EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Annual Review

2015-2016

UNIVERSITY of STRATHCLYDE
CMAC
NATIONAL FACILITY

EPSRC
Engineering and Physical Sciences
Research Council

Contents

Opening Remarks

Welcome to the 5th CMAC Annual Review for the EPSRC Centre for Innovative Manufacturing. This review reports the Centre's progress over the last 12 months across our programmes that include collaborative demand-led research, training and skills development, new facilities development and services, internationalisation and translation. There have been exciting developments across all of these areas with new approaches for continuous manufacturing and crystallisation emerging from our phase II programme; new ICT technologies developed and tested by the ICT-CMAC project; industrial research contributions to major UK AMSCI funded projects, REMEDIES and ADDOPT as well as a vibrant and impactful programme of industry sponsored projects. Delivering the skills needed by industry is major goal of the Centre and 2016 will also see our first cohort of doctoral trainees graduate and enter the next phase of their careers. I am delighted too that our efforts to establish a new National Facility offering world class support to the wider academic and industrial communities was recognised earlier this year by ISPE in their 2016 annual Facility of the Year Awards. We are the first academic research institution to receive this prestigious award.

2016 also marks a major milestone for CMAC with the end of the initial EPSRC Centre for Innovative Manufacturing award. Hence this year's report also highlights key achievements from the last five years. It has been a hugely exciting and challenging few years and it has been a privilege to be part of the CMAC team whose dedicated efforts have helped to establish our reputation as a leading national manufacturing research Centre. I am indebted to our Advisory Board, all of the management team, academics, researchers, students and company representatives from across the research and innovation landscape who have contributed to the success so far.

Partnership and collaboration remains very much at the heart of our activity and we look forward to continue to build on these relationships as we work to accelerate the adoption of continuous manufacturing. Importantly, we are also able to look forward to the next chapter for CMAC with all our industry, charity, academic and public sector partners as we build on the collective achievements to date and embark on an ambitious new 7 year programme in the recently announced EPSRC Future Manufacturing Hub in Continuous Manufacturing and Advanced Crystallisation. These are indeed exciting times, not least as we look at a dynamic international landscape. Myself and the CMAC team look forward to working together with colleagues from across the UK and international communities to deliver the societal and economic benefits that can only be achieved through long term strategic support for manufacturing research.

Professor Alastair Florence
Director

Centre Overview

CMAC is a world class national centre for research and training in advanced pharmaceutical manufacturing. Working in partnership with Industry we are transforming supply chains for the future.

- 137 people
- 74 active researchers
- 4 tier 1 industrial partners
- 7 HEI collaborative institutions
- 56 PhD students
- 5 industry funded PDRAs

National Centre

- National centre supported by EPSRC, industry & academia
- Accelerating the adoption of continuous manufacturing
- Supporting UK collaboration in manufacturing research
- Maximising impact of innovative manufacturing research
- Building the community through dissemination and outreach

Research

- Consistent, better & functional particles
- Better medicines through understanding particle formation and processing
- Continuous manufacturing research through synthesis, crystallisation to formulated product

National Facility

- World class facilities for forming, processing and measuring particles and particulate systems
- World scale manufacturing research facility supporting global partners
- Inspiring researchers and enabling breakthroughs in medicines manufacture

International

- Creating global impact in advanced pharmaceutical manufacturing
- Co-founders of International Institute of Advanced Pharmaceutical Manufacture (I2APM) with partners C-SOPS (USA), and RCPE (Austria)
- Joint International Doctoral Training programme with NTU Singapore

Industry

- Industry demand led research programme
- Influencing policy through world leading collaborative membership organisation
- Enabling supply chains of the future
- Impact through effective research translation for multi-nationals and SMEs

Training

- Delivering the skilled leaders and workforce of the future
- A talent pipeline for industry and academia
- World class multidisciplinary programmes delivering
  - Doctoral and Masters level training
  - Industry and international experience

Centre Overview

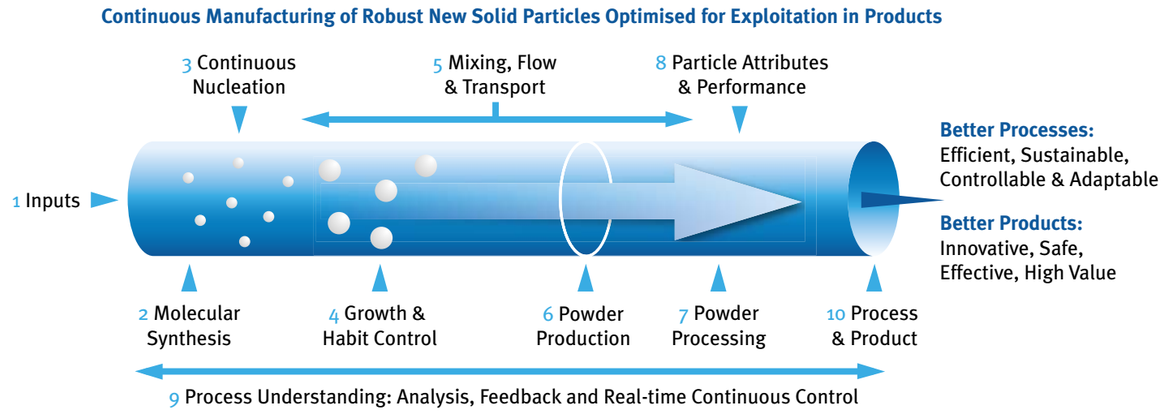
The Centre

Centre Mission

Through partnership and collaboration between academia, industry and public sector stakeholders we have established and will sustain a world class centre of excellence in continuous manufacturing and crystallisation research. The programme will deliver continuous manufacturing research across three main thematic areas that are developing new understanding and supporting innovation across a range of products, processes and operations (Figure 1).

Products	Processes	Operations
Better particles through understanding particle formation and performance in continuous processes	**Better technologies for continuous control, formation, isolation, and processing of particles**	**Optimised high-value chemical manufacturing operations across the value chain**
• Innovative, safe, effective, high-value • Nucleation, growth, agglomeration, breakage • 'dial-a' ...form, size, shape, purity • Tailored bulk and surface structure and function	• Fast, efficient, sustainable, safe • Controllable, scaleable, adaptable and agile • Predictable, optimised • Reconfigurable, modular, plug-play	• Economic, efficient, lean, world class • Wealth creating, sustainable • Deliver regulatory compliance • Reduced time to market
Better Particles	**Consistent Particles**	**Functional Particles**

Figure 1. Key areas for research within the Centre to enable continuous manufacturing of high value chemical products.



Demand-led Scope

The research scope of the EPSRC Centre has been jointly defined by the academic team and our industrial partners. The 10 key challenge areas against the scope are summarised in Figure 2 above and provide a focus for the academic engineering and physical science research activities.

Figure 2. EPSRC Centre research scope highlighting 10 key areas where engineering and physical science research can contribute to accelerate the adoption of continuous manufacturing.

Tier 1 Members and Academic Partners

Academic Members

Multidisciplinary Research and Training

Key to the success of the Centre is the multidisciplinary academic team supporting the research programme. Our team involves 15 academic investigators from 7 institutions working with 19 PDRAs and circa. 50 PhDs and a management, technical and support team of 21, harnessing expertise in chemical and process engineering, synthetic, physical, analytical, structural and materials chemistry, crystallisation science, pharmaceutical science, manufacturing and operations management, Figure 3 & 4.

Additionally we support research activity as part of the National Centre with associate investigators and short term feasibility studies. Our foundation research activity in years 1-2 (2011-2013) was delivered via our flagship research projects against key areas of continuous manufacturing of particles and manufacturing operations in supply chain. The programme has adapted to meet the challenges of the scope in years 3-5 (Phase II) (refer to page 40-41).

The academic team also contribute to the innovative post graduate development programme developed for the EPSRC Doctoral Training Centre in Continuous Manufacturing and Crystallisation and MSc in Advanced Pharmaceutical Manufacturing and other doctoral training schemes (refer to pages 56-59).

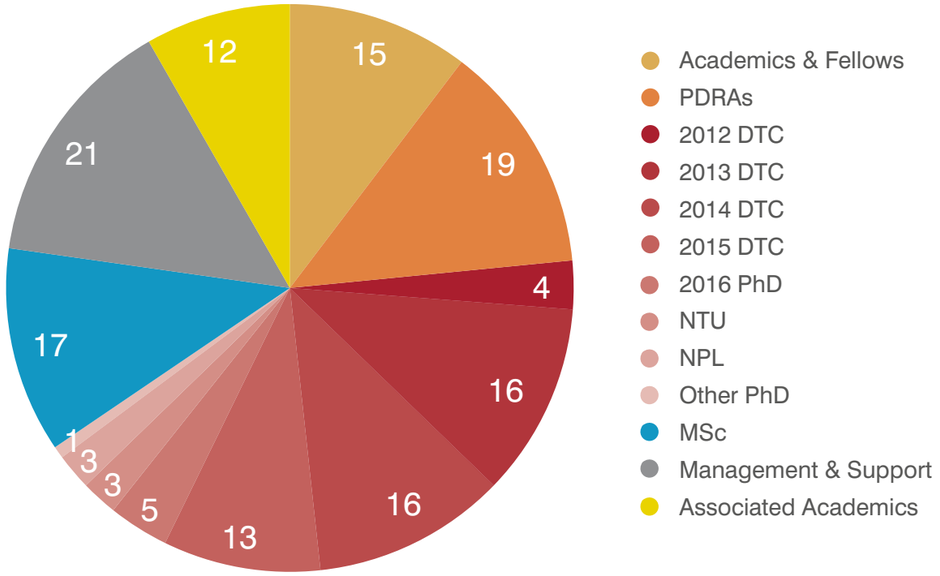


Figure 3. CMAC people category breakdown

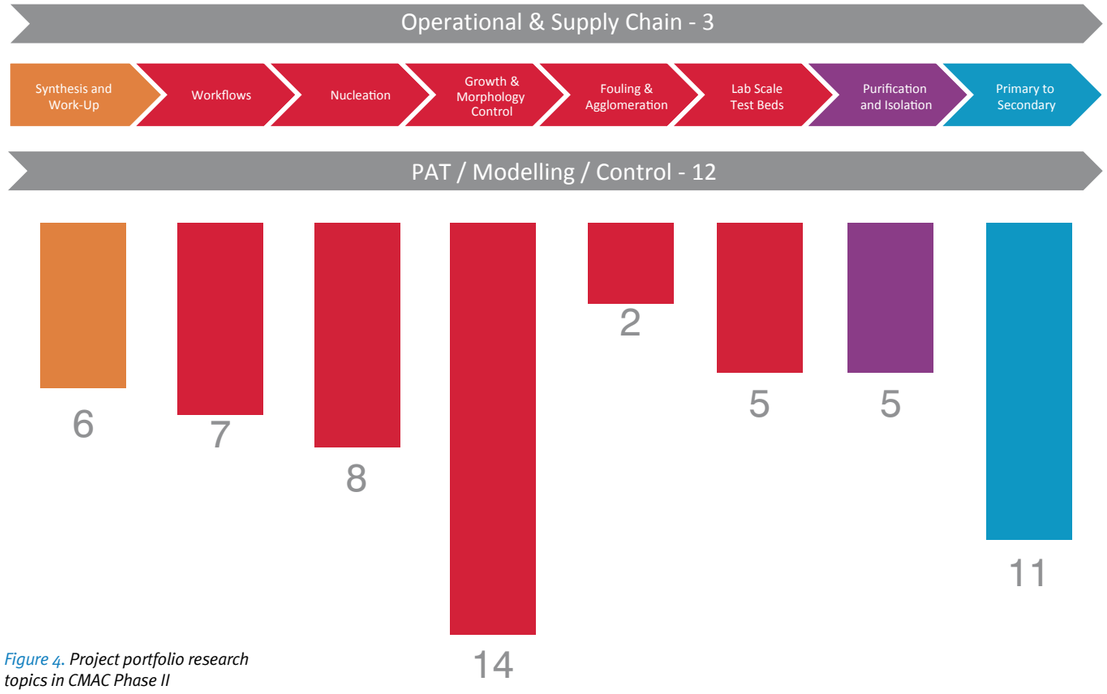


Figure 4. Project portfolio research topics in CMAC Phase II

Centre Overview

Highlights 2011-2016

Date	Item
Oct 2011	EPSRC Centre for Innovative Manufacturing Launch
Sept 2012	CMAC's 1st Annual Open Day, University of Strathclyde
June 2013	Capital Investment of £34.2m awarded by HEFCE's Research Partnership Investment Fund (RPIF) and announced by the Chancellor, George Osborne
Sept 2013	CMAC's 2nd Annual Open Day, Glasgow Science Centre
Oct 2013	2nd Cohort of 17 DTC students begin projects at CMAC
Oct 2013	CMAC joined A.SPIRE as an academic partner which is a formally recognised partner in the EU's Horizon 2020
Jan 2014	Rt Hon Dr Vince Cable MP, Secretary of State for Business, Innovation and Skills marked the Official Opening of Phase I of the UK RPIF
Jan 2014	EPSRC Manufacturing with Light funded awards announced by the Rt Hon Dr Vince Cable MP, Secretary of State for Business, Innovation and Skills
Feb 2014	Innovation in Continuous Manufacturing (iCON) Project kick-off with 7 new academics
Apr 2014	NSF-EPSRC Workshop on Advanced Pharmaceutical Manufacturing with US/UK academics, industry, the FDA and public bodies
May 2014	CMAC and MIT co-hosted the 1st International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP) in Boston, keynote from Janet Woodcock, Head of CDER at the FDA
May 2014	Four Year AMSCI £23m project, Reconfiguring Medicine and End-to-end Supply Chain (ReMediES) aimed at revolutionising pharmaceutical supply
June 2014	Successful Mid Term Review from an International panel
Sept 2014	CMAC hosted the 3rd Annual EPSRC Manufacturing the Future Conference, Glasgow Science Centre, providing a National forum for the UK manufacturing community
Oct 2014	Joint International Doctoral Training Centre in Continuous Manufacturing and Crystallisation of Pharmaceuticals with Nanyang Technological University, Singapore
Dec 2014	New NSF-EPSRC Award Project established $1m from the SAVI seed fund given to support the International Institute for Advanced Pharmaceutical Manufacturing (I2APM)
Dec 2014	Scotland's First Minister Nicola Sturgeon MSP attended the TIC soft opening celebration event hosted by Principal Professor Sir Jim McDonald
Mar 2015	White Papers from the ISCMP published in J. Pharm. Sci Vol 104
July 2015	Her Majesty the Queen officially opened the new Technology and Innovation Centre at University of Strathclyde and visited CMAC labs
Sept 2015	CMAC's 3rd Annual Open Day
Jan 2016	Bayer Healthcare joined CMAC as new Tier 1 Partner
Jan 2016	£20.4m AMSCI Advanced Digital Design of Pharmaceutical Therapeutics (ADDoPT) 4 year project kick-off involving academia, industry and government
Feb 2016	Sir Andrew Witty CEO of GSK visits CMAC
Feb 2016	CMAC are the first academic institution to win ISPE Facility of the Year Award
Mar 2016	Juergen Maier, CEO of Siemens UK, visits CMAC
May 2016	CMAC Tier 2 Engagement event as part of the Engage with Strathclyde wide event brought together academics, researchers and 15 Tier 2 companies to explore collaborations moving forward
Oct 2016	EPSRC CEO Philip Nelson Tours CMAC National Facility

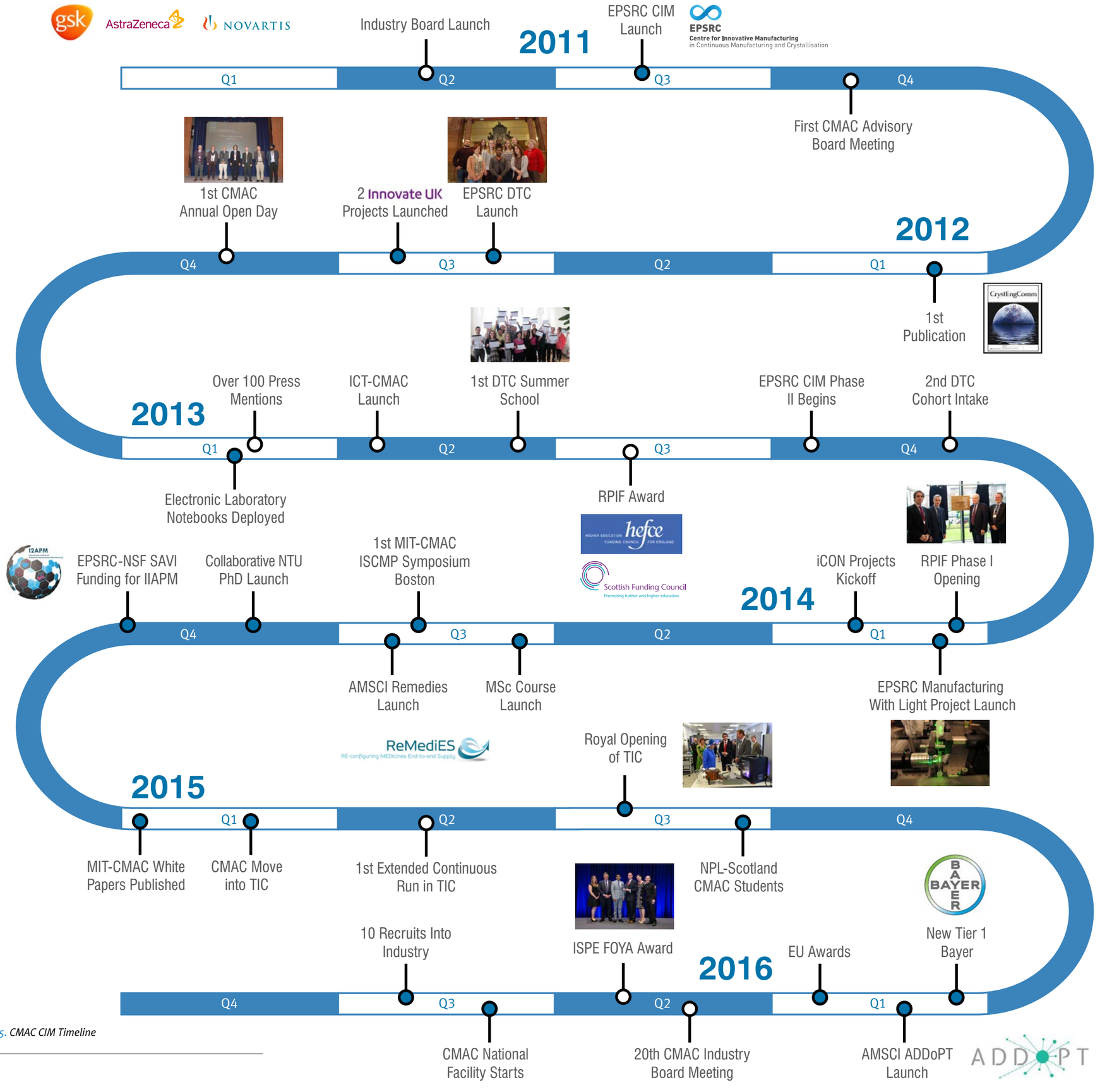


Figure 5. CMAC CIM Timeline

Centre Overview

Outcomes and Impacts

CMAC is delivering outcomes across the manufacturing community, impacting how high value compounds are produced. Three examples of translation to industry in the pharmaceutical and agrochemical fields are presented below:

syngenta

Continuous crystallisation feasibility study learning applied to a Syngenta batch process resulting in a 'de-bottlenecked' fungicide process.

'Overall it was a very valuable collaborative experience. I was really impressed that all the experiments in all equipment scenarios gave meaningful results. The project has led to insights which have changed the way we think about our crystallisation'
David Ritchie, Syngenta

PERCEPTIVE ENGINEERING LTD AstraZeneca cpi

CMAC, Perceptive Engineering, AstraZeneca and CPI collaborated on 'Dial-a-particle' model predictive control for lactose resulting in reduced particle size and improved control.

'CMAC has had an impact both on a national and international level in this area and AZ has benefitted substantially from being associated with the Centre'
Jon-Paul Sherlock, AstraZeneca

NOVARTIS

Use of CMAC's know-how and novel approach for introducing seeds into continuous crystallisation systems installed in Novartis Basel continuous plant.

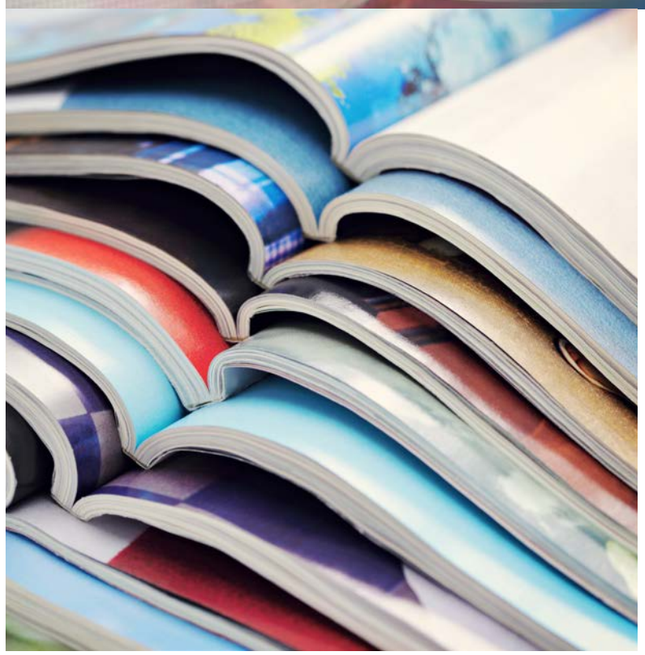
'The introduction of continuous seeding approaches developed with CMAC into our scale-up operations allows for more consistent operation and predictable product properties'
Ruairi O'Meadhra, Novartis

Research: Outputs

CMAC investigators and researchers have published over 75 peer reviewed journal articles, white papers and conference proceedings as a result of our research efforts. Book chapters and online articles have also been published informing the wider agenda in advanced manufacturing of pharmaceuticals and engaging with a global industry, and the academic community of experts. The full list of publications can be found in the appendix page 108.

People

CMAC has a headcount of over 137 including academics, staff, and PhD students across the 7 HEI members. 67% of researchers who have completed PhDs with us have gone on to posts in the Pharmaceutical Industry and Academia both within the UK and Internationally. See talent pipeline (pages 24-25).



Training

An EPSRC Doctoral Training Centre (DTC) started in 2012 and an MSc in Advanced Pharmaceutical Manufacturing in 2014. Additional programmes have been initiated with NTU Singapore and the National Physical Laboratory (NPL). Annually our training calendar includes our DTC Training Weeks and Summer School, Internal Research Days and Communities of Practice and an invited speaker Seminar Programme. With the award of the EPSRC creativity@home funding, the Centre held a creative workshop in May 2013.

Industry

CMAC has 4 Tier 1 Industry Partners who are end users for the advanced manufacturing technology and research: GSK, AZ, Novartis and Bayer. There are currently 17 Tier 2 technology provider companies involved. There is an on-going Industry mentor group scheme, a programme of secondments and placements and regular visits. These various, deep engagements ensure CMAC research is well informed by industry need and provide opportunities for effective KE.

Centre Overview | Outcomes and Impacts

Visits to CMAC

Highlights include her Majesty the Queen visiting our labs in TIC in July 2015 and the CEO of GSK, Sir Andrew Witty, visiting our labs in February 2016, both of which have raised the profile of the EPSRC Centre and our activity and progress.

Organisation of Events

CMAC and the MIT-Novartis Centre co-organised the first International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP) in 2014 and the second in September 2016. CMAC has also organised the 3rd EPSRC Manufacturing the Future Conference and three Open Day events to disseminate our research. Our most recent 2015 Open Day was attended by a total of 232 people from 82 organisations. We will host an Open Day in March 2017 that will showcase research outputs from the Centre from 2011-2016.

Press

CMAC has been featured in the “UK Manufacturing Review 2016” and “A Manufacturing Future for Scotland” in early 2016 highlighting the effectiveness of our engagement approaches in raising the profile of the important research we are carrying out across a wider community.

Awards & Recognition

- The CMAC National Facility in TIC at Strathclyde has been awarded an honourable mention at ISPE FOYA 2016 – see page 37.
- CMAC were nominated for an IChemE award in 2015.
- CMAC were nominated for a Scottish Enterprise Life Sciences Award in the “Innovation” category in 2015.
- Professor Alastair Florence was appointed conference chair of the Academy of Pharmaceutical Science (APS) 2013.
- Professor Alastair Florence is the current chair of the British Association of Crystal Growth (BACG).

Public Outreach

- DTC researcher Vaclav Svoboda won the 2016 Images of Research Competition at University of Strathclyde with his image “Hidden Colours of Crystals”.
- CMAC took part in Explorathon 2016 which took place at the end of September.
- EPSRC funded artist, Fiona McGurk was based at Strathclyde during 2013 to create artwork inspired by continuous manufacturing research for an exhibition at the Hidden Door Festival in Edinburgh in 2014
- The Centre has a website (www.cmac.ac.uk), twitter feed (@EPSRC_CMAC), LinkedIn Group (EPSRC Centre of Continuous Manufacturing and Crystallisation) and newsletter.

Academic Engagement

CMAC researchers have been invited to participate in many national and international conferences and workshops. As part of our National Centre remit we have funded feasibility projects at five universities across the UK engaging with new academic expertise and creating new project ideas for future activities (see pages 18-19 on the iCON Projects). Internationally, we are partners in the EPSRC/NSF supported International Institute for Advanced Pharmaceutical Manufacturing (I2APM)(see page 21) and are partners in the collaborative international PhD programme with NTU Singapore (see page 59).

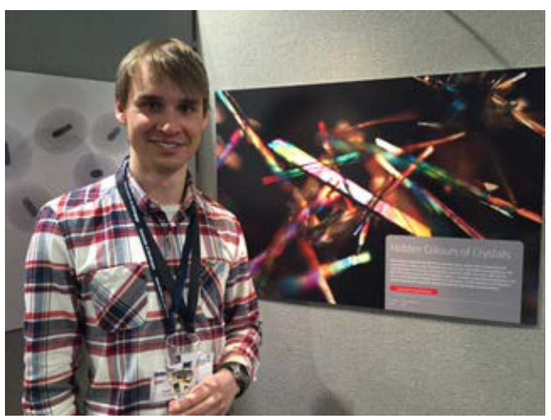


Image: Vaclav Svoboda and his winning image

National Centre

Being A National Centre

- National Centre supported by EPSRC, industry and academia
- Accelerating the adoption of continuous manufacturing
- Supporting UK collaboration in manufacturing research
- Maximising the impact of innovative manufacturing research
- Building the community through dissemination and outreach

Dr Andrea Johnston
National Centre Manager

As a National Centre we have a role to work with and on behalf of the wider community and to act as a focus for the wider research community in this area. Outreach, engagement activities, and collaborations have increased in parallel with the growth of the Centre. We have engaged with the wider community, acting on their behalf e.g. to influence policy, facilitate and support workshops, meetings on topics within scope, support feasibility studies, develop national expertise and facility registers. The Centre holds an important position in the collaborative Research and Innovation Landscape in the UK (Figure 6). Our work as a National Centre included policy influence and strategy development in the area of continuous manufacturing and crystallisation.

To date the Centre has engaged with Innovate UK, SCI, IChemE, KTNs, CIA, RSC, MMIP and is a member of ASPIRE. High profile visits to CMAC have included the Rt Hon Vince Cable who visited our facilities to officially open Phase I of our RPIF award, the Swiss Ambassador Dominik Furgler, in January 2014 the Foreign and Commonwealth Office's Chief Scientific Adviser (CSA), Prof Robin Grime, visited CMAC.

In April 2015 the Strathclyde based CMAC team moved into the new TIC building where the new National facility is housed. The building was officially opened by Her Majesty the Queen on 3rd July 2015. The Queen met with senior industrial and academic partners in the new laboratories during her visit. In early 2016 GSK CEO Sir Andrew Witty visited the CMAC National Facility laboratories and gave great feedback on these. Professor Sir Mark Walport (Government's Chief Scientific Advisor) and Dr Neil Waby (Climate Change & Energy Policy Adviser) visited CMAC's X-ray Suite in February 2016 and Juergan Maier (CEO Seimens UK) met with CMAC in March 2016. In October 2016, EPSRC CEO Prof Philip Nelson visited TIC and toured the CMAC National Facility.

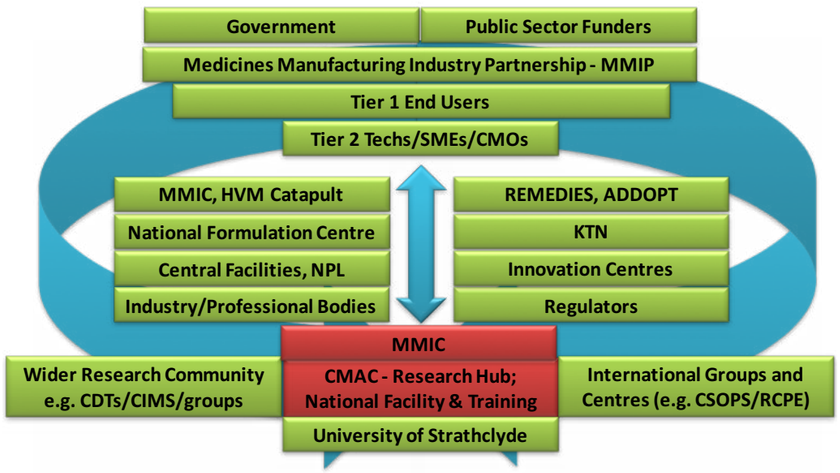
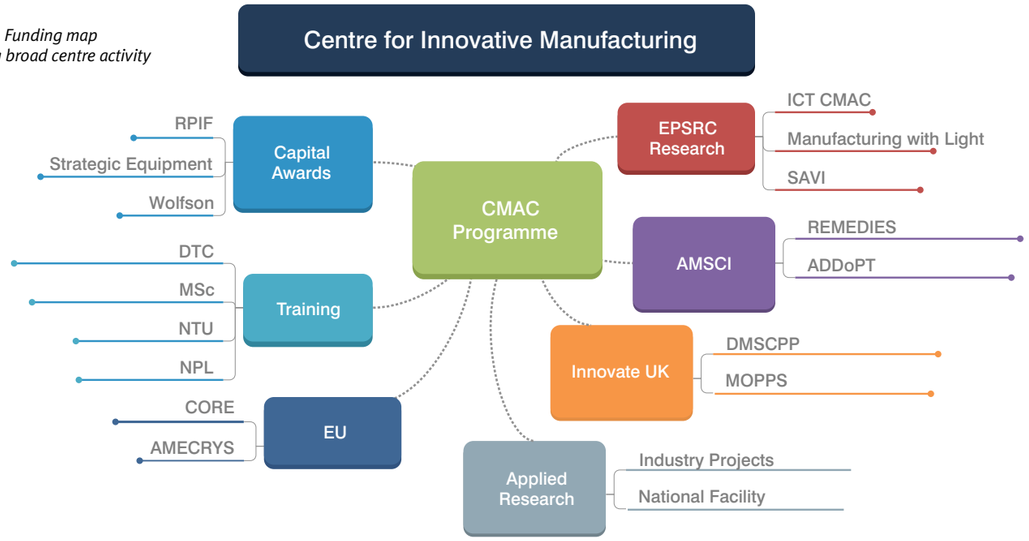


Figure 6. Pharmaceutical manufacturing innovation system landscape stakeholder map

Figure 7. Funding map enabling broad centre activity



CMAC has a broad portfolio of funding to support its activity across its key areas supplementary to the initial Centre award. CMAC acknowledge and thank funding bodies: EPSRC, SF, RPIF (HEFCE/SFC), Innovate UK and Wolfson Foundation.

"EPSRC Centres for Innovative Manufacturing will provide a national focus for areas of early stage basic research that will feed through to Catapult Centres and industry."

EU Grant Success

CMAC's Prof Joop ter Horst has obtained funding for a 4 year postdoc within the Fet-Open 2014/2015 call as part of the AMECRYS consortium (€ 335,500). The Horizon2020 Fet-Open consortium funding opportunity is a very competitive call for fundamental research. This year only 11 proposals were funded out of 669 proposals. AMECRYS aims at revolutionising the manufacture of biopharmaceuticals with innovative membrane crystallization technology.

The field of chiral resolution & deracemization will become increasingly important in pharmaceutical industry and in CMAC. This is exemplified by the funding Prof. Joop ter Horst obtained to set up a Marie Skłodowska-Curie Innovative Training Network on Continuous Resolution and Deracemization of Chiral Compounds by Crystallization (CORE). This European network brings together 15 PhD students, 8 academic and 7 industrial partners from 6 European countries to jointly construct an Industrial Toolbox on Continuous Resolution that provides next generation tools, approaches and methods to industry for the development of continuous resolution processes.

EPSRC Fellowship

In February 2016 it was announced that Dr Iain Oswald won an EPSRC Manufacturing the Future theme Early Career Fellowship of £900k for Pressure-Induced Nucleation for the Continuous Manufacture of supramolecular assemblies.

National Centre

Academic Engagement

CMAC Innovations in Continuous Feasibility Projects

iCON Projects

Continuous work-up was identified as a key gap in enabling the uptake of continuous processing at an industry workshop early in our centre programme. In June 2013 the Centre launched a call for funding "iCON" projects which stimulated the Centre's engagement with the wider UK research community under the Continuous Processing Work-Up theme. On 25th October 2013 seven successful iCON project awards were announced, which included two small scale equipment projects and five longer term research projects ranging from six to twelve months duration. Projects ran from February 2014. A wrap up workshop event, attended by interested parties from CPI, the KTN, industrialists and academics, was held in March 2015 to showcase these projects, and assess the current landscape identifying key gaps, areas requiring continual improvement and other groups/companies that are active in this area.

iCON Feasibility Projects

Name	Institution	Title	Duration
Dr Svetlana Ignatova	Brunel University	Counter-current liquid-liquid processes for continuous manufacture APIs	6 months
Prof Alexei Lapkin	University of Cambridge	Telescoping continuous synthesis of APIs to work-up	6 months
Prof Ian Baxendale	Durham University	Extracting and delivery procedures using phase transfer strategies	12 months
Pro Frans Muller	Leeds University	Recirculating slurry hydrogenation in tandem with continuous product recovery	6 months
Prof Nigel Titchener-Hooker	University College London	An ultra scale-down investigation of the impact of continuous crystallisation performance and recovery by depth filtration	12 months
Prof Steve Ley	University of Cambridge	In-line flow solvent evaporator	Equipment Award
Dr Mark Haw	University of Strathclyde	OMNIFLOW: Optical and Magnetic Non-Invasive Flow and manipulation platform for controlling nucleation using local flow	Equipment Award

Seminar Programme

Academic experts in topics related to continuous manufacturing and crystallisation from around the world have visited CMAC and delivered seminars to our researchers during the CIM.

