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Oral Presentations



Laser-Induced Cavitation for Controlling Crystallization from Solution

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Keywords: Laser-induced crystallization, high-speed microscopy, 1-D FEM simulations, microfluidics

Controlling crystallization from solution, which is central to technological applications ranging from nanomaterial synthesis to pharmaceutical manufacturing, is still challenging our understanding of nucleation [1]. Among the strategies proposed to control kinetics and emerging crystal properties, non-photochemical laser-induced nucleation (NPLIN), where one or more unfocused laser pulses trigger accelerated nucleation in supersaturated solutions, emerged as a promising approach due to its presumed non-chemical nature and ability to influence polymorphic form [2].

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 [3]. 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.

The proposed mechanism, verified by combining experiments and simulations, may shed light on the discussion of the working mechanism(s) behind NPLIN and sonocrystallization via cavitation [4].

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Influence of molecular interactions between inorganic compounds and protein on their crystallization processes

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Keywords: Lithium carbonate, Calcium oxalate, Lysozyme, precipitation crystallization

Crystallization of inorganic compounds attracts more and more attention due to its wide appearances and applications. For example, the crystallization of lithium carbonate can be used as a recycling method for battery materials [1], which tends to be widely used with the increasing demand for batteries on the market. Calcium oxalate is crystallized as kidney stones inside human bodies [2], which is harmful to people. In this work, two inorganic compounds, lithium carbonate and calcium oxalate are used as model compounds to investigate the influence of interactions between macromolecules and inorganic on their crystallization processes. LiCl and CaCl2 were used in lysozyme crystallization by the hanging drop method [3], with adding more LiCl and CaCl₂, the obtained lysozyme crystals tended to become smaller in size and larger in amount. Na₂CO₃ and C₂H₂O₂ were used as precipitation solutions mixed with LiCl and CaCl2 solutions, respectively. With the addition of precipitation solutions, Li2CO3 and CaC2O4 were first crystallized, with lysozyme crystals appearing later at high protein concentrations, shown in Figure 1. With more protein added to the solution, the nucleation tended to be delayed and fewer crystals were obtained during the same crystallization period. The results clearly demonstrated the strong

interactions between the macromolecules and the inorganic molecules, and the mechanism has been discussed, which will be useful to design and control the crystallization processes.



Figure 1. Tiny CaC2O4 crystals and large lysozyme crystals

[1] Liu, H.; Azimi, G. (2021): Process Analysis and Study of Factors Affecting the Lithium Carbonate Crystallization from Sulfate Media during Lithium Extraction, *Hydrometallurgy*, 199.

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Influence of Solution Boundary Layer Structure on Growth and Dissolution

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Keywords: Growth, Dissolution, Solution Boundary Layer, Diffusion, Laser Interferometry

The current kinetics models of crystal growth and dissolution are based on the bulk solution properties, particularly the bulk superstation and undersaturation respectively. It is known that the solute molecules need to diffuse through a boundary layer surrounding the crystal before integrating onto the crystal surface. Due to the solution concentration gradient in the boundary layer, the concentration or supersaturation/undersaturation in the bulk solution is different from the value at the crystal surface. Therefore, the solution boundary layer structure formed, i.e. its thickness and concentration distribution, provide an additional term of resistance for mass transfer and have a great impact on the growth and dissolution kinetics.

For this, a reaction engineering approach has been considered, in which mass transfer in the boundary layer and growth at the crystal surface are respectively considered to be the processes of diffusion and reaction in series [1][2]. However, due to the lack of knowledge based the experimental data about the boundary layer thickness and the growth rate constant at the crystal- solution interface, the application of the diffusion theory remains impractical.



Fig. 1 Interferogram taken during growth of L-alanine.

We have recently measured the concentration distribution and the thickness of the solution boundary, and the growth rate of the $\{120\}$ and $\{011\}$ faces of L-alanine using our newly developed Mach-Zehnder/Michelson laser interferometer system, which measures the refractive index as a function of solution concentration (e.g. figure 1). Under the certain fluid dynamic condition, the boundary layer thicknesses increases with the bulk supersaturation and undersaturation. The supersaturation and undersaturation interface increase with the

bulk supersaturation and undersatruation for growth and dissolution respectively. However, when bulk understaturation for the dissolution exceeds a certain value, the undersaturation at the crystal surface no longer increases. This indicates disintegration of solute from the crystal surface has no resistance and the dissolution rate is controlled by diffusion only, which is associated with the attachment energy of crystal face. With the knowledge of solution boundary layer, the solution concentration at the crystal surface can be predicted and hence to provide a more accurate kinetics model of growth and dissolution for the crystal morphological faces.

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Morphology Development of Hierarchical Vaterite Structures

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Keywords: vaterite, crystal growth, hierarchy, CXDI

Vaterite, an anhydrous polymorph of calcium carbonate, is found in biominerals and has applications in a variety of fields. Vaterite particles are often found as polycrystalline structures with complex, hierarchical morphologies, which are of interest both due to the superior mechanical properties of naturally occurring layered materials, such as nacre, and the obscurity of their formation mechanism. The hierarchical organization of vaterite microstructures have so far been explained either by supersaturation-controlled kinetic roughening and interface instability or particle attachment.[1, 2] Although detailed analyses of vaterite growth revealed certain aspects of their morphology development, contradicting hypotheses prevail due to the non-exclusivity of the experimental methods that depend solely on observation of final particle morphologies and/or lack quantitative data on (time-dependent) supersaturation profile. In order to advance our understanding of the formation pathways of hierarchical vaterite structures and identify the regulating parameters of the crystallization process, we have performed growth

experiments at controlled supersaturation and investigated the three-dimensional (3D) structures of the vaterite microparticles. The experiments were conducted over a supersaturation range of 1.5-5 with respect to vaterite, and a temperature range of 10 to 60 °C. The constant composition experiments revealed the significant dependence of growth mode on the temperature and supersaturation. 3D coherent X-ray diffraction imaging (CXDI) coupled with Bragg diffraction was employed to visualize the internal architecture of particles with a resolution ~20-30 nm, while simultaneously investigating their crystallinity, and facilitated documentation of the distinction between the seed surface and the new growth layer. Our results demonstrate the strong correlation of particle morphology with thermodynamic and kinetic drivers of crystal growth, defined within the framework of classical crystal growth theory.

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The limits and potentials of heat batteries based on salt hydrates

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Keywords: heat batteries, salt hydrates, phase diagrams, (de)hydration

Approximately 80% of the energy consumption in the western world is in the form of heat, for warming houses and, to a lesser extent, for hot tap water. In the search for sustainable energy sources the demand for heat during winter and the supply by the sun in the summer are out of phase. If the source is industrial waste heat, the source and demand often have a spatial mismatch. An efficient form of heat storage is therefore of paramount importance. A highly effective method of heat storage is Thermochemical Heat Storage (THS), for which heat is stored in a chemical reaction during times of limited demand and released when needed through the reverse reaction. One of the most promising reactions is between two or more hydration states of salt hydrates [1]. As an example, the reaction

 $NaI \cdot 2H_2O(s) \leftrightarrow NaI(s) + 2H_2O(g)$

can store 1.5 GJ of heat per m^3 of salt without energy loss by isolating the water product. The heat can be recovered via the reverse reaction on supplying the water vapor back to the reactor. We have shown this salt to be cyclable for at least 10 cycles (*i.e.* 10 seasons).

In this presentation we will address the problems encountered in applying salt hydrates for THS, like limited (de)hydration cyclability, deliquescence, swelling and the ways to tackle them using data obtained from the phase diagrams. Control of crystal morphology is found to be critical for the cyclability and deliquescence should be avoided unless the crystallites are compartmentalized.



Scanning Electron Microscopy image after a single heating cycle of SrCl₂·6H₂O; a. after dehydration/hydration in an open cell; b. after incongruent melting in a closed cell.

[1] P.A.J. Donkers *et al.* (2017): A review of salt hydrates for seasonal storage in domestic applications, *Applied Energy* 199, 45-68.

Kinetics of primary nucleation of various solid forms of griseofulvin

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Keywords: Nucleation, Polymorphism, Solvate, Pharmaceuticals

Nucleation is a poorly understood phenomenon, in part because nuclei are so small that they are difficult to detect. The purpose of this research is to look into the crystal nucleation of griseofulvin (GSF). GSF is a high-molecular-weight (352.76 g/mol) active pharmaceutical ingredient with a complex molecular structure that includes a cyclohexanone ring, a benzofuran moiety, and numerous functional groups. GSF is prone to polymorphism and solvate formation. Visual detection of the onset of nucleation in 20 mL solutions of n-butyl acetate (nBuAc), acetonitrile (ACN), and methanol (MeOH) was used to investigate primary nucleation of GSF. GSF nucleated as the stable form I from MeOH (CSD GRISFL) [1], as a previously reported solvate from ACN (CSD PINMOQ) [2], and as a new solvate from nBuAc, as verified by PXRD in this work. At room temperature, both solvates were found to be unstable, with the GSF- nBuAc solvate transforming to form I and the GSF-ACN solvate transforming to an unreported polymorphic form (GSF Form VI).

At similar supersaturation, the ACN-solvate shows the fastest nucleation, followed by the nBuAc-solvate, and with Form I nucleating in methanol the slowest, as presented in Fig. 1. Both the pre-exponential factor (kinetic) and the interfacial energy (thermodynamic) are highest for nucleation of Form I from methanol, followed by the GSF-nBuAc solvate and the GSF- ACN solvate, as presented in Fig. 2. The nucleation rate is inversely proportional to the interfacial energy and directly proportional to the pre-exponential factor, according to classical nucleation theory. As a result, for this compound in these solvents, the interfacial energy has a greater influence on the nucleation rate than the pre-exponential factor. The solvent affects the resulting solid phase of GSF as well as the nucleation rate, with the unstable solvated forms crystallizing faster than the thermodynamically stable ansolvate.



Fig.1. Classical nucleation plot for GSF nucleating in MeOH, ACN, and nBuAc.



Fig. 2. Values calculated from the CNT plot: a) interfacial energies and b) pre-exponential factor for GSF nucleating in MeOH, ACN, and nBuAc.

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Quantifying the Kinetics of Competitive Polymorphic Nucleation via Microdroplet Approach

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Keywords: nucleation, microfluidics, kinetics, polymorphism, solubility

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] Moreover, in the context of polymorphic systems, the aqueous solubility of the metastable form is often inaccessible using conventional methods[3] because of the risk of polymorphic transformation during measurement. 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. In this work, we develop an original microfluidic approach to measure the aqueous solubility and nucleation kinetics of a metastable form of KDP (KH2PO4), 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, which agrees with experimental reports in the literature. Indeed, our combined experimental and computational study reveals an interesting interplay between thermodynamics and kinetics in competitive polymorphic nucleation.

