EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Annual Review
2014-2015

UNIVERSITY of STRATHCLYDE
CMAC
NATIONAL FACILITY

EPSRC
Engineering and Physical Sciences
Research Council

Contents

Opening Remarks

Welcome to the 4th Annual Report of the national EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC). The last year has seen major developments across our Centre's programme spanning industry engagement, research, training, facilities and internationalisation. CMAC's industrial partnerships continue to flourish, underscoring the continued importance of our contributions to the UK innovation landscape. In particular we welcome Bayer Healthcare who join GSK, AstraZenenca and Novartis as Tier 1 members of CMAC. Further details on the exciting developments in industry collaborations are provided later in the report and highlight the growing community working together in CMAC to accelerate the adoption of advanced manufacturing technologies in pharmaceuticals and other high value chemical products.

Our progress is rooted in the manufacturing research carried out by CMAC researchers across our academic partner network. It has been particularly rewarding to see many of these projects mature over the last few months, leading to an increasing number of high quality research papers and conference papers emerging, a key step towards delivering impact from the engineering and physical science research underway across the Centre. The report also provides highlights of new initiatives including collaborations with the UK National Physical Laboratory and participation in two major new AMSCI funded projects. We have also continued to develop our international partnerships in the US, EU and Singapore. For example, CMAC is one of the founding partners with CSOPS (US) and RCPE (Austria) of the International institute of Advanced Pharmaceutical Manufacturing. The new collaborative training and research projects being developed build on the complementarity between these Centres and aim to provide a forum for new international research activity as well as excellent opportunities for students to gain valuable international experience.

> The shared vision, scope and programme for the national Centre have been developed through close collaboration with industry and in particular our founding strategic partners AstraZeneca, Bayer, GSK and Novartis who continue to provide significant input and support. Together the Centre partners have a shared long-term vision: to enable a step change from the current batch manufacturing paradigm to fully continuous manufacturing processes, systems and plants for the production of high-value chemical products to higher levels of quality, at a lower cost, more quickly and in a more sustainable manner.'

Training and skills development remains of paramount importance and our doctoral training programme continues to develop future leaders in continuous manufacturing and crystallisation with the 3rd cohort now entering the research phase of their studentships. We have also seen talented CMAC alumni taking up posts across industry and academia in the UK and abroad. We continue to work with our industry partners to develop new, tailored training solutions and this year has also seen the first cohort of masters students complete the new Advanced Pharmaceutical Manufacturing MSc course.

One of the most significant developments this year for CMAC was the move into the new £89M Technology Innovation Centre for the Centre team at Strathclyde. Opened by Her Majesty the Queen in July 2015, the building houses the new CMAC National Facility. This facility benefits from over £12M of investment from the UK Research Partnership Investment Fund, the Wolfson Foundation and EPSRC in state-of-the-art processing equipment and instrumentation. Over the coming months we look forward to formally launching the Facility and welcoming our existing colleagues and new partners to explore how these investments can provide benefits not only locally but to the wider manufacturing research community.

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.

- **130 people**
- **70 active researchers**
- **4 tier 1 industrial partners**
- **Involving 7 institutions**
- **5 HEI collaborative institutions**
- **58 PhD students**
- **3 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


Research
National Centre
Facilities
EPSRC
Centre for Innovative Manufacturing
in Continuous Manufacturing
and Crystallisation
Training
International
Industry

Centre Overview

The Centre

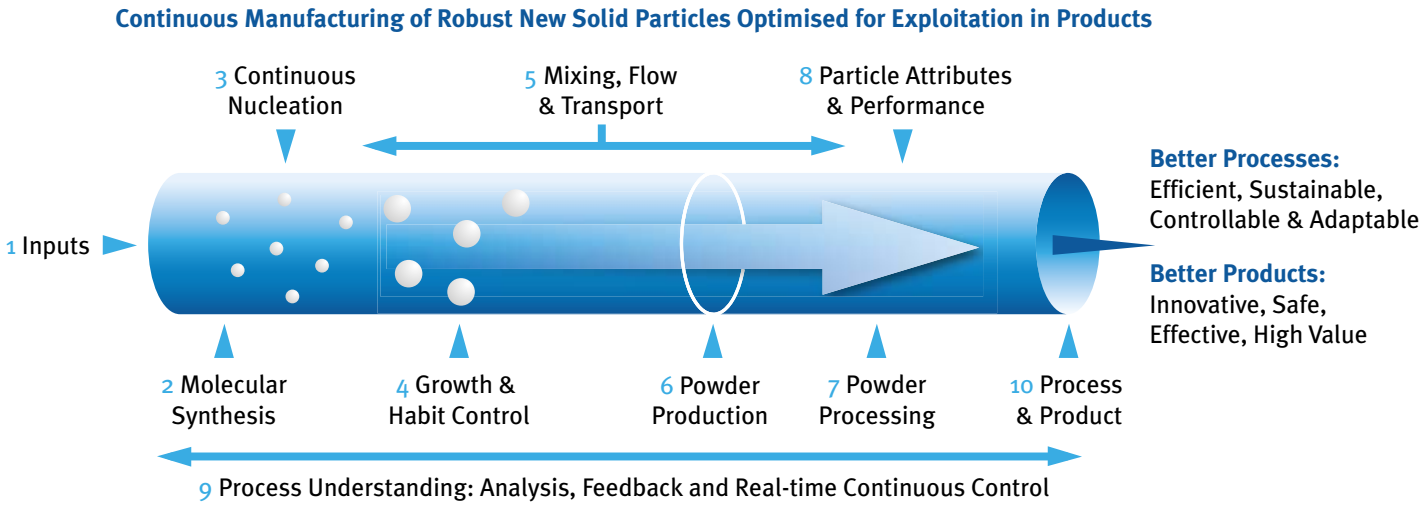
We are a world class national centre for research and training in advanced pharmaceutical manufacturing. Working in partnership with industry to accelerate the adoption of continuous manufacturing we are transforming supply chains for the future.

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 • Innovative, safe, effective, high-value • Nucleation, growth, agglomeration, breakage • 'dial-a' ...form, size, shape, purity • Tailored bulk and surface structure and function	**Better technologies for continuous control, formation, isolation, and processing of particles** • Fast, efficient, sustainable, safe • Controllable, scaleable, adaptable and agile • Predictable, optimised • Reconfigurable, modular, plug-play	**Optimised high-value chemical manufacturing operations across the value chain** • 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 right 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

Centre Overview | The Centre

Multidisciplinary Research

Key to the success of the Centre is the multidisciplinary academic team supporting the research programme. Our team involves 16 academic investigators from 7 institutions working with15 PDRAs and circa. 50 PhDs and a management, technical and support team of 15, harnessing expertise in chemical and process engineering, synthetic, physical, analytical, structural and materials chemistry, crystallisation science, pharmaceutical science, manufacturing and operations management, Figure 3. 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 p9). 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 page 34).

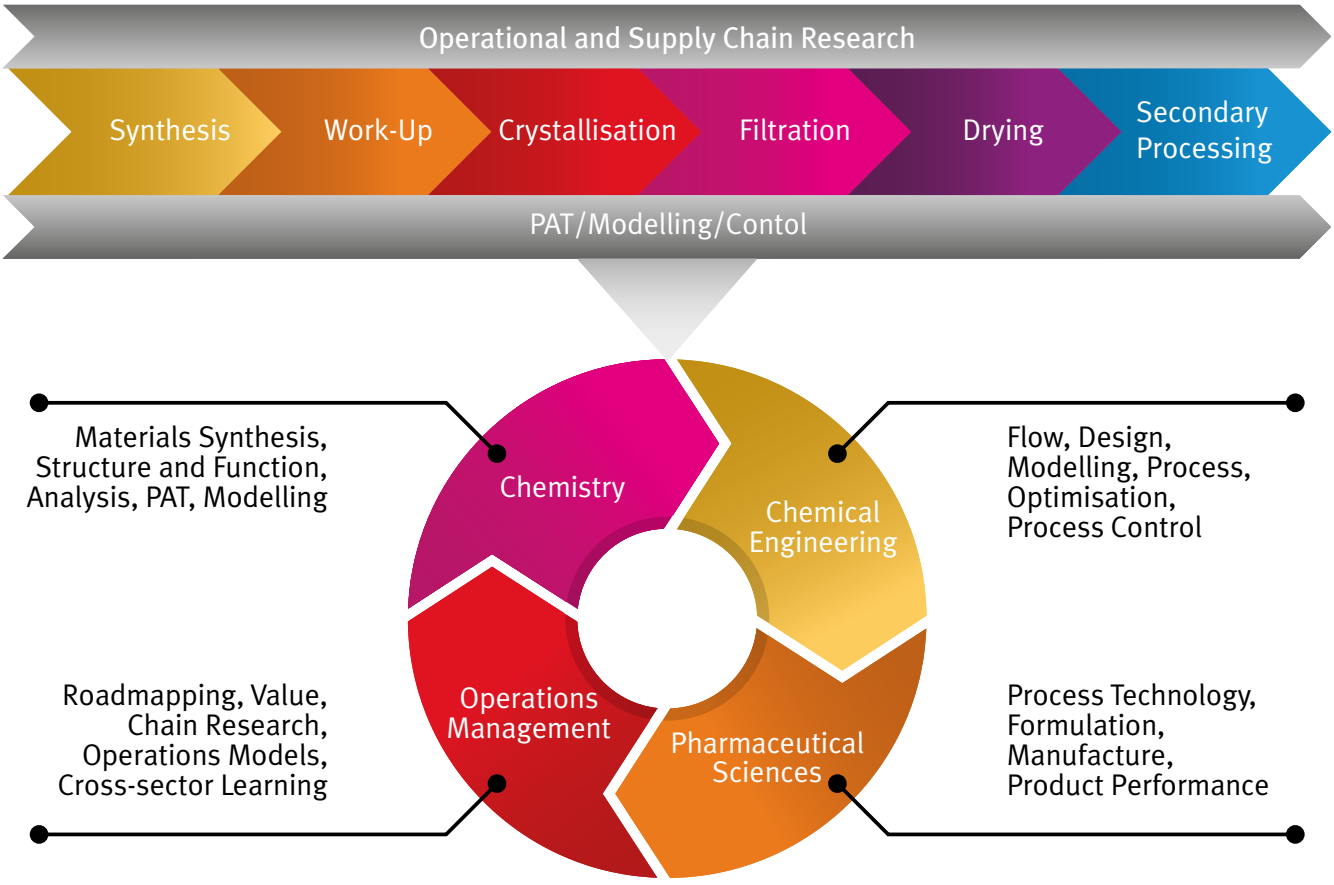
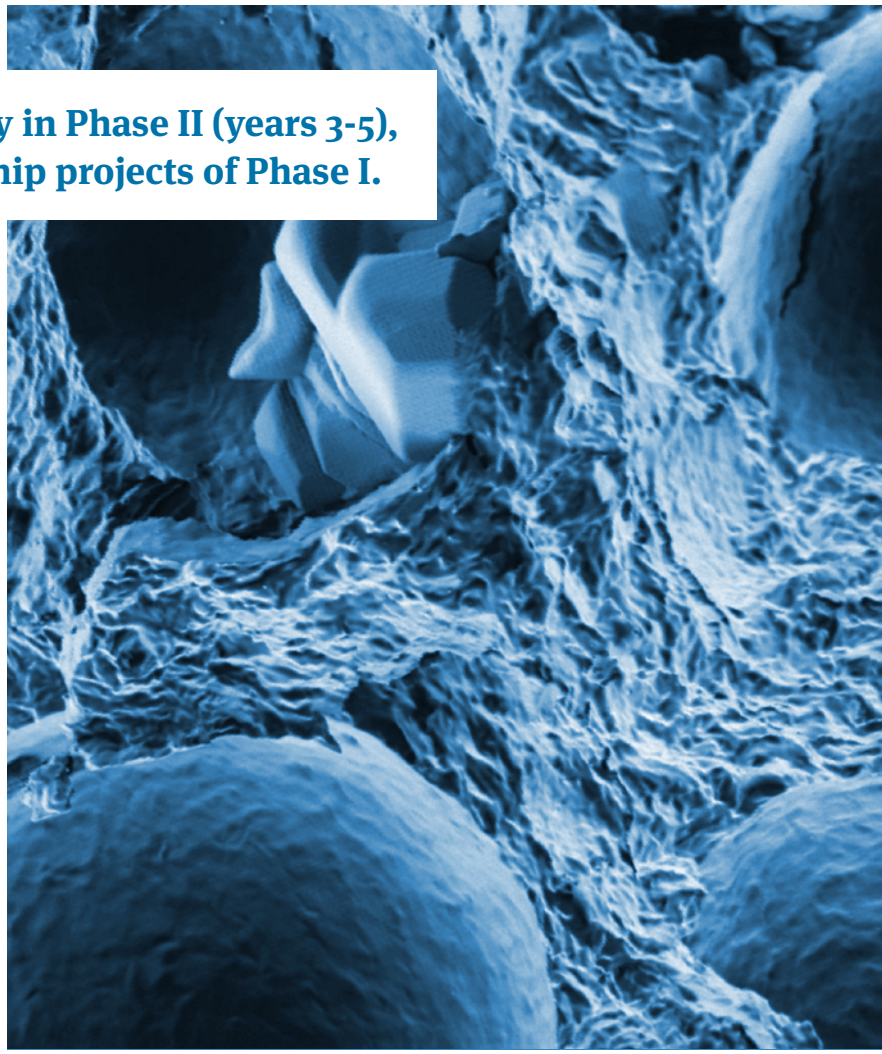


Figure 3. Key disciplines contributing to the initial EPSRC Centre research programme and Doctoral Training Centre programme.

Centre Overview

Phase II Themes and Vision



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

Building on the capabilities established and progress made in Phase I, Phase II is delivering an ambitious co-ordinated programme of research that will transform capabilities for continuous manufacturing of high value chemicals and in particular, pharmaceuticals. The direction of Phase II draws on the technical targets and industry problem statements collated by the Centre's industry technical committee and by extensive discussion across the academic team. Phase II also builds on new and emerging projects involving downstream processing including continuous filtration and drying and secondary processing of API into formulated product. This work includes understanding how particle attributes impact on performance in downstream operations. Key enablers of Phase II are the new processing and analytical capabilities housed within the CMAC National Facility which officially opens in late 2015. The purchase of the state of the art equipment has been supported by the £34m UK RPIF award, Wolfson award and EPSRC strategic equipment funds. The research is being facilitated and undertaken by new academic, research fellow and PhD appointments. The research programme is being delivered through three core work packages supported by the core Phase II Centre funded RAs.

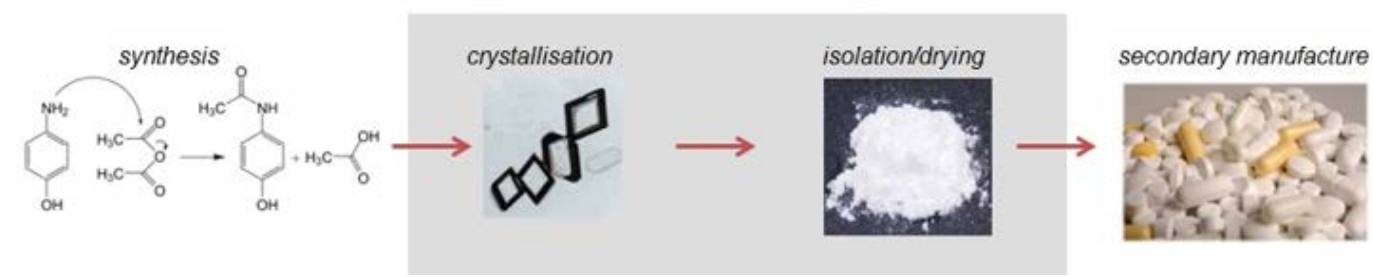


Figure 4. Demand-Led Scope: from synthesis to formulated product

Centre Overview | Phase II Themes and Vision

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

WP1 Laboratory-scale continuous process capabilities to support end-to end manufacturing

Continuous processing at laboratory scale is an important target for CMAC offering a range of benefits including use of less material, improved process understanding, rapid process development, enabling research with a broader range of solvents and API. A suite of continuous platforms is being developed alongside the experimental infrastructure to accelerate process development. These platforms will support specific continuous synthesis, work-up, crystallisation, isolation and secondary processing operations.

