Webinar Series of the Working Party on Crystallization
9th-11th September 2020

About the Webinar

The Working Party on Crystallization of the European Federation of Chemical Engineers (https://efce.info/WPC.html) is pleased to announce a series of webinars on various aspects of crystallization. The talks will cover crystallization fundamentals, processes and industrial applications. A keynote speaker followed by three other speakers will deliver the talks on each day. The webinar is scheduled on the 09th, 10th and 11th September 2020 from 1500 to 1700 (Central European Summer Time, UTC+0200). The schedule for the webinar can be found on pages 3-5 and the abstracts for talks can be found on pages 6-35.

Access details

All webinars will be broadcast on the YouTube channel (https://bit.ly/3jqMTWu) of the Working Party on Crystallization. We recommend the attendees to subscribe to the YouTube channel to get notified about the start of the live streaming.

The attendees can make use of the live chat feature in YouTube to ask their questions. These questions will be forwarded to the chair of the session who will then steer the Q&A session. Note that in order to use the live chat feature in YouTube, the attendees must be logged in YouTube (through a Google account).

Organization

The webinar series is organized by Prof. Dr. Marco Mazzotti, ETH Zurich (marcom@ethz.ch) on behalf of the Working Party on Crystallization, with assistance from Dr. Ashwin Kumar Rajagopalan, ETH Zurich (ashwinr@ethz.ch) and Luca Bosetti, ETH Zurich (bosettil@ethz.ch).

About the Working Party on Crystallization

- Organization of triennial International Symposium on Industrial Crystallization (ISIC) and specialized scientific meetings and workshops.
- Exchange of information about activities of national working parties on crystallization of the EFCE member countries
- Evaluation and standardization of methods of measurement; definition of terminology, symbols and units in the field of industrial crystallization
- Fostering links to other working parties within EFCE which are active in adjacent areas, such as mixing, reaction engineering, filtration and separation, drying, agglomeration, comminution and classification, characterization of particulate systems
- Development of training at undergraduate and postgraduate level

About the EFCE

Founded in 1953, The European Federation of Chemical Engineering (EFCE) is a nonprofit-making association, whose object is to promote co-operation in Europe between non-profit-making professional scientific and technical societies in 30 countries for the general advancement of chemical engineering and as a means of furthering the development of chemical engineering (www.efce.org).

Day 1 – Wednesday, September 9th 2020
Crystallization Processes

Time (CEST)	Author(s)	Title
15:00	Introductory Remarks by the Chair (***Béatrice Biscans,*** Laboratoire de Génie Chimique à Toulouse – CNRS, F)	
15:10	***Martha Grover***, Georgia Tech, USA	A Data-Centric Approach to Optimal Crystallization Control
15:55	**Gaensch, Jonathan;** Huskova, N. (Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, D); Kerst, K. (University of Magdeburg, Magdeburg, D); Mangold, M. (Technische Hochschule Bingen, Bingen, D); Temmel, E.; Lorenz, H.; (Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, D); Janiga. G (University of Magdeburg, Magdeburg, D); Seidel-Morgenstern, A. (Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, D)	Continuous racemate resolution via coupled fluidized bed crystallization: Case study on amino acid asparagine
16:15	***Chen, Ruipeng***; Weng, J.; Chow, S. F.; Lakerveld, R. (Hong Kong Univ. of Science and Technology, Hong Kong, CN)	Integrated continuous crystallization and spray drying of insulin
16:35	***Ng, Denise Zi Ling***; Yeap, E. W. Q.; Khan, S. A. (National University of Singapore, Singapore, SGP)	Engineering Spherical Crystalline Drug-Colloid Composites via Microfluidic Emulsion-based Processing
16:55	Concluding Remarks (***Marco Mazzotti,*** ETH Zurich, CH)	

Day 2 – Thursday, September 10th 2020
Fundamentals of Crystallization

Time (CEST)	Author(s)	Title
15:00	Introductory Remarks by the Chair (***Heike Lorenz,*** Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, D)	
15:10	***Heiko Briesen***, TU Munich, D	Crystallization processes in four dimensions – Tracking full crystal shape information over time
15:55	***Tahri, Yousra***; Gagnière, É.; Chabanon, É. (Univ. of Claude Bernard Lyon 1/LAGEPP, Villeurbanne, F), Bounahmidi, T. (Univ. Euromed de Fès, Fès, MA); Kožíšek, Z. (Institute of Physics of the Czech Academy of Sciences, Praha, CZ); Candoni, N.; Veesler, S. (Aix-Marseille Univ. & CNRS, CINaM, Marseille, F); Boukerche, M. (Process Research & Development/AbbVie Inc., Chicago, USA); Mangin, D. (Univ. of Claude Bernard Lyon 1/LAGEPP, Villeurbanne, F)	Multiscale experimental study and modeling of L-glutamic acid crystallization: a new perspective on the Ostwald rule of stages
16:15	***Rehage, Hendrik***; Kind, M. (Karlsruhe Institute of Technology, Karlsruhe, D)	A New Method for Scale up of Mixing Controlled Precipitation Processes Based on Complete Similarity
16:35	***Das, Gunjan***; Pallipurath, A. P.; Kathyola, T.; Al-Madhagi, L. H. (Univ. of Leeds, UK); Chang, S (Diamond Light Source, Oxfordshire, UK); Leng, J. (Univ. of Leeds, UK); Marathe, S.; Rau, C.; Wanelik, K. (Diamond Light Source, Oxfordshire, UK); McGinty, J; Miller, R.; Sefcik, J.(CMAC/ Univ. of Strathclyde, Glasgow, UK); Schroeder, S. L. M.; (Uni. of Leeds, UK);	Real-Time X-ray Phase-Contrast Imaging of Continuous Antisolvent Crystallisation in a Concentric Flow Microreactor
16:55	Concluding Remarks (***Marco Mazzotti,*** ETH Zurich, CH)	

Day 3 – Friday, September 11th 2020
Industrial Applications

Time (CEST)	Author(s)	Title
15:00	Introductory Remarks by the Chair (***Brian Glennon,*** University College Dublin, Dublin, I)	
15:10	***Jon-Paul Sherlock***, Astra Zeneca, UK	Crystallising Pharma Futures – the need for process engineering and crystallisation science
15:55	Chivavava, Jemitias, Abdul-Malik Lottering, ***Alison E. Lewis*** (Univ. of Cape Town, Cape Town, ZA)	Treatment of brines from power generation using freeze-based crystallization methods
16:15	***De Keyser, Ruben*** (Janssen Pharmaceuticals N.V.,Beerse, B)	Reinventing a commercialized particle-engineered crystallization process using PAT feedback control to obtain the filed solid form
16:35	***Burcham, Christopher (Eli Lilly and Company, USA)***; Calado, F.; Mitchell, N. (Process Systems Enterprise Limited, London, UK); Stout, J. R. (D&M Continuous Solutions, USA); Johnson, M. D; Groh, J. M.; Merritt, J. M.; Myers, S.; Svoboda, V. (Eli Lilly and Company, USA)	Development of a Continuous Crystallization with Periodic Wet Milling for Particle Size Control
16:55	Concluding Remarks (***Marco Mazzotti,*** ETH Zurich, CH)	
17:00	Announcements by the Working Party (***Marco Mazzotti,*** ETH Zurich, CH)	

Note:

Introductory/Concluding remarks
Keynote talk
Invited talk

All times are in CEST (Central European Summer Time, UTC+02:00)
Names in bold and italic face indicates the presenter

Prof. Dr. Martha Grover

School of Chemical and Biomolecular Engineering

Georgia Institute of Technology, Atlanta, Georgia, USA

Ph.D. 2003, California Institute of Technology, USA

Prof. Grover's research interests:

- Feedback control of colloidal crystallization for photonic materials
- Chemical evolution in the origins of life
- Modeling and control of pharmaceutical and nuclear waste crystallization
- Process-structure-property relationships in polymer organic electronics

Abstract

A Data-Centric Approach to Optimal Crystallization Control

The large quantity of data provided by process analytical technologies during synthesis and crystallization of active pharmaceutical ingredients provides a new opportunity to learn optimal control policies directly from the real-time data. Fundamental physical models such as population balance models are not required, as the process model is learned directly from the PAT data—but if available they can be integrated into the calculations. The optimal control policy provides a compact form for online implementation, circumventing the need for computationally intensive online optimization that may hinder the implementation of nonlinear model predictive control in pharmaceutical manufacturing. A key challenge in machine learning is the definition of a minimal set of features to characterize the system state, and methods for automated feature selection will be discussed. Here a minimal feature set is posed using physical intuition and measured by PAT: crystal mass from infrared spectroscopy, crystal chord count from FBRM, and crystal size from microscopy.