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Stabilization and Coagulation of Colloidal Suspensions during Crystallization

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Keywords: Crystallization; Colloid suspension; Particle behavior; Surface interaction

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[1]. However, colloidal suspension could be catastrophic for the phase separation process like crystallization[2]. Due to the high viscosity, colloidal suspension would be a great burden on the equipment, which cause the clogging in pipeline and difficulty in stirring. In addition, due to the collapse of the colloidal suspension, impurities and solvents trapped significantly affect the purity of the final product. Hence, understanding the motion and interaction of particles are crucial and instructive to control the colloid suspension during crystallization. Due to the special thermodynamic properties of cefradine, the mutation of supersaturation usually led to the explosive nucleation, resulting in the formation of large amounts of nanocrystals as the colloidal particles. Via surface analysis of nanocrystal and molecular simulation, the electric double layer on ionized crystal surface was revealed. Then, DLVO model was further derived to analyze interaction between

particles. Combining dynamic light scattering, zeta potential measurements and rheology, the stability of colloidal suspension and motion behavior of particles was understood during the whole crystallization process. The developed knowledge based on the suspension can form a basis for further optimization of purification and crystallization for cefradine.



Fig.1 Stabilization and coagulation of colloidal suspensions during crystallization

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Precipitation of hydrated niobium oxide (niobic acid) from potassium niobate and sulfuric acid solutions

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Keywords: Precipitation, hydrated niobium oxide, thermodynamic simulation, solid characterization

The niobium-based oxides such as niobic acid (hydrated niobium oxide - Nb2O5.nH2O) have received attention due to their application in batteries as well their stability, selectivity and high activity in catalytic reactions, which can be preserved in polar liquids and higher temperatures. The Nb⁵⁺ ion is hydrolysed in water and can be precipitated at lower pH values as niobic acid. The niobium oxide (Nb2O5) in its hydrated form loses most of its surface acidity upon temperature increase (> 500 °C) and the anhydrous crystalline oxide is formed. In this context, we have investigated the precipitation of hydrated niobium oxide from potassium niobate and sulfuric acid solutions. This study aims to evaluate the influence of supersaturation and H2SO4 concentration on the characteristics of niobic acid. Thermodynamic simulation of the niobium- potassium-sulphate-water system was carried out using OLI Studio Stream Analyser to predict the influence of solution composition and pH in the precipitation process. The modelling shows the equilibrium conditions of the system considering only the most stable phase of potassium niobate (KNbO3). In this work, potassium niobate was obtained from an alkaline liquor of Fe- Nb alloy fines leached with KOH. After cooling

crystallization, a solid containing KNbO3 and K4Nb6O17 phases were obtained. Further, the potassium niobate was dissolved in distilled water and the effect of different H2SO4 dosages up to 1 mol was evaluated in batch precipitation for 96 hours. After filtration and drying, the solids were characterized by XRD, XRF, FTIR, Raman and microscopy. The remaining solution was analysed through ICP-OES. The aqueous niobium was also quantified by UV-Vis methodology and confirmed the removal of niobium from the solution. As expected, the XRD shows that an amorphous phase of niobic acid was formed. Raman spectroscopy exhibit characteristic bands of niobic acid (maximum shifts at 450 and 670 cm⁻¹) and for higher sulphate concentrations the broad band sharpens. The experimental results are consistent with the simulation predictions, despite the fact that the OLI Studio database does not contain all potassium niobate phases. The next steps will assess the viability of production of a high-quality niobium oxide from the precipitated niobic acid.

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Machine Learning Based Automatic Crystal Measurement and Growth Analysis

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Keywords: Machine Learning, Mask-RCNN, L-Glutamic Acid, Facet Crystal Growth Measurement, Growth Analysis

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.



Figure 1: Examples of β-LGA crystals from a microscrope which have been measured automatically, left, a single crystal, right, multiple crystals are detected and measured.

Technologies for the Delivery of the Right Particle in Late Stage Pharmaceutical Development

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Keywords: Crystallisation, Particles, Process Development

The complexity in pharmaceutical small molecules is ever increasing, along with increased demands to deliver the API right particle within accelerated timelines to meet early Phase 2b/ Phase 3 clinical timelines. With an ever diversifying portfolio, strategies to deliver the right particle are also having to diversify.

The API right particle is defined by the critical quality attributes (CQAs) of the API, which are critical for downstream processing of the API into the product formulation. Target CQAs should be selected prior to designing the crystallisation, to ensure efficient process design. Furthermore, the right process should deliver the right particle with high yield, short process time and manufacturability. Increasingly, maximizing yields not only reduces batch sizes and cost, but minimizes sustainability risks associated with solvent based crystallisations. A properly designed crystallisation process should ensure delivery of the particle CQAs whilst maximizing productivity.

To meet the demands of a complex Pharmaceutical development portfolio and deliver the right particle, data-rich experimentation methods are being implemented, alongside model-based process design [1]. Modelbased methods have increased utility over empirical approaches to process design, such as Quality-by-Design (QbD), by effectively using limited data sets to model the outcomes of crystallisations to afford the particles of the right form, morphology and crystal size distribution. Furthermore, model-based methods can be combined with data-rich experimentation to develop processes efficiently. By taking a hybrid approach, the time and resources needed to optimize processes ahead of manufacturing is greatly reduced and also frees up material destined for clinic rather than development purposes.

In addition to data-rich and model-based experimentation, crystallisation workflows are being implemented to optimise the way problems are solved on projects. Workflows are designed by collaborators to sequentially eliminate any issues that may prevent crystallisation of the right particle. For example, the use of an impurity rejection workflow has allowed the project to make clear conclusions surrounding the quality of the final API and put in place practical mitigations to prevent the quality profile becoming an issue upon manufacture [2].

To conclude, new routes are being utilized in pharmaceutical process development that can deliver the right particle for increasingly complex particle challenges.

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Towards a solution to prevent encrustation in Couette-Taylor continuous crystallizer set-up

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Keywords: Continuous process, encrustation prevention, Couette-Taylor, Ibuprofen

Traditionally, active pharmaceutical ingredient (API) production is performed through batch processes. Nevertheless, batch production mode has shown some weaknesses over the years, especially batch-to-batch product quality variation. Conversely, the continuous mode ensures more constant product quality [1]. Among continuous operations, the bottleneck is mainly linked to the crystallization step, which is the cradle of one of the main issue in continuous processes: encrustation [1]. The mechanisms of fouling are numerous [2] and can be complex to evaluate.

In this work, encrustation was encountered while performing continuous chiral resolution of racemic Ibuprofen in a mixture ethanol/water 76/24 (w/w) in a Couette-Taylor (CT) crystallizer [3]. Two main sources were identified: generation of local high supersaturation and reduced flow velocity at the inlet of the CT crystallizer.

To avoid such encrustation issue, the preventive implementation of temperature cycling seems to be an attractive solution [2]. The coupling of the temperature increase with pure solvent circulation has proven its efficiency on blockage in previous experiments. Preliminary experiments of periodic cleaning procedure appeared to be quite promising regarding productivity, yield and repeatability.

However, during the cleaning procedure, the continuous crystallizer cannot produce. To address this industrial scale issue, a 4-CT system is proposed and displayed in Figure 1. It is based on a simulated solution involving a system of four independent PFC segments, called Simulated Moving Plug Flow Crystallizer (SM-PFC) [4]. This set-up would include a recycling stream for the cleaning liquors and the filtration liquors.



Figure 1: 4-CT system proposed, including a recycling stream for the cleaning liquors and the filtration liquors.

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Optimization potential of the seeding strategy for continuous enantioselective fluidized bed crystallization

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Keywords: chiral resolution, preferential crystallization, fluidized bed crystallization, continuous operation

The production of pure enantiomers is challenging but of increasing importantance for the life science industries. A cost efficient separation technique is Preferential Crystallization (PC), which allows the direct crystallization of only one enantiomer from a 50:50 (racemic) solution. An enantioselective fluidized bed crystallization (FBC) process applies this technique in continuous operation applying tubular crystallizers. The required continuous supply of enantiopure seed crystals is realized by coupling the conical shaped tubular crystallizer with a milling bypass. The utilization of conical shaped tubes provides a short and narrow residence time distribution of the liquid phase and offers a selective removal of crystal fines. Both effects promise that this process can be operated robust against product contamination by nuclei of the undesired enantiomer. In addition, the conical shape of the tubes causes a size classifying effect, which results in a narrow and easily adjustable product crystal size distribution. Despite these beneficial effects, the coupling of PC with the hydrodynamic effects of the FBC as well as with the breakage kinetic of the milling bypass leads to an auspicious but complex process with limitations for the operating window.

A remarkable steady-state productivity of 150 g/L/h as well as the narrow and easily adjustable product crystal size distribution was achieved in a comprehensive experimental parameter study for the chiral system DL-asparagine monohydrate [1]. Furthermore, the continuous chiral resolution could be demonstrated recently as well for the amino acid DL-threonine and the active pharmaceutical ingredient RS-guaifenesin [2] proving that the enantioselective FBC process is exploitable as well for chiral systems with low solid phase densities and slow crystal growth of needle-like crystals. Despite these achievements, it was also observed that the identification of a suitable seeding strategy, i.e. the shape and size distribution of the seed crystals, is more sophisticated for chiral systems with needle-like crystal growth.

In this contribution, the process and the applied seeding strategies will be explained in detailed. The latter will be evaluated with respect to the comminution rate and breakage distribution. Their impact on the performance of the continuous FBC will be shown for three chiral systems, namely DL-asparagine monohydrate, DL-threonine and RS-guaifenesin. The evaluation of the process performance is based on the steady state productivity achieved in a pilot plant and the corresponding shape and size distribution of the product crystals.

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Fabrication of Spherulitic Hierarchical Energetic Materials via Noncrystallographic Branching Induced by Polymer Additives: A Case Study of 2,2',4,4',6,6'-Hexanitrostilbene (HNS)

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Keywords: energetic materials; hierarchical structure; noncrystallographic branching; crystal defects; polymer additives

The spherulitic hierarchical 2,2',4,4',6,6'-hexanitrostilbene (HNS) was successfully fabricated via noncrystallographic branching induced by polymer additives (Fig. 1), which was promising to solve the problems of nanoscale energetic materials in agglomeration and microscale bulk crystals in low activity. The prepared spherulitic HNS owned nearly 6 times the specific surface area of the raw HNS, with decreased impact sensitivity and advanced melting and decomposition temperatures, demonstrating a good desensitization effect, and a favorable energy release of the hierarchical structure.