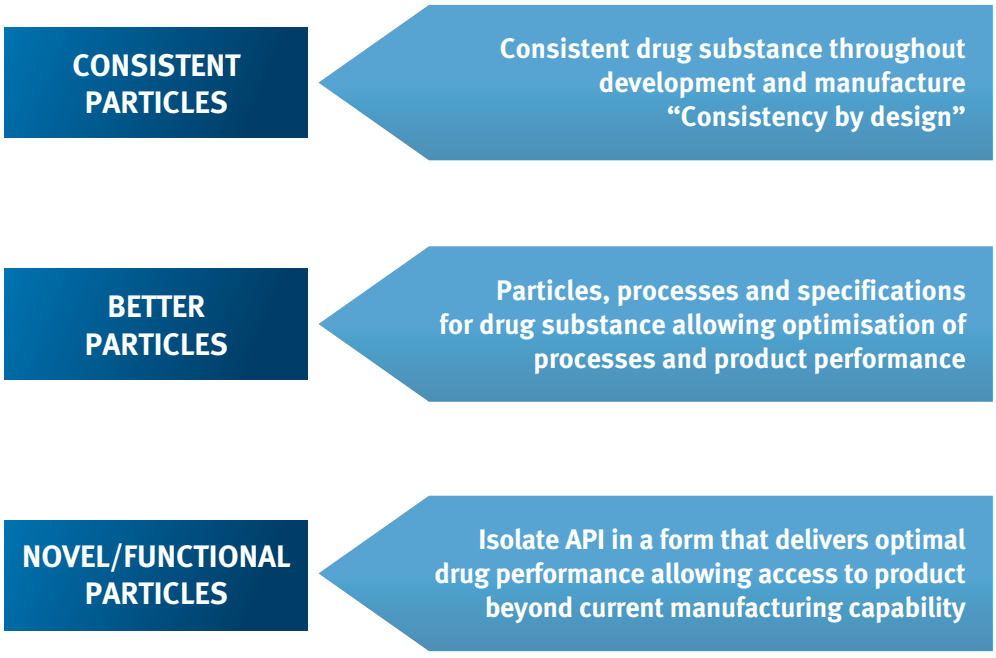
WP2 Tools and workflows for rapid product assessment and continuous process selection

We are developing rapid methodologies for assessing the physical properties of molecules, particles, formulated products and their physical transformation to inform future process and platform selection (e.g. batch vs.continuous, MSMPR vs COBR). By exploiting a comprehensive suite of automation, characterisation and measurement tools, and the developing CMAC informatics infrastructure we will deliver a robust foundation for systematic, rapid continuous crystallisation development including a crystallisation classification approach. With the implementation of a bespoke ELN and data management system and integration of end to end workflows we deliver a robust foundation for systematic, rapid continuous crystallisation development including a crystallisation classification approach.

WP3 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 needs 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.

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



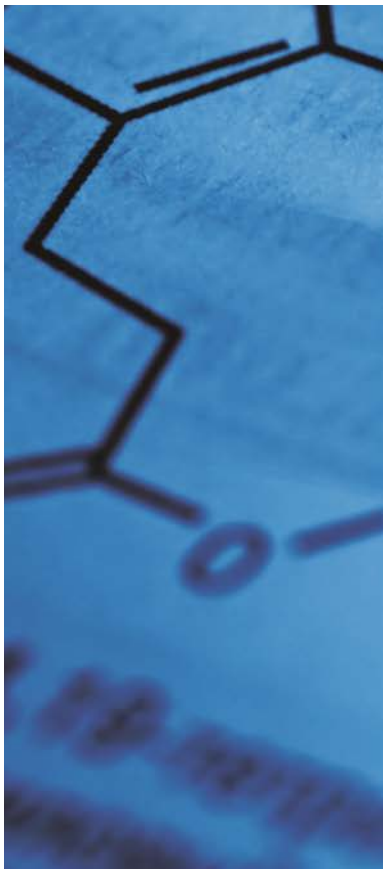


Figure 5. Focus of Phase II deliverables.

Making Medicines

Research in the Centre is now actively targeting 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 and Metformin Hydrochloride as case studies. Other projects will target anti-malarials as well as treatments for HIV, and elevated cholesterol with outcomes demonstrating the ability to improve the medicines supply chain of the future.

Centre Overview

Annual Highlights

Queen Visits CMAC

Her Majesty the Queen opened the TIC building at the University of Strathclyde on 3rd July 2015. During her visit, the Queen visited the CMAC Labs and was introduced to key industry partners and academics and shown our new facilities and equipment by Academic Director Professor Alastair Florence.

First Minister at CMAC

The First Minister of Scotland, Nicola Sturgeon MSP marked the opening of the TIC building to employees at the University of Strathclyde in December 2014. The First Minister met with CMAC representatives including our Academic Director Professor Alastair Florence.

CMAC move to TIC

In April 2015 the Strathclyde based researchers and management team moved into new office and laboratory facilities in the Technology and Innovation Centre (TIC) at University of Strathclyde. The new CMAC National Facility housing state of the art equipment for end to end continuous manufacturing will be opened officially in late 2015.

3rd EPSRC Manufacturing the Future Conference

CMAC hosted the nation's 3rd EPSRC Manufacturing the Future Conference at Glasgow Science Centre in September 2014. The Conference was chaired by Professor Alastair Florence, Academic Director of CMAC. The conference was a huge success with almost 400 delegates and has received outstanding feedback from all who attended. Refer to p49 for more detail.

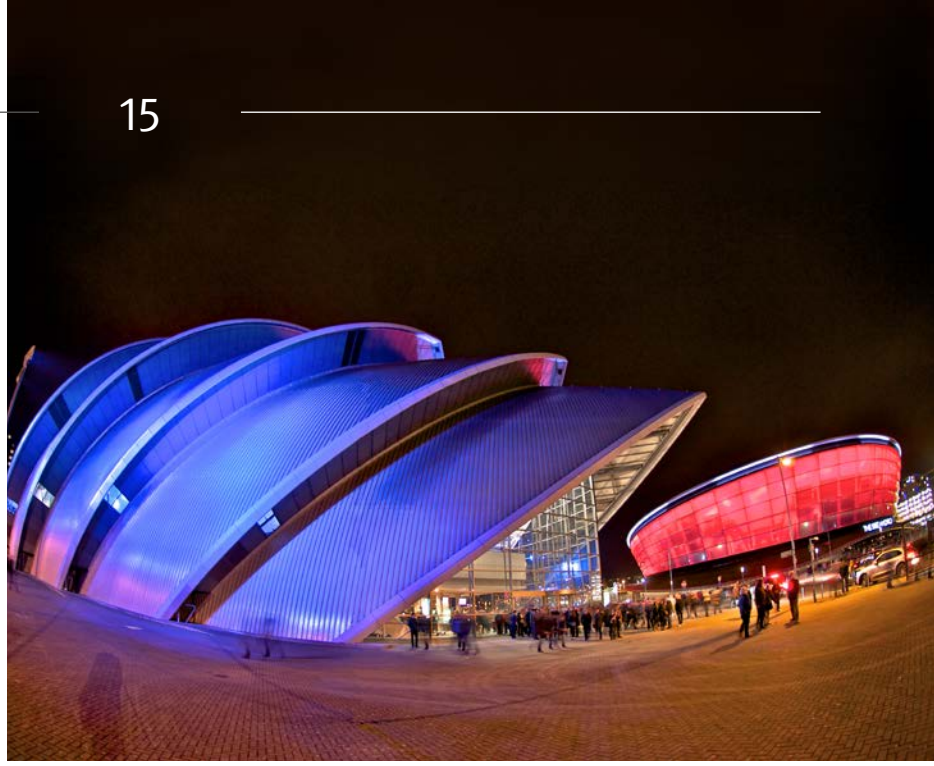
Centre Overview

Outcomes and Impacts

CMAC is delivering impact for the manufacturing research community

Research

- Over the past 12 months the Centre has produced 15 research publications and 5 conference proceedings and has had a dedicated presence at conferences in the manufacturing, crystallisation, flow chemistry and formulation conferences with over 24 oral presentations from investigators and researchers.
- CMAC researchers have been key participants in workshops: Erice 2015, British Council Workshop in Novosobirsk 2015, and 5th BCA/CCG Intensive Teaching School 2015.
- Dr Thomas McGlone secured a place on the 'Young Chemists Crossing Borders' scheme which included attending and presenting at the 250th ACS Conference in Boston in August 2015 as well as visits to MIT, Harvard, Novartis and Genzyme.
- The White Papers from the International Symposium on Continuous Manufacturing of Pharmaceuticals held in 2014 have now been published in the Journal of Pharmaceutical Sciences Volume 104 - March 2015 Special Topic Commentaries on Continuous Manufacturing.
- ICT project generating Intelligent Decision tools that are being implemented in ELNs to automate workflows.



National Centre

- CMAC hosted the annual EPSRC Manufacturing the Future conference at Glasgow Science Centre, and were co-hosts of Bruker Scanning Probe Microscopy Conference and User Meeting at University of Strathclyde in April 2015.
- CMAC were nominated for the “Innovation” category at the Scottish Enterprise Annual Awards in February 2015
- CMAC were shortlisted for an award in Innovative Training (Chem Eng Soc).
- CMAC are cofounders of International Institute of Advance Pharmaceutical Manufacturing which launched during 2015.
- Partners in two new major national projects: Remedies and Digital Design

Training

- CMAC launched a novel MSc in Advanced Pharmaceutical Manufacturing with a cohort of 13 MSc Students who will graduate in September 2015.
- CMAC are producing an exceptional talent pipeline into the fine chemicals manufacturing sector

Press

- CMAC board chair Dr Clive Badman, OBE, was interviewed and quoted in part of an article on Pharma Outsourcing in Chemistry World, in June 2014. The article reference: Extance, A., Reaching Out. Chemistry World 2014, 11 (6), 58- 92.
- CMAC nominated for “Innovation Award” for Scottish Enterprise Life Sciences Annual Awards 2015
- Chemicals in Scotland: Clive Badman, was featured in late 2014 edition
- CMAC (Continuous Manufacturing and Crystallisation) featured in the Scotsman with an article about Clive Badman, CMAC board chair. The article describes how CMAC is at the forefront of research into changing the way pharmaceuticals are manufactured. The article was published in February 2015.

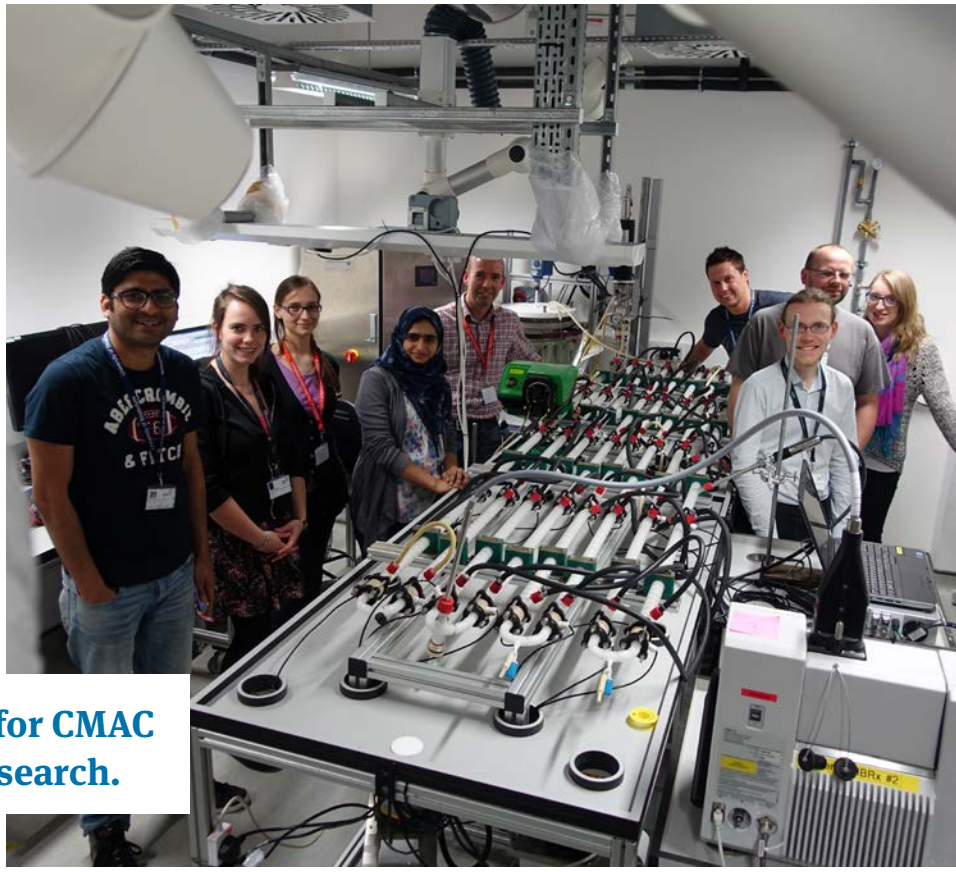
Research Overview

12-Month Review

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

Building on the rich activity of developing techniques and technologies for understanding and controlling continuous crystallisation processes, the programme now integrates 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 (Figure 6) . 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.

This has been a fantastic year for CMAC with major steps forward in research.



First Continuous Crystallisation Experiment in TIC

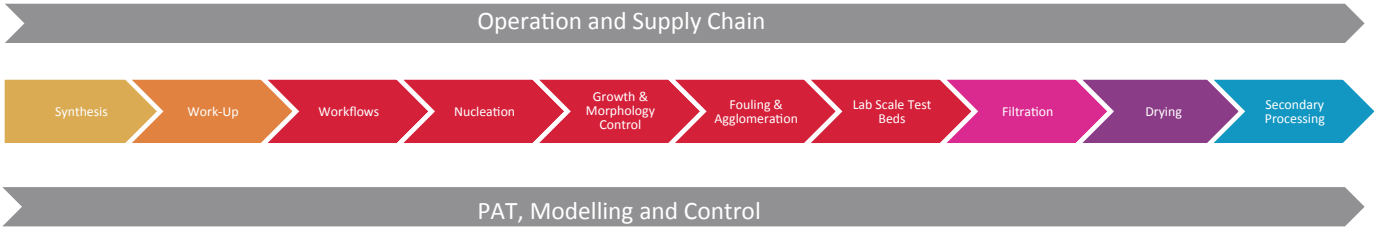


Figure 6. Project portfolio research topics in CMAC Phase II

A primary focus of research across the Centre has been in developing workflows for primary and secondary processing. They have been constantly evolving with continuous learning from past and current projects in addition to scoping out new opportunities with an increasing armoury of analytical and processing equipment.
The aims of having a validated workflow remain clear:

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

Currently we are developing workflows for crystallisation (Figure on Page 56) and for the primary to secondary processing (Fig 7).

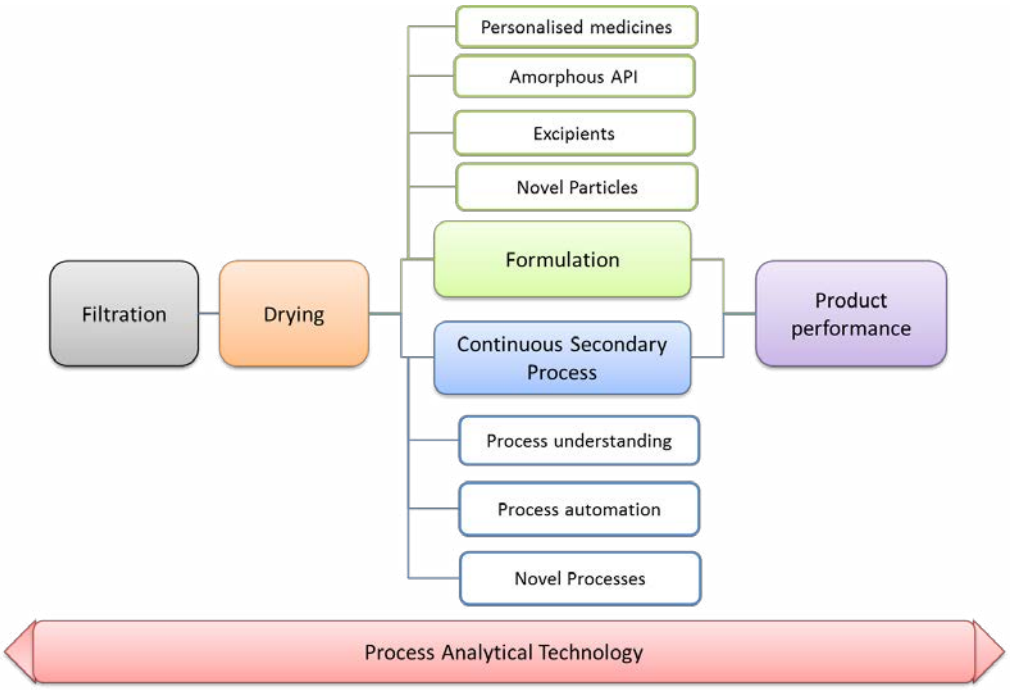


Figure 7. Primary to Secondary Processing Workflow

Key Research Outputs

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

Other key research outputs include controlled continuous generation of seeds, controlled continuous seeded crystallisation of L-glutamic acid, continuous crystallisation of lactose with real time monitoring and control, non-photochemical laser induced nucleation.