Prof. Dr. Heiko Briesen

School of Life Sciences

TU Munich, Munich, Germany

Ph.D. 2002, RWTH Aachen, Germany

Prof. Briesen's research interests:

The transfer and new development of process systems engineering concepts for food and beverage technology and biological processes, with the aid of mathematical and computer science techniques in order to develop new and optimize existing products and processes

Abstract

Crystallization processes in four dimensions – Tracking full crystal shape information over time

The shape of crystals affects both the product value and the processability of crystals. Thus, it is not surprising that crystal shape (engineering) has received increasing attention over the past one to two decades from academia and industry. The presentation will highlight some of the key challenges when addressing crystal shape related questions. It mainly collates the past 14 years of research from our group in the direction of modeling and understanding shape related aspects of crystallization. Briefly touching on suitable modeling and simulations approaches, the main focus will be on experimental characterization with increasing depth of information on crystal shape. Though being an offline-technique and being associated with significant experimental effort, X-ray microcomputed tomography (µCT) provides a way to fundamentally access particle shape in its full three-dimensional complexity even for non-ideal, non-convex or agglomerated crystals. By increasing the number of crystals analyzable by µCT, even tracking the time evolution of shape (distribution) as a fourth dimension becomes feasible.

Dr. Jon-Paul Sherlock

Global Technology Strategy Director

AstraZeneca, United Kingdom

Ph.D. University of Manchester

Dr. Sherlock's bio:

Jon-Paul Sherlock is the Global Technology Strategy Director for AstraZeneca Operations, responsible for implementation of manufacturing technologies that improve quality and process robustness, improve supply chain agility and reduce cost. He joined AstraZeneca after completing a PhD in Chemical Engineering (at Manchester University) and has over 20 years' experience of pharmaceutical research and development. He has held senior roles in chemical, analytical and product development, supporting multiple therapeutic areas and all clinical phases including commercialisation and the regulatory approval of a number of medicines. Immediately prior to his current role he led the development of innovative digital health solutions for emerging and established respiratory medicines. He is a is a chartered chemical engineer and Fellow of the IChemE and has founded significant collaborations between industry and academia in the areas of formulation and physical processing, advanced manufacturing technologies and future pharmaceutical supply chains. He is a Visiting Professor at the University of Manchester and University of Strathclyde, Chairs the Industry Board for CMAC Manufacturing Research Hub and was a member of the EPSRC Manufacturing the Future SAT.

Abstract

Crystallising Pharma Futures – the need for process engineering and crystallisation science

Turning molecules into medicines is an expensive and complex process. The needs of patients, physicians, payers and regulators have evolved and what was previously acceptable is no longer. The complexity of the medicines and the speed with which they need to be brought to market to address unmet patient needs, places pressure on an existing development methodology, whilst increasing R&D productivity means costs must be contained. Despite the bar being raised it is essential that robust manufacturing processes are delivered. The role of crystallisation scientists and process engineers has never been more vital. New technologies such as automation, continuous processing and digital twins offer more opportunity than ever for these scientists and engineers to ensure future medicines are made accessible to patients faster, more sustainably and more robustly. This talk will provide an insight into how the medicines development process is evolving and the importance of crystallisation and process engineering science.

Continuous racemate resolution via coupled fluidized bed crystallization: Case study on amino acid asparagine

J. Gänsch[1], N. Huskova[1,2], K. Kerst[3], E. Temmel[1], H. Lorenz[1], M. Mangold[2], G. Janiga[3], A. Seidel-Morgenstern[1]

[1] Max Planck Institute for Dynamics Complex Technical Systems, Magdeburg/Germany (MPI)

[2] Bingen University of Applied Science, Bingen/Germany (TH Bingen)

[3] Laboratory of Fluid Dynamics and Technical Flows, University of Magdeburg "Otto von Guericke", Magdeburg/Germany (OvGU)

The resolution of racemates is a crucial and challenging separation task for the pharmaceutical, agricultural and for the biotechnological industries. A continuous, robust and efficient racemate resolution can be realized by performing preferential crystallization within two coupled fluidized bed crystallizers [1]. The continuous supply of enantiopure seed crystals to each crystallizer enables the spatially separated, continuous production of both stereoisomers from a racemic solution. Applying for this purpose a conical shaped tubular crystallizer allows achieving a narrow residence time distribution of the liquid phase, as well as the selective removal of smaller crystals as nuclei of the counter-enantiomer. Both effects are essential for creating a robust process, which avoids efficiently product contamination by the unwanted enantiomer. Furthermore, the conical shape of the tubular crystallizers causes a variation of the fluid velocity along the height. The resulting classifying effect causes a narrow and adjustable product crystal size distribution. However, the delicate coupling of the crystallization kinetics with the hydrodynamic effects in combination with continuous seeding leads to a very complex process.

The work to be reported is part of a larger interdisciplinary collaboration project supported by the German Research Foundation (DFG), which aims to demonstrate, analyze and optimize this attractive but challenging process: The MPI works on the demonstration and the experimental investigation. The TH Bingen develops a reduced process model based on population balances and, the OvGU studies the hydrodynamic effects of the two-phase flow applying detailed CFD-DEM-simulations (Computational Fluid Dynamics - Discrete Element Method).

In this contribution, the process as well as the experimental set up will be explained. Selected results of a comprehensive experimental parameter study carried out using asparagine monohydrate dissolved in water as a model compound will be presented and discussed. Numerous stationary operating points are evaluated with respect to the process productivity, the yield as well as the product crystal size distribution [2]. An excellent reproducibility and a remarkable productivity of this process will be demonstrated. Finally, we will show the good agreement between experimental observations and simulation results using the reduced process model [3].

Acknowledgments

The financial support from Deutsche Forschungsgemeinschaft (DFG) within the Research Program SPP 1679 ‘‘Dynamische Simulation vernetzter Feststoffprozesse” is gratefully acknowledged.

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Integrated Continuous Crystallization and Spray Drying of Insulin

R. Chen[1], J. Weng[2], S.F. Chow[2], R. Lakerveld[1]

[1] The Hong Kong University of Science and Technology, Hong Kong

[2] The University of Hong Kong, Hong Kong

Introduction

Insulin injection is commonly used for the treatment of diabetes. Pulmonary delivery through inhalation of dry insulin powders is commercially also available and offers a more convenient route compared to injection.[1] The manufacture of such powders is challenged by the need to produce crystalline particles with an aerodynamic diameter in the narrow range of 1 – 5 µm. Amorphous particles produced from spray drying an insulin solution are limited by their fast dissolution,[2] which leads to a therapeutic effect of only several hours. Particles outside the optimal size range will not deposit well into the lungs. The crystallization of insulin has been studied in various crystallizers.[3–5] However, those processes generally do not deliver crystals in the optimal size range. Therefore, there is a need for novel crystallization processes that can produce insulin crystals with tailored size for dry powder inhalation more efficiently.

The objective of this work is to develop and characterize a novel continuous crystallization process for insulin that is tailored for dry powder inhalation by integrating a segmented-flow crystallizer with spray drying for rapid solvent removal. Continuous crystallization has received growing interest in the fine-chemical and pharmaceutical industries due to typical advantages such as easier process control and a more consistent product quality compared to batch crystallization.[6] Furthermore, continuous crystallization of proteins generally enables different attainable product quality attributes and process conditions compared to batch crystallization.[7] Finally, spray drying naturally operates in continuous flow mode, which enables easy integration, potentially reducing undesirable phenomena such as Ostwald ripening and agglomeration. The benefits of integrating continuous crystallization with spray drying for the manufacture of dry powders for inhalation has been demonstrated by earlier work from our group for different small-molecule active pharmaceutical ingredients.[8] The present work is, to the best of our knowledge, the first demonstration of such process for a therapeutic protein.

Experimental setup and approach

The process (see Figure 1) consisted of a tubular crystallizer and a spray dryer. One feed was prepared by dissolving a certain amount of insulin in a pH 7.2 0.01M citrate buffer containing 15% (v/v) acetone. The other feed was a solution with a 0.01M citrate buffer at lower pH with 0.005M zinc sulphate and 15% (v/v) acetone, which acted as the precipitant. The solubility of insulin at different conditions was measured to determine optimal feed compositions. A calibrated two-channel peristaltic pump was used to introduce the two feed solutions into the crystallizer at the same flow rate through a T-mixer. A gas flow controller was used to introduce nitrogen with a controlled flow rate via another T-mixer to create a

segmented flow, which offers the benefit of a narrow residence time distribution.[9,10] The supersaturation was generated by both cooling and a change in pH. The crystallizer consisted of two connected pieces of tubing of 14m long each. The crystallizer was immersed in a thermostatic bath to allow temperature control. At the outlet of the crystallizer, a buffer vessel was used for separation of nitrogen and to provide a steady flow to the spray dryer using another peristaltic pump with the same volumetric flow rate as the feed to the crystallizer. The spray dryer was operated with an inlet temperature of 150˚C and an atomizer flow rate of 670 L/h. The outlet temperature for all experiments was around 85˚C. Finally, the dry powder was collected in a powder collector located below a cyclone. The morphology of the particles and their approximate size were characterized with optical microscopy and scanning electron microscopy (SEM). The aerodynamic size distribution was measured with a Next Generation Impactor. Initially, the crystallizer was operated stand-alone to identify optimal crystallization conditions. Subsequently, optimal crystallization conditions were applied for the integrated process.