The morphological changes were explored for the effect of the molecular weight and concentration of PVP, which indicated that the molecular weight of PVP presents a more profound effect than the concentration on inducing the spherulitic growth of HNS. Furthermore,

the formation mechanism of spherulitic HNS was experimentally verified that additives acting as the impurities adsorb on the HNS crystals and inhibit the growth steps on the (200) face, introducing stress and generating defects to trigger noncrystallographic branching and further spherulitic growth. The adsorption effect of additives was verified by FTIR, and the crystal defects on the crystal surface and inside the crystals were detected by AFM and SAXS, respectively.



Figure 1. HNS crystals without additives (a), in the presence of polysuccinimide (PSI) (b1 and b2), or polyvinylpyrrolidone (PVP) (c1 and c2).

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Polymer-mediated and Ultrasound-assisted Crystallization of Ropivacaine: Crystal Growth and Morphology Modulation

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Keywords: Pharmaceutical crystallization, Crystal shape and size, Additive, Ultrasound, Molecular simulation

Abstract: The objective of this work was to modify the crystal shape and size of poorly water- soluble drug ropivacaine, and to reveal the effects of polymeric additive and ultrasound on crystal nucleation and growth. Ropivacaine often grow as needle-like crystals extended along the aaxis and the shape was hardly controllable by altering solvent types and operating conditions for the crystallization process. We found that ropivacaine crystallized as block-like crystals when polyvinylpyrrolidone (PVP) was used. The control over crystal morphology by the additive was related to crystallization temperature, solute concentration, additive concentration and molecular weight. PVP with shorter chains showed more profound influence on decreasing the aspect ratio of crystals. SEM and AFM analyses were performed providing insights into crystal growth pattern and cavities on the surface induced by the polymeric additive. In ultrasound-assisted crystallization, the impacts of ultrasonic time, ultrasonic power, and additive concentration were investigated. The particles precipitated at extended ultrasonic time exhibited plate-like crystals with shorter aspect ratio. Combined used of polymeric additive and ultrasound led to rice-shaped crystals, which the
average particle size was further decreased. The induction time measurement and single crystal growth experiments were carried out. The results suggested that PVP worked as strong nucleation and growth inhibitor. The inhibition ability exhibited dependence on supersaturation, molecular weight of additive, concentration of additive, and ultrasound. Molecular dynamics (MD) simulation was performed to explore the action mechanism of the polymer. The interaction energies between PVP and crystal faces were calculated, and mobility of the additive with different chain length in crystal- solution system was evaluated by mean square displacement (MSD). Based on the study, a possible mechanism for the morphological evolution of ropivacaine crystals assisted by PVP and ultrasound was proposed.



Figure 1 (1) MSD plots and snapshots of additive (green) with different chain length adsorbed on (101) face of ropivacaine; (2) effects of polymeric additive and ultrasound on the morphology of ropivacaine crystals

PAT assisted estimation of the kinetic parameters during the crystal growth of paracetamol in isopropanol

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Keywords: Crystallization, Crystal growth kinetics, Secondary nucleation

Crystal growth kinetics parameters are essential to design industrial crystallization units [1]. Crystal growth parameters are also essential to design experimental set-ups required for the continuous manufacturing of active pharmaceutical ingredients [2]. We performed batch crystal growth experiments assisted by the state-of-art Process Analytical Technology (PAT) tools that includes the FTIR and FBRM to study the growth kinetics of paracetamol (an important API) in isopropanol at different operating conditions [3]. The operating variables studied include the initial supersaturation, seed loading, seed size, agitation speed and temperature [1]. The experimentally obtained results were used to obtain the crystal growth kinetic and thermodynamic parameters using the Burton-Cabrera-Frank, spiral nucleation and the birth and spread model [4]. We will show the results correlating the kinetic parameters obtained from the above-mentioned theories with the operating variables that can be used to design industrial scale crystallization units.

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Feasibility assessment of a three-phase reactive crystallizer for pH swing carbon capture processes

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Keywords: spray tower, pH swing, alkaline scrubbing, reactive crystallization, carbon capture

Separating CO2 from flue gas or ambient air is often performed using sorbents that require thermal regeneration. The respective processes often apply a temperature swing approach [1]. However, the growing number of renewable energy plants predominantly provides electrical energy requiring alternative process concepts such as the electrochemical pH swing [2]. The working principle of a pH swing carbon capture process is based on the dissociation equilibrium of CO2. An electrochemical regeneration is performed by directly producing H⁺- and OH⁻-ions. To realize an energy-efficient operation, CO2 needs to be captured as bicarbonate instead of carbonate. That way, only a single H⁺- and OH⁻-ion per absorbed CO2 must be provided to the system. However, in an alkaline scrubbing process, the sorbent capacity is very limited, if the targeted pH predominantly fosters the formation of bicarbonates. Thus, suggest supplementing the alkaline scrubbing process by an *in situ* we precipitation of bicarbonates, so that energy-efficiency can be maintained despite scaling sorbent capacity (See scheme below).

At the Chair of Fluid Process Engineering, a pilot plant of a three- phase reactive crystallizer is set up. A spray tower design is selected, promoting a low pressure drop in the gaseous phase and a high surface-to-volume ratio in the liquid phase. The spray tower is fed with a flue gas surrogate system consisting of 15 mol% CO₂ and 85 mol% N₂. At the top of the tower the alkaline solution containing the precipitating agent is injected through a nozzle plate.



Scheme of the pH swing process with an in situ precipitation

The first experiments successfully demonstrated the absorption with an *in situ* precipitation. The results to be presented include an experimental sensitivity analysis comparing a pure absorption process with an *in situ* precipitation of bicarbonate and carbonate salts under varying liquid/gas flow ratios. CO2 depletion, CO2/OH⁻ ratio and remaining alkaline absorption capacity are examined for the different alternatives. The process imposes several requirements on the selection of the precipitant, which are addressed in particular.

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Recovering Lithium Carbonate Using Gas – Liquid Reactive Crystallization Of Lithium Hydroxide And Carbon Di-Oxide

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Keywords: Crystallization, Lithium carbonate, Lithium recovery, Spent LIBs

Lithium is a vital component in lithium-ion batteries (LIBs), which are the heart of electric vehicles. There is a projected lithium shortage in the future, so some of the de-bottlenecking of the lithium supply chain crisis can be achieved by recovering lithium from spent LIBs [1]. The water leaching process is one of the methods used for selectively leaching lithium from spent LIBs as lithium hydroxide (LiOH), followed by sodium carbonate (Na2CO3) precipitation for lithium carbonate (Li2CO3) recovery [2]. One of the key challenges during this process is the purity of the recovered Li₂CO₃, as there is a potential for sodium incorporation. The semi-batch gas-liquid reactive crystallization of LiOH and CO2 to form Li2CO3 is investigated in this work. We focus on investigating the behaviour of Li2CO3 crystallization at various temperatures as well as the CO₂ flow rate. The Li₂CO₃ solubility decreases with the increase in temperature resulting in higher lithium recovery [3]. During the experiments, pH and temperature were in- situ monitored along with the samples of liquid and solid precipitate to determine % lithium recovery (using microwave plasma atomic emission spectroscopy (MP-AES)) and Li2CO3 morphology (using scanning electron microscopy (SEM)).

The maxima for lithium recovery followed the pH and temperature maxima (Figure 1). SEM images show that the Li2CO3 products are spherulites (Figure 2), which are composed of smaller, plate-like crystals. The size analysis shows that the average size of the Li2CO3 particles at the various experimental conditions is in the range of 50-100 μ m, allowing for efficient filtration. The present work will open the possibility for recovery of high-purity Li2CO3 from spent LIBs which can be used in the resynthesis of cathode active material for new LIBs.



Figure 1: Li2CO3 crystallization (50 °C & 0.525 L/min)



Figure 2: SEM Li2CO3 (50 °C & 0.525 L/min)

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Eutectic Freeze Crystallization Investigations on NiSO4-CoSO4-H2O System

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Keywords: Eutectic Freeze Crystallization, nickel sulfate, cobalt sulfate, recovery, lithium-ion batteries.

Nickel sulfate and cobalt sulfate are essential materials in the battery industry. Particularly in lithium-ion batteries, they are both used as precursor ingredients in producing cathode material and electrolyte additives to improve performance. Recycling raw materials of batteries is crucial because it conserves energy and reduces the demand for new resources, greenhouse gas emissions, and waste. Therefore, investigations have been carried out to recycle valuable NiSO4 and CoSO4 from used batteries. Precipitation, evaporation, crystallization, ion exchange, membrane filtration, biological treatment, and chemical oxidation methods are mainly used to recover NiSO4 and CoSO4 from their aqueous waste solutions.

Eutectic freeze crystallization (EFC) is a unit process that uses the principle of freezing point depression to separate a mixture of two or more components. When an aqueous solution is cooled below its eutectic temperature, as the system reaches eutectic composition, ice and salt crystallize simultaneously and separate from the liquid phase due to their density differences. EFC has several advantages over other separation techniques, including low energy requirement, high purity, simple operation principle, and environmental benefits.

To operate EFC method successfully, accurate knowledge of the NiSO4-CoSO4-H2O phase diagram is needed at low temperatures. In this study, the effect of Co on NiSO4-H2O eutectic point and Ni effect on CoSO4-H2O eutectic point were investigated experimentally. The onset of crystallization upon cooling several solution concentrations allowed to draw metastable lines for ice and salts.

Experiments were also carried out for the composition of the industrial nickel sulfate-cobalt sulfate battery waste stream under EFC. The system's performance was evaluated for the eutectic freeze crystallization treatment method regarding ice and salt qualities, quantities, and economic and technical issues.

Crystallization of vivianite for phosphorus recovery from wastewater

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Keywords: Iron phosphates, precipitation, crystal growing

The efficient way to obtain phosphorus (P) from sustainable sources has become a challenging task to meet the increasing demand of various industrial sectors, for instance, fertilizer production and the battery industry. One of the possible sources of P is wastewater, where the crystallization processes of P-containing minerals could be maintained [1]. However, this approach has not been systematically studied for P-recovery in the form of vivianite Fe^{2+} (PO) \cdot 8H O from solution, and therefore, the forming conditions for optimal crystal growth need to be defined. Our current study focuses on the crystallization of highpurity vivianite from an artificial solution that simulates processed wastewater. The crystallization process was examined under different pH conditions (pH 5.0 to 8.5) using a novel combination of methods, including real-time visualization (Figure 1a), to probe the crystal morphology and other properties. The mineralogical composition and purity of the crystals were characterized by X-ray diffraction (XRD). The shapes of the crystals were observed by scanning electron microscope (SEM) (Figure 1b). The size distribution of the crystals was determined using the Multisizer. The preliminary results of the study provide a comparison of the effect of pH on crystal sizes and shapes at different stages of the crystallization process. According to the size-particle analysis, the

promising optimal range of pH seems to be between 7.5 and 8. We assume that the output of this research will help predict the optimal conditions for effective vivianite recovery from real wastewater.