National Centre Link With Other Major National Projects

This year also saw the kick-off of secondary manufacturing AMSCI project, Remedies. This has enabled a significant increase in research portfolio in the primary to secondary manufacturing area. Further details on Remedies are given on page 26. CMAC are a partner in the AMSCI Digital Design Project which launched 2Q 2015.

Research Outputs

Over the past 12 months the Centre has produced 15 research publications and 5 conference proceedings and has had a dedicated presence at conferences in the manufacturing, crystallisation, flow chemistry and formulation conferences with over 24 oral presentations from investigators and researchers. CMAC researchers have received prizes for conference presentations and have been key participants in cutting-edge workshops such as Erice 2015, British Council Workshop in Novosibirsk, 2015 and 5th BCA/CCG Intensive Teaching School 2015.

Research Overview

Centre Programme

The Centre's research programme has seen tremendous growth over the last 12 months. Now with 70 active research projects (Figure 8) encompassing core Phase II researchers, circa 50 PhD students from our Centre, Doctoral Training Centre, and collaborative NTU programme, and linked projects such as ICT-CMAC, Remedies, MOPPS, Manufacturing with Light and Digital Design.

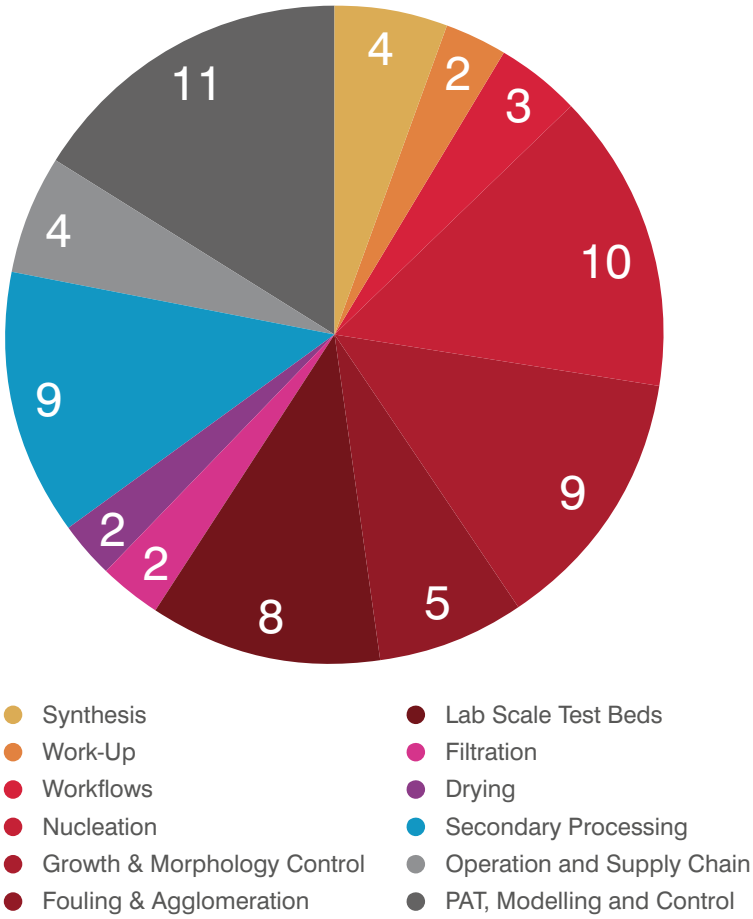


Figure 8. Project distribution across centre scope

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.

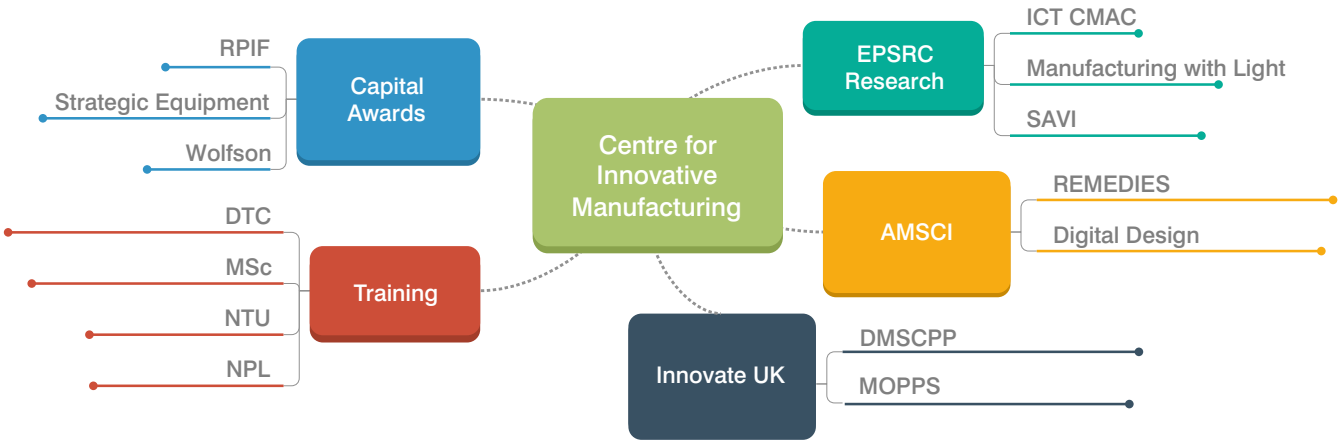


Figure 9. Funding map enabling broad centre activity

Research Overview

Publications

Peer Reviewed Journals

Callahan, Craig J., & Ni, Xiong-Wei. (2014). An investigation into the effect of mixing on the secondary nucleation of sodium chlorate in a stirred tank and an oscillatory baffled crystallizer. CrystEngComm, 16(4), 690. doi: 10.1039/c3ce41467a

Sans, Victor, Glatzel, Stefan, Douglas, Fraser J., Maclaren, Donald A., Lapkin, Alexei, & Cronin, Leroy. (2014). Non-equilibrium dynamic control of gold nanoparticle and hyper-branched nanogold assemblies. Chemical Science, 5(3), 1153. doi: 10.1039/c3sc53223b

Bhardwaj, Rajni Miglani, Johnston, Andrea, Johnston, Blair, & Florence, Alastair James. (2015). A Random Forest Model for Predicting the Crystallisability of Organic Molecules. CrystEngComm. doi: 10.1039/c4ce02403f

Daly, Ronan, Harrington, Tomás S., Martin, Graham D., & Hutchings, Ian M. (2015). Inkjet printing for pharmaceutics – A review of research and manufacturing. International Journal of Pharmaceutics(0). doi: 10.1016/j.ijpharm.2015.03.017

Hunter, Steven, Coster, Paul L., Davidson, Alistair J., Millar, David I. A., Parker, Stewart F., Marshall, William G., . . . Pulham, Colin R. (2015). High-Pressure Experimental and DFT-D Structural Studies of the Energetic Material FOX-7. The Journal of Physical Chemistry C, 119(5), 2322-2334. doi: 10.1021/jp5110888

McGlone, Thomas, Briggs, Naomi, Clark, Catriona, Brown, Cameron, Sefcik, Jan, & Florence, Alastair J. (2015). Oscillatory flow reactors (OFRs) for continuous manufacturing and crystallization. Organic Process Research & Development. doi: 10.1021/acs.oprd.5b00225

Powell, K. A., Saleemi, A. N., Rielly, C. D., & Nagy, Z. K. (2015). Periodic steady-state flow crystallization of a pharmaceutical drug using MSMPR operation. Chemical Engineering and Processing: Process Intensification(0). doi: 10.1016/j.cep.2015.01.002

Reus, Marloes A., van der Heijden, Antoine E. D. M., & ter Horst, Joop H. (2015). Solubility Determination from Clear Points upon Solvent Addition. Organic Process Research & Development. doi: 10.1021/acs.oprd.5b00156

Su, Qinglin, Nagy, Zoltan K., & Rielly, Chris D. (2015). Pharmaceutical crystallisation processes from batch to continuous operation using MSMPR stages: Modelling, design, and control. Chemical Engineering and Processing: Process Intensification, 89(0), 41-53. doi: 10.1016/j.cep.2015.01.001

Tachtatzis, Christos, Sheridan, Rachel, Michie, Craig, Atkinson, Robert C., Cleary, Alison, Dziewierz, Jerzy, . . . Sefcik, Jan. (2015). Image-based monitoring for early detection of fouling in crystallisation processes. Chemical Engineering Science(0). doi: 10.1016/j.ces.2015.01.038

Ward, Martin R., Rae, Alasdair, & Alexander, Andrew J. (2015). Nonphotochemical Laser-Induced Crystal Nucleation by an Evanescent Wave. Crystal Growth & Design. doi: 10.1021/acs.cgd.5b00854

Wittering, K. E., Agnew, L. R., Klapwijk, A. R., Robertson, K., Cousen, A. J. P., Cruickshank, D. L., & Wilson, C. C. (2015). Crystallisation and physicochemical property characterisation of conformationally-locked co-crystals of fenamic acid derivatives. CrystEngComm, 17(19), 3610-3618. doi: 10.1039/C5CE00297D

Yang, H., Rasmuson, Å. C. (2015). Phase equilibrium and mechanisms of crystallization in liquid-liquid phase separating system. Fluid Phase Equilibria 385, 120-128. doi: 10.1016/j.fluid.2014.11.007

Yang, Huaiyu. (2015). Relation between metastable zone width and induction time of butyl paraben in ethanol. CrystEngComm, 17, 577-586. doi: 10.1039/C4CE01625D

Conference Proceedings

Badman, C., & Trout, B. L. (2015). Achieving continuous manufacturing. May 20-21, 2014 continuous manufacturing symposium. J Pharm Sci, 104(3), 779-780. doi: 10.1002/jps.24246

Baxendale, I. R., Braatz, R. D., Hodnett, B. K., Jensen, K. F., Johnson, M. D., Sharratt, P., . . . Florence, A. J. (2015). Achieving continuous manufacturing: technologies and approaches for synthesis, workup, and isolation of drug substance. May 20-21, 2014 continuous manufacturing symposium. J Pharm Sci, 104(3), 781-791. doi: 10.1002/jps.24252

Brandel, Clement, & ter Horst, Joop H. (2015). Measuring induction times and crystal nucleation rates. Faraday Discussions, 179(0), 199-214. doi: 10.1039/C4FD00230J

Harrington, T.S., Alinaghian, L., Srai, J.S. (2014a). 'Integrating industrial sub-systems in complex, multi-tier value networks: A Pharmaceutical industry case study', Industry Studies Association (ISA) Conference, Portland OR. (2014).

Harrington, T.S., Alinaghian, L., Srai, J.S. (2014b). 'Making the business case for Continuous Manufacturing in the Pharmaceutical Industry', 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA. (2014).

Jawor-Baczynska, Anna, Moore, Barry D., & Sefcik, Jan. (2015). Effect of mixing, concentration and temperature on the formation of mesostructured solutions and their role in the nucleation of dl-valine crystals. Faraday Discussions, 179(0), 141-154. doi: 10.1039/C4FD00262H

Srai, J. S., Badman, C., Krumme, M., Futran, M., & Johnston, C. (2015). Future supply chains enabled by continuous processing-opportunities and challenges. May 20-21, 2014 continuous manufacturing symposium. J Pharm Sci, 104(3), 840-849. doi: 10.1002/jps.24343

Srai, J. S., Harrington, T.S., Alinaghian, L. (2014). 'Implications of Continuous Flow Technologies on Pharma Supply Chains', RSC Continuous Flow Technology in Industry II conference, Cambridge, UK (2014).

Book Chapter

CMAC's Professor Joop Ter Horst has recently published a book chapter. Reference is:
J.H. ter Horst, C. Schmidt, J. Ulrich, Fundamentals of Industrial Crystallization, In: Nishinaga T, Rudolph P, editors, Handbook of Crystal Growth, Vol. II., Elsevier, 2015, pp. 1317–49.

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**

We are delighted that Bayer HealthCare has formally joined CMAC as a tier 1 member, joining founding members AZ, GSK and Novartis. Bayer Healthcare's key reasons for joining is their technical interest in CMACs pre competitive and 1:1 projects, access to talent pipeline and research quality. Also CMAC acts as an efficient portal to broader activities internationally. Bayer also hosted the 14th CMAC board meeting in Leverkusen in May at their Invite facility. Their wholly owned subsidiary Bayer Technology Services has also joined the group as a tier 2 member.

Olaf Queckenberg, Bayer Senior Vice President

Board Meeting

The most recent quarterly board meeting was held at Bayer's Invite Facility in Leverkusen, this included an annual strategy review facilitated by PwC.

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, GSK and Novartis and Bayer all get an individual seat on the CMAC Board and an opportunity to influence the direction of future research and Centre activity. The quarterly board meeting makes certain the centre's Industrial strategy stays on track with a demand led research programme, whilst providing Industry with the skills and the facilities to ensure translational research for multi-nationals and SME's represented by Sean Bermingham (PSE) and enabling supply chains of the future.

CMAC 14th Industry board meeting at Bayer Leverkusen in June

CMAC @ Achema 2015

In June, at the international Achema trade fair in Frankfurt, the Swiss division of the UK Science and Innovation Network supported a manufacturing event for CMAC. It was an opportunity to share knowledge with current members and inform potential technology partners of the benefits and future opportunities of working with CMAC.

Representatives from CMAC Tier 2 technology companies who presented at Achema

Industry & Knowledge Exchange

Tier 2 Partners

CMAC has increased its tier 2 company members to fourteen over the period: Mettler Toledo, Perceptive Engineering, Process Systems Enterprise (PSE), Cambridge Reactor Design, NiTech Solutions, AMtech, Clairet, Sirius, Technobis (Avantium), Alconbury Weston Ltd (AWL), Siemens with Price Waterhouse Cooper, Bayer Technical Services, and Booth Welsh. These companies bring a wide range of enabling technologies, equipment, experience and value to the CMAC industrial group. We look forward to increasing engagement and support from and with these businesses.

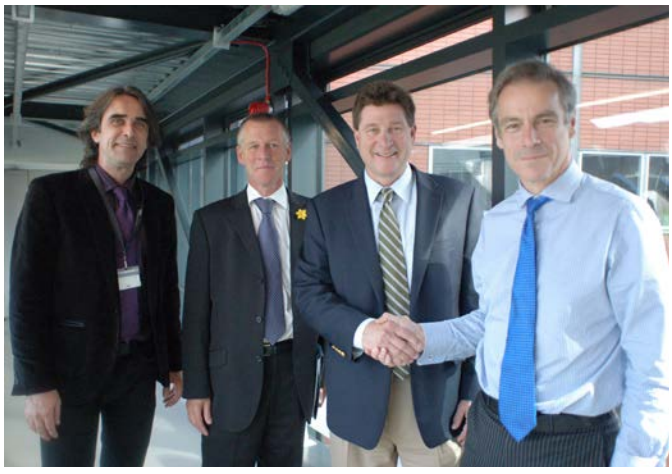
Collaborators

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

Mentor groups

Technical Committee

A separate 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. 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.



Mettler Toledo are strategic partners of CMAC having donated significant lab equipment and expertise in kind. Their equipment is used on CMAC workflows and their staff involved in a variety of projects. This includes a recent joint publication on particle sizing combined with image analysis

Mentor groups

The CMAC mentor scheme has been relaunched this year to enhance industry – academia knowledge exchange. The scheme is key for delivering industrially led research through detailed interactions in all technology areas.