Academic
Prof Raj Suryanarayanan, Department of Pharmaceutics, University of of Minnesota
Professor Baron Peters, Chemical Engineering, UC Santa Barbara
Dr Jerry Heng, Department of Chemical Engineering, Imperial College London
Prof Joop Ter Horst, TU Delft (now joined CMAC at University of Strathclyde)
Prof Jim Litster, Chemical Engineering, Purdue (from Jan 2016 Chemical and Biological Engineering at Sheffield)
Nuno Reis, Department of Chemical Engineering, Loughborough University
Prof Sven Schroeder Institute of Particle Science Engineering, University of Leeds
Prof Tim Foster, Food Science, University of Nottingham
Prof Roger Davey, School of Chemical Engineering and Analytical Science, University of Manchester
Prof Claire S. Adjiman, Chemical Engineering, Imperial College London
Professor Harris Makatsoris, Cranfield University

Public Outreach

CMAC Researchers have been active in a number of ways in raising visible awareness of CIM research and its potential impact.

Explorathon ‘16

Explorathon ’16 took place across Scotland on 30th September 2016. As part of this, a group of CMAC researchers visited Aultmore Primary School in Glasgow to give a series of demos on crystallisation.

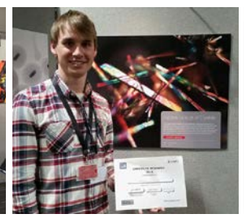
The team, Andrew Dunn, Alex Cousen, Alice Turner, Clarissa Forbes, Elanor Brammer, Rebekah Russell, Sarahjane Wood, then exhibited at the Explorathon Extravaganza at Glasgow Science Centre in the evening. The crystal builders demo proved to be very popular and used 14kg of marshmallows and 3000 cocktail sticks!

Image: Outreach Team at Aultmore Primary School in Glasgow

Images of Research

CMAC PhD researcher Vaclav Svoboda was the overall winner at this year’s University of Strathclyde Images of Research, an annual competition that offers a unique opportunity to captivate an audience through an eye catching image as winning images are showcased to the public throughout the west of Scotland.

Vaclav who is in Professor Jan Sefcik’s group, had won the “Innovative Engineering” category for his image “Hidden Colours of Crystallisation” which was taken using the Leica DM6000 M microscope housed in the CMAC National Facility. Research associate Rene Steendam, who is in CMAC Academic Joop Ter Horst’s group, was runner up in the “Size Matters” category with his Image “Manufacturing the Right Crystals”.



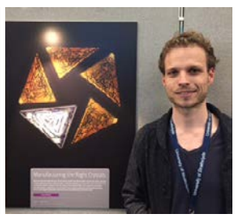


Image: Left to Right: Vaclav receiving prize, Vaclav and his image, Rene and his image

Artist in Residence

Following an eight-month residency with CMAC, artist Fiona McGurk created a multidisciplinary installation of visual artworks. The works - inspired by the TIC build project and observations of continuous manufacturing research and data collection – were showcased at Hidden Door Festival, Market Street Vaults, Edinburgh (28th March – 5th April 2014).

The event attracted over 7500 visitors and gained national press reviews.

© Fiona McGurk 2014. All rights reserved

Internationalisation

CMAC is recognised as a world leading Centre for research and training in the area of continuous manufacturing and crystallisation.

I²APM: International Institute for Advanced Pharmaceutical Manufacturing

I2APM (http://www.i2apm.org/) brings together world-leading academic expertise to deliver new end-to-end continuous manufacturing capabilities that will transform the global supply chain for medicines. The joint programme leverages existing extensive investments in the UK and US and creates a vibrant international manufacturing research community that will accelerate progress through excellence in research. Furthermore, by engaging with regulators the research will be targeted to maximise impact for end users.

CMAC, C-SOPS (US) and RCPE (Austria) are the co-founders of the I2APM. Circa $1m in funding has been obtained from the SAVI scheme, and joint NSF-EPSRC funding, which supports coordination of activities.

Building on the links established at the Puerto Rico workshop in 2014 and the Graz workshop in 2015, the I2APM has formed four working groups.

The research workgroup is investigating how modifications at the crystallisation stage of API production translate to behaviour in the secondary formulation stage. This project leverages CMAC’s expertise in crystallisation and aligns this with the expertise C-SOPS has in secondary processing.

The regulatory workgroup have input into a draft continuous manufacturing Regulatory Guidance Document, which has been prepared by C-SOPS and will be submitted to the FDA. A University of Strathclyde Impact Accelerator Account (IAA) grant has been awarded to enable CMAC to work with RCPE to further engage the European Regulatory Authorities.

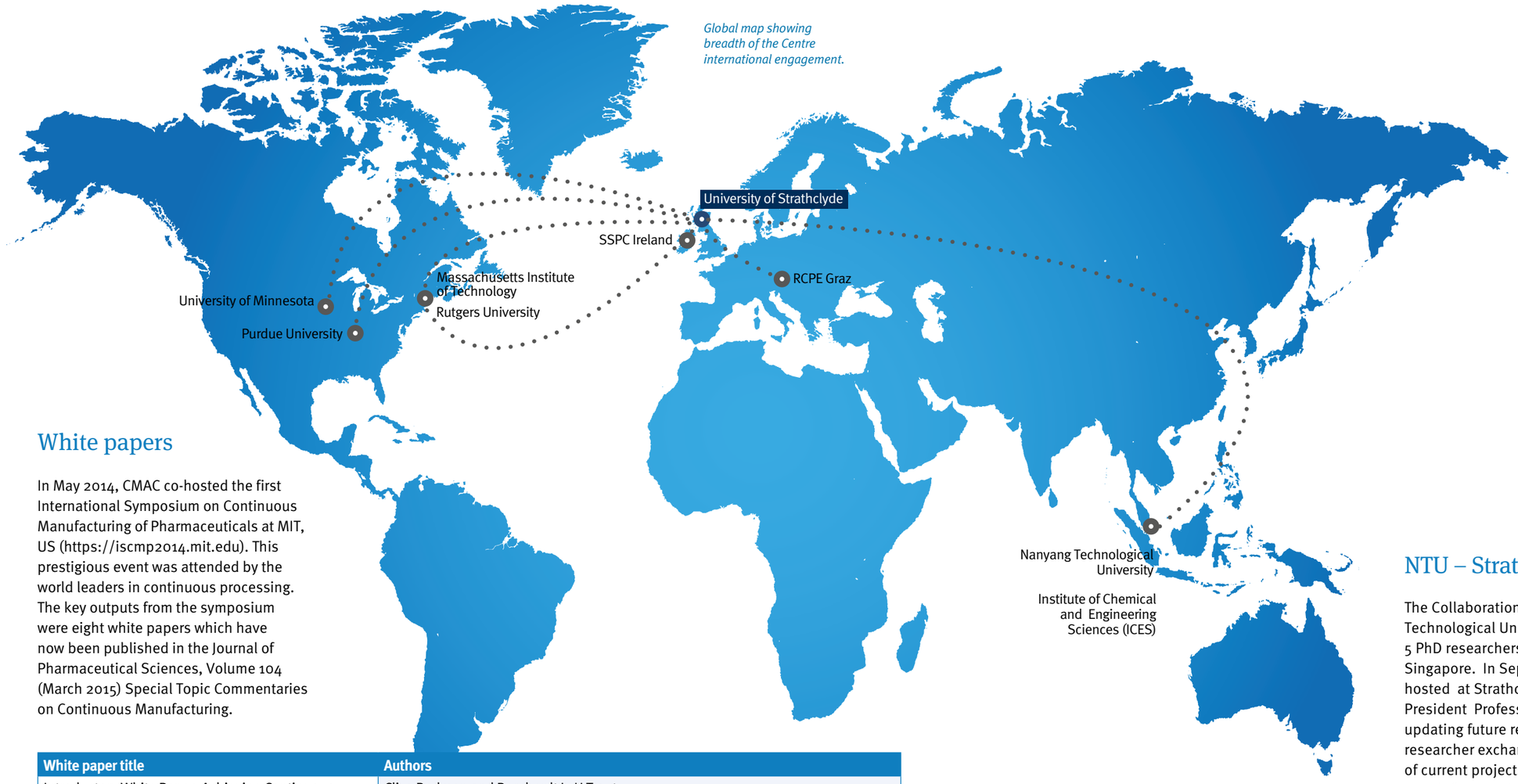
The events workgroup will be organising the first I2APM International Symposium, to be held at CMAC on 30th November 2016 which will showcase research from all three centres who will come together to learn about research being carried out across all institutions.

The training workgroup aims to produce a training package of teaching material in various aspects of continuous manufacturing which can be offered to industry. This workgroup will co-ordinate a day of training at CMAC on 1st December, immediately following the I2APM International Symposium.

CMAC also saw visits from Prof Fernando Muzzio (C-SOPS) and Prof Johannes Khinast (RCPE) in September 2015, and Prof San Kiang from C-SOPS in May 2016. CMAC is hosting Assistant Professor Heidi Gruber-Woefler (RCPE) on a secondment from September – December 2016. CMAC DTC researchers have also attended a workshop in continuous manufacturing hosted by C-SOPS at Rutgers University in summer 2016.

Purdue Placement

From March 1st to April 30th 2016 John McGinty went on secondment to Purdue University facilitated by the I2APM. He spent the time working on a combination of experimental and modelling to learn new approaches and techniques used in Zoltan Nagy’s group. John is working on PAT based monitoring of the crystallisation of an organic polymorphic salt and the subsequent estimation of its crystallisation kinetics. In particular he utilised PAT to monitor the crystallisation of his model compound, ethylenediamine 3,5-dinitrobenzoate (EDNB), and will use the data obtained to estimate its crystallisation kinetics in collaboration with Dr Qinglin Su.



Global map showing breadth of the Centre international engagement.

White papers

In May 2014, CMAC co-hosted the first International Symposium on Continuous Manufacturing of Pharmaceuticals at MIT, US (https://iscmp2014.mit.edu). This prestigious event was attended by the world leaders in continuous processing. The key outputs from the symposium were eight white papers which have now been published in the Journal of Pharmaceutical Sciences, Volume 104 (March 2015) Special Topic Commentaries on Continuous Manufacturing.

White paper title	Authors
Introductory White Paper: Achieving Continuous Manufacturing	Clive Badman and Bernhardt L. H Trout
Technologies and Approaches for Synthesis Work-Up and Isolation of Drug Substance	Ian R. Baxendale, Richard D. Braatz, Benjami K Hodnett, Klavs F. Jensen, Martin D Johnson, Paul Sharratt, Jon-Paul Sherlock and Alastair Florence
Achieving Continuous Manufacturing for Final Dosage Formation: Challenges and How to Meet Them	Stephen Byrn, Maricio Futran, Hayden Thomas, Eric Jayjock, Nicola Maron, Robert F. Meyer, Allan S. Myerson, Michael P. Thien, and Bernhardt L. Trout
Regulatory and Quality Considerations for Continuous Manufacturing	Gretchen Allison, Yanxi Tan Cain, Charles Cooney, Tom Garcia, Tara Gooen Bizjak, Oyvind Holte, Nirdosh Jagota, Bekki Komas, Evdokia Korakianiti, Dora Kourti, Rapti Madurawe, Elaine Morefield, Frank Montgomery, Moheb Nasr, William Randolph, Jean-Louis Robert, Dave Rudd and Diane Zezza
Continuous Bioprocessing	Konstantin B Konstantinov and Charles L. Cooney
Equipment and Analytical Companies Meeting Continuous Challenges	Trevor Page (GEA), Henry Dubina (Mettler Toledo), Gabriele Fillipi (IMA), Roland Guidat (Corning), Saroj Patnaik (Emerson) Peter Poechlauer (DSM) and Craig Johnston (CMAC)
Control Systems Engineering in Continuous Pharmaceutical Manufacturing	Allan S. Myerson, Markus Krumme, Moheb Nasr, Hayden Thomas and Richard D. Braatz
Future supply chains enabled by continuous processing – opportunities and challenges	Jag Srai, Clive Badman, Mauricio Futran, Markus Krumme and Craig Johnston
How Development and Manufacturing Will Need to be Structured – Heads of Development/Manufacturing	Kevin Nepveux, Jon-Paul Sherlock, Mauricio Futran, Michael Thien and Markus Krumme

2nd International Symposium on Continuous Manufacturing of Pharmaceuticals

CMAC and MIT co-hosted the 2nd International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP) in Boston on 26-27 September 2016. There was a strong CMAC presence at the symposium. CMAC Director Prof Alastair Florence chaired a session on small molecules on day one. There were also sessions on bioprocessing, learning from other industries, and regulatory and quality. One of the major outputs of the 2016 ISCMP will be writing a regulatory white paper on continuous manufacturing of pharmaceuticals. The paper will incorporate all of the learnings, discussion, and comments of the meetings and post-meeting discussions. The event highlighted the enormous progress that has been made and the emerging challenges for industry adoption.

NTU – Strathclyde Symposium

The Collaboration between CMAC (Strathclyde) and SCBE (Nayang Technological University - NTU) was initiated in 2012 and there are now 5 PhD researchers in place across the University of Strathclyde and NTU Singapore. In September 2016 an NTU-Strathlyde Symposium event was hosted at Strathclyde by Strathclyde Principle Sir Jim McDonald and NTU President Professor Bertil Andersson. Workshop Outputs consisted of updating future research funding plans and scoping projects for future researcher exchanges. There were updates from both centres on progress of current projects and discussions on future plans including demonstrating proof of concept studies relating to real industry challenges.

Lauren Connor and Thidarat Wongpinyochit have gone on 3 month placements to NTU Singapore and there an additional 3 further placement planned for 2017.



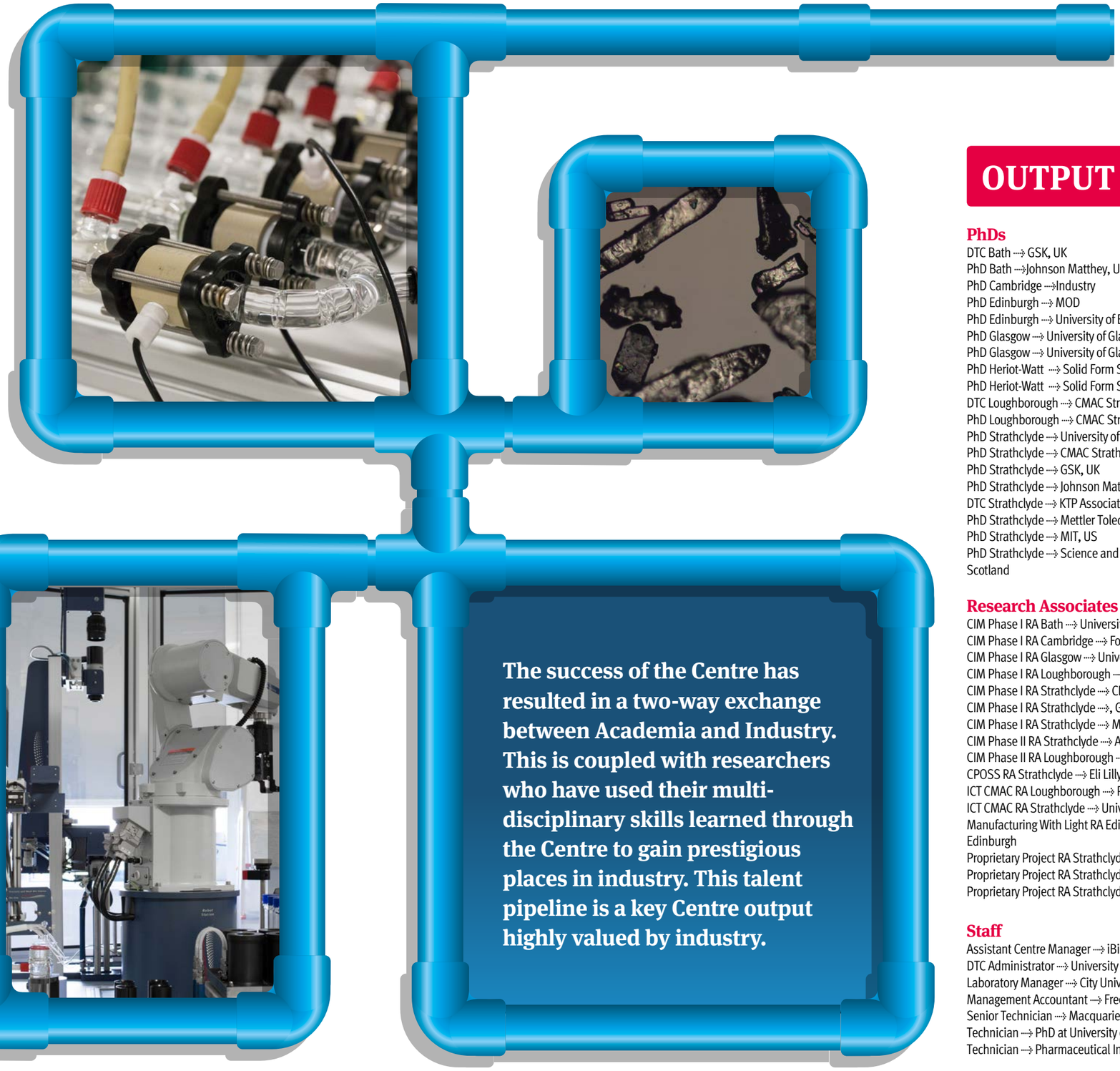
Images. Left to Right Lauren Connor, Sebastion Davidson & Thidarat Wongpinyochit

National Centre

Talent Pipeline

October 2011 - December 2016

People are at the core of our success and developing a talent pool has been a key achievement.



INPUT

79 PhD Researchers

39 Research Associates

CIM Phase I (Bath, Cambridge, Glasgow x2, Strathclyde x3)
CIM Phase II (Cambridge, Loughborough x3, Strathclyde x6)
ADDoPT (Strathclyde)
COST (Strathclyde x2)
CPOSS (Strathclyde x2)
ICT CMAC (Loughborough, Strathclyde x7)
Manufacturing With Light (Edinburgh)
MOPPs (Strathclyde)
Proprietary Projects (Strathclyde x7)
Remedies (Strathclyde)

26 Management & Support Staff

CIM (Strathclyde x10)
Industry Team (Strathclyde x4)
National Facility & Technical Staff (Strathclyde x11)
ICT CMAC (Strathclyde)

The success of the Centre has resulted in a two-way exchange between Academia and Industry. This is coupled with researchers who have used their multi-disciplinary skills learned through the Centre to gain prestigious places in industry. This talent pipeline is a key Centre output highly valued by industry.

OUTPUT

PhDs

DTC Bath ⇢ GSK, UK
PhD Bath ⇢Johnson Matthey, UK
PhD Cambridge ⇢Industry
PhD Edinburgh ⇢ MOD
PhD Edinburgh ⇢ University of Edinburgh
PhD Glasgow ⇢ University of Glasgow
PhD Glasgow ⇢ University of Glasgow
PhD Heriot-Watt ⇢ Solid Form Solutions, UK
PhD Heriot-Watt ⇢ Solid Form Solutions, UK
DTC Loughborough ⇢ CMAC Strathclyde
PhD Loughborough ⇢ CMAC Strathclyde
PhD Strathclyde ⇢ University of Strathclyde
PhD Strathclyde ⇢ CMAC Strathclyde
PhD Strathclyde ⇢ GSK, UK
PhD Strathclyde ⇢ Johnson Matthey
DTC Strathclyde ⇢ KTP Associate, University of Strathclyde
PhD Strathclyde ⇢ Mettler Toledo, Germany
PhD Strathclyde ⇢ MIT, US
PhD Strathclyde ⇢ Science and engineering sector industry, Scotland

Research Associates

CIM Phase I RA Bath ⇢ University of Bath
CIM Phase I RA Cambridge ⇢ Ford
CIM Phase I RA Glasgow ⇢ University of Nottingham, UK
CIM Phase I RA Loughborough ⇢ GSK, UK
CIM Phase I RA Strathclyde ⇢ CPACT, UK
CIM Phase I RA Strathclyde ⇢, GSK, UK
CIM Phase I RA Strathclyde ⇢ MacFarlane Smith, UK
CIM Phase II RA Strathclyde ⇢ AZ, Macclesfield, UK
CIM Phase II RA Loughborough ⇢ Loughborough
CPOSS RA Strathclyde ⇢ Eli Lilly, US
ICT CMAC RA Loughborough ⇢ Purdue, US
ICT CMAC RA Strathclyde ⇢ University of Strathclyde
Manufacturing With Light RA Edinburgh ⇢ University of Edinburgh
Proprietary Project RA Strathclyde ⇢ AZ, Macclesfield, UK
Proprietary Project RA Strathclyde ⇢ University of Bradford, UK
Proprietary Project RA Strathclyde ⇢ Imperial College London

Staff

Assistant Centre Manager ⇢ iBioIC, UK
DTC Administrator ⇢ University of Strathclyde, UK
Laboratory Manager ⇢ City University of New York, US
Management Accountant ⇢ Freelance Accountant
Senior Technician ⇢ Macquarie University, Australia
Technician ⇢ PhD at University of Glasgow, UK
Technician ⇢ Pharmaceutical Industry, Ireland

Industry & Knowledge Exchange

- **Industry demand led research programme**
- **Influencing policy through world leading collaborative membership organisation**
- **Enabling supply chains of the future**
- **Impact through effective research translation for multi-nationals and SMEs**

A key part of the original Centre bid was sustainability with strong industry engagement and leadership. Following the 5 year award of the EPSRC Centre, an industry led membership organisation (CMAC) was created. The membership organisation operates under a pre-competitive, collaborative research and development model with senior level company support. The main industry partners (AstraZeneca, Bayer, GSK and Novartis) get an individual seat on the CMAC Board and an opportunity to influence the direction of future research and Centre activity.

CMAC 14th Industry board meeting at Bayer Leverkusen in June

Image: Dr Olaf Queckenberg Bayer Senior VP meets with Her Majesty the Queen at the Royal Opening of TIC

Image: Sir Andrew Witty, CEO GSK during CMAC visit

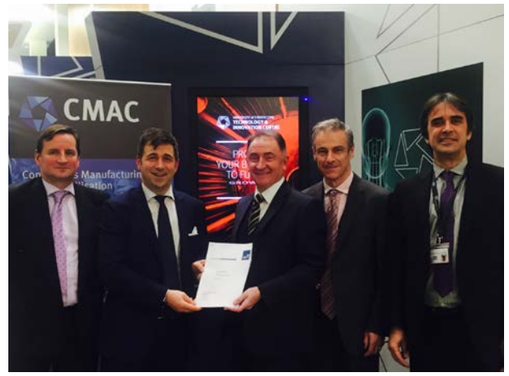


Image: Right to left: Phil Shering, AstraZeneca with Dr Juergen Maier, Siemens meet with Prof Sir Jim McDonald, Prinicple of University of Strathclyde, Craig Johnston and Prof Alastair Florence of CMAC

CMAC Technical Committee

A Technical Committee comprising industrial experts and representatives of the EPSRC Centre defines the core industry research programme and provides support and steer on future Centre plans e.g. research, training, facilities and international and regulatory engagement. The EPSRC Centre Director and Industrial Director are members of these committees to ensure that optimal alignment of the programmes across TRLs is maintained. In accordance with the Centre's business plan, the aim is to populate the innovation landscape with parallel research activities across the TRLs using a range of appropriate funding mechanisms to address industry needs in a structured manner.

Industry & Knowledge Exchange

Technical Committee

The technical committee continues to provide high level technical input on a monthly basis regularly discussing PhD placements, proprietary projects, funding proposals as well as keeping abreast of, and advising on, technical progress across CMAC. They also provided invaluable input to the scope of the CMAC Hub renewal bid.

1:1 Proprietary projects

Working on both launched and developmental pharmaceutical compounds, the projects have delivered immediate impact from CMAC's academic research into live projects. The PDRAs have worked at both company and CMAC facilities including one 6 month project developing a continuous crystallisation alongside the team developing the batch process.

Project areas include:

- Developing continuous crystallisation of APIs to deliver desired particle attributes
- Using continuous processing to provide understanding of existing batch processes: particularly where variability between different equipment/sites exists
- Modelling of crystallisation processes to inform future experimentation
- Understanding new analytical capabilities at CMAC to assess levels and stability of amorphous compounds
- Improving understanding of twin screw granulation

CMAC also runs a number of directly funded projects developing platform continuous capability in spherical agglomeration, investigating impurity profiles in a commercial product and manufacturing products with defined product shape and PSD.

Industrial placements

This year, 5 PhD researchers went on industrial placements of 8-12 weeks. The aim of the placements are:

The Researcher: experience industrial environment to help with career decisions, get a different perspective and input to their research, access to different equipment or techniques and to broaden their experience.

The Company: implement academic research into industrial practice, learn new methods and techniques, an opportunity to do something they wouldn't have been able to do on their own, identify future talent.

Researcher	Company	Projects Area
Anneke Klapwijck (Bath)	Bayer	Habit Control using Templates
Laura Martinez-Marcos (Strathclyde)	GSK	Increasing Process Understanding in Twin Screw Extruders
Iyke Onyemelukwe (Loughborough)	GSK	Set-up, Characterisation and Demonstration of Continuous Crystallisation Platforms
Sara Ottoboni (Strathclyde)	AZ	Investigating Novel Equipment for Continuous Filtration and Washing (REMEDIES project)
Francesca Perchiballi (Strathclyde)	AZ	Optical Imaging and Automated Processing for Assessing Levels of Agglomeration

We are currently arranging placements for over 10 researchers for 2016/17! See pages 69-70 for case studies of two of the industry placements.

Mentor Groups

The mentor groups are well established as a key conduit for ensuring industrially relevant research and enabling access to cutting edge research for fast application in industry. The mentor groups are multi-university, multi-company groups with a common technical theme who meet every 2-3 months to discuss the students research in detail providing guidance and suggestions from industrial and other CMAC colleagues.

Tier 2 companies will join the mentor groups later this year.

Figure 8. Industry interactions

Multi-partner Collaborative Projects

CMAC is involved in over 7 active collaborative projects providing an efficient and effective way for Tier 1 companies to keep informed about the progress in all the projects whilst not necessarily being active in all of them. CMAC collates and provides end-user feedback from the Tier 1s. Several projects are covered in more detail but we will briefly cover 2 Innovate UK projects here.

Made To Order Processing Plants (MOPPs)

Perceptive Engineering Ltd, CMAC, Centre for Process Innovation and AstraZeneca developed an Advanced Process Control system that can be used to control a range of continuous processing equipment including both reactors and crystallisers. A 5 day continuous crystallisation was demonstrated at CMAC with dial-a-particle size capability. See pages 67-68 for more.

Left to right: Dr Ian Houson, Ewan Mercer, David Lovett, Craig Johnston, Karolina Krzemieniewska , Furqan Tahir, John Mack.

Developing Innovative Modular Systems for Continuous Chemical Processing

CMAC, working with GSK and Blacktrace (previously Syrris) are developing the next generation of large lab to pilot scale continuous flow processing units. As many pharmaceutical compounds increase in potency, the annual demand of API falls with many requiring only 10's or 100's of Kg per annum. This project is delivering novel pumps, reactors and residence time units, with supporting ancilliaries for the 10s to low 100's ml/min scale which will provide, in many case, full commercial scale.

CMAC is carrying out baseline characterisation of equipment such as heat and mass transport, mixing times and CFD modelling. Further processing units are being developed through the REMEDIES project.

Industry & Knowledge Exchange

Tier 2 Partners

CMAC now has seventeen Tier 2 members. All our tier 2 members were represented at the CMAC Open Day in 2015 with the majority of them having exhibit stands and a number giving excellent presentations. We have hosted and facilitated face to face sessions with the companies, hosted workshops and training sessions, and made a number of business to business and academic introductions with over 40 meetings in 2015/2016. We will continue to promote and facilitate collaboration and introductions wherever the opportunity presents itself. Tier 2 members have been integral to our centre support, hub renewal and projects such as ICT, Remedies and ADDOPT.

Collaborators

In addition to our Tier 1 & 2 partners, we also work with a range of technology providers and companies from other chemical sectors including those who contribute to the technical programme, for example, through access to new processing and measurement technologies. We also continue to develop further links with other companies that can contribute a range of expertise to advance the developing programme in continuous manufacturing research.

Image: PwC - Scott Lawson on RHS

Image: Sean Bermingham, PSE, Tier 2 Board Representative

Image: Perceptive Engineering - John Mack on RHS

Image: Mettler Toledo, with Dr Stewart Mitchell, CMAC Tier 2 Project Manager

Tier 2 Engagement Event

On 4th May we held an event with Engage with Strathclyde. This event brought together CMAC Tier 2 companies and our academics and researchers to explore how we can collaborate moving forward. There were 26 flash presentations hosted within half a day to give an excellent overview of the projects, technology and collaborations between the Tier 2 Technology companies and CMAC researchers. We also had a pre-event networking session around the Images of Research where discussions took place, and an afternoon event where PwC hosted and presented an excellent showcase. Thanks to all the companies, researchers, academics and Engage with Strathclyde who made this event a great success.

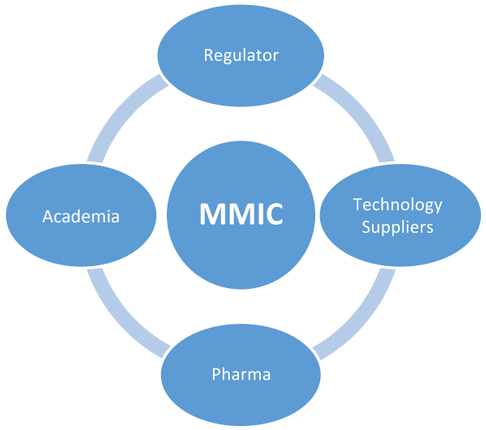
Image: Steve Leech, Siemens at the CMAC Tier 2 Event at Engage With Strathclyde

Industry & Knowledge Exchange

Forward Directions

Medicines Manufacturing Innovation Centre (MMIC)

Accelerating the translation of promising research into commercial adoption in small molecule pharmaceutical manufacturing



CMAC have been working with the Centre for Process Innovation (CPI), Medicines Manufacturing Industrial Partnership (MMIP) and Scottish Enterprise (SE) to make MMIC a reality. The current projected investment for the initial phase of the MMIC facility and initial operating costs is circa £56m. The business case will be submitted separately to Scottish Enterprise and InnovateUK for government funding support this summer. GSK has conditionally offered their support for up to £10m. The project team is scheduling meetings with other potential pharma partners to obtain additional support for MMIC.

MMIC will offer pharmaceutical companies the potential to save time, save capital and reduce risk. MMIC will be a first-in-class, global facility that offers a sustainable and flexible means to accelerate the adoption of emerging and novel manufacturing technologies and transform pharma manufacturing. MMIC will cover the end-to-end manufacturing supply chain within a bespoke, quality driven and safe environment. MMIC will be an enabler in terms of taking advances in manufacturing research and providing a facility for proving concepts before launching them into commercial operations.

CMAC is leading the facility and equipment design concept work with the intent of developing a state of the art, end-to-end, pilot scale, proof of concept facility that will showcase the ready-now technologies in continuous manufacturing.

MMIC will allow pharmaceutical manufacturers to do what cannot be done by themselves currently and will focus on the "triple helix" of bringing together industry, academia and regulators. MMIC will be technology neutral, transparent, open access and future focused on the supply chains of tomorrow. MMIC will build on the synergy created by the research and collaboration at CMAC with SMEs and technology providers, allowing SMEs and start-ups to innovate and grow. CMAC will be providing thought leadership to MMIC and the broader UK pharmaceutical innovation community.

MMIC will integrate activities across the continuum from research to commercialisation, including a current Good Manufacturing Practice (cGMP) facility for production proving.

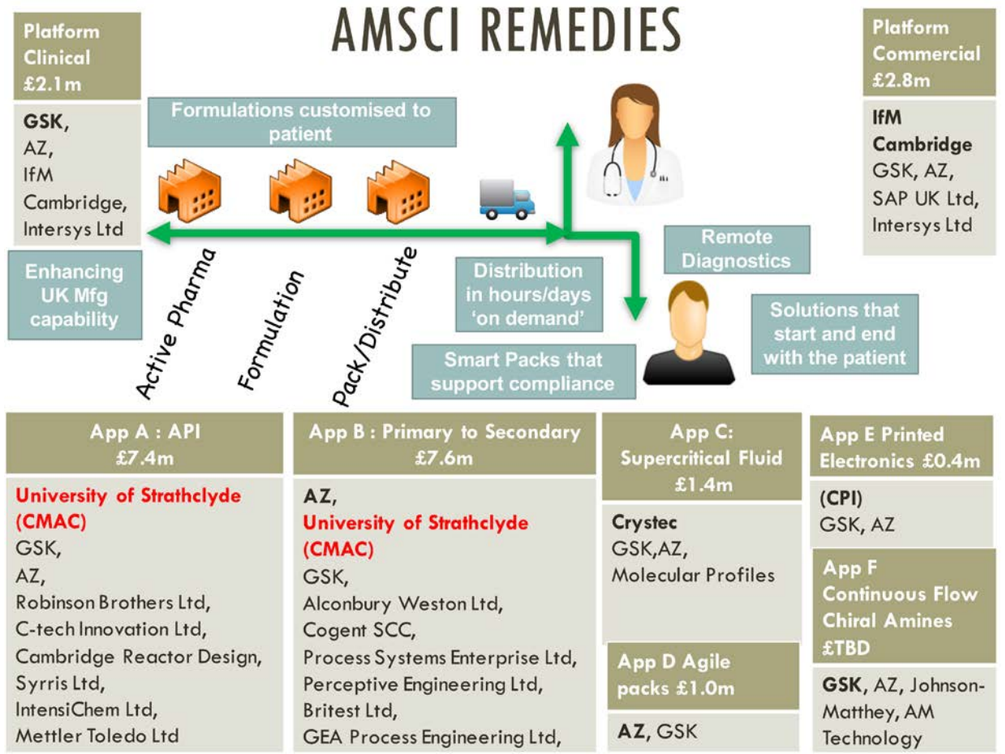
REMEDIES Project

REMEDIES: RE-configuring MEDIcines End-to-end Supply

The REMEDIES project is part of the Advanced Manufacturing Supply Chain Initiative (AMSCI) programme whose goal is to improve the global competitiveness of UK advanced manufacturing supply chains. AMSCI is funding research and development, skills training and capital investment to help UK supply chains achieve world-class standards and encourage major new suppliers to locate in the UK. The £23m project will be completed over the next 20-months and involves 22-partner organisations in the UK.