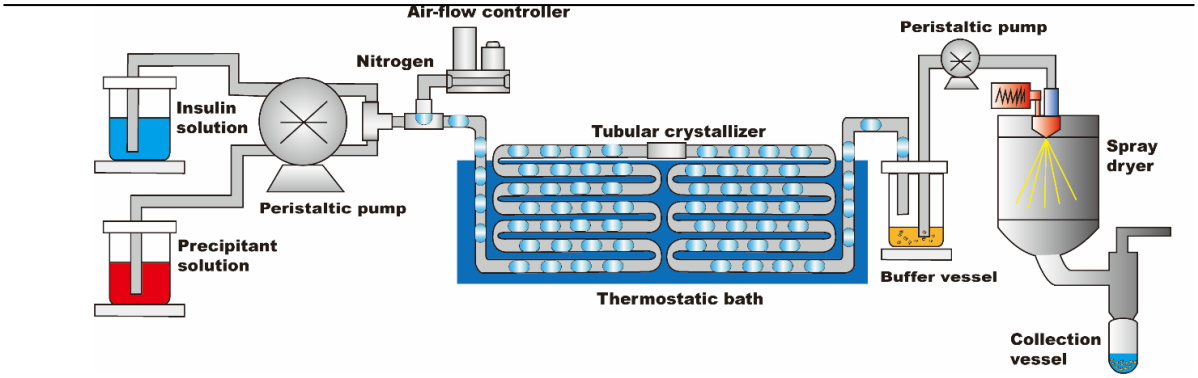

Figure 1. A schematic of the integrated process of continuous tubular crystallization and spray drying

Results

The recovery of insulin from stand-alone crystallization experiments was in excess of 90% when using a low combined flow rate of 1.2 ml/min and a high insulin concentration of 2.4 mg/ml (see Figure 2). A lower recovery was obtained at higher combined flow rates, and thus shorter residence times, in the range of 1.8 ml/min to 2.4 ml/min. A constant recovery could be approached in a short period of about 10 to 15 minutes when running at a high initial concentration in the range of 2.0 mg/ml to 2.4 mg/ml (see Figure 2). Such fast start-up indicates plug-flow conditions, which is an inherent benefit of a segmented-flow crystallizer compared to a mixed-suspension mixed-product-removal crystallizer. The produced particles appeared crystalline and were close to the desired size range for pulmonary drug delivery (see Figure 3). The particles produced with the integrated process under optimal conditions (an initial insulin concentration in the range of 1.6-2.4 mg/ml and a liquid flow rate of 0.6 ml/min) were characterized by a mass median aerodynamic diameter (MMAD) in the range of 2µm to 6µm (see Figure 4a) and a fine particle fraction (FPF) of 20-40% (see Figure 4b), which indicates a good potential for pulmonary drug delivery. In conclusion, the demonstrated benefits of the novel process include a short total residence time, high recovery from crystallization, and suitable product quality attributes for pulmonary drug delivery without any

added excipients. Future work may focus on scale-up, process control, modeling, tailored equipment design to increase the recovery of fine particles, and formulation design to optimize bioavailability.

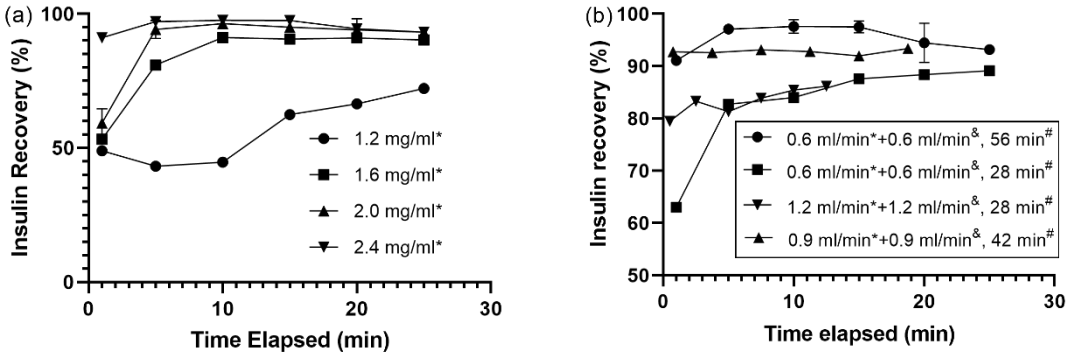

Figure 2. (a) Effect of initial concentration on insulin recovery at different times based on 0.6 ml/min+ 0.6ml/min, 56 min residence time (* initial concentration). (b) Effect of flow rate and residence time on insulin recovery at different times at 2.4 mg/ml initial concentration (* combined liquid flow rate, & gas flow rate, # residence time). Error bars represent the standard deviation from at least duplicate experiments. The data are obtained from stand-alone crystallization experiments.

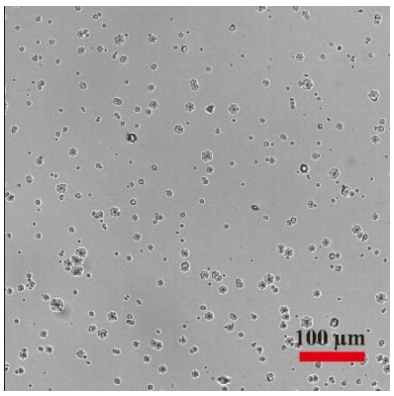

Figure 3. Microscope image of the product from stand-alone crystallization experiment

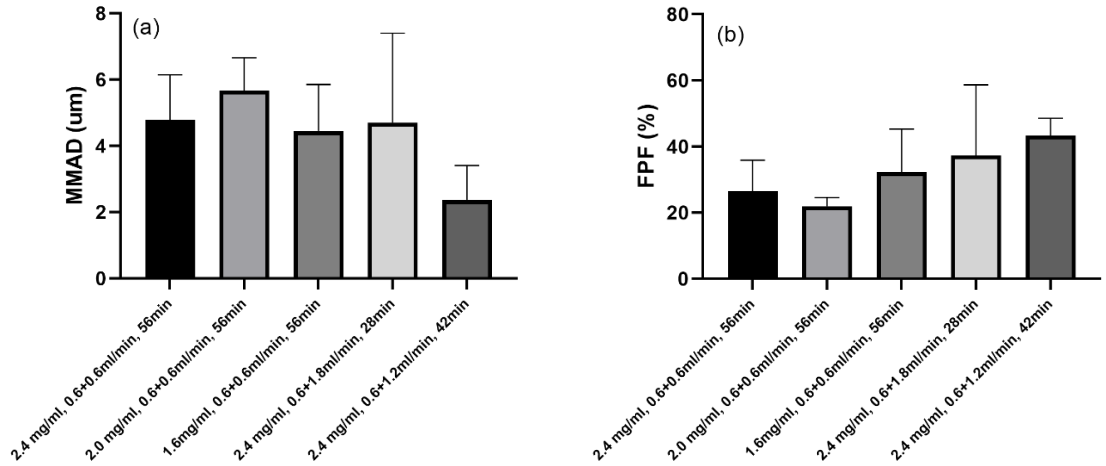

Figure 4. (a) MMAD of the insulin crystals obtained from the integrated process. (b) FPF of the insulin crystals obtained from the integrated process. Error bars represent the standard deviation from at least duplicate experiments.

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Engineering Spherical Crystalline Drug-Colloid Composites via Microfluidic Emulsion-based Processing

D. Z. L. Ng[1], E. W. Q[1]. Yeap, S. A. Khan[1]

[1] National University of Singapore, Singapore

Introduction

The crystallization of molecular solids is ubiquitous in various contexts and forms the basis of pharmaceutical drug product design and manufacture. As drug molecules get more complex, their crystallization into well controlled crystal forms becomes more challenging yet unquestionably important, from a process and product perspective. We have recently demonstrated the fabrication of co-formulated drug-(polymeric) excipient microparticles with exquisite control over particle size, shape and polymorphism, using microfluidic emulsion crystallization and model hydrophobic drugs such as ROY and Carbamazepine [1-2]. In some cases, the co-formulation of polymeric excipients and drugs, depending on their mutual interactions, may lead to problems of drug-polymer miscibility and result in amorphous solid dispersions. [3-4] These amorphous solid dispersions may present storage problems, as they can crystallize over time and result in changes in therapeutic efficacy. Here, we demonstrate the use of colloidal silica particles as excipients in microfluidic emulsion crystallization of a model hydrophilic drug, lamivudine. Colloidal silica, conventionally incorporated in solid dosage forms at the later stages of formulation, function as glidants or fillers. In contrast, in our work, colloidal silica enables drug crystallization into well controlled sizes and polymorphic forms, while retaining a spherical macrostructure for good flowability.