The regular meetings provide a mechanism for 2-way interactions

- Industrialists are able share experience and provide guidance to the research projects ensuring industrial relevance and providing a context for the research.
- As a conduit for novel research approaches, methods and equipment from academia to be transferred and directly applied on live industry projects.

This close interaction facilitates matching student and companies for industrial placements and CMAC producing DTC researchers with industrially relevant knowledge and skill.

The growth of CMAC means that the scheme now comprises 7 groups with over 60 researchers and 25 industrialists involved. The mentors were initially from tier 1 companies, with tier 2 companies and collaborator companies becoming involved over the summer.

The mentor groups are multi-University and multi-company to benefit from the wide range of approaches and experience across CMAC. They act as an efficient way for industrialists to interact with 3-6 researchers from a minimum of 2 universities in each group rather than the classical 1:1 approach. With 4 telecons per year and two face-to-face meetings (held at different locations).

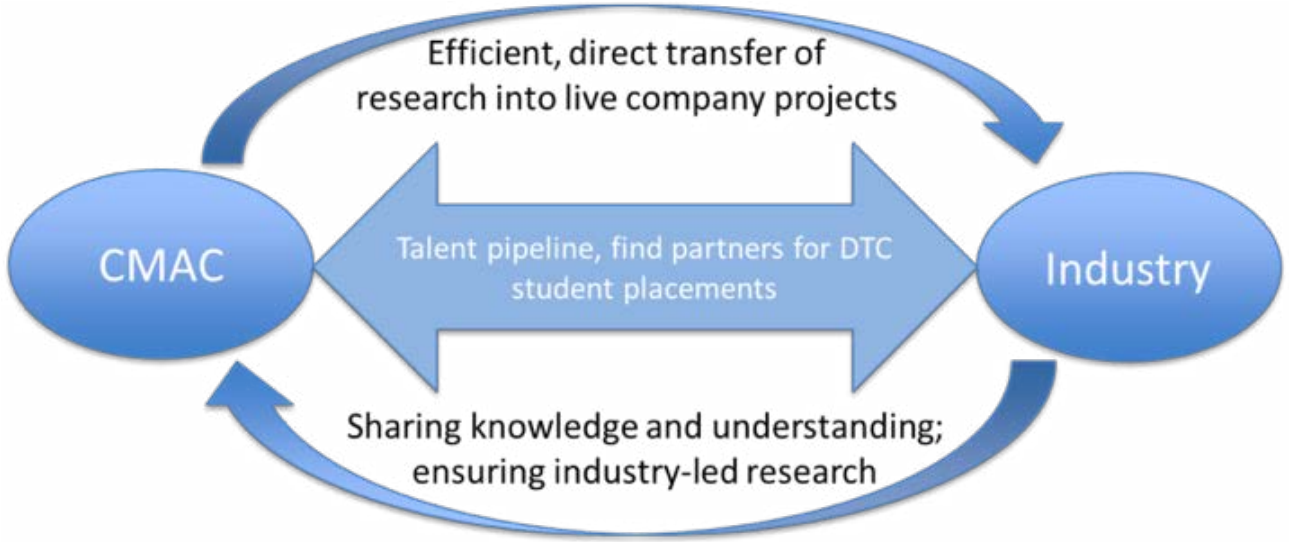
Examples of some benefits

- Rebecca Halliwell (Strathclyde University) has been working closely with Dr Mike Quayle, AZ to help shape her research into spray drying for inhaled pharmaceutical products.
- Juliet Adelukan (Heriot Watt University) visited Dr Mark Hartshorne at FujiFilm to test some different filtration equipment for her melt-crystallisation work.
- The Chick Wilson Group (Bath University) visited AZ, Macclesfield to better understand the characterisation of particles and the impact their properties can have in downstream processing.
- Jo Lothian (Strathclyde) worked alongside GSK. Her work at GSK looked into new and existing PAT for the monitoring and optimization of a continuous twin screw granulation (TSG) process.
- AstraZeneca find it a great opportunity to "Identify students to come on industrial placements which benefit both the student and the company".

Industry & Knowledge Exchange

Knowledge Exchange

Mentor Group



“Ideal format to Interact with our counterparts in other pharma companies in a pre-competitive environment.”

Dr Helen Wheatcroft
Senior Crystallisation Scientist, AZ

“Access to, experience and in particular the diversity of perspectives has been refreshing and thought provoking.”

Dr Peter Aspin
Particle Scientist, GSK

“Being part of CMAC mentor group is a great opportunity to discuss your PhD project with industry experts and highlight the “magic bullet” element to enhance your research towards industrial applications.”

Laura Martinez-Marcos

Industry & Knowledge Exchange

Industrial Placement Case Study: Kate Wittering Visits AstraZeneca

Kate Wittering (final year PhD, University of Bath) has recently completed a 3 month placement with Dr Sophie Janbon at AstraZeneca, Macclesfield where she was able to work on both live AZ projects as well as continue her own PhD research. Her experience working with the "Right Particle" team gave Kate a real insight into how particle formation and controlling particle attributes are critical to delivering high quality medicines. Kate worked on a live AZ compound to further optimise the continuous system that Dr Anna Jawor-Baczynska had initially developed during her placement at AZ in 2013, where she went on to become a member of staff. As part of this work, Kate ran demonstrations for AZ staff discussing various pro's and con's of the system as well as presenting the results to the whole department, thus significantly enhancing the profile of continuous processing and crystallisation within Chemical Development at AZ.

Dr Alexandria Parker, AZ Team Manager said

> "Kate's demo kick-started the consideration of continuous crystallisation on this project, something that would not have occurred on this timescale if she had not spent time with us."

During her PhD, Kate has developed the urea-barbituric acid co-crystal system from an evaporative crystallisation to a continuous crystallisation; scaling from a few mgs to 100's grams. The continuous crystallisation has been demonstrated in both an OBR and an MSMPR system (in collaboration with Loughborough University). Kate says "Access to the equipment and analytical capabilities at AZ at this critical stage of completing my PhD has offered me real added value".

Kate particularly benefitted from her placement through; training and understanding the extensive analytical capability at AZ, further characterisation of her products, extra data analysis and understanding additional features in the CCDC (Cambridge Crystallographic Data Centre) suite.

Industry & Knowledge Exchange

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 executed over the next three years 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 through five areas:

- Active pharmaceutical ingredient manufacturing
- Primary to secondary manufacturing
- Super-critical fluid technology
- Agile packaging
- Printed electronics

REMEDIES is led by GlaxoSmithKline (GSK), which will provide major inputs on clinical supply chains, with the University of Cambridge's Institute for Manufacturing (IfM) leading on commercial supply chain and overall research coordination, AstraZeneca (AZ) focusing on formulation developments, and the University of Strathclyde team within CMAC developing processing. Other industrial partners include major contract manufacturing organisations, equipment manufacturers and technology and system providers spanning the end-to-end pharmaceutical supply chain.

In addition to inputs from industrial partners, the collaboration also involves key institutional bodies across the UK pharmaceutical ecosystem – skills agencies, user representatives, regulators and health sector specialists – to ensure future, more adaptive supply chain models are supported by consistent standards and a unified approach to regulation. Activities will include two sector-wide platform projects focused on the end-to-end clinical and commercial supply chain, and several technology-specific application work streams.

CMAC is leading one of the technology-specific application work streams: Application A (App A) and technical lead Application B (App B).

REMEDIES APP A: Development of Mobile Continuous Process Equipment

The goal of REMEDIES App A project is the development of mobile continuous process equipment capable of a range of chemistries. App A will lead to cheaper, more efficient, higher quality manufacture of medicines that shorten the supply chain and are better able to deliver products with desired product characteristics/attributes to improve product performance. There are 8 partner organisations coming together in an effort to overcome the historic barriers to innovation in medicines manufacturing by reducing risk through a collaborative approach in a pre-competitive environment.

This project seeks to create an asset network for use by CMOs and primes. Each of the equipment providers will design and manufacture novel continuous reactor systems in a mobile skid format for demonstration on CMO's and Prime's specific molecules and at their manufacturing facilities which will allow the continuous processing of chemistries that cannot be done now.

App A is split into six strands to deliver the overall aims. There are two cross-cutting strands that 1) provide pre-competitive guidance, steering and the opportunity for all project members to be involved in setting specifications and agreeing on high-level goals for the chemistries to be targeted and 2) demonstrate and assess the value and benefit derived from the novel asset network. There are four equipment/inventor led strands which allow the inventor companies to work with end users in a protected IP environment to design and build flexible, modular continuous equipment to address key unmet technical needs.

> "Remedies project not only provides monetary support for our Innovation activity, but also allows us to demonstrate the value of our process technology"
>
> Ollie Tames, Intensichem

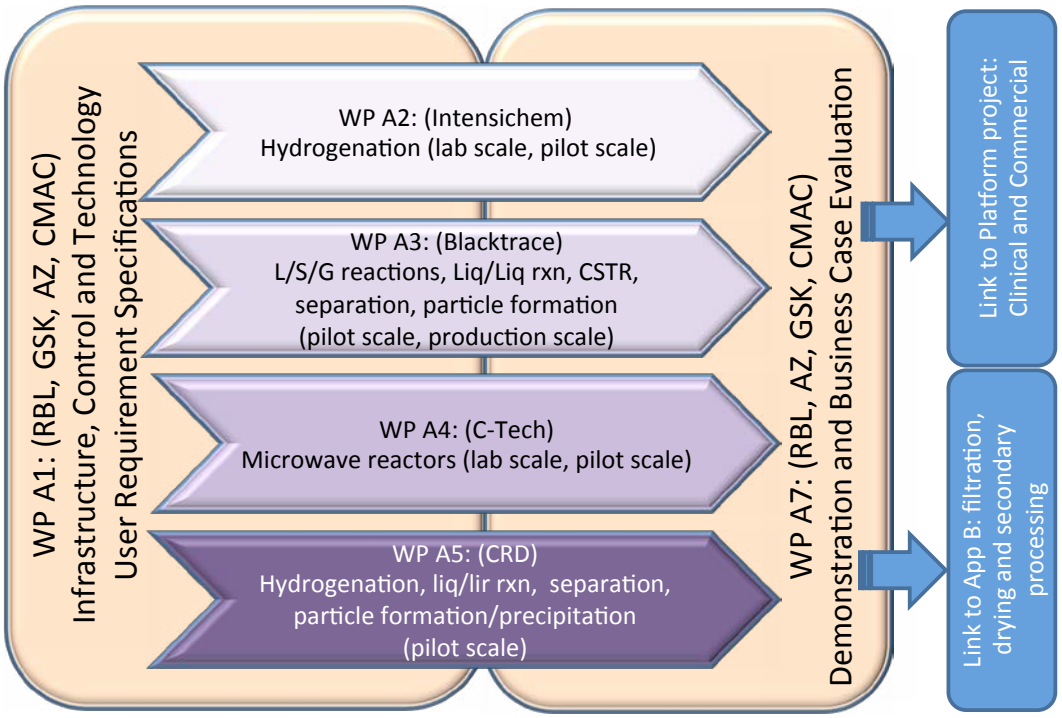


Figure 10: The partners supporting App A are Robinson Brothers, GSK, AZ, CMAC, C-Tech, Cambridge Reactor Design, Blacktrace, Intensichem and Mettler Toledo.

REMEDIES APP B: Primary / Secondary Formulation

REMEDIES App B is focussed upon linking primary to secondary processing.

The key objectives are:

- Generate understanding around the impact that API physical properties have on drug product process robustness and product quality.
- Develop API filtration/drying strategies that reduce processing time/cost and minimise negative impact on API physical properties
- Demonstrate flexible and agile drug product manufacturing capabilities which implement continuous processing operations, where product is monitored during processing and the process is adjusted based upon input API properties and in-process measurements.

To achieve this, App B has three technology strands:

Strand 1: Continuous filtration of drug substance: The strand will design equipment for continuous filtration of drug substance with the ability to reduce processing time, improve linkage to continuous drying and to deliver enhanced control over particle properties rendering the material more compatible with downstream drug product processes.

Strand 2: Continuous direct compression. This strand will define a design space for the implementation of continuous blending and direct compression (DC) in terms of critical material attributes and critical process parameters. Demonstrate potential for the wider application of continuous blending and direct compression.

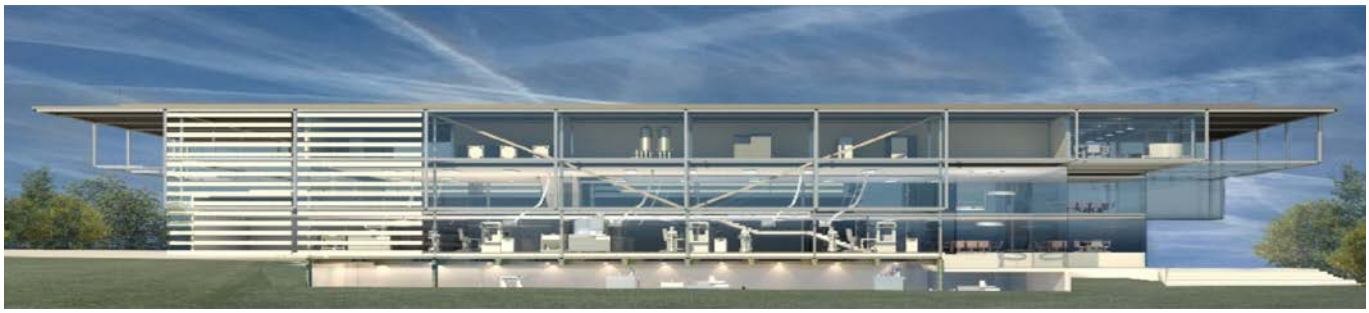
Strand 3: Hot melt extrusion. This strand will demonstrate the ability of hot melt extrusion technology to produce oral solid dosage forms in one continuous process. Demonstrate potential for the wider application of hot melt extrusion.

All strands will support the development of new methodologies and training packages to support advanced manufacturing technologies.

The partners supporting App B are GSK, AZ, CMAC, PSE, AWL, Cogent, Perceptive, GEA and Britest.

Industry & Knowledge Exchange

Medicines Manufacturing Innovation Centre (MMIC)



MMIC

The Medicines Manufacturing Innovation Centre has a very clear focus - to help the pharmaceutical industry make the switch to the ready now, new technologies. To do this it will pull technology from research centres (like CMAC), develop and then deploy into commercial facilities.

MMIC will be initially conceptualised and led by collaboration between Medicines Manufacturing Industry Partnership (MMIP), The Centre for Process Innovation (CPI) and Continuous Manufacturing and Crystallisation (CMAC) with steering from industry and other stakeholders.

Amongst its strategic aims, the centre will:

- Link primary and secondary manufacturing within one state of the art facility.
- Provide space for developing, demonstrating and deploying new innovations in pharmaceutical processing and technology platforms.
- Be flexible/adaptable in design, opening with a focus on continuous as the ready now technology but capable of handling new technology platforms as they come through.

To do this the MMIC will aim to:

- Reduce the cost and risk involved with the development and deployment of novel technology through collaboration.
- Provide a mechanism for industry to engage with key partners as a sector eg equipment suppliers, Contract Manufacturing Organisation's (CMO's), regulatory agencies.
- Develop people with the right skills to provide a future proof workforce.
- Provide space to stabilise processes, or equipment before deployment.
- Provide space and knowledge to experiment with future supply chain designs and developing business cases.

The facility has cross industry support, helping with the development of the facility concept. Both Scottish Enterprise, who are providing support for the project and Innovate UK who have representation on the steering team are fully engaged and supportive of this project. This will be a National Centre with links across the UK and a global reputation.

The centre will support the deployment of novel manufacturing technologies into manufacturing sites. The benefits these new technologies will deliver have been well documented. Product quality, manufacturing cost, capital spend at risk will all be positively affected and the benefit to patients will come from the move to agile supply chains delivering more stratified medicines. The facility will be able to run proprietary projects, but it will also enable the sector to work together when beneficial, in the development of regulatory standards, development of standardised technology platforms and the training of people with the right skills.

This facility has the opportunity to transform the supply chain of both new and existing pharmaceutical products. With regulators, pharmaceutical companies, equipment suppliers and academia all working together, the ambition of transforming supply chains of years to months will be realised.

