity. The wettability of surfaces is used to describe the hydrophilicity of a given system. Linking particle surface wettability to their crystal structure using particle informatics would allow for the early detection of challenging systems.

Historically, surface roughness has been studied as a mechanism for adjusting the hydrophobicity of a material. However, surface chemistry can also have an impact on the wettability of a surface [2,3].

In this contribution, we present the findings of correlating surface descriptors and interaction data from the Cambridge Structure Database (CSD) with experimental contact angle measurements.

The surface descriptors explain the density of hydrogen forming functional groups, surface roughness, and the probability of interactions with hydrophilic/phobic probes. With the help of these descriptors, the application of predictive tools upstream can quickly determine whether a structure will cause processing problems and reduce the resources required to achieve an optimum formulation product.

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Systematic Framework for Model-Based Digital Design of Polymorphic Crystallization

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Polymorphism is prevalent and important in pharmaceutical manufacturing. Polymorphism is a challenging issue during crystallization as it significantly affects the properties of the active pharmaceutical ingredients (API). Different polymorphs of the same API can have different bioavailability, stability, solubility, and manufacturability. In this work, a study on a chemotherapeutic agent, Imatinib Mesylate, is demonstrated to show the potential of selective crystallization for its two polymorphs: the needle-shaped metastable α-form and the cubic-shaped stable β-form. The polymorphic transformation of imatinib mesylate is investigated using a systematic experimental design together with population balance modeling. The kinetics of isothermal antisolvent crystallization of α-form and β-form imatinib mesylate are determined for the first time. The solvent-antisolvent (methanol-isopropanol) ratio affects the dissolution and growth rates of different forms. In order to have more yield, the minimum solvent composition used in the experiments is chosen to be 50% MeOH-50% IPA (v/v). In-situ Raman spectroscopy is used to detect the polymorphic transformation during experiments. This study aims to reduce experimental efforts and resources by utilizing the validated polymorphic model for in-silico design of experiments to study the effect of various process parameters on product quality. The results yield a feasible design space for the crystallization of the desired stable β-form. This work demonstrates the potential of model-based digital design in rapid process development for polymorphic crystallization.

Computer-Aided Solvent Selection for Designing API Crystallizations to be Nucleation or Crystal Growth Dominant

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As development timelines for new small molecule therapies become increasingly compressed, attention has turned to the creation of new tools and methodologies to streamline the laboratory process development effort. For the crystallization of active pharmaceutical ingredients (APIs), the particle size outcome represents a critical design requirement for which target values may already be known at a phase in the process development where solvent choice for the crystallization remains open. Computational approaches for the prediction of solubility are now widely used in the design of industrial crystallization processes to aid solvent selection and reduce development timeframes and material needs.1 However, despite the significant influence of solvents on the crystallization kinetics and thus particle size outcomes, there have been limited examples of computational methods being used to guide solvent selection with consideration of the particle size goals of the process.

In this contribution, a new computer-aided workflow is presented for choosing solvents to design API crystallizations to be either nucleation or crystal growth dominant, thus expediting the journey to develop processes that deliver the particle size requirements for the API. A relationship between nucleation difficulty and solvent-solute interaction strength has been predicted computationally and demonstrated experimentally for a range of different organic molecules, strongly suggesting that the desolvation of a solute molecule is one of the key elements governing nucleation kinetics.2 Leveraging this knowledge, this contribution demonstrates how computational predictions (quantum-mechanical and force-field based molecular simulations) of physical parameters closely related to the solvent-solute interaction strength (e.g., intermolecular binding energy and solvation free energy) can be effectively used to select solvents that facilitate either a nucleation dominant or a growth dominant crystallization regime to drive smaller or larger particle size outcomes as required.

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P1.1

Investigation on the effect of mutarotation in lactose crystallization: Measurement and mechanistic assessment

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Lactose is a key component in infant formulae, pharmaceutical tablets, inhalers and processed food. Its production relies on batch cooling crystallization. Like other sugars, lactose has two anomeric forms with only α-lactose crystallizing during batch cooling. Furthermore, α- and β-lactose can interconvert via an equilibrium reaction called mutarotation, which can replenish α-lactose during crystallization. Thus, a complex interplay of nucleation, growth and mutarotation arises that is highly dependent on process conditions.

In our study, we utilized inline ATR-FTIR spectroscopy to investigate the impact of mutarotation on crystallization in pure lactose-water solutions. We modified the setup to enable measurements at high solids concentrations at which lactose crystals tend to deposit on the probe, allowing us to observe an inhibiting effect of mutarotation on growth and nucleation kinetics at common crystallization conditions. We also used a simple ratio of kinetic rates to theoretically analyse the impact of mutarotation on crystallization, which avoids the need for extensive experimentation or population balance modelling while still enabling us to evaluate the effect of process conditions on the anomeric ratio and mutarotation limitation. As part of this, we have developed a state diagram that maps the relevance of mutarotation throughout the process as a phase plot dependent on various process parameters, including supersaturation, temperature, crystal load, and distance of the α-lactose fraction from the equilibrium value. (see supplementary, Figure 1). In addition, we wanted to evaluate the influence of mutarotation on crystallization from whey permeate. However, one challenge we faced was performing ATR-FTIR calibration for α- and β-lactose concentration in whey permeate. With our theoretical analysis, we were able to evaluate the influence of mutarotation on crystallization from whey permeate despite this difficulty.

Crystallisation: An Alternative to Chromatographic Separation of Oligosaccharides

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Oligosaccharides are polymeric carbohydrates, that are found in all living organisms, which are made of 1-10 monosaccharides.

Extracting of oligosaccharides from plant tissues results in several different chain lengths of the oligosaccharide and expensive chromatographic methods are normally required to narrow down the distribution of the chain lengths in the final product. Herein, the aim was to use the method of fractional crystallisation, which is the process of separating two or more crystalline solids based on the differences in their solubilities in the same solvent.

For this work, fructooligosaccharides (FOS) was used which consists of glucose-(fructose)n chains. The starting material was chosen as the 'worst-case' scenario, exhibiting a broad distribution of chain lengths which had 1-60 monomer units with an average degree of polymerisation of >10.

To produce a more crystalline form of FOS by designing a crystallisation procedure to isolate fractions of FOS containing smaller chain length distributions.

The supplied material was characterised before a solubility screen was conducted in a variety of solvents including pure organic and organic water solvent systems, covering the temperature range of 5 °C to 80 °C.

The XRPD results showed that the residues isolated from water-based systems displayed a slight increase in crystallinity via XRPD and the best scalable methods included slow cooling and maturation.

A 20 g scale crystallisation was performed using EasyMax and OptiMax vessels equipped with PAT (Blaze900 metrics probe).

The LC-MS data showed the final product to contain the longer chain lengths suggesting the shorter chain lengths were present in the mother liquor. Further processing of the mother resulted in the smaller fractions being isolated as a solid. FOS was successfully isolated with increased crystallinity, reduced chain length distribution and lower hygroscopicity between 0-90% RH, via a multi-step crystallisation process.

Solid Form Screening and Crystallisation of Peptide-based therapeutics

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Research into therapeutic peptides started with studies of natural human hormones, including insulin (1921), oxytocin and vasopressin (1962), and leuprorelin (1984). Overall there are now more than 33 non-insulin peptide drugs approved worldwide since 2000.

In the present example, internal studies were performed on an FDA approved glycopeptide molecule, to show the type of solid state and crystallisation screening available at Pharmorphix on peptide-based therapeutics (PbTs).

Once a stable, pure peptide form was obtained, this was crystallised and scaled up to multiple grams and crystallisation development studies performed, in order to develop a controlled and robust crystallisation process. A full batch characterisation was performed on vancomycin (an HCl salt form, e.g. RP-HPLC, NMR, GVS, etc).

One salt form (bis-phosphate) showed stability to storage at elevated conditions (40 °C/75% RH, > 1 week) and was selected for study.

Single crystal growth studies were performed on this and similar salt forms in organic/aqueous solvent mixtures initially to provide a structure solution using in-house SCXRD instrument. Single crystals grown provided a unique structure of the mono-phosphate.

A multi-gram preparation of the bis-phosphate form was developed, and material scaled initially at gram scale on a Polar Bear reactor, then multigram on EasyMax system with PAT monitoring using BlazeMetrics 900 probe.

The resulting salt was a crystalline hydrate and showed an uplift in purity compared to the HCl salt (ca. 96.5 to > 98%) and high crystallinity (HCl and free form are amorphous).

SAXS for Monoclonal Antibodies Batch Crystallizations

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The large-scale crystallization of monoclonal antibodies (mAbs) represents an attractive approach to downstream drug substance (DS) processing as opposed to the more classic, costly solution manufacturing. mAb crystallization holds great promises for simplifying and improving the purification of protein DS. mAb crystalline suspensions additionally offer the opportunity to investigate highly concentrated drug product (DP) formulations (e.g., for subcutaneous delivery) and are expected to be more stable at ambient conditions resulting in increased shelf-life stability. Highly concentrated formulations are currently very challenging for mAb solutions, which typically suffer from elevated viscosity and chemical instability together with the need of freezing temperature for storage.

While single crystals of mAbs have been widely investigated by single crystal x-ray diffraction, polycrystals made from batch-crystallizations and their bulk characterization remain more complex compared to that of traditional small molecule active pharmaceutical ingredients (APIs). The intrinsic properties of mAb molecules such as high molecular flexibility typically result in crystallites being shear sensitive and having a strong propensity to dehydration and crystallinity loss.

Due to their large unit cells, bulk mAb crystals remains challenging to characterize with typical wide-angle scattering (WAXS) tools such as laboratory x-ray powder diffraction (XRPD). Small-angle x-ray scattering (SAXS) offers the ability to probe crystalline Bragg peaks at angles lower than conventional XRPD instruments enabling detection of x-ray diffractions from mAb crystals.

In this presentation, we present how SAXS was used to support development of the crystallization process of a mAb.

The challenges of crystallisation development in the Pharmaceutical Early Phase

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Crystallisation is one of the fundamental steps in the isolation of Active Pharmaceutical Ingredients (APIs) in the pharmaceutical industry [1-3]. It transforms an API from being just an individual chemical entity to a solid with 'desirable' physical properties (i.e. solid-state Form, particle and bulk properties) for use in the drug product.

But the road to developing these crystallisation processes is by no means straight-forward and no more so than at the early development stage, prior to even the first phase of clinical trials. Here, project demands are high, working to tight timelines for consecutive, sometimes parallel, drug substance manufactures. Often API material is in limited supply and with little knowledge prior to process development, generating 'fit for purpose' processes for the delivery of the final API for onward studies can most certainly be a challenge.

In this presentation, a range of AZ projects will be showcased highlighting some of the challenges faced during the early phase. The focus will be on how both the solid-state Form and particle properties can be controlled for formulation development and supply to clinical studies. There are many successes that can be attributed to these projects but it is also important to reflect on where the desired outcome was not achieved and the lessons learnt going forward for future deliveries.

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Crystallisation process design of a solvate forming API

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The increasing structural complexity of novel active pharmaceutical ingredients (APIs) results in materials with ever more elaborate solid form landscapes. This includes an increased occurrence of solvated forms, where solvent is incorporated within the crystal lattice, and leads to numerous problems in achieving a robust API crystallisation process during drug development. Although both stable and transient solvates are possible, the removal of solvent from the lattice whilst also achieving desired solid form and particle size characteristics is challenging and leads to the exclusion of many preferable solvent systems during early development. This is frequently a facet of the difficulty in characterising transient solvates and their mechanism of desolvation, leading to their presence being missed or poorly understood and resulting in issues in drying upon scale-up.

Within this work we present the workflow used to design an industrial crystallisation process for a novel API which exhibits a complex solid form landscape due to the formation of numerous stable and transient solvated forms. This required a pragmatic approach to solvent selection during process development; balancing compound stability, solvate formation and solvent toxicity (ICH QC3). Despite the complex form landscape, a robust particle formation process was developed that delivered the desired unsolvated form with preferential particle attributes via a cooling crystallisation of the transient solvate which subsequently underwent desolvation during drying. Specific process understanding of the stability of the transient form was obtained through crystallographic and engineering techniques to determine the robustness and mechanism of desolvation during agitated filter drying. Successful scale-up to multi-kilogram scale demonstrates that although solvates can be challenging for developing reliable processes, thorough understanding of the mechanism of desolvation during drying can yield robust crystallisation processes with preferable solvent selection.

P1.7

The mechanism of crystallization-induced deracemization

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Since the discovery of Viedma ripening in 2005 (10.1103/PhysRevLett.94.065504), crystallization has increasingly been studied as a means of deracemizing mixtures of enantiomers. In the presence of a racemizing agent, Viedma ripening and associated deracemization strategies based on temperature cycling enable the amplification of an initial enantiomeric excess in a suspension of crystals up to enantiopurity.

In the past, our group has derived population balance-based models from first principles for both Viedma ripening (10.1021/cg2008599) and temperature-cycling induced deracemization (10.1021/acs.cgd.8b01292) which indeed showed that crystallization enables deracemization under certain conditions. Despite the success of these contributions, the precise mechanism of deracemization has yet to be revealed. This is mainly because the mechanistic nature of this models inherently makes them rather complex; complete sensitivity studies to fully understand the underlying mechanisms hence have been unfeasible due to the large computational costs.
Here, we present a new mathematical formulation for crystallization-induced deracemization that significantly reduces this complexity but still is fully mechanistic: we have derived an analytical solution for deracemization and obtained explicit expressions both for the direction and for the rate of deracemization. We show that the condition for deracemization is fulfilled under general conditions; homochirality thus must be considered as the natural long-term outcome of the crystallization of conglomerates in presence of a racemizing agent. Such process hence provides a natural pathway for the emergence of homochirality on Earth.

Formation of Skeleton Crystals of Sodium Chloride by Continuous Crystallization using Micro-flow Reactor

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The solubilities of organic compounds consisting of pharmaceuticals in water are very low. In order to be exerted a pharmaceutical benefit of their compounds well, it is necessary to be improved the dissolubility of their compound crystals in water. Dissolving rates of crystals depend on surface areas of their crystals. Although Sodium chloride (NaCl) crystals are generally cubes surrounded by (100) faces, it is reported that "skeleton crystals" that are hollowed on the inside of crystal or are only frames, of NaCl are obtained by anti-solvent crystallization. The purpose of this study is to establish the way to produce skeleton crystals of NaCl continuously.

The operating conditions were determined by a batch crystallization. Anti-solvent was poured into a small beaker and it was agitated by a magnetic stirrer. NaCl saturated aqueous solution was added into anti-solvent rapidly, they were mixed a certain duration. Suspended solution was filtrated by a membrane filter and the shapes of obtained particles were observed by a field emission – scanning microscope (FE-SEM). As a result, skeleton crystals of NaCl were obtained when methanol (MeOH) was used as anti-solvent, the mixing ratio of NaCl aqueous solution to MeOH was 1:3 and the mixing duration was 30s.

Continuous crystallization of skeleton crystals for NaCl was produced using a micro-flow reactor. NaCl aqueous solution and MeOH, that were fed by peristaltic pumps, were mixed by a micro-flow reactor, and suspension was flowed in a tube. Suspension was filtrated and the shapes of obtained crystals were observed by a FE-SEM. The skeleton crystals of NaCl were obtained when the operating conditions were the same as batch crystallization. After a few minutes, however, a tube was blocked by suspending NaCl crystals. Therefore, the feeding methods of liquid into a micro-flow reactor are discussing.

Continuous chiral inversion by coupling enantioselective fluidized bed crystallization with enzymatic racemization

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The production of pure enantiomers is challenging but increasingly on demand for the life science industries. The enantioselective separation technique Preferential Crystallization (PC) allows the direct crystallization of enantiopure crystals from a 50:50 (racemic) mixture. Since in many cases only one enantiomer is needed, the yield is limited by 50%. To overcome this yield limitation, Carneiro et al. studied a coupling of PC with an enzymatic racemization. Despite the achievements, drawbacks of the coupled process can be concluded, i. e. the high dosage of enzyme required to facilitate the PC. Currently a new process concept, which couples a packed bed reactor of immobilized amino acid racemase [Carneiro, 2020] with the enantioselective fluidized bed crystallization [Gänsch, 2021] is developed. The process under study promises a much more efficient utilization of the enzyme as well as the continuous and complete chiral inversion of an undesired enantiomer. In the contribution, the process and its advantages will be explained in detail and demonstrated via experiments on the substance system DL-asparagine-monohydrate/water at pilot plant scale.

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Crystal nucleation in 3D printed polymer scaffolds

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This study of the literature provides a thorough examination into the use of heterogeneous nucleation in 3D printing of crystalline polymeric biomaterials for tissue engineering applications. The major goal is to investigate the theoretical underpinnings and offer a method for discovering probable nucleation particles customised to various polymeric materials. Understanding and regulating nucleation processes is crucial for achieving desirable crystal structures and improving the mechanical and biological properties of printed scaffolds. This study intends to contribute to current knowledge in the field of 3D printing for tissue engineering by reviewing important research findings and theoretical frameworks, with a particular emphasis on the significance of nucleation phenomena and their implications for scaffold creation. This review's observations and proposed methods will be useful

Effects on the separation efficiency of a wash column and the production rate in a freeze concentration process

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Suspension freeze concentration (FC) is a technology for dewatering aqueous solutions by crystallization of water. With sub-zero process conditions, the technology is favorable for thermally sensitive components like liquid food as it preserves flavor and nutrients. Additionally, the significantly lower latent heat of crystallization than evaporation provides a great potential of energy savings and with the growing trends towards renewable energy, FC could be an alternative for dewatering processes like wastewater treatment since only electricity is needed. To utilize the full potential of FC, the solid-liquid separation and purification of ice crystals are essential, which are efficiently combined in continuously operated wash columns. The operation of a piston-type wash column can be separated into four steps. The downward movement of the piston feeds the suspension into the column. The subsequent upward movement is similar to a pressure filtration. The solid phase is compressed to form an ice bed and separated from the concentrated liquid, which exits the column via the filter scree as the piston head. In the top section the ice bed is scraped off and molten to obtain water, which is partly fed back as pressurized wash liquid. The wash liquid is pushed through the ice bed and displaces adhering concentrate, recrystallizes at crystal surfaces or melts crystals inside the bed. In stable operation, all phenomena result in a temperature and concentration gradient with a sharp step, which is visualized by a horizontal interface (wash front) inside the ice bed, which separates the washed and unwashed region. Therefore the position is crucial for the purification efficiency, but dependent on the pressure and temperature of the washing liquid, hence these parameters determine the washing efficiency. The correlation and effects of these parameters are going to be presented to create a better understanding of the wash column purification efficiency.

Antisolvent Crystallization of Carbamazepine Dihydrate using a Fluidic Oscillator

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The pharmaceutical industry is rapidly evolving the prevailing crystallization systems to achieve better control over the critical quality attributes of the Active Pharmaceutical Ingredient (API) produced. Fluidic devices provide superior mixing and scale-up possibilities compared to conventional crystallizers, while also facilitating control of the particle size distribution (PSD). The advantages of implementing fluidic devices such as a fluidic oscillator, helical coil, and coiled flow inverter, for the crystallization of paracetamol from methanol solutions using anti-solvent crystallization, have been demonstrated by Yu et al., and, Madane and Ranade (Yu et al., 2022) (Madane & Ranade, 2022). In this study, we investigated the effect of using the fluidic oscillator as a crystallizer for the crystallization of carbamazepine dihydrate (CBZ-DH) from aqueous solutions of ethanol using water as an antisolvent. A loop setup was introduced for the continuous mode of operation of the fluidic device as a crystallizer. Its performance was compared with the performance of batch mode and continuous mode (using a Continuous Stirred Tank Reactor (CSTR)) at the same supersaturation ratio and residence time. The effect of varying the process parameters of the fluidic oscillator such as inlet velocity and recirculation time was also investigated. The acicular dihydrate crystals were monitored online using the Focused Beam Reflectance Measurements (FBRM), and offline PSD characterization was performed using a laser diffractometer. Population Balance Modelling (PBM) was used to simulate continuous crystallization and the kinetic parameters were estimated by fitting the simulated PSD to the experimental data. This study will help understand the applicability of the fluidic oscillator for the production APIs with needle-like particles.

Development of Baffle Exchangeable Continuous Oscilately Baffled crystallizer

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A Continuous Oscillating Baffle Crystallizer (COBC) is a tubular crystallizer. Baffles are evenly spaced inside the tube, dividing it into smaller compartments. The reciprocating piston moves the solution back and forth, creating intense vortices around the baffles. In each chamber, the solution is agitated like a stirred-tank crystallizer. A conventional COBC has used orifice plates as a baffle. However, since it is not designed specifically for a crystallizer, various troubles occur, such as clogging inside the tube and adhesion of crystals to the inner wall.

In this study, we developed a new baffle exchangeable COBC that can use any kind of baffle as well as orifice baffle. First, we evaluated the mixing characteristics of fluids by CFD (Computational Fluid Dynamics) and aimed to design a baffle suitable for crystallization. Sixteen types of baffles were designed, and 44 simulations were performed under different conditions. Simulation results showed that the best mixing was realized using the No. 14 baffle, named the cyclone baffle. Following CFD results, the cyclone baffle was actually manufactured.

Reaction crystallization of glutamic acid was carried out using the cyclone baffle. The outlet concentration was measured by HPLC, and the yield was calculated. When using the cyclone baffle, the yield increased from 66% to 82% compared to the conventional orifice baffle. The obtained crystals were observed by SEM, and the particle size distribution was evaluated. Larger and more uniform crystals were obtained by using the No. 14 baffle. It was revealed that the baffle's shape is critically important in COBC suitable for continuous crystallization.

To Mill or Not To Mill – A Pharmaceutical example on how to "tune" API particle properties

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Pharmaceutical industry constantly investigates new ways to control Active Pharmaceutical Ingredient (API) physical attributes in drug substance (DS) manufacture to ensure a seamless transition into drug product (DP). These attributes relate to solid form and particle properties to ensure that the DP administrated to patients meet critical safety and efficacy endpoints and therefore quality is assured.

The final API stages tend to be the control point for these attributes, but sometimes conflicts emerge between DS and DP requirements. The main conflict comes from the particle size; for example, particles less than 10 microns can prevent the isolation and drying to be effective and hence batch cycling times and/or purity profiles can be negatively impacted.

For such compounds a dry milling approach is typically required. There is often a lack of understanding around dry milling and a development phase is needed to identify critical process parameters (e.g. pressure, feed rate…) to ensure the desired particle properties are achieved. Additionally, a particle size distribution method is developed to monitor the dry milling outputs, which should generally be different from the one used for the bulk API.

All these aspects can take time and can impact the drug development especially when transitioning DS to DP. Ideally, removal of the dry milling step should be pursued when manufacturable-suitable particle sizes can be generated directly from the final API stage.

This presentation will focus on an AZ project which exhibited poor milling properties and how the removal of the dry milling process was performed using a wet mill in the final API stage. When possible, eliminating the particle size reduction step should be attempted to improve sustainability and simplify the supply chain. Finally, other technology will be presented on how particle properties can be engineered to ensure DP quality.

Growth dynamics of aspirin crystals in microfluidic antisolvent crystallization

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Controlling crystal size is a significant challenge for industrial crystallization with immense implications on product quality and performance. This research investigates the potential of antisolvent crystallization using microfluidics to achieve crystal size control. In the experiments, a poor solution, saturated with aspirin, replaces a good solution in the microfluidic channel, which leads to a supersaturation pulse that moves through the channel and induces the growth of aspirin seeds. The hypothesized supersaturation pulse could be visualized by measuring the linear growth rate during the experiment. The results show that the linear growth rate scales with Peclét, in line with boundary layer behaviour around a crystal, according to $dR/dt \sim Pe^{3/2}$. Boundary layer behaviour was visible for crystals that experienced rough diffusion-controlled growth at sufficiently high supersaturation levels. However, the given relationship was only shown for a specific range of flow rates (300 - 900 µL/min) because the dispersion behaviour changed at lower flow rates (< 300 µL/min), and a growth rate limitation was attained at higher flow rates (> 900 µL/min). A relationship between Peclét and the final volume was not yet discovered due to large variations in the results. However, this research could be the foundation for crystal size control in antisolvent crystallization.

Effect of laser exposed volume, irradiation position and solvent composition on non-photochemical laser induced nucleation of potassium chloride solutions

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We study the influence of the laser exposed volume, the irradiation position and the solvent composition on non-photochemical laser induced nucleation (NPLIN) of supersaturated potassium chloride solutions in water or water/methanol mixtures as solvent. Effect of exposed volume on NPLIN probability is studied by exposing distinct volumes of aqueous potassium chloride solutions stored in vials of millilitre volume at two different supersaturations (1.034 and 1.050) and laser intensities (10 and 23 MW/cm^{2}). Higher NPLIN probabilities were observed with increasing laser-exposed volume as well as with increasing supersaturation and laser intensity. The measured NPLIN probabilities at different exposed volumes are questioned in the context of dielectric polarization mechanism and classic nucleation theory. No significant change in NPLIN probability was observed when samples were irradiated from the bottom, top or middle of the vial. However, a significant increase in nucleation probability was observed upon irradiation through the solution meniscus. Additionally, increasing the methanol content in the solvent to 20 wt.% at constant supersaturation decreased the NPLIN probability significantly. We discuss these results in terms of mechanism proposed for NPLIN.