Results and Discussion

Here, we demonstrate the evaporative solidification of an anti-retroviral drug molecule (Lamivudine,4-amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone) into spherical crystalline particles in the presence of colloidal silica or polystyrene with exquisitely tunable needle-like crystals by co-confinement of a highly supersaturated drug−colloidal dispersion within submillimeter droplets. (**Figure 1**). We are able to tune the crystalline microstructure of the drug at the submicron level by using various colloid sizes. (**Figure 2a-c**) This tunability of the microstructural length scale with colloid size (**Figure 2a-c)** and the surface-agnostic nature of the microstructure control (**Figure 1d-i**) are unprecedented observations that are not captured by currently available theories. Furthermore, differences in the polymorphic outcome of the crystallization conducted in the presence or absence of colloids are also observed. (**Figure 2d-e**)

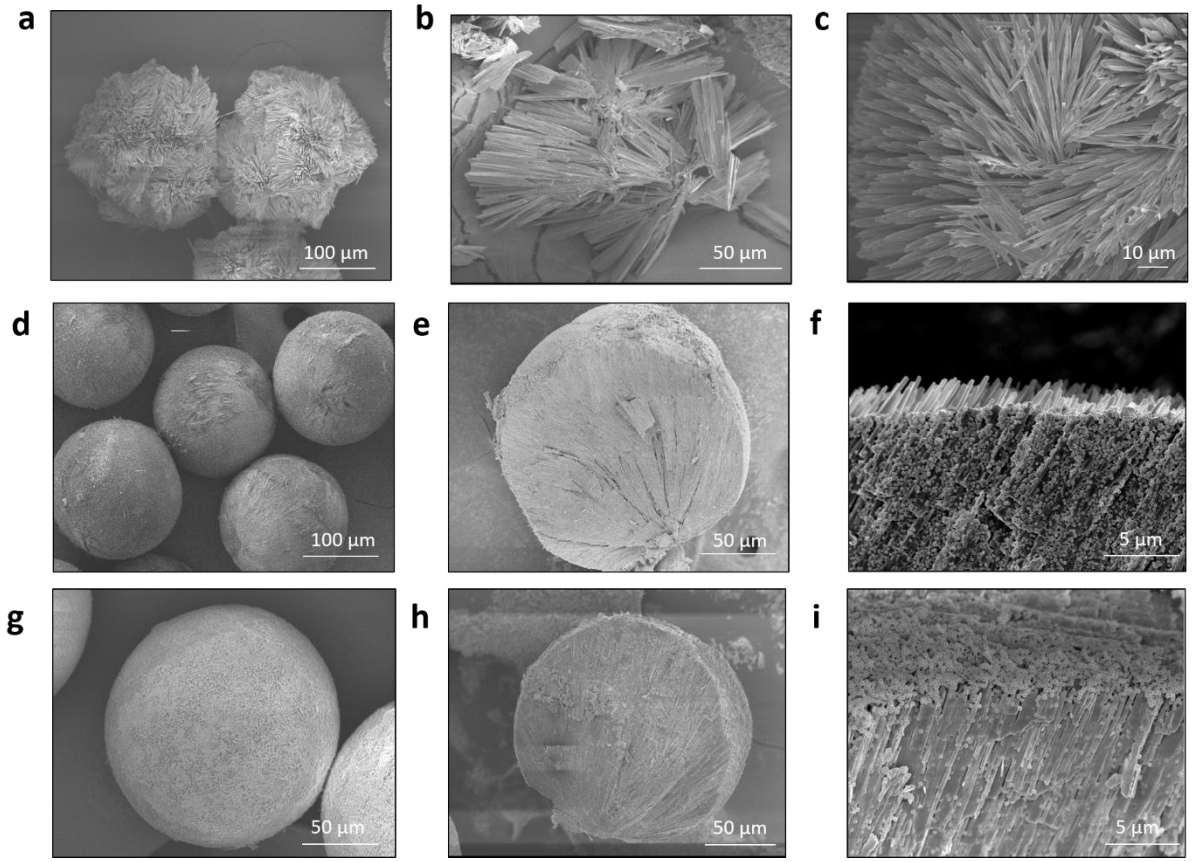

Figure 1: Scanning electron microscopy (SEM) images of (a−c) neat lamivudine microparticles, (d−f) lamivudine-silica (165 nm) microparticles, and (g-i) lamivudine-polystyrene (375 nm) microparticles. (a−c) Lamivudine microparticles are irregularly shaped, and are composed of large, loosely packed and lamellar needles. (d,e,g,h) Lamivudine-silica and lamivudine-polystyrene microparticles have a well-controlled spherical macrostructure and are composed of tightly packed, fine lamivudine needles of high aspect ratio (up to 300), spanning the extent of the microparticles. (f,i) These needles are of submicron cross-sectional dimensions, and highly aligned.

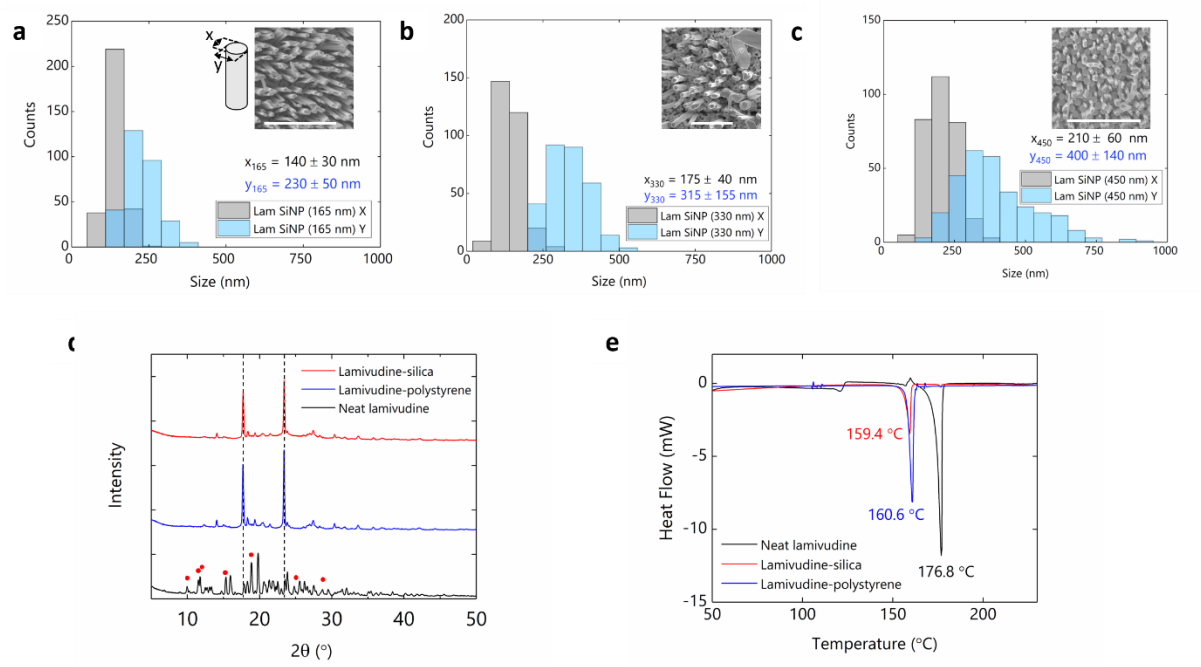

Figure 2: (a-c) Histograms of cross-sectional dimensions of the lamivudine needles in the microparticles, when colloidal silica of diameter (a) 450 nm, (b) 330 nm, and (c) 165 nm is used. The needles are typically of elliptical cross section, and the reported measurements are of width along the two principal axes (x and y), made from top-down SEM micrographs (see inset of (a)). The cross-sectional dimensions of the needles are seen to increase with colloid size. Scale bars represent 1 μm. (d) Powder X-ray diffraction spectra of lamivudine from neat lamivudine particles, lamivudine-silica (330 nm) particles, and lamivudine-polystyrene (375 nm) particles. The red dots above the neat lamivudine spectra mark out characteristic peaks for lamivudine polymorphic Form I. Two distinct characteristic peaks at 17.7° and 23.4° (marked with vertical dotted lines) were seen for both lamivudine-silica and lamivudine-polystyrene spectra, matched those of lamivudine Form V. (e) Differential scanning calorimetry (DSC) thermograms of lamivudine from neat lamivudine particles, lamivudine-silica (330 nm) particles and lamivudine-polystyrene (375 nm) particles. The melting point of lamivudine in the neat lamivudine particles at 176.8 °C corresponds to the Form I melting point.[5] There lowered melting point for the lamivudine within the lamivudine-silica and lamivudine-polystyrene particles at 159.4 and 160.6 °C, respectively, corresponds to the Form V melting point.[6]

Another notable advantage of using colloidal silica is its general applicability to a wide range of drugs, since the silica particles can easily be functionalized [7] and applied to hydrophobic drugs. Furthermore, there is considerable interest in the development of nanocrystalline drugs, which dramatically increase the bioavailability of poorly soluble drugs. From all these perspectives, our findings, which describe how controlled colloid addition and confinement within droplets can be used to tune crystalline microstructure at the submicron level as well as polymorphic outcome, while still retaining control over the spherical macrostructure, pave

the way for the design and manufacturing of crystalline solids for application in next generation pharmaceutical dosage forms.