Figure 1. Scheme of the experiment (a); SEM image of vivianite crystal at pH 7.5 (b).

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Vanadium Crystallization from High Tenor Bayer Liquor

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Keywords: Vanadium, Acetone, Crystallization, Anti-solvent

The valorisation of waste produced during metal extraction has become an integral component of minimizing negative environmental impacts. The bauxite ore used exclusively in the production of aluminium oxide via the Bayer process, contains besides Al, several trace elements like rare earth elements (REEs), V, Li, Sc, Ga that are currently not valorised. Vanadium and Gallium both dissolve during the Bayer process forming a constant impurity in the Bayer liquor, the sodium aluminate solution which is the heart of the process. Vanadium finds application in multiple industries ranging from steel and battery manufacturing to aircraft and defence industries; this has made it a metal of interest. The extraction of vanadium involves pyrometallurgy, leaching, SX, and ammonium treatment of strip liquor to the precipitate the vanadium salts, ammonium metavanadate (AMV) and vanadium pentoxide [1, 2]. Vanadium precipitation techniques presently in use have the drawback of generating copious amounts of highly saline ammonium containing wastewater coupled with solid waste that is difficult to handle safely or recycle [3, 4]. This study seeks to understand the crystallization of vanadium salts (measured through yield and purity) from a synthetic vanadium laden leach liquor using antisolvent crystallization in a temperature-controlled jacketed batch reactor. The aqueous vanadium concentration ([V⁵⁺]) was varied from 20 to 40 g/L with different organic to aqueous ratios (O/A =0.5; 0.75; 1) whilst using acetone as the antisolvent. The primary precipitates were analysed for yield, purity, morphology, structure, particle size and composition. The preliminary results showed that an increase in O/A ratio, from 0.5 to 1, led to an increase in yield. This

increase was accompanied by time dependent changes in mean particle size, number of particles, and micro-structure that arose from conditions that favoured agglomeration. It is anticipated that the enhanced agglomeration will have impacts on product purity.

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Effect of crystallization rate on the thermal conductivity of paraffins

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Keywords: Crystallization; Paraffins; Thermal Conductivity; Heat Transfer.

Thermal energy storage is an essential item in the development of energy generation and supply systems. Phase change materials (PCMs) can be a solution to this demand by transferring heat associated with the latent heat of phase change [1]. A major problem with paraffins is their low thermal conductivity, around 0.2 W·m⁻¹·K⁻¹ [2]. The effect of the crystallization rate on the thermal conductivity of the solid formed has not been adequately studied. This study presents the effect of the crystallization rate on the thermal conductivity of paraffins, evaluated by means of experimental measurements of solid thermal conductivity and by performing layer crystallization experiments and modeling using an internally cooled cylindrical tube, denominated "cold finger" which uses water as cooling fluid.

Was used paraffin 120/125-6, with temperature of the crystallization at 49.75°C. For the conductivity measurements, two paraffin samples were made by first melting then at 70°C in two steel vessels. The fast crystallized paraffin sample was then placed inside a thermostatic bath containing water at 4°C until complete solidification and the slow crystallized sample vessel was exposed to ambient air at 23°C. Figure 1A shows the locations of the measurements and the average values. Mean thermal conductivity increased 14% (HSD test, 5% significance) by fast crystallization and was statistically significant. Layer growth experiments were done under several conditions. Cooling fluid at 10°C and heating fluid controlling the molten paraffin temperature kept at 55, 57, 60 and 63°C. For the cooling fluid kept at 20°C, the heating fluid temperatures were kept at 55, 60°C. For each run, three measurements of layer thickness with a digital caliper. The mathematical model consisted of heat transfer and crystallization phenomena such as the convection in the cooling fluid, conduction in the cold finger wall and solid paraffin layer, and natural convection in the molten paraffin. Most of the input variables and physical properties were measured experimentally, e.g., the liquid paraffin viscosity and density. Figure 1B shows the results related to the average crystal growth rate. Faster crystallizations cause higher thermal conductivities in solid paraffin.



Figure 1. A, direct thermal conductivity measurements. B, cold finger model results

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Metal carbonates recovery from Lithium-Ion Battery (LIB) hydrometallurgical recycling process

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Keywords: LIB recycling, carbonates, simultaneous crystallization, multicomponent systems, thermodynamic simulation.

The energy transition in Europe brought to light the limited resources in terms of raw materials required for the production of batteries to feed the increasing demand and the environmental repercussions in their primary extraction. Urban mining comes as a possible solution to recover these metals. In this process, end-of-life batteries are collected and dismantled, and pyro- and/or hydrometallurgical processes are applied for the recovery of high purity metal salts that can later be used in the production of new batteries. Despite being considered a highly efficient process, it is a laborious and expensive process, yet to surpass many challenges such as the great variation in the input stream result of different brands and models of batteries mixed in the recycling step and the heavy use of chemicals in successive extraction processes. Simultaneous and fractional crystallization show great potential in process intensification in reducing steps and, consequently, costs, on the recovery of dissolved materials, as it comprises the recovery of several compounds by the crystallization from a multicomponent solution such as the lithium-ion batteries (LIB) liquor. 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 untreated LIB-liquor to

reduce the number of solvent extraction steps currently implemented, and consequently decrease the need for harsh chemicals. We used thermodynamic simulations (OLI Studio Stream Analyzer) to predict the behavior of the metal- containing systems in the precipitation of carbonates using sodium carbonate as a precipitant agent. The simulations were used as guidelines for batch precipitation experiments. The solutions contained (in g.L⁻¹) Li = 2.8; Co = 8.4; Ni = 7.4; Mn = 6.8 and 2M H2SO4. Sodium carbonate is added at once and the mixture was kept under stirring for 24h. The product was characterized using XRD, SEM and microscopy. The remaining solution was characterized through ICP-OES. Results show that cobalt, nickel and manganese can be recovered simultaneously, with recovery rates higher than 99.9% for Co and Mn and 92% for Ni. In opposition to the simulations, lithium had a maximal recovery of 56% compared with the theoretical 86.5% shown in OLI. We hypothesize that the competition for the carbonate ion during the simultaneous crystallization of the metal-carbonates along with different kinetics slows the lithium carbonate formation, which may require longer time to achieve higher recoveries. 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.



Melt crystallization of phytosterols

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Keywords: Melt crystallization, Phytosterol, Purity

Phytosterols, known as plant sterols and stanols, commonly exist in nuts, seeds, vegetables, fruits, and vegetable oils. There are over 200 types of sterols and most common phytosterols are β-sitosterol, stigmasterol, campesterol, and brassicasterol. The main advantage of phytosterols is to inhibit blood cholesterol absorption as well as increase excursion of cholesterol since they are a family of molecules related to cholesterol. [1, 2] Owing to health benefits and wide range of applications in pharmaceutical, food and cosmetic industry, more and more research has been focused on separation and purification of phytosterols. Maximize Market Research [3] stated in their recent analysis report that phytosterol market size in 2022 was \$950 million with a CAGR of 8.8% in 2023-2029. Extraction, chromatographic separation, solvent crystallization, and enzymatic process have been used for separation technologies of phytosterols. However, low purity of the end products, toxic solvents and high costs of the complex process are the drawbacks of those techniques [4]. An economical downstream process which gives maximum purity and yield is critical and needs to be developed.

Melt crystallization is considered as a green purification technology since it does not need any additional chemical/solvent and the process performance is quite simple, which thus lower the capital cost and energy consumption [5]. To our best knowledge, there is no available reference concerning melt crystallization of phytosterols and it has great potential with competitive advantages compared to other techniques. Therefore, the current work focuses to develop a melt crystallization process for purification of phytosterols extracted from crude tall oil. The aim is to pursue food grade phytosterols fulfilling certain product profile criteria. Commercial pure phytosterol will be used as a reference standard compound for feasibility studies and process development. The effect of operational variables, such as cooling rate, temperature of the melt and seeding on the product purity, yield, and profile will be discussed.

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Facet Crystal Growth Kinetics of β-Form L-Glutamic Acid for Growth Kinetics Determination with Machine Learning

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Keywords: L-Glutamic Acid, Microscopic Crystal Imaging, Facet Growth Rate Measurement, Facet Growth Kinetics, Machine Learning

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. Mansemi-automatic and full-automatic (with machining learning) ual. tools were used to compare and their assess 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 are used to compare with that from this study. Finally, the growth mechanisms of both capping and side faces are obtained.



Fig. 1 The growth rates of β-form LGA single crystalsin individual face directions vs. supersaturations

Recovery of vanadium oxide from spent carbon capture solvents

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Keywords: Vanadium pentoxide, ammonium vanadate, precipitation, carbon capture.

To comply with the Paris Climate Agreement to keep global warming below 2°C, many countries including the European Union aim at becoming carbon neutral by mid-century. Reaching this goal requires decarbonization of industries and the transportation sector. However, it is realized that some emissions will remain as their abatement would be too demanding from a technical and/or economical viewpoint. To compensate for these remaining emissions, negative emission technologies need to be in place. [1] Bioenergy carbon capture and storge, or BECCS, offers a viable option to produce negative emissions. BECCS includes an absorption unit where a liquid solvent is used to remove CO2 from the flue gas originating from the conversion of biomass.

The current work investigates the recovery of vanadium from spent absorption solvents used for carbon capture. Absorption solvents such as aqueous potassium carbonate (K2CO3) contain vanadium pentoxide at concentrations around 2-3 w% to enhance the absorption rate of CO2 [2]. Vanadium is a critical material, and it is thus of interest to develop methods to recover vanadium once the solvent is wasted (the solvent will gradually accumulate dust and impurities such that it eventually needs to be replaced, creating waste). Being able to utilize the wasted solvent improves the economic and ecological performance of BECCS, while at the same time increasing its public acceptance and strengthen its role as a sustainable climate technology.

The work explores a possible route for the recovery of V from a spent BECCS solvent via precipitation. Literature [3] showed that vanadium compounds in sodium carbonate could be recovered via the addition of ammonium salts. Our research showed that this process also is applicable when dealing with K2CO3 solution. Via the precipitation route, recovery of vanadium from a synthetic solvent via an excess addition of ammonium salts was possible. When washed and dried, ammonium vanadate of high purity was achieved. A series of tests was conducted to examine the effects on the precipitation efficiency by varying pH and reaction time. The experiments showed that pH has a strong effect on the precipitation ammonium vanadate. Reaction times were found to be relatively long and precipitation of vanadium salt at room temperature required around 24 h.