Applications of Sublimation in Synthesis and Crystal Growth of Organosulfones

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Sublimation has been established as a successful method of producing solvent-free high-quality single crystals of several APIs (1-3). Further applications of sublimation in combined organic synthesis through thermal transformation and crystal growth of organosulfones are currently investigated in this work.

Aromatic sulfones are valuable intermediates in industrial applications and organic synthesis. Diaryl sulfones are of particular importance in pharmaceuticals. Diphenyl sulfone is an intermediate in the synthesis of Dapsone (4,4'-diamino diphenyl sulfone) which is used in the treatment of leprosy (4). Substituted diaryl sulfones were also found to suppress the replication of human immunodeficiency virus type-1 (HIV-1) in vitro (5).

The preparation of 4-phenylsulfonyl biphenyl typically involves multistep reactions that require the use of catalysts and solvents (4). An in-house low thermal gradient sublimation apparatus (1–3) (Figure 1) has shown success in eliminating phenylsulfinic acid from trienes (Compounds 1a – 1f) to produce biphenyls (Compound 2).

1 was synthesized by reacting [(E)-3-(benzenesulfonyl)allyl]sulfonylbenzene with an equivalent amount of a substituted trans-cinnamaldehyde and 33 equivalents of aluminum oxide (Figure 2) to produce a family of substituted derivatives of 2. In the case of 1a yellow crystalline needles of the starting compound were transformed into colorless crystalline blocks of the phenyl derivative of 4-phenylsulfonyl biphenyl in quantitative yield (Figure 3).

Controlled thermal transformation and crystal growth through sublimation has proved to be a green method that provides a single-step process for the efficient production of a quantitative yield of organosulfones without the need for solvents, catalysts, or further purification.

Evaporative crystallization of sessile droplets using electrowetting

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We study the evaporative crystallization of sessile droplets of aqueous glycine solution on substrates with different wetting properties and characterize the morphologies as well as polymorphs emerging from the solution. On a hydrophilic surface, a mixture of bipyramidal α and needle-like β crystals was observed in the coffee stain. On a hydrophobic surface, the droplets evaporated without contact line pinning, and small bipyramidal α crystals formed. Further, we tune the surface wettability dynamically through electrowetting as the sessile droplet evaporated. In this case, glycine crystallized with a distinct polymorphic form and morphology than crystals nucleating on hydrophilic and hydrophobic surfaces. Our results highlight electrowetting as a promising tool to control the evaporative crystallization of sessile droplets.

Crystallization rate effect on the thermal conductivity of paraffin as phase change material

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Temperature swing adsorption (TSA) is used in CO2 capture systems. Paraffin as phase change material (PCM) has been used to improve adsorption rate and bed capacity by absorbing or releasing adsorption heat [1]. However, a drawback of solid paraffins is their low thermal conductivity (0.2 W·m-1·K-1), which slows the PCM response [2]. This study presents the effect of the crystallization rate on the thermal conductivity of paraffins.

Direct thermal conductivity measurements were performed first. Paraffin with a crystallization temperature of 47.97°C was first molten in a static container and then allowed to crystallize until complete solidification either in a thermostatic bath containing water at 4°C or in ambient air at 23°C. The mean thermal conductivity was 14% higher with fast crystallization (HSD test, 5% significance). In situ thermal conductivity determination was done in a setup designed to emulate macro-encapsulated PCM devices. The thickness of paraffin layers grown in a cold finger was measured with a digital caliper and the thermal conductivity was determined as the adjustable parameter of a detailed 1D mathematical model for the process of phase change. It was found that the thermal conductivity of paraffin increases by 40% to a value of 0.30 W m-1 K-1 when the crystal growth rate increased from 0.06 to 0.19 kg m-2 s-1. Also, a 2D mathematical model showed that the experimentally found truncated cone shaped paraffin layer was caused by natural convection in the molten paraffin. It is concluded that the crystallization rate should be considered for designing PCM devices with improved thermal response.

Insoluble and soluble impurities' influence on crystallisation of polymorphic forms

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The presence of impurities can have a significant effect on solubility and crystallisation kinetics, directly influencing key attributes such as crystal habit, form, size, and chemical purity. Multiple impurities can lead to a complex interplay of competing/cooperative effects that can be difficult to decouple.

In this work, we detail the experimental findings of an antisolvent cooling crystallisation of an agrochemical active ingredient, compound A, in the presence of process impurities. Compound A has three known polymorphs that are all enantiotropically related, the target form being stable up to 55°C and required for stable formulation design. Our aim was to find the crystallisation conditions to ensure a robust process that consistently delivers the required form with the highest possible yield, productivity, and purity.

Our results show differing crystallisation behaviour in the presence of impurities:
•	Effect of insoluble impurity: we show that insoluble impurity S provides a surface that reduces the energy barrier for secondary nucleation producing undesired forms of differing habit (Figure 1), which is not observed in pure solvent. We detail studies that demonstrate its impact on form, habit, and rate of polymorph transformation.
•	Effect of soluble impurity: we show that the soluble impurities provide favourable conditions to aid polymorphic robustness. We detail studies on the conversion rate to the stable form under process conditions and find a "sweet spot" in temperature for rate and yield. We also detail how the solubility changes with impurities and antisolvent, indicating a need for care with the seeding regime.

Our work outlines the experimental workflow used to decouple the effects of impurities and demonstrates an industrial case study where the fundamental understanding obtained has led to key recommendations on the plant process.

Loading of Aceclofenac Nanocrystals in Drug Delivering Liposomes

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Liposomes are promising drug delivery vehicles that can be utilised as highly concentrated crystal reservoirs. For crystallisation to occur, the concentration of the encapsulated compound must exceed the solubility within the liposome's aqueous core. Then, validation that this supersaturation has led to crystal formation inside the liposome is needed.

The liposomal aqueous core can be filled with solute by creating a pH or ion gradient between the interior and external environments. This gradient is highly tuneable to allow either hydrophilic or hydrophobic compounds to be encapsulated in the liposomal cores with great efficiency. In this study, aceclofenac is loaded into liposomes using a sodium acetate ion gradient. The solubility of aceclofenac in 0.15M sodium acetate is low (0.12 mg/mL) and loading at a drug to lipid ratio of 0.01 g/g we would require 55% drug loading to exceed the supersaturation ratio. We achieved drug loading of >85%. The solid forming within the liposome core would be aceclofenac sodium.

Despite the liposomes' miniscule interior volume, the generated supersaturations make it likely that nanocrystals are formed within. Nanocrystal presence within liposomes can be difficult to ascertain due to their small size and the interference of the lipids in standard crystal analysis techniques such as IR spectroscopy and microscopic observation. However, small angle x-ray scattering (SAXS) can be used to identify key crystal properties of the encapsulated solid material. Indeed, the scattering of the liposomes could be accounted for, allowing data to be gathered on the encapsulated aceclofenac nanocrystals.

Acetate gradients make it possible to load weakly acidic drugs, like aceclofenac, into liposome cores with great efficiency, even up to highly supersaturated conditions. Furthermore, SAXS provides a suitable method for confirming the presence of aceclofenac nanocrystals within liposomes. This technique allows the study of the crystallisation behaviour of the nanocrystals inside the liposomes.

Gaining kinetic insight into the crystallisation of metal-organic frameworks via non-invasive Raman spectroscopy

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Metal-organic frameworks (MOFs) are typically synthesised via solvothermal crystallisation processes and comprise metal centres or clusters connected by multidentate organic linkers. Such materials are highly tuneable, arising from opportunities to tailor the properties of both the metal and organic components. Whilst MOFs have applicability to addressing global challenges in energy, healthcare, and environment, the ability to reliably scale-up MOF synthesis poses a significant challenge to their commercialisation. Recent advances in understanding the formation of MOFs are reliant on complex and expensive instrumentation such as synchrotron radiation.

Invasive Raman and infrared spectroscopy have been used for in situ monitoring of different components within MOF reaction mixtures. However, the effects of an invasive probe upon nucleation and crystallisation are unknown and add complexity to the experimental setup. Here, non-invasive wide area illumination Raman spectroscopy has been employed for monitoring the progress of a known MOF reaction. The extent of crystallisation derived from the Raman data showed good agreement with reported kinetics for the system that were determined using a synchrotron X-ray diffraction technique. The Raman technique also provided mechanistic insight into species in solution within the reaction medium, such as the ligand source and acid modulator. Raman spectroscopy benefits from sensitivity to materials in both the solid and solution state, whereas X-ray diffraction only detects species in the solid state. Non-invasive wide area illumination Raman spectroscopy is advantageous in terms of cost, portability, and accessibility compared to a synchrotron. Therefore, non-invasive Raman spectroscopy is more easily deployable in a real process environment and is potentially a key enabling tool for understanding the crystallisation of MOFs.

Harnessing Birefringence for Real-time Classification of Molecular Crystals using Polarized Light Microscopy, Microfluidics and Machine Learning

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Molecular crystals are ubiquitous in a variety of industrial contexts, from foods to chemicals and pharmaceuticals. The timely identification of different molecular crystal forms (and transformations between forms) is critical in both manufacturing and chemical/pharmaceutical product design, as they possess different physicochemical properties (e.g., solubility, melting and boiling point etc.) that could affect product attributes such as stability and dissolution rate. However, current characterization methods typically involve a time delay between sampling and analysis and are unable to directly quantify forms/ transformations in crystal ensembles at a single crystal level in real-time. Here, we introduce a new methodology to accomplish such measurements, which utilizes a combination of microfluidic flow cells and a rotating polarizer-analyzer pair with orthogonally aligned polarization axes for automated access to interference colours of birefringent molecular crystals that are characteristic of the polymorphic form. When coupled with machine learning, this methodology enables unprecedented real-time and in situ classification of crystal ensembles (~3000 crystals classified in under 10 s) at a single crystal level. We demonstrate ~94% and ~86% accuracy in classification of two model systems comprising of polymorphs (α-glycine and β-glycine) and hydrates (azithromycin sesquihydrate and azithromycin dihydrate) respectively. We then apply the method to monitor dynamic transformation of molecular crystals from one form to another over time in crystal ensembles, through simultaneous form classification of crystals and direct crystal area measurements. This sheds quantitative insight into the dominant crystallization phenomena such as nucleation, growth or dissolution, potentially enabling both process monitoring as well as extraction of crucial kinetics data needed for crystallization process modelling and control. We envision the applicability of this methodology in accelerating the exploration of storage, process condition or additive dependent polymorphic form outcomes that are of interest during early-stage research and development when limited quantities of materials are available.

Verification of the Nanoparticle Heating Mechanism in Laser-Induced Nucleation

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Non-photochemical laser-induced nucleation (NPLIN) refers to using short (usually nanosecond) laser pulses to induce crystallization and brings no photochemical damage to the system. Some reports proposed the nanoparticle heating mechanism where heating of nanoparticles in solution under laser causes vapor bubbles and provides nucleation sites near the interface. More work is still required to explore the effect of impurity nanoparticles in NPLIN.

We propose two hypotheses to further prove the nanoparticle heating mechanism on the basis of the vapor cavitation model.
1) Increasing the size of the nanoparticles would form larger bubbles and lead to higher nucleation probability;
2) Using nanoparticles with larger absorption efficiency would form larger bubbles and lead to higher nucleation probability.

Different sizes and materials of single nanoparticles are added to filtered urea solution with various supersaturation and the nucleation probability are tested under laser (532 nm) to verify these two hypotheses and the nanoparticle heating mechanism.

Controlling crystal properties of curcumin microparticles via anti-solvent crystallization

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Flavonoids and polyphenols, like curcumin, are attractive crystalline materials to be used as nutraceuticals, food ingredients, and formulation stabilizers (e.g., Pickering effect) due to their health benefits, antioxidant properties, safety for human consumption, and cost effectiveness. However, functional attributes of curcumin, such as solubility, bioavailability, and surface properties (e.g., water wettability) are strongly dependent on crystal properties such as size and shape distribution, as well as polymorphism. Curcumin is characterized by low water solubility, low bioavailability, and poor chemical stability under different pH conditions, which makes the crystallization of this compound very challenging.

Anti-solvent precipitation is a widely spread technique to obtain particles of uniform and reduced (< 10 µm) size distribution for heat sensitive and unstable compounds, such as curcumin. This aim of this work is to determine the impact that the operating parameters of anti-solvent precipitation have on the crystal properties of the obtained curcumin micro-particles. Water was used as anti-solvent to precipitate curcumin particles from an ethanol solution, while a high shear rotor-stator mixer allowed fast mixing and uniform supersaturation. The effect of curcumin concentration, solvent / anti-solvent ratio, batch volume, stirring conditions, and pH were tested. Design of experiment (DoE) was used to optimize the experimental campaign. Polarized microscopy and Raman spectroscopy, in addition to static light scattering, were used to characterize the obtained crystals.

Crystallisation kinetics of different solid forms of griseofulvin

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Nucleation is a poorly understood phenomenon, partly because the small size of nuclei makes them difficult to detect. The aim of this work is to investigate the crystal nucleation of griseofulvin (GSF). GSF is an active pharmaceutical ingredient with high molecular weight (352.76 g/mol) and complex molecular structure containing a cyclohexanone ring combined with a benzofuran moiety along with many functional groups. GSF is prone to polymorphism and solvate formation due to its chemical structure and geometrical characteristics that inhibit efficient crystal packing. Primary nucleation of GSF was investigated in n-butyl acetate (nBuAc), acetonitrile (ACN), and methanol (MeOH) by visual detection of onset of nucleation in 20 mL solutions. The PXRD solid-state analysis indicated that GSF nucleated as the stable form I in MeOH (CSD GRISFL), as a GSF-ACN solvate in ACN (CSD PINMOQ), and as an unreported GSF-nBuAc solvate in nBuAc. Both solvates were found to be unstable at room temperature, with the GSF-nBuAc transforming to form I and the GSF-ACN transforming to an unreported polymorphic form. At similar supersaturation, the nucleation rate was the highest for the ACN-solvate followed by the nBuAc-solvate, and the form I nucleation in methanol was the slowest. The pre-exponential factor (kinetic) and the interfacial energy (thermodynamic) were the highest for GSF form I, followed by GSF-nBuAc, and the lowest for the GSF-ACN. According to the classical nucleation theory , the nucleation rate is inversely proportional to the interfacial energy and directly proportional to the pre-exponential factor. Hence, for this compound, the interfacial energy has a higher impact on nucleation rate than the pre-exponential factor. In conclusion, the solvent choice affects the resulting solid-state of the GSF crystals, as well as the nucleation rate where crystallization is faster for the unstable solid-state solvated forms.

Pre-nucleation aggregation of caffeine-benzoic acid as a tool for crystallisation solvent choice

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Pharmaceutical co-crystals are promising alternatives for the formulation of some drugs because of their improved physicochemical properties.[1] While the standard experimental co-crystal screening employing mechanochemical methods, slurry conversion, and evaporation, is trial-and-error based and may miss harder to nucleate co-crystals, [2] computational prediction methods are an alternative but suffer from being based on thermodynamics driving the formation of the final co-crystal form without taking into account whether they can be obtained via solution co-crystallisation.[3]
Here, we report a fast, efficient and reliable experimental method to chose the solvent for co-crystal formation from solution. We study the model system of caffeine (CAF)-benzoic acid (BA) due to its reported difficulty to co-crystallise spontaneously.[4] The formation of CAF-BA co-crystal can be predicted using nuclear magnetic resonance (NMR) spectroscopy titration for three solvents (acetonitrile, acetone, and methanol). The large apparent binding constant and apparent Gibbs free binding energy between CAF and BA in acetonitrile indicate strong heteromeric, coinciding with the ease to co-crystallise from this solvent. Although we initially did not obtain the co-crystal from acetone and methanol, the NMR results show strong interactions between the two solutes in these solvents indicating the possibility of the co-crystal formation. This result was further corroborated by the ternary phase diagrams of these systems, and the co-crystal could be obtained by changing the molar ratio of the co-formers. Weak interactions between CAF and BA in dimethyl sulfoxide (DMSO) suggests DMSO is an unsuitable solvent in the formation of the co-crystal, and the co-crystal could not be obtained from solution. Hence, NMR spectroscopy is a promising, easy and timesaving technique to screen for suitable co-crystallisation solvents.

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The effect of milling on the surface energy heterogeneity and different crystal planes

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Crystalline materials can be energetically anisotropic, meaning the surface chemistry is not homogeneous or different crystal planes can exhibit different chemistry. Therefore, even for crystalline materials, it is important to treat them as energetically heterogeneous materials, and their surface energy may not be adequately described by a single value. Finite concentration Inverse Gas Chromatography (IGC) experiments allow for the determination of surface energy distributions which more accurately describe the anisotropic surface energy for real materials. Previous studies have investigated the anisotropic nature of mannitol. In this study, we investigate the affects of milling on the heterogeneity of crystalline D-mannitol. In addition, the particle aspect ratio as a function of milling will be correlated to the surface energy heterogeneity and different crystal planes.

Exploring the Crystallisation of Pharmaceutical Molecules using Liquid Phase Electron Microscopy

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The pharmaceutical industry spends a significant amount of energy mapping the crystallisation landscape of their drug molecules to achieve high purity crystalline drugs, and to achieve a desired morphology. The crystallisation operating conditions determine the physical properties of the products such as purity, size, crystallinity, and shape. In turn, these properties determine the downstream process efficiency such as filtration, drying and formulation along with the product efficacy such as bioavailability and shelf-life. Therefore, approaches to control the crystallisation process are needed to reduce the time to market these products, increase the drug manufacturing efficiency and to improve product consistency. Liquid phase transmission electron microscopy (LPTEM) has the potential to elucidate the mechanisms involved in the nucleation and crystal growth of pharmaceutical crystals from solution. General LPTEM experiments create an environment that overcomes the barriers to nucleation leading to crystallisation at extremely undersaturated concentrations. To control crystallisation processes, extensive solubility data, to determine supersaturation levels under different conditions, is required. In this work, solubility data for flufenamic acid (FFA) in ethanol, methanol, and isopropanol and for mefenamic acid (MFA) in ethanol, ethyl acetate and dimethyl formamide at temperature ranges of 25 to 40 °C has been generated. Structural characterisation of the solid phase at equilibrium has been done using PXRD and DSC. Upon loading of extremely undersaturated solutions of FFA (10mM) in the liquid phase sample holder, crystallisation was observed at ambient conditions under the electron beam (>200 e−/Å2/s) using a FEI Titan Themis3 working at an acceleration voltage of 300 kV, mounted with a monochromator. Different concentration ranges (lower to higher) will be further explored along with binary solvents to further map the crystallisation of flufenamic acid and mefenamic acid under the electron beam.

Crystal Nucleation Induced using Optical Tweezing near the edge of Sessile Droplets

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Following the discovery that pulsed lasers could induce crystal nucleation from solution, it was observed that optical tweezing could induce nucleation by locating the tweezing focus at the solution-air interface. To systematically investigate this phenomenon, nucleation was investigated in solutions of glycine in H2O and D2O using a 1064nm laser beam focused at or near the three-phase contact point (solution, air and supporting glass coverslip). A range of conditions where the bulk supersaturation, lateral displacement of the focus from the droplet edge and the presence of a trapped silica microparticle were varied, repeats were performed to obtain a distribution of induction times for nucleation under isothermal conditions.

Our experiments demonstrated that the nucleation of glycine can be induced by optical tweezing from both D2O and H2O, including from undersaturated solutions. The results showed that the likelihood of nucleation does not have a significant dependence on bulk solution concentration above a certain critical value (dependent upon solvent isotopologue and laser power) which is less than the corresponding solubility. Lateral distance from the edge of the sessile droplet was found to significantly impact the likelihood of nucleation, which decreased with increasing distance from the droplet edge. A single silica microparticle trapped within the laser beam focus appeared to partially inhibit nucleation by reducing the proportion of times nucleation was observed.

Observations of crystal nucleation and growth induced by the optical tweezing focus near the edge of sessile droplets in undersaturated bulk solutions indicate that the local glycine concentration near the beam focus is significantly higher than in the bulk solution for moderately undersaturated and supersaturated solutions, but this effect vanishes as the beam focus moves away from the droplet edge. This provides a novel insight into nucleation mechanisms using optical tweezing and expands our abilities to localise nucleation of crystals from solutions.

Co-crystallization of Praziquantel : conglomerate and racemic compound nucleation rates

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Praziquantel (PZQ) is widely used to treat schistosomiasis. However, this chiral pharmaceutical is still produced as a racemic compound (both enantiomers crystallize together in the crystal lattice) while only the R enantiomer is active. A possible way to control the solid properties of chiral APIs and herewith to separate the enantiomers is their co-crystallization with a coformer, either to form a salt or a co-crystal. The crystallization behavior of such systems is still not well-understood. For instance, the nucleation rate of such co-crystals can be low compared to the nucleation rate of pure components and therefore, co-crystal nucleation can require a higher driving force.

A previous co-crystal screening has identified vanillic acid (VA) as a coformer able to form two different co-crystals with PZQ.1 Further analysis shows that these two co-crystals exist at different molar ratios: PZQ:VA crystallizes as racemic compound and PZQ:VA2 is a conglomerate. The phase diagram of this system has been established to identify the thermodynamic stability and the solubility of the different solid forms. This system offers the opportunity to study the crystallization kinetics using the probability distribution of induction times2 of the racemic compound and the conglomerate co-crystals in comparable conditions, as the same components are involved. The crystallization kinetics of the conglomerate co-crystal are much slower than those of the racemic co-crystal compound, perhaps due to self-poisoning in the conglomerate. The comparison of the crystallization behavior of these different solid forms should lead toward an improved understanding of the crystallization behavior of co-crystals as well as racemic compounds and conglomerates.

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CNT effective interfacial energy and pre-exponential kinetic factor from measured NaCl crystal nucleation time distributions in contracting microdroplets.

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Nucleation, the birth of a stable cluster from disorder, is inherently stochastic. Yet up to date, there are no quantitative studies on NaCl nucleation that accounts for its stochastic nature. Here, we report the first stochastic treatment of NaCl-water nucleation kinetics. Using a recently developed microfluidic system1 and evaporation model2, our measured interfacial energies extracted from a modified Poisson distribution of nucleation time show an excellent agreement with theoretical predictions. Furthermore, analysis of nucleation parameters in 0.5 pL, 1.5pL and 5.5 pL microdroplets reveals an interesting interplay between confinement effects and shifting of nucleation mechanisms. Overall, our findings highlight the need to treat nucleation stochastically rather than deterministically to bridge the gap between theory and experiment.

Two new hydrate morphologies formed by the self-assembly of diphenylalanine in ethanol and acetone

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Dipeptide diphenylalanine (FF) has been studied from mesoscopic to nanometric levels for its self-assembly by crystal and amorphous solid-state structures.1,2 Diphenylalanine is the core recognition motif of Alzheimer's β-amyloid peptide, which has the ability to self-assemble into nanotubes, nanowires, and nanofibrils, making it suitable for a range of applications including drug delivery, 3D cell culture, and nanofabrication.3 Despite being extensively studied for constructing nanostructures, there is limited information available on the fundamental properties of diphenylalanine, such as solubility, crystallizability, and hydrate/solvate formation propensity.

In this study, the solubility of diphenylalanine dihydrate was investigated using the static method in different solvents (water, ethanol, and acetone) at 5°C and 35°C. The results showed that diphenylalanine dihydrate has an inverse solubility relationship with solvent polarity, with solubility decreasing as solvent polarity increases due to the hydrophobic side chains on the phenylalanine residues. Morphology screening experiments for diphenylalanine were also conducted in ethanol and acetone to investigate the effect of solvents on the peptide self-assembly. The PXRD patterns (Figure 1) suggest two different crystal morphologies for the diphenylalanine obtained from the cooling experiments in ethanol and acetone. Raman spectrum shows the shifting of peak at 2850-3000 cm-1, contributed to change of the bonded C-H stretching in the new crystal structures, suggesting the different interactions between water and peptide molecules. Further, the 12% weight loss in TGA is indicative of potentially new hydrate morphology for these crystal forms. Interestingly, SEM micrographs shows the nanotubular shape for the new morphologies similar to the raw materials which has already been published as diphenylalanine dihydrate (Figure 2).4

In summary, diphenylalanine exhibits new crystal from when crystallised from ethanol and acetone, which could potentially be new hydrate forms. However, further research is needed to fully understand the new crystal from and the underlying mechanisms that led to the formation.

Molecular and thermodynamic mechanisms of cosolvency of amino acids: experiments and molecular simulations

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Cosolvency is an interesting and important thermodynamic property that is frequently used in the pharmaceutics and fine chemicals industries. For example, the addition of organic solvent to aqueous solution of amino acid to generate the supersaturation is a very effective method for amino acid crystallization. However, in some amino acid systems, the solubility tends to increase and then decrease with the addition of organic solvents, which makes the nucleation uncontrollable and further affects the product quality. However, the molecular mechanism of the phenomenon of cosolvency, including the differences in molecular conformation before and after cosolvency and the changes in inter/intra-molecular interactions in single pure solvents and binary co-solvents, has been less studied, and the molecular mechanism of amino acid cosolvency is still unclear. In this work, cosolvency phenomenon was investigated at the molecular level using online spectroscopy and molecular simulations, in which L-alanine, L-phenylalanine, and L-tryptophan were used as model substances. The results indicate that in binary solvent mixtures, amino acid molecules undergo a shift in molecular conformation due to different solvents, resulting in a change in inter/intra-molecular interactions, which in turn leads to the latent solubilization phenomenon. With this knowledge in hand, the cosolvency point of other amino acids were successful predicted through the utilization of quantitative calculation method proposed by us, which is further verified by the experimental solubility data. These favorable results prone to provide an elegant approach for predicting solubility enhancement of amino acid-like substances.