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Multiscale experimental study and modeling of L-Glutamic acid crystallization: a new perspective on the Ostwald rule of stages

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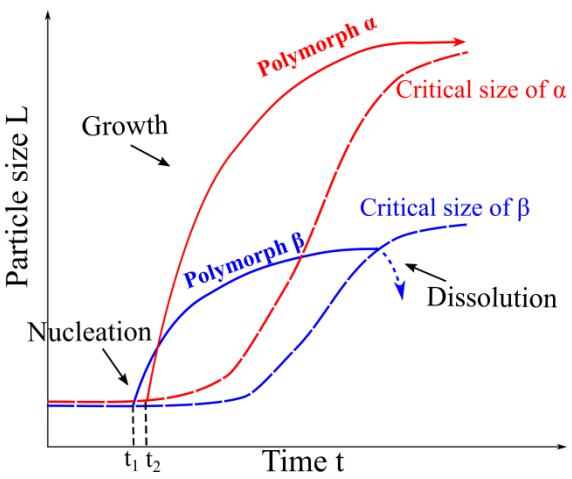
When a polymorphic system is said to follow the Ostwald Rule of Stages (ORS), a metastable phase is expected to appear first then undergoes a transition toward a more stable phase. In this work, a multiscale experimental study and simulations were used to validate our explanation to the ORS involving the Gibbs Thomson effect. The product used was the L-Glutamic acid (LGlu), a monotropic system with two polymorphs (metastable α and stable β). In the experimental section, we compared the results of LGlu cooling crystallization in three different devices: a liter scale crystallizer, a milliliter scale stagnant cell, and a microfluidic device. In the modeling section, we used a kinetic model that was previously built[1] to show the behavior of each LGlu polymorph at early stages of crystallization.



The results gave a new explanation of ORS, i.e. growth of the metastable phase at the expense of the stable phase: at the beginning of the crystallization process, several polymorphic phases are likely to nucleate, including the stable form. However, depending on the respective growth rates of each phase, the nuclei of the polymorph of higher growth rate will grow faster than the others and will consume the supersaturation. In the same time, the nuclei of the slow growing phases will find themselves under the critical size and will be doomed to dissolve. For LGlu α and β polymorphs, this behavior is illustrated in the figure [2].

Consequently, the Gibbs Thomson effect could drive the dissolution of the stable phase clusters in favor of the metastable phase, leading to the absence of stable phase crystals, in agreement with the ORS.

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A New Method for Scale-Up of Mixing-Controlled Precipitation Processes Based on Complete Similarity

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Precipitation is an important solids formation process in chemical or pharmaceutical industry. During precipitation, supersaturation is generated by mixing and reaction of educt fluids. In such precipitation processes a rather higher level of supersaturation prevails, due to which the timescale of solids formation is small. It often is even smaller or at the same order of magnitude than the timescale of mixing. Hence, an influence of mixing on the resulting crystal size distribution (CSD) can be observed. As the timescale of mixing depends on the scale of the reactor, the final CSD of the production scale is difficult to predict and might deviate drastically from laboratory-scale experiments. Hence, precipitation still poses a problem for process development and optimization.

Several scale-up rules for precipitation have been developed in the past. All these rules come from the idea of keeping a specific variable (e.g. energy dissipation, impeller tip speed, …) constant between both reactor scales. However, as different mechanisms are involved in precipitation processes, which do not rely on a single variable, only insufficient results can be obtained by these scaling-techniques. Generally valid scale-up rules, considering all relevant mechanisms, could not be identified yet.

We recently proposed a novel scale-up theory enabling advanced usage of competitive-parallel chemical model reactions (CCMRs) [1]. CCMRs, e.g. the Villermaux-Dushman reaction, are typically used for characterizing mixing reactors or fundamental studies. In [1] we were able to proof that, for a confined-impinging jet mixer (CIJM) with equal inlet velocities, only the Reynolds number (Re), the Damköhler number of the slow reaction β, Da_{β}, and the dimensionless concentration ratios affect the product distribution [1]. We, furthermore, demonstrated that literature has misinterpreted the impact of Re on the product distribution of CCMRs, since the influence of Da_{β} has not been considered correctly. In previous studies, Da_{β} was either not defined or defined in a way which can be shown to be generally incompatible to the concept of the Reynolds similarity [2].

Within this contribution, we transfer the idea of complete similitude to the issue of mixing-influenced precipitation. Under consideration of some simplifications, we propose that complete similarity is possible and enables the derivation of new scale-up functions based on complete similarity. We show that the dimensionless CSD is a function of Re, a solids formation Damköhler number, Da_{sf}, and the dimensionless concentration ratios only in a CIJM with equal inlet velocities. Thus, our results solve the issue on how to use Re for scale-up, as scale-up by Re requires consideration of Da_{sf}. Furthermore, we can show that literature has misinterpreted the impact of Re on the precipitate's CSD, since the influence of Da_{sf} has not been considered.

This contribution introduces our new theory of complete similitude, presents latest results and illustrates, how this theory can be used to develop new methods for scale-up of technical precipitation processes in future.

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Real-Time X-ray Phase-Contrast Imaging of Continuous Antisolvent Crystallisation in a Concentric Flow Microreactor

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Microscopic imaging of mixing, nucleation and pre-nucleation stages of organic molecule crystallisation in organic solvents presents formidable challenges to conventional microscopy techniques due to the low absorption, scattering or refraction contrast between organic phases. Using coherent X-rays from a synchrotron source we have now developed a system for real-time X-ray imaging of processes taking place inside continuous-flow crystallisers. The enhanced contrast is achieved through slightly different phase shifts experienced by coherent X-rays travelling through adjacent phases, which lead to constructive and destructive interference between X-rays near interfaces in multi-phase mixtures. This X-ray phase contrast allows imaging of multi-phase multi-component mixtures of organic materials with strongly enhanced contrast. In this presentation we will show how such X-ray phase contrast imaging (XPCI)[3] overcomes the limitations of conventional absorption contrast X-ray microscopy and tomography, and how such *in situ* XPCI microscopy under practical conditions can be used to gain deep insight into the spatiotemporal dynamics of the processes taking place inside crystallisers.

We used a previously described concentric flow crystalliser[1] for antisolvent crystallisation, modified by an outer vessel with X-ray transparency of the reactor walls (Fig. 1). We have been able to resolve mixing, phase separation and crystallisation processes in both time and space, thereby providing deep insight into the processes taking place in the mixing, nucleation and crystal growth zones of anti-solvent flow crystallisers. We have so far achieved time resolution of about 50 milliseconds and spatial resolution of ~1 µm over a field of view of about 2 x 2 mm.

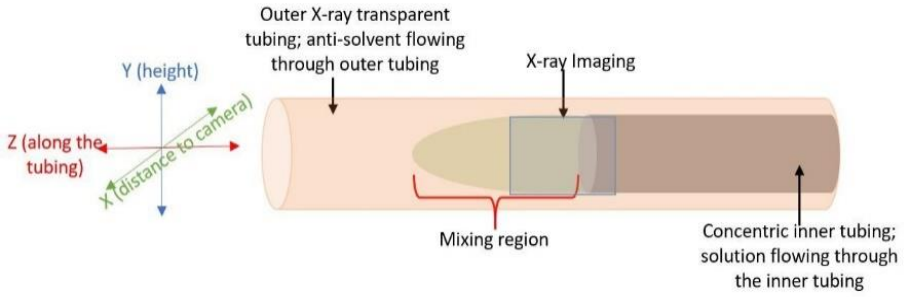

Figure 1. Schematic of the concentric flow crystallisation X-ray imaging experiment.