The project team are looking to complete the business case, economic assessment and scoping exercise ready to apply for funding in September from both the UK and Scottish Government. If successful the aim is to have the facility operational by 2018.

The project team are also working on the details of concept development. This is led by CMAC with input from a broad spectrum of industry and academic contributers. EPSRC and Innovate UK are also key steering team members.

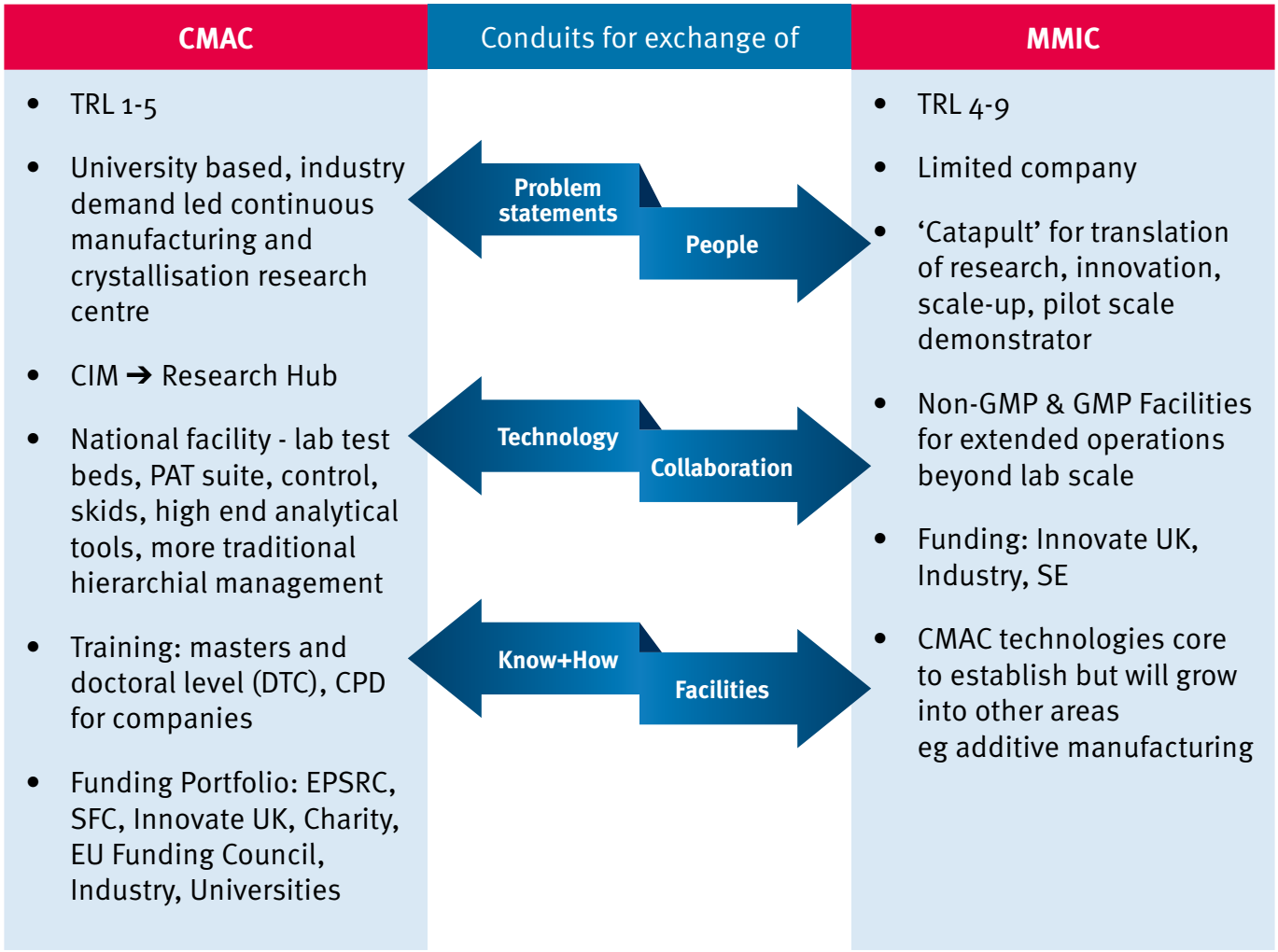


Figure 11: CMAC fit with proposed MMIC

Regulators

The University of Strathclyde hosts a cGMP formulation unit funded by Cancer Research UK. It is led by Prof Gavin Halbert who is also a QP. Ph 1 and 2 clinical material is produced with several products being commercialised. With this background CMAC are further developing their interactions and training with regulators. MHRA visitors pictured at a training event prior to audit with Prof Alastair Florence, Dr John Robertson and Dr Elke Prasad. CMAC is also developing strategic relationships with international partners. There are several initiatives with EMA and FDA. As a leading international group request for information was provided to FDA / BARDA.

MHRA visitors

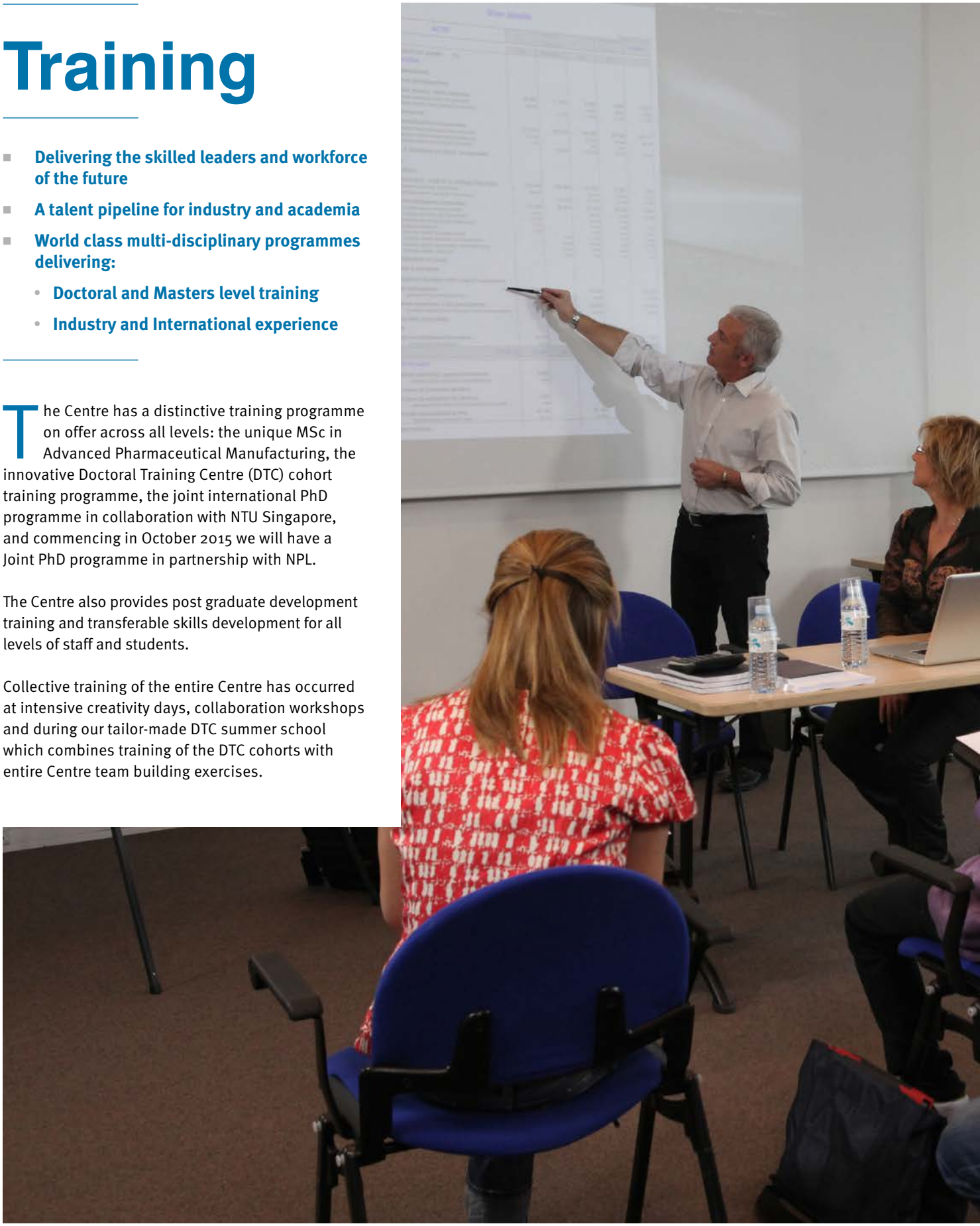
Training

- **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**

The Centre has a distinctive training programme on offer across all levels: the unique MSc in Advanced Pharmaceutical Manufacturing, the innovative Doctoral Training Centre (DTC) cohort training programme, the joint international PhD programme in collaboration with NTU Singapore, and commencing in October 2015 we will have a Joint PhD programme in partnership with NPL.

The Centre also provides post graduate development training and transferable skills development for all levels of 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 students and researchers benefit from support from internationally leading supervisors and expert industry practitioners and opinion leaders through the established industrial mentor scheme.

Mentor groups meet regularly to enable industry experts to coach the students in their research and provide industrial relevance and context for their work. The meetings are a mixture of telecon/webex and face-to-face meetings and involve both Tier 1 members as well as several Tier 2 companies. These mentor meetings have already enabled a student to access industrial analytical equipment and it is anticipated that they will also facilitate placements within the companies as students move into their second and third year. This is a key avenue for the research and learning in CMAC to be transferred into industry and an efficient way for companies to access and influence the ongoing research.

Training

The Doctoral Training Centre

The CMAC Doctoral Training Centre (DTC) commenced in October 2012, and offers a vibrant, world-class, multi-disciplinary four-year training programme that will equip graduates with leading edge skills in pioneering continuous processes. 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 (Figure 12) whereby year 1 of the PhD encompasses residential training weeks throughout all of the partner institutions with visits and input from industrialists.

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

i. Relevant fundamentals across each discipline,
ii. Current state-of the-art knowledge and the challenges in continuous manufacturing and crystallisation,
iii. Existing research activities both within the Centre and internationally and
iv. 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:

i. A range of taught modules covering the different aspects of the programme;
ii. Individual and group miniprojects;
iii. Transferable skills training.

To date three cohorts have completed their first year residential training weeks and are now in the research phase of their projects. A fourth cohort of ten students commence training in October 2015.

Cohort Building
- Induction
- Residential Training
- Open Days
- Industry Days
- Team building events
- Student forums
- Summer Schools
- Annual Colloquium/Dinner

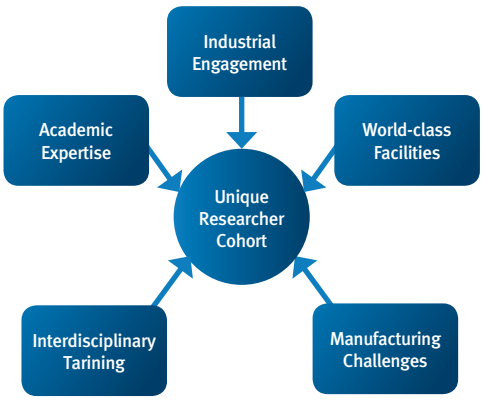
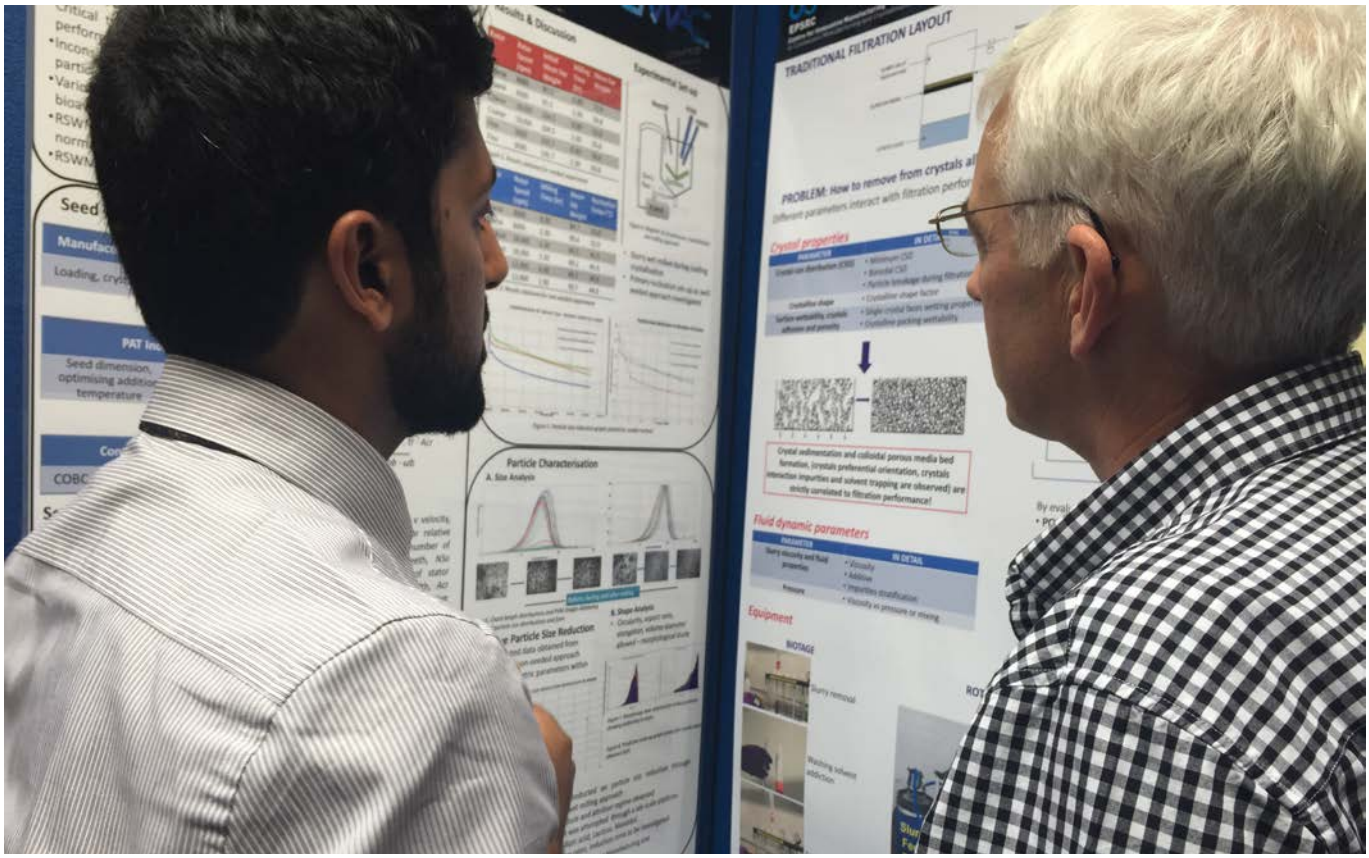


Figure 12. The DTC will create a new community of continuous manufacturing researchers.