In Search of Relationships between the Kinetics of Anti-Solvent and Cooling Crystallisation

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Anti-solvent crystallisation can provide access to polymorphic forms of organic crystalline products that cannot be obtained by cooling crystallisation. This is possible because mixing with the anti-solvent opens additional molecular pathways that are further removed from thermodynamic equilibrium, e.g., through high local supersaturation ratios. However, achieving precise, let alone predictive control over these processes remains problematic, as the thermodynamics and kinetics are intertwined with complex mass transport and fluid dynamics. For example, incomplete mixing of anti-solvent and solution, local temperature fluctuations during mixing and the complex interactions between the solvated solute and solvent phases can be expected to create a complex network of parallel molecular processes and lead to the formation of alternative polymorphic forms. To shed light on the significance of these non-equilibrium phenomena we have embarked on a systematic study of L-histidine crystallisation kinetics in solvent/anti-solvent systems, comparing cooling with anti-solvent crystallisation observables while keeping the composition of the solvent mixtures constant. This approach allows prediction of the nucleation rates expected for ideal mixing of solvent and anti-solvent from solubility measurements close to thermodynamic equilibrium. This provides a reference for identifying/predicting conditions far from equilibrium, and how the associated nucleation and crystal growth kinetics combine to determine the structure, habit and size distribution of the crystallised product.

Stabilization and Coagulation of Colloidal Suspensions during Crystallization

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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 destruction of colloidal metastability, 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. The suspensions and colloidal particles during cefradine crystallization were studied using different characterization tools, and the stability of colloidal suspension was revealed. 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 colloidal stability is significantly affected by pH. Besides, the particle concentration and external ions would also affect the interaction and electric double layer of nanocrystals, which could destroy the colloidal stability, leading to the aggregation of nanocrystals and coagulation of suspensions. The developed knowledge based on the suspension can form a basis for further optimization of purification and crystallization for cefradine.

Crystal nucleation of sodium sulfate

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Mineral precipitation is the formation of crystalline salts, such as carbonates or sulfates, from solution. Precipitation of salts, such as sodium sulfate, is a challenge in a variety of fields, including geothermal technology where it can block pores and hinder extraction, and historic building preservation where it can cause damage by crystallising in porous rock and forming cracks. Sodium sulfate has several different crystal hydrate forms but it is not well understood how different surfaces influence its heterogeneous nucleation and which hydrate nucleates. The aim of this project is to develop a procedure to investigate the nucleation of sodium sulfate hydrates.

The experimental set up used a vial nucleation procedure previously used for glycine induction experiments [1,2]. A sodium sulfate stock solution of concentration of 3.2 molal was prepared by dissolving anhydrous sodium sulfate in deionised water at a temperature of 32.4 oC. The solution was pipetted to glass vials and cooled for isothermal crystallisation in a Polar Bear cooler. The nucleation of heptahydrate and mirabilite is exothermic, and the nucleation rates were obtained by monitoring the temperature of the solutions. Distinct signatures corresponding to heptahydrate and mirabilite were observed, and results of nucleation induction at several isothermal temperatures will be presented. The developed procedure will form the basis for studies of heterogeneous nucleation of sodium sulphate hydrates.

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Model-based Scale-up of Attrition-Prone Crystallisation Processes

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This work focuses on developing a workflow that allows for the scale-up of crystallisation processes that are prone to attrition. Attrition is defined in this work as the mechanical process that produces small fragments from large crystal particles. These small fragments are a source of new crystalline particles, i.e., nuclei, but their production is distinct from the formation of nuclei through a liquid-solid phase transition that would constitute a true nucleation mechanism. The presence of attrition in a process can be beneficial in that, if controlled, it can provide a source of new crystalline particles required to maintain steady state operation in continuous crystallization processes. However, it can have detrimental effects on the particle size distribution, for example in a batch crystallization process where the production of fines can create problems for downstream processing.

The use of a systematic experimental workflow to investigate crystallisation systems will allow the different parameters affecting the scale-up of attrition to be determined. The use of non-solvents for the testing of attrition in seeded suspensions allows for the effects of other crystallisation mechanisms (nucleation, growth, agglomeration) to be removed from consideration. The coupling of image analysis techniques with both Crystalline and EasyMax setups allows the attrition rate to be quantitatively assessed under an array of experimental conditions. Considerations of relevant dimensionless numbers (Stokes, Reynolds) can be used to assess flow conditions where attrition is likely to be relevant due to particle-impeller collisions [1]. Population balance models of attrition will be incorporated alongside the experimental work to facilitate scale-up and a deeper understanding of the attrition process.

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Quantifying the Risk of Acute Kidney Injury caused by drug induced Crystalluria

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Acute Kidney Injury (AKI) is often diagnosed late, ineffectively managed and has been recognised as a condition of global concern. As such, the most effective approach to reduce the healthcare burden of this condition is primary prevention. Precipitate induced Acute Kidney Injury (pDAKI) is one of the most common causes of AKI, resulting from the precipitation of crystals in the kidney which can cause direct toxicity. pDAKI often occurs after a drug treatment intervention, when clinicians are trying to balance unknown patient specific pharmacokinetics to avoid toxicity whilst ensuring therapeutic concentrations are reached. I summarise the exogenous drug compounds that have been reported to cause pDAKI and describe the physicochemical behaviour of the antibiotics nitrofurantoin and ciprofloxacin in real and artificial urine. This information has enabled my team to develop a technique which couples physicochemical and pharmacokinetic data and can offer a means to predict pDAKI. This methodology requires simple laboratory equipment and can inform diagnosis and treatment.

Drug nanoparticle attachment to carrier particles for solid dose formulations

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The nanosizing of active pharmaceutical ingredients (APIs) has been widely used to solve challenges in the pharmaceutical industry such as poor API dissolution rate and bioavailability. However, API nanoparticles, once formed, are unstable and tend to agglomerate and undergo Ostwald ripening when isolated to dryness. In the past, a one-step approach was developed in our group to isolate API nanoparticles produced via antisolvent precipitation without the need for soluble stabilizers. As such, montmorillonite (MMT), a clay particle, was selected as the carrier particle to adsorb API nanoparticles onto its surface and the resultant API nanocomposite solid exhibited excellent performance in terms of the rapid API dissolution rate. However, the properties of MMT that produced these promising results are as yet unknown. Therefore, this work uses carrier particles with known surface properties (namely a mesoporous silicate (SBA-15), a mesoporous organosilane (ESE) and non-porous silica (SIL)) instead of MMT to isolate API nanoparticles and to study how known surface properties affect the adsorption and subsequent dissolution behaviour of these API nanoparticles. API nanocomposites with different drug loadings (up to 33.3% w/w for SBA-15 and SIL, and up to 50% w/w for ESE) were prepared via liquid antisolvent precipitation using valsartan as a model API. The dissolution behaviour of the resulting nanocomposite powders in deionised water was found to be poorer than that of a valsartan nanosuspension freshly prepared in the presence of a soluble stabilizer (~50 nm particle size), but significantly better than that of valsartan as received (~11 μm particle size). In particular, ESE nanocomposites, which showed the fastest dissolution rates, exhibited comparable results to those published in the past by our group for valsartan adsorbed onto functionalized MMT.

Piezo responsive multicomponent crystals of L-amino acids – a case study using carboxylic acid coformers

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Piezoelectricity is the generation of electric current by the application of mechanical force on a material. The naturally occurring material, quartz (1.4 pC/N), and inorganic materials such as aluminium nitride (AIN; 8 pC/N) and lead zirconium titanate (PZT, 350-500 pC/N), are known to be piezoelectric in their own range of low, medium and high actuating piezo materials. However, the above materials are non-environmentally friendly, and offer limited designability and structure-property control. Naturally occurring organic chiral materials, e.g., amino acids, are a possible alternative to traditional inorganic systems, because of being biocompatible and are known to exhibit considerable piezo response. Further, organic molecules like amino acids possess functionalities, which makes them perfect coformers for the design and synthesis of multicomponent crystals using principles of crystal engineering.

Cocrystallisation of piezoelectric L-Amino acids with selected coformers leads to scalable amounts of multicomponent crystalline systems that could be used for eco-friendly actuation. In this study the piezoresponses of the parent L-amino acid and resulting multicomponent systems are measured, to understand the performance modulation that can be achieved via cocrystallisation. DFT calculations are used to calculate the optimal orientation axis for maximum electrical output under an applied force validating the applicability of cocrystallisatio as a tool to design next generation biological piezoelectric.

The case studies confirmed that cocrystallisation can be a useful method to modulate the piezoresponses of a parent conformer. However, the extent of the influence cocrystallisation can bring about, depends on the conformer that has been used. Further, cocrystal screening of basic L-amino acids with various coformers, is presently being performed to derive concrete design rules for high piezoelectric output.

Amino acid crystals as high-performance, eco-friendly structural health monitors.

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In the past ten years, biological piezoelectric materials have emerged as the potential next generation of cost-effective, green electromechanical sensors1, 2. The piezoelectric voltages produced under an applied force are inversely proportional to the dielectric constant of the material and so even 'weak' organic piezoelectrics (with modest piezoelectric constants compared to inorganic ceramics3, 4), can generate large voltages in response to strain. Amino acids are the simplest biological units, and are inexpensive and easy to crystallise5-7, and demonstrate measurable piezoelectricity in single crystal8-10 and polycrystalline forms11, 12.

Recently we have experimentally validated flexible glycine-based sensors for pipe leak detection and monitoring in real-time, for a variety of flow rates and leak sizes using a custom fluid test rig developed for the validation of PVDF patches13. This is the first time that glycine crystals have been grown and characterised as a high-concentration, polycrystalline aggregate for piezoelectric sensing14. However a key limitation of this study is that the piezoelectric response of the film was less than that of glycine single crystals due to the random orientation of glycine crystallites11.
In this work, we will systematically study the effect of crystallisation growth parameters on a number of polycrystalline amino acid films in order to modulate the piezoelectric response and increase the detection sensitivity and voltage output of amino acid-based piezoelectric devices. Moreover, we will investigate and optimise different parameters involved in the polycrystalline film growth and characterise the formed polycrystalline films using Scanning Electron Microscopy, X-Ray Diffraction, and Scanning Probing Microscopy. The study will highlight the potential of low-dielectric, non-centrosymmetric biomolecular crystal films for widespread monitoring of built infra-structure systems by showing how reliably and sustainably they may be used as sensors for pipe structural health monitoring (SHM) applications.

Density Functional Theory (DFT): A tool for rational design of crystalline piezoelectrics

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Accelerating the identification of a biomolecular crystal with an extraordinarily high piezo response is one of the main objectives of our group's research project Pb-FREE. Crystallizing biomolecules creates a network of unit cell dipoles identical to the mechanisms of classical inorganic piezoelectrics, that allows for biological single crystals to easily fulfill the role of piezoceramics. Biomolecular piezoelectric materials are considered a strong candidate material for biomedical applications due to their robust piezoelectricity, biocompatibility, and low dielectric property. A combination of modeling and characterization can provide much-needed insight into how piezoelectric properties are modulated by unit cell properties- dipole moments, molecular packing, and composition. Using automation, computer simulations can make the integration of high throughput screening simpler. We are exploring biomolecular crystals for excellent piezoelectric performance using high throughput DFT computations. It utilizes periodic boundary conditions to simulate bulk material behavior and can quantify material physical properties of crystals, including the dielectric, elastic, and piezoelectric constants. By studying biomolecular crystals this way, the predicted physical properties can be directly related to single crystal experiments, allowing effective screening of organic crystals for experimental investigation.

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From natural products to valuable fine chemicals by crystallization

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Compared to synthetically derived products, natural ingredients are favored nowadays as they are expected to be safe, health-promoting and environmentally sustainable. They include medicinal plants and nutraceuticals such as turmeric and the dragon fruit, which both are subject of our investigation.

Turmeric, a plant used to produce curry spice, has attracted increasing interest due to its many therapeutic effects. It contains three bioactive components, namely Curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). While Curcumin is the most extensively studied of the curcuminoids, DMC and BDMC have not received much attention. Interestingly, studies reveal different biological activities for the individual substances.[1] Due to their structural similarity, and the low content of DMC and BDMC in the ternary mixture, it is still challenging to purify curcuminoids in a large scale and sustainable way. For purification, crystallization is a preferred method but it has rarely been reported in the context of curcuminoids. In previous projects, the separation of Curcumin by a seeded cooling crystallization approach was studied,[2] and BDMC was characterized regarding its various solid-state forms.[3] Our future work will focus on isolating BDMC and DMC via crystallization. DMC characterization, solubility screenings, and phase diagram data act as a basis for defining the crystallization parameters.

The dragon fruit contains many nutrients, seed oils, and natural products such as Betacyanin pigments. Recently, Vietnam has faced an overproduction of this fruit. We intend to reduce food waste and recover the valuable products of the fruit peel by crystallization.
In the contribution, first results of the two projects will be presented.

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Design of Additive Manufacturing for Crystalline Solid Dispersion with Polymorphic Control

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Modafinil (MOD) is an anti-narcoleptic drug prescribed to treat narcolepsy, obstructive sleep apnea, or shift work disorder [1,2]. MOD is commercialized as a tablet under the brand name Provigil®. Manufacturing such type of solid dosage formulation demands multiple unit operations and handling of powders for every stage of the formulation process, which is known to be more challenging compared to liquids. Using liquids or suspensions to manufacture a solid dosage form can circumvent these challenges. This study demonstrates a novel polymer-based solid dosage formulation strategy to obtain crystalline solid dispersion (CSD) for MOD [3]. The 3D printing process consists of dissolving MOD in a saturated solution of methanol – polyethylene glycol (MeOH – PEG) and dispensing it dropwise into a capsule for crystallization by solvent evaporation. By understanding the critical process parameters (e.g., temperature, concentration, evaporation rate, residence time) of the crystallization conditions, the crystallization process and the polymorphic form of MOD can be tuned and controlled. The drug loading was controlled by the number of drops added and measured offline via UV-vis spectrophotometry. The obtained CSDs were also characterized by PXRD, DSC, TGA and Raman spectroscopy. In addition, dissolution and stability studies were conducted following US Pharmacopeia methods. Ultimately, this study demonstrates that thorough understanding of the thermodynamic and kinetic boundaries of an active pharmaceutical ingredient–polymer system leads to polymorphic control in CSDs.

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Amplification of polycrystalline biomolecular piezoelectricity through solution and gas phase crystal growth

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The piezoelectric effect is a property of crystalline materials to generate an electrical potential upon the application of mechanical stress. Piezoelectric sensors, traditionally utilizing perovskite lead zirconium titanite (PZT), find use in industrial and consumer products including medical devices and energy harvesters. Lead free alternatives are desirable but current alternatives focus on ceramics containing niobium, bismuth and barium which come with their own environmental difficulties. Biomolecular materials, i.e., amino acids and peptides have come under increasing interest as alternative materials, possessing many advantages, being biocompatible, biodegradable and ease of fabrication with piezoelectric responses approaching that of PZT (350-550 pC/N). Piezoelectric activity in crystalline materials dependant on the formation of non-centrosymmetric crystalline lattices due to charge separation upon application of mechanical force. With chiral molecules naturally existing in non-centrosymmetric space groups, these exhibit a significant body of potential piezoelectric materials with β-Glycine the first known biomaterial approaching the piezoelectric response performance of PZT.

In this study we focus on the growth of amino acid thin films through the drop cast method and by gas phase vapour deposition with the ability to modulate piezoelectric responses. The piezoelectric response of polycrystalline organic film layers is greatly affected by crystalline morphology, directionality, and thickness of layers. The presence of solvents and additives in the solution phase can have a large impact on the crystal morphology and polymorphism while through our gas phase deposition method we show the ability to control directionality by epitaxial growth. Through close control over crystal growth conditions and use of tailor-made additives, we show the ability to maximise the piezoelectric response for these materials. For example, DL-alanine has been shown to give variable responses between 0 to 80 pC/N. This work demonstrates a significant step forward into the development of green, biocompatible piezoelectric devices with a potentially facile synthetic process.

Preparation, stabilization, and carrier mediated isolation of curcumin nanoparticles

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Aqueous solubility of newly developed pharmaceutical drugs is a crucial challenge to the pharmaceutical industries to bring new drugs to the market. Nowadays, the development of poorly soluble drugs is increasing because of their potential to target specific treatments. Nanosizing of the drug particles is the most efficient formulation strategy to increase the solubility of drugs. In our work, we prepared the stable nanoparticles of curcumin by bottom-up approach. Curcumin is a main ingredient found in the natural spice product turmeric. Curcumin has several potential pharmaceutical properties like anti-inflammatory, antimicrobial, anticancer and anti-HIV. The clinical application of curcumin is limited by its poor aqueous solubility. To enhance the solubility of curcumin, we prepared the stable nanoparticles by self-assembling the curcumin molecules with soluble stabilizer. The size and morphology of the nanoparticles were analyzed using dynamic light scattering (DLS) and transmission electron microscope (TEM). Our experimental results show that we could be able to successfully form the spherical nanoparticles with size ranging from 60 nm to 75 nm. The size stability of particles in the nanosuspension was monitored by DLS over a period of one month and the particles remained stable. Curcumin nanoparticles were isolated from the suspension using carrier particle by filtration method. The nanoparticles were further characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and UV-vis spectroscopy. The dissolution rate of curcumin nanoparticles is increased many folds compared to the commercially available curcumin.

Electric field-assisted microbatch crystallization of lysozyme

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Electric fields have been used to control the protein's crystallization outcomes, such as the crystal size and the number of crystals. Previous studies have demonstrated that electric field-assisted crystallization of proteins results in a lower number and larger size of protein crystals. In this study, we show contradictory results where the application of the electric field on the crystallization of lysozyme using the microbatch under-oil technique has produced a higher number of crystals with smaller sizes. In addition, both positive and negative polarities of high voltage were used, which showed a similar effect with a greater extent when negative voltage was used.

CFD modelling of batch pressurized freeze crystallization

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Objectives

The aim was to develop a model of pressurized freeze crystallization (PFC) by CFD simulation. The pressurized freeze crystallization device consisted of a pressurized jacketed chamber whose geometry and dimensions were taken into account in the CFD calculations.

Introduction

Freeze crystallization process consumes less energy than evaporation process due to the lower latent heat of fusion than evaporation. By utilizing higher pressure, more efficient wastewater treatment process could be achieved due to increased ice crystallization rate. Moreover, this process has potential applications in various industries, such as wastewater treatment, desalination, and concentration of fruit juices. According to experimental data reported in literature, almost instantaneous freezing of water occurred at high-pressure ranges, which greatly affects the efficiency of the PFC. However, the influence of high pressure on ice crystallization kinetics is still largely unexplored (Myint et al., 2018).

Modelling

In this study, the effect of batch time in the freezing behaviour of the fluid is investigated. An enthalpy-porosity technique (Voller & Prakash, 1987) was used for modelling the pressurized freeze crystallization process. This was achieved using a combination of different ANSYS Fluent modules such as solidification/melting. The CFD simulation results showed that the pressure has a significant role in ice crystallization: a pressure increase from 1 bar to 800 bar shortens freezing time from the magnitude of minutes to microseconds, with respect to initial observed ice formation. Experimental results obtained with an IC High Pressure Desalination Technology (IC HPD) device are to be used in the CFD model validation.

Understanding the manufacturability of pharmaceuticals: Real insights from virtual crystals

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The manufacturing complexity of drug products of crystalline small molecule active pharmaceutical ingredients (APIs) is highly dependent on their processability next to stability and dosage form. Processes such as dry or wet milling, granulation and compaction are key unit operations that must be optimized as part of pharmaceutical development. Such optimization, however, usually relies on tedious efforts to obtain accurate experimental data, hence it is very scarce in early development phases when only limited resources are available—in particular, representative quantity and quality of the candidate API.

The intrinsic mechanical properties of an API crystalline solid form are, in principle, fully determined by its crystal structure. Thus, molecular modeling approaches should provide key insights that informs on their developability. The advent of crystal structure prediction (CSP) approaches enables early access to high-quality structures of different potential API polymorphs. As a result, a unique opportunity has emerged to virtually screen and assess the manufacturability of different API forms in silico during early stages of development. Such an approach informs drug development, guides form selection and can be used as a risk-assessment for project planning and resource expenditure.

In this contribution, we will discuss our efforts to establish a flexible modeling pipeline for the computation of energetic and mechanical properties of molecular crystals. We aim to identify which molecular-level descriptors can be correlated with macroscopic manufacturability characteristics, therefore process performance and where modeling results can guide focused experimentation on small amounts of API for validation.

Estimating the Three Characteristic Lengths of Plate-like Particles in Suspension

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The particle size and shape distribution (PSSD) of a powder influences its macroscopic properties, such as flowability, filterability, and compressibility[1]. Needle and plate-like crystals commonly occur in the pharmaceutical industry and present major challenges for downstream processing.

State-of-the-art characterization techniques, such as laser diffraction, focused beam reflectance measurement, or Coulter counter, typically rely on the assumption of particles being spherical, and therefore characterize them with a single size descriptor. Due to their lower symmetry, needle and plate-like crystals require two and three generic length descriptors, respectively, for an accurate size and shape characterization.

For needle-like crystals, both mono and dual imaging systems have been successfully used to obtain the PSSD[2,3]. Thanks to the higher quality of information gathered, dual imaging offers both improved accuracy and reliability.

For the case of plate-like crystals, no commercial device can accurately estimate their three characteristic lengths. Recently, a neural network-based machine learning model built on the information extracted from stereoscopic images has been proposed[4], as an approach to handle particulate systems that require a 3D characterization.

In this contribution, we experimentally validate the aforementioned machine learning model and demonstrate the possibility of an accurate online characterization of plate-like particles to obtain three characteristic lengths, i.e., length, width, and thickness.

Since no analytical standards are available for plate-like particles of different sizes and shapes, we produced populations of custom-designed "LithoPlatelets" through photolithography, (see Figure1a). Several monodisperse population with a wide range of sizes and aspect ratios have been successfully characterized to obtain a 3D PSSD (see Figure 1b), thus proving the applicability of the characterization technique in real world applications[5].

The availability of such an accurate online characterization will enable monitoring, modeling and control of the evolution of size and shape of plate-like crystals.

The figure and references can be found in the supporting information.

Crystallisation Parameter Estimation Using an Autonomous Continuous Flow Platform: A Simulation Study

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Rigorous optimisation of crystallisation processes can be simplified with accurate models of the crystallisation kinetics. Determining these kinetics, however, is an often labour intensive procedure requiring a suite of unique experiments.

To streamline this procedure, an autonomous continuous flow platform is proposed using an MSMPR. A system controller changes the experimental conditions (temperature, initial concentration etc.) to explore the experimental space. Continuous measurements (HPLC, CSD etc.) are recorded and retain transient data for maximum data efficiency, improving parameter predictions. Autonomous continuous flow platforms have been demonstrated to great effect in the chemical reaction engineering field, and to our knowledge, this is the first application in the crystallisation field.

Crystallisation data is generated via simulations from a pre-defined model: simulated experiments. The autonomous continuous flow platform workflow is simulated using ML to 're-discover' the kinetic parameters used in the data generation. The system controller then selects experiments which it predicts will best improve the parameter estimates. System controller algorithms are then compared with respect to parameter estimation accuracy and experimental efficiency. The results aim to help identify the best experimental exploration strategy with respect to parameter prediction accuracy, while also balancing API resource availability.

Solubility of organic salts in solvent-antisolvent mixtures: A combined experimental and molecular dynamics simulations approach

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Solubility is a critical property in the development of crystallization processes, in particular in the pharmaceutical industry [1]. One common method for modifying the solubility and dissolution rates of drugs is through salt formation. However, estimating and tailoring solubility of salts through purely experimental means can be a time-consuming and inefficient process.

Molecular dynamics (MD) simulations have emerged as a powerful tool for studying crystallization phenomena on the atomic scale [2] and can be used to predict the solubility of crystals in a given solution. MD can therefore be used to support and accelerate experimental campaigns.

In our study, we employed molecular dynamics simulations to estimate the solubilities of organic salts in complex growth environments [3]. To predict solubility, we performed simulations of the growth and dissolution of ions at crystal surface kink sites at varying solution concentrations. We determined the solubility as the solute mole fraction at which the energy difference between an ion pair dissolved in solution and the ion pair crystallized at the kink site is equal to zero.

We applied this simulation setup to anhydrous sodium acetate dissolved in various solvent-antisolvent mixtures [3]. We compared our simulations to in-house experiments conducted under moisture-free conditions, given sodium acetate's hygroscopic nature. Our simulations were found to closely replicate the experimental results.

The agreement between the experiments and simulations, as well as the mechanistic insights on the role of the solute ions, solvent and antisolvent provided by the simulations, enable us to complement experimental tasks. This will additionally reduce the time and resources required for designing complex industrial crystallization processes for organic salts.