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Pilot scale production of Magnesium Hydroxide: evaluating the potential of natural saltworks bitterns

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Keywords: Mineral recovery; reactive crystallization; pilot-scale prototype.

Nowadays, sustainable and renewable productive processes and resources are the only alternatives to tackle the continuously growing global population and high living standards requirements. For the case of bitterns, i.e. the by-products streams of sea salt production in saltworks, magnesium concentration can reach values up to 20-60 times than seawater [1]. Magnesium compounds, such as magnesium hydroxide, Mg(OH)2, are widely adopted in numerous industrial applications [2]. These compounds are primarily manufactured from mineral ores causing environmental, and geopolitical concerns about landing mining consumption and supply risk availability. In this context, the present work deals with the production of Mg(OH)2 at a pilot scale from unconventional sources, namely natural bitterns. Mg(OH)2 was extracted from a bittern collected from the Margi saltwork located in Trapani, Italy. Magnesium concentration of ~50 g/l was found in the bittern. Sodium hydroxide, NaOH, was used as the alkaline reactant. A proprietary multi-plug flow reactor designed in the framework of the Europan SEArcularMINE project and patented by ResourSEAs was employed. The reactor is made of two adjacent fluid compartments where the bittern and NaOH solutions flow. The bittern is injected into the alkaline solution through multiple nozzles to ensure good reactants

homogenization all over the reactor volume. Produced Mg(OH)2 suspensions are recycled back to the inlet section of the reactor to achieve a total conversion of Mg ions and to promote a seeded Mg(OH)2 precipitation. The influence of several operating parameters was investigated on Mg(OH)2 suspensions and powders characteristics: (i) bittern and NaOH flow rates, (ii) NaOH concentrations (iii) final suspension pH values (stoichiometric or OH⁻ excess amounts). Mg(OH)2 suspensions exhibited the best thickening and filterability performances when produced (i) at stoichiometric conditions, (ii) at low reactants mixing degree and (iii) by adopting low NaOH concentrations. Magnesium recovery was always > 99.9 %, thanks to the slurry recycling strategy. In addition, Mg(OH)2 powders mass purity reached values > 97 %, complying with commercial specifications. Results demonstrate that saltworks bitterns are promising sources for the sustainable industrial production of Mg derivates from waste.

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Industrial crystallization of new pseudo-polymorphs: root cause analysis and characterization

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Keywords: Pseudo-polymorphs, crystallization process, storage conditions, impurities.

In production, crystals can enter in contact with water (from the surrounding atmosphere or from the solvents) along the solid chain process (crystallization, filtration, washing, drying) and all the following steps (packaging, storage, and transport).

Depending on the product, the presence and amount of water can impact the quality of the crystals resulting for example in lumps formation, a degradation and/or the crystallization of pseudo-polymorphs. In this regard, new pseudo-polymorphs were unexpectedly isolated in production upon changing the conditions in the upstream and downstream process. Thereafter, the crystallization conditions and the solid-state characterization of three pseudo-polymorphs were investigated by X-Ray diffraction, DVS, Raman and IR analyses.

A DVS analysis shows that Form III can be obtained by a transformation of Form I at 70% Relative Humidity (RH) at 25 °C within 24 hours. Such conditions could have occurred during the drying step (if operational parameters are not properly controlled, for example the surrounding atmosphere could be saturated with water) or while handling the powder (sealing issues) resulting in the conversion of Form I into Form III. The *in-situ* Raman analyses performed with a suspension of Form I in methanol/water at 25 °C show that the conversion from Form I to Form III is achieved within 24 hours. This transformation could therefore also have taken place during an extended forced storage of the suspension in the reactor due to technical issues before the filtration step.

The presence of impurities, even at ppm level [1], can enhance or inhibit [2], the nucleation and crystal growth of a specific form. A stable pseudo-polymorph Form II crystallized unexpectedly in production. The root cause analysis showed that the presence of impurities coming from a change in the upstream process has enhanced the crystallization of Form II and inhibited the one of Form I. The process had to be adapted in such a way that the impurities were below a given threshold, where the crystallization of Form I solely is enhanced.

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

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Keywords: Cosolvency; Molecular conformation; Intermolecular interactions; Intramolecular interactions

Cosolvency is an interesting and important thermodynamic property that is frequently used in the pharmaceutics and fine chemicals industry [1]. 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 make the nucleation uncontrollable and further affects the product quality [2]. However, the molecular mechanism of the phenomenon of cosolvency, including the differences in molecular conformation before and after cosolvency and the changes in inter/intramolecular interactions in single pure solvents and binary co-solvents, has been less studied. 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/intramolecular interactions, which in turn leads to the latent solubilization phenomenon (Figure 1-2). 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.



Figure 1. Molecular conformational changes before and after cosolvency.



Figure 2. Solubility and simulated inter/intra-molecular interaction changes of L-alanine, L- phenylalanine and L-tryptophan in water + 1-n-propanol at 293.15 K.

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Influence of hydrodynamic conditions on the formation of spherical crystals

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Keywords: ceritinib, granulometric properties, hydrodynamic conditions, spherical crystallization

In the production and purification process of an active pharmaceutical ingredient, small crystals often cause problems in filtration and drying, as well as in handling and packaging of the final product. Controlled crystal agglomeration during the process of spherical crystallization can prevent such problems. Using spherical crystallization to obtain suitable particulates for direct tableting appears to be an effective alternative. The excellent flowability and compression properties of spherical crystals facilitate the tableting procedure.

Spherical agglomerates of an active pharmaceutical ingredient, ceritinib, were prepared by a combination of the spherical agglomeration method and quasi-emulsion solvent diffusion technique. According to the solubility test, a THF-heptane-water system was used to produce ceritinib agglomerates. Heptane was employed as a bridging liquid, while THF was used as a suitable solvent because of ceritinib's high solubility in THF. Water was used for the fast precipitation of ceritinib since it is practically insoluble in water. Spherical crystallization was carried out in a heterogeneous area of three solvents, with a bad solvent, good solvent, and bridging liquid mass ratio of 7:1:1. Heptane was dispersed in a 1 wt.% PVP-water solution, then ceritinib-saturated THF solution was added, and spherical crystals were formed. The hydrodynamic conditions in the crystallizer determine the size of the heptane droplets that form in the PVP-water solution and the crystals that shape when the saturated THF solution is added to the water. A six-pitch blade turbine impeller, a six-blade Rushton turbine impeller, and a spiral propeller agitator were utilized to generate spherical crystals of ceritinib. Since various stirrers result in different vessel flows, crystals with different granulometric properties form. The minimum mixing rate required to disperse the bridging liquid in the aqueous PVP solution was determined for all types of stirrers. It was determined by how the mixture rate influenced the granulometric properties of the crystals.

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Effect of salts on the solubility and crystallization of L-histidine polymorphs

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Keywords: crystallization, L-histidine, polymorph, solubility

L-histidine is an essential amino acid that used in the biosynthesis of proteins. It is also an important substance in the pharmaceutical and food industries. Crystallization is the most widely used process because the crystal form is benefits to the development in drug and medical fields. L-histidine can be crystallized into two crystal forms-form A and B. Differ forms present in different physical properties i.e. solubility. From literature, the difference crystal forms provided different the ability of dissolution in any salts solutions. Nevertheless, the studied of both forms of L-histidine on their solubility as well as the effect of salts on its solubility are necessary for the application needs especially in pharmaceutical field since it might have to vary for distributed the dissolution considered. The effect of sats on the crystallization of L-histidine polymorph need also to be studied. Thus, this work is focus on the solubility of L-histidine crystal form A and B at different concentrations in the various salts concentrations of the solution. The effect of salts concentrations on its solubility was investigated using the Focus Beam Reflectance Measurement (FBRM) during the dissolution process of L-histidine. The crystallization and polymorphic transformation were investigated using Raman spectroscopy for the
measurement of solute and solid concentrations, and EasyViewer for image analysis.

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Dandelion-sowing Hydration Mechanism of the Water-insoluble Drug Aripiprazole

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Keywords: Aripiprazole, Water-insoluble, Hydration, Mechanism

Hydrate of APIs has received a lot of attentions as it can broaden the options for final dosage forms and can also enrich the methods for developing new crystal forms.^[1,2] In this work, aripiprazole whose solubility in water is quite low^[3] was used as model compound to investigate the mechanism of hydration and low solubility. Based on single crystal structures of Form H1 and anhydrous Form III, molecular surface electrostatic potential (MSEP) was calculated to localize strong intermolecular interaction sites. The conformational energies and cohesive energies of Form III and Form H1 were calculated and their stabilities were compared. The energy calculation results show that the relative stability of Form III and Form H1 can be determined by the cohesive energy. Furthermore, the insolubility mechanism of Form III in water was explored based on the synthetic analysis of the crystal structure, crystal energy, and molecular dynamics simulation results. It was found that the overall decrease in polarity caused by the formation of

APZ diamide dimer structure and the strong binding effect on APZ molecule clusters due to strong hydrogen bonds and van der Waals interactions lead to the water insolubility of Form III. Finally, a dandelionsowing mechanism for the solid-phase transformation process (hydration process) of Form III to Form H1 in water was explored by suspension crystallization experiments and molecular dynamics simulations. The core step of the mechanism lies in the detachment of APZ molecules or small molecular clusters from the surfaces of Form III molecular clusters induced by external input energy, like the detachment of dandelion pappi from blowballs blown by the wind. The whole dandelion-sowing type hydration mechanism is demonstrated in Figure 1.



Figure 1. The dandelion-sowing type mechanism of the hydration process from APZ Form III to Form H1.

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Recovery of MnSO4 by Eutectic Freeze Crystallization

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Keywords: Eutectic Freeze Crystallization, Lithium-ion battery recycling, Urban mining, Sustainable separation technology.

Lithium-ion batteries are widely used in portable electronics and electric vehicle applications today due to their high energy, power density, and enhanced cycle life. The batteries often contain high amounts of precious metal such as Li, Ni, Mn, and Co where most of these valuable elements are lost in landfills or hoarded in households after the product life cycle has been reached. Therefore, the compiled quantity of waste in the future will be considerable unless significant progress is achieved in recycling of these critical elements . Although there are existing recycling technologies such as evaporative crystallization to recover the precious metal from lithium batteries, this process is energy intensive and not efficient. Furthermore, these acidic solutions are highly corrosive and form toxic fumes at high temperatures. To try to avoid this hazardous environment, Eutectic Freeze Crystallization method is taken in consideration due to its operation at subzero temperatures where limited vaporization of acids take place.