Although UK pharmaceutical firms lead global markets, significant challenges lie ahead of them relating to the affordability of drugs, product portfolio fragmentation and the ability of existing supply chains to embrace emerging technologies. These challenges compound existing problems of inventory across the end-to-end supply chain, and poor 'right-first-time' processing which costs the industry £20bn per annum globally. The REMEDIES project will seek to address these challenges.

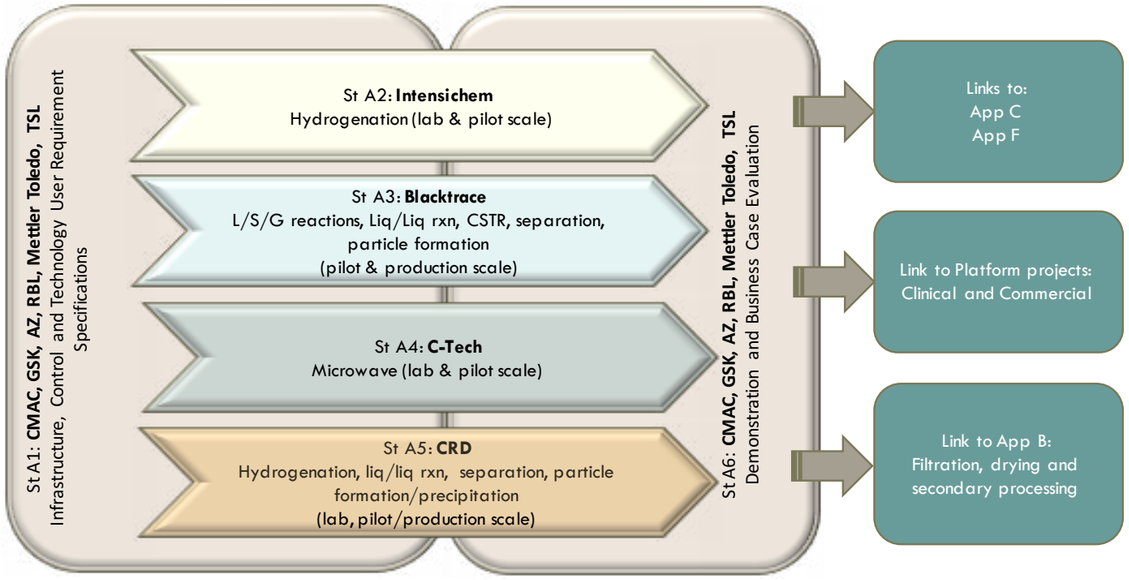
CMAC is leading workstream (App) "A" – Active Pharmaceutical Ingredients and Registered Starting Materials and technical lead on workstream (App) " B" – Primary to Secondary Formulation. Since last year, App A and App B have progressed significantly. App A and B are looking to strengthen the links with the other REMEDIES workstreams and the platform projects in the coming months.



Industry & Knowledge Exchange

APP A | Active Pharmaceutical Ingredients and Registered Starting Materials

The four technology companies in App A have progressed with design, fabrication and even begun testing of continuous platforms with end-user chemistries. App A was successful in adding another CMO to join the project, Thomas Swan & Company Ltd.



App A Technical Update:

STRAND 1: High-level URS development completed.

STRAND 2: Intensichem's continuous lab scale hydrogenator has been built and is being prepared for demonstration on RBL chemistry.

STRAND 3: Blacktrace - has recently launched their Titan Series, a Pilot & Production Scale Continuous Modular platform (L/S/G rxns, L/L rxns, CSTR, separation, particle formation). Beta prototype for module 1 & 4 complete; Testing for beta prototype for module 1 on-going; Building alpha prototype for module 2 & 4; design alpha prototype for module 3. More details on each module will be forthcoming shortly, however the first module launched, the Titan Syringe Pump, will be included in the App A testing phase. The syringe pump is a continuous flow chemical processing module, extremely chemically-resistant single channel pump combining powerful drive motors, clever valve design and software control to deliver ultra-smooth flow rates from 1 to 250 ml/min.

STRAND 4: C-Tech - Lab & Pilot Scale Continuous Microwave Reactor - Prototype MW reactor built and have begun preliminary testing on RBL chemistries which will require further modifications to test rig.

STRAND 5: CRD has been developing the next generation Baffled Reactor Geometry (Xryst platform) with a comprehensive plan and technical specifications drafted. The design specifications are to be reviewed and approved July/Aug 2016 and assembly of kit to begin Aug/Sept 2016. CRD's lab scale Gas Liquid Mixed Reactor has been built and initial testing utilising RBL chemistry was successful. CRD is in discussions with TSL on testing chemistries on the Tubular Reactor Geometry lab scale kit that has just been assembled.

STRAND 6: Demonstration and business case evaluation discussions have begun to identify how App A will link into the Clinical and Commercial Platform Projects.

APP B | Primary to Secondary Formulation

App B has been full of activity with testing of continuous filtration, direct compression and hot melt extrusion test rigs with lab scale CFC prototype run at AZ with CMAC evaluation of lab scale prototype V2 taking place from June to August 2016. Continuous DC test rig set up at GEA with PharmaMV for process data capture installed by Perceptive and initial data analysis is underway at AZ, GSK and Perceptive. Hot melt extruder with Raman PAT probe has been assembled and initial extrusion work on excipient is in progress at CMAC to establish operating windows for process parameters. Preliminary paracetamol/polymer runs have been carried out with analysis ongoing AZ and CMAC. App B is assessing the possibility for direct link from extruder to 3D printing and injection moulding.

Image: Strand 1: Continuous drug substance filtration: AWL lab scale prototype

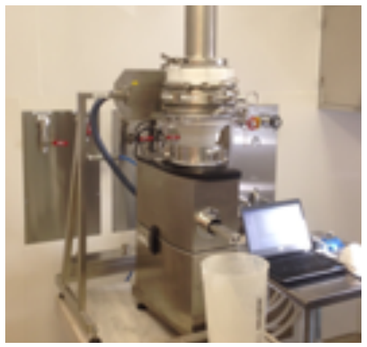
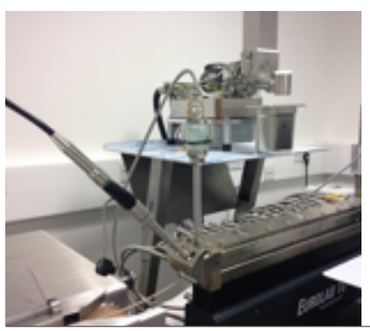


Image: Strand 2: Continuous direct compression: GEA CDC50 test rig, PAT enabled, for continuous feeding, blending and compression



App B Technical Update

STRAND 1: CONTINUOUS DS FILTRATION

Limited lab scale prototype V1 experience gained at AZ, feedback to AWL indicated areas for system improvements not initially anticipated (application for additional funding is underway). CMAC evaluation of lab scale prototype V2 planned for June-August 2016. Experimental DoE on paracetamol as model compound (CMAC PhD student). Providing feedback to AWL to assist with design and build of pilot scale unit for Q3/Q4 2016. PSE predictive models for filtration in place, further model development specific to AWL design to continue Q3/4 2016, verification with experimental data anticipated.

STRAND 2: CONTINUOUS DIRECT COMPRESSION

CDC50 continuous direct compression test rig is set up at GEA and the PharmaMV for process data capture installed by Perceptive. A detailed design of experiments on the compact feeder has been completed by GEA, while AZ, GSK and Perceptive are performing material and data analysis. Formulation optimisation (compaction simulator work) has been completed at GSK, the composition for a model formulation (paracetamol 10% drug load) has been established to be able to explore the interaction between variable DS particle properties and feeding/blending parameters on product quality attributes. Further feeding/blending/compression trials based on formulation variants identified above due in Q3-Q4 2016. Empirical models for feeding, blending & compression reside with PSE. Further work in 2016 will be to test and validate those models using experimental data being generated.

STRAND 3: HOT MELT EXTRUSION

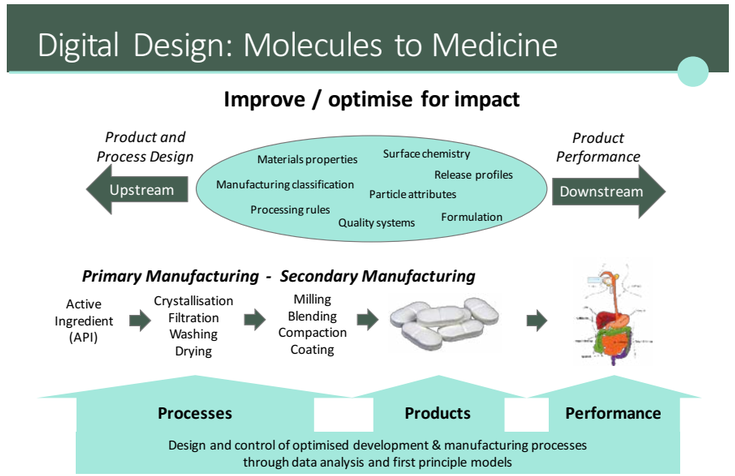
16mm twin screw extruder with Raman PAT probe at the die is set up at CMAC, fully PharmaMV ready with remote access for Perceptive. Initial extrusion work on excipients designed for HME is in progress (Affinisol, Plasdone) to establish operating windows for process parameters. Preliminary paracetamol loaded polymer runs carried out, analytics ongoing at AZ/CMAC. Full design of experiments to commence Q3 2016 to explore the interaction between variable DS particle properties and process parameters on extrudate quality attributes. The possibility of producing 3D printer ready strands from HME or directly linking the extruder to a 3D printer or injection moulder is being explored to establish a fully continuous process for dose form manufacture. Modelling work ongoing at PSE, currently a single phase system with refinement continuing based on equipment set up and material properties.

Image: Strand 3: Hot melt extrusion/3D printing: twin screw extruder at CMAC, PAT enabled

Industry & Knowledge Exchange

ADDOPT: Advanced Digital Design Transforming Pharmaceutical Development and Manufacture

The ADDoPT (Advanced Digital Design of Pharmaceutical Therapeutics) project is addressing the pharmaceutical industry's desire to deliver medicines more effectively to patients. CMAC is a partner in ADDoPT developing advanced digital design techniques that eliminate non-viable drug candidate formulations as early as possible, streamlining design, development and manufacturing processes. ADDoPT is a £20.4m, four-year collaboration between pharmaceutical companies, solution providers and academia. Part-funded under the Advanced Manufacturing Supply Chains Initiative (AMSCI) and supported by the Medicines Manufacturing Industry Partnership (MMIP), it aims to make existing and new Digital Design approaches widely usable within the pharmaceutical industry and thereby increase efficiency and effectiveness of drug development and manufacture.



Within ADDOPT, Dr Blair Johnston (CMAC) is working on the following research challenges:

- Precise control in manufacturing of solid particles using continuous manufacturing technologies.
- Control and exploitation of nucleation and growth of particles via crystallisation under continuous flow.
- Continuous crystallisation platforms; process analysis tools and strategies to manufacture 'perfect particles' for different applications.
- Deliver the tools to achieve exquisite control over crystal structure, particle shape and particle size distribution to meet the needs of advanced manufacturing of innovative chemical products.
- Continuous manufacture of medicines and nanomaterials with kinetic, co-crystallisation and impurity control.
- Understand key particle properties for enhanced formulated product performance.
- Manufacturing operations and supply chain management challenges in continuous manufacturing of chemical particles to include: manufacturing operations and supply chain configuration; management control systems and learning from experiences of other industries.
- Optimise manufacturing industries operations and supply chain to enable the effective adoption of continuous manufacturing.

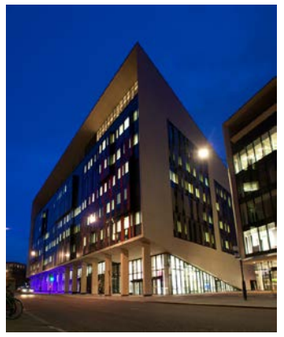
Alison Clough, Acting Chief Executive of the Association of the British Pharmaceutical Industry, commented,

"This project will help to put the UK in a position to make innovative medicines available to UK patients more quickly by futureproofing our advanced pharmaceutical manufacturing sector."

Image: Dr Blair Johnston, CMAC's technical lead in the ADDoPT Project

Facility of the Year (FOYA) 2016 Award

CMAC and University of Strathclyde are the first academic institution to win an award from the FOYA programme. FOYA is the premier global awards programme recognising innovation and creativity in facilities serving the regulated healthcare industry. John Bournas, President and CEO of the International Society of Pharmaceutical Engineers (ISPE), said "ISPE is proud to honour these nine teams for their exemplary projects and outstanding dedication to creating high quality medicines for people around the world."



The FOYA judges chose CMAC within TIC because of the exemplary collaboration between industry, academia and government which the FOYA judges felt represents the future of pharmaceutical manufacturing and supply chain R&D framework. Prof Alastair Florence, the Centre Director believes, "The FOYA award is a fantastic achievement for CMAC and our partners, in particular as it recognises the unique world class facilities and high quality collaborative environment that has now been established in TIC to support our research and training activities. CMAC look forward to continuing to extend our collaborative approach and welcome new partners to come and work alongside us within the new CMAC National Facility". In addition the FOYA judges said that the students working with such technology and in such a collaborative environment will be the pipeline for the Pharmaceutical professionals of the future. "Being chosen as the first academic institution for this international prestigious award programme is a real honour and further validates the world class capabilities of CMAC and relevance to industry", said John Mulgrew, CMAC Project Manager.

FOYA 2016
Facility of the Year Awards
Honorable Mention

Image: Primary Processing Equipment Housed in the CMAC National Facility

Industry Recognition for Category Winners

The 2016 Facility of the Year Awards Winners was formally recognized at the ISPE Facility of the Year Awards Banquet on 7th June 2016 in North Bethesda, Maryland, USA. The banquet was held in conjunction with ISPE/FDA/PQRI Quality Manufacturing Conference. Andrea Johnston, Stewart Mitchell, Vishal Raval, Naomi Briggs, John Mulgrew and Scott McPhee were there to accept the award on behalf of CMAC. CMAC's labs were lauded for both the design of the 2,900-m2 of world-class lab facilities and for the £34m worth of cutting-edge equipment they house.

Visit: www.FacilityoftheYear.org for more information.

Image: CMAC receive FOYA award

Research Overview

- **Consistent, better & functional particles**
- **Better medicines through understanding particle formation and processing**
- **Continuous manufacturing research through synthesis, crystallisation to formulated product**

The CMAC research portfolio is made up of around 80 projects that cover the CMAC research pipeline from synthesis through primary and secondary processing and includes supply chain considerations. The individual projects are supported through the various initiatives shown in the diagram (Figure 9).

Building on the rich activity of developing techniques and technologies for understanding and controlling continuous crystallisation processes, the CMAC research programme now integrates projects from upstream synthesis and work-up processes, as well as downstream filtration, drying and secondary processing stages. Work from the Cambridge team in mapping and managing Supply Chains informs practical aspects of the research programme. The Centre has also been actively developing automated workflows, our cross-centre ELN platform and a comprehensive data management infrastructure, building on the links with the ICT CMAC project. This will exploit the rich value in the data being collected across our projects. This is a key aspect of our strategy to deliver new tools to support process development and control through rigorous understanding.

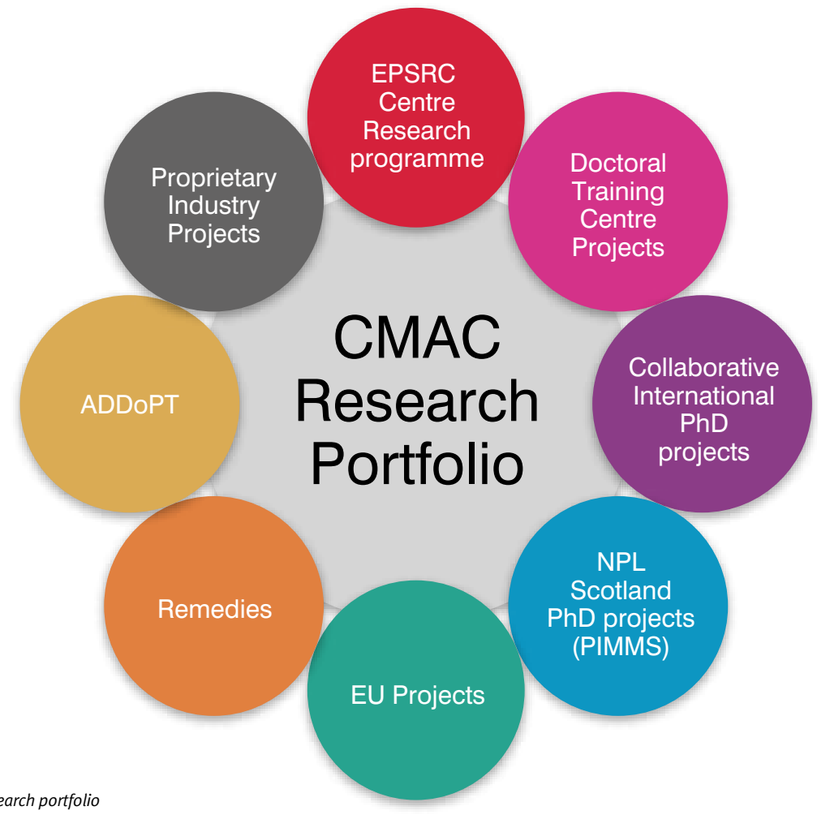
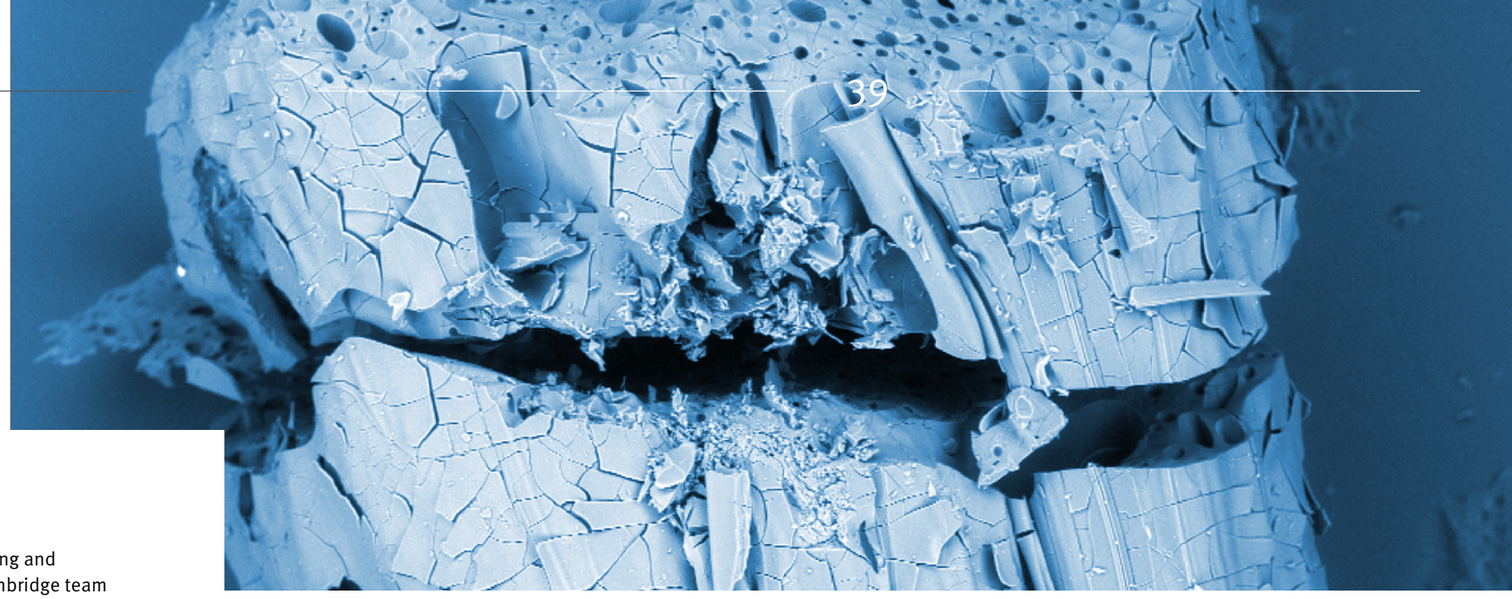


Figure 9. CMAC research portfolio



A primary focus of research across the Centre has been in developing workflows for primary and secondary processing. These have been constantly evolving though learning from past and current projects and scoping out new opportunities created by our new analytical and processing capability.

The benefits of having a validated workflow include:

- A clear and systematic approach for delivering a process with data driven decision points
- Automated data processing steps minimise repetitive tasks
- Minimised input of researcher and material resource and maximised output of data via design of experiment approaches
- Realistic estimations of project timescales

Currently we are developing workflows for crystallisation Case Study on pages 60-62 and for the primary to secondary processing (Fig 10).

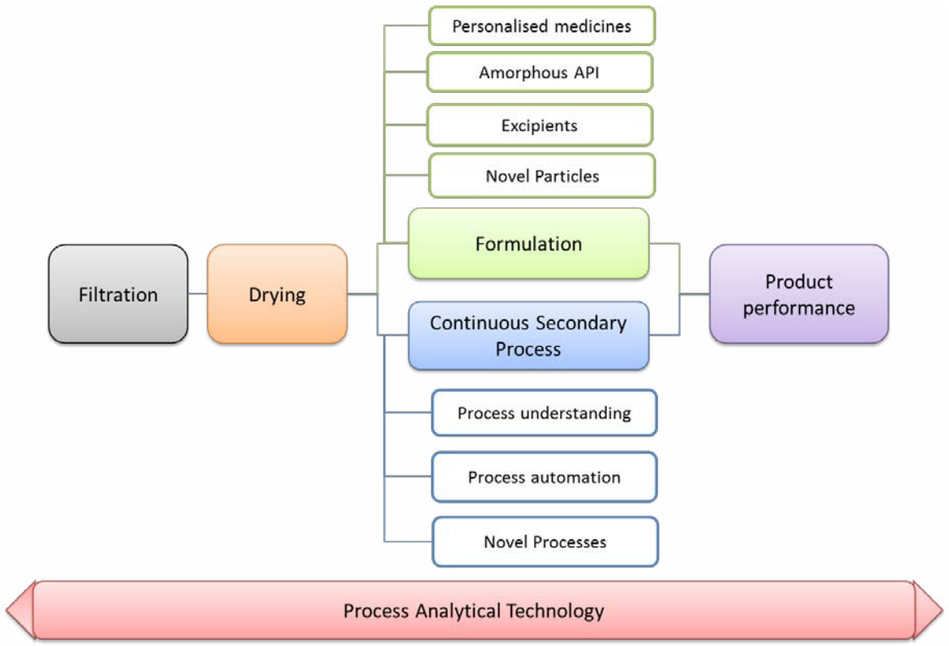


Figure 10. Primary to Secondary Processing Workflow

Research Overview

Research Themes and Vision

The Centre programme is currently in Phase II (years 3-5), following work on the initial flagship projects of Phase I.

Phase II builds on the capabilities established and progress made in Phase I. It delivers an ambitious co-ordinated programme of research that will transform capabilities for continuous manufacturing of high value chemicals and in particular, pharmaceuticals. Technical targets and industry problem statements collated by the Centre's industry technical committee and extensive discussion across the academic team have directed Phase II. Phase II also builds on downstream processing capability that includes isolation, drying and secondary processing of API into formulated product. The new processing and analytical capabilities housed within the state of the art CMAC National Facility (see pages 48-55) are key enablers of the programme. The research programme is being delivered through three work packages supported by the core Phase II Centre funded RAs.

Within the Centre scope from synthesised API to formulated product in Phase II, our programme is delivering across three key themes:

Laboratory-scale continuous process capabilities to support end-to end manufacturing

Continuous processing at laboratory scale offers a range of benefits including use of less material, improved process understanding, and rapid process development. This enables research with a broader range of solvents and APIs. A suite of continuous platforms are being developed to accelerate process development. These platforms support specific continuous crystallisation, isolation and secondary processing operations.

Tools and workflows for rapid product assessment and continuous process selection

We are developing methodologies for fast assessment of the physical properties of molecules, particles, formulated products and their physical transformations. This will inform future process and platform selection. We have a comprehensive suite of automation, characterisation and measurement tools, and a developing CMAC informatics infrastructure that we are using to deliver a robust foundation for systematic, rapid continuous crystallisation development. This will include a crystallisation classification approach.

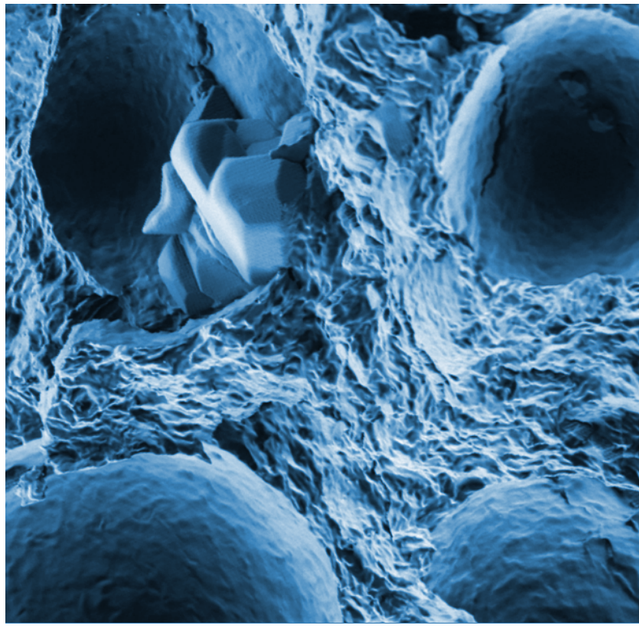
Product-process archetypes that support supply chains of the future

The widespread adoption of continuous manufacturing and crystallisation processes in pharmaceutical industrial practice is not solely dependent upon the technical requirements of each process step. For such technologies to become more generally accepted the business case and impact on current industry supply chain configurations need to be understood. This work package is focussed on addressing these issues and providing an informed view of the combinations of product and process attributes that would benefit from continuous manufacturing and the potential impact on future supply chain configurations.

Figure 11. Demand-Led Scope: from synthesis to formulated product

Making Medicines

Research in the Centre now actively targets specific pharmaceutical products where there is a clear opportunity to develop new manufacturing technologies that can aid access to medicines in developing countries as well as addressing the healthcare needs of western economies. We are in the process of exemplifying our workflows in Phase II using Paracetamol as the first case study. We will follow this up rapidly with other APIs of interest. Other projects will target anti-malarial drugs as well as treatments for HIV, and elevated cholesterol with outcomes demonstrating the ability to improve the medicines supply chain of the future.



A Focus on Particles
Our intention is to exploit continuous manufacturing to deliver:

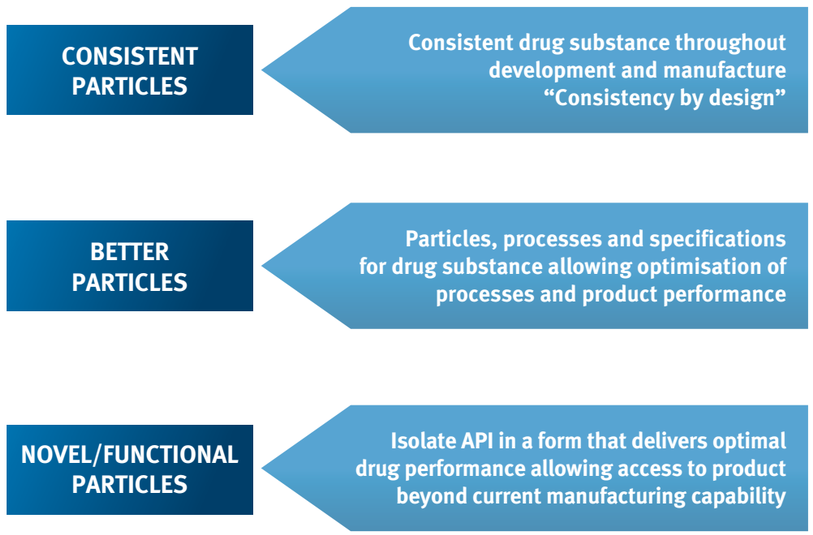


Figure 12. Focus of Phase II deliverables.

Research Overview

Review 2011-2016

Researcher Outputs

Between October 2011 and June 2016 the Centre has produced over 75 research publications, conference proceedings and white papers. CMAC has had a dedicated presence at conferences in the manufacturing, crystallisation, flow chemistry and formulation areas. CMAC Academics and researchers have been invited to chair and give plenary lectures at key conferences such as the 10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, the British Crystallographic Association (BCA) Young Crystallographer's Meeting,and BACG. CMAC researchers have received prizes for conference presentations and posters and have been key participants in cutting-edge workshops such as Erice, British Council Workshop in Novosibirsk, BCA/CCG Intensive Teaching School. CMAC's Professor Joop Ter Horst recently organised and hosted the European Nucleation Summer School, and Centre Director Professor Alastair Florence was on the organising committee for the 10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology.

Key Research Outputs

Workflow Development

Phase II of the Centre research programme has focussed on developing a seeded cooling crystallisation workflow as a core activity upon which others can build. See the case study on pages 60-62 for full details. This workflow has been used for several model compounds including Paracetamol and a publication on this work will be submitted before the end of 2016. The seeded cooling crystallisation provides a basis for further processes to integrate with crystallisation up and downstream and can also be adapted and updated for alternative types of crystallisation processes. Ultimately we plan to map types of API particle to archetypical product processes.

Platform Development

During 2011-2016 the Centre actively developed several existing technology platforms at the University of Strathclyde, Loughborough, Heriot-Watt and Bath, including the mixed suspension mixer product removal (MSMPR) crystalliser, continuous stirred tank reactors (CSTRs), the meso-scale and full scale continuous oscillatory baffled crystalliser (COBC) (See pages 90-92 for full details). We also have the Custom made reconfigurable integrated modular crystallisation miniplant (Microinnova) that are housed in the CMAC National Facility. A patent was filed for a device for inducing nucleation at Heriot-Watt University. Other work included bespoke nucleation units to obtain suitable seed suspension at the University of Strathclyde, establishing parameters necessary as a precursor for continuous crystallisation on MF-OBC and the design of a new flow crystallisation technology for the development of multicomponent agrochemicals at the University of Bath.

Image: Custom made reconfigurable integrated modular crystallisation miniplant housed in CMAC National Facility

Supply Chain Management

This research explores future value network configurations which may enable novel routes to medicines production, and the delivery of added value to 'end-users', i.e. payers and patients. We are using case studies to assess end-to-end (E2E) benefits and emerging patterns in a variety of contexts. The business case for transformation from batch to continuous processing can be assessed using the techniques explored through this research (see pages 65-66).

First Continuous Extended Run

Dr Humera Siddique successfully ran a 5 day continuous crystallisation of lactose experiment using the Cambridge Reactor Design Rattlesnake oscillatory flow reactor in Early 2014. The Continuous crystallisation was successfully performed at a throughput of 300-500 g/hr of desired alpha-lactose for 96 hours without any fouling or blockage. 26% higher yield was obtained in the continuous process as compared to batch. The system reached steady state after one and half residence times. Mean particle size can be easily tuned by varying the operating conditions. The XRPD analysis confirmed the product purity with no unwanted primary nucleation and consistent crystal habit was obtained throughout the process.

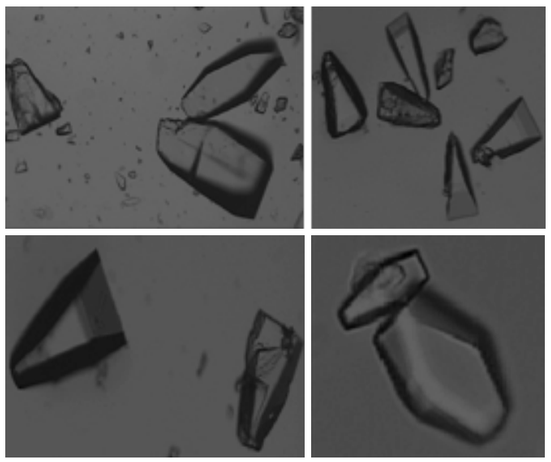


Image: Product crystals from different residence times showing consistent habit.

First Continuous Experiment in New National Facility

The first continuous experiment in the CMAC National Facility took place in May 2015. A continuous seeded cooling crystallisation of Lactose was performed in the NiTech DN15 continuous oscillatory baffled crystalliser. Step tests were performed on seed flow rate to build predictive models for concentration control and were validated real-time. The system was run for three days to achieve "dial a particle" capability. This work was done in partnership with Perceptive Engineering.

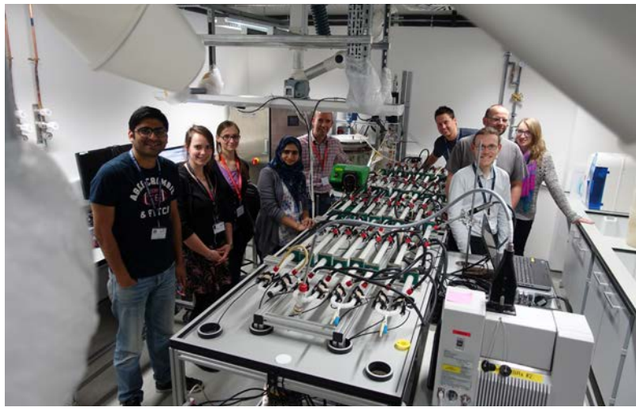


Image: First Continuous Crystallisation Experiment in TIC

National Centre Link with Other Major National Projects

2015 saw the kick-off of secondary manufacturing AMSCI projects, Remedies which has enabled a significant increase in research portfolio in the primary to secondary manufacturing area. CMAC are a partner in the AMSCI Digital Design Project which launched 2Q 2015. Further details on Remedies are given on pages 33-35 and ADDoPT on page 36.

Research Overview

Select Publications

For full list of publications please see appendix on pages 108-110

Seeded Crystallization of β-l-Glutamic Acid in a Continuous Oscillatory Baffled Crystallizer (Briggs et al., 2015)

In 2015 CMAC published a paper outlining research that resulted in continuously seeded, cooling crystallization process that gave controlled polymorphic and phase pure β-l-Glutamic Acid (LGA). The process ran in a Continuous Oscillatory Baffled Crystallizer (COBC). Steady-state operation was demonstrated consistently after two residence times. Bulk supersaturation levels determined whether or not the polymorphic phase purity of the thermodynamically stable β polymorph could be achieved. In the absence of seeding the system could not be operated in a controlled way, whereas a continuously seeded approach allowed robust processing for at least 10 hours.