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Application of Novel BlazePAT for Drug Substance and Drug Product Manufacturing. Multiple Best-in-Class PAT in a Single Probe

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Process Analytical Technology (PAT) has dramatically expanded in capability over the last decade. Today's PAT enables an in-depth understanding of process behaviour on both macroscopic and molecular levels, allowing users to accurately track the impact of process variables on system behaviour. Whether in a reactor, a continuous flow line, or a filter/dryer, kinetic mechanisms such as nucleation, growth, breakage, agglomeration, and "oiling out" play a major role in downstream drug product manufacturing. Using next generation Blaze PAT, these mechanisms are understood in real-time such that they can be related to final crystal morphology, surface, size, and structure, which ultimately drive downstream processability. The application of PAT to these downstream efforts presents new opportunity for deeper process understanding and control through further steps of the drug product cycle.

In this talk, we will review the enabling improvements to the PAT landscape as they relate to drug substance and drug product manufacturing. In particular, the application of particle focussed Raman spectroscopy and novel, in-process particle generated polarization and provide examples of how those improvements deepen process understanding, speed process development and in some cases enable new paths to process optimization in common applications such as crystallization and fluidized bed granulation.

CrystalGrower: Dialing Up Particle Design

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Particle shape engineering is a fundamental part of any industry that requires the use of solid matter, whether that be pharmaceuticals, materials, energy etc. Therefore, understanding how to manipulate the shape of particles on a molecular or intermolecular level would provide a level of control that would be hard to understand without knowing the behaviour of the building blocks that make up the particle. Here, the power of CrystalGrower is showcased by predicting all possible morphologies of a crystal structure, along with growth and dissolution rates, effect of impurities and screw dislocations. Thus, providing the user the knowledge to design and control the desired properties of their crystals. The CrystalGrower software utilises a 3-Dimensional kinetic Monte-Carlo model that uses free energy of crystallisation (ΔGCryst) as a probability of growth and dissolution of growth units. CrystalGrower can be used in simulating and predicting the growth of many different types of crystal systems, ranging from molecular or ionic to framework systems such as zeolites and MOFs.1,2 In this talk I will be discussing the many different uses CrystalGrower has in particle design from molecular systems to zeolite frameworks. These include the uses in the pharmaceutical industry and the building of zeolites to optimise their capability.

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Digital Design of Crystallization Process: The potential value of moving from concentration to activity driven crystallization kinetics

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One of the major technological processes in the pharmaceutical industry is crystallization. Kinetics of crystal nucleation and growth represent the main controlling factors in crystallization processes. Both primary nucleation and crystal growth strongly depend on the thermodynamics driving force, the supersaturation. Hence, to have an accurate description of the crystallization process we need to accurately express the driving force.

The supersaturation is defined as the difference in chemical potential between the solute in the supersaturated solution, and the solute in the saturated solution. Since the chemical potential might be defined in terms of the activity coefficient, we refer to this approach as the activity-driven kinetics.

To evaluate the chemical potential as well as the activity coefficient in a supersaturated solution might be challenging due to the non-equilibrium conditions [1-3]. Therefore, the difference in chemical potential is often approximated to a ratio between the difference in concentration of the solute at saturation and the actual concentration in the supersaturated solution. We referred to this approximation as the concentration-driven kinetic.

The aim of this work is to investigate the impact on the crystal growth when changing the crystallization kinetics from concentration-driven to activity-driven. We use the group contribution approach SAFT-γ Mie equation of state [4-5] to evaluate the difference in chemical potential between the equilibrium and non-equilibrium states.

Using experimental data on the growth rate of ibuprofen in ethyl acetate, we developed two models considering concentration-driven and activity-driven kinetics and predict the ibuprofen growth rate in other solvents (see Figure 1).

The model developed using the activity-driven kinetics demonstrates higher transferability and robustness than the concentration-driven model. In fact, by considering the activity-driven kinetics with the difference in chemical potential we are able to capture solvent effects, resulting in an improvement of the estimation of the crystal growth kinetics.

Computer Vision-Assisted High-Throughput Screening of Surfactants for Crystal Morphology and Powder Properties Optimization

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Solution crystallization is an important technology for chemical separation and purification, and more importantly is used in recently years for crystalline product refining and functional regulations such as optimizing crystal size, morphology, and controlling crystal polymorphism. The optimization targets of the crystals usually prefer large size with regular morphology and narrow size distribution to avoid potential risks such as agglomeration, solvent residue, encrustation and low efficiency in downstream processing stages. It is reported that trace amount of additive may effectively impact crystal morphology and inhibit agglomeration etc. While the additive screening using traditional batch crystallization method requires high amount and tedious screening experiments, which is material- and time-consuming. To address this challenge, we propose a computer vision-assisted high-throughput additive-screening system (CV-HTPASS) composed of a 24-well crystallization plate, imaging device, and deep learning-based image analysis model. In this study, succinic acid (SA) was chosen as model compound due to its various morphology outcomes in industrial crystallization processes. Using the CV-HTPASS, high-throughput SA crystallization experiments with 12 surfactants and 4 concentration conditions were performed, then in-situ optical microscope images captured four different morphologies of flake, bulk, rod, and needle structures with varying sizes. By intelligently analyzing large amounts of information on SA crystals, such as the percentage of each crystal morphology, sizes, and aspect ratios, suitable additives are screened efficiently. The results of scaled-up crystallization experiments demonstrate that the SA crystal products under the optimized conditions exhibit satisfactory bulk morphology, reduced agglomeration, and improved powder properties. Finally, scaled-up experiments verified the consistency and feasibility of the intelligent high-throughput additive screening method. In conclusion, this unique and effective CV-HTPASS offers a promising guidance and enabling platform technology for quantitative surfactant screening and crystal morphology optimization in industrial crystallization process development.

Separation of bis(2-hydroxyethyl) terephthalate from ethylene glycol for a simplified PET bottle-to-bottle recycling concept

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Recycling plastics is one of the most pressing issues today, not only to avoid environmental pollution but also to conserve natural resources. Plastic bottles made of poly(ethylene terephthalate) (PET) offer a great opportunity due to the purity of the material and the absence of additives. Although PET bottles are generally a very clean material, many processes in the past have not succeeded in obtaining a sufficiently large quantity of PET of the required quality.

This project now aims at bottle-to bottle recycling of PET by glycolysis. Waste PET is depolymerised in the presence of ethylene glycol at about 190 °C, producing bis(2-hydroxyethyl) terephthalate (BHET) as the main product. To achieve the BHET quality required for PET production, purification is recommended, which includes filtration and recrystallisation steps. After glycolysis, BHET can be crystallised by cooling the ethylene glycol solution. On a laboratory scale, the solubility of BHET is further reduced by the addition of water. However, an industrial process would require the subsequent separation of water and ethylene glycol, which is one of the most energy-intensive processes in chemical engineering.

As an alternative route, the direct crystallisation of BHET from ethylene glycol is investigated in this work. A BHET solution is cooled from 40 to 0 °C at different cooling rates, reducing the concentration from 80 to 10 g/kg solution. Crystallisation is accelerated by seeding. The experimental data are used to model the crystallisation process in gPROMS. The model will be used to make assumptions for an industrial process in terms of the space time and the optimal initial BHET concentration. Another important aspect is the consideration of the ethylene glycol viscosity, which changes by several orders of magnitude in the temperature range of an industrial process and could have a strong influence on the final properties of the slurry.

A Machine Learning Based Automatic Crystal Measurement and Growth Analysis

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In this work, we present a novel approach for automating the measurement and growth analysis of crystals using machine learning techniques. The traditional manual methods of measuring and analysing crystal growth are time-consuming and prone to human error. Our proposed system utilises an established machine learning method, Mask-RCNN, to automatically detect multiple crystals from images captured either by a microscope or from an in-process flow. We also implement a method for fitting a 2D polygonal shape, with opposite sides' parallel, to the image boundary of the detected crystals By tracking the changes in crystal size and shape over time, we can perform growth analysis and derive insights into the underlying crystallisation processes.

Our system was evaluated using a dataset of images captured during the growth of β-LGA crystals. The results indicate that the approach achieves high accuracy in detecting and measuring crystals and allows the user to analyse the growth rates of crystals with ease. Moreover, our approach significantly reduces the time and effort required for crystal measurement and growth analysis, enabling more efficient and accurate studies of crystal growth.

Our proposed system provides a reliable and efficient method for automating crystal measurement and growth analysis. The system's ability to detect crystals using machine learning and to fit a shape model to the crystal boundaries, provides a powerful tool for understanding the complex mechanisms of crystallisation.

The Effect of Particle Shape on Packing Structure for Elongated and Flat Particles: Experiments and Simulations

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The performance of filtration processes downstream of a crystallization step is affected by the filter cake resistance, which is determined by the cake structure. The packing structure of an ensemble of particles is affected by material properties, the physical environment, and the particle size and shape distribution. The latter is thought to be the most significant factor[1].

Previous works relating particle shape to packing structures have considered a variety of relatively equant shapes[2,3], and elongated particles[4]. Despite the progress, several challenges still exist, including the consideration of plate-like shapes and their experimental validation.
The goals of this work are two-fold. First, the development of a model capable of predicting the packing structure for populations of equant, elongated, plate-like particles, and everything in between. Second, the systematic experimental investigation of the effect of shape on packing for all the aforementioned shapes.

To address the first goal, we develop a Monte Carlo model to simulate the formation of a pile of particles. The settling process is simulated through stochastic, preferentially downwards, movements of particles. We simulate several populations that exhibit a wide range of shapes (see Figure 1).

To address the second goal and to validate the trends observed in the Monte Carlo simulations, we produced 3D-printed particles to match the simulated ones. These particles were poured into containers and imaged with a medical computed-tomography scanner[5]. From the tomographs, metrics such as the overall void fraction of the packing, vertical and radial porosity profiles, particle orientations, and the tortuosity of paths through the packing were extracted.

In both experiments and simulations, we observe a significant dependence of packing behaviour on the particle shape. More importantly, we have a good agreement between the model and the experiments, thereby facilitating the prediction of packing structure of ensembles of irregularly shaped particles[6].

Effect of Particle Size and Shape Distribution on Filterability of Crystal Populations

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The particle size and shape distribution (PSSD) strongly affects filterability1. However, the exact quantitative link between the two has not yet been established. The filter cake resistance depends on the cake structure, and intermediate to achieve this goal is to predict packing structures based on a PSSD. This was investigated in a previous work by developing a predictive model trained on millimeter-sized 3D-printed particles2. Despite the PSSD being the biggest factor in determining packing structure3, other factors like crystal material properties, fluid environment, and scale also play a role. Therefore, micrometer-sized crystals packed during filtration will exhibit different a packing behavior than their millimeter-sized analogue. Additionally, even if the packing structure is known, the filter cake resistance cannot be directly inferred from that. The aim of this study is to investigate the link between the PSSD of crystal populations and their filterability.

For this purpose, populations of needle-like β L-glutamic acid and plate-like adipic acid are prepared through various processes, resulting in a wide variety of populations with different aspect ratios, dispersity, etc. The crystal populations are characterized using two independent offline and online characterization devices capable of measuring the lengths, widths, and thicknesses of thousands of crystals5,6.

Subsequently, these crystal populations are filtered and washed with both vacuum and pressure filtration at various constant pressures. During washing, the filtrate flowrate is tracked to calculate the resistance of the filter cake (see Figure 1 for 2D PSSDs of crystal populations and the height-normalized filter cake resistances αh). The information from these experiments can be used to build a model to obtain the filter cake resistance using population characteristics such as the average sizes, aspect ratios, or fraction of fines.

The ability to predict filter cake resistances will enable better design and control of the production chain of crystalline powders.

Fight off the metastable form with in silico modelling

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As part of the ongoing development process of a drug candidate molecule of Gedeon Richter Plc, our task was to design a new crystallization process. Our goal was a robust technology for the production of the Form I polymorph of this API. Several polymorphic forms of this material are already known, but the two relevant to the development of the process are polymorphs Form I and Form II. Although Form I is the thermodynamically stable form, the kinetically favoured one is Form II in all investigated solvent systems.

Because of the already capital-intensive synthesis of the API, it was not an option to produce Form I with low yield. A suitable solvent for a cooling crystallization with adequate yield had not been found, so we had to opt for an antisolvent crystallization process which unfortunately promotes the formation of the metastable Form II polymorph in general. Seeding with Form I seeding crystals was inevitable, but identifying the seeding point, and the elaboration of an antisolvent dosing profile which does not yield Form II in the product just Form I proved to be a challenge. The information provided by the in-line probes (solubility curves) was indispensable. With the use of the API concentration data measured by the IR probe and offline measured PSD data, we could start a project for a model building and the estimation of the kinetical parameters of the crystallization using MATLAB software. Using this model and its identified parameters we could do the optimization of the dosing profile and the process in silico, which has saved us many working hours, many grams of API and solvents as well.

Improving the Process Performance of Continuous Crystallization of L-Glutamic Acid through Theory and Experiments

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In this work [1], the crystallization of two L-glutamic acid (LGA) polymorphs is carried out in a continuous process [2-4], and its performance is evaluated according to different key performance indicators. The study aims at identifying suitable operating conditions for producing either αLGA or βLGA with high polymorphic purity, yield and productivity. To this end, we investigate the process both from a theoretical perspective and through experiments using either a single stirred-tank crystallizer or a cascade of two stirred-tank crystallizers in series. In terms of theory, we extend the steady-state stability analysis of Farmer et al. [4] developed for a mixed-suspension mixed-product removal (MSMPR) crystallizer, by accounting for the possibility of a non-representative withdrawal of the solid phase from the crystallizer, as established in our previous work [5]. Additionally, the process is simulated using population balance equations, solved numerically [6].

Guided by the model-based conclusions, suitable operating conditions were identified and tested experimentally. The experimental campaign has demonstrated that βLGA can be successfully and continuously produced in both process configurations (single crystallizer and cascade) in good agreement with theory and simulations, whereas the same was not possible for αLGA. The difference between the two cases is the heavy agglomeration of prismatic αLGA particles, making it difficult to suspend and effectively withdraw them from the crystallizer. Conversely, needle-like βLGA particles exhibit no agglomeration, but tend to be slightly oversampled (i.e., the withdrawn suspension density at the outlet is higher than the suspension density inside the crystallizer). This consideration represents not only an interesting outcome, offered by both experiments and simulations, but at the same time also a conclusion, which enables a more realistic understanding of a continuous stirred-tank crystallizer, and thus opens additional opportunities in process intensification.

Continuous deracemization of the solid-phase via temperature cycles in a tubular crystallizer: A simulation-based study on conglomerate forming compounds

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Separation of enantiomers is of paramount importance in the pharmaceutical industry due to the differences in therapeutic activities. Crystallization process with various configurations is shown to be an attractive means for the separation of the enantiomers. In particular, it has been shown that in the presence of liquid phase racemization, temperature cycling can lead to complete chiral resolution [1,2]. Several simulation and experimental studies on the mixed suspension mixed product removal crystallizer (MSMPRC) configurations are reported in literature [2]. There are also some experimental studies that demonstrates the effectiveness of the tubular crystallizer with spatial temperature cycles achieving complete chiral resolution [3]. However, there has been no simulation-based studies on tubular crystallizers.

In this study, a population balance-based model is used to describe the crystallization of a conglomerate forming chiral compound with liquid phase racemization in a tubular crystallizer. Spatial temperature cycle is applied along the length of the crystallizer so that the crystals are subject to growth and dissolution cycles. The supersaturation in the crystallizer is maintained at a very low level to supress the nucleation. Fresh feed to the crystallizer is a slurry containing racemic solution. It has been found that after about 20 hours the enantiomeric excess (ee) reaches the steady-state value of 1.0. The results are also compared with MSMPRC with equivalent temperature cycling in time domain for which the ee reaches an average value of 0.87. Moreover, the productivities are found to be 3.15 and 1.34 g/(kg solvent-h) in the tubular crystallizer and MSMPRC, respectively. Further studies will be carried out to investigate the effect of initial ee, residence time etc on the product crystals.

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Reactive Crystallisation of Benzaldehyde Sodium Bisulfite

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Bisulfite addition is a commonly used reaction in the purification of aldehydes and reactive ketones in organic synthesis [1]. This is done through reactive crystallisation or precipitation, where the reaction product is the only species to exceed the solubility of the system and drops out of the solution as a recoverable solid [2]. The bisulfite addition reaction specifically involves a nucleophilic attack of the carbonyl carbon of an aldehyde or reactive ketone by a bisulfite ion, creating an aldehyde bisulfite adduct (Figure 1). Whilst the addition reaction is well-characterized in literature [3-6], there is little known about the crystallisation and solid-state information (solubility, crystalline structure). In this work we develop a fundamental understanding of benzaldehyde sodium bisulfite crystallisation in order to facilitate designing crystallisation processes for aldehyde sodium bisulfite adducts. Benzaldehyde sodium bisulfite can be rapidly produced by mixing of benzaldehyde in an organic solvent (such as ethanol) with an aqueous solution of sodium bisulfite, which results in reactive/antisolvent crystallization of the adduct. This work will address relevant liquid-liquid and liquid-solid equilibria, including solubility of benzaldehyde sodium bisulfite as a function of temperature and solvent composition in ethanol-water mixtures; solid state characterization, including determination of the adduct crystalline structure; selection of process analytical technologies for in-situ process monitoring; as well as preliminary crystallization process design

Digital design of a robust continuous crystallization process: Using mechanistic modelling tools to minimize material requirements at the R&D stage

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Crystallization is a key unit operation in the isolation of many active pharmaceutical ingredients. The crystallization process commonly has a significant impact on the quality of drugs and the efficiency of downstream processes, including filtration, milling, and drying1. One of the key challenges in industry is the integration of Quality-by-Design methods when designing unit operations and processes. Continuous crystallization is seen as a means of achieving that by reducing process costs and maximizing operational efficiency2. The aim of this work is to enhance and redefine a continuous crystallization workflow by implementing a mechanistic modelling approach at an earlier stage and a smaller scale of observation to limit material used for experimental data gathering, yet allowing for the development of continuous crystallization processes.

A recent study demonstrated the use of a systematic, science-based workflow that aims to counter the uncertainty in crystallization processes by reducing the risk from an early stage. This allows for the development of robust and consistent continuous crystallization processes2. The same workflow has been modified for this work to incorporate modelling tools and enable for a reduction in material consumption and time spent performing lab-scale experiments for solvent screening and crystallization (Fig. 1).

Experimental data from an initial solvent screen and a final mefenamic acid and diglyme-water system was collected from a series of micro-scale experiments (Crystalline from Technobis Crystallization Systems). The results were subsequently used to calibrate a mechanistic crystallizer model. The solvent screen predictions showed some differences to the experimental results, however the final predicted solvent ranking matched the experimental ranking. The crystallizer model was shown to provide a good prediction of the crystallization behaviour, particularly the final product particle size. A design space exploration was then conducted to understand the key process parameters that affect both the product particle size and the yield.

Impurity Removal during Filtration and Washing – A Mechanistic Modelling Approach

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The pharmaceutical industry is starting to adopt continuous active pharmaceutical ingredient (API) manufacturing in order to reduce production costs, improve manufacturing flexibility, and improve sustainability. To facilitate the transition, digital design tools are being adopted to enable design space exploration, optimal and robust performance. This work focuses on the development of a mechanistic model-based workflow for the optimization of an integrated filtration and washing model, with a view to minimize impurities.

A Carman-Kozeny filtration model is integrated with custom diffusion within an axial dispersion washing modelling approach. To effectively track impurities in the cake, the wash model considers dissolution of the solid phase. The integrated modelling tool uses information on the product crystal suspension characteristics to predict filtration time, filtrate flow rate, and the composition of the filter cake and filtrate generated during filtration. The washing of the wet filtered cake is then simulated to predict washing efficiency.

Mefenamic acid and paracetamol were selected as representative test compounds. Three different crystallization solvents were used for mefenamic acid and for paracetamol, with relative structurally related impurities derived from synthesis.

The objectives included the following:

1. Identify the product purity reached with a fixed wash ratio.
2. Optimize process conditions to minimize impurity content in the isolated cake.
3. Predict the potential risk of particle dissolution during washing steps

A model validation approach was used to estimate cake properties (specific cake resistance, cake volume, cake composition after washing, washing curve). The data used for validation was generated via small-scale batch pressure filter experiments. Subsequently, the validated model was used to explore the design space and identify critical process parameters. The optimization problem was then configured to reduce the impurity concentration in the final cake after washing. The findings from this were translated to a final model to simulate the optimal operating point.

Application of Eutectic Freeze Crystallization in Recycling of Lithium-ion batteries

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Different types of Li-ion batteries (LIBs), based on different cathode materials, have been designed for various applications. One of the most common cathodes in Li-ion batteries is lithium nickel manganese cobalt oxide (NMC). Several of these metals are valuable and/or associated with a critical status, most notably cobalt. Thus, a lot of work has focused on developing processes to recover these metals in recent years (Wang et al., 2019).

In the recycling of LIB the batteries are first crushed and processed into so-called black mass. The most common hydrometallurgical process routes to recover Ni, Mn and Co from spent batteries are based on sulfuric acid leaching of the black mass (Ma et al., 2022). In the final stages of such processes, Ni, Mn and Co sulphate hydrates are often crystallized by evaporative crystallization. However, the process requires a lot of energy. A possible replacement is eutectic freeze crystallization (EFC), a cutting-edge technique. In the EFC process, operated at the eutectic point, ice and salt crystallize concomitantly. The solids can then be separated based on differences in density compared to water (Randall et al., 2011).

The present work looks at the potential to use EFC for the recovery of nickel and cobalt from Ni-Co-water mixtures, and at the possibility to further purify the product through recrystallization into lower-order hydrates. The eutectic point of nickel and cobalt has been investigated for different concentrations of compounds in the ternary system nickel, cobalt, and water. The salts produced via EFC are mainly higher order hydrates. Transformation of metal sulphate heptahydrates, obtained by EFC, into hexahydrate salts at elevated temperatures has been investigated. Experimental transition temperatures have been compared with temperatures obtained by modelling (using the software OLI stream analyzer), and the kinetics of the transformation process at different operational temperatures and driving forces evaluated.

Vivianite crystallization for Phosphorus recovery from digester supernatant in wastewater treatment plants

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It has been discovered that the supernatant resulted from the dewatering of the digester sludge in wastewater treatment plants (WWTPs) contains significantly amount of both phosphorus (P) and iron (Fe), and furthermore the ferrous cation (Fe2+) is the predominant Fe fraction due to the reduced condition in the anaerobic digestion. For the recovery of P from such digester supernatants, crystallization of vivianite ($Fe_3(PO_4)_2 \cdot 8H_2O$) might be the most feasible process compared with the recovery route of struvite and hydroxyapatite since the solubility of vivianite is extremely low at pH > 7. However, a particular challenge lies in the small/fine particle size of the produced vivianite during the process, affecting the overall recovery potential and further downstream processing. Very few works have been done to investigate the crystallization mechanisms of vivianite.

To understand the vivianite crystallization, our previous work investigated the metastable zone width of the vivianite system, which was found very narrow under the studied operating conditions. Therefore, it was found difficult to control supersaturation to promote crystal growth and hence, to produce larger particles of vivianite. We have developed a multi-stage cascade crystallization process for crystallizing vivianite from digester supernatant, and we have found that the growth of vivianite particles could be promoted to a certain degree, however, it is difficult to produce the particles with the size larger than 100 µm. Thus, in the present work we will investigate the feasibility of using membrane crystallization to produce vivianite with optimal particulate properties. The effects of different parameters including the concentration of the ferrous ion, and the flowrate of the ferrous solution, on the particle size distribution of vivianite will be investigated with different membranes. The obtained results will be used to design and optimize a membrane crystallization process that can produce vivianite with preferred particulate properties.

Production of sustainable soda ash: crystallization in Na2CO3-NaOH-H2O system

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Half of the worldwide soda ash (Sodium carbonate) is produced by the Solvay process, which emits significant amounts of fossil CO_2 and generates waste streams containing potentially hazardous substances. The CODA (Carbon-negative sODA ash plant) research project aims to replace this conventional process by a new environmental friendly process. In the CODA process, NaOH solution and CO_2 (directly absorbed from air) react to Na_2CO_3 to provide the feed composition for crystallization. The required NaOH will be generated by electrolysis of rock salt brine using renewable energy from wind and solar power plants1. As a particular challenge the generation of renewable electricity, the absorption of CO_2 directly from air, and consequently the obtained feed composition for crystallization would depend on the weather conditions.

Based on the solid-liquid equilibria (SLE) data of soda ash in the Na2CO3-NaOH-H2O system e.g. 2, possible crystallization strategies are evaluated with respect to their mass and energy balances to identify the most economic process version. These strategies integrate the absorption process of CO_2 from air into the crystallization of soda ash and downstream processes, which should also assure the target product (anhydrous Na_2CO_3) quality with regard to crystal size, bulk density, and purity.

Accordingly, crystallization of $Na_2CO_3 \cdot 10H_2O$ (as an intermediate product) and $Na_2CO_3 \cdot 1H_2O$ by cooling and vacuum evaporation are promising in terms of energy. Besides, in the day-night cycles crystallization of $Na_2CO_3 \cdot 10H_2O$ can already occur in the CO_2 absorber.

In the conference contribution recent results in crystallization process design including SLE and growth kinetics studies are presented.