In this study, the binary EFC solubility diagram of MnSO4 was measured at eutectic freeze crystallization conditions in 1L setup at atmospheric pressure. The temperature of the saturated solution was periodically decreased in steps of 5 °C to reach the eutectic conditions. The Eutectic Freeze

Crystallization point of MnSO4 was obtained at Teutec = -10.5°C and Ceutec = 35.41 wt%. The produced pink crystals were MnSO4 heptahydrate. In order to determine the crystal morphology and size distribution of the produced MnSO4 heptahydrate crystals online digital image microscopy and image post-processing analysis were applied. The sequential time image acquisition during the crystallization process inside the reactor at these operating conditions allowed to determine the nucleation and growth rates from the time line crystal size distributions.

Ice and MnSO4·7H2O crystals were easily separated in the reactor by gravitational separation at low mixing speeds.

Influence of Cooling Rate on Crystal Growth Kinetics of Borax During Sonocrystallization

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Keywords: sonocrystallization, borax, crystal growth, cooling rate

The influence of the cooling rate on the crystallization kinetics of a certain substance is usually one of the first parameters to be examined because of its noticeable influence on the kinetics of the process and the product properties [1,2]. The aim of this work was to investigate the influence of the cooling rate during the sonocrystallization of disodium tetraborate decahydrate (borax) on the process of crystal growth. Tests were performed in a laboratory batch crystallizer with stirring, equipped with an ultrasonic homogenizer (24 kHz, 400 W) operating continuously at 20% amplitude. Crystallization was carried out from a solution saturated at 30 °C by cooling to a temperature of 10 °C at rates of 4, 6, 8, 10 °C h⁻¹. After nucleation, at a defined process time, the magma was withdrawn from the crystallizer to determine the mother liquor concentration using a sodium ion-selective electrode. The properties of the growing crystals over process time were observed by measuring the crystal size distribution, the volume mean diameter of the crystal, coefficient of variation and the specific surface area of the crystal using a laser diffraction particle size analyzer. The final products were subjected to sieve analysis to determine differences in the crystal shape and agglomeration ratio. From the results, it was observed that during sonocrystallization,

regardless of the cooling rate, the properties of the crystals do not change significantly with regard to the crystal size distribution and average size. The influence of the cooling rate was mostly reflected in concentration changes of the mother liquid and the specific surface area of the crystal, which indicated the intensity of secondary nucleation in the examined systems. By comparing the properties of the crystals obtained, at the applied cooling rates, in sonicated and silent systems it was found that the crystals obtained in sonicated systems are very similar in properties, in contrast to those obtained in silent systems, which differ significantly with regard to the cooling rate. The above leads to the conclusion that the influence of ultrasound significantly exceeds the influence of the cooling rate in the process of crystal growth of borax.

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Solubility Behavior of L-Homophenylalanine in Aqueous Solution

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Keywords: L-Homophenylalanine, Solubility, Solid liquid equilibria, pH

L-Homophenylalanine (L-HPA) is a non-natural amino acid that acts as a precursor for other pharmaceutically important drugs such as inhibitors and antibiotics [1, 2]. Due to the need for high purity, crystallization is applied to achieve this goal. In this regard, L-HPA solubility is required in a range of operating conditions w.r.t. temperature and pH. However, in open literature, very few information considering the effect of pH on the solubility of L-HPA was found [3]. This work aims to experimentally determine aqueous solubilities of L-HPA as a function of pH and temperature. Solubility measurements were performed by fixing the pH at specified values using buffering solutions. Isothermal solubility measurements were conducted at 25 and 55 °C. The concentrations of the saturated solutions were determined using High Performance Liquid Chromatography (HPLC). The solubility of L-HPA does not change over a wide pH range around its isoelectric point at both temperatures. However, at sufficiently low or high pH values, the solubility increases more than three fold. We are currently working on theoretical modeling of the obtained data as well as extending the data set to cover a wider temperature range.

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A comparative study of mesoscale clusters and nanoparticles of flufenamic acid

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Keywords: Mesoscale clusters, flufenamic acid, dynamic light scattering, nanoparticle tracking analysis, particle nature

The nucleation and prenucleation stages of crystallisation play an important role in determining the characteristics of the resulting crystal. However, the underlying molecular mechanisms of these early stages of crystallisation remain poorly understood. Even though nonclassical nucleation via mesoscale clusters elegantly explains the nucleation mechanism, experimental evidence for its applicability to organic molecules is limited. Furthermore, from the standpoint of the pharmaceutical industry, a thorough mechanistic understanding would aid in the rational design of the crystallisation process, which would be a step forward from the current empirical approach. Therefore, the aims of the current study are to determine the dependence of cluster properties on solute concentration as well as identify how similar mesoscale clusters are to 'classical' nanoparticles. To accomplish this, dynamic light scattering and nanoparticle tracking analysis of flufenamic acid in ethanol solutions were utilised. Initial examinations of unfiltered samples at varying concentrations revealed the presence of mesoscale clusters, even in undersaturated samples. In addition, while the cluster sizes were

independent of solute concentration, the cluster number concentration was directly proportional to solute concentration. To determine the degree of similarity between mesoscale clusters and particles, nanoparticles of FFA in the same size range as the observed clusters were prepared. Nanoparticles of FFA were removed by filtration, as evidenced by the significant change in concentration and size distribution following filtration. In contrast, the mesoscale cluster peak disappeared from the size distribution following filtration, despite change in solute concentration. This indicates the fragility of no mesoscale clusters. This was further confirmed when, despite being smaller than filter pore size, mesoscale clusters disappeared from the size distribution. Further, the clusters did not reform even after 72 hours of incubation at 40 °C, indicating the presence of a significant kinetic barrier to reformation. In conclusion, clusters, unlike FFA nanoparticles, are extremely fragile, breaking under filtration pressure.



Figure 1: Graphical abstract

Separation and purification of high-value products by melt crystallization

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Keywords: High-purity products, melt crystallization, Process optimization

Melt crystallization is a cost-effective method for the separation of compounds produced in various industrial sectors to meet high purity standards. Our findings suggests that melt crystallization offers advantages for the purification of azeotrope forming, close boiling point, heat sensitive compounds and high viscosity melts by selective crystallization of the desired compound. Our research is focused on the purification of diols and polyols as important biorefinery products derived from renewable biomass resources.

To develop an efficient crystallization process, the actual driving force of crystallization can be quantified as a measure to optimize the process conditions which ultimately effects the growth kinetics and purity of final products. It also gives insight on the influence of additives/ modifiers employed to remove purification barriers and reducing the need for further purification steps. The actual driving force is the difference in chemical potential of solute between supersaturated and saturated liquid phase [1]. To determine this driving force, the activity coefficient of liquid phase was estimated based on the measured equilibrium phase diagram. The solid-liquid equilibrium data were measured by a dynamic approach (Differential Scanning Calorimetry) or an equilibrium approach depending on the characteristics of the compounds. To optimize an efficient separation, the role of applied driving force was evaluated by studying the layer growth rates against quality of final product.

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A Coffee Smell Agent Optimization for Unseeded and Seeded Batch Cooling Crystallization

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Keywords: crystallization, cooling temperature, smell agent optimization, crystal size distribution

A Coffee Smell Agent Optimization (COSAO) algorithm for optimal operating recipes in batch cooling crystallization is presented in this paper. The COSAO algorithm is based on the Smell Agent Optimization (SAO) algorithm, which uses the phenomenon of a dog (agent) sniffing and trailing solution points. As a logical consequence, the SAO has three modes: sniffing, trailing, and random. When the agent is in trailing mode, we modified the SAO with a "drop of coffee" diffusion pattern to create a grid search array. This would assist the agent in tracking down more optimal cooling process solutions. The algorithms' optimality and effectiveness are demonstrated using unseeded batch cooling and seeded batch cooling crystallizations of paracetamol and potassium nitrate, respectively. The individual objectives used to determine the optimal temperature range for the two crystallization processes are mean size, nucleated mass, and coefficient of variation. In optimizing the temperature trajectory, we also took into account the initial mean size of seeds as an additional decision variable. The results of mean size and coefficient variation optimizations for unseeded paracetamol crystallization are analyzed, and the solution from COSAO depicts a more optimal

cooling trajectory in lesser time than SAO and Genetic Algorithm (GA). The COSAO algorithm also outperforms the other algorithms for potassium nitrate seeded crystallization. The optimal temperature profiles, as well as some different seed properties, were also investigated in order to improve crystal size distribution.

Selective recovery of potash from HCl-based leaching solution of feldspar ore via anti-solvent-crystallization

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Keywords: potash; feldspar; anti-solvent; crystallization; PLS

Feldspars are one of the most prevalent minerals in the Earth's crust [1] and are commonly found in igneous rocks such as granite, as well as in metamorphic and sedimentary rocks [2]. Due to their toughness and corrosion resistance, feldspars have been widely employed in the glassmaking and ceramic industries [3]. Recent studies have shown that feldspar minerals have the potential to be a source of potash, a valuable fertilizer that is commonly used in agriculture [4]. The global consumption of potash for agricultural application is expected to increase by 15% or 53 million tons in 2025 [5]. Despite possessing more than ample recognized and undiscovered resources for the commodity, an estimation of 10 billion tons of known resources, the EU has assessed the commodity as being within the region of supply risks [6]. Potash production is now restricted to a few nations mainly due to the geological availability of potash deposits and the high cost of production. The top producers of potash in the world are Canada, Russia, Belarus, and China, which together account for a significant portion of the global production of potash. Other countries with significant potash production include Israel, Germany, Jordan, and the United States. This restriction of suppliers can have significant geopolitical implications [7].

As a result, new unconventional sources of potash must be investigated, to meet the demand in fertilizer industry.

The present study, as the part of the POTASSIAL Project of ERA.MIN investigates the zero- waste valorization of K-bearing feldspathic ore to produce high-value added products. In this project, a hydrometallurgical flowsheet has been suggested to produce potash, alumina, and other silicon-based materials from K-feldspar. The main challenges associated with the hydrometallurgical recovery of the metallic content of the feldspar are the dissolution of elements and the recovery of different components with the proper specifications in terms of purity for the intended purposes. The high Al-Si ordering in the K-feldspar structure results to a stable structural K⁺ in the pores or interstitial sites of the mineral, making it difficult to break or in other words, more difficult to dissolve [8]. To overcome this challenge, mechanical activation followed by HCl leaching has been suggested in this project. This approach results in complete dissolution of all main components, namely K, Al, Fe, and Na. The presence of iron, aluminum, and other impurities in feldspar and their subsequent recovery with potash reduces the potash quality, which reduces its chemical stability and more importantly, results in a dramatic drop in its trading value [9].