From discovery to scale-up: α-lipoic acid: nicotinamide co-crystals in a continuous oscillatory baffled crystalliser (Zhao et al., 2014)

α-lipoic acid : nicotinamide co-crystals were discovered via co-crystal screening and the structure determined by single crystal X-ray diffraction and used for subsequent phase identification. The process of co-crystallisation was investigated in a COBC and then scaled up. This process produced over 1 kg of solid co-crystals at 99% purity.

From Evaporative to Cooling Crystallisation: An Initial Co-Crystallisation Study of Cytosine and Its Fluorinated Derivative with 4-chloro-3,5-dinitrobenzoic Acid (Wittering et al., 2014)

Two new multi-component molecular complexes of cytosine and 5-fluorocytosine with 4-chloro-3,5-dinitrobenzoic acid were synthesised. This was achieved initially by evaporative crystallisation. Analysis by XRPD and DSC confirmed the process was successfully transferred to a controlled small scale cooling crystallisation. Turbidity measurements were shown to be a valuable process analytical technology probe for characterising the initial stages of molecular complex formation in solution.

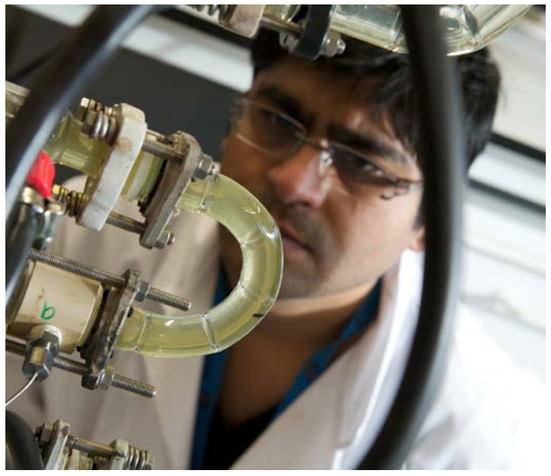


Image: Continuous Oscillatory Baffled Crystalliser

Probing into Nucleation Mechanisms of Cooling Crystallization of Sodium Chlorate in a Stirred Tank Crystallizer and an Oscillatory Baffled Crystallizer (Callahan & Ni, 2012)

This work investigated the crystallisation of sodium chlorate. The nucleation mechanism of a seeded crystallization in a novel oscillatory baffled crystallizer (OBC) was investigated by comparing the enantiomorphism of the product crystals to that of the seed crystals. The mechanism in the OBC was found to differ from that in the traditional stirred tank crystallizer (STC).

Oscillatory flow reactors (OFRs) for continuous manufacturing and crystallization (McGlone et al., 2015)

A review of oscillatory flow reactors (OFRs) was published in 2015. It outlines known operating principles and applications and highlights areas where further development is needed. Opportunities include: scale down, materials of construction, mitigating encrustation and blockage, automation and control.

Estimation of particle size distribution and aspect ratio of non-spherical particles from chord length distribution (Agimelen et al., 2015)

ICT CMAC work resulted in a comprehensive algorithm which produces estimates of particle size distribution and particle aspect ratio from measured CLD data. It does not require any additional information about particle size range and shape. It can be used with any optical or geometrical model for particle detection.

Nonphotochemical Laser-Induced Crystal Nucleation by an Evanescent Wave (Ward et al., 2015)

Laser-induced nucleation of potassium chloride was achieved using an evanescent wave. Unprecedented localization of the time and position of nucleation, within 5 ns and within 100 nm of the glass–solution interface, respectively, has been achieved with this method.

Investigation of an 11mm diameter twin screw granulator: Screw element performance and in-line monitoring via image analysis (Sayin et al., 2015)

The performance of two different screw elements was studied in an 11 mm twin screw granulator (TSG) with various liquid-to-solid (L/S) ratios. The kneading element configuration was found to be most efficient and produce narrower granule size distributions. Granules were analysed using the Eyecon™, a real-time high speed direct imaging system, which captured accurate particle size distribution and particle count. The size parameters and particle count were then assessed in terms of their ability to be a suitable control measure.

Image: Loading the twin screw granulator

A Random Forest Model for Predicting the Crystallisability of Organic Molecules (Bhardwaj et al., 2015)

This work is the first report of a random forest model helping to predict crystallisability of organic molecules. Accuracy of ~70% was achieved using a model based on calculated molecular descriptors and published experimental crystallisation propensities of a library of substituted acylanilides.

Image-based monitoring for early detection of fouling in crystallisation processes (Tachtatzis et al., 2015)

An automatic algorithm to detect early stages of fouling has been designed and can be used for in situ monitoring of early signs of encrustation. This gives an early warning for corrective actions to be taken when operating continuous crystallisation processes. The algorithm can distinguish crystal appearance in the bulk solution and at the crystalliser walls. Online real-time detection of induction time at the surface and in the bulk is achieved as a result.

Mathematical Modeling, Design, and Optimization of a Multisegment Multiaddition Plug-Flow Crystallizer for Antisolvent Crystallizations (Su et al., 2015)

As part of a larger project to build dynamic simulations of continuous crystallization and downstream secondary manufacturing operations, to optimize performance and test out control strategies for an integrated pharmaceutical production plant flow sheet, this paper presents an example of the first stage, which considers the mathematical modeling, design, and optimization of tubular crystallizers for antisolvent crystallization, to provide a better understanding of flexible design, and to improve the process performance accordingly. The method is quite general and can be adapted to take into account different definitions of the process objective and to target a variety of product quality attributes. Nevertheless, the simulations require input in the form of kinetic rate laws, which should be obtained from experiments conducted under the relevant flow conditions.

Research Overview | Select Publications

Solvates, Salts, and Cocrystals: A Proposal for a Feasible Classification System (Grothe et al., 2016)

Work on an unambiguous classification system for multicomponent crystals was tested using organic crystals in the Cambridge Structural Database (CSD). These were analysed and seven subclasses found, each illustrated by an example of an isonicotinamide crystal structure that can be found in the CSD.

Tuning crystal morphology of succinic acid using a polymer additive (Klapwijk et al., 2016)

This work has shown that Succinic Acid crystal growth can be controlled in a reproducible manner using small quantities of Pluronic P123 (a triblock co-polymer). The crystal morphology can be modified from plate-like to block-like to needle-like depending on the quantity of PP123 added. The mechanism and effect of PP123 have been investigated. See also page 80.

Amino acids as highly efficient modulators for single crystals of zirconium and hafnium metal-organic frameworks (Marshall et al., 2016)

This project shows that amino acids, in particular L-proline, are highly efficient modulators of zirconium and hafnium metal–organic frameworks (MOFs) of the UiO-66 series. The synthesis and characterisation were explored comparing the thermal stabilities and porosities for Zr and Hf analogues. Synthesis was extended to a microwave protocol. The modulating ability varies dramatically across a series of amino acids. It is expected that our protocols will enable the discovery of new Zr and Hf MOFs as well as offer new insights into their materials properties.

Evaluating the potential for the continuous processing of pharmaceutical products—a supply network perspective (Srai et al., 2015)

Evaluating the potential supply chain benefits of continuous processing technologies for a diverse set of pharmaceutical products is necessary to provide a business case for adoption. This approach integrates upstream ‘continuous’ processing considerations with the downstream implications for packing and distribution. Current practise decouples these, whereas the approach presented in this paper identifies opportunities for more case-specific integrated end-to-end supply chains enabled by continuous flow technologies. This is demonstrated using 3 case studies.

Periodic steady-state flow crystallization of a pharmaceutical drug using MSMPR operation (Powell et al. 2015)

Periodic mixed suspension mixed product removal (PMSMPR) crystallization process has been demonstrated. PAT and in-house developed crystallization process informatics system software (CryPRINS) were used to monitor the periodic steady-state flow crystallization of paracetamol. Periodic steady-state is a new concept defined as a state of a system that maintains itself despite transitory effects caused by periodic, but controlled disruptions (state of controlled operation). This work also illustrates the concept of “state of controlled operation” instead of “steady-state operation” as a state that can characterize continuous (periodic) operation. The results illustrate the use of PAT and information system tools together to determine when the periodic operation reaches a state of controlled operation (periodic steady-state).

Patent

A patent was filed for a device for inducing nucleation. (Ni, X.-W.; Callahan, C. J.: Device for Inducing Nucleation. 2013, WO 2013/088145.) The device, which separates the two operations of crystal nucleation and crystal growth, can be described as being similar to a two stage COBC.

Facilities

UNIVERSITY of STRATHCLYDE
CMAC
NATIONAL FACILITY

- **World class facilities for forming, processing and analysing particles and particulate systems**
- **Pilot scale manufacturing capability supporting global partners**
- **Inspiring researchers and enabling breakthroughs in medicines manufacture**

Vision:

To support a world class manufacturing research facility, inspiring researchers, supporting innovation

Mission:

To provide cost effective access and support to all users within a safe, well managed and collaborative environment

The CMAC National Facility delivers world class research, training and knowledge exchange on a global scale as well as operating as a National Facility supporting users from both academia and industry. Our advanced pharmaceutical manufacturing research facility is easily accessible by academics and businesses in the UK and internationally.

The National Facility has the additional benefit of co-locating multidisciplinary teams of academic and industry researchers within the state of the art Technology and Innovation Centre (TIC) at the University of Strathclyde.

The facility is equipped using £11.4 m funding awarded by the Higher Education Funding Council for England (HEFCE)'s UK Research Partnership Investment Fund (UKRPIF) and supported with £22.8 m industry and charity contributions. The National Facility features world class capabilities in:

- Primary Processing
- Secondary Processing
- PAT/Spectroscopy
- X-ray Diffraction
- Surface Analysis
- Materials Characterisation

The National Facility has end-to-end continuous manufacturing and crystallisation research capability under one roof. This capability features key items of equipment:

- Modular skid-mounted crystallisation platforms (batch and continuous)
- Pilot scale filtration and drying
- Secondary processing including spray drying, hot melt extrusion (HME), granulation and tableting
- TOF-SIMS
- Atomic force microscopy (AFM)
- Nuclear magnetic resonance (NMR) spectroscopy
- World class X-ray suite including single crystal, powder (crystalline & amorphous), small angle scattering (SAXS) and nano computed tomography (CT).

Strathclyde's Technology and Innovation Centre will help transform Glasgow and Scotland. Based on our reputation for high quality research with industrial impact and relevance, it will attract millions of pounds of inward investment to the city, drive global businesses, and create jobs - helping develop highly-qualified graduates and postgraduates.

"We believe that this project will be in the vanguard of exciting new investments that fully realise our potential to capitalise on academic excellence, contribute to economic development and position Scotland as a global competitive player in key sectors. The Centre will raise Glasgow's profile internationally and help restore the city's reputation as an engineering and technology centre of excellence.

"But beyond that, this is about transforming the way we share knowledge and find solutions to challenges that affect every area of society – including energy, pharmaceuticals, manufacturing and economics"

Professor Sir Jim McDonald, Principal of the University of Strathclyde

With £22.8m industry and charity support, the award of £11.4m from UK Research Partnership Investment Fund (RPIF) has enabled a step-change in the research capability of CMAC.

This has specifically benefitted the following key areas:

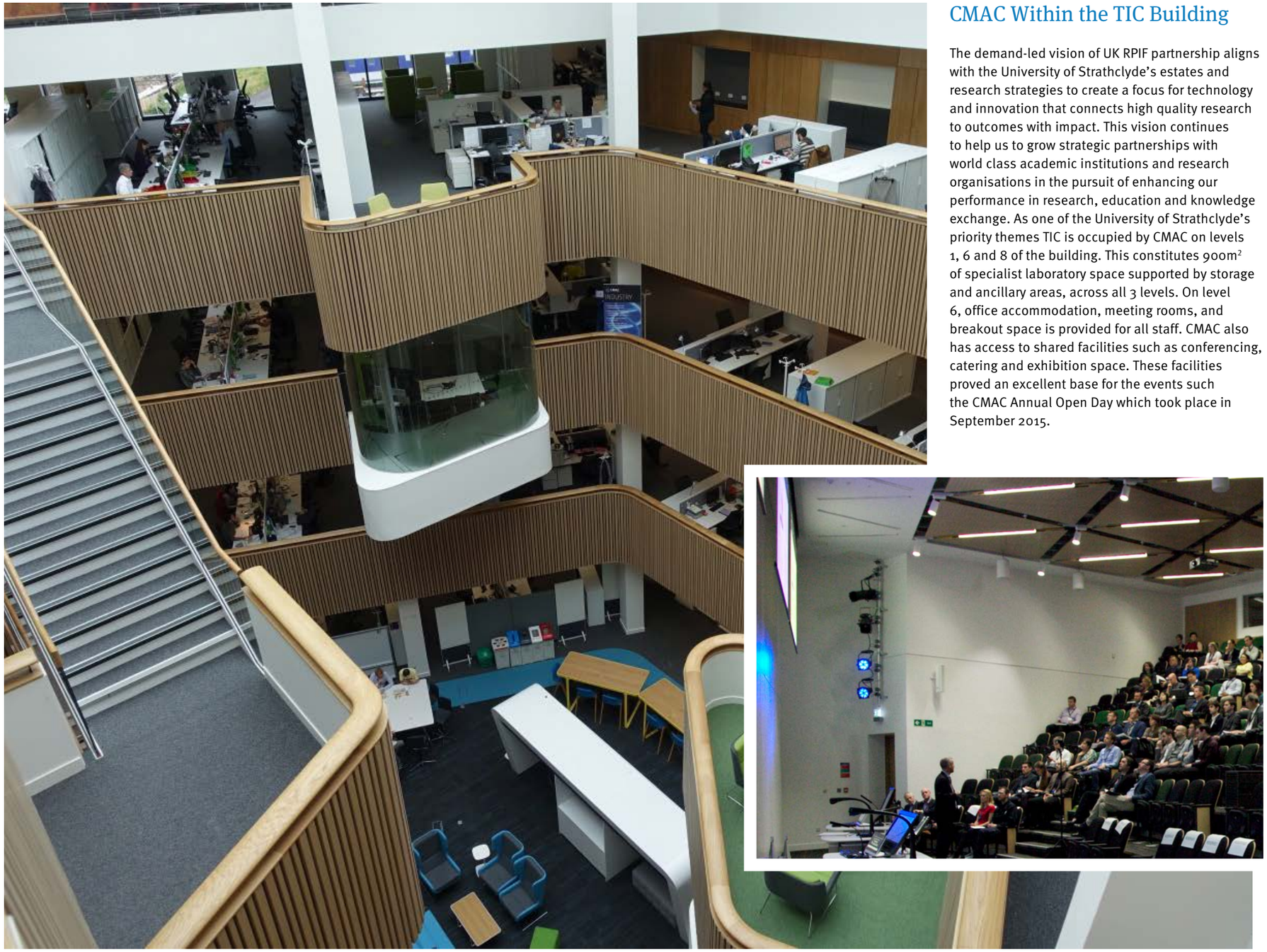
- Establishing a physical hub within TIC at the University of Strathclyde with a full complement of research equipment and instruments to create a world leading National Facility housed within a dedicated laboratory. This supports a range of high-value, state-of-the-art processing equipment, novel monitoring and control research systems and off-line characterisation capabilities. Thus, the National Facility offers unparalleled research capability to identify, understand, monitor and control critical aspects of continuous manufacturing and crystallisation.

- Enabled the construction of pilot scale processing equipment platforms. These modular, reconfigurable platforms (including skid-mounted set-ups) together with control systems exploit current understanding and develop new laboratory-scale technologies that aim to meet the need for continuous manufacturing capability, primarily from particle evolution to complex formulated product.

- Provision of additional equipment to our partner university laboratories aligned with the National Centre. This has supported the establishment of a linked network with shared access to continuous processing, control and process monitoring in addition to off-line analysis.

- Facilitated access to dedicated high-value equipment locally within other departments and organisations in the university. This includes Physics imaging equipment, Chemistry NMR facility and the Advanced Manufacturing Research Laboratories (AMRL), Advanced Forming Research Centre (AFRC) and high performance computing (ARCHIE - WeST).

- Creation of a base for a collaborative and open culture with industry partners such that their staff are able to spend periods of time within the National Facility alongside researchers in order to advance new technologies and develop ideas. In addition, the multidisciplinary nature of the researchers (chemists, pharmacists and engineers) provides a productive and stimulating environment for both industrial and academic researchers.



CMAC Within the TIC Building

The demand-led vision of UK RPIF partnership aligns with the University of Strathclyde's estates and research strategies to create a focus for technology and innovation that connects high quality research to outcomes with impact. This vision continues to help us to grow strategic partnerships with world class academic institutions and research organisations in the pursuit of enhancing our performance in research, education and knowledge exchange. As one of the University of Strathclyde's priority themes TIC is occupied by CMAC on levels 1, 6 and 8 of the building. This constitutes 900m^2 of specialist laboratory space supported by storage and ancillary areas, across all 3 levels. On level 6, office accommodation, meeting rooms, and breakout space is provided for all staff. CMAC also has access to shared facilities such as conferencing, catering and exhibition space. These facilities proved an excellent base for the events such the CMAC Annual Open Day which took place in September 2015.

Facilities | CMAC National Facility

Laboratories and Equipment

The laboratory accommodation in TIC is over 900m² including a cluster of 12 multi-functional walk-in fume cupboards and a dedicated enclosure for multi-phase batch and continuous primary processing. Additionally, there are dedicated analytical areas for advanced understanding of particulate formation and processing and a secondary processing suite. Stores and ancillary areas have been designed to complement the unique activities carried on in the laboratories to support the programme.

Images: *Primary processing lab and equipment*

Primary Processing Laboratory

Our largest laboratory in TIC houses our 12 walk-in fume cupboards. These bespoke units are highly reconfigurable both meeting the needs of current research and, in liaison with supplier Premier Labs, will be able to meet future demands as our research grows. Key features of these fume cupboards include: removable rear baffles to accommodate a 3.8 m long process; the 2 clusters of 4 fume hoods have side windows to accommodate processes side by side; 80 mm diameter pass through ports for PAT probes and fibres plus data communications. In addition there is good access to 3 phase power, ethernet, compressed air and nitrogen, and water.

Secondary Processing Suite

A purpose built collection of laboratory areas adjacent to the primary processing facility house our entire secondary and formulation units. These areas are equipped with flexible exhaust ventilation for powder handling. The units include 11mm and 16 mm twin screw extruders, a mini-injection moulder, bin blender, high-shear wet granulator, fluid bed drier, conical/hammer mill, dry granulator and a tablet press.

Image: *Secondary Processing Suite*

Image: *X-ray Analysis Suite*

X-ray Analysis Suite

The National Facility includes a dedicated, world-class X-ray suite housing 3 Bruker D8 Advance powder instruments in addition to a D8 Discover and a PANalytical Empyrean for amorphous studies. Furthermore, a Kappa Apex II and D8 Venture facilitate advanced single crystal work. A significant investment for the National Facility was the Nano-CT instrument. The Centre, together with colleagues from BioNano and Physics have purchased a Xenocs Small Angle X-ray Scattering (SAXS) instrument. A benchtop D2 instrument is also available in the primary processing area for rapid sample analysis at-line.

Process Development Laboratory

This laboratory provides additional preparation space with four regular 2m wide fume hoods for smaller scale activities. It houses a Zinsser screening robot platform, various 3D printing platforms and a Circular Dichroism unit.

Image: *Process Development Laboratory*

Material Characterisation Laboratory

Our largest analytical laboratory houses all of our capability in terms of off-line characterisation across multiple forms - powders, tablets, slurries etc. Instrumentation allows for chemical analysis: gas and liquid chromatography and mass spectrometry in addition to physical methods such as porosity, density, surface area analyses, dynamic vapour sorption (DVS), inverse gas chromatography and powder and liquid rheometry. New generation instruments are available for advanced particle size and shape analysis. Furthermore, dissolution testing, solubility screening and compression testing equipment complete the scope of capability.

Wolfson Pharmaceutical Surfaces Laboratory and AFM Facility

We are hugely grateful to the Wolfson Foundation for the award of £750k and an additional contribution from UK RPIF allowing the purchase a TOF-SIMS instrument. This was a second major investment item for the National Facility. This instrument, in addition to two AFM systems allow a new level of nanoscale physical and chemical understanding with surface characterisation.

Microscopy Suite

Within a vibration sensitive laboratory, the National Facility houses extensive optical and electron microscopy capability. This includes automated compound and inverted optical microscopes, off-line IR and Raman instruments with surface mapping features plus a benchtop SEM. This allows physical samples to be imaged and chemically analysed.

Image: Wolfson Pharmaceutical Sciences Laboratory

Image: Filtration and Drying

Continuous Filtration and Drying Capability

An increasingly important area for the National Facility has been the installation of continuous filtration and drying process set-ups including a filtration robot designed by Cambridge Reactor Design, donated to the National Facility by GSK. This comprises of a custom built rotary drum system and a prototype combined filtration and washing platform.

Image: Continuous Work Up

Facilities

Training for Researchers and Staff Within the National Facility

The National Facility regularly hosts training events, both following the commissioning of new pieces of equipment and to support the uptake of new techniques. Such events are a great way to engage with technology providers (in particular, our Tier 2 partners) and give students excellent hands on experience as part of their training programme. As the facility continues to strengthen, we are regularly asked to host company demonstrations of specific equipment items, serving as a geographical hub for some of our partners. Safety and wellbeing is at the centre of our focus, with expert training and guidance provided in order to generate a high quality student and staff pipeline as individuals move through the various programmes.

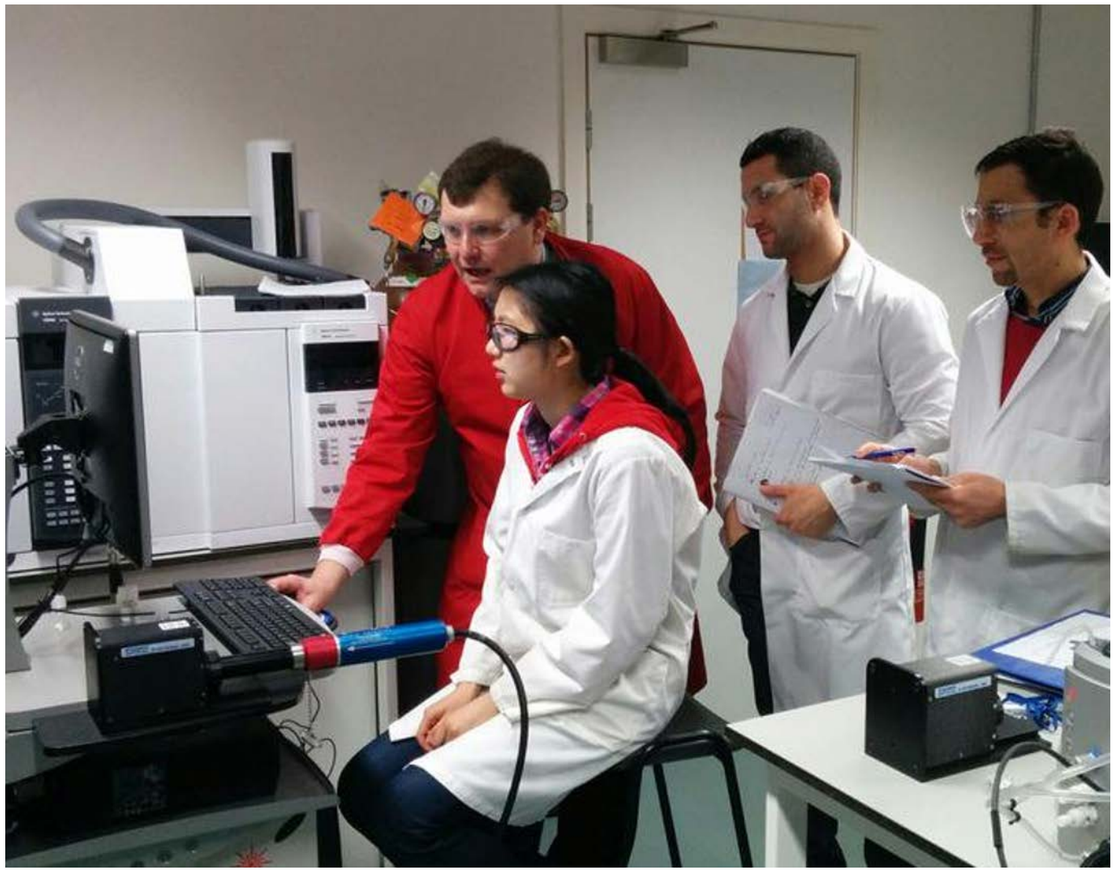


Image: Researchers training in CMAC National Facility

Training

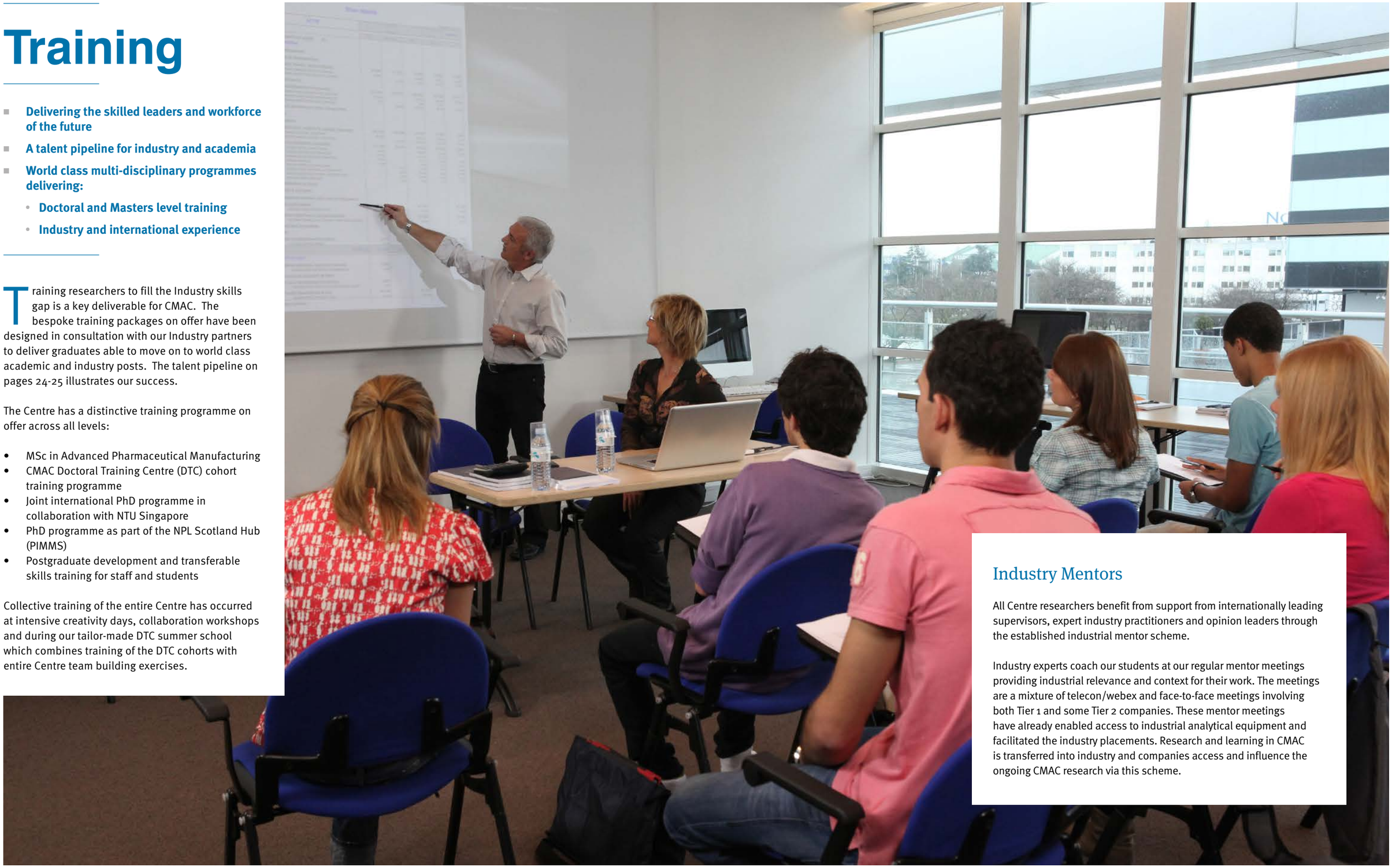
- **Delivering the skilled leaders and workforce of the future**
- **A talent pipeline for industry and academia**
- **World class multi-disciplinary programmes delivering:**
  - **Doctoral and Masters level training**
  - **Industry and international experience**

Training researchers to fill the Industry skills gap is a key deliverable for CMAC. The bespoke training packages on offer have been designed in consultation with our Industry partners to deliver graduates able to move on to world class academic and industry posts. The talent pipeline on pages 24-25 illustrates our success.

The Centre has a distinctive training programme on offer across all levels:

- MSc in Advanced Pharmaceutical Manufacturing
- CMAC Doctoral Training Centre (DTC) cohort training programme
- Joint international PhD programme in collaboration with NTU Singapore
- PhD programme as part of the NPL Scotland Hub (PIMMS)
- Postgraduate development and transferable skills training for staff and students

Collective training of the entire Centre has occurred at intensive creativity days, collaboration workshops and during our tailor-made DTC summer school which combines training of the DTC cohorts with entire Centre team building exercises.



Industry Mentors

All Centre researchers benefit from support from internationally leading supervisors, expert industry practitioners and opinion leaders through the established industrial mentor scheme.

Industry experts coach our students at our regular mentor meetings providing industrial relevance and context for their work. The meetings are a mixture of telecon/webex and face-to-face meetings involving both Tier 1 and some Tier 2 companies. These mentor meetings have already enabled access to industrial analytical equipment and facilitated the industry placements. Research and learning in CMAC is transferred into industry and companies access and influence the ongoing CMAC research via this scheme.

Training

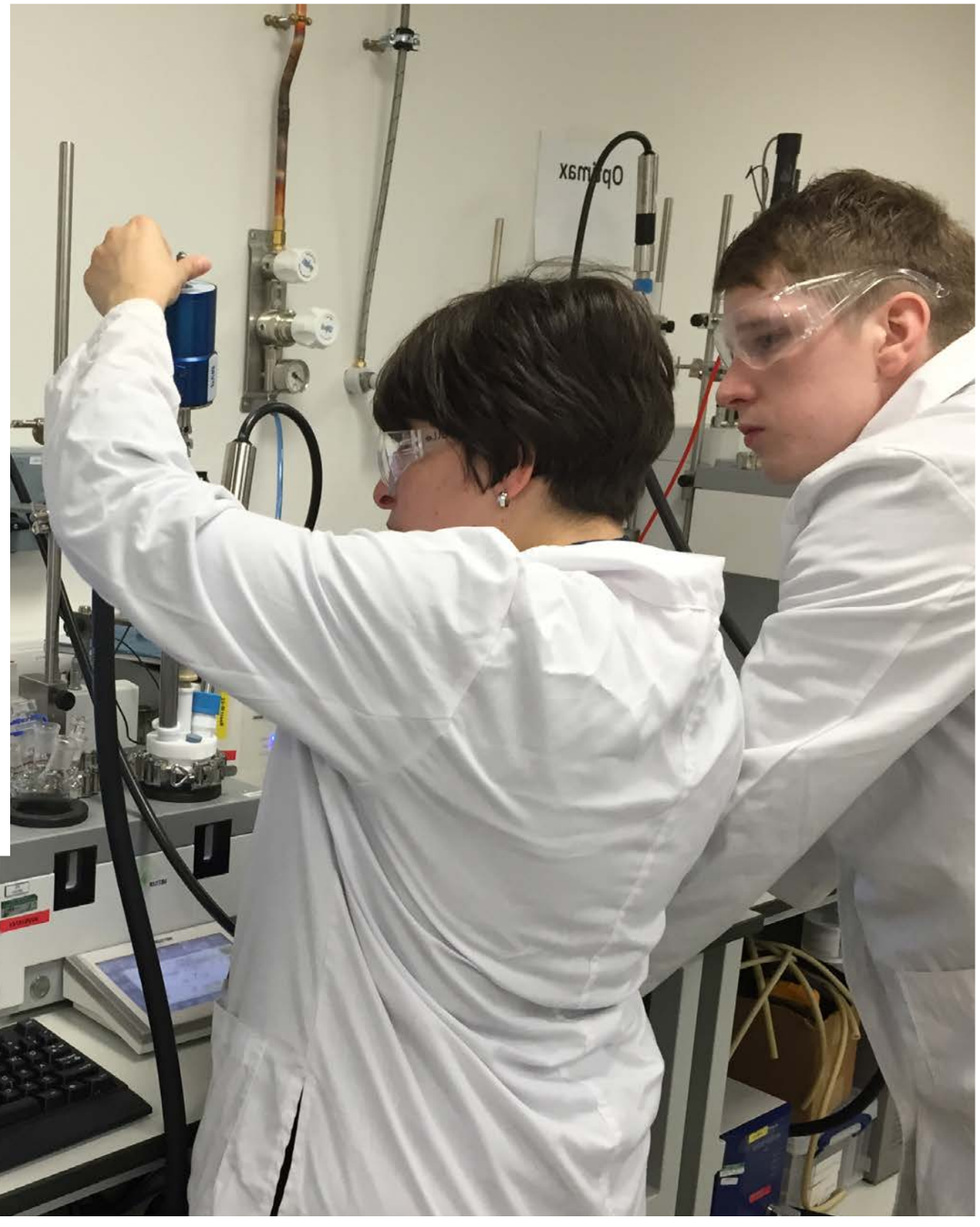
The Doctoral Training Centre

The CMAC Doctoral Training Centre (DTC) commenced in October 2012 and offers a vibrant, world-class, multi-disciplinary training programme that equips graduates with leading edge skills in pioneering continuous processes. The DTC is funded through combined support, from a £4.2m award from EPSRC, a £668k contribution towards training costs from AstraZeneca, GSK and Novartis and significant support for studentships, training and infrastructure from the seven Centre universities. This DTC employs a novel approach to cohort building and training whereby year 1 of the PhD encompasses residential training weeks delivered by the partner institutions with visits and input from industrialists.