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One-pot hydrothermal transformation of seashell calcium carbonate waste to apatite and doped-apatite particles

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Waste seashells from the fishery industry represent an important environmental issue. Its valorization by transforming the $CaCO_3$ into apatite micro/nanoparticles may have a positive environmental impact besides economic profitability since the global apatite market is expected to grow at 6.5% to around USD 3.085,00 million by 2027. Many of methods to transform biogenic $CaCO_3$ into apatite particles are two-step processes involving calcination to CaO at 900-1000 °C followed by titration with a phosphate reagent (typically H_3PO_4). Here we present a one-step hydrothermal method using oyster shells of the species Crassostrea gigas as model raw material. Shells were treated with NaClO 5% v/v, crushed, milled, and sieved (Ø<45 μm mesh), before submitting to hydrothermal conversion. Firstly, we explored the influences of KH_2PO_4 and K_2HPO_4, P/Ca molar ratios (0.24, 0.6, and 0.96), and temperature (25-200°C) in the transformation process. The minimum temperatures to obtain full transformation when using KH_2PO_4 and K_2HPO_4 for P/Ca molar ratios 0.6 (stoichiometric) were 160 ºC and 120ºC respectively, while for P/Ca ratios 0.96, they were 120 ºC and 80 ºC. The precipitates (Mg-doped carbonated-apatite micro/nanoparticles) are the result of a dissolution/re-precipitation mechanism driven by pH variation. Secondly, we explored the influence of osteogenic ions Mg(II), Mn(II), and Co(II) at P/Ca molar ratios of 0.6. Full transformation of $CaCO_3$ was obtained at 160 ºC, yielding platy-shaped apatite nanoparticles doped with either 0.22 mol% Mg, 0.012 mol% Mn, or 0.16 mol% Co, and sizes within the range 75-90 nm. Compared to the previous two-step processes, the one reported here is straightforward, one-pot, easy to scale up, and can be operated at relatively low temperatures without any pH adjustment.

Data Mining-Enabled Process Design and Operation for Second Order Asymmetric Transformation: Advancing the State-of-the-Art

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Improving the flexibility and capabilities of pharmaceutical technologies and lowering the process development time while satisfying regulatory constraints translate to highly desired resilient supply chains. Generating and validating the necessary knowledge in-silico before experimentation or plant-scale intervention with minimized human implications is the dream this paper aims to contribute to. The idea is demonstrated through the case study of particle size-controlled second-order asymmetric transformation of enantiomers (SOAT), a crystallization and racemization-based resolution technique. The fundamental processes of crystallization, dissolution, fragmenation and racemization separated in time (dissolution vs. crystallization) and space (crystallization vs. external wet mill) form a complex network, which is difficult to predict. Integrated wet milling is proposed in this study for SOAT, which is promising technology but has limited general, and no SOAT-specific operation experience. Hence, a suitable engineering tool is developed to solve this challenging design problem. The developed computational framework has three steps: (1) skilled scientists draft potential technologies to solve a well-defined problem; (2) all alternatives are modeled with high fidelity first principle models, followed by high throughput parametric optimizations (3) data mining is deployed to extract key information from the synthetic database of optimal solutions and take the effectiveness of process design and operation to the next level. In this work, population balance-based models were applied to describe the crystallization, fragmentation, and chemical reaction in the crystallizer and wet mill. The wet mill is modeled with a cascade of three mills (e.g., IKA MagicLab). The efficient implementation enabled the execution of nearly 1300 global multiobjective process optimizations. Carefully trained classifiers reliebly predicted the with or without milling and with or without T-cycling decisions (AUC score exceeding 0.85). Regression methods estimated the product property profile with Pearson coefficients over 0.95. The results agree with the existing SOAT literature, but some conclusions point beyond the state-of-the-art.

Experimental and Computational Understanding of Template-Assisted Crystallisation of Peptides: Case Study of (Poly)glycine

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Crystallization 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. Increasing demand for high product throughput led to the development of quick, efficient, and controlled nucleation processes using external stimuli such as templated nucleants. The template-induced nucleation works by attaching the drug to the surface of the template resulting in faster crystallisation and reducing the need for higher supersaturation. Template nucleation could be subdivided into soft-template and hard-template induced nucleation, depending on the ability of templates to dissolve or not in the crystallising solution. This study demonstrates that using the hard template (glass beads) with functional group complementarity to the nucleating solutes (glycine, diglycine, and triglycine) resulted in a 2-4-fold acceleration in the nucleation rate of crystallising solutes. In addition, experimental data suggest that the presence of templates did not dramatically influence the interfacial energies of glycine, diglycine, and triglycine, but instead increased the pre-exponential factor by at least 2-fold. This study led to the development of templated crystallisation, wherein two factors were identified. Firstly, hydrogen bond complementarity between the template surface and nucleating solute, and secondly, the extended lifetime of adsorbed compounds, created from the adsorption of single molecules or small clusters. This phenomenon was further explored using Molecular Dynamics simulation suggesting that larger molecules exhibit faster nucleation in the presence of glass beads due to an increased number of interactions (Figure 1b) as observed with the longest hydrogen bond lifetime for triglycine, followed by diglycine and glycine, as seen in Figure 1a. Hence, templated nucleation is potentially a smart approach to enhance/improve the crystallisation of peptides.

The effect of size, shape and the number of suspended crystals on scale formation dynamics

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In suspension-type cooling crystallization, crystallization on the cooling surface, namely scale formation becomes a serious problem. Many of the previous studies have reported the effect of supersaturation, chemical interaction between the surface material and crystal component, or the geometrical structure of the surface on scale formation. The author has reported that the dynamics of scale formation during the start-up operation in melt crystallization of organic compound. In addition, the author has reported that the shape of suspended crystals can affect the dynamics of scale formation in seeding crystallization. This present study focuses on the effect of characteristics of suspended crystals such as size or shape, and suspension amount in terms of the number of suspended crystals on scale formation and the deposition of suspended crystals during suspension crystallization. Melt crystallization of ethylenecarbonate containing 5 mass% of water was carried out under the several seeding conditions to clarify how the characteristics and the suspension amount affect scale formation and to suggest the seeding conditions to mitigate scale formation and enhance the deposition of suspended crystals. The experimental results showed the following three things in early stage of scale formation: (i) The seed crystals having large size in the major axis direction lead to rapid linear growth rate of scale layer. (ii) The seed crystals having high aspect ratio (AR) lead to rapid linear growth rate of scale layer. (iii) The large number of seed crystals lead to rapid linear growth rate of scale layer. Therefore, it was found that small size (in the major axis direction), small aspect ratio (AR), and the appropriate number of crystals might be preferred for suspension cooling crystallization to suppress the linear growth rate of scale layer and enhance/improve the deposition of suspended crystals.

Crystallising natural products using nanolitre-scale high-throughput crystallisation protocols.

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Natural products are a rich source of inspiration for the development of new medicines. Natural products and their derivatives have been used to treat a host of diseases and conditions, such as, cancer, heart disease and infection.[1, 2] In fact, more than 50 % of small molecule drugs approved for use in the United States between 1981-2019 were derived from natural products or semisynthetic derivatives.[2] However, absolute structure determination of new bioactive molecules – an essential step in the development of a clinical drug – remains a time-consuming practical impediment. Therefore, methods to increase the speed at which the absolute structure of a natural product can be solved must be developed to alleviate this "bottleneck" in the discovery process of clinical compounds.

Herein, we report the successful deployment of a new crystallisation approach to rapidly access crystals of complex organic molecules that are otherwise challenging to crystallise. Using encapsulated nanodroplet crystallisation (ENaCt) protocols, a significant number of natural products have been crystallographically characterised (Figure 1).[3] Numerous natural products, which were only supplied on the milligram scale, have been unambiguously confirmed structurally by single crystal X-ray diffraction analysis, both at Newcastle University and through collaboration with the UK National Crystallography Service and Diamond Light Source. ENaCt protocols have been shown to succeed where traditional crystallisation methods have previously failed.

Figure 1. Examples of compounds crystallised using ENaCt protocols.

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Development of Continuous Nucleators

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Consistent seeding is crucial to industrial large-scale crystallisation, where processes are often designed to be seeded with a specific number of seed crystals of a desired solid form with a particular size. However, maintaining a consistent seed pot is potentially a time consuming and labour-intensive process. Nucleators, devices that can be used to generate crystal suspensions with a targeted particle size and solid loading, provide an attractive prospect to reduce this burden.

In order to be viable for seeding, we aim to generate a suspension of small particles (< 100 μm) of the required solid form with a suitable solid loading (solid volume fraction 0.01 – 0.05). To produce such a suspension in a convenient time frame, it is necessary to achieve high nucleation rates within the nucleator device, and so methods to enhance the primary nucleation rate may be required. To facilitate the development of a nucleator platform, this work aims to develop small-scale screening protocols to allow suitable conditions to be identified that will achieve the rapid nucleation rates required for a range of different crystallisation methods while using minimal amounts of starting material.

We have investigated approaches designed to quickly assess the nucleation and growth rates in order to identify rapidly nucleating crystallisation processes on the mL scale, including rapid mixing of solution and antisolvent; combined cooling and antisolvent crystallisation; quench cooling crystallisation; and crystallisation enhanced by high fluid shear. We will present results for range of different API systems as case studies to demonstrate how these approaches can be used to identify suitable conditions to generate seeding suspensions with the desired attributes, speeding up process development for a nucleator device with minimal material consumption.

Optimization of particle breakage during combined crystallization-wet milling – A Mechanistic Modelling Approach

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The pharmaceutical industry is starting to adopt continuous active pharmaceutical ingredient (API) manufacturing in order to reduce production costs, improve manufacturing flexibility, reduce infrastructure costs, reduce manufacturing lead time (from typically 6 months to 10 days) and to improve sustainability. To facilitate the transition, digital design and modelling are being adopted to aid in exploring the design space and study the optimal performance of important unit operations such as crystallization and milling. The combination of crystallization and wet milling processes is an increasingly studied area of pharmaceutical manufacturing and presents several benefits for industrial application[1][2]. However, given the complex interplay of crystallization and wet milling mechanisms, there is a need for mechanistic understanding and modelling to control the particle attributes through identifying the important controlling parameters.

The focus of the work reported here aims to decouple and better understand the mechanisms involved in a combined cooling crystallization-wet milling process. Carefully designed lab-scale experiments were performed in stages to isolate the rate processes; nucleation, growth and breakage from the combined process. This informed the development of a population balance model which captures and estimates the effect of both crystallization and milling mechanisms in a single intensified unit operation to predict the particle size. In detail, this work focuses on the development of a mechanistic model-based workflow for the optimization of an integrated crystallization and wet milling model, with a view to parametrize the breakage kinetics as well as optimize the milling performance. Results from model validation showed that with the dataset used for modelling, the model was able to effectively estimate the crystallization and wet milling breakage performance. These kinetic estimations were used to understand the design space and optimize the process.

Crystallization of Battery Grade Lithium Hydroxide Monohydrate – Challenges with regards to purity

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Driven by the EV (electric vehicle) revolution and the increasing demand for energy storage capacity the global need for battery-grade lithium compounds, namely $LiOH \cdot H_2O$ and Li_2CO_3 is steadily increasing, and even a shortage in supply chain is expected for the upcoming years.

Up today the term "battery-grade" is not well defined by international norms or standards and is defined individually by the relevant producers of lithium products.

Thereby, and this is in contrary to other bulk chemicals, the focus is set to individual impurity species instead of defining three, four or even five nines for the product purity.

On the one hand, the limits for common impurities like sodium, potassium or sulfate were steadily lowered during the last years and expectations of less than 20ppm are not unusual today anymore.

On the other hand, the list of impurities to be considered steadily increased and species like borates and silicates emerged. Furthermore, impurities like nickel, cobalt or copper are to be taken into account which is mainly related to future battery recycling industry.

GEA has an advanced toolbox for the industrial crystallization which, in combination with the sophisticated in-house laboratory, creates confidence for customers that the expected product purity in combination with high yields can be achieved. This toolbox including some examples will be presented and discussed.

An impression on challenges for the analytical work will be touched as detection limits of well-established analysis methods partly exceed defined impurity concentration limits in the $LiOH \cdot H_2O$.

Crystallisation DataFactory: Cyber-Physical Infrastructure for Digital Transformation of Crystallisation Development

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The CMAC Future Manufacturing Research Hub at the University of Strathclyde is developing an autonomous robotic platform for high throughput small-scale crystallisation experiments of active pharmaceutical ingredients (API). For API crystallisation, understanding the size, shape, kinetics and physical form of crystals is key to developing models that can predict crystallisation outcomes across a broad chemical space. Digital predictive tools such as machine learning (ML) and mathematical models can significantly reduce the time and resources required in these processes, but generalisable machine learning models usually require reliable interoperable datasets with hundreds to thousands of data points. Currently, no such database exists in this area. Therefore, we're establishing and integrating the cyber-physical infrastructure at CMAC to capture data for crystallisation kinetics, habit, and physical form across a wide chemical space. We're developing the capabilities to collect this data robotically and autonomously with the next best experiment being determined by algorithms that are in turn informed by past experiments, integrated expert knowledge and predictive models. This data collection strategy aims to ensure reliable repeatable high-throughput data collection that can feed into a FAIR (Findable, Accessible, Interoperable & Reusable) data structure.

Laser-Induced Cavitation for Controlling Crystallization from Solution

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We demonstrate that a cavitation bubble initiated by a Nd:YAG laser pulse below breakdown threshold induces crystallization from supersaturated aqueous solutions with supersaturation and laser-energy dependent nucleation kinetics. Combining high-speed video microscopy and simulations, we argue that a competition between the dissipation of absorbed laser energy as latent and sensible heat dictates the solvent evaporation rate and creates a momentary supersaturation peak at the vapor-liquid interface. The number and morphology of crystals correlate to the characteristics of the simulated supersaturation peak.

P2.7

Laser-Induced Cavitation for Controlling Crystallization from Solution

Mr Nagaraj Nagalingam[1], MSc Aswin Raghunathan[1], MSc Vikram Korede[1], Assistant Prof Remco Hartkamp[1], Johan Padding[1], Assoc.prof.dr. Burak Eral[1]
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Development of additive-assisted continuous crystallization for improving drug processability

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Additive-assisted crystallization is a well-known method for manipulating all physical properties, thus the effectiveness and processability of active pharmaceutical ingredients (APIs). Besides the impact on crystalline quality, additives can also affect the mechanism of crystallization through their influence on nucleation, induction time, and solubility. The available additives have a wide range of chemical and functional diversity and can be purposefully fine-tuned. However, the adaptation of knowledge on the subject into continuous crystallization, which would utilize both the beneficial attributes of the different additives and continuous technologies on product quality control is overlooked.

Our goal was to develop an additive-assisted continuous crystallization to produce a crystalline drug with good flowability, thus possibly reducing the need for otherwise necessary downstream formulation procedures. In accordance, the crystallization of famotidine (FMT), an antihistamine in the presence of polyvinylpyrrolidone (PVP), a tableting excipient in batch operation was investigated through a 24-1 factorial design. The aim of these preliminary experiments was to select the most appropriate process conditions for a three-unit continuous cooling MSMPR crystallizer cascade. The effect of different process parameters, such as the amount of PVP, residence time (RT), mixing rate and presence of the buffer element on product quality and yield were screened and statistically analyzed. The most promising settings were tested in continuous operation as well. Adding PVP to the API solution enabled the selective crystallization of FMT Form A and could be operated for more than 6 RT (4 hours) without clogging. The system can be characterized by a very short run-up period (< 1 RT) and the product had excellent flowability. By contrast, continuous crystallization without any additive resulted in a mixture of Form A and needle-like Form B polymorphs, poor flowability, and yield, as well as a much longer run-up period (> 5 RT or 3.5 hours).

Upscaling of continuous crystallization process conditions from the laboratory scale to pilot scale

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The use of capillary reactors enables the control of spontaneous nucleation conditions for a solute in solution. The use of this principle has enabled Secoya Technologies to build process skids at different scales: from the gram-scale parameter testing instrument SCT-LAB, over a pilot unit producing kilograms of solute, up to a full scaled industrial skid, able to produce at ton-scale.

By the example of spontaneous nucleation of adipic acid and lactose, the screening of important parameters such as reactor volume, solution concentration, flow velocity inside the reactor, nucleation temperature, crystal maturing and others are discussed using the laboratory scaled instrument. It is found that adipic acid rapidly nucleates inside low-volume reactors at limited supersaturation values. Its fast crystal growth kinetics results in limited crystal maturation time after gathering the slurry out of the nucleation reactor. Lactose on the other hand requires a very high supersaturation value inside long reactors to reach a sufficient degree of nucleation inside the slurry, whereas the growth kinetics are much lower when compared to adipic acid.

It will be demonstrated how minor changes in this parameter set may have a drastic impact on the final retrieved crystalline material after filtration and drying.

When the scale of testing is increased towards the pilot scale, the identical opimal parameter set is simply translated from lab to pilot conditions. It is demonstrated that there are no changes in material attributes for both lactose and adipic acid when upscaled from laboratory to pilot scaled testing, with excellent reproducibility between different tests. Again, small changes in the optimal parameter set are induced to demonstrate that deviations from the ideal case immediately give rise to e.g. increased crystal size and different crystal shapes. An outline to industrial production and incoporation with continuous filtration methods will be given for both compounds.

Investigation of melting point depression of hydrates in dependence on melt composition.

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Macro and micronutrients, like nitrogen (N), phosphor (P), potassium (K), sulphur (S) and magnesium (Mg) play a key role in crop development and growth and need to be added to agricultural soils due to declining nutrient levels in many parts of the world. Many fertilizers are produced as prills from melt. Prilling technology forms beads from molten materials by solidifying mono-sized droplets, offering higher flexibility and lower recycle stream in multicomponent fertilizer prills production. Increased controllability over microstructure, nutrient release, uptake and loss to the environment is currently pursued in industrial prilling.

We investigate the melting point depression as a function of composition of fertiliser hydrates, as well as melt viscosity, surface tension and crystal structure. Viscosity and surface tension are key parameters influencing jet breakup and droplet formation during industrial prilling. Homogeneity of crystal structure, size distribution and surface properties increase controllability of nutrient release, uptake and loss to the environment.

Hydrates exhibit lower melting points than their anhydrous counterparts and allow crystallization from solution at lower temperatures. Different mineral fertilizer hydrates are homogenized in molten state. We investigate melting point and measure density and viscosity as a function of shear rate and temperature. Droplets are formed to determine surface tension and analyse crystal structure and dispersion.

We prill calcium nitrate and related hydrates at low temperature from melt. Evaporation of water during prilling influences the micro structure of the final product. The product is of an industrial fertilizer production quality. Melt point depression of mixed fertilizer hydrates increases homogeneity and quality of the final product and reduces energy required during processing. We can model behavior, like droplet formation and jet breakup, of mixed hydrate melts and design suitable process equipment for the manufacture of micro and macro prills as fertilizer and animal feed.

P2.11

Fertilizer grade magnesium sulphate from flue gas desulfurization

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The paper deals with discussion concerning research and project of the industrial scale plant for magnesium sulphate (MgSO4.7H2O) fertilizer production after flue gas desulphurization (FGD) by means of magnesium method.

The paper consists of (i) investor requirements, (ii) chemical composition of magnesium sulphate solution after flue gasses absorption, (iii) results of a research, (iv) discussion, (v) final conclusions and at last but not at least (vi) the industrial scale plant proposition, respectively.
The Authors also described untypical conditions of crystallization process kinetics together with necessary pre-processing of the raw inlet fluid.

Bridging the gap between experimental and computational approaches for rapid pharmaceutical crystallization scale-up

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Scaling up pharmaceutical crystallization processes is challenging due to the nonlinear nature and the high mixing sensitivity of fundamental crystallization mechanisms. Practitioners and academic research groups proposed several scale-up support tools. The former methods rely on averaged values of mixing related descriptors, from the Re number to mean turbulence dissipation rates but have shown modest success due to the tight pharmaceutical constraints. The latter calculates the flow field explicitly with an appropriate turbulence model in a computational fluid dynamics (CFD) simulation. Besides the flow, material, energy, and population balances can also be embedded, allowing direct simulation of crystallization processes. This was successful in several applications. That said, the immense computational burden of full-scale CFD simulations and the substantially different workflow delimit its application. We propose a novel approach to consider the CFD results in a workflow and toolset similar to the currently used experimentation-centric process development. The method has two key assumptions: the process is developed already on a laboratory scale, and the difference in flow fields between the small and large scales is the root cause of product property deviations. Obtaining a prediction model is realized in three steps: (i) keep the recipe and vary the mixing properties (volume, stirring rate, etc.) in systematic small-scale experimentation; (ii) conduct the CFD simulations for the corresponding experiments without or with minimal dynamics and without material, and population balances for effectiveness; (iii) apply data-mining: select the variables from the plethora of CFD results that have the predictive power on the measured output(s), then, create a regression model. Finally, this predictive model can estimate the product properties expected from a flow field characterizing a larger-scale reactor. The approach will be presented through the successfully executed case study of L-glutamic acid crystallization from water in 0.5 L nominal volume (0.35-0.5-0.65 L actual volumes).

Purification and Crystallization of a Solvent-Free, High Temperature Melt Reaction

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The development of practical crystallizations for active pharmaceutical ingredients (APIs) requires a thorough understanding of the upstream unit operations. Oftentimes, synthesis and crystallization development occur in parallel, and knowledge must be continuously communicated between development teams to realize a robust and resilient process. Here, we discuss the process development for a generic benzodiazepine that hinges on an acid-mediated decarboxylation at high temperatures under solvent free conditions, where effective interdisciplinary collaboration resulted in a process that consistently gives high-quality API. Based on the academic and patent literature, crystallization development was initially focused on the effective removal of an isomeric impurity; typical processes resulted in a 9:1 product to isomeric impurity ratio, and the team leveraged this knowledge to kick-start development work. In parallel, our synthetic colleagues identified suitable batch conditions that minimized impurity formation (~470:1 product to isomeric impurity), where the primary challenges for the downstream process were to remove the isomeric impurity to less than 0.1% and purge the dark color formed during upstream processing. A two-stage crystallization/recrystallization sequence was developed that gave API that met specifications of the relevant United States Pharmacopeia (USP) monograph. Prior to scale-up of the process, a hazard analysis indicated the temperature of reaction was close to the temperature of thermal decomposition, and concerns of a potential run-away reaction led the team to evaluate a continuous manufacturing platform. Upon implementation of the synthesis in flow, the purification no longer resulted in material that met specification, and an impurity not observed throughout development was identified. The team leveraged solubility data from early in the development process and a single stage crystallization was identified and implemented to give high-quality API.

Coating by cooling crystallization of sugar on metformin hydrochloride tablets

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Metformin hydrochloride tablets was coated with sugar (sucrose, glucose) solution by cooling crystallization. There were two parts for coating in this research. The first part was the investigation of the solubility, metastable zone width, viscosity and the contact angle measurement of coating material in form of solution. These studies are very important to know before coating by crystallization because they are an essential effective crystalline coating, which is very compact in structure without cracking and uniform in shape, is achieved. The second part was the coating process. This investigated on the optimum operating conditions that affect the surface morphology and the crystal growth rate that included concentration, agitation speed, retention time. The result investigated that metformin hydrochloride tablets coating by cooling crystallization is feasible and can be applied in the pharmaceutical industry.

Amorphous precipitation: Learning from failures

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The amorphous form of an active pharmaceutical ingredient (API) may be selected for several reasons, such as the poor solubility and bioavailability of the stable crystalline form or because a developable crystalline form is yet to be identified.[1-3] However, the amorphous form is inherently unstable and tends to convert to a crystalline structure over time.[3] This transformation can vary depending upon the material itself, the processing route taken to generate and isolate the amorphous API and the storage conditions. Amorphous APIs can be generated during the drug product formulation and stabilised by additional components, i.e., as an amorphous solid dispersion (ASD).[2,4] An amorphous API can also be generated as part of the drug substance without any additional components.

An example of direct amorphous precipitation of an active API will be presented, for which an anhydrous crystalline form is currently unknown, and it is found to solvate readily from a wide range of solvents. The steps taken to understand the parameters will be presented and discussed. These parameters may accelerate or inhibit the crystallisation. With accelerated timelines and limited API supply accepting failing is important to ensure that bouncing back fast and rapid learning is quickly embedded into ways of working. Being resilient was paramount for this project to better understand the direct precipitation process, the solid form landscape and evaluating technologies for generating API as an amorphous solid.

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Determination of solid-state properties of conformational rotamers of an API and their impact on purity in crystallization pathways.

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A common characteristic of organic molecules is their ability to adopt multiple conformations due to their high degrees of freedom compared with inorganic substances. This has important consequences in terms of accessibility of the conformational polymorph during crystallization processes, as well as for their physicochemical properties. In the present work we discuss the challenging case of an active pharmaceutical ingredient (API) that crystallizes as a mixture of two rotational conformers having similar relative energies. Firstly, the investigation of the solid-state properties of the API will be described, elucidating the relationship between the two conformers and their ability to interconvert. After carrying out an attempt to isolate the most stable conformer exploiting variable temperature techniques, the purified material is used as seeds in a crystallization process with the aim to produce the desired conformer. Given the possibility of the two conformers to be interchangeable in the crystal lattice as well as their strong structural analogy, the present work is intended to rationalize the ability of structurally similar molecules, like conformers, to exhibit miscibility in the solid state, hence forming solid solutions. Solid-state analyses are performed to explain structural aspects of the compound and its ability to form a solid solution. The present contribution is also intended to clarify the applicability of the definition of polymorphism in case of molecular entities exhibiting structural similarities. Minor differences in crystal structure, as for the case of the two conformational entities of the studied API, might be interpreted subjectively as they don't generate a unique fingerprint of one structure. Furthermore, due to the difficulty to access the pure form of the conformers, the characterization of their physical-chemical properties as well as the understanding of their function at regulatory levels such as bioavailability and formulation of a single entity is limited.