The recovery of potash from HCl feldspar leaching solution often requires the removal of impurities through separation and purification techniques such as solvent extraction, precipitation, and crystallization. To achieve this, anti-solvent crystallization was chosen for its potential benefits, including direct potash production, suitability for very acidic solutions, and selective potash recovery without pre-treatment operations. In this study, five different anti- solvents were tested to determine their effectiveness in recovering potash. Table 1 presents the major characteristics of these anti-solvents that could be useful in the procedure. The results of the experiment, presented in Table 2, demonstrated that both acetone and 2-propanol were effective in selectively recovering potassium in the form of potash. The efficiency of the process using these anti-solvents was found to be comparable. Therefore, antisolvent crystallization can be considered a viable technique for the purification of HCl feldspar leaching solution in the recovery of potash.

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Anti-solvent		Molecular weight g.mol ^{-1 b}	Density g.ml ^{-1 c}	Boiling point °C ^d	Dielectric constant ^e	Viscosity cP ^f
Methanol	н нон н	32	0.792	64.6	32.7	0.59
Ethanol	Н Н Н ОН Н Н	46	0.789	78	24.5	1.1
Acetone	H ₃ C CH ₃	58	0.784	56	20.7	0.36
2-propanol	OH H ₃ C CH ₃	60	0.786	82.4	18.6	2.4
Ethylene glycol	НООН	62	1.11	197	37	18.4

Table 1- The specifications of the anti-solvents used in this study

^a The longer the alkyl chain is the organic compound, the more hydrophobic it is.

^b One of the effective factors on dielectric constant. Typically, the higher the molecular weight is, the lower the dielectric constant is.

^c Density affects the weight of the consumed anti-solvent.

^d Boiling points affects the energy consumption and selectivity of the anti-solvent recovery after crystallization.

^e One of the most important factors affecting the process. Dielectric constant reflects the polarity of the solvent, which is effective to reduce the amount of the free water.

f Viscosity affects the efficiency of the PLS mixing with the solvent

PLS													
Element/compound	К		Al		Na		Fe		HC1				
Concentration*	9 g/L		9 g/L		1.5 g/L		0.1 g/L		2 M				
Experimental resul	ts**				I								
	Methanol		Ethanol		Acetone		2-propanol		Ethylene glycol				
O/A***	4	5	4	5	4	5	4	5	4	5			
K recovery (%)	0.00	0.38	0.11	12.09	50.55	68.01	51.04	68.81	1.22	1.24			
Na recovery (%)	0.00	0.00	0.00	0.33	0.00	0.54	0.00	0.48	0.43	0.00			
Al recovery (%)	1.78	0.87	4.29	0.55	2.57	0.00	0.38	0.00	3.86	1.29			
Fe recovery (%)	0.00	0.00	0.00	0.00	0.00	0.12	0,00	0.98	0.00	0.31			

Table 2- Experimental results

* Concentrations based on the concentration of the elements in the utilized feldspar sample and the optimum leaching condition.

** In all the experiments, the following conditions were constant: T=25°C, t=72h, RPM=125. The aqueous solution after each experiment was analyzed by ICP-MS. Experiments were repeated three times to ensure the obtained results. For analysis, samples were diluted 1000 times with 5% v/v HCl solution.

*** The volume ratio of the organic anti-solvent to the PLS

Sustainable Soda Ash Production by CO2 Direct Air Capturing: Crystallization in the Na2CO3-NaOH-H2O System

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Keywords: CO2 DAC- soda ash- SLE- short-cut method.

Soda ash (anhydrous sodium carbonate) is worldwide mainly produced by the Ammonia Soda (Solvay) process or can also be obtained from natural minerals. However, the Solvay process emits significant amounts of fossil CO₂ and generates waste streams containing potentially hazardous substances. Thereby, the new environmental friendly CODA (Carbon-negative sODA ash plant) process is planned to avoid the mentioned emissions and mining of the natural sources. In the CODA process, NaOH solution and CO₂ (directly absorbed from air) react to Na₂CO₃ to provide the feed for Na₂CO₃•xH₂O crystallization. The required NaOH will be generated by electrolysis of rock salt brine using renewable energy from wind and solar power plants [1]. As a particular challenge the generation of renewable electricity, the absorption of CO₂ directly from air, and consequently the obtained feed composition for crystallization depend on the present weather conditions.

Possible Na₂CO₃•xH₂O crystallization strategies were evaluated with respect to their mass and energy balances to identify the most economic and sustainable process version based on the solid-liquid equilibria (SLE) data of the Na₂CO₃-NaOH-H₂O system from both experimental and literature studies [2]. Moreover, the growth kinetics of these crystallization strategies are studied using a novel short-cut method [3]. The latter is based on evaluating the evolution of the crystal size distribution during well-planned experiments. In the conference contribution, recent results in crystallization process design including SLE and growth kinetics studies will be presented.

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Purification of the antimalarial artemisinin from a crude plant extract using a combination of adsorption and cooling crystallization

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Keywords: artemisinin, natural products, multi-component mixture, combined process, pre- adsorption unit, cooling crystallization

The secondary plant metabolite artemisinin (ARTE), chemically a sesquiterpene, is a key substance to produce effective antimalarial drugs. The main source for ARTE is the extraction from the plant Artemisia annua. Depending on growing conditions, cultivars contain up to 1.4 wt% of ARTE in dried leaves. Effective extraction of the dried plant material can be carried out using a counter-current process [1], which is studied at our institute using toluene as the extraction solvent. The starting point for the purification of ARTE is a complex multicomponent mixture that contains about 20% of ARTE within the total extracted substances, and a high number of co-extracted mostly unknown substances, such as hydrocarbons, waxes, flavonoids, and terpenoids including other sesquiterpenes. For the purification of ARTE, a combined process concept consisting of a pre-adsorption and a final cooling crystallization process is considered. Pure ARTE possesses very high solubility in toluene (~200 g·L⁻¹ at 25 °C). In addition, co-extracted substances act as a solubility enhancer. For this reason, preliminary small-scale investigations on the purification of ARTE were performed in ethanol after a solvent exchange. The solvent exchange in

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combination with a freezing-out is able to remove about 10 % of the total extracted substances with almost no effect on the concentration of ARTE. Flavonoids were proven to impede the final crystallization of ARTE [2]. Thus, the pre-adsorption process focused on the removal of this group of substances. It was found that γ - Al2O3 is a promising adsorbent for that task. By combining adsorption and a single-step cooling crystallization in batch experiments, a final purity of ARTE of >90 % could be achieved. This proof of concept was then used to study the underlying thermodynamic and kinetic foundations, like adsorption isotherms, solubility and supersolubility in detail with the goal to purify ARTE in a larger scale and towards higher purities (> 99 %) and yields. Results and challenges of this process upscaling and optimization will be emphasized in this contribution.

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Water impact in the binary solvent system on phytosterol profile, crystal characteristics and processability

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Keywords: phytosterols, profile, binary solvent system, water, crystal dimensions

Phytosterols (PS), known also as plant sterols (C29H50O) are high value biomolecules with wide range of applications in the pharmaceutical, nutraceuticals, food and cosmetic industries. Phytosterols occur as a group of different phytosterols, which differ only slightly from each other by the structure. Stanols forms, which are saturated forms of phytosterols, are also classified as phytosterols. [1,2]

The current binary solvent research focuses on developing a batchcooling crystallization process for food-grade phytosterols, where both the total purity and phytosterol profile have strict quality requirements. It has been observed that by varying the water concentration in the solvent system, the produced phytosterol profile can be tuned towards the favorable product profile, especially regarding the sterol/stanol ratios. This is due to the water concentration impact on the solubility and due to the hydrate formation. It has been identified that phytosterols can form three different hydrates (monohydrate, hemihydrate, anhydrate) [3].

Commercial grade phytosterols have been used as a reference starting material. Batch cooling crystallization experiments have been carried out with precise temperature control and particle tracking (FBRM) system. Phytosterol purity and profile are analyzed by GC-FID, DSC and TGA. The water impact in the hydrate formation, crystal characteristics and crystal dimensions are studied mainly by laser diffraction -based particle size distribution analysis, X-ray crystallography, SEM and optical microscopy. The water impact on the overall processability is also emphasized, e.g., the impact on the crystallization process conditions, mixing, filterability, and drying.

It can be concluded that the water concentration in the solvent system has an important role to tune the final product profile. These findings are important as it enables to modify the chosen crystallization solvent system based on the starting material purity and profile, which may differ based on the feedstock and fractionation/extraction technologies used earlier in the process. Water as an antisolvent, decreases the phytosterols overall solubility and thus affects the temperature profile used in the cooling crystallization experiments. The concentration of water affects also downstream process conditions and further crystal characteristics.

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Fe precipitation for the recovery of a marketable product in a NdFeB magnet recycling process

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Keywords: NdFeB magnets; Recycling; Solvent extraction; Anti-solvent; Precipitation

The economic importance of rare-earth elements (REEs) has risen sharply in recent years due to their application in magnets for various renewable energy technologies such as electric vehicles and wind turbines. The dominance of China for both the supply and refining of REEs globally has led to the large supply risk of REEs and price volatility observed in metal markets [1]. Recycling magnets can provide a rich source of REEs as well as metals like Co and Fe, which are used widely in NdFeB and SmCo magnets. This study evaluated the separation of the valuable REEs from Fe which accounts for 65 wt.% of the metals in the NdFeB magnets.

NdFeB waste magnets were shredded to <2 mm and leached with CuSO₄ according to a patented process by MEAB, enabling >90% dissolution of all metals [2]. Solvent extraction, anti-solvent precipitation, and neutralization were all evaluated for the separation of the REEs and the Fe. Solvent extraction showed the highest separation of the REEs and enabled >99.5% REE extraction in 3 countercurrent stages with D2EHPA while the co-extraction of impurities was limited to <7%. The REEs were stripped with 1.25M H₂SO₄ and separated into individual fractions by extraction chromatography. Each REE fraction can subsequently be precipitated with oxalic acid and calcinated before being sent for molten salt electrowinning. The solvent extraction raffinate contains >55 g/L Fe with traces of B and ~3 g/L Co. Anti- solvent precipitation with ethanol precipitated nearly 80% Fe recovery but led to the co- precipitation of Co. The precipitation of Fe by combined neutralization/oxidation to produce jarosite produced selective Fe precipitation with low Co entrainment [3]. The major benefits of targeting jarosite over goethite or hematite were the fast kinetics and good filterability of the Fe product. More than 95% Fe precipitation was achieved within 4 hours with <10% Co and B precipitation.