By embedding the DTC within our National Centre, our students are exposed to:

- Relevant fundamentals across each discipline
- Current state-of-the-art knowledge including the challenges in continuous manufacturing and crystallisation
- Existing research activities both within the Centre and internationally
- Unparalleled opportunities to engage in leading-edge research projects as part of a National team
- The formal training programme is coordinated by Prof Jan Sefcik and has three main elements:
  - A range of taught modules covering the different aspects of the programme
  - Individual and group mini-projects
  - Transferable skills training

To date four cohorts have completed their first year residential training weeks and are now in the research phase of their projects.



Collaborative International PhD Programme

A Joint International Doctoral Training Centre in Continuous Manufacturing and Crystallisation of Pharmaceuticals was initiated as part of an EPSRC Global Engagements award in 2012/2013. The Centre established links with Nanyang Technological University (NTU) in Singapore via workshops and exchanges. We have built on these links, and with support from the University of Strathclyde and established a joint doctoral training programme which commenced in October 2014. This unique PhD scheme started with a cohort of 6 students; 3 based at the University of Strathclyde and 3 at NTU.
The main research themes of Pharmaceutical Particle Formation, Optimising Pharmaceutical Performance and Multi- Scale Pharmaceutical Systems are being explored via projects at the University of Strathclyde and at NTU (see page 85).

Pharmaceutical Innovation and Manufacturing Metrologies

CMAC is a key theme within the NPL Scotland Regional Hub, a partnership between the National Physical Laboratory (NPL) and the University of Strathclyde. The partners have successfully developed a joint Doctoral Training Programme with underpinning investment in the key research themes: initially three joint CMAC-NPL PhD studentships started in October 2015 with researchers splitting their time between the CMAC National Facility at Strathclyde and NPL laboratories in Teddington. Students receive state of the art training in measurement science applied to a range of scientific disciplines and industrial challenges.

Led by joint Head of Science at NPL, Prof Ian Gilmore, three new research projects in Metrology for Pharmaceutical Manufacturing, Measurement of Surfaces and Big Data Management are being explored by new PhD researchers in the PIMMS collaboration as part of the NPL Scottish Hub at University of Strathclyde (see pages 86-87).

MSc in Advanced Pharmaceutical Manufacturing

In 2014 the Scottish Funding Council (SFC) awarded CMAC at the University of Strathclyde 20 fully funded places per year for a new MSc in Advanced Pharmaceutical Manufacturing. This unique Masters course provides training in key aspects of modern manufacturing approaches suitable for pharmaceuticals and high-value chemicals. It is designed to produce highly-skilled graduates in continuous manufacturing science and technology to meet the growing demands for expertise in this area. Graduates will be equipped to take up jobs in the food, chemical and pharmaceutical industries. The curriculum was designed with input from CMAC industry partners (AstraZeneca, Bayer, GSK & Novartis).

Students undertake the following compulsory classes:

- Continuous Manufacturing of Pharmaceutical Particles and Products
- Crystallisation and Formulation for Manufacture
- Generic Biomedical and Pharmaceutical Research Skills
- Industrial Pharmacy
- Pharmaceutical Project Management
- Process Analytical Technology (PAT) and Quality by Design in Continuous Pharmaceutical Manufacturing

Research Case Studies

Seeded Cooling Crystallisation Workflow

Academics:
Prof Alastair Florence
Dr Andrea Johnston
Dr Blair Johnston
Dr Chris Price
Prof Chris Rielly
Prof Jan Sefcik

Researchers:
Dr Cameron Brown
Dr Pol MacFhionnghaile
Dr Thomas McGlone
Dr Humera Siddique
Dr Murray Robertson
Dr Anna Trybala
Stephanie Yerdelen
Bilal Ahmed
Maria Bruiglia
Dimitrios Fysikopoulos
Rajesh Gurung
Fraser Mabbott
Hector Polyzois

The Phase II (see pages 40-41) research campaign's core activity has been focused on the design and implementation of a workflow for continuous crystallisations. Initially we concentrated on seeded cooling crystallisations.

As there a many considerations to be made when designing a crystallisation process, the following qualifying statements were made to standardise the approach to retain process design. Future versions of the workflow will be expanded to address each of these:

- Polymorphic form is largely pre-determined (not actively from screening)
- Feed composition is fixed (no varying levels of impurities)
- Nucleation is managed by seeding (seed generation considered in auxiliary workflow)

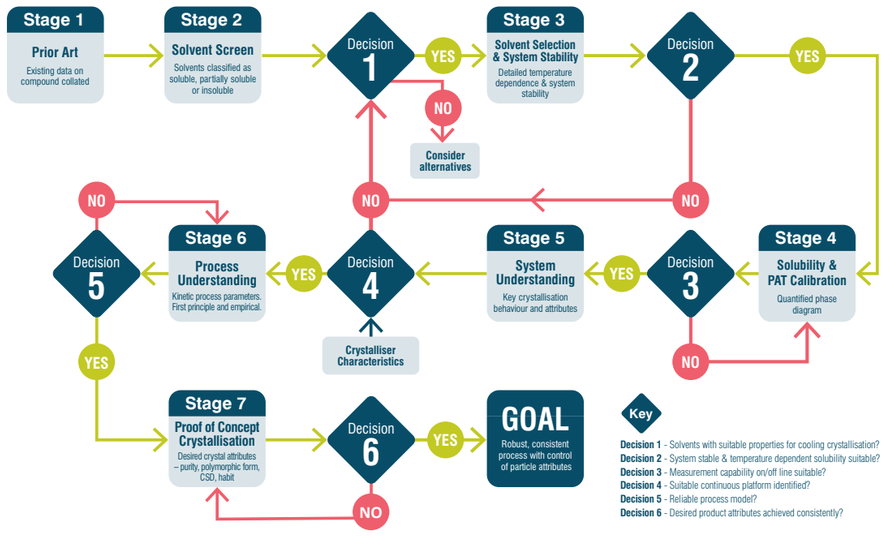


Figure 13. High level overview of the current cooling crystallisation workflow showing the critical stages and the decision points for each.

The workflow is broken into 7 high level stages, each with a clear objective and criteria which inform progression to the next. If critical criteria are not met, the stage is re-visited after which it may actually be concluded that it is not feasible to continue the development of a cooling crystallisation process. These data driven decision points will ensure that optimal conditions are used and that specific processes are directed towards the most suitable platforms.

Stage 1: Prior Art

This stage fully characterises and reviews known information on the API under consideration. This informs the rest of the workflow and provides a benchmark to monitor the purity and form of the API during the process.

Stage 2: Solvent Screening

From a library of 97 solvents, a fixed concentration of compound is analysed at three temperature values using the Crystal16 platform and each solvent is classed as soluble, partially soluble or insoluble. A design space has been determined which considers each solvent's dissolution class across the three temperatures, hazards and practicality. All solvents which fall within this design space are carried forward to Stage 3.

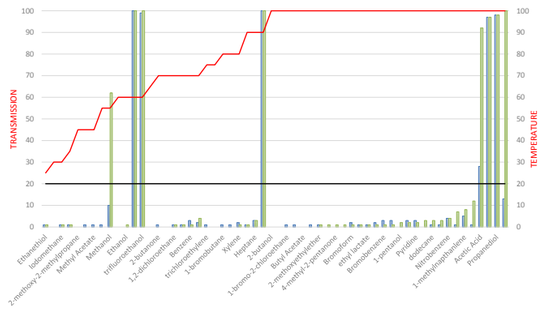


Figure 14. Typical output from the solvent screening stage.

Stage 3: Solvent Selection & System Stability

Of the reduced number of solvents carried forward from Stage 2, a more detailed investigation of the temperature dependent solubility is performed using the Crystalline platform. Exposing multiple known concentrations to a heating and cooling cycle allows an approximate phase diagram to be produced. In-situ imaging also allows valuable visualisation. As with the previous stage a design space was determined which considers the potential operating temperature range, yield of solute, final solid mass fraction, metastable zone width, form and chemical stability. These are in addition to qualitative observations relating to agglomeration and fouling. From solvents which fall within this design space a single solvent is selected for the following stages.

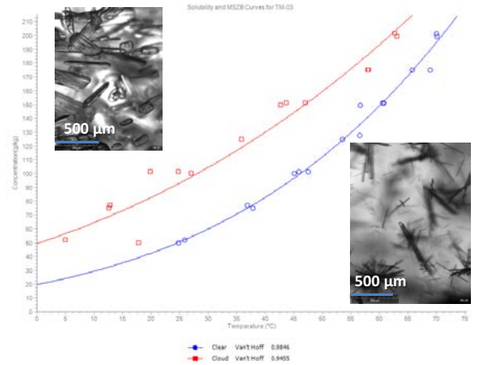


Figure 15. Typical output of an approximate phase diagram for Stage 3.

Stage 4: Solubility (Thermodynamic)

With the selected solvent system from Stage 3, an assessment of a suitable solution concentration monitoring technique (UV, IR, Raman) is performed. A multivariate calibration is completed incorporating PLS modelling to remove the effects of temperature. The phase diagram is then accurately determined using a specific, stepped heating approach to ensure equilibrium solubility. This is validated by an additional, off-line technique.

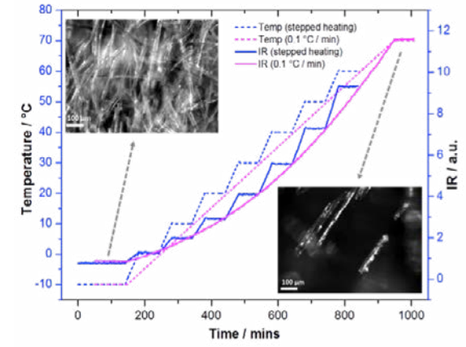


Figure 16. A specific, ramped heating profile is used to determine accurate temperature dependent solubility diagrams.

Seeded Cooling Crystallisation Workflow

Stage 5: System Understanding

The process conditions for a desired crystallisation are investigated with the primary objective being platform selection. A series of studies are performed to investigate the relative magnitudes of the crystallisation's: primary nucleation, secondary nucleation, growth rate (measured both as single crystal and in bulk), agglomeration and fouling. Automated evaluation platforms including the Optimax, Crystalline and MF-OBC are used to determine these system parameters.

Figure 17. Examples of platforms used in Stage 5 a) Optimax, b) MB-OBC and c) fouling cell.

Stage 6: Process Understanding

While it is entirely feasible to proceed from Stage 5 to Stage 7 using data driven model predictive control approaches which have been developed in partnership with Perceptive Engineering for the processing platforms, we have adopted a hybrid approach where parameter estimation for population balance modelling is used. Parameters for nucleation, growth, agglomeration and breakage, based on experimental results from a DOE approach, are used to assess process conditions (cooling rate, concentration, seed loading) via gCRYSTAL and Matlab.

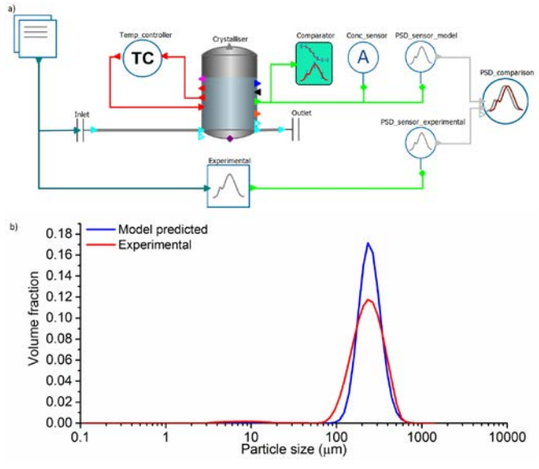


Figure 18. a) Model flow diagram and b) comparison of model predicted and experimental particle size distribution.

Stage 7: Proof of Concept Crystallisation

From the detailed outputs of Stage 5 and 6, demonstration of a pilot/production scale operation for the chosen solvent/solute system in the selected platform is performed. The objective is the achievement of critical crystal attributes over an extended period of operation under controlled steady state conditions.

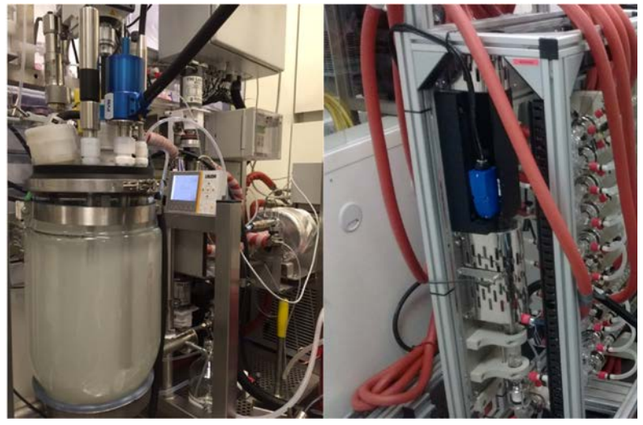
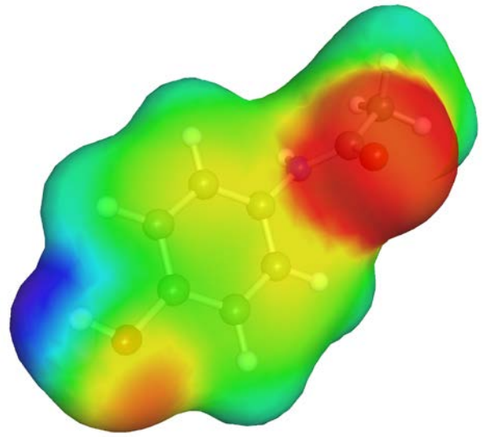


Figure 19. Modular skid mounted crystallisers utilised in Stage 7.

Research Case Studies

Automated Workflows for Rational Solvent System Selection



Academic:
Dr Blair Johnston

Researchers:
Dr Cameron Brown
Dr Murray Robertson
Bruce Wareham

The Challenge

Solubility is the thermodynamic driving force in all crystallisations. Being able to predict solubility with some degree of accuracy is an extremely useful tool in the pharmaceutical industry. The ability to implement a fast, reliable and accurate, automated *in silico* modelling system for effective solvent selection that is incorporated into designing the continuous crystallisation process is the key objective of this project. The approach is strengthened by using available experimental data to refine the model. This approach is being developed in parallel with CMAC's Phase II seeded cooling crystallisation workflow (see pages 60-62).

The Technology

This project uses several methods (the *ab initio* COSMOtherm, UNIFAC and SAFT) to predict solubility. It involves parameterising new molecules (using COSMOconf and Turbomole, which are quantum chemical and thermodynamic packages) and building the model using techniques such as Random Forest and AMBER.

The Method

These solubility prediction models will be incorporated into the digital workflows accessible via the CMAC ELN. This will allow our researchers easy access to a predictive solvent screen that is able to rank solvents at three different temperatures (high, mid and low) and help select solvents for cooling crystallisations.

Research Case Studies

Rapid and Efficient Method of Solvent Screening of Organic Solvents

Academics:
Dr Andrea Johnston
Dr Blair Johnston
Prof Alastair Florence

Researchers:
Dr Thomas McGlone
Rajesh Gurung

Properties such as solubility, crystal habit, polymorphism and crystallinity of an API are greatly influenced by the choice of the solvent used. Thus, finding an ideal solvent for a crystallisation process is of great importance. An ideal solvent should be chemically compatible in the first instance and when considering cooling crystallisation, dissolve the API at higher temperature but be sparingly insoluble at low temperature. Impurity retention is a critical issue to consider and economic and safety concerns are also addressed. Finding an ideal solvent is often challenging.

In this study, Random Forest, an approach typically used for various predictive applications, has been introduced to perform a rapid and efficient solvent screen of different pharmaceutical compounds based on a quantitative chemoinformatics approach. Random forest is an ensemble of randomly constructed independent and fully grown decision trees based on the bootstrap sampling technique. It is ideal for handling quantitative structure-property relationship tasks and offers features such as estimation of prediction accuracy, measure of descriptors importance and a measure of similarities between compounds. It gives highly accurate predictions whilst being computationally much faster and more robust than other ensemble techniques (Breiman, 2001).

Experimental data for the solvent screening was collected using the Technobis Crystal16 platform which measures the turbidity of solute in various solvents at varying temperature ranges. The outcomes of the experimental dataset can be used as the response variable (training set) in the Random Forest model and divided into three categories of highly soluble, soluble and completely insoluble at a certain set temperature. The predictors for the random forest model consisted of a set of 2-D and 3-D molecular descriptors which were calculated using MOE software from Chemical Computing Group.

The random forest classification model was trained using both the 200 calculated molecular descriptors and the training dataset. A multidimensional scaling of proximity matrix was plotted which showed three distinctive zones indicating Highly Soluble, Soluble and Completely Insoluble. The predictive accuracy of the trained model was noted. Mean decrease in accuracy of a variable was also determined which indicated which molecular descriptors were more important for the classification of the data. The predictive accuracy of the random forest model was tested by removing some of the outcomes in the training dataset, followed by rebuilding the model and then subsequent prediction of their outcomes which resulted in the similar predictive accuracy as the older model.

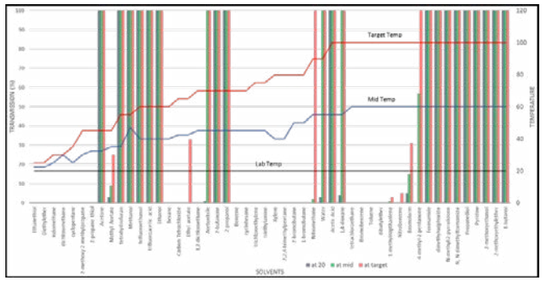


Figure 20. Experimental outcome for Paracetamol indicating the three outcomes: 1) Highly Soluble 2) Soluble 3) Completely Insoluble

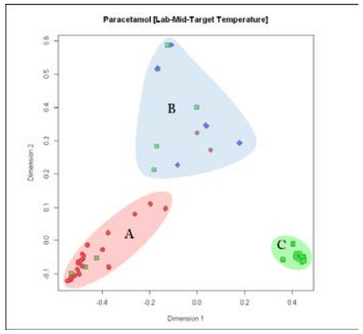


Figure 21. Multidimensional Scaling Plot in Random forest showing classification into three distinct zones of 'Completely Insoluble' indicated by Red circle, 'Highly Soluble' indicated by the Green circle and 'Soluble' indicated by the Blue circle.

Breiman L, (2001) **Random Forest** Statistics Department, University of California, Berkeley Vol. 5-32 pg. 45 [Accessed: 7th August 2015] [Available at: http://link.springer.com/article/10.1023%2FA%3A1010933404324]

Research Case Studies

Manufacturing Operations and Supply Chain Management Challenges in Continuous Manufacturing

Academic:
Dr Jagjit Singh Srai

Researchers:
Dr Tomás Harrington
Dr Ettore Settanni
Mark Phillips

This research explores possibilities to align future value network configurations and disruptive shifts in manufacturing and information technologies (e.g. digitalisation, continuous manufacturing) to enable novel routes to medicines production, and deliver added value to 'end-users', i.e. payers and patients. While evidence exists that continuous processing delivers financial benefits for single-purpose plants, a business case for transformation assessing the resultant impact across the end-to-end (E2E) value chain is needed for such a technology to be better understood and quantified, and for the upstream and downstream linkages to emerging continuous process technologies (e.g. in synthesis and work-up, filtration, drying, secondary processing) to be effectively exploited.

To assess value network reconfiguration opportunities enabled by targeted technology interventions a 4-step approach[1] developed as part of this research at Cambridge is applied to explore opportunities with respect to new and established markets where interventions in continuous crystallisation and adjacent unit operations may create attractive value network opportunities.

[1] Srai, J.S., Harrington, T.S., Alinaghian, L.S., Phillips, M.A. (2015) 'Evaluating the potential for the continuous processing of pharmaceutical products - a supply network perspective', Chem. Eng. Process., Vol. 97, pp. 248-258.

Manufacturing Operations and Supply Chain Management Challenges in Continuous Manufacturing

Pre-screening In the case of more established generic products, we often choose to examine traditional batch processing routes that may be considered uneconomical in delivering on future requirements and changing markets. As part of CMAC phase II activities (see pages 40-41), paracetamol was selected as a case demonstrator.

Current state mapping and future state models The proposed approach extends prior work on industrial systems analysis and supply chain mapping techniques, and provides a characterisation and visualisation of the 'current state' for the candidate drug product, in terms of unit operations and the supply network. This mapping exercise scopes out those unit operations where an existing batch production process may be amenable to a series of continuous technologies, in terms of current state and future potential. It is estimated that up to 80% of production, currently located in India, may remain via a p-nitrochlorobenzene (PNCB) batch route. Opportunities were identified in the areas of inventory, flexibility (both mix and volume), process control, sustainability, and quality (purity), and future state scenarios for processes technologies and network configurations were derived accordingly.

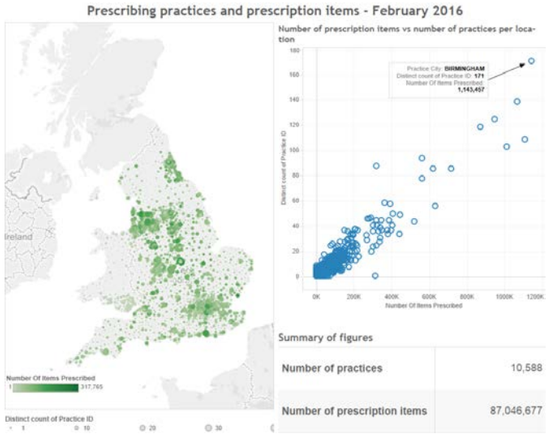


Figure 24. Tableau – data visualisation and statistical analysis

Figure 22. Supply Chain Guru – Network Design and Optimisation

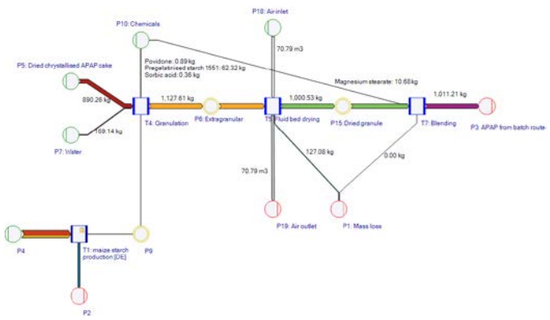


Figure 23. Umberto – Sustainability assessment, material and energy flow cost analysis

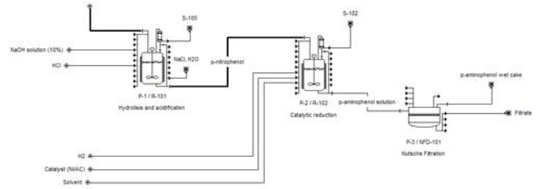


Figure 25. SuperPro Designer – Manufacturing Operations modelling

An E2E assessment of benefits and emerging patterns is carried out in a variety of product/delivery/patient scenarios. Key to this our capability to model complex systems, using Cambridge's Network Design Process Laboratory suite of tools.

Building the business case for transformation Finally, we build the business case for transformation. This involves integrating (1) outputs from the previous steps, (2) business context and viability considerations - balancing the transformation versus the investments required (potential impact on revenue, margin, inventory reduction), informed by key economic evaluation criteria in terms of batch versus continuous (direct fixed capital, plant throughput, manufacturing cost, unit production cost), and (3) technology readiness inputs (from supporting technology roadmaps and specific technology interventions with realistic timescales). Growing demand may contribute to an attractive batch-to-continuous transformation agenda in certain scenarios (e.g. a move to more localised and market/country-specific supply) where continuous crystallisation may support smaller plant footprints, with associated capital cost reductions.

Research Case Studies

A Made to Order Processing Plant

Academics:
Dr Ian Houson
Prof Alastair Florence

Researchers:
Dr Humera Siddique

Partners:
Perceptive Engineering
AstraZeneca
CPI
CMAC

The "Make To Order Processing Plants" (MOPPs[1]) project involving CMAC, CPI, AstraZeneca and led by Perceptive Engineering has the aim of designing a single, flexible control system software infrastructure and work process that will work across a whole range of equipment including reactors, crystallisers, spray driers. The same model predictive control system has been demonstrated on 1 continuous reactor (Corning Plate Reactor) at CPI and two continuous crystallisers (Nitech's DN15 and Cambridge Reactor Design's Rattlesnake) at CMAC. This case study will focus on the crystallisers.

[1] the MOPPs project team would like to thanks EPSRC and Innovate UK for funding (project no. 101334)

The team has systematically developed a continuous crystallisation process for lactose from an existing batch process maintaining or enhancing the crystal attributes. The use of in-line PAT (IR, UV, FBRM, Raman etc) provides real-time information and feedback that the model predictive control system (see Figure 26) uses to control the process variables. A robust, reliable crystallisation system has been developed that has been run in continuous mode for over 5 days.

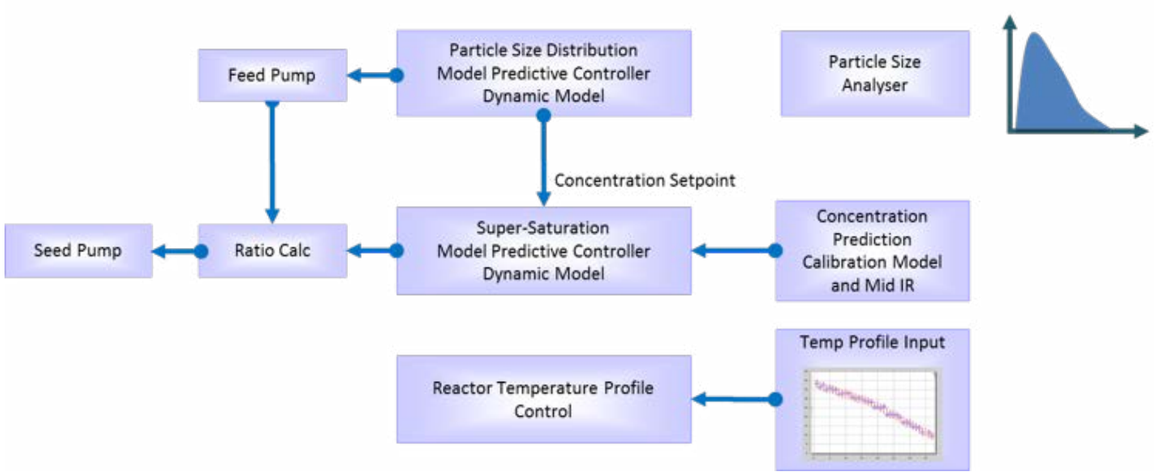


Figure 26. A control strategy for "Dial a Particle" in continuous crystallisation

Key benefits from the project are:

1. Proven ability to run for 5 days and 26% higher yield (vs batch) in continuous crystallisation => improved yield
2. 2 fold reduction in span of PSD vs stirred tank reactor => consistent & higher quality (Figure 27)
3. Reduction in Lactose crystallisation time from 16 hour to 5 hours => intensified process
4. Reduced manpower and waste requirements
5. 'Dial a Particle' capability achieved (Figure 28)
6. Advanced process control capable of controlling available Crystallisation platforms

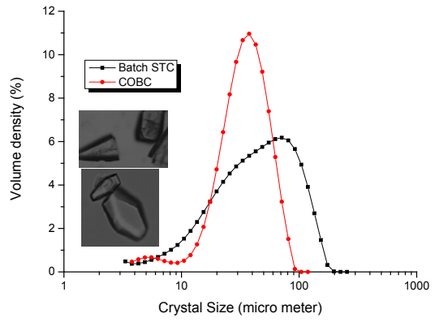


Figure 27. reduction in particle span in continuous crystallisation process

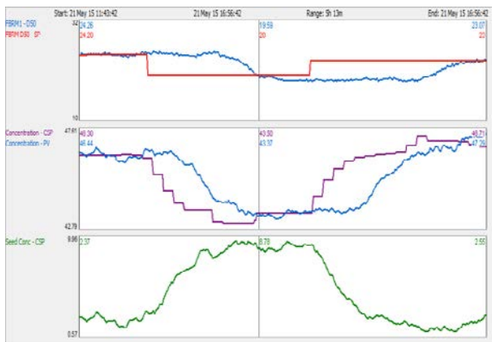


Figure 28. Dial a particle capability using model predictive control

Full characterisation of the hydrodynamics of the batch and continuous equipment has enabled seamless transfer from batch to continuous processes. Shear has been shown to be a particularly useful scale-independent factor for transfer between equipment. Developing process understanding within a model predictive control environment has been shown to deliver real control and enhanced product characteristics over the equivalent batch process.

The project has been such a success that CMAC has commissioned perceptive Engineering to install the control systems on 6 different platforms. Future research will focus on application of model predictive control to delivering consistent particles with variable raw material feed as well as impurity rejection during crystallisations. The National Facility will provide access to these platforms and control systems for companies to test and evaluate novel processes.

Research Case Studies

Industrial Placement: Development, Demonstration and Comparison of Two Continuous Crystallisers

Academic:
Prof Chris Rielly

AZ Supervisors:
Dr Helen Wheatcroft
Dr Anna Parsons

Researchers:
Iyke Onyemelukwe

Iyke Onyemelukwe, a final year DTC CMAC Research Student at Loughborough University, completed a 3 month industrial secondment with Dr Helen Wheatcroft and Dr Anna Parsons at AstraZeneca, Macclesfield in 2016. During this time, Iyke was able to investigate the continuous crystallisation of a number of live AZ projects, as well as continue his own PhD research.

A key outcome of the secondment was the successful development of a robust continuous Mixed-Suspension Mixed-Product Removal (MSMPR) Crystallisation platform (made up of a series of CSTRs) which incorporated both process analytical technology (PAT) to aid process monitoring, and an intermittent vacuum transfer system to overcome potential problems with the blockage of transfer lines. His experience working with the Crystallisation team gave Iyke real insight into the challenges of controlling particle attributes and isolating desired forms that are unique to each drug development project. As part of his work, Iyke developed an easy-to-use gCRYSTAL model of the MSMPR platform, and ran demonstrations for AZ staff. He also presented the findings of the investigations to the whole department, thus significantly enhancing the profile of continuous processing and crystallisation within Chemical Development at AstraZeneca.

In the course of his PhD, Iyke has focused on the application of oscillatory flow devices to continuous crystallisation processes, particularly the mesoscale Continuous Oscillatory Baffled Crystalliser (meso-COBC). A key part of his work has to do with the use of in-line PAT including FBRM, Raman, ATR-UV for process understanding, parameter estimation, and implementation of control strategies for continuous crystallisation.

Iyke particularly benefitted from his placement through training on extensive analytical capabilities and softwares at AZ, as well as understanding approaches and standardized SOPs used at AZ to rapidly develop reliable and robust crystallisation processes.

Statement from Anna Parsons, AZ Senior Process Engineer: "We got great value from hosting Iyke for a 3 month placement. He was able to use his experience of continuous crystallisation to make significant improvements to our lab scale MSMPR facility. He characterised the system using Glycine as a model compound and compared it to the COBC platform at Loughborough University. He was able to run two of our projects through the system to assess feasibility. We have gained an additional platform for crystallisation process development." Anna Parsons, AZ Senior Process Engineer

Industrial Placement: Development of an Engineering Mindset in Twin-Screw Granulation at GSK

Image: Twin-screw granulator set-up

Academic:
Prof Gavin Halbert

GSK Supervisor:
Dr. Richard Elkes

Researcher:
Laura Martinez-Marcos

Final year PhD student, Laura Martinez-Marcos, completed a 2 month industrial placement at GSK (R&D, Stevenage) under the supervision of Richard Elkes. This industrial project focused on the optimisation of twin-screw granulation (TSG) processes to understand the impact on growth behaviour and final particle attributes which are essential to deliver high quality medicines.

Evaluation of TSG processes from an engineering perspective:

- Optimisation of TSG processes and assessment of the impact of processing conditions on main particle attributes were performed
- Different engineering approaches were implemented and studied
- Successful results provided a deep understanding of the correlation between process variables, growth mechanisms involved and product attributes in the area of TSG
- A wide range of different off-line characterisation techniques were applied

A twin-screw granulator was used to perform the granulation experiments.

Different engineering approaches were applied to assess the impact of mechanical as well as processing conditions on granules particle size and homogeneity properties.

Next steps:
The level of understanding gained during this industrial placement will allow us to establish a robust design of space approach. This can be applied as a screening or selection tool in further TSG manufacturing processes based on the intermediate product requirements and specifications.

Reactive Crystallisation & Work Up Characterisations

Academics:
Prof Xiong-Wei Ni
Dr John Robertson

Researchers:
Meifen Jiang
Arabella Johnston

Characterisation of a Reactive Crystallisation

The reactive crystallisation of paracetamol is being studied to understand how to link reaction kinetics with crystallisation kinetics so that the reaction and crystallisation steps can successfully be combined into a single continuous process. The effect of how reaction kinetics and parameters could affect target crystal specifications will also be investigated. Paracetamol synthesis using the 4-aminophenol and acetic anhydride route has been chosen as the model because this reaction is significant in pharmaceutical industry. Process analytic tools are used to monitor concentrations of species, extract reaction kinetics and inform process design and operation.

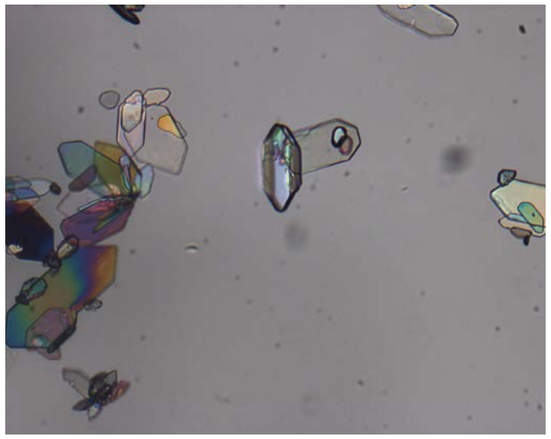


Image: Paracetamol crystals

Characterisation of Solid Dosing and Degassing in Work Up

The technological goal of this project is to establish operational and control protocols for a lab scale continuous work-up process. Firstly it investigates the operational principles, kinetics, and problems affecting accurate solid dosing in current batch systems. It also investigates solid dissolution rates in devices with either stationary or flow of solvents and it addresses the problem of the presence of minute gas bubbles in solvent feeds prior to the continuous crystalliser by degassing.

The initial model API/solvent is paracetamol in water/IPA. Three grades of paracetamol (micronised, powder and granules) will be investigated. The stationary system in this study is a stirred tank reactor and the flow systems consist of a twin screw extruder and a wet mill. Dissolution kinetics will be measured using in-line PAT and the data obtained will be used to design a prototype device for solid dosing.