2014 Cohort receiving their certificates on completion of the first year DTC training programme

Training

Joint International PhD Programme



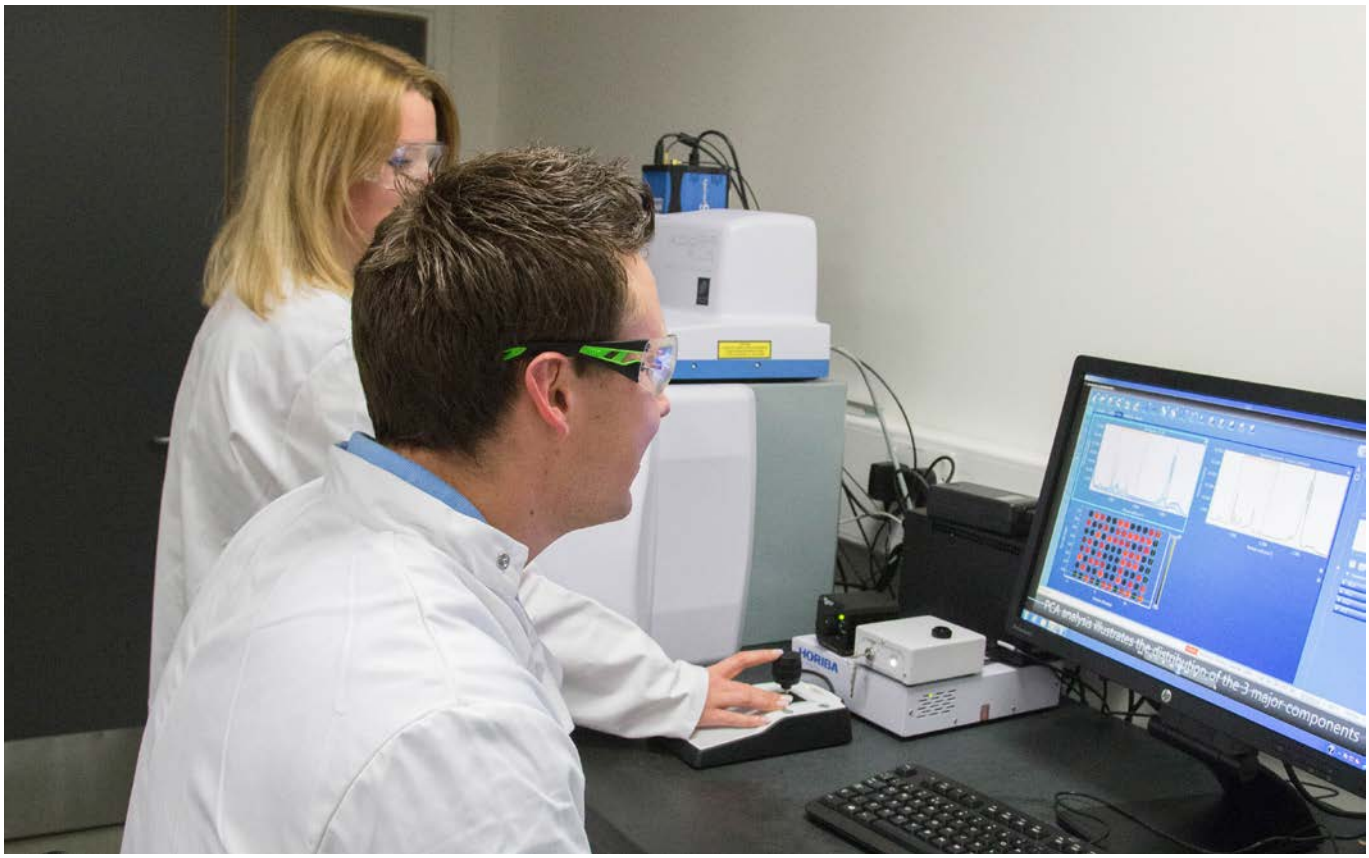
A Joint International Doctoral Training Centre in Continuous Manufacturing and Crystallisation of Pharmaceuticals was initiated as part of an EPSRC Global Engagements award in 2012/2013. The Centre established links with Nanyang Technological University (NTU) in Singapore via workshops and exchanges. 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. The first year of 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.

Academic Team:
Prof Alastair Florence (Strathclyde)
Prof Joop Ter Horst (Strathclyde)
Dr Iain Oswald (Strathclyde)
Prof Gavin Halbert (Strathclyde)
Dr Blair Johnston (Strathclyde)
Dr Philipp Seib (Strathclyde)
Dr Kunnito Ong (NTU)
Weiman Lau (NTU)
Zaher Judeh (NTU)
Samir Mushrif (NTU)

Training

Pharmaceutical Innovative Manufacturing Metrologies (PIMMs)



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 there will be three joint CMAC-NPL PhD studentships which will start in October 2015 with researchers splitting their time between the CMAC National Facility at Strathclyde and NPL laboratories in Teddington. Students will receive state of the art training in measurement science applied to a range of scientific disciplines and industrial challenges.

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.

Academic Team:
Prof Alastair Florence (Strathclyde)
Dr Dimitrios Lamprou (Strathclyde)
Dr David Watson (Strathclyde)
Prof Jan Sefcik (Strathclyde)
Dr Blair Johnston (Strathclyde)
Dr Alison Nordon (Strathclyde)
Prof Ian Gilmore (NPL)
Dr Alex Shard (NPL)
Dr Melissa Passarelli (NPL)

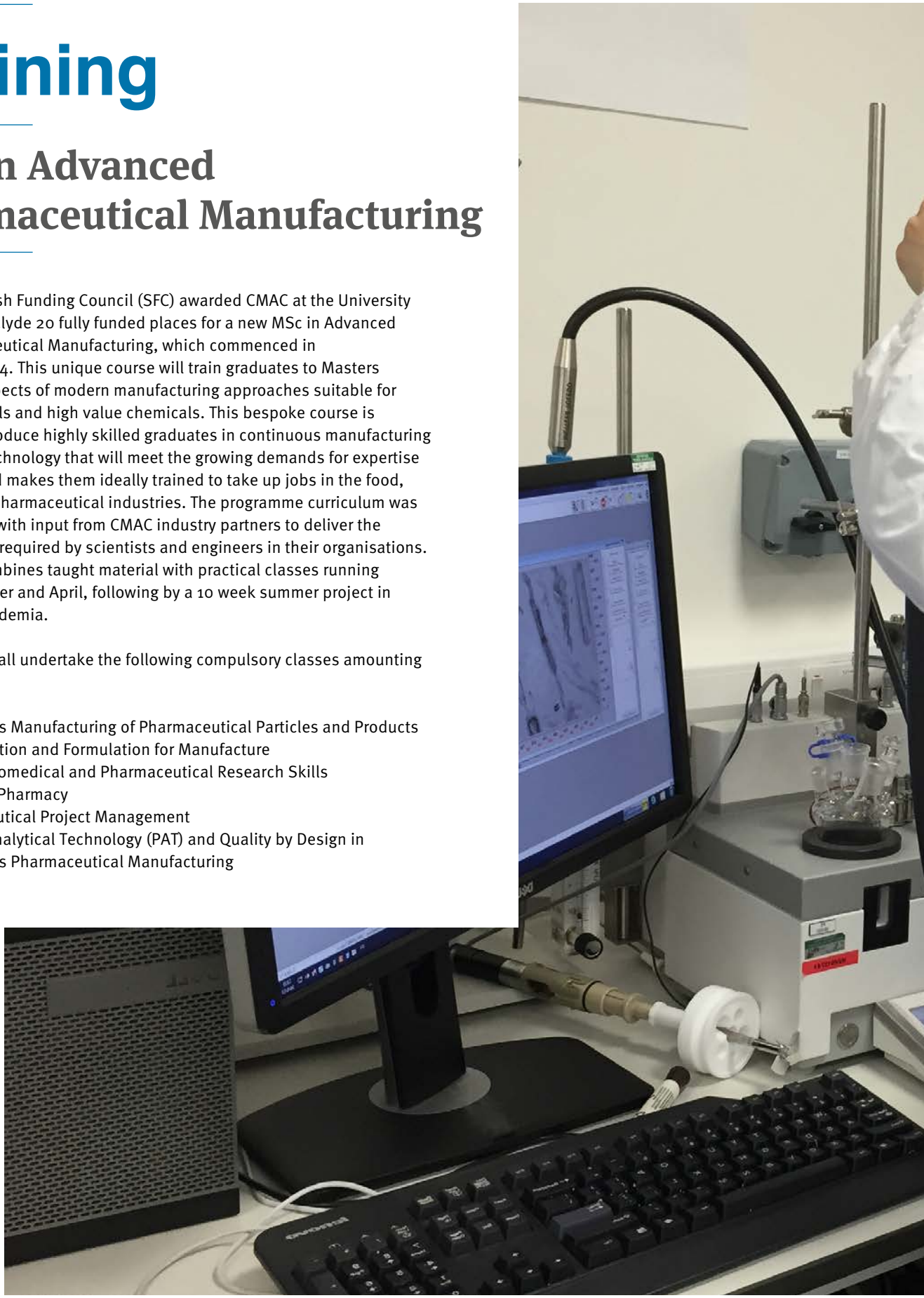
Training

MSc in Advanced Pharmaceutical Manufacturing

The Scottish Funding Council (SFC) awarded CMAC at the University of Strathclyde 20 fully funded places for a new MSc in Advanced Pharmaceutical Manufacturing, which commenced in September 2014. This unique course will train graduates to Masters level in key aspects of modern manufacturing approaches suitable for pharmaceuticals and high value chemicals. This bespoke course is designed to produce highly skilled graduates in continuous manufacturing science and technology that will meet the growing demands for expertise in this area and makes them ideally trained to take up jobs in the food, chemical and pharmaceutical industries. The programme curriculum was also designed with input from CMAC industry partners to deliver the practical skills required by scientists and engineers in their organisations. The course combines taught material with practical classes running between October and April, following by a 10 week summer project in Industry or Academia.

All students shall undertake the following compulsory classes amounting to 120 credits:

- 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




Optimax

Facilities

UNIVERSITY of STRATHCLYDE
CMAC
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**

Vision:

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

Mission:

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

The CMAC National Facility will deliver world class research, training and knowledge exchange with global reach as well as operating as a National Facility supporting users from industry and academia. Our advanced pharmaceutical manufacturing research facilities will be easily accessible by academics and businesses in the UK and internationally.

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

The facility is equipped using £11.4m funding awarded by the Higher Education Funding Council for England (HEFCE)'s UK research Partnership Investment Fund (UKRPIF) and supported with £22.8m industry and charity contributions. The National Facility will establish 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 crystallization and research capability under one roof and the capability includes key items of equipment:

- ToF-SIMS is only one of its type in Scotland
- CRD filtration Robot – one of only 5 in existence
- Secondary Processing Suite
- Modular Skids
- AFM is the most advanced model available in Europe
- SEM is the only benchtop field emission source model currently available
- World class, extensive suite of X-ray diffractometers

"

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

Facilities | CMAC National Facility

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 will benefit four key areas:

- **Equip a physical hub within the Strathclyde TIC with a full complement of research equipment and instruments**. CMAC will establish a world leading National Facility housed within a dedicated laboratory within the new Technology Innovation Centre (TIC) building at Strathclyde. This will support 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 Centre will have a main physical hub that offers unparalleled research capability to identify, understand, monitor and control critical aspects of continuous manufacturing and crystallisation.

- **Allow the Centre to build bespoke manufacturing research skids**. These modular, reconfigurable process platforms and systems will exploit current understanding and develop new laboratory-scale technologies that will meet the need for continuous manufacturing capability from molecular synthesis to complex formulated product.

- **Provide state-of-the art facilities across our strategic National Centre HEI partner laboratories**. Aligned with our National Centre strategy, this will establish a linked network of shared and common continuous process monitoring and control tools across the wider community, ensuring access to dedicated high-value equipment locally.

- **Prototype a novel open access culture for the UK pharmaceutical and high value chemical development community**. In addition to the flagship TIC facility, this will include open access facilities offered by companies including AstraZeneca as part of the RPIF support.

CMAC within the TIC Building

The demand-led vision of the UKRPIF partnership perfectly aligns with the University of Strathclyde's estates and research strategies creating a focus for technology and innovation that connects high quality research to outcomes with impact. This vision will 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 Strathclyde's priority themes tailor-made high quality accommodation is now occupied by CMAC on levels 1, 6 and 8 of the TIC building. This constitutes 900m^2 of specialist laboratory space supported by storage and ancillary areas, across all 3 levels.

On level 6, environmentally friendly office accommodation, meeting rooms, and breakout space is provided for all staff.

Being located within the TIC building, CMAC now has access to shared facilities such as a clean room suite, workshops, conferencing facilities, Knowledge Exchange area, café and exhibition space. These facilities will be put to good use in late 2015 when the Centre hosts the Annual CMAC Open Day in the new TIC building. Office areas are fully furnished to a high standard and will provide all facilities to support the Researchers activities.

Facilities | CMAC National Facility

Laboratories and Equipment

The laboratory accommodation in TIC is over 900m^2 including a cluster of 12 multi-functional walk-in fume cupboards and a dedicated enclosure for primary processing. The three main areas of laboratory space include: dedicated analytical areas for advanced understanding of particulate formation and processing; a secondary processing suite; and a primary process area with reconfigurable walk-in fume hoods for the development of advanced multi-phase continuous processes. Stores and ancillary areas have been designed to complement the unique activities carried out in the laboratories to support the programme.

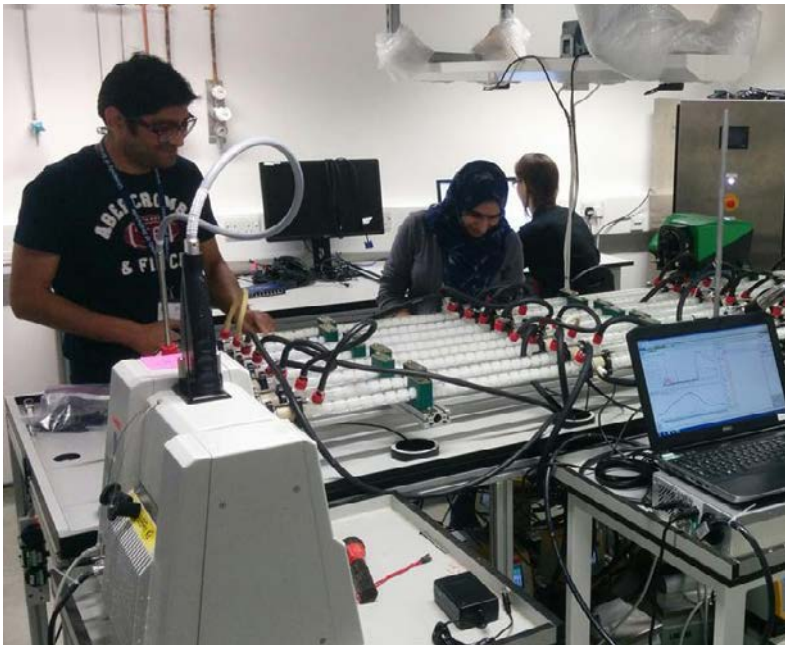


Image. DN15 up and running with model and control software from Perceptive Engineering

Images. Level 8 lab before and after equipment arrived

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 cupboards 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.

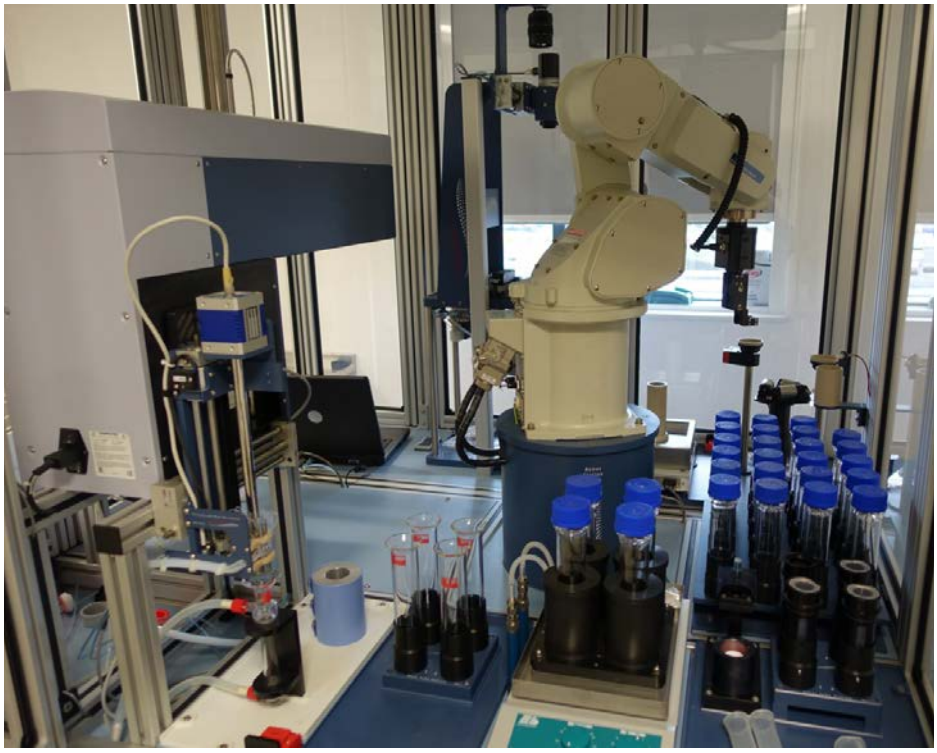
Secondary Processing Suite

A purpose built collection of rooms will house our entire formulation capability. These rooms are equipped with flexible exhaust ventilation, 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

X-ray Analysis Suite

We have a dedicated X-ray suite housing 3 Bruker D8 Advance XRPDs, a D8 Venture single crystal, new Bruker powder XRD and PANalytical. The X-ray Nano-CT will be operational late September. CMAC, together with colleagues from BioNano and Physics, were successful in a recent EPSRC equipment award which will fund a Small Angle X-ray Scattering (SAXS) instrument.