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The role of water in the formation of crystal structure: a case study of valnemulin hydrochloride

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Keywords: crystal structure, Polymorphism, water

In this work, to better understand the role of solvents during formation of solvate/hydrate and the effect of existence of solvent molecules on the properties of the host molecule, valnemulin hydrochloride (VH) was used as model compound to investigate the effect of water on formation of crystal structure. Valnemulin hydrochloride is a new semisynthetic pleuromutilin derivative. It is mainly used to prevent and cure mycoplasma disease and Gram-positive bacterial infection in pigs, cattle, sheep and poultry [1-4]. At present, amorphous valnemulin hydrochloride is mainly used as commercial material. The amorphous form has many shortcomings, such as low stability, strong hygroscopicity, low bulk density and heavy irritating taste^[5]. Many efforts have been made to prepare crystalline product of valnemulin hydrochloride. However, only two kinds of crystalline solvates, methanol-water solvate(VHWMS) and ethanol-water solvate (VHWES), have been successfully developed and characterized^[6]. Although the hygroscopicity of these two solvates are better than those of amorphous valnemulin hydrochloride, the thermal stability of them are still not ideal

and they will loss some associated solvents continuously at around 40 °C, which limits its application.

In this study, one new form of valnemulin hydrochloride, valnemulin hydrochloride dihydrate (VHW), was devoloped for the first time and was characterized. Since water molecules are involved in all obtained crystal forms of valnemulin hydrochloride, it is speculated that water plays a key role in the crystal formation of valnemulin hydrochloride. Therefore, the single crystal structures of different crystals are determined and analyzed to explore the role of water in the stabilization of these structures. At the same time, the change of molecule conformation in different forms was also analyzed. The transformation process of VHW to VHWMS and VHWES was investigated by infrared and Raman spectroscopy and discussed in detail. The results show that, in addition to stacking similarity, the conformation may also have significant impact on the crystallization kinetics.

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The preparation high-performance energetic crystals by solvates: in-situ mediated phase transition and autologous surface molecular reconfiguration

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Keywords: energetic materials; solvates; phase transformation; core-shell; nano structure

In our research, the unique properties of solvates were used to develop high-performance energetic materials (EMs). 4,4 ',5,5 'tetranitro-1H,1 'H-[2,2 '-biimidazole]-1,1 '- diamine (DATNBI) was selected as the model energetic compound due to its excellent detonation properties and mechanical sensitivity. Using EMs products with impure solid forms or a single structure in practical application scenes will lead to a series of serious consequences in terms of safety, mechanics, storage, detonation, and reliability properties. First, prediction combined with experiments were successfully screened DATNBI solvates. Then, a novel approach to obtain the scarce and superior performance solid form of EMs was developed by the strategy of rapid in-situ solvate-mediated phase transformation (Fig. 1). A mechanism of this solvate-mediated method was studied by exploring the types of solute clusters and intermolecular interaction of DATNBI in the microscopic view. It is found that solute molecules tend to exist as solvated monomers resulting in the prior precipitation of solvate in saturated solution of tetrahydrofuran (THF). From the perspective of crystal structure and transformation energy, the solvates consisting of DATNBI and THF can easily transform to the scarce α form of DATNBI.



Figure 1. The comparison of the previous preparation of solid forms using solvates and the preparation method of solid forms in this work.

Meanwhile, core-shell structured explosives (CSEs) are becoming increasingly prominent in the energetic materials, however, some fatal defects of CSEs including inadequate two-phase adhesion, insufficient shell coverage and thickness, and poor chemical stability seriously impact the security and dependability of weapon systems. We present a novel core-shell material in the field of organic crystals, the core@self-shell structure, constructed by an original strategy of autologous surface molecular reconfiguration. According to the propensity that solvate dioxane (DIOX) of DATNBI form a unique nanostructure after drying, we successfully designed the core@self-shell structure with a hierarchical nano-surface and proposed the "solvate micro- dissolution shell" formation mechanism. The core@self-shell nanoenergetic materials significantly improve impact sensitivity without greatly decreasing energy density through the eco-friendly and effective method.



Figure 2. A novel core@self-shell hierarchical structure with excellent performance was constructed using an eco-friendly and effective strategy of autologous surface molecular reconfiguration.

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Uncovering the role of impurity sugars on the crystallization of D-tagatose crystal: experiments and molecular dynamics

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Impurity sugars produced in upstream process of functional sugars are significantly impacting the product quality. D-tagatose (D-TAG) is an emerging functional sugar with good prebiotic properties and is used broadly in food and medicine. It is generally prepared from galactose by chemical or biotransformation isomerization reactions, in which impurities such as D-fructose (D-FRU) and D-maltose (D-MAL) are produced, thus affecting the downstream process, especially for the crystallization process of D-TAG. In this work, the effect of congeners (D-MAL, D-FRU, D-glucose (D-GLU)) on primary and secondary nucleation of D- TAG crystals was investigated (Figure 1). Interestingly, impurity sugars showed an inhibition on primary nucleation of D-TAG crystals, while a promotion on the secondary nucleation of D- TAG. The order of inhibitory ability for primary nucleation was D-FRU+D-MAL > D-GLU+D- MAL > D-FRU > D-GLU > water, while the sequence for secondary nucleation was reversed. The diffusion ability, hydrogen bond formation ability and interaction energy of D-TAG crystal surface and
impurity sugars were evaluated by molecular dynamics (MD) simulations to reveal these nucleation and growth behaviors. At the molecular level, it was explained that the congeners affect the nucleation ability by hindering the diffusion of D-TAG molecules (Figure 2) [2]. On the other hand, the adsorption energy of the D-TAG surface was calculated by constructing MD simulation system, and the results (Figure 3) showed that the adsorption of impurity sugars on the D-TAG crystal surface hindered the growth of D-TAG crystals. Moreover, crystallization experiments were designed, and D-TAG crystals with uniform particle size distribution and regular morphology were obtained by control the concentration and types of the impurity sugars. This study helps to understand the effect of impurity sugars on crystallization and guide the industrial production of functional sugars.



Figure 1. SEM images of D-TAG crystals in the absence and presence of impurity sugars.



Figure 2. RDFs (a) and MSD (b) of D-TAG molecules under different impurity sugar additions.



Figure 3. Optimized geometries of the interaction between D-MAL and D-TAG crystal before and after MD simulation. The blue lines stand for the hydrogen bond interaction.

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Impurity Uptake During Eutectic Freeze Crystallization for Recovery of Nickel Sulfate Hydrates

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Although originally created for portable electronics, lithium-ion batteries (LIBs) are today utilized in a wide range of daily items, such as electric vehicles, power tools, medical equipment, smart watches, drones, satellites, and utility-scale storage¹. One of the most common cathodes in Li-ion batteries is lithium nickel manganese cobalt oxide (NMC) which is produced using raw materials such as NiSO₄ and CoSO₄ ^{2, 3}.

Highly soluble salts like nickel and cobalt sulfate hydrates are typically produced from their concentrated aqueous solution using either cooling or evaporative crystallization; classical methods employed in the industry. The evaporative method tends to be expensive and require a lot of energy. Because of the residual solubility at a low temperature, cooling crystallization is not a very efficient process⁴. Another method is eutectic freeze crystallization (EFC). In the EFC process, which takes place around the eutectic point, both salt and ice crystallize simultaneously. The separation of these solids is then done according to differences in density between the liquid and solid phases⁵.

The current study investigates the feasibility of using EFC to crystallize nickel sulfate heptahydrate from an aqueous solution in the presence of impurities, as well as the prospect of further purifying the product via recrystallization into lower-order hydrates. The eutectic point of nickel in an aqueous solution containing various impurities has been determined. At increased temperatures, metal sulfate heptahydrates produced by EFC transform into hexahydrates. The experimental transition temperatures were compared to temperatures estimated by the software OLI stream analyzer, and the kinetics of the transformation process at various temperatures were examined.

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Hydrometallurgical recovery of rare earth elements using antisolvent crystallization

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Keywords: Rare earth elements (REEs), Antisolvent, Recovery, Purity

Rare earth elements are recognized as building blocks of modern-day technology [1] because of their crucial role in various advanced applications such as electric vehicles, wind turbine generators, and consumer electronic appliances [2]. The increasing demand and limited resources have led to the exploration of innovative and sustainable methods for their recovery from various sources. Typical methods for the separation of rare earth elements are ion exchange, solvent extraction, and precipitation in extraction from primary and secondary sources [3]. These can involve complex and environmentally harmful processes, leading to the need for sustainable and efficient alternatives. Antisolvent crystallization provides a novel approach for the recovery of rare earth elements based on solubility reduction within a solvent-antisolvent matrix, inducing supersaturation and facilitating the crystallization.

This study targets recovery of rare earth elements of specific industrial interest i.e., neodymium, praseodymium and dysprosium in various mixtures using antisolvent crystallization from acidic (H_2SO_4) solution. Ethanol is used as an antisolvent and added at a controlled rate. Crystallization of rare earth sulphates, and incorporation of Fe (II) and Fe (III) as impurities is investigated under different experimental conditions. The process parameters studied are controlled addition rate and seeding. The effect of supersaturation control on the crystal size and size distribution, shape and purity are investigated. Optical microscopy, SEM-

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EDX and powder-XRD are used to investigate product quality. The outcomes of the work can offer valuable insights into refining the process of recovering rare earth elements as a high purity concentrate from leach solutions during the recycling of magnetic waste.

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The impact of impurities on controlled antisolvent crystallization of nickel, manganese, and cobalt from a citric acid system

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The exponentially growing use of lithium-ion batteries (LIBs) couples with their limited life span emphasizes the importance of developing efficient recycling methods. Due to its lower energy costs and pollutionreducing potential, antisolvent crystallization has aroused interest in the precipitation and separation of metals from the leaching solution of LIBs [1]. As LIBs consist of different components such as cathode, anode, separator, and shell, it is not feasible to completely prevent impurity metals like aluminum and copper to become mixed into the solution of target metals during leaching [2]. Despite this, limited research has explored the precipitation process of metals in a LIB leaching solution in the presence of impurities. This work explores the influence of metallic impurities on the controlled antisolvent crystallization of nickel (II), manganese (II), and cobalt (II) from a citric acid system. Antisolvent crystallization experiments have been performed with ethanol as antisolvent, and the effects of controlled operating conditions including the amount of antisolvent, antisolvent addition rate, and agitation

conditions on the precipitation efficiency of metals, and properties of crystal products have been investigated. The purity, morphology, size distribution, and crystalline phase of the product have been characterized and analyzed. The results show that limited copper and no aluminum was precipitated in the crystals. However, the impurity aluminum plays a dominant role for the recovery of the target metals in the citric acid system. A higher amount of antisolvent affected the morphology and size of the product crystals because of the higher driving force for nucleation and crystal growth. Additionally, a slower addition rate of antisolvent strongly contributed to increasing the size of crystals due to the reduced rate of supersaturation generation.

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