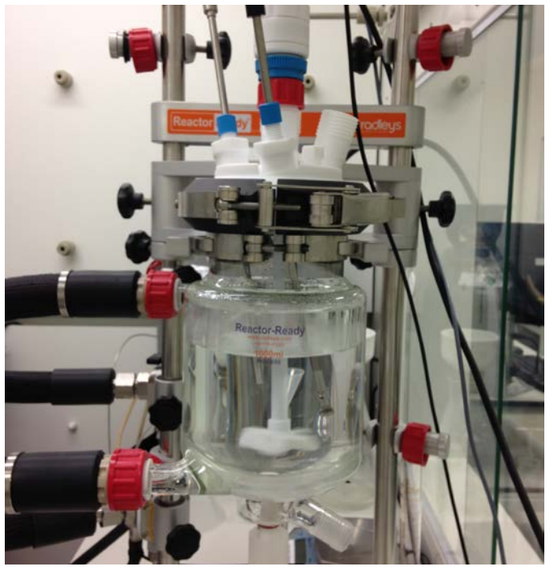


Image: Continuous work up

Scale-Up, Yield, Purity and Selectivity in the Continuous Production of Multi-Component Targets

Academics:
Professor C.C. Wilson
Professor Joop ter Horst
Dr Chris Price

Researchers:
Alexander J. P. Cousen
Ruth Lunt

Industrial and commercial interest in multi-component materials (MCMs), such as co-crystals, salts, solvates, etc., has recently increased dramatically. MCMs offer the opportunity to manipulate solid-state structure and hence deliver improved physicochemical properties.

Developing pharmaceutical MCMs relies on inclusion of a secondary (or ternary) component with Active Pharmaceutical Ingredient (API). However, controlling their solid-state form is not facile. MCMs can not only exhibit polymorphism, but also stoichiometric variations. Both phenomena must be appreciated during production to ensure selectivity towards the desired MCM form.

This case study presents previously un-demonstrated, selective preparation of the various stoichiometric forms of the oxalic acid : urea co-crystal model system, which can exhibit both 1:1 and 1:2 MCM solid forms. Preparation utilised low solvent mechanochemical and solvent-mediated (slurrying) methods.

Across all conditions implemented, the 1:2 phase is preferentially generated with starting material stoichiometric ratio of 1:2. However, with a 1:1 component ratio, selectivity towards the corresponding phase is not observed. Instead either no co-crystal formed or the 1:2 form is produced, depending upon the solvent environment utilised. Similar observations are seen through slurrying, providing further evidence of the importance of starting material stoichiometry in low solvent complexation methods. In addition to producing bulk stoichiometric selectivity, these mechanochemical methods offer a convenient pathway for generating phase pure seeds for directing improved selectivity in solution-based crystallisation methods.

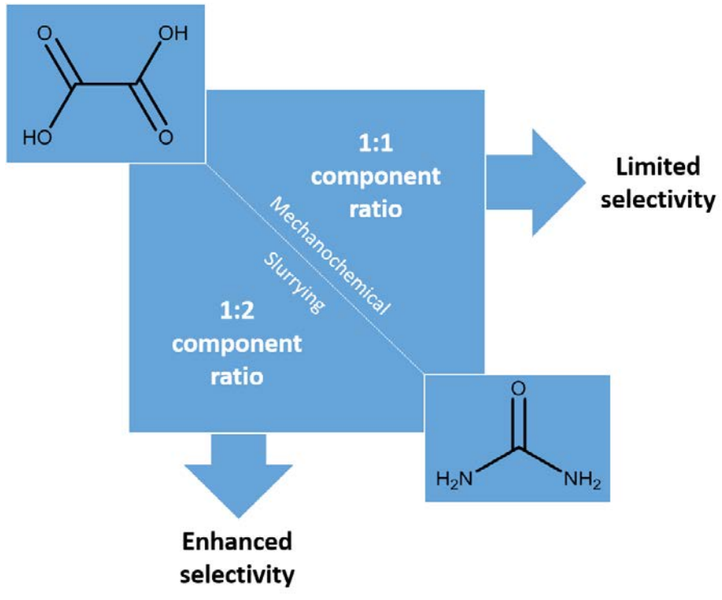


Figure 29. Selective Preparation of Oxalic Acid : Urea Co-crystal Model System

Seed Production via Wet Media Milling Approaches

Academics:
Professor Alastair Florence

Researchers:
Dr Cameron Brown
Bilal Ahmed

Wet media milling has a range of applications in continuous processing including seed generation, size reduction and particle property control. The aim of this work is to develop a better understanding of how particle attributes and process parameters interact to achieve consistent controllable processes. Some of the key drivers towards adopting wet milling technologies over dry milling include reduced cost, reduced crystal lattice deformation, reduced operator exposure and better process control.

Experimental evaluation of a toothed rotor-stator wet mill is demonstrated through applying an IKA MagicLAB in a recycle loop configuration coupled with a crystallisation unit. Manipulating milling conditions such as rotational speed (rpm), and number of teeth within each rotor-stator pair has consistently delivered small monodispersed particle sizes (20-50µm). Studies conducted on paracetamol, a brittle compound by nature, have given insight into the unique breakage mechanisms occurring within the mechanistic framework of the mill. Implementing a scaling energy dissipation rate term (E*) and Design of Experiments (DoE) approach through systematic experimental protocols have allowed for key milling factors at various recycles to control particle size and shape characteristics

A rotor-stator wet mill can be applied as an in-line batch and continuous seed generator with the ability to provide large seed surface areas for a growth-dominated continuous crystallisation process. Hence, the flexible nature of this approach can be incorporated through a semi-batch recycle loop or as a continuous in-situ nucleating device.

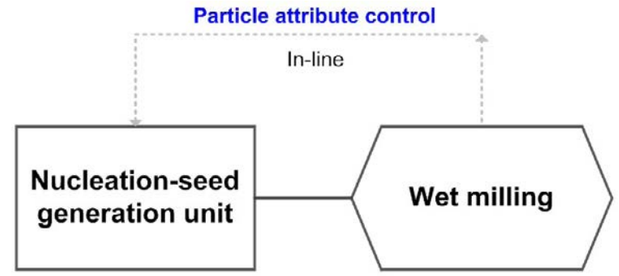
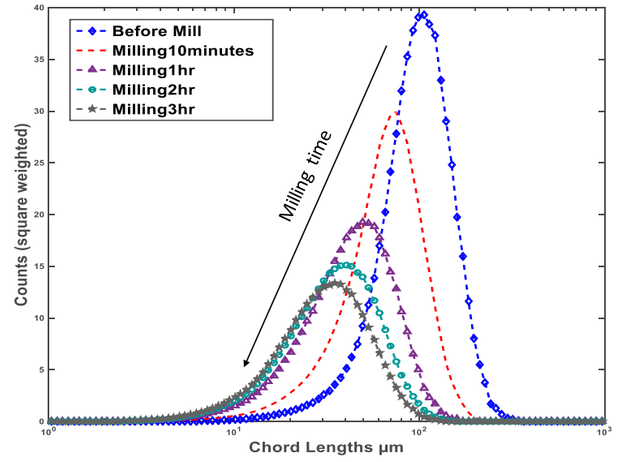
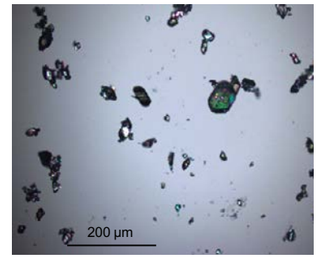


Fig. Fundamental understanding of in-line milling impact via recycle-loop mode





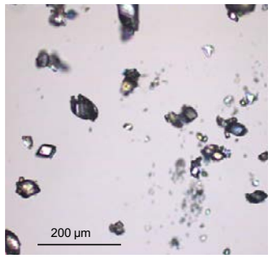


Figure 30. Seed Production

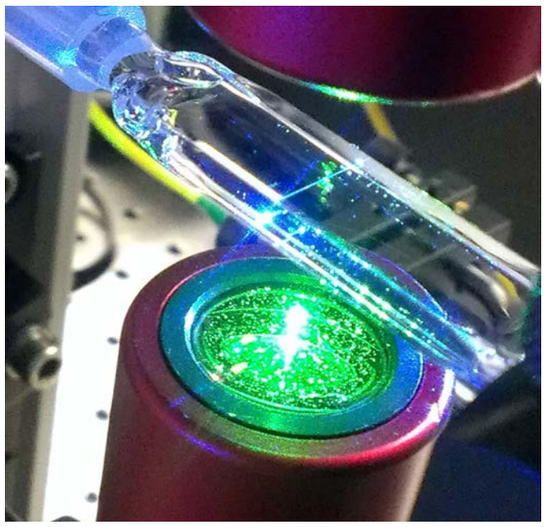
Laser-Induced Nucleation

Academics:
Professor Colin Pulham
Dr Andrew Alexander
Professor Jan Sefcik

Researchers:
Dr Nadeem Javid
Dr Martin Ward
Thomas Kendall

Manufacturing with Light

Through Manufacturing with Light we seek to revolutionise the use of light for manufacture of solid materials. Our project is exploring new techniques to induce nucleation under flow conditions, to control product particle attributes such as size, morphology and solid form (polymorph). We use short (nanoseconds) laser pulses to induce nucleation in metastable (e.g. supersaturated) fluids. Using light allows us to induce nucleation remotely—without the need for a seed—and to access fluid conditions that would be difficult to obtain by other methods. So far, laser induced nucleation of a wide range of substances has been demonstrated, from simple salts to proteins.



Laser Induced Nucleation in Continuous Crystallisation

Non-photochemical laser-induced nucleation (NPLIN) is a relatively new method of crystallisation that has demonstrated great potential in controlling polymorphism and the number of crystals formed. The biggest challenge to NPLIN being adopted as a viable crystallisation technique is that the mechanism is currently unknown. We aim to add new information that could aid in understanding how NPLIN works.

We demonstrate that nanofiltration of aqueous glycine solutions has a pronounced effect on laser-induced nucleation. Filtration of the solutions prior to irradiation greatly suppresses the nucleation efficiency, for all supersaturations studied. A clear effect of laser irradiation on crystal polymorphism was also observed in irradiated solutions at a lower supersaturation which exclusively yielded the α-polymorph at higher supersaturations there was significant presence of the γ-polymorph. On the other hand, non-irradiated solutions almost exclusively yielded α -polymorph of glycine at all supersaturations studied. These surprising results challenge some established ideas about laser-induced nucleation, showing that previously reported laser-induced nucleation phenomena in glycine aqueous solutions can be effectively suppressed by filtration, so that the underlying mechanism is unlikely to be based on molecular scale interactions involving just the solute and the solvent alone. Instead, laser-induced nucleation in this system appears to be related to either colloidal scale solution clusters or foreign solid or molecular impurities that can be removed by nanofiltration.

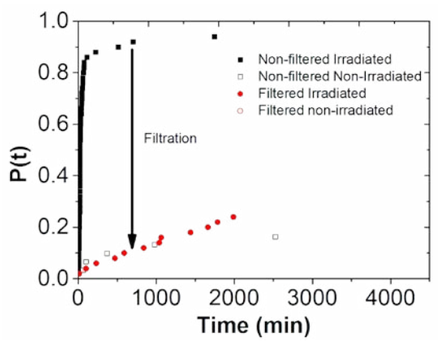


Figure 31. Effect of filtration on laser-induced nucleation

Start-Up Approaches to Continuous Manufacturing Processes

Academics:
Professor Joop H. Ter Horst

Researchers:
Dr René Steendam
Andrew Dunn

This project aims to provide strategies for continuous crystallisation start-up and steady state adjustments in complex multicomponent systems. The start-up period and adjustment of a continuous crystallisation process can take substantial time and thus valuable material, before the continuous process reaches steady state to produce product with the desired specifications. Deeper process understanding is needed to mitigate loss of valuable material during start-up and change of steady state. The start-up and steady state switching will become even more complex in complex multicomponent process mixtures, for instance in elaborate separations.

The system currently under study is that of L-asparagine monohydrate (L-asn.H2O) in water. The current work focuses on the preferential crystallisation of L-asn. H2O from a solution of DL-asn.H2O. Once preliminary experiments have been carried out using a single MSMPR crystallizer (shown in Figure 32), a coupled crystalliser set up will be used to preferentially crystallise both chiral forms. Subsequently, the effect of additives will be studied to determine what effect these have on the steady state e.g. time to steady state.

FBRM is being used is being used to monitor particle counts and chord length distribution, and give an indication that steady state has been achieved. Polarimetry is being used for concentration and enantiomeric excess determination. Calibration experiments on both concentration on the polarimeter, and enantiomeric excess have already been completed with further calibration experiments on temperature still to be carried out.

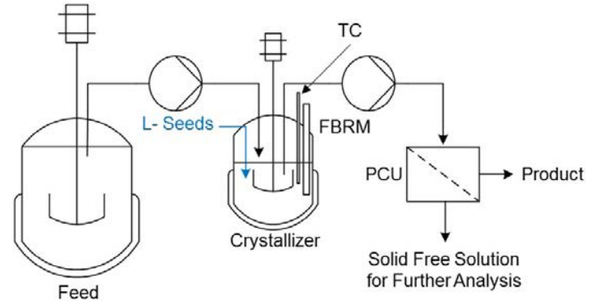


Figure 32. Crystalliser set-up

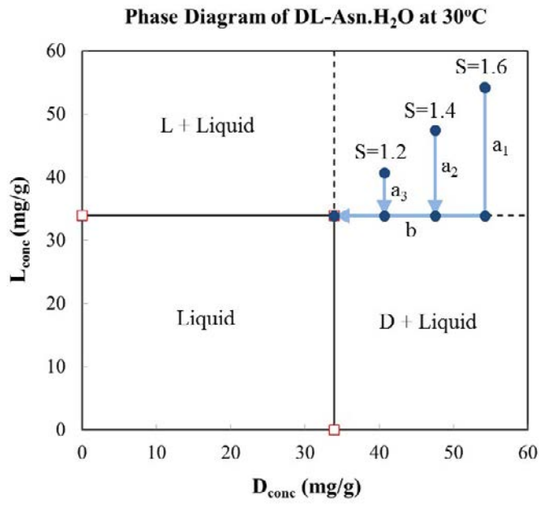


Figure 33. Operation of preferential crystallization in single vessel (a_1, a_2, a_3) and coupled vessel ($a_{1,2,3}$ + b) setups

Research Case Studies

Continuous Manufacture of Chiral Crystals

Academics:
Professor Joop H. Ter Horst

Researchers:
Dr René Steendam
Andrew Dunn

Separations involving chiral pharmaceutical compounds are increasingly important in industry. Chiral molecules are mirror-symmetrical molecules which, like hands, cannot be superimposed onto each other (Figure 34a). The biological activity of left- and right-handed molecules can be completely different. For example, (S,S)-ethambutol is used to treat tuberculosis whereas its mirror image causes blindness. The separation of such chiral compounds is a challenge because the physical properties of chiral molecules are the same.

This project integrates a reaction and a crystallisation process to continuously manufacture only one of the two crystalline chiral forms. Our approach involves continuous cooling crystallisation of a racemising (i.e. in solution, the left- and right-handed forms interchange) feed solution (Figure 34b). At start up, the crystalliser is seeded with only one chiral form. To control the crystallisation of only this desired form, we exploit the racemisation reaction and secondary nucleation to prevent primary nucleation of the unwanted chiral form. In this way, continuous crystallisation will proceed to give more crystals of the seeded chiral form through secondary nucleation.

We could maintain a steady state over the course of days in which crystals of the model compound could be produced continuously with high chiral purity (Figure 35a) allowing us to study the effect of process parameters on the chiral outcome of the experiment. We found increasing the residence time and suspension density has a positive effect on the chiral purity (i.e. cee) of the product (Figure 35b).

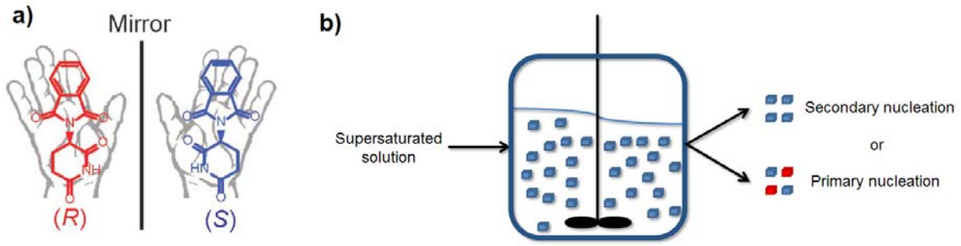


Figure 34. a) Chirality or "handedness" of molecules; b) Cooling crystallisation where desired chiral form is produced

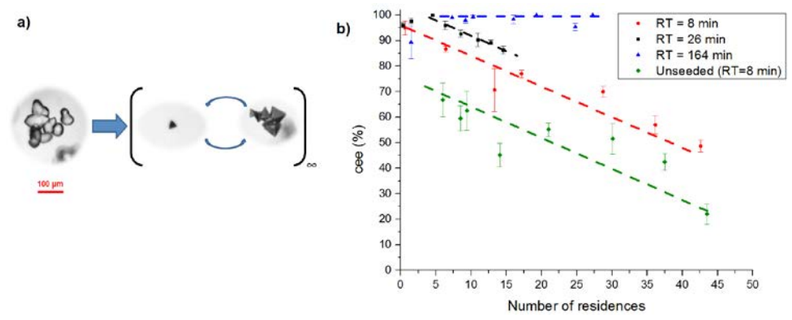


Figure 35. a)Producing a crystal with high chiral purity b)Effect of residence time and suspension density on chiral purity

Research Case Studies

Continuous Antisolvent Crystallisation of a Multi-Component System

Academics:
Professor Jan Sefcik

Researchers:
Dr Pól MacFhionnghaile
John McGinty
Vaclav Svoboda

Multi-component systems include salts, co-crystals, solid solutions and solvates. These can be used to modify physical properties of APIs, however, the manufacturing process is complex. This project has investigated producing solid solutions and co-crystals using antisolvent crystallisation in a continuous platform, with the focus on producing the desired solid forms. Antisolvent crystallisation of multi-component systems involves solutions of at least four components with multiple potential solid phases. This makes solvent selection both highly important and less straightforward. The work demonstrates control of a continuous nucleation process by achieving consistent solid phase crystallisation.

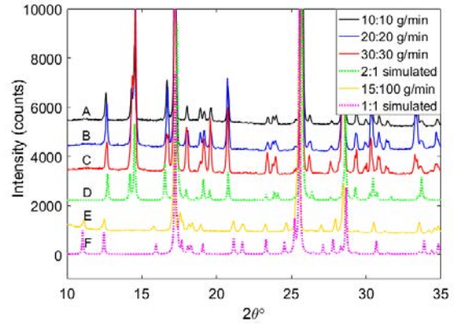


Figure 36. XRPD verification of solid phases

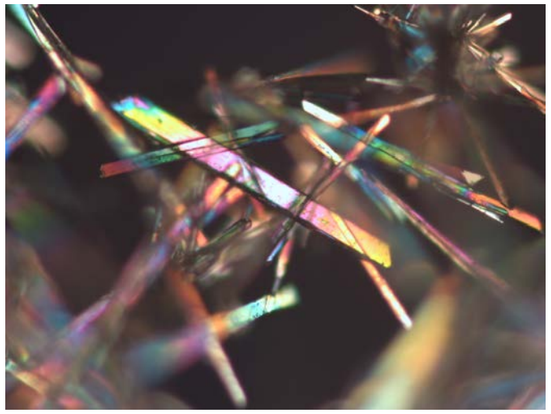


Image: Microscope image of 2:1 co-crystals

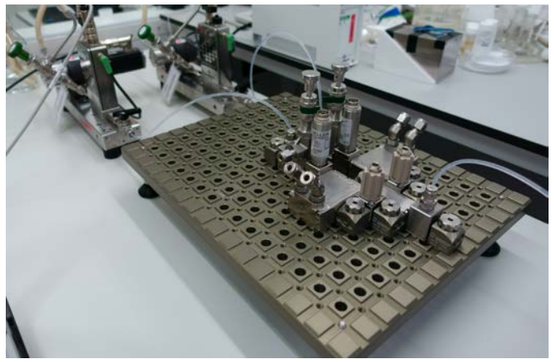


Image: Ehrfeld modular micro-reaction system

The process development within this project utilised a Design of Experiments vial screening approach to find suitable conditions for continuous crystallisation. The factors examined were yield, solid phase, induction time and flow properties. With well controlled flow rates and rapid mixing, continuous antisolvent crystallisation can generate consistent supersaturation. Steady supersaturation is the key to delivering control over solid phase and particle properties. The continuous setup has also demonstrated control of antisolvent crystallisation to selectively produce various stoichiometric ratios (2:1 and 1:1) of the model co-crystal.

Research Case Studies

Improved Manufacture of a Melt-Cast Explosive

Academics:
Professor Colin R. Pulham

Researchers:
Paul L. Coster
Daniel W. Ward

The development of insensitive munitions that are less susceptible to accidental initiation and hence increase safety is an area of major interest. One candidate material is 2,4-dinitroanisole (DNAN). DNAN is attracting significant interest as a replacement for the commonly used trinitrotoluene (TNT) in melt-cast formulations on account of the dramatic sensitivity improvements demonstrated during qualification testing. Despite DNAN-based formulations already being in use, there remains several issues associated with the replacement of TNT by DNAN. These include the thermal behaviour of pure DNAN and DNAN-based formulations. In particular, temperature-cycling experiments on DNAN-containing compositions have demonstrated irreversible volume increases of up to 15% with potentially deleterious consequences. One potential cause of this volume increase is the polymorphic transition from form-II to form-III that occurs at 266 K in pure DNAN. Repeated cycling across this transition is believed to disrupt the packing of microcrystallites, either as a result of the anisotropic expansion and contraction of the unit cell, or through some form of "ratchet" mechanism.

By looking at the relative crystal structures of DNAN form-II and form-III it can be observed that there is a jump in the β-monoclinic angle, a decrease in the unit cell volume and an ordering of disordered nitro- groups that are present in form-II. Our current working hypothesis is that the ordering of the nitro groups occurs when the unit cell volume decreases – which occurs as a function of decreasing temperature. At this point DNAN-II will fully convert to DNAN-III. Hence by introducing more space into the structure the disorder will be able to persist to lower temperatures therefore suppressing the polymorphic transition. We are currently achieving this by substituting dopants directly into the crystal lattice of DNAN. These dopants have slightly smaller molecular volumes and therefore provide more space within the crystal lattice. It follows therefore that increasing the amount of dopant will provide more space within the crystal structure and further suppress the transition. This proved to be true. Introducing 5 mole% of 2,4-dinitrotoluene suppresses this II-III transition to below 240 K. Increasing the dopant level to 10 mole% further suppresses the transition to below 220 K.

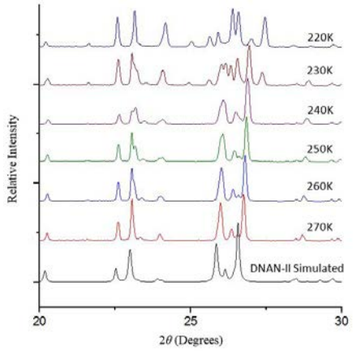


Figure 37. VT-PXRD for DNAN doped with 5 mole% 2,4-dinitrotoluene showing the II-III transition occurring below 240 K. The same transition usually occurs at 266 K in undoped DNAN.

Furthermore, when doped with 5 mole% dinitrotoluene, pellets of doped DNAN showed no sign of irreversible expansion when repeatedly cycled (40 cycles) in the temperature range from 260-274 K. In contrast, the undoped sample showed significant radial expansion when cycled under the same heating and cooling regime.

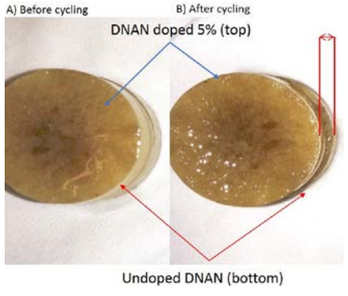


Figure 38. Images of doped (5 mole% 2,4-dinitrotoluene, top) and undoped (bottom) pellets of DNAN after thermal cycling, showing substantial difference in expansion of undoped sample

Our most recent exciting result shows that a new additive present at a level of 5 mole% completely inhibits the II-III transition over the entire operational temperature range. This has significant implications for the manufacture and processing of DNAN, as well as for the ultimate safety of DNAN-containing formulations. These studies have also provided valuable insight into nucleation and crystallisation processes encountered in melt systems.

Research Case Studies

Growth & Morphology Control

Academics:
Professor Chick Wilson
Professor Zoltan Nagy

Researchers:
Dr Karen Robertson
Dr Elena Simone
Dr Thomas McGlone
Lauren Agnew
Alex Cousen
Anneke Klapwijk
Ruth Lunt

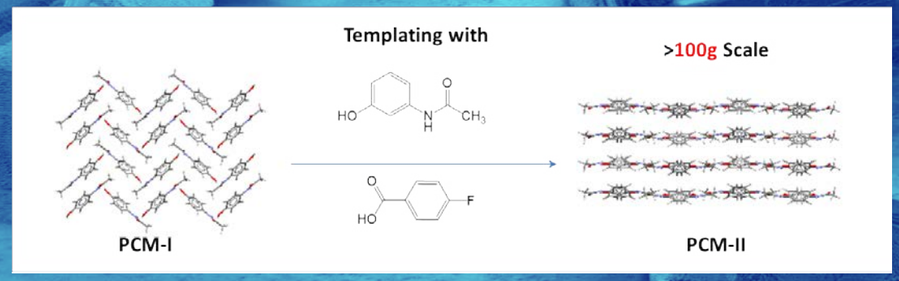


Figure 39. Templating strategy to produce PCM form II

Control over particle attributes such as crystal morphology is critical for the function and properties of materials produced in crystalline form and for the ease of their downstream processing. There are several strategies that address this challenge.

Templating

Lauren Agnew has developed a novel method of targeting metastable paracetamol form II (PCM-II) by using a templating molecule. A template is a molecule that forces the adoption of a particular polymorphic form of an active pharmaceutical ingredient (API) without itself being present in the final crystal structure. The Wilson group has shown we can template metastable paracetamol form II with a variety of benzoic acid derivatives in an evaporative crystallisation environment. This work uses metacetamol as a templating molecule to the scale of the production of PCM-II to volumes as high as 800 ml. This scaled up batch crystallisation was performed in the Mettler Toledo OptiMax CMAC instrument at the CMAC National Facility and then transferred to a continuous COBC set up at Bath. The product of these continuous runs is predominantly PCM-II (importantly, there are no traces of PCM-I in the product), although there remains a small quantity of a second crystalline phase (metacetamol hydrate, recently identified within CMAC by Pulham et al). Current work is thus looking to optimise this process.

Additives

The relative growth rates of individual faces of crystals can be influenced by a number of external factors such as the choice of solvent, mixing conditions and the presence of impurities/additives. This affects the shape of the crystals that are formed. Anneke Klapwijk has studied the effect of a polymeric additive, Pluronic P123, on the crystal morphology of succinic acid crystallised from water. See Tuning crystal morphology of succinic acid using a polymer additive (Klapwijk et al., 2016) page 46 and page 80.

Multi-Component Continuous Crystallisation

Polymorphism is the ability of a molecule to crystallise in more than one distinct packing arrangement in the solid state, with different polymorphs often displaying markedly different physicochemical properties. Co-crystallisation is commonly used to enhance physical properties of APIs; targeting polymorphic forms of these co-crystals can provide further enhancement, an area that has been largely unexplored. Dr Kate Wittering and Dr Ali Saleemi studied the polymorphic multi-component system urea-barbituric acid (UBA), in which the solubility of the target barbituric acid precursor is enhanced. High yield, high volume runs have been achieved in the DN15 COBC, and optimised for the selective production of UBA Form I (verified by PXRD). This was the first fully selective continuous scaled-up crystallisation of a polymorphic multi-component system and was a CMAC breakthrough. Further work by Ruth Lunt will investigate seeding strategies to directly access UBA Form III.

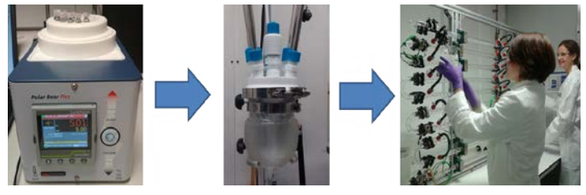


Figure 40. Scale-up of urea-barbituric acid crystallisation from small scale cooling crystallisation in the PolarBear (Cambridge Reactor Design) through to continuous crystallisation using the COBC.

Disorder and Additive Control of Solid Form and Morphology in Continuous Crystallisation

Academics:
Professor Chick Wilson
Professor Zoltan Nagy

Bayer Supervisors:
Dr Wolfgang Beckmann
Dr Michal Sowa
Dr Guillaume Levilain
Dr Britta Olenik

Researchers:
Anneke Klapwijk
Dr Elena Simone

Control over particle attributes is critical in determining the function and properties of materials produced in crystalline form. This in turn affects ease of downstream processing. For example plate shaped crystals often show poor filtration properties due to their tendency to pack as an impermeable layer on the filter media whereas block-like crystals may filter more easily.

The relative growth rates of individual faces of crystals can be influenced by factors such as solvent choice, mixing conditions and the presence of impurities. Impurities may disrupt crystal growth by adsorbing onto and inhibiting growth on crystal faces. Impurities added deliberately to engineer the growth of crystals are known as additives.

The effect of a polymeric additive, Pluronic P123, on the crystal morphology of succinic acid crystallised from water has been studied at scales from 3 ml to 350 ml using PAT to monitor the crystallisation. Succinic acid displayed a plate-like morphology when crystallised from water. Crystallising in the presence of low concentrations of polymer additive produced block-like morphology at both scales (Figure 41). Increasing the concentration of additive or succinic acid tended to produce less favourable needle-like crystals. Despite the large change in crystal shape, the succinic acid adopted the same polymorphic solid form under all conditions.

The change in morphology suggests that growth perpendicular to the side faces of the crystals is being inhibited by the additive. SEM imaging and face-indexing using single crystal X-ray diffraction (Figure 42) allowed a mechanism to be proposed based on the correlation of the inhibition of face growth with interactions of the succinic acid CH_2 groups. Further studies confirmed that the hydrophobic polypropylene glycol (PPG) block of the polymer interacts with the CH_2 groups and inhibits growth in the direction perpendicular to the hydrophobic (111) and (1-11) faces resulting in a block-like morphology. This supports an observation of an optimal concentration range in which the favourable morphology can be obtained, which is broadened when just the hydrophobic PPG is used as an additive.

Initial steps have been taken to transfer the system into the continuous environment. The additive-modified morphology has successfully been reproduced in the continuous oscillatory baffled crystalliser, the first example of polymer additive control of morphology in a continuous crystallisation process, while other studies have involved crystallisation under segmented flow conditions.

Klapwijk, A. R.; Simone, E.; Nagy, Z. K.; Wilson, C. C., Tuning crystal morphology of succinic acid using a polymer additive. Crystal Growth & Design 2016.

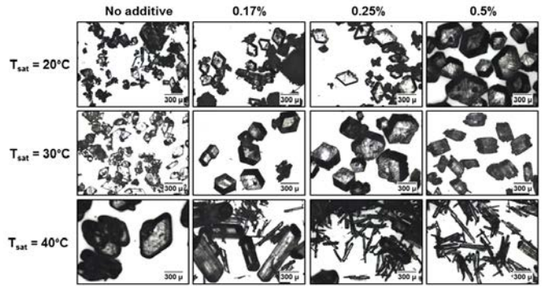


Figure 41. Morphologies of succinic acid with polymeric additive, pluronic P123 in various amounts

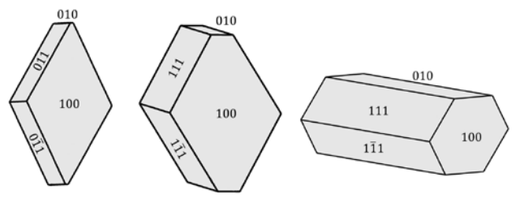


Figure 42. Crystal faces were indexed using single crystal X-ray diffraction to understand which functional groups are present on the surface of the crystal faces.

Development of Sono-Mechanical Processes to Enhance Product Purity in Continuous Crystallisation

Academics:
Dr Chris Price
Dr Richard O'Leary

Researchers:
Clarissa Forbes
Thai Nguyen
Layla Mir Bruce

The objective of this research is to develop a novel sono-crystallisation process that exploits ultrasound in order to improve product purity, yield and process velocity through precise and active intervention in molecular processes at growth surfaces to remove impurities from the surfaces of crystals. It will attempt to determine the optimal ultrasonic intervention to displace impurities from growing crystal surfaces whilst minimising the disruption to the growth process. In order to design and construct the ultrasonic transducer for single crystal growth cell, rapid prototyping approaches will be deployed and acoustic field modelling will be carried out with PZFlex, a finite element analysis software package. As illustrated below (Figure 43), by building a model of a particular geometry, the acoustic pressure can be simulated and a pressure field map is obtained. Then, a scale up strategy for bulk crystallisation will be developed by linking the single crystal growth and suspension crystallisation process understanding derived by experimentation. This will allow a mechanistic model to be built and will provide a platform to design and build prototype ultrasonic crystallisation systems to apply the same intervention in other platforms. The development of a novel continuous sonocrystallisation process is expected to deliver both significant time and cost savings for industrial crystallisation processes.

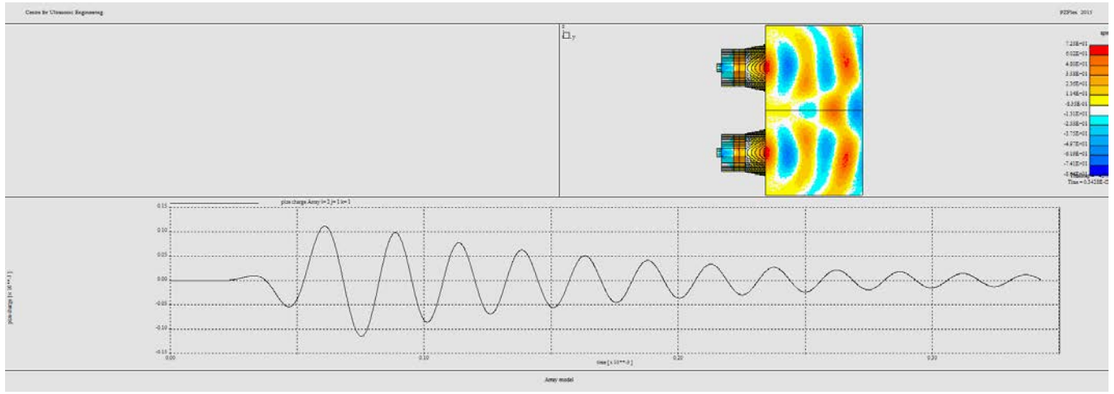


Figure 43. Acoustic simulation of an ultrasonic transducer array

Understanding Fouling Mechanisms in Continuous Crystallisation Processes

Academics:
Professor Alastair Florence

Researchers:
Dr Cameron Brown
Dr Nadeem Javid
Fraser Mabbott

The importance of mitigating or preventing fouling within continuous crystallisation campaigns is significant as it allows extended operation periods and the achievement of a crystalline product with desired properties including specified yield, polymorphic form and crystal habit.