Antisolvent crystallisation studies were carried out with two model systems, glycine and lovastatin, with various solvent/antisolvent systems and flow-rate ratios. Our initial aim was to spatially resolve the expected sequence of mixing, nucleation and crystal growth zones that are believed to be associated with the initial formation of supersaturated solution by mixing and subsequent phase separation by homogeneous nucleation of crystals. Indeed, real-time *in situ* XPCI imaging of the glycine system reveals the size and shape of the concentric mixing flow cone. We will also show an XPCI movie of homogenous glycine nucleation from the mixing zone. The results clearly indicate that additional heterogeneous nucleation and growth of crystals take place at the mouth of the inner tube feeding the solution, raising the possibility that seeding and secondary nucleation may take place downstream. There is also evidence for time-dependent gradient-induced mass transport variations in the continuous phase flowing over the growing crystals.

In contrast, our investigation of the lovastatin crystallisation system provides evidence for a much more complex scenario, raising interesting questions about the sequence of events leading to nucleation.[2] We will show real-time XPCI movies of the microscopic phase behaviour in the metastable zone that reveals a complex interplay between initial mixing, liquid-liquid phase transitions as well as heterogeneous and homogeneous nucleation processes. Spherical droplets are evident of a new phase formed by what we presume is a liquid-liquid phase separation driven by the extremely high local supersaturation achieved in the mixing zone. This phase interacts strongly with the reactor walls, forming a heterogeneous thin film phase near the mixing zone (Fig. 2), from which crystallisation of the final needle-shaped crystals takes place. This suggests that heterogeneous surface templating could potentially be a better strategy to morphology control in this system than the addition of homogeneously dissolved growth modifiers.

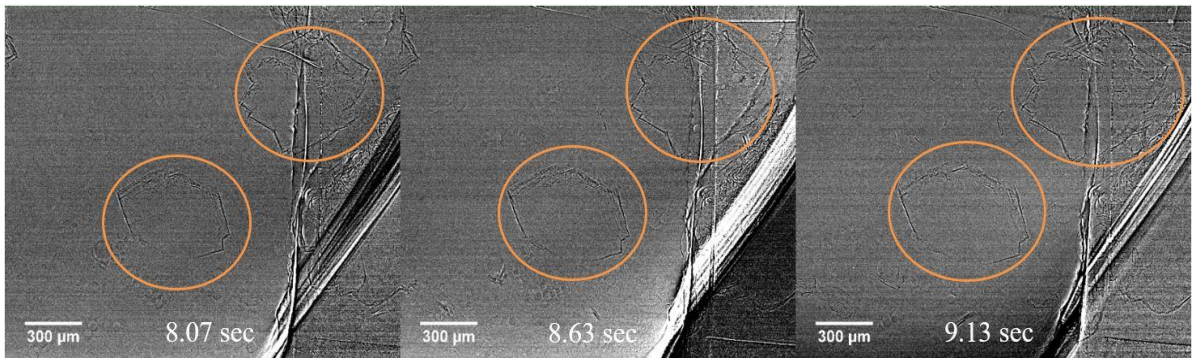

Figure 2. XPCI 2D time-lapse of thin film deposition during lovastatin anti-solvent crystallisation as a function of the elapsed time.

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Treatment of brines from power generation using freeze-based crystallization methods

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Introduction

Freeze-based technologies offer a promising alternative to evaporation with respect to lower operating costs, high salt/by-product recovery efficiency[1], and can generate pure products[2, 3] that can be reused. Eutectic Freeze Crystallization (EFC) has been used to treat wastewaters from mining[3-6], pharmaceutical[7], flue gas desulphurisation[8] and textile industries and has potential to treat wastewaters where traditional technologies are unable to perform.

The aim of this study was to test the treatment of a moderately dilute brine, produced from flue gas desulphurisation (FGD). Brines from (FGD) have been treated using EFC before[2, 8]. However, these brines had compositions near the eutectic value for the $MgSO_4$-H_2O system. A combination of treatment technologies is required for brines characterised by compositions far from the eutectic values[9]. This is capital intensive, but it also means more water or salt(s) can be recovered than when the feed has a eutectic composition.

Materials and methods

The FGD brine used in this study contained 8037 mg/L Mg^{2+},11 100 mg/L of Cl^- and 18 100 mg/L of SO_4^{2-}as the major components. The stream also contained minor concentrations of Br^-, F^-, Na^+ and Ca^{2+}. The treatment of the brine using cooling-based crystallization methods was simulated using OLI Stream Analyser[10], which uses the Helgeson-Kirkham-Flower equation of state to predict equilibrium constants of species from multi-component aqueous solutions. The nucleation temperatures, identity and yields of the potential products obtainable from the brine were predicted.

A model synthetic stream was prepared and treated using a cooled 1L batch crystallizer which was operated in a refrigerated laboratory. Each experiment was run for three hours from the point of nucleation. After harvesting the ice product, the residual solution from each experimental stage was employed as the feed to the next stage [3]. The salt product was harvested only in the last stage.

Results and Discussion

Thermodynamic modelling showed that, as the temperature is reduced, the first solid to crystallize out is ice, which nucleates at -1.5°C. This indicates that the brine is relatively dilute, as this is a very low freezing point depression. $CaSO_4.2H_2O$ (gypsum) also crystallizes out at this temperature, but at a very low yield of 224 mg/L. With a further operating temperature decreas, more ice crystallizes out at progressively lower temperatures. At -2°C, MgF_2 crystallizes out, also at a very low yield of 53 mg/L.

This is illustrated in Figure 3, which shows the effect of decreasing the operating temperature on the ice and salt nucleation temperatures as well as the yields of the different salts and ice.

With a decrease in temperature and with more ice crystallizing out, the concentrations of all spectator species increase until $MgSO_4.12H_2O$ nucleates at -10°C. Simultaneous crystallization of ice and $MgSO_4.12H_2O$ occurs at a significantly lower temperature than the eutectic point of the binary $MgSO_4$-H_2O system, which is -3.9°C [1, 9]. This depression in the eutectic point was attributed to the magnesium chloride species which usually crystallizes out at a eutectic temperature of -34°C[9].

The yields of ice and $MgSO_4.12H_2O$ continue to increase as the operating temperature is decreased until the yields become relatively constant at 873 g/L and 50 g/L at -20°C, respectively. The predicted yield of $MgSO_4.12H_2O$ is significantly higher than that of MgF_2 and gypsum.

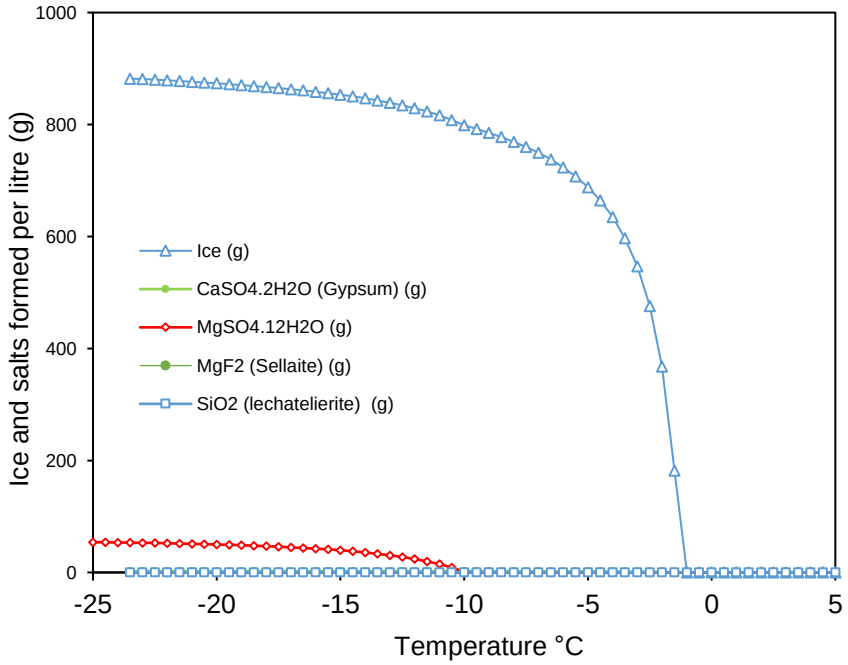

Figure 3: Effect of temperature on ice and salt nucleation temperatures and yields for the freeze/EFC of the FGD brine

The treatment of this brine using cooling-based crystallization would be dominated by the recovery of significant amounts of water, as ice, and the recovery of small amounts of $MgSO_4.12H_2O$. The overall theoretical water recovery in this case is 88% and the Mg recovery is 46% at -20°C. It would be difficult to operate the process, at -20°C, in a single stage. Therefore, several sequential stages were proposed for the recovery of ice at this operating temperature. It was decided that the first stage be operated at a temperature close to -1.5°C.

The batch experiments showed that ice nucleated from the synthetic brine at at -1.5°C upon introduction of ice seeds. An operating temperature of -3.17°C was achieved after the brine was treated in four stages, from which at least 60% of the water was recovered from the brine as ice (Figure 4a). Although gypsum and MgF_2 were predicted to crystallize simultaneously with ice at -1.5°C and -2°C, respectively, no salt was harvested until an operating temperature of -3.17°C was reached. Gypsum then crystallized out of the residual solution obtained from this stage (Figure 4b).

