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GlaxoSmithKline, Novartis, and AstraZeneca Fund Center Focused on Advancing Commercial-Scale Continuous Crystallization

By Cynthia Challener, PhD

Through partnerships and collaborations between academia, industry, and the public sector, the Center for Continuous Manufacturing and Crystallization is advancing continuous crystallization technologies.

The Center for Continuous Manufacturing and Crystallization (CMAC) was co-created with industry to address long-term manufacturing challenges and emergent market opportunities. Its scope is from reaction through to formulation, with a particular focus on particle production, and one of its core technology areas is continuous crystallization. The main research platform is the Engineering and Physical Sciences Research Council (EPSRC) Center for Innovative Manufacturing in the United Kingdom, which was established in 2011. The vision of the CMAC, according to its industry director Craig Johnston, is to accelerate the adoption of continuous manufacturing and crystallization processes, systems, and plants for the production of high quality, high-value chemical products at lower costs, more quickly and sustainably, and to do so through effective collaboration between industry, academia, and public bodies.

Administrative details

CMAC was established in 2011 with support from founding members, such as GlaxoSmithKline (GSK), Novartis, and AstraZeneca. Equipment is also provided by various engineering and instrumentation firms, including Cambridge Reactor Design, NiTech Solutions, Amtech, Avantium Crystallization Systems, PSE, Perceptive Engineering, Clairet AWL, Mettler Toledo, and Bruker. There is broad engagement with other pharmaceutical and fine-chemical companies, such as Pfizer, Sanofi (Genzyme), Fujifilm, Syngenta, and Johnson Matthey, to name a few. The physical hub is at the University of Strathclyde (Glasgow), with Glasgow, Heriot-Watt, Edinburgh, Cambridge, Loughborough, and Bath Universities rounding out the multidisciplinary academic team. The center has raised nearly $100 million in two years, initiated several research projects, implemented a doctoral training program across the network (45 PhD students), and is starting a masters program.

Research focus

The research program at the CMAC looks to make significant technology advances across a range of products, processes, and operations, according to Johnston. “With respect to improved particle-based products, we want to develop effective continuous processes for particle formation that address all stages of crystallization, as well find efficient, cost-effective methods for precisely controlling the form, size, shape, purity, surface structure, and functionality of crystallized products that are scalable and sustainable,” he notes. There are 10 key areas that the center has targeted for investigation, including the investigation of appropriate raw materials and synthetic methods, continuous nucleation, growth and habit control, mixing, flow and transport, powder production and processing, and particle properties and performance.

To tackle these issues, the center takes a multidisciplinary approach, with experts in chemical and process engineering, synthetic, physical, analytical, structural, and materials chemistry, crystallization science, pharmaceutical science, and manufacturing and operations management contributing as needed. Projects range from curiosity-driven research through to short-term applied, one-on-one consultancy projects.

Currently, CMAC is tackling two main research projects: the continuous manufacturing of solid particles (continuous crystallization) and manufacturing operations and supply chain management challenges.

Progress in continuous crystallization

CMAC researchers at the University of Strathclyde and Loughborough, Heriot-Watt, and Bath Universities have been involved in efforts to develop effective, commercial-scale continuous crystallization processes. Some of this work has focused on the use of existing equipment, such as a mixed-suspension mixer product removal (MSMPR) crystallizer, continuous-stirred tank reactors (CSTRs), and meso-scale and full-scale continuous oscillatory baffled crystallizers (COBCs). Others are developing new technologies for which patents have been filed, including a device for inducing nucleation (Heriot-Watt University), customized nucleation units for seed suspension (University of Strathclyde), and a moving fluid oscillatory baffled crystallizer and new flow crystallization technology for multicomponent products (University of Bath).

Continuous seeded crystallization

At the University of Strathclyde, for example, modeling and experimental studies, along with the use of process analytical technology (PAT), have led to a greater understanding of heat transfer and growth kinetics in continuous crystallization processes in existing crystallization equipment. A custom nucleation system for the continuous antisolvent precipitation of seed suspensions and controlled addition of the seeds to a continuous growth unit has also enabled the production of particles with desired physical properties.