General role of amorphous aggregates in crystal nucleation

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Nucleation of crystals from solution is traditionally described in the framework of classical nucleation theory, in which the critical size of a nucleus that grows by attachment of solute molecules is the key criterion. However, classical nucleation theory has been challenged by observations of nanoscale and mesoscale metastable solute species in super- and even undersaturated solutions without initiating crystal growth. Accordingly, an alternative mechanism, called non-classical or two-step nucleation theory, was proposed in which nucleation involves formation and reorganization of pre-nucleation clusters.

Here, we will show that a wide range of amino acids as well as di- and tripeptides in supersaturated aqueous solution form aggregates and investigate their role in laser-induced nucleation and crystallisation. Using light scattering, we can demonstrate that these aggregates are far from monodisperse but have a wide range of sizes. They form on a timescale of about a day and redissolve on a timescale of hours, while in situ Raman spectroscopy confirms their amorphous nature. Mass spectrometry is used to confirm that the solute molecules cluster over a very wide range of sizes. All but one of the samples investigated shows aggregate-assisted laser-induced nucleation. These results suggest a general role of amorphous aggregates in crystal nucleation and a universal role in laser-induced nucleation. The wide range of observed sizes of the aggregates is inconsistent with both classical nucleation theory as well as non-classical theories involving liquid–liquid phase separation, requiring a new theory of crystal nucleation.

Effect of the precursors morphologies on the electrochemical properties of NMC811

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Lithium-ion batteries are important in exploiting renewable sources and they are growing exponentially in diverse applications like electric portable devices, electric vehicles and stationary energy storage. In the case of electric vehicles (EV) the most used cathode materials are the layered nickel-manganese-cobalt oxides (NMC), which can be made from calcinating Ni1-x-yMnxCoy(OH)2 with a Li source, which in turn is traditionally obtained by reactive co-precipitation in a continuous stirred tank reactors (CSTR) in presence of ammonia and sodium hydroxide. In this work, we focus on studying the effect of different aging time on precursor morphologies and, in turn, on the electrochemical properties. To synthesize the metal hydroxide and ensure a correct reactants mixing, it was employed a micromixer, which enable us to collect the precipitated metal hydroxide suspension within a few seconds after its precipitation, and to age the material with a top stirrer, at 60°C under N2 atmosphere. More experimental details can be found in [1]. Then, the cathode active material (CAM) is obtained by calcinating the precursor with a Li source and is tested electrochemically in coin cells (2032), while their morphology analyzed by SEM. The NMC material synthesized from the overnight aged precursor have smoother and more compact primary particles (Figure 1 a, b). The well-ordered structure impacts the electrochemical performance; indeed, the aged precursor produces NMC with higher specific capacity, better cyclability and lower capacity fade (Figure 1 c, d).

Developing new approaches for estimating crystallisation kinetics from small-scale seeded crystallisation experiments

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Small-scale crystallisation experiments performed in Crystal16 and Crystalline units typically rely on primary nucleation at high supersaturations to generate crystal suspensions. Crystallisation kinetics, including primary and secondary nucleation and crystal growth, can be estimated from these unseeded experiments but as the data is collected at high supersaturations, it can be difficult to extrapolate the nucleation and growth rates to lower supersaturations where many crystallisation processes are operated. For this reason, this work is concerned with estimating crystallisation kinetics from seeded experiments at low to moderate supersaturations.

The seeded experiments are performed with two different approaches. One approach is to use a large single seed crystal to seed the system. This is the previously established approach [Briuglia et al., 2018; Cashmore PhD thesis, 2022] but has the drawback of requiring the preparation of a seed crystal with sufficient size which is free from surface artefacts. The novel approach being developed in this work is to avoid the need to prepare seed crystals and instead provide seed crystals in-situ by partial dissolution of suspended solids present in the system. This has the benefit of minimising experimental time and opens up the possibility of automation for controlled dissolution to achieve required seed size and loading. The resulting seed suspensions are than brought to a target temperature (and supersaturation), where secondary nucleation and growth can be observed from imaging with the corresponding kinetics being determined from image analysis.

Briuglia et al., 2018
Cashmore PhD thesis, 2022

Comparison of One Dimensional and Two-Dimensional Population Balance Model for Optimization of a Crystallization Process

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Crystallization is a key unit operation in the isolation of many active pharmaceutical ingredients. The crystallization process commonly has a significant impact on the quality of drugs and the efficiency of downstream processes such as filtration, milling, centrifugation, drying, granulation, and tableting[1]. One of the key challenges in industry is the integration of Quality-by-Design methods when designing unit operations and processes. This would provide potential ways to improve quality while reducing variability and is being actively encouraged by pharmaceutical regulatory agencies[2]. Two-dimensional population balance modelling (2D PBM) allows for the modelling of two different growth kinetics, along perpendicular major & minor axes of a particle. This approach has several advantages for the modelling crystallization processes that generate non-spherical particles, such as needles and plates, commonly encountered for active pharmaceutical ingredients (API)[3]. The 2D PBM approach is also able to account for morphological evolution during a crystallization process; something that cannot be successfully accomplished with a 1D model.

This work outlines a stepwise approach to configuring, validating and optimizing a 2D PBM model. As a first step, the experimental data gathered is used to configure and validate a 1D PBM model. The initial validated 1D model showed that while the desupersaturation behaviour is well predicted and can be optimized using a 1D approach, the particle size did not match the PSD quantiles observed experimentally. Therefore, to investigate this further, a 2D PBM model is configured and validated using the estimated model parameters from the 1D approach as initial guesses. The results indicated that the 2D approach is better equipped to predict the particle shape evolution during the process. The 2D model was then used to explore the design space with a view of identifying process parameters which may result in an improved product particle, namely lower aspect ratio (major axis/minor axis).

Effect of fluid shear on secondary cross nucleation of different polymorphs

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Controlling the polymorphic form of crystalline compounds can be challenging due to the propensity for secondary cross nucleation, which refers to the formation of new crystals on the surface of seeds of a different form. This effect can lead to the formation of unwanted impurities and multiple crystal forms. Our goal is to investigate and measure this occurrence by examining how distinct polymorphs can be generated through secondary nucleation, initiated by single crystal seeds of known composition.

We have chosen to study the crystallization of glycine as a model compound, as it has been extensively researched and has well-documented nucleation characteristics. Prior studies involving the impact of a single-polymorph seed of this compound onto surfaces have resulted in the creation of secondary nuclei with various polymorphs, as described in Myerson's paper [1]. Nevertheless, distinguishing between the effects of attrition and fluid shear was not feasible in this case since the impact of the seed resulted in its surface abrasion.

To avoid this, we have used a "seed-on-a-stick" method instead, to better discern the mechanisms of secondary nucleation in our research. This entailed attaching onto a stick a crystal seed of the stable form of glycine, gamma, immersing it in a supersaturated solution, and subjecting it to fluid shear using an overhead stirrer. This approach enabled us to isolate the influence of fluid hydrodynamics surrounding the seed from the effects of attrition. Secondary cross nucleation could be employed as a tool in the scale up of crystallization processes of polymorphic compounds, allowing us to assess the impact of various secondary nucleation mechanisms on the final product.

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P2.22

Recrystallization of ammonium perrhenate from multicomponent systems

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The application of rhenium includes various branches of industry such as aviation, defense, petrochemicals, medicine, and electricity. One of the main market products of rhenium is ammonium perrhenate (APR) salts, and therefore, the purity of the salt is an important issue for its application. Apart from available techniques such as electrodialysis or ion exchange, the crude APR salt is treated by recrystallization. Nowadays, recrystallization of crude APR salt is carried out using ammonia salt systems. A small amount of research has been conducted on the solubility of rhenium salt in a pure solvent and in systems containing ammonium salts, which is a new direction for researchers. Crystallization takes place in a multicomponent system. Therefore, knowledge about the solubility of ammonium perrhenate in ammonia salt solutions is essential for further industrial crystallization.

The effect of sonication time, frequency and power on the sonofragmentation of p-aminobenzoic acid

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The application of ultrasound during crystallisation has been shown to result in fragmentation (sonofragmentation), leading to a decrease in average crystal size and narrowing of the crystal size distribution. Shorter crystals that are more uniform in size have higher tabletability [1], are less likely to cause blockages in equipment, and are of higher value, particularly in the pharmaceutical industry. In addition to providing crystals of higher value, understanding the mechanisms of sonofragmentation, as well as the extent of its effects, is important for understanding the larger mechanisms of sonocrystallisation. Despite this, existing research on sonofragmentation is often limited to one frequency, predominately 20kHz, and continuous sonication for the duration of the crystallisation process. Cavitation bubble dynamics varies with frequency and power, therefore, an understanding into how fragmentation varies with frequency, power and sonication time would provide further insight into the sonocrystallisation mechanism and allow greater control and efficient sonocrystallisation operation. To the best of the authors' knowledge, this study demonstrates for the first time the effect of different ultrasound frequency (22kHz to 1 MHz) and power on the fragmentation rates of PABA crystals, and the impact of different sonication durations on average crystal length, width, and aspect ratios.

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Deracemization by Mechanochemistry: green access to pure enantiomers

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When a molecule is chiral, it exists as two enantiomers. In the pharmaceutical field, most of the time only one of the enantiomers is desired (eutomer). Its opposite enantiomer (distomer) can exhibit limited therapeutical properties or, in the worst-case scenario, cause lethal effects. Therefore, half of the mass of a racemic mixture (50/50 mixture of enantiomers) obtained after organic synthesis is considered as impurity to be removed.

Among all the developed methods to obtain pure enantiomers (asymmetric synthesis, chiral chromatography), those using crystallization, such as deracemization, are generally preferred, often due to economic reasons. Deracemization allows the total conversion of racemic mixture into an enantiopure solid by an interplay between solution racemization and crystallization mechanisms. Even if this method gives attractive yield, it exhibits an important drawback: the necessity to use solvent (often toxic) that need to be removed in an additional step.[1]

To tackle this issue, mechanochemistry and deracemization could be associated to create a new method: the mechanical deracemization through abrasive grinding. Mechanochemistry refers to the chemical reactions occurring upon mechanical energy input. It serves for co-crystal preparation but has been also used for organic synthesis. This approach gives the advantage to use only few amounts of solvent while maintaining a similar (or even better) yield. Only one study concerning mechanochemical racemization has been reported so far and the field of mechanochemical deracemization remains unexplored,[2] in spite of its potential as a green tool to reach enantiopurity.

The preliminary results that will be communicated prove that deracemization and racemization are possible under milling conditions and occurs faster than regular deracemization processes from solutions. The impact of process parameters will be highlighted and discussed.

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Investigation of calorimetric and solubility behavior of racemic ketoprofen in different organic solvents

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As a poorly water-soluble chiral molecule, ketoprofen (KTP) is a highly potent nonsteroidal anti-inflammatory drug (NSAID). In this work, we couple solution calorimetry, and the gravimetric method to respectively measure heat of solution and solubility of KTP in different organic solvents. Moreover, Perturbed Chain-Statistical Associating Fluid Theory (PC-SAFT) model is used to successfully represent the solubility curves using a small amount of data for fitting the model parameters. The results showed a good agreement between different experimental techniques. Finally, study of primary homogeneous nucleation of KTP is an ongoing work, which will extend our understanding of the kinetic behavior of KTP.

Effect of initiators on crystallisation of sustainable polymers

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Polycaprolactone (PCL) is a biodegradable polymer that has a wide range of applications (adhesives, paints and coatings, protective films, compostable packaging) and should be tailored to the specific applications. The properties of PCL are often dependent on crystallinity, and for some applications it is desirable to increase the rate of crystal nucleation and degree of crystallinity, whereas for others crystallisation should be inhibited. The properties of PCL can be varied by changing the initiator molecule and the aim of this project is to explore how different initiators change polycaprolactone crystallisation using molecular dynamics (MD) simulations.

We use a modified Kremer-Grest polymer model [1,2] to study polymer crystal nucleation. This model reproduces key polymer phenomena and the results are thus expected to be transferable to PCL. To mimic different initiators used to make PCL variants, the properties of polymer chain sections were modified. The systems were cooled from the melt using an NPT ensemble, and the crystal fraction was estimated from straightening of chain segments. The rate and degree of crystallinity for different model systems will be presented. This work provides insight into how different types of initiators affect polymer crystal nucleation and growth, enabling the selection of initiators for desired PCL crystallisation properties.

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Investigating novel phase behaviour in molecular mixtures

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While there has been some debate about the exact definition of a cocrystal material, there is broad agreement that such materials are solids, generated by reacting together by various methods, two different molecular solid materials. Solvent -free synthesis of co-crystal materials is well documented. There are many examples in the literature in which grinding of the solid drug and conformer, without solvent medium, results in the spontaneous formation of a new material comprising a synthon formed from hydrogen bonding between the two molecular entities. The resulting solid material is a cocrystal.

This contribution examines novel behaviour in which molecular materials are observed to form a new material in the same way, but producing a liquid product, rather than a solid. Co-formers reacting with thymol display such novel behaviour and the nature of the resulting liquid material is yet to be fully understood. The possible nature of such cocrystal liquids is explored and the observed behaviour examined to consider whether such liquid products should expand the definition of a cocrystal product.

Atmospheric crystallization of potassium niobate from Fe-Nb alloy fines liquor.

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The consumption of niobium-based compounds has increased in the later decades due its large range of applications such as in ceramic capacitors, material for medical implants, batteries, microelectronic components, fine chemicals for catalysis and optical lenses. Brazil has the largest reserves of niobium worldwide and is the major producer of this metal in the world market. About 90% of niobium is commercialized as Fe-Nb alloy and extracted using hydrothermal methods (high temperature and pressure). The alloy fines which are usually out of commercial specifications contain significant amounts of niobium. In this context, we have investigated the crystallization at atmospheric temperature and pressure of niobium-compounds from the alkaline leachate of the Fe-Nb alloy fines. We conducted a thermodynamic evaluation of physical-chemical properties and speciation of niobium using OLI Studio Stream Analyzer to evaluate the influence of process parameters (composition, pH, temperature and supersaturation) on the crystallization. Experimentally, the Fe-Nb alloy fines (~ 65% of Nb) were leached with KOH and an atmospheric cooling crystallization of potassium niobate was carried out from the liquor, after a pre-concentration step through evaporation. The solids obtained from atmospheric crystallization were characterized by XRD, XRF, FTIR and microscopy. The XRD associated with the chemical analysis indicated that potassium niobate was formed in different crystalline phases ($KNbO_3$ and $K_4Nb_6O_{17}$) and the optical microscopy showed mostly isolated plate-like crystals. The chemical composition of the solid was 42.3% of Nb, 24.7% of K, 23.3% of O and 9.7% of impurities. The potassium niobate shows great potential to be used as a precursor in the synthesis of other niobium compounds. These results are essential to develop scientific and technological knowledge about niobium in aqueous media, which is scarce in the literature. Moreover, it provides the basis for future recovery and valorisation of niobium-containing products from waste materials towards circularity.

Analysis of the US assistance on nucleation and the crystal size during the precipitation process in the selected reactors.

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The paper deals with conclusions regarding the precipitation process and focused on the relation between the reactor type, US (ultrasounds) assistance, nucleation intensity, as well as crystals' characteristics. As model reactions, the precipitation of calcium fluoride and hydroxyapatite, in both silent and US-assisted systems, have been carried out, by the use of a typical stirred tank reactor, and the Koflo static mixer.

The experiments have clearly shown that the influence of US presence on CSD and nucleation rate is not univocal and that the differences are connected with diverse mixing profiles in the examined reactor types. For reactors with close to a homogeneous distribution (i.e. static mixers), the only effect is the increased turbulence intensity. For reactors with non-uniform profiles (i.e. STR), one may observe both the increased turbulence and the alignment of the mixing characteristics.

Due to that, a significant effect of US on the nucleation stage has been observed in STR, depending mainly on the relation between the unit mixing power and the unit US power, presented as the relative mixing intensity εrel. Following its value, three different areas of i) not significant, ii) moderate, and iii) dominant influence of US on the nucleation stage have been distinguished. In comparison to the silent system, one may observe an increase in the nucleation rate up to 100 for the second area, or even much greater for the third one.

The US contribution in the turbulence intensification, well correlated by means of a developed equivalent Reynolds number (Reeqv), is even more complex because it acts not only on the particle size or shape but also to some extent on the agglomeration phenomenon. For properly selected US parameters (mainly PUS) one may observe the reduction of the clustered structures, but for the systems with overestimated values secondary sono-aglomeration phenomenon may occur.

Influence of processing conditions on the industrial crystallisation and stability of iron (II) sulphate heptahydrate

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Keywords: Crystallisation, Crystal Morphology, Iron (II) Sulphate Heptahydrate

Iron (II) sulphate heptahydrate, hereinafter IS7, is a green coloured crystalline material, which finds industrial applications for example as a flocculant in water treatment processes. It is formed as a co-product from titanium dioxide manufacture using the sulphate process (1). It is known that the crystallisation process and resultant crystal morphology can be affected by processing conditions such as variation in cooling and agitation rates, and solution pH. The latter can also influence the solubility and stability of IS7, which can readily dehydrate to other hydrate forms and/or oxidise to iron (III) under ambient conditions (2). Each of the hydrated forms has a distinct crystalline structure and colour and hence it is important to understand how processing conditions affect the crystal growth and stability of IS7 (2).

Examination of the solubility of IS7 in aqueous solution as a function of temperature and pH revealed the solubility to be directly proportional to the solution pH. Characterisation of the crystal morphology following recrystallisation revealed an essentially prismatic morphology, albeit with evidence for oxidation to iron (III) as characterised by yellow/brown solution colouration. The latter effect was much reduced in the presence of sulphuric acid and whilst the resultant crystals were initially found to be prismatic, successive recrystallisations resulted in a much more plate-like morphology. These results are currently being cross-correlated with the rate of solid state dehydration of IS7 using dynamic vapour sorption (DVS) as a function of relative humidity and temperature. Overall, this study demonstrates how the stability, solubility and crystal morphology of IS7 are affected by process conditions to enable its optimisation for obtaining the prismatic form to improve product filtration and drying.

Tautomerism unveils a self-inhibition mechanism of crystallization and its applications for tuning bending deformation and nanomechanical properties

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Modifiers are commonly used in natural, biological, and synthetic crystallization to tailor the growth of diverse materials. They often exhibit structures and/or compositions that differ from a solute molecule but often contain similar functional motifs that facilitate molecular recognition for modifier binding to crystal surfaces. In this presentation, we will report a new class of modifiers, tautomers, that produce via the dynamic interconversion from solutes. The unique effect of tautomers on crystallization and the underlying impact on crystalline materials will be discussed.

In the first part, we employ a combination of high-resolution experimental techniques and density functional theory (DFT) calculations to unveil that tautomers, which constitute a minor fraction of solute, function as potent native growth inhibitors (NGIs) that nearly suppress crystal growth at select solution alkalinity and supersaturation. Our study initially focuses on ammonium urate crystallization and has extended the generalizability of this phenomenon to two additional tautomers with relevance to biological systems and pharmaceuticals. The macroscopic and microscopic effects imposed by inhibitor-crystal interactions reveal dual mechanisms of inhibition where tautomer occlusion within crystals leads to natural bending and selectively alters the rate of crystal dissolution.

Then, we explore the autodeformation mechanism of natural bending crystals that are less commonly observed in small molecular crystals. Using a combination of spatially resolved atomic experimental techniques and calculations, we show that the inhomogeneous strain produced by keto-enol tautomer occlusion results in the macroscopic deformation of crystals. High-resolution TEM imaging shows numerous edge dislocations with curved lattice strips and reveals plastic deformation by interlayer and cross-layer slippery mechanisms. Moreover, we demonstrate crystal curvature impacts the nanomechanical properties of molecular crystals. To our knowledge, this is the first report using tautomerism to strategically engineer crystal defects for tunable curvature and nanomechanical properties in a naturally grown bend molecular crystal.

Particle Breakage using Hydrodynamic Cavitation: Breakage modeling and mechanisms

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Particle Size Distribution (PSD) is a critical quality attribute for a wide range of solid products in chemical and pharmaceutical industries. Particularly, in pharmaceutical industry, a uniform PSD ensures a uniform dissolution rate, flowability, and compressibility which in turn affect the drug effectiveness, quality, and bioavailability. Milling techniques such as high shear wet milling and ultrasound grinding have often been studied to alter the PSD of the Active Pharmaceutical Ingredient (API) crystals.[1-12] In the present work, Hydrodynamic cavitation is sought to break particles and alter their PSD. A suspension of paracetamol particles is passed through a vortex diode (VD) which causes hydrodynamic cavitation to break the particles. The particle size distribution before and after the treatment with hydrodynamic cavitation is measured using a laser diffractometer. Hydrodynamic cavitation is compared with other grinding techniques such as Ultrasound grinding and High-Shear Wet mill. Kapur function[13] analysis is used to arrive at the breakage kinetics under varying operating parameters for the vortex diode. The breakage rates and daughter distribution functions obtained will be used to validate a breakage model which will be further used in Population Balance Modelling for crystallization of APIs. The effect of operating parameters of the vortex diode on the breakage mechanisms has been studied. Both abrasion and fragmentation has been observed in the breakage process. Hydrodynamic cavitation also resulted in a higher breakage rate for smaller particles compared to high shear wet mills and ultrasound because of the localised high energy dissipation during cavity collapse at the diode outlet. The energy dissipation in the vortex diode was 1/6th of the energy dissipation in the wet mill for similar breakage kinetics. The results will help in creating a population balance model for a crystallization process intensified using hydrodynamic cavitation.

Purifying rare earth scandium salt from metallurgic production residue by controlled antisolvent crystallization

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Scandium is a rare earth metal salt with low availability but many useful applications. Small amounts of scandium can strengthen an aluminum alloy so components can be constructed with weight reductions, which is popular for lightweight applications [1]. In Europe, scandium is not mined and must be imported from countries such as China, or Russia, severely limiting its availability. One possibility for secondary scandium production is metallurgical wastewater streams from aluminum or nickel-cobalt production, which contain small amounts of multiple rare earth elements [1]. Scandium can be concentrated by selective and reactive solvent extraction and back extraction using ammonium fluoride. Subsequent antisolvent crystallization with ethanol leads to the crystallization of the scandium salt, which is then filtered and calcined to obtain scandium fluoride, which then can be integrated into an aluminum alloy [1]. High yields can be generated using ethanol as an antisolvent, however, very high local concentration gradients are generated when the two fluids are mixed. As a result, strong nucleation leads to many small crystals, which are difficult to filter and agglomerate strongly when dried, rendering them hard to handle in an industrial process. For the crystallization process and subsequent solid-liquid separation to get manageable, nucleation must be controlled, and crystal growth benefited. Therefore, nucleation and growth kinetics were determined in a fed-batch process, by measuring the metastable zone width and CSD over time [2]. This allowed the determination of process parameters, such as the antisolvent dosing rate, stirrer speed, or the dilution of the antisolvent, which enable the growth of crystals. Scandium salt crystals can be further purified by filtration and washing from other salts that form in the process, that do not grow as much.

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Real-time Synchrotron X-ray Phase Contrast Imaging of Glycine Cooling Crystallisations

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Synchrotron X-ray phase contrast imaging (XPCI) allows rapid microscopic imaging of multiphase systems with low absorption contrast between the phases, such as organic crystals in solvents. It permits time-resolved studies of the structural evolution in crystallising systems. We have captured in situ videos of aqueous glycine during cooling crystallisations at the ANATOMIX beamline of the Soleil synchrotron facility in Orsay, France. A custom-made flow-cell was constructed to allow X-ray monitoring of the process with a flow loop attached to a larger jacketed vessel. Solutions were supersaturated by cooling until nucleation and crystal growth were observed. The process was imaged in real time with an exposure time of 10 ms per image (100 frames per second), with videos taken over 5 minutes. Each frame is a 16-bit image of 1024 x 2048 pixels, with an effective pixel size of 1.3 µm, resulting in a field of view of 1.33 mm x 2.66 mm. The advantage of using X-ray imaging over optical microscopy techniques is that crystals are imaged across the whole sample volume captured by the image. To obtain the temporal evolution of the particle size distribution and of the crystal habits, we have developed image analysis software that segments crystals against the solution and vessel background. Possibilities and limitations of XPCI and other synchrotron X-ray techniques, e.g., combining X-ray imaging with diffraction, will be discussed.

Experimental and Modeling Study of Lactose Crystallization

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Minimizing waste production in the dairy industry requires new valorization strategies to exploit cheese whey, a major by-product of cheese production. Particular attention is paid to the recovery of lactose, one of its main components, which is a promising starting material for the production of high-value chemicals, such as prebiotics or bioplastics.