The gypsum continued to crystallize from the residual solution at room temperature (i.e.~22°C) after the experiment had been terminated. Gypsum remained in solution although it was supersaturated probably due to the slow crystallization kinetics under the conditions employed in this study. This behaviour is well known for gypsum[3].

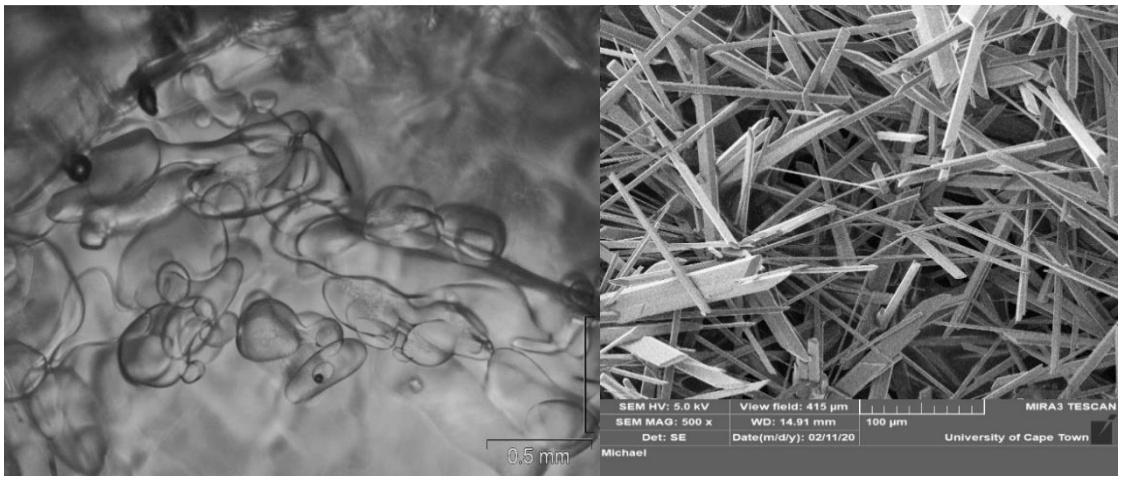

Figure 4: Micrographs of (a) Ice product and (b)Gypsum recovered from a dilute FGD brine

Conclusions

Ice, gypsum, MgF_2 and $MgSO_4.12H_2O$ were predicted as potential products from the freeze-based treatment of the moderately dilute, multi-component brine from power generation operations. Theoretically, ice was expected to first crystallize out at -1.5°C and this was confirmed experimentally in a cooled batch crystallizer. However, gypsum was only recovered from a residual solution that was obtained from a stage operating at -3.2°C. MgF_2 has not been recovered yet but further experimental work is still being conducted.

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Reinventing a commercialized particle-engineered crystallization process using PAT feedback control to obtain the filed solid form.

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Introduction

During the development of an Active Pharmaceutical Ingredient (API), an extensive polymorph screen identified a hemihydrate as the stable solid form. However, during commercial manufacturing of the multi-ton API a previously unidentified monohydrate was obtained which was later found to be thermodynamically more stable under the process conditions employed.

A detailed phase diagram was constructed (Figure 5) which revealed that the hemihydrate could only be obtained in a narrow temperature-water activity region in the crystallization solvent system (Isopropyl acetate/water) whilst the process conditions of both the crystal engineering step and the isolation were found to favor the undesired monohydrate form. Initial mitigation strategies to stabilize the metastable process were inadequate (lowering water content, high shear mill loop rinsing, gowning procedures, and the inability to reprocess due to shortened induction and form transformation times from hemihydrate to monohydrate).

Therefore, a new crystallization process had to be developed to ensure the hydrate form was thermodynamically favored whilst delivering the same chemical and physicochemical API quality attributes. (considering the process consists of a necessary PSD and crystal habit tuning step). Furthermore, the new process had to fulfill commercial process equivalency in terms of yield and throughput to avoid any negative impact on cost of goods.

Discussion

Initially, different solvents were evaluated in which a broader window of water activity is acceptable than in the isopropyl acetate/water system, but these were found to be suboptimal towards yield, throughput, and crystal habit.

A continuous crystallization was considered due to the potential for crystallizing the API at a specific location within the phase diagram where the hemihydrate is favored (point “B3” in Figure 1). However, amongst the process yield, the water content control and current production plant design were unfavorable to meet timely implementation.

Eventually a batch cooling crystallization process in the same solvent system was developed and successfully introduced and validated in our commercial plant. Both the original metastable process (Blue trajectory “A”) and the newly designed thermodynamically stable

processes (Green trajectory “B”) are schematically depicted in the phase diagram of the isopropyl acetate/water system (Figure 1).

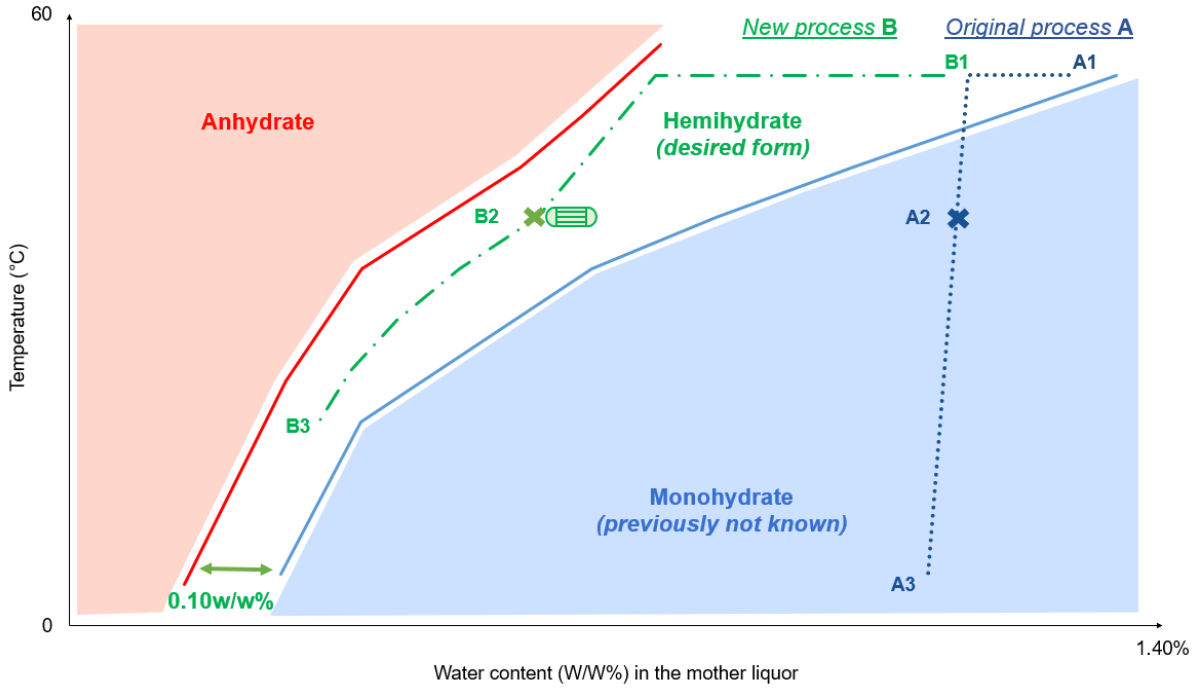

Figure 5: Original metastable API process trajectory A (blue) and new thermodynamically stable API process trajectory B (green) overlaid onto the phase diagram of the API in isopropyl acetate/water. Stage A1 and B1 are the seeding points, Stage A2 and B2 (crosses) is the crystal engineering step and Stage A3 and B3 are the isolation points

In both processes at stage 1 (A1 and B1) the crystallization is initiated by seeding in the hemihydrate zone. Prior to seeding, in the new process, the water content and product concentration are controlled using Near Infrared Spectroscopy as an in-process control in order to meet the very narrow water content requirement at the isolation point. By taking advantage of the inherent water consumption during the formation of the hemihydrate crystals, at the seed point the water content was lowered. In order to remove sufficient water from the system the crystallization was performed at a high API concentration (40g/100ml) allowing the system to maneuver within the hemihydrate “safe zone”.

To ensure a narrow PSD (Dv50 of 40µm with a span of 1.7) and to alter the crystal habit, a crystal engineering step is performed at stage 2 (“A2” and “B2”). Initially, the needle-like crystals are broken by the in-line high shear mill into short rods and fine particles. In contrast to the metastable process trajectory “A”, the shear milling step is performed within the region favoring the hemihydrate.

The suspension is then heated in order to re-dissolve the generated fines. Therefore, in the metastable process, the content of the crystallizer is re-heated and cooled over time.