Mechanistic understanding of fouling within a continuous crystallisation process is limited (Vendel and Rasmuson 2000). Process understanding considerations within continuous process operations should extend to include fouling. This project investigates the effect of three main parameters on fouling: (1) influence of different solute/solvent systems (2) influence of hydrodynamics and (3) influence of different materials of construction (MOC). Batch and flow platforms to explore fouling have been set up in CMAC as part of this study.

A simple batch fouling set up was developed to explore the influence of supersaturation, hydrodynamics and MOCs upon fouling nature. Within this small-scale batch set up, an array of inexpensive HD webcams were employed to monitor each vial for nucleation and fouling events. MOC coupons made of either stainless steel 316L or PTFE were studied. These were agitated by a PTFE magnetic bar on a multi-position stir plate. Statistical design of experiments (DoE) was implemented and fouling was quantified in terms of mass deposits, area coverage and mass coverage over the first 10 minutes of fouling (Figure 44).

To explore the influence of continuous flow upon fouling in continuous crystallisation, a flow set up comprising a novel flow cell was developed in conjunction with Cambridge Reactor Design (CRD). This was used to explore the three parameters highlighted above and in addition to measure the impact of heat transfer (Figure 45).

The overall objective of this research is to use a DoE approach to determine which investigated parameters have the greatest influence upon fouling and, ultimately, enhance the understanding of fouling mechanisms in continuous crystallisation processes. This experimental approach has been successfully applied within the systematic workflow for continuous process design to identify high risk conditions where fouling is likely to occur, informing process design.

Vendel, M. and Å. C. Rasmuson (2000). “Initiation of Incrustation by Crystal Collision.” Chemical Engineering Research and Design 78(5): 749-755.

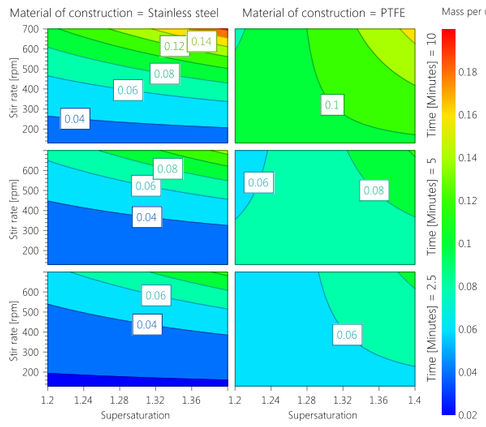


Figure 44. DOE response plot for all explored conditions with mass per unit area selected as model response

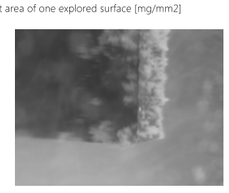


Image: Imaging study of fouling mechanism

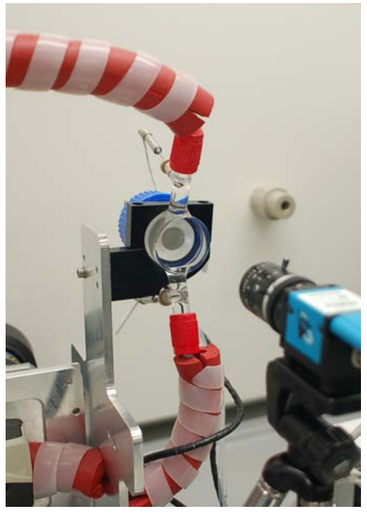


Figure 45. Image of the developed flow cell comprising an optical window for monitoring of the investigated MOC and incorporation of Pt100 sensors to monitor the efficiency of heat transfer

Exquisite Particles: Towards Predicting Agglomeration in APIs

Academics:
Professor Alastair Florence
Dr Ian Houson

Researcher:
Dr Cameron Brown

The Challenge

Along with nucleation and growth, agglomeration is a commonly occurring process in crystallisation operations. Agglomeration becomes an interesting process to control as, depending on the product requirements, it can be both desired and undesired. Undesired agglomeration can have drastic effects on product consistency. The entrainment of mother liquor and impurities between the primary particles of an agglomerate lead to diminished washing efficiency and lower final product purity. Furthermore, fragile agglomerates can break under the stress of filtration, resulting in blockage of filter medium. Whilst it is generally understood what drives agglomeration, quantification of that driving force and prediction of agglomeration behaviour is lacking. This lack of understanding in compounded by the difficulty in being able to regularly quantify the degree of agglomeration occurring.

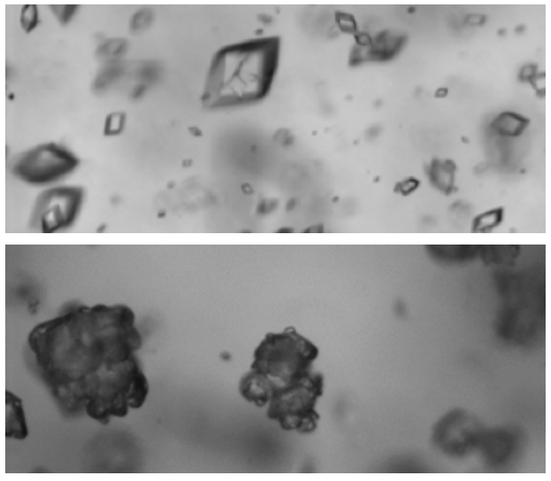


Figure 46. Unagglomerated (top) and heavily agglomerate (bottom) paracetamol crystals

The Technology

It is very easy for an individual to visually identify an agglomerated particle in comparison to a single crystal. However, manual segregation of every particle into agglomerates and single crystals would be incredibly tedious, time consuming and subject to bias. Whilst not 100% accurate, simple image analysis methods can lead to significant automation of the segregation process. Coupling this with in-situ time lapse images from the Mettler-Toledo PVM probe, trends of particle number, size, shape and transparency can be determined. These trends can then be semi-quantitatively linked to the agglomeration process.

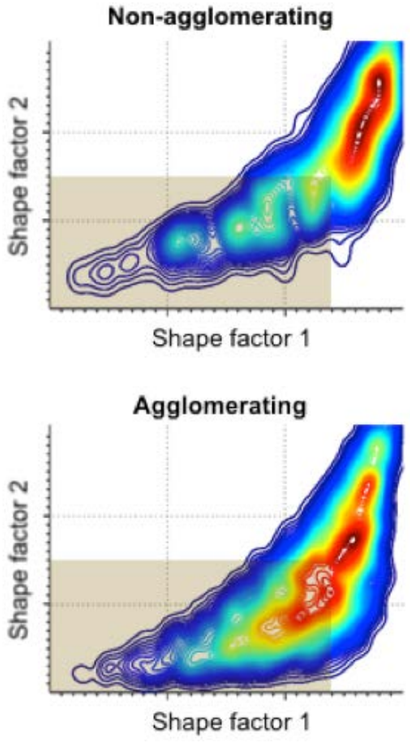


Figure 47. Population density plots of particle shape factors. Shaded area represents agglomerated particles

The Outcome

Agglomeration has been shown previously to be driven by a combination of physico-chemical and hydrodynamic processes. For active pharmaceutical ingredients such as paracetamol this is believed to be linked to the hydrogen bonding potential of the various functional groups on the crystal faces. As a result, the hydrogen bonding ability of the solvent used strongly influences the occurrence of agglomerates. A screening methodology was developed in which seed crystals of known concentration and size where allowed to agglomerate. Over the process in-situ images were recorded and analysed by the developed image analysis algorithms. The result of which was the classification of solvents into 3 classes: rapid agglomerating (‹ 2 min), agglomerating (› 8 min) and non-agglomerating. Agglomerating solvents were then subject to further tests covering a range of hydrodynamic conditions revealing that the solvents which showed rapid agglomeration where unaffected by increasing shear rates. In contrast to the agglomerating solvents demonstrated that the agglomeration process could be influenced by the shear rate, and in some cases prevented entirely.

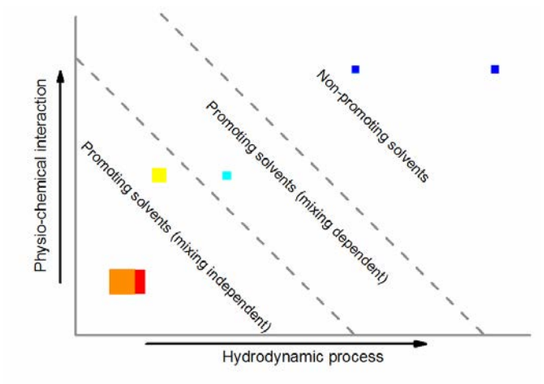


Figure 48. Conceivable solvent classification map. Symbols coloured based on shape factor 2 (red to blue – low shape factor 2 to high shape factor 2) and sized based on CED (larger symbol – higher CED)

The Impact

Presentation of results from this project along with training on the image analysis algorithms and general discussions on particle imaging have taken place at AstraZeneca, Macclesfield and GSK, Stevenage (with similar visits to Novartis and Bayer planned). This has led to a 3 month industrial placement of Francesca Perciballi at GSK, Stevenage, working on the implementation of the agglomeration screening methodology to an active ingredient.

Although developed initially solely for this project, the image analysis algorithms have grown into a set of programs bundled into the PVMA Toolbox (Particle Vision and Measurement Analysis), which has already seen use in projects at both AstraZeneca and GSK.

The outcome of this project has highlighted the importance of particle surface properties in driving agglomeration. To address this a follow up student project has been started which aims to characterise the surface of a number of seed particles from different production methods and relate these surface properties to the measured rates of agglomeration.

Acknowledgements

Thanks are given to all members of the Exquisite Particles steering committee for their help and financial support throughout the project.

Research Case Studies

Collaborative International Research Programme - Nanyang Technological University

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Dr Blair Johnston
Dr Iain Oswald
Dr Philipp Seib

Researchers:
Lauren Connor
Sebastion Davison
Thidarat Wongpinyochit

Crystal Engineering of Multicomponent Constructs and the Impact of High Pressure

This project investigates the formation of novel high density API-excipient constructs at high pressure and compare them with those assembled at ambient pressure. The constructs will be formed using Diamond Anvil Cells which enables the application of up to 10 GPa of pressure. Benzoic acid:nicotinamide, indomethacin:saccharin and lactide:API are currently under investigation. Single crystal X Ray diffraction analysis will be used to examine the effect of high pressure assembly.

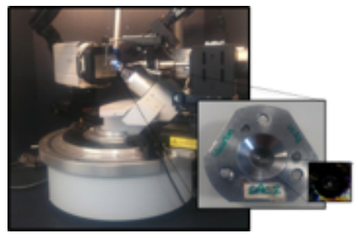

Figure 49. Diamond Anvil Cell on Diffractometer

Multicomponent Crystallisation in a Continuous Oscillatory Baffled Crystalliser

The suitability of the COBC platform for alternative crystallisation methods is being investigated. This presents an opportunity to exploit the unique mixing conditions this system offers and explore their effect on crystal products. A continuous antisolvent (drowning-out) crystallisation platform based on a COBC has been developed by the introduction of liquid in-line with the net flow of the feed solution. This liquid can be antisolvent, feed solution or a mixture depending on the mode of crystallisation and desired crystal attributes. This platform is currently under investigation by a single-addition setup to assess if it is viable for primary nucleation. Then multi-addition processes can be explored. Reactive crystallisation is also under consideration, as the platform does not require any significant modifications to achieve this. The entire setup is jacketed, which allows for the combination of cooling crystallisation with other techniques, which may prove more effective than using either in isolation.

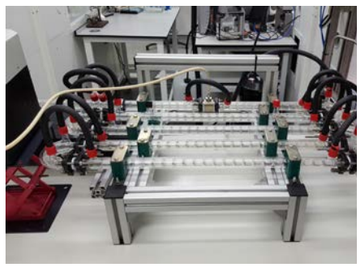

Image: Modified COBC set-up

Silk: A Biopolymer for Engineering Defined Nanomedicines

This project is investigating the interaction of silk with drug molecules and developing molecular simulation methods which can accurately model the experimentally determined structure/thermodynamic data for silk fibroin protein. The molecular dynamic simulation results will be compared to the experimental results. Moreover, silk nanoparticles are being experimentally prepared and used to study biodegradation in lysosomal enzymes and protease enzymes.

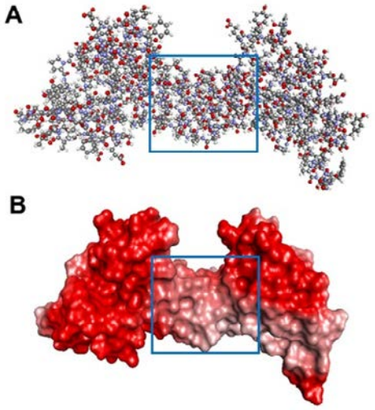

Figure 50. Determination of electrostatic potential of silk structure. (A) multidomain silk structure. (B) Electrostatic potential surface on the silk structure. The blue squares are crystalline regions of the silk structure.

NPL Scotland Hub: Pharmaceutical Metrology

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Prof Gavin Halbert
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Dr Dimitrios Lamprou
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* NPL academic

Pharmaceutical Innovative Manufacturing Metrologies (PIMMs)

Three joint CMAC-NPL projects are currently in progress with a focus on metrology and managing big data sets. See also page 57.

Managing Multiple Data Flows in Continuous Pharmaceutical Manufacturing: Fusion of Big Data Sets for Enhanced Product and Process Understanding and Control

Laboratories in industry and academia produce extraordinary amounts of files and data that require rigorous research and time costly analysis. For some analytical techniques such as in-line probes used for real time analysis of processes, direct manual analysis of the data is near impossible and automated methods are put in place to control these systems. This project will utilize newly developed and largely successful sections of the open source Berkeley Data Analytics Stack in an attempt to develop an easily scalable system to manage, store, search and analyse large data sets in real time. With particular focus on the fusion of different analytical data sets the vision is to apply machine learning approaches to enable the analysis of said "big" data sets and visualise them in a comprehensible and meaningful way. Currently the back-bone of the analytical framework has been set up and progress is made towards the analytical platform selected to be incorporated as an introductory-concept.

Metrology for Pharmaceutical Manufacturing: Understanding Activity From Surface Sub-microscale Chemistry

The aim of this project is to study, define and understand structure-property relationships in continuous pharmaceutical manufacturing processes and products, in order to forecast and control the final product performance. ToF-SIMS and 3D nano SIMS techniques will be applied to the problem. The spectroscopic identification of active ingredient, excipients, impurities and degradation products will also be used to explore the effect of processing and storage on particles' disposition in complex mixtures at the micron and submicron scale.

Image: TOFSIMS housed in the Wolfson Pharmaceutical Surfaces Laboratory

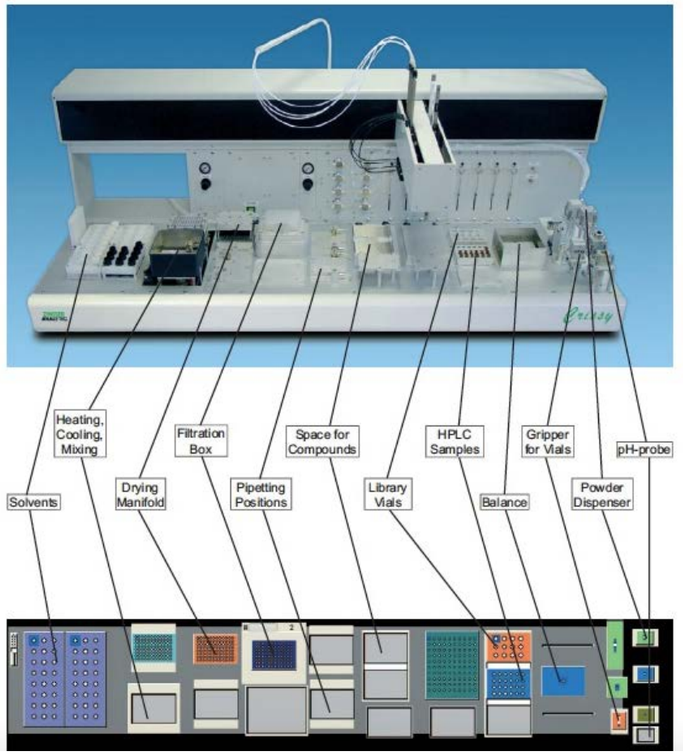

Figure 51. Crissy by Zinsser

Fabrication and Measurement of Nano-/micro-structured Surfaces for Nucleation/templating Studies Combined With Molecular Imaging

This project aims to deliver new insight into the interaction between surfaces, process operating conditions, and solutes for the purpose of delivering unparalleled control over the nucleation process. Crystallisation will be assessed from the vapour phase and from solution and the surface templates that will be studied in the first instance are metal substrates. The model compounds of interest will be the anti-convulsive drug carbamazepine and its structural analogues. Crystallisation from vapour will be investigated through a series of sublimation experiments. For the assessment of solution crystallisation, polymorph screening studies will be conducted using Crissy by Zinsser Analytic, a highly automated liquid and powder handling platform that enables the screening of a broad range of solvents and automates the crystallisation process using different solvents, concentrations, temperature gradients, agitation, and pH measurements

Modelling & Control of Crystallisation

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Professor Zoltan Nagy
Professor Xiong Wei Ni
Dr Brahim Benyahia
Dr Valerie Pinfield

Researchers:
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Dr Qinglin Su
Dr Ali Saleemi
Dr Anna Trybala
Dr Wei Li
Iyke Onyemelukwe
Emmanuel Kimuli
Dimitrios Fysikopoulos
Guillermo Jimeno Millor
Ravi Parekh
Louisa Ejim
Gurdeep Sagoo

CMAC has projects at Loughborough and Heriot Watt that use Computational Fluid Dynamics (CFD) modelling to improve process understanding for continuous crystallisation in several platforms.

Characterisation of Solid-Liquid Mixing in a Continuous Oscillatory Baffled Crystalliser Using CFD

At Heriot-Watt three approaches are being applied to collectively address the effects of the presence of gas bubbles and/or solid particles on global two/three phase mixing: a) pressure drop profile; b) pressure drop profiles with the presence of minute gas bubbles; c) mixing profile with the presence of solids.

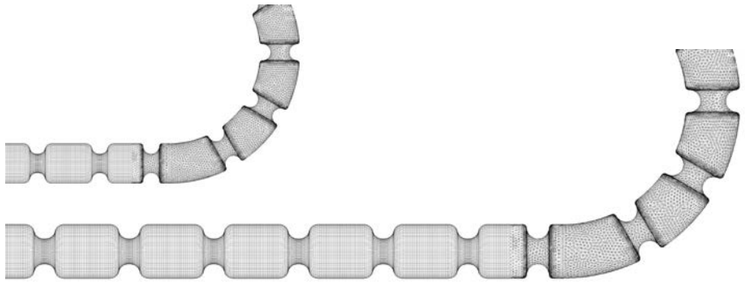

Figure 52. Characterisation of COBC

Model-Based Optimization of Continuous Crystallisation

The objective of this project is to develop an automated robust population balance model-based framework for modelling, parameter estimation and optimisation of continuous crystallisation processes. Hence, towards this direction a library of robust models has been developed that can be used for modelling and optimisation of crystallisation processes. However, the development of a model is only one part of the process, since virtually all mathematical models of chemical processes contain unknown parameters that have to be estimated from experimental data. Due to a number of factors (e.g. limited experimental data, correlation between the model parameters etc.) PBM models may contain more parameters than can be accurately identified from the available experimental data. Considering these challenges a novel approach has been proposed that incorporates hybrid non-convex optimisation model based approaches in conjunction with estimability and uncertainty analysis for the improvement of the current parameter estimation procedure. The framework was validated with experimental data and it was proven that although noisy data were used, the most influential and the least correlated parameters could be identified, providing sufficiently accurate inputs for the dynamic evolution of the crystal size and shape distribution in terms of model prediction capability.

Comparative Investigation of Continuous Crystallisation Approaches

The continuous crystallisation of α-Glycine in the mesoscale continuous oscillatory flow crystalliser has been developed at Loughborough, following the characterisation of the heat and mass transfer performance of the crystalliser. A novel camera technique was developed to measure the residence time distribution (RTD) of both liquid and solid phases in the crystalliser. Process understanding and investigation of various operating strategies was carried out with the aid of PAT tools and engineering equipment incorporated into the mesoscale oscillatory flow crystalliser such as ATR-UV, Raman, FBRM/Mastersizer, and the magicLAB homogeniser. A study of the Mixed-Suspension Mixed-Product Removal (MSMPR) Crystalliser was also carried out with the aid of PAT tools, with an intermittent vacuum transfer method implemented to solve transfer line blockage issues and enable the investigation of various operating conditions. The last stage of the project is to carry out a parameter estimation of crystallisation kinetic rates and use both steady-state and dynamic models of the crystallisers as a guide for determining the optimum operating conditions.

Coupled CFD/PBE Modelling of Continuous Crystallisation Processes

The aim of this research project is to develop CFD models for continuous crystallisation processes to analyse the flow fields and mixing patterns prior to applying population balance modelling to predict the effects of flow conditions on the crystallisation process. Detailed CFD simulations will allow in silico optimisation of the crystalliser geometry and operating conditions leading to narrower RTDs which in turn will lead to the consistent delivery of better crystal products. The next stage is to introduce detailed population balance equations within the CFD framework. This coupled model will help eliminate the assumptions made about the flow characteristics (either plug flow or completely mixed) in most existing crystallisation models therefore facilitating better process understanding that will capacitate the delivery of products possessing the desired critical quality attributes.

Multi-Objective Model Predictive Control (MPC) of an Integrated Continuous Crystallisation and Filtration Process

Process understanding and forward prediction can lead to better productivity and waste reduction in an effort to minimise production costs and lead-times of drugs to patients. This project focuses on moving a step closer to end-to-end process optimisation using a model-based predictive controller. A global linearisation method has been applied to a crystallisation process for supersaturation control. The resulting MPC performance shows effective supersaturation control for a batch and continuous crystallisation process. Robustness testing also shows the controller can effectively reject input uncertainties. Further investigations will involve more complex crystallisation kinetics, control of competing objectives (multi-objective) and laboratory implementation of the MPC controller to control a real process.

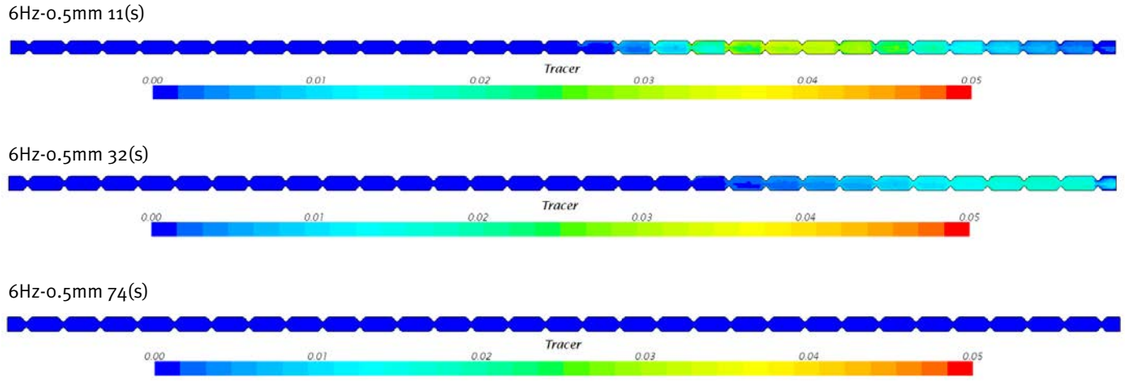

Figure 53. Contour plots showing the transportation of scalar through the fluid domain and the velocity profile

Novel Crystallisation Platforms

Academics:
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Prof Chick Wilson
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Researchers:
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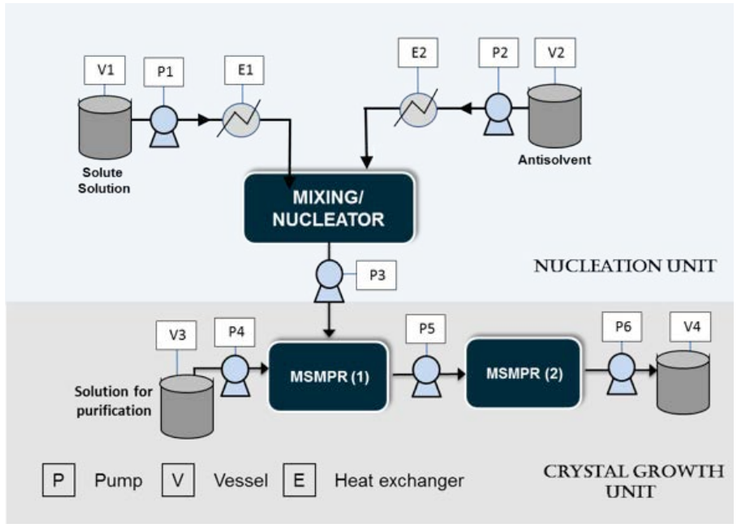
Dr Keddon Powell
Dr Anna Jawor- Baczynska
Dr Karen Robertson
Vishal Raval
Stephanie Yerdelen
Iyke Onyemelekwe
Louisa Ejim

Novel Nucleator Platform

The particle engineering research group under the supervision of Prof Jan Sefcik has designed and investigated a novel continuous seed production unit (nucleator) wherein the particles are formed by the rapid antisolvent crystallisation process, see Figure 54. The control of crystal nucleation kinetics is achieved by adjusting the mixing efficiency, solvent-antisolvent ratio, supersaturation and residence time. The generated seed crystals can be directly transferred to the next crystallisation unit (growth unit) for example Continuous Oscillatory Baffled Crystalliser (COBC) or Mixed Suspension, Mixed Product Removal (MSMPR) crystalliser where crystals are grown to desired size while required purification/isolation objectives for an incoming upstream feed are achieved.



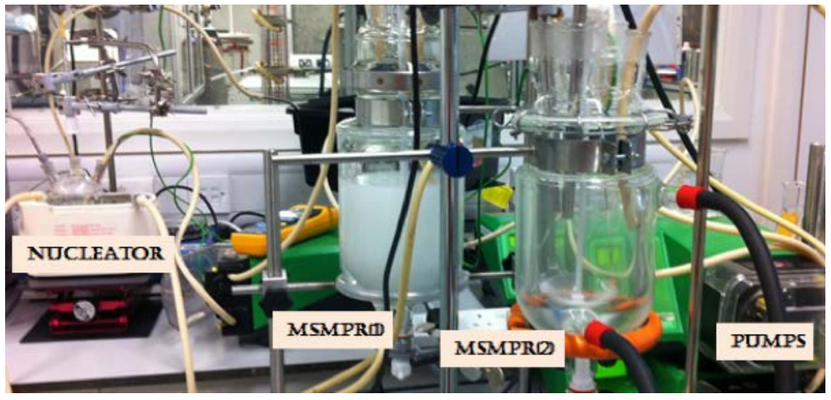
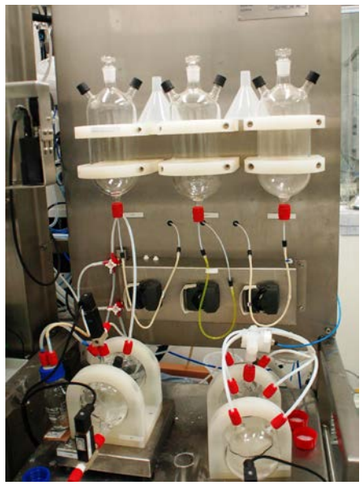


Figure 54. Continuous seed crystals generation (nucleator) followed by two-step MSMPR cascade.



MSMPR

A mixed suspension mixed product removal (MSMPR) crystalliser unit that avoids common problems encountered during continuous crystallisation such as fouling, encrustation and blockage of transfer lines has been developed at Loughborough. A novel periodic flow crystallisation operating strategy using a modified MSMPR crystalliser unit has been demonstrated to work effectively when tested on model pharmaceutical compounds paracetamol (PCM) and glycine (GLY). The periodic flow crystallisation method involves periodic transfer of slurry (addition and withdrawal) at high flow rates between several stirred tank vessels arranged in series. This type of operation involves alternating periods of true continuous and batch operations. The work also introduces for the first time, the concept of "state of controlled operation" instead of "steady-state operation" to describe the periodic flow crystallisation process. It is defined as a state of the system, which maintains itself despite transitory effects caused by periodic but controlled disruptions. State of controlled operation can characterize both continuous and periodic operation in MSMPR.

Image: MSMPR cascade

Moving Baffle- Oscillatory Baffled Crystallisers (MB-OBC)

The MB-OBC has been developed in CMAC by Vishal Raval et al at Strathclyde. It will now be used to make alpha Lactose monohydrate via a continuous process that integrates with filtration and drying. The work aims to successfully produce phase pure lactose particles with a narrow particle size distribution. The crystallisation process will be monitored via PAT (FBRM and ReactIR) alongside offline characterisation techniques (particle size distribution, X-ray powder diffraction for phase analysis and microscopy and HPLC for purity determination).

Image: MB-OBC

The KRAIC

The KRAIC has been developed as a flexible platform both for crystallisation and as a link to upstream elements of flow chemistry. It offers a range of reconfigurable inputs, mixing options and temperature regimes within the crystallisation process. The KRAIC has been designed, constructed and developed within CMAC by the Bath group, principally by Dr Karen Robertson, in partnership with Asynt (Cambridge) who have provided both design and construction input. By operating in segmented flow, the KRAIC offers complementary, smaller scale capabilities to those available from some other platforms within CMAC. Originally designed to operate with air-liquid segmentation, recent enhancement of the KRAIC, enabled by additional funding provided by RPIF, has allowed implementation of liquid-liquid segmentation. This offers improved consistency and performance on the flow crystallisation process. The KRAIC has been deployed on both single and multi-component systems, and is currently tackling target materials in the areas of polymorph and stoichiometry control, templating, and additive control of morphology.

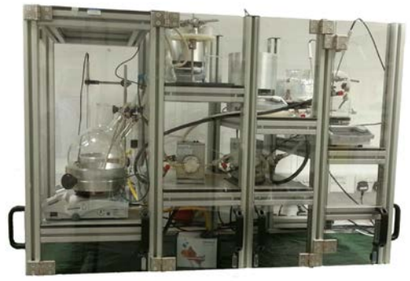


Image: KRAIC developed at Bath

Small Volume cSTR

The Bath group has also designed and constructed a continuous crystalliser based on a cascade of small-volume STRs in collaboration with Cambridge Reactor Design. Individual STR volumes are around 7-10 ml with an ingenious weir arrangement that harnesses gravity for transport between vessels negating the need for more pumps or a pressurised system. The BCCL cSTR offers a fully reconfigurable platform with a flexible number of STRs in series, and full temperature control over each section of the device.

Continuous Evaporative Crystallisation (CMEC) Platform

An entirely complementary approach to continuous has been taken in the membrane-mediated evaporative crystalliser (CMEC). Designed by the Bath group in collaboration with (and constructed by) ChemTrix BV (Netherlands), the CMEC offers a small scale solution in which solvent evaporation, rather than cooling, is used as the means to control nucleation and growth. The innovative design will allow a high level of process control to be achieved within an extremely compact arrangement. Although compact, the CMEC crystalliser offers a relatively large sample volume (diameter of flow channels 3 mm), and overall path length (2 m) in a compact device, 20 ×20 cm2 in area. The CMEC device should find particular use in cases where control of solvent behaviour is critical, including the production of solvates and hydrates, and adds a further capability within the CMAC continuous crystalliser portfolio.

Both the cSTR and CMEC platforms were fully funded from the CMAC RPIF award

Platform Development – DN10

To meet the challenges of scale down, a 10 mm platform has been designed and developed by Loughborough and Strathclyde researchers.

Key features of the new design include smooth periodic constrictions (SPCs) as opposed to sharp edged baffles for improved particle suspension, a staggered, angled arrangement of the tubular sections with customised jacketed bends for air bubble minimisation, spiral inserts in the cooling jackets to optimise heat transfer and direct connections with enhanced PAT ports to remove additional materials of construction exposed to the process fluid.

Practical operation within a fume cupboard includes a robust piston arrangement, incorporation of the Perceptive Engineering PharmMV control software and facile addition of in-line ATR UV probes. Non-invasive process monitoring via Raman and high resolution imaging will also be implemented. The fluid mixing conditions allow operation at relatively low flow rates and a reactor length of ca. 15 m provides a residence time in the range 1 – 1.5 h. The total working volume is ca. 1 litre. There is also the possibility of extending the system as the reactor has been designed to be completely modular.

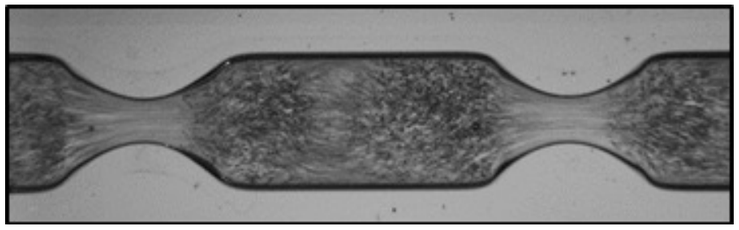
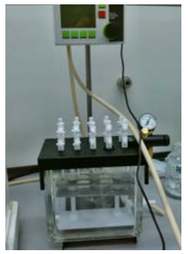


Image: DN10 Baffles

Image: DN10

Continuous Isolation Research Programme



Biotage filtration unit

CRD /GSK Automated platform

Rotary drum filtration unit

AWL CFD20 Carousel filtration unit

Academics:
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Dr Blair Johnston
Dr John Robertson

Researchers:
Dr Cameron Brown
Dr Nadeem Javid
Dr Murray Robertson
Sara Ottoboni
Bruce Wareham

The continuous isolation research program is focused on the assessment of filtration performance by using different filtration methods. Batch systems studied at CMAC include the Biotage and the CRD/ GSK filtration robot. Continuous filtration equipment under investigation are a bespoke rotary drum filtration prototype and the AWL CFD20 carousel filtration unit.