In aqueous solution, lactose undergoes an intramolecular reaction leading to two diastereomers, α- and β-lactose, that slowly interconvert until equilibrium: the reaction is called mutarotation. Below 93 °C, α-lactose is the least soluble compound and is traditionally recovered from whey as monohydrate via seeded batch cooling crystallization. This process is governed by the complex interplay between secondary nucleation, growth, agglomeration, and mutarotation. However, little attention has been focused so far on experimentally investigating how the interplay among the different phenomena affects the evolution of the α- to β-lactose ratio during crystallization. Therefore, the purpose of this research is to assess the impact of mutarotation on the process and to provide preliminary guidelines on the optimal design, operation and control of industrial lactose crystallizers.

A prerequisite for studying the interplay between lactose mutarotation and crystallization is a remarkably robust and accurate analytical protocol to characterize the behavior of the system: thus, a novel chromatographic method has been developed and employed as offline monitoring tool to track the evolution of α- and β-lactose over time, while laser diffraction has been used to measure the particle size distribution. The evidence is taken into account in a rigorous population balance model and the system of equations has been solved with a high-resolution finite volume method (FVM). State-of-the-art parameter estimation techniques have been used to evaluate different growth rate expressions by comparison with data from batch desupersaturation experiments.

Quantifying the Kinetics of Competitive Polymorphic Nucleation via Microdroplet Approach

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Nucleation plays a key role in polymorph selection which profoundly impacts the physicochemical properties, processability, and overall quality of the final crystalline product. For this reason, understanding the kinetics of competitive polymorphic nucleation is essential in controlling the polymorphic outcome.[1] Given that nucleation is inherently stochastic, experimental platforms allowing large number of experiments are needed to enable a reliable statistical analysis.[2] Given that solubility is a pre-requisite in quantifying nucleation kinetics, new methods for measuring the aqueous solubility of metastable forms are of fundamental interest.[3] In this work, we develop an original microfluidic approach to measure the aqueous solubility and nucleation kinetics of a metastable form of KDP (KH_2PO_4), one of the most important opto-electronic crystals[4]. Using our measured solubility, we estimated its interfacial energy from its probability distribution of nucleation time measured in evaporating microdroplets.[5] We show that the nucleation barrier measured in our microfluidic experiments is in reasonable agreement with molecular simulations. Then, with our measured nucleation parameters, we used the classical nucleation theory (CNT) to model the competitive nucleation of both polymorphs and the simulation results show that the stable form is favored at lower supersaturation while the metastable form is favored at higher supersaturation. Indeed, our combined experimental and computational study reveals an interesting interplay between thermodynamics and kinetics in competitive polymorphic nucleation.

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Reactive Crystallization of CaMg(CO3)2 Nanoparticles by CO2 Fine Bubble Injection and Ultrasonic Irradiation into Concentrated Brine and Conversion to Inorganic Phosphor

Lecture Yoshinari Wada[1], Shunrin Chin[1], Shinnosuke Kamei[1], Koji Masaoka[1,2], Masakazu Matsumoto[1]
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To build an efficient salt production process using seawater as raw material, a novel method to recover and upgrade Ca2+ and Mg2+ from the concentrated brine discharged by salt manufactories in Japan is desired. From a salt solubility viewpoint, the synthesis of dolomite (CaMg(CO3)2) by reactive crystallization between the dissolved Ca2+ and Mg2+ in concentrated brine and CO2 at pH below 10.5 can be considered as an effective separation/recovery method. If the increase in Mg/Ca ratio and nanoparticulation of CaMg(CO3)2 can be achieved during the reactive crystallization, applications as a mother crystal of inorganic phosphor with superior luminescent properties would become possible. In this study, the minute gas-liquid interfaces around CO2 fine bubbles (CO2-FB) activated by ultrasonic (US) irradiation were applied to the reactive crystallization of CaMg(CO3)2 from concentrated brine. In the regions around the minute gas-liquid interfaces, local higher supersaturation generates because of the accumulation of Ca2+ and Mg2+ caused by the negative electric charge on the fine bubble surface and the enhancement of CO2 gas absorption due to minimizing the bubble formation. In addition, when US irradiated to concentrated brine containing CO2-FB, CO2 mass transfer is further promoted by pressure oscillation and carbonate solubility decreased locally with an increase in local temperature surrounding the gas-liquid interfaces. Thus, local supersaturation further increases and CaMg(CO3)2 nanoparticles with high Mg/Ca ratio can be expected to crystallize.

Consequently, US irradiation into concentrated brine containing CO2-FB helped to crystallize the nanosized CaMg(CO3)2 particles with higher Mg/Ca ratio. Additionally, when the obtained CaMg(CO3)2 with different Mg/Ca ratios and particle sizes was converted to the inorganic phosphor by immersion into TbCl3/CeCl3 solution, CaMg(CO3)2 nanoparticles at average size below 700 nm and Mg/Ca ratio of approximately 0.5 were found to be suitable for the synthesis of green inorganic phosphor with a high emission intensity.

Precipitating solvent for CO2 capture: Systems characterization and microfluidic approach

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To tackle down climate change and maintain a restrictive world warm up below 2°C, an estimated 15 to 30% of the global effort must come from Carbon Capture Utilisation and Storage strategies. Today, the number of such deployed technologies remains far below the required guidelines in order to respect the modelled projections. Indeed, heavy infrastructures construction, more energy efficient solutions, CO2 reservoirs capacities and government policies are the main parameters which need to gain in intensity and be orchestrated for large CO2 capture acts.

Thus concerning the technology key parameters, important resources are today focused on the research and innovation of new capture methods. The presented work is centred on the treatment of large emitters stream: coal power plant, steel manufactory, cement and natural gas plant, which the effluents are homogeneous through the time (temperature, pressure, composition), CO2 concentrated and available to be treated by retrofit operations.

Solvent precipitation was commonly seen as problematic during carbon capture operations. But now, this phenomenon could be used for intensive capture methods. Indeed, following precipitation characteristics, multiple advantages could take place, such as: 1) a shifted chemical equilibrium through precipitation of CO2 containing materials, 2) favourable shaped isotherms for solvent capacity, and 3) corrosion reduction for instance. In this study, the interests of precipitation are studied through liquid/vapor equilibrium experiments for solvent capacity measurements and benchmark with conventional formulations, and through non-equilibrium states with different operating parameter impacts for dynamic measurements of precipitation process and its regeneration. Precipitates will be characterised at different steps to determine the key process parameters and formulations configuration impacts on precipitation performances. Finally, a microfluidic approach will be developed in order to formalize a high throughput device, to evaluate its applicability to the targeted/desired properties and thus to characterize the precipitation process.

Tailor-made xanthone crystals for Pickering stabilisation and multiphase systems formulation

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Xanthone crystals offer a promising alternative to surfactants as Pickering stabilisers. Advantages include low toxicity, biodegradability, and sustainability. They can be used without surface modification or with surface functionalisation to stabilise foams and both water/oil (w/o) and oil/water (o/w) emulsions. There is a gap in the understanding of the mechanism of stabilisation of xanthone particles at air/water or liquid/liquid interfaces.

In this work, foams and emulsions were prepared using handshaking, agitation with a milk frother and high shear homogenisation. The concentration of xanthone crystals were varied between 1% - 10% w/w of the continuous phase; whereas the disperse phases in emulsions ranged from 10-40% w/w (using medium chain triglycerides, orange oil and tetradecane as oils).

Preliminary results indicate that foam stability is correlated to the size and aspect ratio of the xanthone crystals as well as the concentration of the crystals used. Crystals with a high aspect ratio (3:1-6:1) produced more stable foams and emulsions than those with a low aspect ratio (1:1), possibly because of the different level of coverage of the disperse phase surface. This is also confirmed by the fact that at the lowest crystal loadings (1-3%), both W/O and O/W emulsions were unstable. Above 5% of crystals the coverage of the interface improves, and the mean droplet size is reduced.

The polarity of the oil used was also found to affect formulation stability. Emulsions prepared with medium chain triglycerides are more stable than those prepared with orange oil and tetradecane. Future studies will focus on exploring the interaction of specific facets at the interface and the impact of pH on these interactions.

Structural Insights into the Highly Solvating Behavior of Axitinib via Binary and Ternary Solvates

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As a common phenomenon, the majority of chemical reactions and virtually all biological processes take place in a liquid-state environment, therefore, solvation as a topic is thus at the very heart of chemistry as well as chemical engineering. Moreover, the application of solvates in many frontier fields is attracting researchers, such as drugs, fluorescent materials, dynamic crystals, making it one of the important topics of crystal engineering. However, the structural driving forces leading to the formation of solvates are not clear, especially for the complex systems above ternary, because of the lack of an unambiguous comparison parameter. Therefore, the understanding of the reasons for solvate formation and exploration of a solid form landscape is important and necessary during drug development.

Axitinib is used for the second-line treatment of metastatic renal cell carcinoma. The various strong hydrogen bonding groups lead it a highly solvating polymorphic system with nearly seventy different solvates. The structures of two new ternary solvates and five binary solvates were selected as the main research object. Meanwhile, we discovered the peculiar isostructural classification event of binary solvates. Seven solvates were thoroughly characterized with various analytical techniques.

Meanwhile, the crystal structures of seven crystals were determined for the first time. The stacking similarity combined was quantitatively calculated by XPac and COMPACK in detail. The thermal stability of the solvates upon heating was also investigated and the corresponding processes and products of the desolvation were analyzed. A strong correlation between the interaction energies of solvents with the thermal stability of solvates was observed. Moreover, the key factors to determine the classification results of binary solvates was explored. The intermolecular interactions of these solid forms were visually compared by Hirshfeld surface and energy framework analysis. Finally, the main driving force for solvates formation of Axitinib was discussed.

A Conglomerate Cocrystal of the Racemic Compound Praziquantel

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Chiral compounds can crystallize from a racemic solution into a conglomerate (a mixture of enantiopure crystals) or into a racemic compound (a 1:1 co-crystal compound of the two enantiomers). For enantiomer separations, conglomerate systems are favored as then relatively simple separation techniques such as preferential crystallization can be performed. However, most chiral compounds form racemic compounds, only about 10% form a conglomerate. In principle, a racemic compound can be changed into a conglomerate co-crystal using the right achiral co-former. Up to now, literature has only reported racemic co-crystal compounds of the racemic compound pharmaceutical praziquantel. In a co-crystal screening study, we tested 20 achiral co-formers with functional groups not yet tested previously on their ability to form co-crystals with praziquantel. Only two formed co-crystal compounds with praziquantel, as confirmed by XRPD. Second Harmonics Generation allowed the identification of a potential non-centrosymmetric co-crystal structure with the co-former 1,3-dimethyl thiourea (DMTU). The binary melting phase diagram determined by DSC further indicated that the co-crystal of praziquantel and DMTU was a conglomerate system. Single crystal determination showed that indeed the system is a conglomerate co-crystal compound. Various crystallization-based deracemization methods using this conglomerate co-crystal compound were tested to identify the optimal route towards enantiopure praziquantel.

Assessing recrystallisation of co-amorphous form products

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Keywords: Co-amorphous; Recrystallisation; TEM

Amorphous drug delivery systems can improve the stability, mobility, and dissolution properties of poorly soluble active pharmaceutical ingredients (APIs) for category II of the Biopharmaceutical Class System. Co-amorphous systems can be obtained by combining an API with a suitable excipient that has a strong intermolecular interaction with the API. It is however critical that recrystallisation is inhibited because crystallinity hampers solubility, reducing efficacy. In this study, model co-amorphous systems of valsartan (VAL), an anti-hypertensive API, and nicotinamide (NIC), a highly-water soluble form of vitamin B3, used here as an excipient, are investigated following the work of Turek et al., 2021 (1).

Co-amorphous systems were prepared by heated slurry and melt amorphisation. Powder X-ray diffraction (PXRD) patterns revealed formation of fully amorphous powders. Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR) identified homogeneity and hydrogen bonding within the systems, key factors in maintaining the co-amorphous phase stability (1). To investigate the early stages of recrystallization, material was aged in 85% relative humidity atmospheres. Transmission electron microscopy (TEM) detects the presence of low levels of crystallinity, at earlier ageing times than by PXRD analysis (2). TEM also provides morphological, compositional, and structural information, providing insight into recrystallisation pathways. Further work will explore the solubility of the co-amorphous phases before and after recrystallization.

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Forming Multicomponent Crystal between Two Racemic Compounds – the Case of Solid Solution

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A growing trend towards producing enantiopure drugs is currently observed in the chiral drug market in the pharmaceutical industry [1]. Even though the two enantiomers of chiral molecules have similar chemical and physical properties, the biological activities of the two enantiomers may be remarkably different. There are many methods to separate enantiomers from racemic mixtures. A recent process achieves resolution by forming a cocrystal with another chiral compound. In our previous work, we developed a resolution process for racemic baclofen (RS-BAC) by forming a cocrystal with L-mandelic acid (L-MAN) [2]. RS-BAC was dismantled by L-MAN to form the R-BAC:L-MAN cocrystal. The system was studied further by combining two compounds in other combinations of chiral configurations. The interesting result was that RS-BAC:DL-MAN showed a similar XRPD pattern as R-BAC:DL-MAN which suggests the possibility of having a solid solution, a very rare mode of racemate crystallization. The structures of both compounds were obtained from crystallizing crystals suitable for analyze by SC-XRD. The similarity of both structures confirmed the formation of a solid solution. Unlike the RS-BAC and L-MAN, R-BAC was unable to dismantle DL-MAN. Instead, the R-BAC:DL-MAN cocrystal was formed which is impossible to develop into a resolution process. In conclusion, if an enantiomer of one species can dismantle a racemic compound of another species, this does not suggest the opposite process (i.e. the racemic compound of the first species can be dismantled by a pure enantiomer of the second species) is sure to work.

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Discovery and Applications of a Novel Solid-state arrangement: Water bridge Salt Form

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Salt formation is the most preferred technique to enhance the solubility and bioavailability of pharmaceutical drugs. However, when basic excipients are mixed with the salt form of a weakly basic drug, the counterion dissociates from the salt leading to a process known as disproportionation. Disproportionation, an ion-exchange reaction and the reverse of salt formation can reduce the bioavailability and dissolution rate of the drug [1].

It has been reported that the rate and extent of salt disproportionation for Miconazole Mesylate (MM) salt (amorphous AMO, anhydrous AH, dihydrate DH) in the presence of excipient is significantly different. MM DH showed stability beyond the pHmax value and was resistant to disproportionation over the time period studied. The stability of MM DH and resistance to disproportionation may be because of the unique and stable crystal lattice arrangement. The molecule of miconazole does not directly hydrogen bond to its counterion but interacts through a bridging water molecule; this is the "water bridge". It is believed that this hydrogen bonding pattern provides stability to disproportionation.

The aim of this project is to build a fundamental understanding of the MM salt "water bridge". For example, its stability and physical property relationships under different experimental conditions. To monitor the disproportionation process, the pH solubility profile of MM DH was investigated using different buffers through the shake flask method and compared with reference data of miconazole-free base. During the pH-dependent stability experiments (in HCl/KCl, phosphate, acetate, citrate phosphate buffers), MM DH and miconazole-free base both underwent a sudden change in the pH together with instant solid precipitation. The subsequent solid-state analysis confirmed an ion exchange reaction between miconazole and counterions in the different buffer systems. XRPD and thermal analysis of each product confirmed that the same novel crystalline phase was created from both MM DH and miconazole-free base.

Evaluation on a combined Cocrystal Screening Method and its Application on Synthesis of Multicomponent Crystals: A Case Study

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Multicomponent crystals, particularly salts and cocrystals, are increasingly gaining attention for their ability to modify the physicochemical properties of molecules while preserving their molecular structures. However, screening suitable coformers is a significant challenge during the development of cocrystals. The successful synthesis of cocrystals often involves multiple experimental trials to find a suitable coformer. To guide and simplify the cocrystal synthesis process, we evaluated three different predictive methods, as well as their combinations, during the cocrystallization of 2-Amino-4,6-dimethoxypyrimidine (MOP) with 63 components.

The conductor-like screening model for real solvents (COSMO-RS) approach offered the best predictive results among the three methods, with an overall success rate of 84.1%. When combined with molecular complementarity (MC) analysis, the success rate increased to 85.7%. However, the Hansen solubility parameters (HSP) method did not provide satisfactory results, whether used individually or in combination for the MOP system.

Based on the screened results, twenty-one new solid phases of MOP were experimentally observed. Among them, the crystal structures of ten multicomponent crystals (cocrystals and salts) were revealed by single crystal X-ray diffraction analysis (SCXRD), and their thermodynamic and spectroscopy properties were also characterized. Hirshfeld surface analysis and molecular electrostatic potential (MEP) surfaces analysis were conducted to explore the interactions in multicomponent crystals and the origin for salts and cocrystals.

The cases in this study not only enriched the solid forms of MOP, but also demonstrated the feasibility of the combined screening method, and set an effective example for choosing potential coformers to prepare multicomponent crystals.

Digital Design of Crystallization Process: Why particle size and shape measurement matters!

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Crystallization is the most widely used method for separating an active ingredient from a reaction product mixture. It functions to control purity, crystal form, particle morphology, and particle size distribution (PSD). The application of population balance modelling (PBM) to aid crystallization process understanding and development has been growing with improvements in process analytical tools (PAT) and numerical software packages.

There are numerous sources of error associated with the measurement inputs for PBMs that directly impact the estimation of crystallization rate parameters, and hence the predictive capability of these models. In turn, both measurement and model influence one another and can be co-optimised to better understand the process. Using an agrochemical case study, our work details method development for PSD measurements and the direct impact on the output of a mechanistic model of a crystal growth process.

Our results show the effects of measurement error for particle size and shape measurements during crystallization model calibration activities across several applications. We provide recommendations for Standard Operating Procedures (SOPs) and workflows when performing particle size and shape analysis to ensure the data is of sufficient quality for developing a mechanistic model. Specifically, we demonstrate the significant impact of the optical model used for laser diffraction measurements on mechanistic modelling parameters. We also detail a new workflow using single crystal microscopy growth data to calibrate a 2D morphological crystallization model for the prediction of particle size and shape. With these models, we explore the crystallization design space for our agrochemical system (Figure 1) and show the potential for improving particle properties for downstream processes and end performance. Our results aid in identifying robust process conditions which provide bounds on the minimum aspect ratio of the product material based on seeding strategy.

Computational Fluid Dynamics-Population Balance Modelling of Batch Cooling Crystallisation Processes: Effects of Agitation and Cooling Rates

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Batch cooling crystallisation is a widely used unit operation for product separation and purification in a range of industries, e.g. bulk/fine chemicals and pharmaceutical industries. The process development and scale up however is difficult owing to complex hydrodynamics/mixing within the crystallisers, which can lead to non-uniform distributions of process parameters such as temperature and supersaturation. These can directly influence product crystal properties, such as crystal size distribution (CSD), morphology, purity and yield. Modelling of crystallisation processes is generally based on a lumped-parameter mechanistic approach, which assumes that the solution is well-mixed. However, this assumption may lead to under/overprediction of nucleation and crystal growth rates, and hence CSD.

This abstract summarises a modelling study on the effects of crystalliser operating conditions on CSD using a distributed-parameter model based on multiphase computational fluid dynamics coupled with a 1D population balance model. It focuses on unseeded batch cooling crystallisation of alpha L-glutamic acid from aqueous solution in a 20L kilo-scale crystalliser with a single beavertail baffle and agitated by a retreat curve impeller [1]. The solution was cooled from 75 °C to 20 °C at a cooling rate of 0.6 °C min-1 and at agitation rates of 100, 150, 200 and 250 rpm. The predicted final CSDs show a good agreement with the experimental data. As the agitation rate increases, the predicted and measured CSD curves shift toward smaller particle sizes. This implies that nucleation is enhanced over crystal growth, as higher levels of supersaturation and turbulence are achieved. The predicted CSD curves in line with measurements [1, 2] shift toward larger particle sizes with increasing cooling rates of 0.1, 0.2 and 0.6 °C min-1 for 100 rpm. The predicted spatial distributions of process parameters provide a detailed insight into the effect of agitation and cooling rates on the crystallisation process.

Understanding diffusive mixing and anomalous mass transfer in an antisolvent crystallization system.

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Antisolvent crystallisation is a process widely applied within the pharmaceutical industry, reliant on the difference in solubility of a solute in two miscible liquids—the solvent and the antisolvent—to create supersaturation. Since local supersaturation values affect the properties of the final product, mixing plays a major role in this process. However, mass transfer in this context is not well understood, leading to undesired outcomes such as unwanted crystal phases or oiling out.

Mixing in the microscale is commonly described through Fick's second law. However, this model considers composition gradients as the driving force for mass transfer, failing to explain non-idealities such as uphill diffusion. Additionally, it assumes ideal behaviour, while the unwanted phenomena mentioned occur when non-idealities lead the system to unexpected regions of the phase diagram.

In this work, experimental micromixing studies of mixtures formed by water, ethanol and glycine are conducted, using Raman microscopy to generate composition maps of these binary and ternary systems. The maps are then used to compare the accuracy in predicting the mixing behaviour of two models: Fickian diffusion and a combination of the Cahn-Hilliard phase-field model with Maxwell-Stefan diffusion (CaHiMaS). The latter considers the minimization of the system's free energy as the mass transfer driving force, can model non-ideal solutions and considers the interfacial free energy. Thus, it can potentially model the oiling-out phenomenon. Therefore, the hypothesis tested is that the CaHiMaS model and Fick's law will adjust similarly to binary systems, while the former will allow to model the non-idealities and phase transformations in the ternary system.

This framework can greatly enhance our understanding of diffusive mixing processes and liquid-liquid separation phenomena in any chemical process involving diffusion of non-ideal solutions. Ultimately, this untapped knowledge will lead to safer and more robust manufacturing of chemical and pharmaceutical products.

Offline Size and Shape Characterization of Crystalline Powder through a Combined Imaging and Chromatic Confocal Microscopy Technique

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Needle- and plate-like particles of fine chemicals can be challenging to process. The ability to quantify and predict their impact on product processability requires accurate characterization of the size and shape of the particles that constitute the powder. Tools that can characterize the size and -- most importantly -- the shape, of ensembles of cuboidal crystals are seldom available.[1,2] The overarching goal of this work is to propose a fast and accurate offline approach to tackle this issue. To this aim, we have designed and experimentally validated a combined imaging[3] and chromatic confocal microscopy technique, as shown in the Figure. The tool can be used in two modes: one that facilitates the 3D reconstruction of the particles at the expense of characterization time; and the other that facilitates rapid characterization without the need to 3D-reconstruct the particles. We evaluated and validated the performance of our technique, using a commercial technique as a reference, on several crystalline compounds that exhibit differences in size and shape, and optical properties. We show that our technique can be used to accurately obtain three characteristic lengths (length, width, and thickness) for thousands of particles, making it a valuable addition to existing process analytical technology.

Multiple scales and crystal formation kinetic characteristics in a single mathematical model: Population Balance modeling, validation, and optimization of an industrial crystallization process

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The model-based design and development of production processes can facilitate the industry's pursuit to meet quality and regulatory requirements as effectively as possible. Now, we present the model-based optimization of a crystallization process of an undisclosed API on laboratory and industrial scales, including experimental validation.

A PB model with adequate predictive performance was built to simulate and optimize an industrial crystallization process step. With the application of Evans's secondary nucleation equation, the model confidently handles two different scales (laboratory and plant) and can overcome the difficulties of large-scale cases (persistent drop in the product size of first batches) through an integrated conditional seeding simulation strategy (Fig.1.). An essential feature of the simulation's input measurements is that none was prepared directly for the simulation: all were previously made historical data. The data used as information for the large-scale experiments are results of generally available measurements (process temperature, product size), which makes this study a robust and ready-to-use method for the industry. FBRM measurements were performed during the laboratory scale experiments to investigate the change in the crystal size; however, due to the crystals sticking to the surface of the probe, only induction time could be used as additional information about the system. This was substantial knowledge for decoupling and tuning the parameters of the secondary and primary nucleation equations sufficiently. Alongside temperature profiles and the product size, the induction time of the laboratory scale experiments served as inputs for the parameter estimation of the model.

With the fine-tuned model, the optimization of the temperature profile was performed: the process time and energy consumption were minimized for both first-batch and non-first-batch cases while respecting the quality requirements regarding the CSD of the product (Fig.2.). The optimized temperature profile was validated on a laboratory scale and may be applied on an industrial scale.

Population Balance Modeling in a Multicomponent Simultaneous Crystallization from an Aqueous Brine Solution

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A population balance mathematical modeling approach was applied for a multicomponent simultaneous crystallization from a NaCl/KCl aqueous solution in a batch evaporative crystallizer. A high-resolution method was applied to solve population balance (growth, nucleation and aggregation) coupled with mass balance for both solutes. In order to solve a set of differential equations from population balace discretization a Runge-Kutta method embedded in the Scipy library for Python was used. Good fit was reached comparing model outputs with previous experimental data.