Process Development Laboratory

This lab provides four regular 2m wide fume hoods for smaller scale activities. It houses the filtration robot designed by Cambridge Reactor Design and donated to CMAC by GSK, as well as the Zinsser Process Understanding Platform.

Image. Filtration Robot donated to CMAC by GSK

Facilities | CMAC National Facility

Material Characterisation Laboratory

Our largest analytical lab houses all of our capability in terms of being able to fully understand and characterise materials, be it powders, tablets, slurries etc. Instrumentation includes: gas and liquid chromatography; porosity, density, and surface area analyses; dynamic vapour sorption (DVS) including organic vapours; inverse gas chromatography using a Surface Energy Analyser (SEA); powder and liquid rheometers; particle size and shape analysis using Malvern and Sympatec instruments; dissolution testing following protocols USP 1, 2, 4, 5 and 6; 2D-UV dissolution testing; solubility screening; and compression testing.

Microscopy Suite

Inside a vibrationally sensitive laboratory, CMAC houses its microscopy capability. This includes automated compound and inverted optical microscopes, IR and Raman microscopes, plus a SEM. This represents a step-change in the manner in which physical samples can be imaged and chemically analysed. It also represents the first piece in the workflow around surface imaging.

Wolfson Pharmaceutical Surfaces Laboratory

We are hugely grateful to the Wolfson Foundation for the award of £750k, with UK RPIF contributing the rest, for the ability to purchase a TOF-SIMS instrument. This instrument will sit in its own dedicated laboratory. The TOF-SIMS and both AFMs are located on level 1 in TIC. As a result nanoscale physical and chemical understanding will be easily achievable for all CMAC researchers.

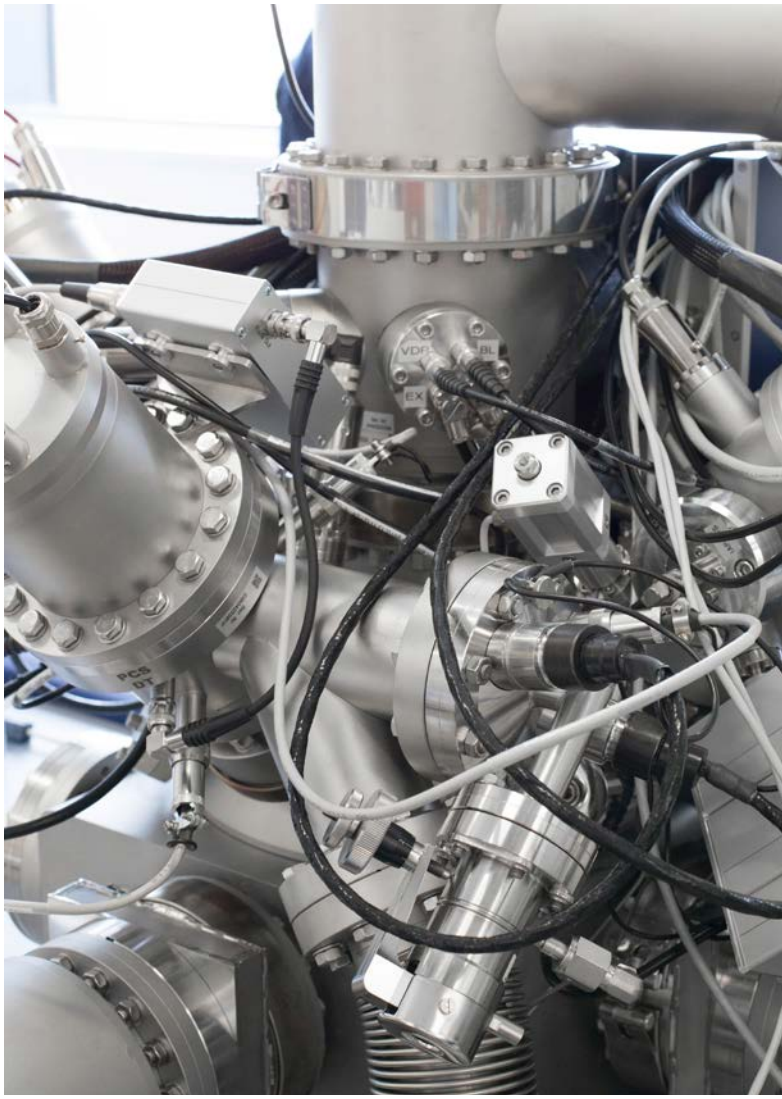


Image. TOF-SIMS Instrument in CMAC National Facility

Facilities

Technology Events at TIC

CMAC has hosted training events to support the commissioning of new pieces of equipment and uptake of new techniques as a result of purchasing through the UK RPIF award. Such events are a great way to engage with technology providers and give students excellent hands on experience as part of their training programme.

- Bronkhorst demonstrated Mass Flow meters and controllers
- Leica held part one of the microscope training course
- Bruker trained us on IR spectroscopy across PAT and microscopy
- Horiba training on the Raman microscope
- Radleys held a mini-workshop on their Reactor Ready stirred tank reactors
- Ocean Optics on their UV/Vis, NIR, and Raman PAT
- Malvern showed us how to use the new HydroSight accessory for the Mastersizer 3000
- Perceptive Engineering held a 2 day workshop on PharmaMV in relation to all process platforms at CMAC that have been automated by Perceptive
- Powder Technologies informed us about powder rheology
- Photron provided training on the high speed cameras
- Mettler Toledo gave a demo of the new V19 PVM probe

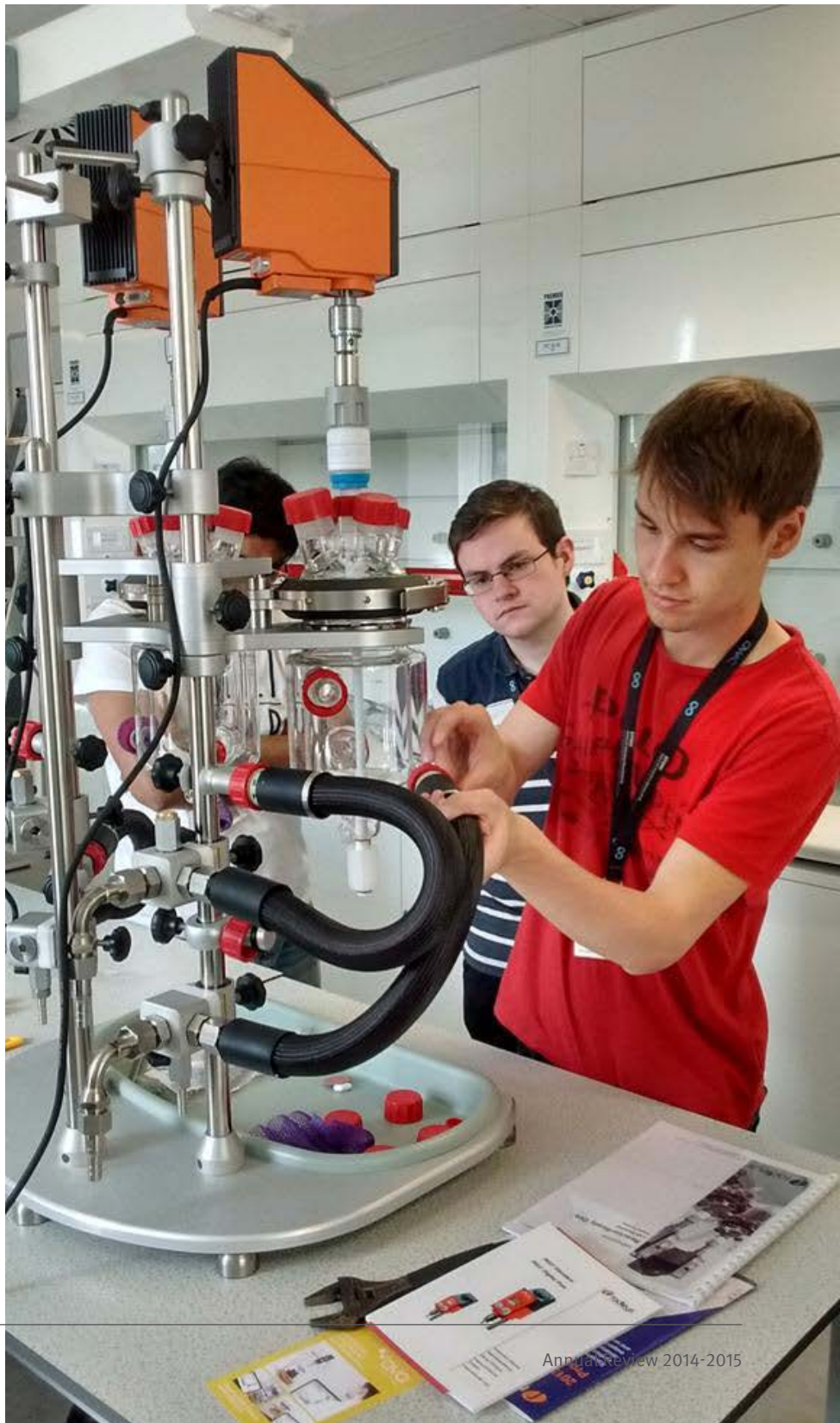


Image. Radleys training workshop

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. In accordance with the growth of the Centre, outreach activities and events and academic and industry collaborations have also escalated. We engage 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 13) and has an abundance of engagements including those with EPSRC Grand Challenge networks, iCON PI's, CPI (HVM catapult), KTNs and collaborative TSB R&D projects. As a National Centre there has been a high degree of developing strategy and influencing policy in the area of continuous manufacturing (Figure 13).

To date the Centre is enthusiastically engaged with TSB, SCI, IChemE, KTNs, CIA, RSC, MMIP and is a member of ASPIRE. We have received press coverage from announcements from Rt Hon David Willets and Rt Hon Vince Cable visited our facilities to officially open Phase I of our RPIF award. We have been visited by the Swiss Ambassador Dominik Furgler, to discuss potential UK – Swiss opportunities. Also in January 2014 the Foreign and Commonwealth Office's Chief Scientific Adviser (CSA), Prof Robin Grime, visited CMAC.

In April 2015 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.

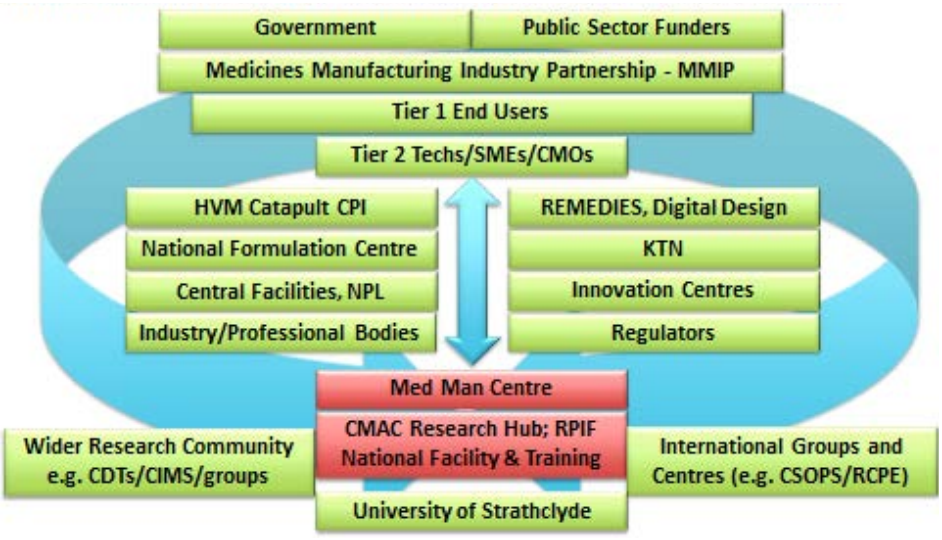


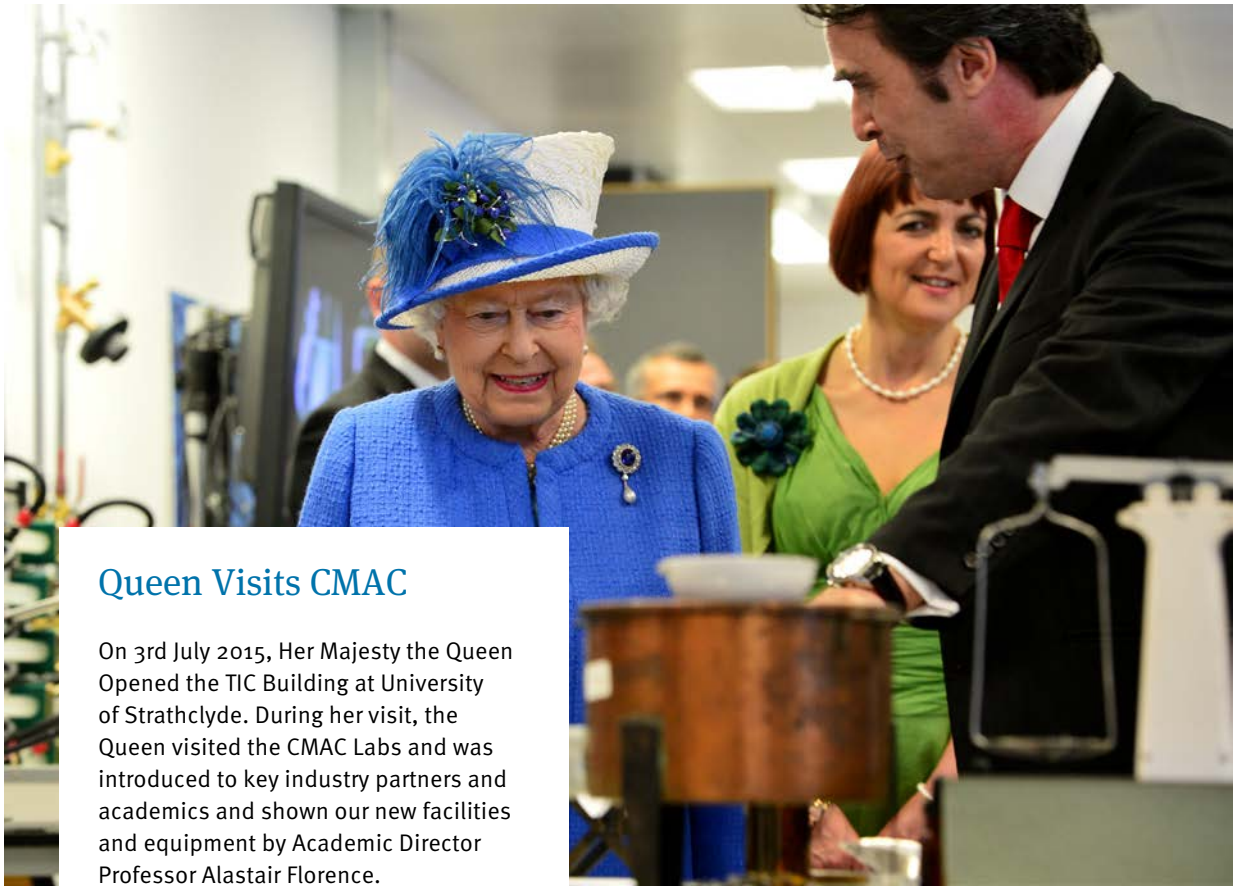
Figure 13. Pharmaceutical manufacturing Innovation System Landscape: CMAC Stakeholder Map

“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.”

National Centre | Being A National Centre

2015 Open Day and National Facility Launch

CMAC Annual Open Day 2015 will take place on 23rd and 24th September at the Technology and Innovation Centre, University of Strathclyde, Glasgow. The programme will include talks from industry and invited academic speakers, posters presented by all Centre researchers, exhibitions from a range of world leading technology companies and will feature the official opening of the new CMAC National Facility.



Queen Visits CMAC

On 3rd July 2015, Her Majesty the Queen Opened the TIC Building at University of Strathclyde. During her visit, the Queen visited the CMAC Labs and was introduced to key industry partners and academics and shown our new facilities and equipment by Academic Director Professor Alastair Florence.