The development of a continuous seeded crystallization process for polymorphic compounds using a continuous oscillatory baffled crystallizer was achieved using L-glutamic acid (LGA). “LGA has two known crystalline forms. There is extensive information in the literature about controlling the polymorphic phase formation during batch crystallization, so it was an ideal test compound,” Johnston notes. The key to the success of the new continuous operation was the use of a modular approach, in which crystal nucleation control is first achieved via rapid antisolvent seed generation using a newly designed system, and then the crystal growth is controlled with cooling using the COBC. Notably, the COBC was modified to allow the insertion of PAT probes for focused-beam reflectance measurements at the bending sites in the reactor in order to monitor the crystallization and determine when a steady state was reached. The result: optimal desupersaturation behavior was achieved, steady-state operation was attained in just one residence time, the crystals were of the desired phase and particle size, and no encrustation or sedimentation occurred.

More modeling, PAT studies

Meanwhile, at Loughborough University, different crystallization techniques, including cooling crystallization, anti-solvent crystallization, and in-line seeded crystallization, as well as the effect of impurities and polymorphism behavior in continuous crystallization in an MSMPR crystallizer are being investigated using PAT. Researchers at both Loughborough and Bath are also jointly studying the application of PAT for continuous cocrystallization monitoring, control, and scale-up. A meso-scale COBC has been rebuilt and fully commissioned and future studies will use results from heat transfer modeling to design and optimize the jacket configurations for precise control of the temperature during continuous crystallization.

Additional work on the development of process monitoring tools and the modeling of continuous crystallization processes is underway at Heriot-Watt University, and professor Xiong-wei Ni and graduate student Craig Callahan have filed a patent for a recently developed nucleation device that separates the crystal nucleation and growth operations into two stages. At the University of Bath, the control of polymorphic forms during continuous crystallization of multicomponent molecular complexes in a COBC is being explored, while crystallization using nonphotochemical laser-induced nucleation for polymorph control is a key research topic at the University of Edinburgh. Finally, at the University of Glasgow, researchers are demonstrating that crystallization conditions can be autonomously controlled via in-line analysis of the solution phase, and that evolutionary algorithms combined with analytical feedback can be used to optimize the desired product attributes.

Extensive industry engagement

CMAC is an industry-led membership organization that focuses its research efforts on addressing the specific technology needs of its members, who support the research with both funding and through the provision of equipment and expertise. In one example, Perceptive Engineering, Astrazeneca, and the Center for Process Innovation are working with CMAC to develop make-to-order processing plants (MOPP). An automated control system is being installed on a Rattlesnake Oscillatory Flow Crystallizer from Cambridge Reactor Design that will include in-line PAT systems (infrared, ultraviolet-visible, FBRM, and/or Raman spectroscopy) for monitoring and control. The system will first be evaluated for the cooling crystallization of lactose in an aqueous solution, and then using a complex API in an organic solvent.

In a second example, researchers at the University of Strathclyde and Heriot-Watt University, with the support of NiTech Solutions, have developed several moving fluid batch oscillatory baffled crystallizers (MF-BOBCs) that can serve as intermediate evaluation platforms when moving from batch to continuous crystallization. “Crystallization behavior in a batch reactor can be very different from that in a continuous reactor due to the very different hydrodynamic environments in these different systems. There has, however, been a dearth of intermediate systems available for the evaluation of crystallization behavior of a compound under continuous conditions,” observes Johnston. The new systems mimic the mixing in a COBC and make it possible to effectively evaluate continuous behavior on a batch scale. “With this capability, it will be possible to more efficiently transition a crystallization process from batch to continuous production,” Johnston states.

Moving to Phase II

In Phase II, the center will focus on three main research initiatives: development of laboratory-scale continuous crystallization; development of tools for rapid product analysis and process monitoring; and development of systems that will be effective for future supply chains, according to Johnston. “Overall, we will continue to investigate the basic properties of particles and crystallization processes in order to achieve highly controlled, continuous methods for the crystallization of complex molecules with desired properties. And we will do so through extensive collaboration with recognized experts in the field,” asserts Johnston.

Adds Clive Badman, chairman of the CMAC board and vice-president of investigational material supply with GlaxoSmithKline: “The team continues to work with GSK, AstraZeneca, Novartis, and other partners to progress innovative research against a well-defined, user-led scope. For GSK, this [collaboration] has resulted in a deepening and broadening engagement over the year.” He also notes that additional funding for a new Technology Innovation Center ($150,000) that will open its doors in 2014 will provide a space for industry and academic researchers to work together to capitalize on new manufacturing technologies and create a new supply chain to meet the increasing needs of patients worldwide.