Cake filtration can be classified according to the slurry flow configuration as either dead end filtration or cross flow filtration. The Biotage, the robotic platform and the AWL CFD20 carousel unit operate in dead end filtration mode, while Rotary drum unit operates in cross flow filtration mode.

All four units are being evaluated by investigating the effect of crystal size distribution, solid loading and suspension properties and the choice of primary solvent and wash solvent. The flexibility of operation of the different units allows optimisation of operating parameters to be evaluated efficiently. A D-optimal design of experiment (DoE) is being used to design a suitable set of experiments to find out which quantitative and qualitative parameters determine filtration and wash time, cake purity, crystal agglomeration phenomena and solvent content after drying.

In order to reduce cost of pharmaceutical isolation linked to large scale solvent usage, supercritical CO_2 washing will be evaluated as an alternative to conventional drying.

An Ultra-Scale-Down Platform For Filtration

Academics:
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Prof Alastair Florence
Dr Andrea Rayat
Prof Mike Hoare

Researchers:
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Sara Ottoboni

The aim of this iCON project (see page 18) is to establish a high-throughput platform for the study of the recovery of crystallised APIs. Ultra scale-down methodologies will be used to inform large-scale processing of crystals eg. the impacts of process shear stress on crystal recovery by filtration. This will be coupled with the implementation of a design of experiment (DoE) approach for process optimisation. The need for accelerated process development of APIs and reduction in time to market of drugs requires the implementation of automated scale-down process development platforms. The platforms enable early process understanding and development at low cost and reduced time.

The ultra scale-down technologies developed at UCL include a small scale (20 mL) rotating disc device for controlled exposure of crystal suspensions to shear stresses to mimic those which might be experienced at process scale and small scale (~5 mL) filtration pods (filter area ~0.12 cm^2) housed within an automated robotic platform. Up to eight filtration operations may be studied in parallel. A laboratory scale high vacuum master (HVM) filtration platform developed at CMAC-Strathclyde allows study up to the 50 mL scale using 5.72 cm^2 filters. The UCL ultra scale-down platform provides a base for rapid process screening (eg the impact of process shear stress or choice of filter media on filterability). The CMAC-Strathclyde platform allows prediction of large scale filtration.

During filtration operation, the process performance (i.e. achievable flux rates) is largely dependent on the interacting variables: (a) crystal size, (b) operating pressure and (c) crystal load. A DoE approach was implemented for modelling and optimising the filtration process using lab scale HVM. Filtration conditions investigated were crystal load (10 – 30% wv-1), pressure driving force (100 – 700 mbar) and crystal sizes ranging from micronised to coarse.

Pressure difference and particle size have a significant effect on the volumetric flux. The volumetric flux increases with increase in particle sizes and pressure difference and decreases with increased crystal concentration. The probability of failure (%) plot (Figure 55) shows a region of hypercube representing conditions under which the process performs optimally. At USD scale (results not shown) the impact of process shear stress did not affect filterability for the type of crystal studied, but other crystals studied are more susceptible to process shear stress. Micronisation of the crystals did lead to a very large reduction of filterability. Implementation of the automated platform for linked filtration and wash steps will further enable accelerated wash solvent screening and selection in the future.

Response contour plot for DoE optimisation (PLS) of volumetric flux for acetaminophen filtration process using lab scale high vacuum master system. The maximum point (Max) represents an allowable maximum volumetric flux limit specified for the DoE. The hypercube on the probability failure plot represents the design space under which acetaminophen filtration process performs optimally using lab scale.

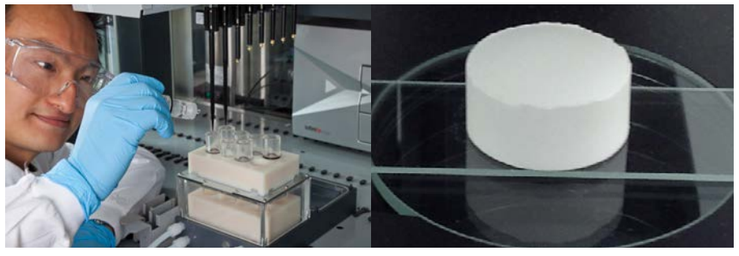

Image: USD automated platform and the vacuum block housing eight filter pods.

Image: Paracetamol cake recovered after deliquoring step using the HVM platform

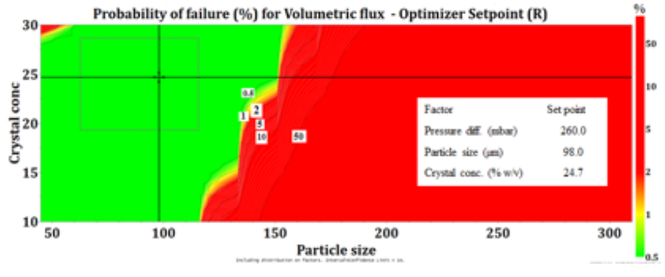

Figure 55. Probability of failure (%) plot

Formulation

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Alice Turner
Sarahjane Wood

CMAC is involved in several research projects that explore how to link continuous crystallisation to continuous isolation and formulation techniques.

Twin Screw Processing

Twin screw extrusion processing is a continuous secondary manufacturing platform that allows for a setup suited for continuous hot-melt-extrusion, as well as a setup for continuous granulation.

Image: Feeding API into the Twin Screw Granulator

Continuous Wet Granulation

We are developing continuous wet granulation with in-line assessment of products. The Twin Screw Granulator (TSG) is being investigated to achieve this using a Quality by Design (QbD) approach. Currently a model is being developed as a combination of discrete element method (DEM) and experimental results. Next steps will be establish the influence of the screw elements configuration on the granule properties and then introduce of this effect in the DEM model. The effect of various binders on the finished granule properties will also be investigated.

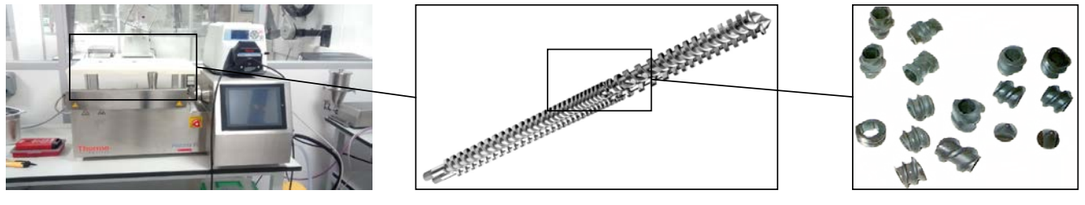


Figure 56. Twin screw extruder used for continuous wet granulation

Research Case Studies | Formulation

Continuous Extrusion

The relationship of processing parameters in HME on material properties of a solid dispersion formulation has been explored using a model drug molecule with an associated low solubility, a class II compound of the Biopharmaceutical Classification system, in combination with a variety of polymers. Product performance indicators were measured as an increase in solubility and/or dissolution rate, as well as the stability of the amorphous drug content of these solid dispersions are assessed. In addition, the use of ultrasound to increase the miscibility of polymer and API during the hot melt extrusion process has been looked at.

Innovative Strategies

CMAC has the ability to combine continuous hot-melt extrusion with innovative manufacturing techniques such as 3D printing and Injection Moulding to selectively produce “personalised medicine”.

An example of this involves incorporating the API of choice within a polymer using HME where, both low and high drug loadings can be achieved. Output from this technique is then transferred to a 3D printer for manufacture of the final dosage form. The dose is further controlled by changing the size of the printed tablet, or varying the infill percentage of the tablet’s internal structure. Currently several models of 3D Printer are being investigated as well as a variety of polymers to determine a suitable process.

Another strategy is the uses an injection moulder to form the tablet. Research will focus on two key areas: achieving immediate release doses of product, and gaining control over API distribution within the dosage units. To reach these goals various excipients will be investigated and new moulds containing smaller cavities will be explored.

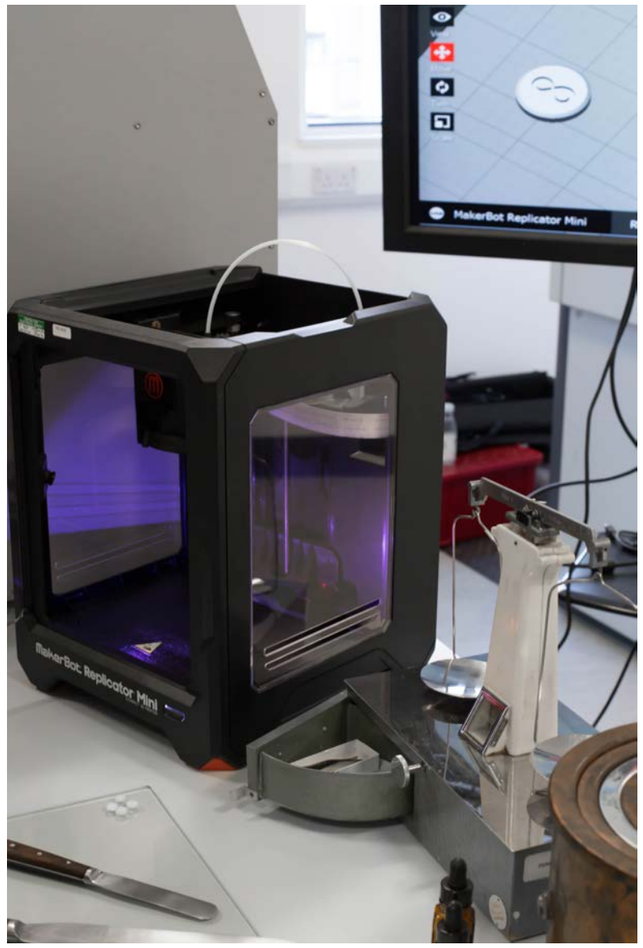
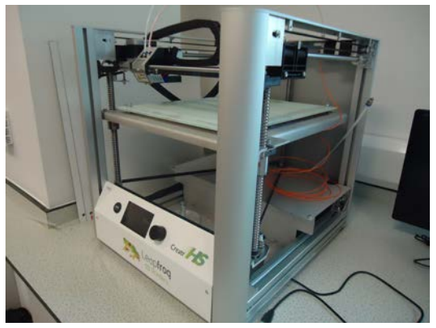
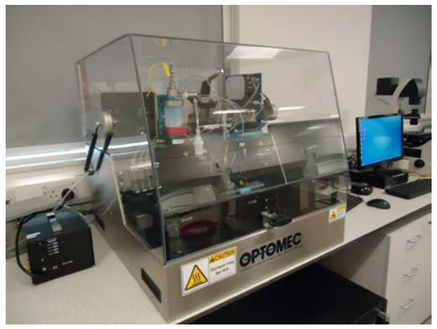


Image: 3D Printers





Spray Drying

Spray drying is an established technique used to produce dried powders. In pharmaceutical manufacturing secondary processing, spray drying is commonly used to produce amorphous products and particles for inhalation delivery. It can also offer a route to engineer particle properties such as, particle size, structure and form for a wider range of formulations and delivery methods.

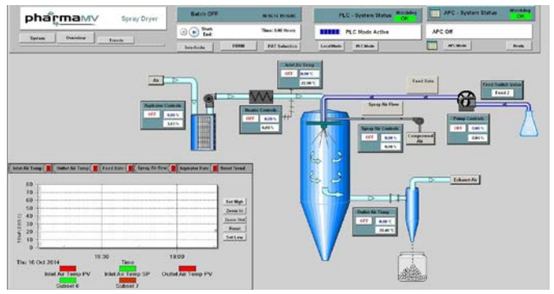
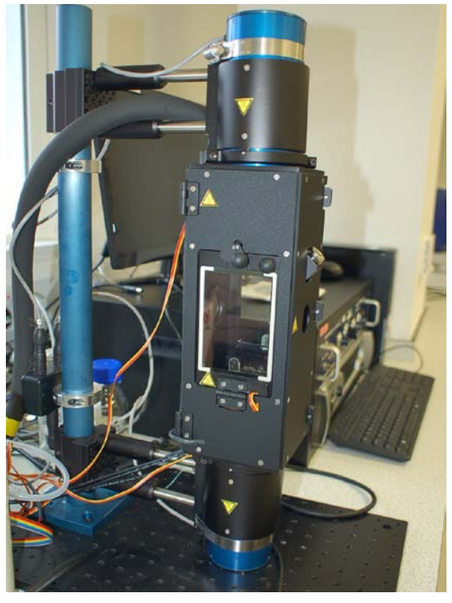


Figure 57. Spray drier control

This project supports the development of the Büchi B-290 Mini Spray Dryer within the CMAC workflow to provide a different method for particle engineering and highlight spray drying as a technique that can be adapted for different applications.

CMAC has collaborated with Perceptive Engineering LTD to automate the spray dryer through the PharmaMV software. Parameter management and real-time data responses of each parameter are recorded and linked with the CMAC ELN. We now have the ability to program and manage each parameter independently which allows for deeper understanding of each parameter’s significance and influence over the different particle attributes. A key challenge is the limited mass density at various key locations in the process to support reliable PAT measurements. The solidification of single droplets can be characterised in an acoustic levitator. The adaption of the Büchi platform to semi-continuous operation will further enhance the chances to integrate this unit operation into different multi-stage continuous process workflows as a crystallisation, formulation or isolation step.

Spray Drying - Particle Engineering



Single Droplet Evaporation Experiments (Acoustic Levitator)

Spray Drying Process Characterisation (Büchi B-290 Mini Spray Dryer)

Images: Particle engineering strategies in spray drying need to address parameters of the compound system and the spray drying process. The solidification of single droplets can be characterised in an acoustic levitator. On lab scale, the drying process is implemented using a Büchi B-290 Mini Spray Dryer.

Process Analytical Control

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Researchers:
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Dr Keddon Powell
Joanna Lothian
Carla Ferreira

Quantitative Solid-State Analysis of Amorphous and Crystalline Forms of Sulfamerazine Using THz Raman Spectrometry

This research is looking at the preparation of three different forms of sulfmerazine, a widely used sulfonamide antibacterial drug. A new novel portable THz Raman spectrometer will be used to investigate the solid state properties of sulfamerazine.

Sulfmerazine forms I and II are enantiotropically related such that form II is more stable at room temperature whereas form I is more stable at higher temperature. The ladder crystalline structure and slip planes of form I allow for an easy conversion into form II by application of mechanical shear. Small amounts of form II can be prepared by ball milling form I at room temperature, and bulk samples of form II have been prepared via a solvent mediated phase transformation in a mixture of acetonitrile and water. The amorphous form can be prepared by cryomilling at low temperatures.

The effects of ball-milling and cryomilling on the solid state properties of Sulfamerazine are to be investigated using THz Raman spectrometry. New filter technologies provide access to both the THz "structural" regime and the traditional "chemical fingerprint" region.

Off-line THz Raman spectra have been obtained of the variously forms of sulfamerazine. In the next stage, calibration models will be built to determine the crystallinity of samples and results compared with off-line solid state analysis techniques such as X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopy (FTIR).

Image:
Ondax THz Raman spectrometer

Providing Quantitative Particle Size and Shape Information from Measurements for Continuous Monitoring of Crystallisation Processes

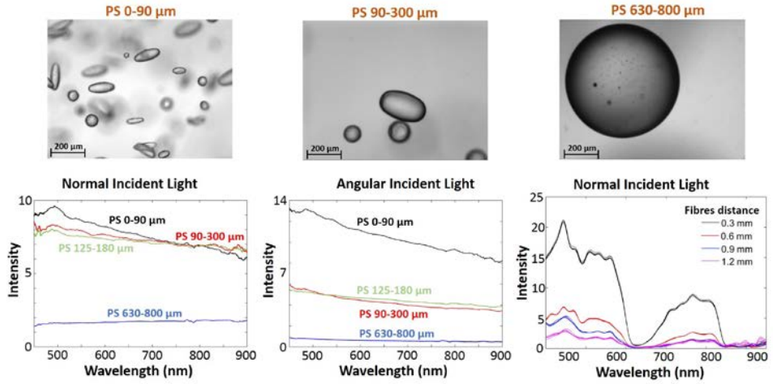
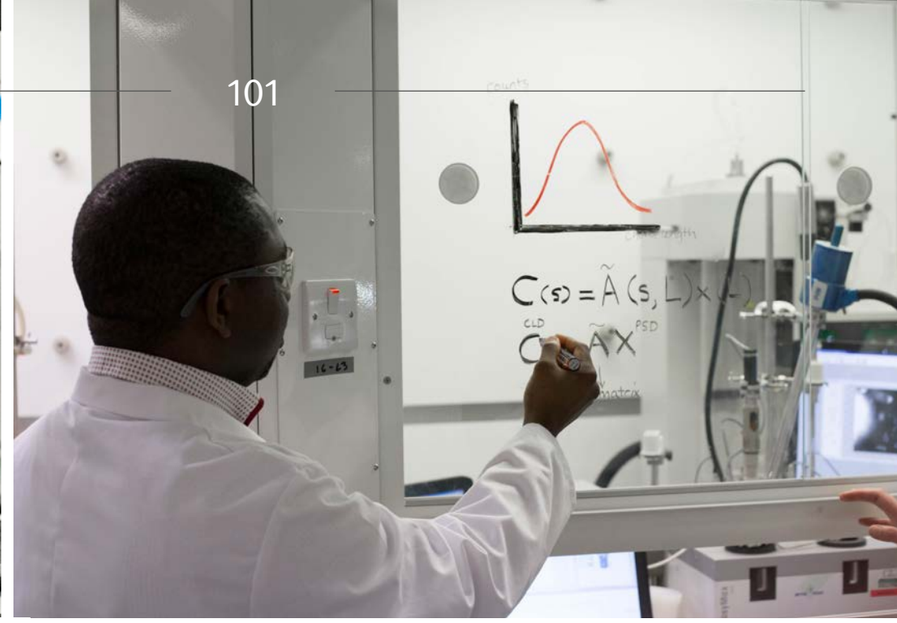


Figure 58. SAR-DRM measurements

An innovative spatially and angularly-resolved diffuse reflectance measurement (SAR-DRM) system has been developed for in-line monitoring in chemical manufacturing applications. The platform collects multi-wavelength (UV-visible-NIR) diffuse reflectance spectra from optical fibres of multi-angle multi-space arrangements, making use of scattering and absorption coefficients that are wavelength dependent to measure chemical composition, concentration and particle size in suspensions. The work carried out so far on SAR-DRM has allowed the establishment of a reliable setup to collect and process measurements.

The SAR-DRM technology is complementary to other Process Analytical Technology (PAT) tools such as Focus Beam Reflectance Measurement (FBRM), Particle Vision and Measurement (PVM) and laser diffraction.

In-situ real-time measurement of particle shape and size distribution is challenging due to the complexity of interpreting measurements from polydisperse samples of particles of various shapes and lack of adequate in-situ sensors. A single sensor is often not enough to extract reliable quantitative information. Implementation of multiple sensors to monitor the crystallisation process inline is crucial for efficient operation and quality control. Upon successful completion, this project aims to contribute with new equipment and methodologies for rapid continuous crystallisation process design. It is believed the new equipment will improve manufacturing quality and efficiency, especially in conditions with high solid loading where current PAT tools face particular problems. The anticipated multiple measurements platform will provide improved assurance of product quality and safety to develop novel, and support existing pharmaceutical manufacturing technologies.



Research Case Studies

ICT - CMAC Platform Project

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Professor Alastair Florence
Professor Tony Gachagan
Dr Blair Johnston
Dr Andrea Johnston
Professor Stephen Marshall
Dr Craig Michie
Dr Tony Mulholland
Professor Zoltan Nagy
Dr Alison Nordon
Profesor Chris Rielly
Dr Christos Tachtatzis
Professor Massimiliano Vasile

Researchers:
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Dr Akos Borsos
Dr Javier Cardona-Amengual
Dr Alison Cleary
Dr Jerzy Dziewierz
Dr Murray Robertson
Dr Qinglin Su

The Challenge

The 5 year £2.5m EPSRC Platform, ICT-CMAC (Intelligent Decision Support and Control Technologies for Continuous Manufacturing and Crystallisation of Pharmaceuticals and Fine Chemicals) is now in its fourth year, and is moving towards integrating the outputs from each of the Work Packages together, and providing a usable interface through the Electronic Laboratory Notebook (ELN) environment. The purpose of the project, co-funded by the EPSRC and a number of industrial co-creators (AZ, Bayer, GSK, Infinity Automation, Mettler Toledo, PSE, Perceptive, Siemens), is to enable the migration from batch to continuous production through extracting quantitative information on particle shape, size and form in near-real-time, and to use this information to inform intelligent decision support and control. In particular, the goal is create a comprehensive Intelligent Decision Support and Control platform using state-of-the-art data acquisition, signal processing, analysis and control mechanisms, interfaced with the ELN.

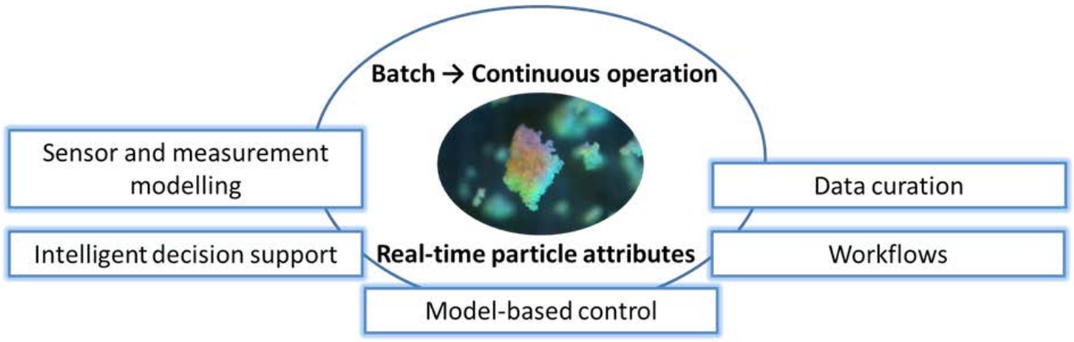


Figure 59. ICT-CMAC work packages

Work is under way to demonstrate the full end-to-end project capabilities, starting from data acquisition, through the required calculations and algorithms to display of information in a Graphical User Interface (GUI) and link to ELN.

The Technology: Work Package Highlights

Data capture and conditioning work has seen significant progress in validating the use of Hyperspectral Imaging (HSI) in the quantification of mixing conditions, therefore introducing a new process development tool. This Work Package highlights one of the major benefits of multidisciplinary projects such as ICT CMAC; combining the domain expertise from CMAC with the in-depth knowledge of signal and image processing techniques in Electronic and Electrical Engineering allows quantitative information to be extracted from HSI measurements that could not previously be achieved.

Sensor and measurement modelling personnel have further developed the FBRM by adding the FBRM inversion routine capabilities to add processed PVM image information, therefore allowing a faster calculation and faster feedback to the user mid-experiment. The purpose of the inversion is to take measured chord length data from the FBRM and estimate the particle aspect ratios present in the original sample.

The Intelligent support platform team has developed a suite of software relating to image processing of real data, which fuses data from projection modelling of particles with real image data. The purpose of this work is to extract further value from image measurements, giving qualitative particle shape information, but also to evaluate the range of particle sizes that could be observed by an imaging system, as the image of a non-spherical particle will very rarely be captured showing its true size due to its orientation with respect to the camera.

Plant-wide modelling and control personnel at Loughborough have developed a number of crystalliser models, as well as secondary process models using a combination of PSE gCRYSTAL and gSOLIDS software, and building additional modules in Matlab. A recent success has been the implementation of a nonlinear model-predictive control strategy using Just-in-Time Learning (JITL) and Extended Prediction Self-Adaptive Control (EPSAC).

Work on People and processes has concentrated on CMAC Phase II (pages 40-41) and in creating digital workflows for cooling crystallisation. A number of automated data processing protocols have been created, for example for Residence Time Distributions (RTD). These automated protocols eliminate complex or time consuming calculations and ensure that the calculations are repeatable. Additional highlights include the transfer and curation of data from Perceptive automated platforms to the CMAC database.

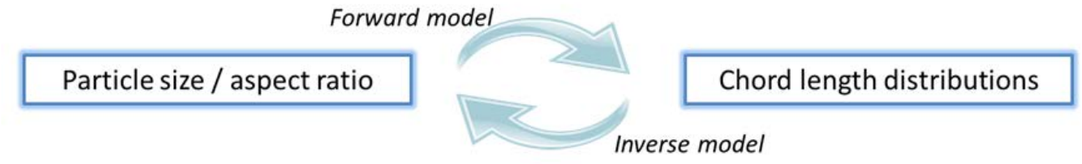


Figure 60. Sensor and measurement modelling

Centre Boards and Committees

The Centre's key activities are overseen by the Advisory Board and the Centre Academic Committee. The Centre **Advisory Board** is chaired by Prof Paul Sharratt from ICES Singapore. Full membership is shown below. Centre representation on the Board includes the Director, Industry Director and EPSRC. Additional members of the Board are an experienced grouping of academics and industrialists. The Board meets three times per year with at least two meetings face to face.

Responsibilities of the Board include:

1. Provide independent input from leading academics and industrialists not directly involved in the Centre;
2. Gather views that will influence the running of the research of the EPSRC Centre and DTC;
3. Advise on strategy, reporting, project monitoring etc.;
4. Provide input from researchers from different fields and from stakeholders from sectors other than pharmaceuticals;
5. Carry out an annual review of Centre performance.

Name	Institution	Status
Chair		
Prof Paul Sharratt	ICES, Singapore	International independent academic
Dr Clive Badman OBE (deputy-chair)	GSK	Non-independent industry
EPSRC Centre Representatives		
Prof Alastair Florence	EPSRC Centre	Centre Director
Craig Johnston	EPSRC Centre	Industry Director
Dr Andrea Johnston	EPSRC Centre	Centre Manager
Independent Academic Members		
Prof Brian Glennon	University College Dublin (SSC)	International independent academic
Prof Nigel Titchener-Hooker	UCL	Independent academic; EPSRC Centre Emergent macromolecular therapies
Prof Kevin Roberts	University of Leeds	Independent academic
Prof William Jones	University of Cambridge	Independent academic
Non-independent Industrial Members		
Dr Jon-Paul Sherlock	AZ	Non-independent industry
Independent Industrial Members		
Kenny Gilmour	Victrex	Independent industry
Dr Colin Groom	CCDC	Independent non-academic
Dr Kevin Girard	Pfizer (US)	International Independent industry
Ian Laird	Moorbrook Textiles	Independent industry
Dr Paul Stonestreet	Roche	Independent industry
EPSRC/Innovate UK Members		
Dr Rebecca Williams	EPSRC	EPSRC representative
Dr Gerry Flynn	Innovate UK	Innovate UK representative

The **Academic Committee** consists of the core management team plus co-investigators. The committee meets monthly and responsibilities of the committee include:

1. Review project progress against milestones;
2. Refine and shape the vision and research programmes in line with user needs;
3. Conduct an annual review and assess proposals for future work packages/DTC themes;
4. Responsible for wider functions such as ensuring that the work of the Centre is appropriately disseminated/published and ensure exploitation pathways are optimised;
5. Oversee the financial aspects of the programme;
6. Grow activities and secure future funding towards delivering the Centre vision.

Centre Structure

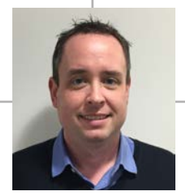
Management and Support Team

Centre Director
Alastair Florence

Industry Director
Craig Johnston

Academic DTC
Jan Sefcik

Tier 1 Technical Project Manager
Ian Houson



Project Manager REMEDIES
John Mulgrew

Project Manager CMAC Technology Companies
Stewart Mitchell

Centre Manager
Andrea Johnston

Assistant Centre Manager
Helen Feilden

Modern Apprentice
Rebecca O'Hare

International Collaboration Coordinator
Claire Ordoyno

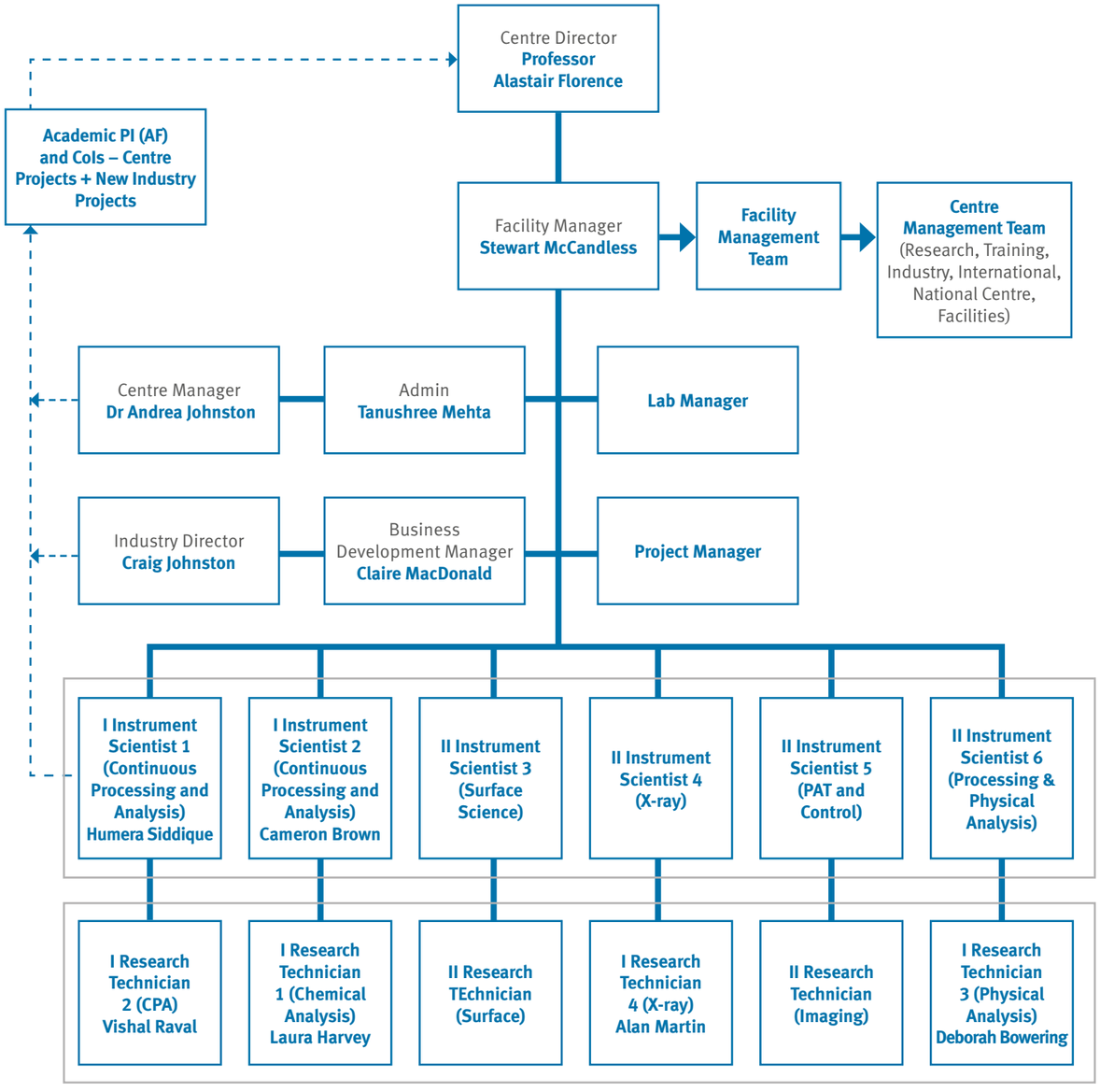
Centre Administrator
Lorna Gray

Postgraduate Development Administrator
Karen Graham

Administrative Assistant
Rebekah Russell

Centre Structure | Meet the Teams

National Facility Team



Academic Team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Professor Joop ter Horst


Dr Blair Johnston


Professor Lee Cronin


Professor Gavin Halbert


Professor David Littlejohn


Dr Alison Nordon

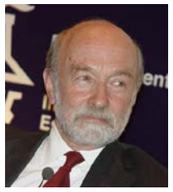

Professor Zoltan K Nagy


Professor Chris Rielly


Professor Xiong-Wei Ni


Professor Colin Pulham


Dr Andrew Alexander


Professor Sir Mike Gregory


Dr Jag Srai


Professor Jan Sefcik


Professor Chick Wilson


Dr Chris Price


Dr Dimitrios Lamprou

Centre Structure | Meet the Teams

Researchers

University of Strathclyde

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Francesca Perciballi

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Arabella Johnston
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Emmanuel Kimuli

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Dr Ross Forgan Group
PhD Researcher:
Sarah Griffin

Professor Lee Cronin Group
PhD Researcher:
Sergio Martin

Appendix - Full list of publications

1. Agimelen, Okpeafoh S., Hamilton, Peter, Haley, Ian, Nordon, Alison, Vasile, Massimiliano, Sefcik, Jan, & Mulholland, Anthony J. (2015). Estimation of particle size distribution and aspect ratio of non-spherical particles from chord length distribution. Chemical Engineering Science, 123, 629-640. doi: http://dx.doi.org/10.1016/j.ces.2014.11.014
2. Agimelen, Okpeafoh S., Jawor-Baczynska, Anna, McGinty, John, Dziewierz, Jerzy, Tachtatzis, Christos, Cleary, Alison, . . . Mulholland, Anthony J. (2016). Integration of in situ imaging and chord length distribution measurements for estimation of particle size and shape. Chemical Engineering Science, 144, 87-100. doi: http://dx.doi.org/10.1016/j.ces.2016.01.007
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Closing Remarks

CMAC has made great strides forward in the last year and is delivering outcomes of real value. Researchers have been recruited into industry to apply their skills and knowledge. Exciting publications are arising from many of the projects and new research themes are being defined and explored. The National Centre at Strathclyde now houses an outstanding experimental facility with the potential to significantly reduce the barriers to both new science and industrial innovation; the continuous processing community is eagerly anticipating seeing it fully operational."

Paul Sharratt, ICES

As we approach the end of year 5 as a CIM I think we can look back with some pride at our achievements over the last year and the five year period.

- **Four Tier 1 partners with a further two going through due diligence**
- **17 Tier 2 partners with an increasing impact on our programme**
- **67% of graduates moving into industrial roles**
- **An increasing number of proprietary projects showing application of CMAC output in industry**
- **A proposal to create a £55M Medicines Manufacturing Innovation Catapult to enable the translation of CMAC innovation into industry**
- **The submission of a Research Hub proposal for £10M over 7 years with three new academic institutions , Imperial, Sheffield and Leeds joining Strathclyde, Cambridge, Loughborough and Bath**

What a great achievement in such a short time. I look forward to accelerating our progress in the next year."

Dr Clive Badman OBE, GSK, CMAC chair

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