Process condition optimisation for small-scale batch cooling crystallisation across fast and slow kinetic parameters

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Multiple-objective Bayesian optimisation (MOBO) has been implemented here in a pharmaceutical crystallisation application. MOBO was able to greatly reduce the number of experiments required to perform an optimisation of crystallisation process conditions with respect to target kinetic parameters. The MOBO algorithm was benchmarked against a traditional experimental plan method – Design of Experiment (DoE), coupled with minimization of the surface of the experimental space. Determining the global minimum of the surface was largely independent of whether genetic algorithm (GA), differential evolution (DE), covariance matrix adaptation evolution strategy (CMA-ES), Nelder-Mead or pattern search was used. Aspirin and lamivudine were used as case studies to demonstrate that MOBO outperforms traditional experimental optimisation methods for active pharmaceutical ingredients (APIs) with either fast or slow kinetics. MOBO reduced material usage tenfold, highlighting the algorithm's value in driving net-zero and greener sustainable chemistry strategies. MOBO was integrated into an experimental planning algorithm that was used in the DataFactory collection of kinetic parameter estimations. The DataFactory aims to incorporate logical workflows, smart decision-making (presented in this study) and robotics to allow autonomous data collection.

Synthonic modeling and experimental characterization of different solid forms of quercetin and its derivatives

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Molecular modeling of intermolecular interactions, or "synthons", has been instrumental in predicting important particle properties such as morphology as well as surface properties of crystalline materials.

Synthonic modelling allows the determination of the type, strength and directionality of intermolecular interactions of different nature, such as hydrogen bonding and π-π stacking. Intrinsic synthons are those characterizing the bulk of a crystal structure; whereas, extrinsic synthons are defined as those located at the terminal surfaces of the crystals (thus mediating interaction with the surrounding environment).

In this case study, quercetin, a bioflavonoid substance widely used in the food and pharmaceutical industries, is used as model compound. Its different solid forms (e.g., anhydrous quercetin) and other structurally related compounds were analyzed in terms of structure, packing, and conformation energetics. These characteristics, together with the surface topography of the crystal face, are involved in the mechanisms by which crystals grow and they determine the physical and chemical properties of the resulting particles.

In this work, conformational analysis and synthonic modeling have been performed using Materials Studio and Mercury CSD software. These tools were integrated with experimental work to enable the validation of the modeling results. Within Mercury software, Visual Habit is a tool that calculates intermolecular interaction energies for crystal structures using atomistic potentials (e.g., Dreiding, Momany) . The lattice energy of different crystal forms can be measured, and the crystal shape predicted by applying the attachment energy model.

Size and Shape Characterization of Ensembles of Crystals: A Comparison of the Common and the Not-so-common Techniques

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Accurately characterizing the size and shape of ensembles of crystals is crucial for process design, modeling, and control. Several techniques have been proposed and implemented at lab and pilot scales in the pharmaceutical and agrochemical industries. While laser diffraction and focused beam reflectance measurement are the industry standard; fast-emerging alternatives such as Malvern's Morphologi and BlazeMetrics probes are complementing traditional techniques due to their ability to resolve the shape of ensembles of crystals. Often, these techniques provide a 1D particle size distribution lumping all the shape features into a single characteristic length. Although this assumption might suffice for quality control purposes, it may mislead the user when designing, modeling, or troubleshooting processes with crystalline products that exhibit elongated or cuboidal morphologies. Non-commercial imaging techniques such as the DISCO and the combined imaging-confocal microscopy can also resolve the shape of ensembles of crystals. They have been and are being successfully used to model and control the evolution of the size and shape of needle- and plate-like particles. Despite the availability of several techniques, literature lacks a study that compares the performance of these to characterize 1D, 2D, and 3D particle size and shape distributions (PS(S)D). Therefore, we conducted a systematic study to compare the accuracy of six different techniques to characterize particles that exhibit elongated and cuboidal morphologies. Depending on the technique, the obtained distributions varied significantly (see figure for an example population characterized using four techniques). Interestingly, despite the differences in the operation (online vs. offline), the two non-commercial imaging devices yield similar 1D and 2D distributions. It is expected that a study of this nature can help practitioners in the crystallization and the broader particulate technology community to gain a better understanding, leading to an informed decision-making process on the choice of the technique based on the end-use.

Evaluation of crystallization kinetics using image analysis to improve the morphology of an acicular active pharmaceutical ingredient.

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The crystal morphology or external shape of crystalline substances can have a significant impact on their behavior in downstream processes after crystallization and, as a result, their end-product performance. Considering the importance of crystal morphology, incalculable contributions have aimed to control it. In contrete terms, to drive the crystal growth towards isometric morphologies. In this study, we conducted a thorough analysis of the primary, secondary nucleation, and growth kinetics of an acicular active pharmaceutical ingredient to provide a fundamental morphological landscape of the resulting crystals and improve its morphology.

The experimental setup consists of a commercial miniaturized crystallization system (Crystalline, Technobis) outfitted with CCD cameras for inline imaging, which were also exploited in this work for the determination of the primary, secondary nucleation and crystal growth kinetics. The experiments were carried out isothermally at various supersaturation ratios, temperatures, and in different solvents.

The findings show that the supersaturation has a significant impact on the exarcebation of crystal growth rate disparities. Low supersaturation ratios promote the formation of more isometric crystals, as other scientific contributions have also shown. Furthermore, the results clearly depict the trade-off in terms of induction times. Lower supersaturation ratios for isometric crystal formation are accompanied by induction times of several days. Further seeded experiments with the obtained isometric crystals at lower supersaturation ratios allow for the enhancement of crystal morphology whilst also keeping the crystallization time within an improved realistic range of hours.

This systematic approach can be repeated for additional active pharmaceutical ingredients to identify the most favorable process conditions for the crystal design and assess a priori the feasibility of preconceived crystallization routes.

Shaping crystals with fundamental and informatics tools. Using Particle Informatics to understand growth rates

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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, temperature, 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 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.

Data-driven approaches for the classification of crystallisation outcomes from imaging sensors

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In chemical and pharmaceutical manufacturing, data-driven approaches for in-line monitoring of particle attributes are becoming more prevalent to optimise process performance and ensure product quality. These approaches utilise process analytical technology (PAT) and machine learning algorithms to analyse and process data in real-time, allowing for identifying patterns and trends that can be used to make adjustments to the manufacturing process. By monitoring key particle attributes such as size, shape, and composition, the potential issues can be detected and addressed before they result in defects in the final product leading to reduced production costs, increased production yields and improved product quality. In addition, data-driven approaches can provide valuable insights into the root causes of process variability, enabling manufacturers to make targeted improvements and enhance traceability and reproducibility, essential for regulatory compliance and maintaining optimal quality control.

In this study, a Convolutional Neural Network (CNN) is adapted to categorise three distinct crystal shapes - needle, plate, octahedral - and detect images without any crystals. The image data was collected from various crystallisation experiments performed using different solute-solvent combinations using the Technobis Crystalline equipment. The model was trained using 2000 images, with 500 images for each class, and then evaluated to measure the accuracy of its predictions on unseen test data.

This paper studies the CNN model illustrating its capabilities and limitations in combining PAT data with deep learning modelling. A confusion matrix assessed the model performance against the test data showing that it has the ability to differentiate between the crystal classes with an overall accuracy above 90%. This illustrates that the model can see the distinguishable features within the data. The model can be extended to consider additional elements, including contaminating impurities, oiling out, and agglomeration, as these phenomena can determine the crystallisation outcome.

Development of Transferable Mie Potential Force-Fields for Crystal Structure Prediction

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Failure to characterize possible crystal polymorphism can lead to severe ramifications for manufacturers and consumers alike, especially since different crystal forms can have highly distinct physico-chemical properties [1]. Crystal structure prediction (CSP) seeks to elucidate the structure and thermodynamic stability of crystals in silico [2], in the hope that unforeseen transformations may be avoided. The Cambridge Crystallographic Data Centre Blind Tests indicate that the field has progressed considerably since its advent [3,4]. In particular, models based on a combination of ab initio calculations and transferable empirical force-fields (FFs) have been found to afford a good balance of computational cost and accuracy, suitable for application towards larger molecules of industrial interest.

In previous work, we have developed CrystalEstimator for parameterizing these FFs [5]. Here, we investigate a different functional form of the transferable potential. We depart from the Buckingham potential, which is used in most CSP FFs [6,7], and instead seek to parameterize FFs with the Mie potential form. Because Mie potential parameters may be directly associated with explicit features of the interatomic pair-potential (e.g., repulsive wall distance), it is possible to obtain potential shapes which are unattainable using a Buckingham potential. To parameterize these FFs, our database of periodic DFT reference geometries and intermolecular energies [5] has been further expanded to include more training structures, as well as an independent validation set. Using CrystalEstimator to estimate the FF parameters, the resultant Mie FFs perform as well as the Buckingham FFs. Moreover, unlike the Buckingham FFs, the Mie FFs exhibit potential shapes which are better aligned with chemical intuition, reinforcing that they are physically meaningful. Testing the Mie FF on our validation set further demonstrates its excellent transferability. Ultimately, we illustrate that the Mie potential could be a good substitute for the Buckingham potential that is conventionally used in CSP.

Computational study on the polymorphism and crystallisation behaviour of sulfadiazine and sulfamerazine

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Sulfadiazine and sulfamerazine are two pharmaceutically active sulfonamides with antibacterial properties. They differ by only the addition of a methyl group in place on the pyrimidine ring of sulfamerazine but exhibit markedly different properties, namely differing solubilities across a range of solvents as well as different numbers of polymorphs upon crystallization (sulfamerazine has three while sulfadiazine has one). We attempt to rationalise the significant differences reported between these two molecules through a crystal structure prediction (CSP) study and a study of the relative conformer populations of the molecules in variety of solvents, captured by combining enhanced sampling molecular dynamics with unsupervised clustering techniques.

Applications and limitations of PAT tools on oiling out crystallisation and protein crystallisation processes

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PAT tools have been used in many research on crystallisation process, which are very useful to observe the crystallisation process and characterization of crystal product during the process, as well as collecting data for process modeling. In this work, we have demonstrated the application of PAT tools in design and control the crystallisation process, and also reported the limitation of PAT tools in complex solution environments.

With the assist of PAT, we have identified different stages of the crystallisation processes in oiling out crystallisation and protein crystallisation process. Four stages of the oiling out crystallization process of paraben in ethanol and water mixture have been observed [1,2], including formation of the dispersed droplet phase (Stage 1), pre-nucleation (S2), nucleation and crystal growth in liquid-liquid phase separation (Stage 3), and further growth in homogeneous solution (Stage 4). Three stages of the protein crystallisation of lysozyme in sodium acetate buffer solution and sodium chloride precipitation solution have been identified [3], including slow nucleation stage (Stage 1), rapid nucleation and growth stage (Stage 2), and slow growth and breakages stage (Stage 3) were observed.

However, it is sometimes difficult to collect the correct process information due to fouling and UV/IR absorption in the solution [3]. Moreover, other limitations of PAT tools were recorded, including inconsistency among the concentration (by in-situ UV), droplet size distribution (by FBRM), and the off-line measurements, due to observation range of the PAT tools [1,2]. It is sometimes essential to consider, compare and correct the in-line and off-line measurements for a better understanding the crystallisation process.

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Simulations of mother liquor and crystal suspension flows in baffled stirred tank crystallizer

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The industrial crystallization is commonly carried out in baffled stirred tanks. Depending on rheological nature of mother liquor, the suspension mixedness and flow patterns of fluid and particles can vary significantly. Several factors can affect the quality of solid-liquid mixing, including tank geometry, impeller geometry and speed, baffles, density, and rheological properties. Thus, mixing conditions usually affect crystallization, especially with higher mixing intensity, high thick suspensions, and long residence times crystals may break due to secondary nucleation. Changing the mixing conditions in a crystallizer can directly impact the kinetics of the crystallization process and the final crystal size.

Many mixing characteristics such as the average energy dissipation, crystal collision energy, and power number required for mass transfer rate calculation can be calculated using a VisiMix software. In addition to process optimization, it is possible to make process up-scaling simulations. The present work studied the scaling-up process of erythritol and xylitol batch cooling crystallization from 40 °C to 20 °C in terms of constant tip speed and energy of dissipation. Xylitol is very soluble in water, and saturated xylitol solutions usually have relatively high viscosities, while saturated erythritol solutions are not viscous. In addition, the mixedness of the suspension in the batch cooling crystallization in the beginning of the nucleation process and in the end of crystallization was compared.

Purifying biorefinery by-products: A kinetics and thermodynamics approach using solvent-aided layer crystallization

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Production processes in biorefineries results in by-products that can be used directly as raw materials in various manufacturing processes or converted into valuable products . Therefore, developing a process in a sustainable manner entails utilizing the process by-products rather than their disposal. Due to presence of impurities in by-product streams, further downstream purification is required to meet the desired purity level.

Solvent-aided melt crystallization is a promising technology for purification of relatively viscous melts. However, the choice of solvent has a significant effect on thermodynamics and crystallization kinetics. This study aimed to examine and compare the impact of use of different additives, single1 and binary solvents, on crystal growth rate and the purification of glycerol as a by-product of a bioprocess. The different compositions of solvents within the solubility range in the targeted component were evaluated based on liquid-liquid phase equilibrium data estimated by Aspen plus V11.0 software. The influence of each solvent system on melting point depression of the melt was estimated by modified UNIFAC Dortmund model. The kinetics of layer crystallization of each system were evaluated using in-situ image analysis maintained at different crystallization driving force based on predicted solid-liquid equilibrium data. The effect of solvent on purity of final products were evaluated by high-performance liquid chromatography (HPLC). The results ultimately lead to optimization of the process in terms of operating conditions and more efficient use of the solvent, leading to improved downstream purification performance and product quality.

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Acknowledgement

A technique for utilization of hard clam shells as a source of calcium-based materials

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Hard clams (Mercenaria mercenaria), an invasive species in Japan, are increasing in population every year. In this study, we discussed the effective utilization of discarded hard clam shells by analyzing their properties. X-ray diffraction patterns and Fourier transform-infrared absorption spectra of powdered shells confirmed their structure to be of a single-phase aragonite-type. In addition, calcium carbonate was reprecipitated by dissolving the shell powder in hydrochloric acid and blowing in CO_2 and NH_3 gases.

First, the prepared shell powder was dissolved in hydrochloric acid (35.0–37.0%; Kanto Chemical Co., Inc., Japan) to prepare a calcium solution (200 ml). Reprecipitation was then performed using glass ball filters at CO_2 and NH_3 blowing rates of 0.53 mmol/(L·min) and 2.68 mmol/(L·min), respectively. A 300 ml beaker was used as a reactor (10 cm in diameter), with a glass ball filter G3 (20-30 μm pores) for CO_2 gas blowing set 3 cm from the bottom on the left side and a glass ball filter G1 (100-120 μm pores) for NH_3 gas blowing set 3 cm from the bottom on the right side, and reprecipitation method were conducted at 100 rpm using a stirring bar (ϕ; 8 mm, diameter; 30 mm). The calcium solution was reacted with the gases for 5 min under stirring, following which the resulting precipitates were filtered and washed to obtain the final $CaCO_3$ reprecipitates.

X-ray diffraction measurements of the obtained reprecipitated calcium carbonate showed the formation of a single-phase calcite-type structure. The particle shape was uniformly spindle-shaped, and the particle size was approximately 5 μm. Lastly, EDS results confirmed that the calcium carbonate composition was homogenous. The dissolution and reprecipitation of the hard clam is expected to avail calcium carbonate that can act as a valuable industrial source for calcium-based materials.

Synthesis of carbonates by reactive crystallization between CO2 and Ca·Mg in industrial wastes -Controlling the crystal properties with bubble diameter and [Mg2+]/[Ca2+] ratio in bulk solution-

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The carbonation process with reactive crystallization between Ca2+ or Mg2+ in industrial wastes (waste concrete, steel slug, or concentrated brine) and CO2 can be considered as an effective CO2 recovery/utilization method. When the all of Ca or Mg in waste concrete, steel slug, and concentrated brine discharged from industry in the world can be converted to carbonates, CO2 emission reduction is anticipated approximately 1.51 Gt/y which is equivalent to 38 % of global reduction target by 2050. To build up an efficient carbonation process that is adaptable to a carbon neutral society, the increase in conversion ratio of CO2 and improvement of carbonate crystal quality are indispensable during reactive crystallization. In this study, the fine bubble formation technique was applied to the reactive crystallization of carbonates from industrial wastes. In the regions near the minute gas-liquid interfaces, Ca2+ and Mg2+ accumulate because of the negative electric charge on the fine bubble surface, and the concentration of CO32- increases because of the acceleration of CO2 mass transfer caused by minimizing the bubble diameter; hence, local supersaturation increases and the yield of carbonate with superior crystal quality is expected to enhance.

At solution temperature of 298 K and pH of 9.7, CO2 bubbles with dbbl of 40 – 2000 μm were continuously supplied to waste concrete powder extract, steel slug powder extract, or concentrated brine using a self-supporting or dispersing type bubble generator, and carbonates were crystallized. Consequently, minimizing the bubble diameter led to the increase in carbonate yield based on supplied CO2, the uniformization of crystal structure, and the micronization of carbonate produced. Additionally, in the case where [Mg2+]/[Ca2+] ratio in the bulk solution increased at dbbl of 40 μm, the crystal structure of carbonate obtained from industrial wastes changed in the order: vaterite CaCO3, calcite CaCO3, aragonite CaCO3, and CaMg(CO3)2.

Recovering Lithium through Precipitation with Carbon Dioxide after Wet-Shredding of Lithium-Ion Batteries

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The growing lithium-ion battery production capacity causes a steadily increasing demand for high-purity lithium. Due to lithium deposits being concentrated in only few countries outside of Europe, the European Union has declared lithium as a critical resource. Therefore, it is necessary to increasingly recover lithium from secondary sources, that is in particular the recycling of lithium-ion batteries, and thus close local raw material cycles in the sense of the circular economy concept.
In this contribution, the recovery of lithium from an aqueous process stream within a lithium-ion battery recycling process is presented. The aqueous process stream results from the shredding of spent lithium-ion batteries in an industrial shredder while water is added through spraying. Water-soluble salts are washed out of the solid matter and dissolved into the resulting aqueous phase. Especially lithium ions accumulate in the aqueous phase, while only lesser amounts of other cations are found. The dominant anionic contaminants are fluorides and phosphates, which come from the battery electrolyte.

The aim of the investigation is to develop a process for recovering lithium from the aqueous process stream. To remove the relevant contaminations from the aqueous process stream, suitable unit operations are selected and designed accordingly. The lithium is then recovered by heterogeneous precipitation as lithium carbonate by gassing a concentrated lithium salt solution with carbon dioxide. Controlling the pH value during the lithium precipitation is of crucial importance for the product yield. Thus, the focus of the investigation is on the study of the predominant lithium precipitation phenomena. Based on these findings, the continuous operating mode of lithium precipitation is being developed in order to ensure that the research results can be transferred to an industrial scale.

Purification of ε-Caprolactam Monomers via Crystallization from a Depolymerization Reaction Mixture

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In the recent years, recycling of polymers has become more important in industry regarding the need for re-use and for higher sustainability. For example, nylon 6 can be depolymerized into ε-caprolactam (ε-CL) monomers in aqueous solution using a homogeneous phosphotungstic heteropoly acid (HPA) catalyst [1]. After the depolymerization, ε-CL needs to be removed from the reaction mixture. Thus, its separation from the catalyst, reaction educts, and potential byproducts such as oligomers is required. This separation imposes further challenges due to the extremely high solubility of ε-CL in water (~85.5 wt.% at 25 °C). In this study, in-depth solid/liquid equilibria investigations will be conducted for pure components as well as in the reaction mixture. The resulting solubilities of ε-CL and its impurities will be modeled with predictive PC-SAFT models. Such models can be implemented into existing models of the depolymerization to deepen process understanding. Based on these predictions, a separation process concept is developed to efficiently purify ε-CL and recycle HPA to the reaction mixture. Both the crystallization process conditions and various downstream unit operations are investigated to maximize product purity. Due to fast crystallization kinetics, ε-CL is expected to entrap mother-liquor in the crystals and thus requires additional downstream processing such as washing, sweating, etc. for further purification [2]. In this contribution, first results of the aforementioned topics will be presented and discussed.

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Melt and Freeze Crystallization: Enabling technologies for Sustainable Products

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The Circular Economy drives emerging areas like bio-based chemicals, plastics recycling and chemicals for electrical vehicles batteries. High product purities are needed to guarantee the right functionality. Bio-based plastics, recycled plastics and electric cars obviously contribute to sustainability, but there is a growing awareness that also the production processes then need to be sustainable.

Most impurities are excluded from the crystal lattice and therefore the crystals from a single stage crystallization are often already 100-1000 times purer than the liquid from which they were grown making crystallization a perfect technology for high purity products. Wash columns can separate the pure crystals almost completely from the impure mother liquor. Melt/freeze crystallization often use is significantly less energy than distillation/evaporation due to the lower operating temperature and the fact that the heat of crystallization is usually 4 and 7 times lower than the heat of evaporation for respectively organic chemicals and water. In contrast to alternative separation technologies like extraction or adsorption melt/freeze crystallization do not use process aids like organic solvents or adsorbents thus avoiding costs and energy for recycling, recovery and/or disposal.

For the above reasons, melt and freeze crystallization have been recognized as sustainable purification technology. Our paper describes the application of melt/freeze crystallization – wash column technology for the purification of the following sustainable products: lactide, the monomer for the bio-based, bio-degradable plastic PLA; ethylene carbonate, a solvent for electrolytes in Li-batteries; and concentrated vinegar with reduced transport, storage and packaging costs. The developed processes have all been implemented in industry and are perfect examples for the use of crystallization for sustainable products. We will also present an outlook for other areas and products related to the Circular Economy that may benefit from (melt) crystallization as sustainable separation technology.

Minimum Solution Shear Stress Preventing MgSO4⬚7H2O Incrustation on Stainless Steel Plates

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Incrustation of MgSO4°7H2O is investigated on steel (X5CrNi18-10) plates with different finishing qualities. By supercooling of 9 °C, MgSO4°7H2O deposits are found on all plates for tested Reynolds numbers (laminar flow). Shear stress is found to have a noticeable influence on the researched phenomenon. In the range of investigated variables, it increases deposition and removal rates. These rates are the highest for mirror-like surface (plate I). On the other hand, contact angle of solution (wettability) has no clear impact on the process under investigation. Solution minimal shear stress preventing incrustation on the plates is also investigated. It is done experimentally and then by extrapolation on the plot of Geff vs τ. Data analysis shows that simple surface parameters such as Ra, Rz, Rq, Sa, Sp, Sv, St and Sq have no substantial influence on these values. On the contrary, more complex parameters like Sku and Ssk, which are measures of nonconventional finishing and sharpness profile shape, respectively, do have a significant effect. According to the norms skewness is a measure of symmetry of the surface profile about a mean line, which offers a convenient way to illustrate load carrying capacity, porosity and characteristic of nonconventional machining processes. However, kurtosis is a measure of the Amplitude Density Function sharpness and quantitatively describes the randomness of profile's shape relative to a perfectly random surface.

Understanding your API

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Understanding the solid form properties of your API (Active Pharmaceutical Ingredient) is essential for its development. The solid form of an API impacts properties such as solubility, dissolution rate, morphology, and tableting characteristics. Therefore, the selection of a suitable solid form is vital for successful pharmaceutical development, IP protection and the development of a robust crystallization process.

This poster presents the capabilities of Ardena Solid-State Research and provides examples of how a better understanding of the solid-state properties of your API is essential for its development. At Ardena, we help you to identify optimal solid forms of your API through polymorph, salt and co-crystal screens. Our high- and medium-throughput solid-state services in combination with a wide array of state-of-the-art analytical techniques are tailored to provide fast insight into the solid form properties of your API, using only a small amount of material. Once the desired solid form of your API has been selected, Ardena can assist in developing crystallization method that reliably delivers the targeted crystalline form at different scales (100 µL to 1L).

Soft Templates for Controlling Peptide Crystallisation: Case of Leuprolide Acetate

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Peptides are a category of biomolecules that closely mimic natural pathways and can exhibit increased potency and high selectivity. The development of novel synthesis strategies to produce peptides with modulated pharmacokinetic properties and target-specificity has resulted in more accessible pharmaceutical-grade peptides. Due to this advancement, about 80 peptide-based therapeutics have been approved by different drug agencies and are launched on the market. However, in the peptide manufacturing process, separation and purification processes (liquid chromatography process) represent a time-intensive and cost-intense downstream operation from the standpoint of product purity and process yield. Alternatively, precipitation can be used to purify and isolate peptides, but precipitation can result in amorphous solids, amorphous solids, or significant solvent-adsorbed volumes.

This work aims to develop an innovative templating crystallization approach for peptide purification. Link et al. have shown that dissolved amino acids such as L-arginine and L-leucine acted as soft templates, resulting in enhancing insulin nucleation significantly. The model peptide selected for this work is Leuprolide acetate (LA), a synthetic nonapeptide that is a potent gonadotropin releasing hormone receptor (GnRHR) agonist. A sitting drop vapor diffusion crystallization screen resulted in block-shaped particles and spherulites of LA after the addition of potassium sodium tartrate tetrahydrate (PSTT) and ammonium sulphate, respectively, which acted as soft templates. Both, block-shaped particles and spherulites exhibited birefringence under a polarized light microscope and strong absorbance under the UV microscope due to the presence of tryptophan amino acid in LA, confirming the particles are crystals formed of LA molecules. The block-shaped LA crystals exhibited an overlapping diffraction pattern (as shown in Figure 1), when analysed using single crystal x-ray diffraction, confirming the presence of multiple crystals forming the block-shaped particle. Thus, soft-templated approaches are useful for controlling the nucleation and crystallization of peptides, providing new routes for purification and separation protocols.

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