However, for the thermodynamically stable process a new time-efficient technology platform is implemented; The combined use of an in-line high shear mill and an in-line heat exchanger**.** Before re-entering the isothermal crystallizer, the fines generated by the in-line high shear mill are dissolved in the heat exchanger (HE) (Figure 2).

To maneuver through the narrow hemihydrate zone, simultaneous cooling and dosing (move from stage “B2” till “B3”) is required. If not diluted, isolation conditions would be within the monohydrate zone as in the metastable trajectory of “A”. By dosing dry isopropyl acetate, the water activity decreases while the suspension cools to the isolation temperature, guaranteeing solid form control with a high yield (93%) and comparable throughput (20g/100mL). As such the new process is completely thermodynamically stabile.

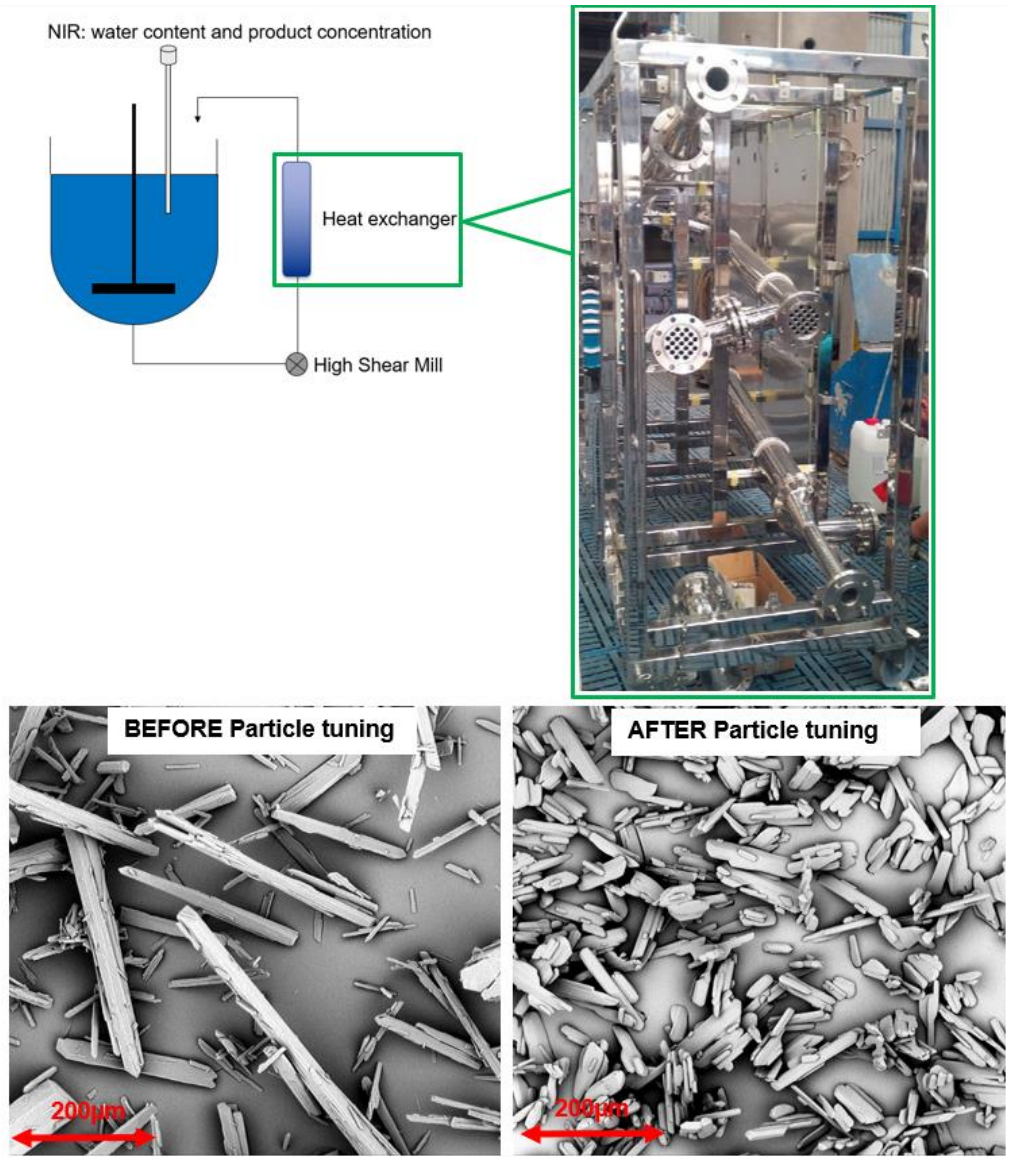

Figure 2: Schematic reactor setup with high shear mill loop and heat exchanger (top left), Picture of a production scale shell in tube heat exchanger (top right), SEM picture before HSM and HE (bottom left) and SEM picture after HSM and HE (bottom right)

Summary

A new thermodynamically stable process is developed and commercialized in which the final hemihydrate solid form is controlled requiring a thigh control of the water content which is achieved via a NIR in-process control prior to seeding. The PSD and crystal habit are altered and controlled by combining in-line high shear milling with in-line temperature cycling by means of a heat exchanger.

Development of a Continuous Crystallization with Periodic Wet Milling for Particle Size Control

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Introduction

The design and testing of a continuous crystallization process with an in-situ mill for the purpose of particle size control is the focus of this effort. This work is an evolution of a continuous crystallization process developed for the supply of an active pharmaceutical ingredient that was executed previously in a Lilly manufacturing facility. The initial continuous crystallization process was not able to directly achieve the desired particle size distribution though it did achieve exquisite product purity, higher than achieved through a batch crystallization process. As a result, a hybrid approach was utilized for initial production of the product during development. The hybrid approach consisted of a batch wet milling process that followed the continuous crystallization and isolation of the Active Pharmaceutical Ingredient (API). The suspension of the crystalline API produced from a continuous reaction and crystallization process was collected on a pressure filter. The collected suspension was then reduced in size using a batch wet milling process for ultimate particle size control. This hybrid approach though effective was not desirable due to the need for larger batch equipment on the back end of the fully continuous process as well as a larger equipment set for the hybrid approach. The approach also added cycle time to the process, and ultimately defeated the advantages of a fully continuous process.

Summary

In this presentation, the stepwise approach to develop a continuous particle size control process will be described. The approach utilized a model driven experimental program to define the final process. Physical property control through continuous crystallization alone was not possible due to the slow nucleation kinetics relative to growth kinetics. Continuous wet milling was also not able to control particle size due to the high brakeage rate of the material. Ultimately, intermittent milling was found to be the solution. Crystallization modelling and lab automation allowed for the rapid development of the ultimate process.

Vetter et al (2004) discuss the concept of an attainable region for particle size control. This approach was utilized to determine that particle size control was not achievable in the via continuous crystallization alone. The development and utilization of a model for continuous crystallization avoided a long development process. Instead, experimentation and development efforts were focused on the integration of a wet mill into the continuous cascade cooling crystallization to manufacture the API. The mechanistic model for continuous crystallization and wet milling was first validated using batch crystallization data. It was then subsequently applied to describe the continuous crystallization and wet milling process, and to explore the impact of varying process parameters and process configurations (namely the position of the wet mill unit in the continuous crystallization process) on the attainable processing regions for particle size and purity, subject to various process constraints.

The background experiments for characterizing and modeling breakage and implementation of the wet mill in continuous crystallization of recrystallized and crude material will be described. The mill is highly effective at producing target particle size providing a significantly narrower particle size distribution compared to terminal milling. Scale-up considerations and manufacturing scale breakage experiments with an immersion mill are discussed.

The crystallization model confirmed the experimental observations that the continuous crystallization process was unable to achieve the desired product particle size distribution due to very low levels of secondary nucleation in the system. Optimal PSD quantiles (x_{10}, x_{50} and x_{90}) predicted for the product were higher than the target PSD quantiles required to achieve the desired product performance for this compound. The combined continuous crystallization and milling model significantly increased the lower end of the attainable region in terms of PSD, conceptually allowing the process to comfortably achieve the desired range for product PSD quantiles. The output of the model provided an optimized conceptual design that was used as a starting point to investigate the operation and positioning of the wet mill to achieve the desired particle size distribution within a relatively tight particle size constraint.

Conclusions

Experimental validation of the model demonstrated that incorporation of a wet mill did indeed substantially reduce the particle of the product, but to a size that was undesirable for powder handling. Periodic milling was utilized to bridge the gap between the size controlled achieved with a wet mill in continuous operation and one without a wet mill. Surprisingly, a periodic milling cycle did not negatively impact the width of the particle size distribution. The results and utilization of the process model will be discussed.

References

1. Vetter, T., Burcham, C.L., and Doherty, M.F. (2014) *Chem. Eng. Sci.* 106 pp. 167–180