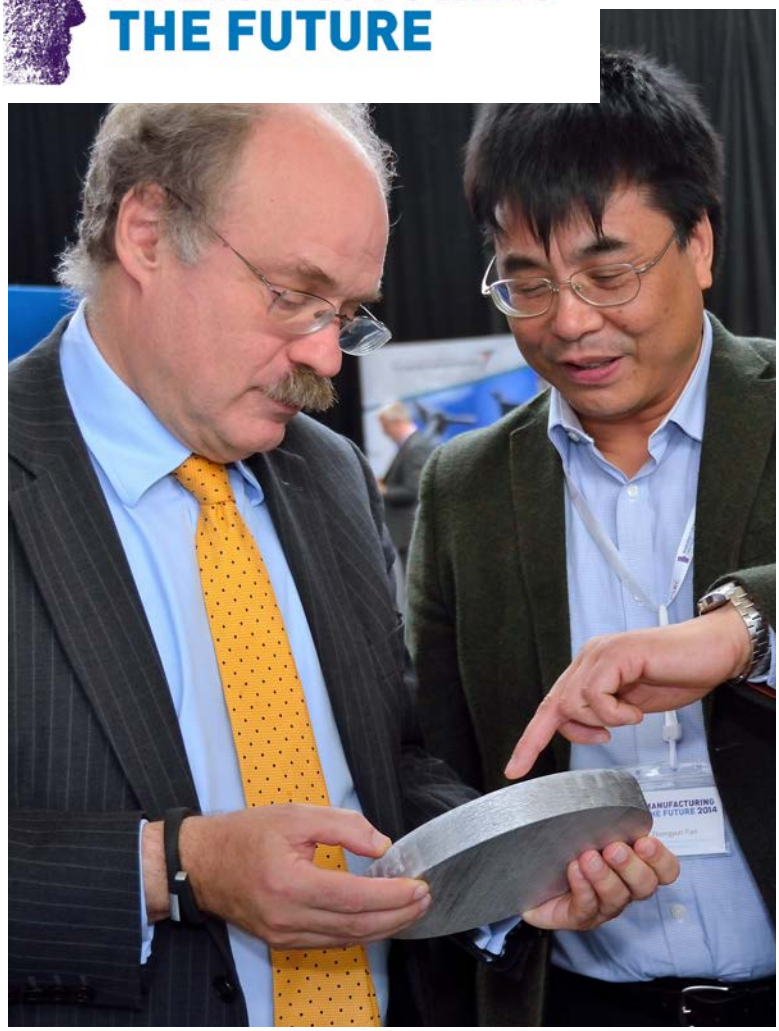
3rd EPSRC Manufacturing the Future Conference

CMAC hosted the nation's 3rd EPSRC Manufacturing the Future Conference at Glasgow Science Centre in September 2014. The Conference was chaired by Professor Alastair Florence, Academic Director of CMAC. The conference was a huge success with almost 400 delegates and has received outstanding feedback from all who attended.

The annual conference provides a national forum for the UK manufacturing research community to share experience, progress and challenges in progressing UK manufacturing. The event also provided a platform for early career researchers to showcase their excellent contributions to the manufacturing research community and contribute to debate on how to move forward.

Mr Atti Emecz, Director of EPSRC, opened the conference. CMAC featured highly in the programme, with CMAC Chair Prof Paul Sharratt, ICES; CMAC Co-Investigator Prof Sir Mike Gregory, University of Cambridge and CMAC Board member Dr Mark Buswell, Head of Advanced Manufacturing Technologies, GSK giving Plenary Lectures. Other Plenary speakers were Sir Mark Walport, Government Chief Scientific Adviser and Archie MacPherson, AFRC. Principle Sir Jim McDonald; Mark Claydon-Smith, EPSRC; and Alastair Florence, Academic Director of CMAC closed the conference.

There were over 120 posters and 26 exhibitors, including all of the EPSRC Centres for Innovative Manufacturing, EPSRC, Mettler Toledo, Alconbury Weston Ltd, and the Welsh Centre for Printing and Coating/Swansea University to name a few.



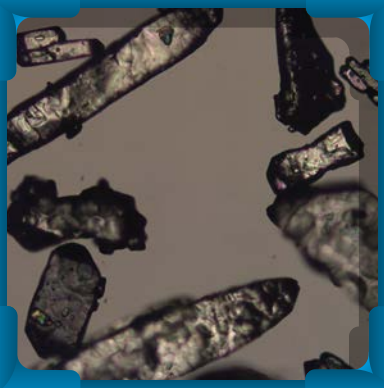
The conference dinner was held in Kelvingrove Art Gallery in Glasgow

National Centre

Talent Pipeline

INPUT

- Dr Nazer Rajoub (PDRA Strathclyde), Heriot Watt-Total company
- Dr Anna Trybala (PDRA Loughborough)
- Dr Nadeem Javid (PDRA Strathclyde), Prof. Ulijn's Group Strathclyde
- Dr Elke Prasad (PDRA Strathclyde), Pharmaceutical Project Manager at Biofilm Limited
- Helen Feilden (Assistant Centre Manager), Network Co-ordinator for SMSdrug.net
- Nina Denver (Lab Technician). MSc Uniwersytet im. Adama Mickiewicza and Paris Sud 11 University
- John Mulgrew (Project Manager App A REMEDIES), Integra Life Science
- Dr John Robertson (Senior Research Fellow App B REMEDIES), GSK
- Dr Pol MacFhionnghaile (PDRA Strathclyde), AbbVie (formally Abbott)
- Tim Faehnrich (Management Accountant) Consultant in Financial Services and Accounting in Higher education sector in the UK
- Dr Muhhamad Tariq Islam (PDRA REMEDIES AppB), PhD from University of Greenwich, UK
- Dr Vijay Srirambhatla (PDRA CPOSS) Solid Form Solutions, UK
- Dr René Steendam (PDRA Strathclyde) PhD from Radboud University in Nijmegen, the Netherlands.
- Claire Ordoyno (International Collaboration Co-ordinator), Drug Delivery International



OUTPUT

- Dr Peter Hamilton(Strathclyde), GSK, UK
- Rajan Talati (Strathclyde), MacFarlane Smith, UK
- Dr Laura Palmer (Strathclyde), Johnson Matthey, UK
- Dr Ulrich Schacht (Strathclyde), Mettler Toledo
- Dr Ali Saleemi (Loughborough), GSK, UK
- Dr Craig Callaghan (Heriot Watt), Solid Form Solutions, U.
- Dr Rasjni Miglani (Strathclyde), pharmaceutical industry, US
- Jaclyn Dunn (Strathclyde), CPACT, UK
- Dr Victor Sans Sangorrin (Glasgow), University of Nottingham, UK
- Dr Catriona Clark (Strathclyde), iBioIC, UK
- Dr Anna Jawor-Baczynska (Strathclyde), AstraZeneca, UK
- Dr Naomi Briggs (Strathclyde), MIT, US
- Thomas Ball (Strathclyde), pharmaceutical industry, Ireland
- Nina Denver (Strathclyde), PhD at University of Glasgow, UK

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.

National Centre

Academic Engagement

CMAC Innovations in Continuous Work-up Workshop

The Centre launched a call in June 2013 for funding "iCON" projects which stimulated the Centre's engagement with the wider UK research community under the Continuous Processing Work-Up Theme. Continuous work-up is an area outside the Centre's core research but was identified as a key gap in enabling the uptake of continuous processing at the initial industry workshop held at Novartis, Basel to identify key problem statements. This allows the project outputs to expand the Centre's knowledge and understanding of the pre-crystallisation supply chain. 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. Industrial mentors provided steering and stimulated interest in this area. In February and March 2014, project kick-off meetings took place for all seven projects as detailed below.

iCON Day

A workshop was held in March 2015 where all project leads showcased their work. The event was also attended by interested parties from CPI, the KTN, industrialists and academics where the portfolio was conceived to be key to driving the uptake of continuous processing.

The morning comprised 6 stimulating presentations from Frans Muller (University of Leeds), Alexei Lapkin Cambridge University), Svetlana Ignatova Brunel University), Paulo Filliponi (Ian Baxendale group, University of Durham), Andrea Rayat and Mike Hoare (UCL), Eric Sliwinski (Steve Ley group, Cambridge University). The afternoon was spent assessing the current landscape identifying key gaps, areas requiring continual improvement and other groups/companies who are active in this area. There was also time for networking and detailed 1:1 discussions. CMAC has provided a short report to attendees and any other interested parties and will use this to drive and influence funders in this under-researched 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

Internationalisation

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

I2APM: International Institute of Advance Pharmaceutical Manufacturing

CMAC are co-founders of this International Institute alongside C-SOPS (US) and RCPE (Austria), Figure 14. The I2APM 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.

SAVI

Institute members, CMAC and C-SOPS have already obtained circa $1m in funding from the SAVI scheme, joint NSF-EPSRC funding. This funding allows the Institute to coordinate researcher and faculty exchanges in addition to holding workshops to develop cutting edge technology road maps and work with regulators to accelerate the adoption of continuous manufacturing. The funds will also be used to establish a core set of training modules that will be offered by the institute to academic researchers, staff and industrialists.

Graz Workshop

In February 2015, the second face to face workshop took place in Graz, Austria hosted by RCPE Director Professor Johannes Kinnast. This workshop was a follow-up to the 2014 Puerto Rico workshop and participants included representatives from GSK, AZ, Johnson and Johnson, Bayer and Novartis as well as academic institute members. Discussions took place which sought to align and connect research projects which require specific collaboration between centres. Feedback was obtained from industry representatives on I2APM and how the needs of industry are met by participating in this project.

I2APM conference

The first showcase for the institute is scheduled for March 2016. This will be combined with a unique training event.

2015 also saw visits to the new CMAC National Facility by C-SOPS centre director Fernando Muzzio in May, and Alberto Cuitino (Rutgers)and Rajesh Davé (NJIT) in July. CMAC also hosted Ridade Sayin from Purdue University for 12 weeks under the supervision of Prof Gavin Halbert.

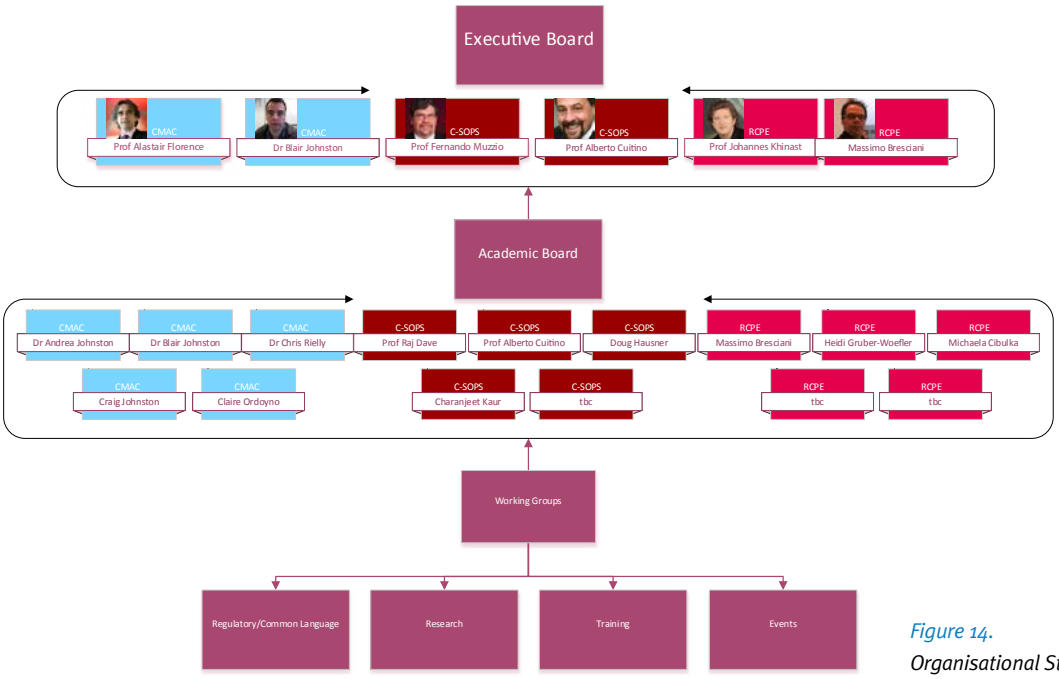


Figure 14.
Organisational Structure of I2APM

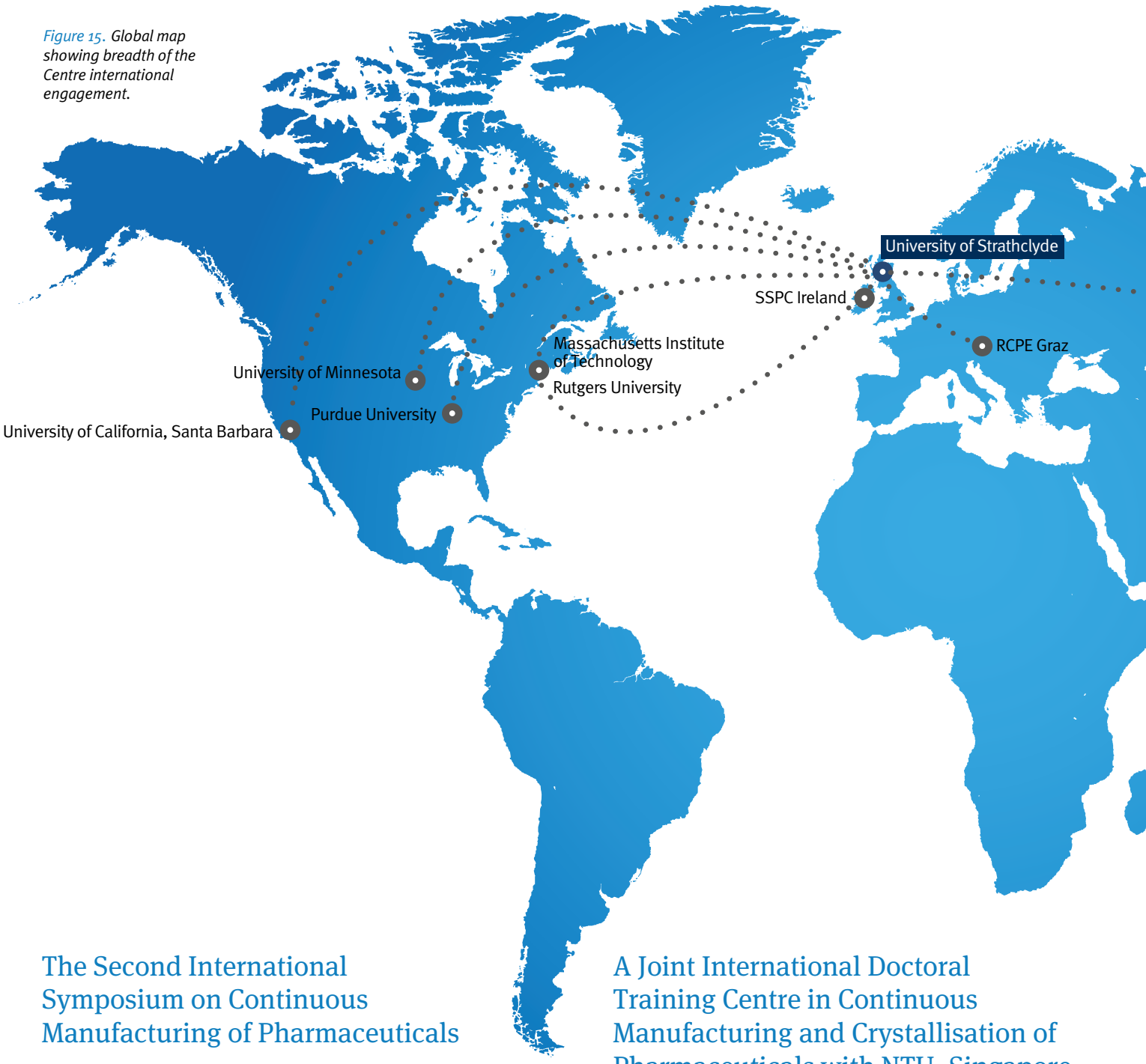


Figure 15. Global map showing breadth of the Centre international engagement.

The Second International Symposium on Continuous Manufacturing of Pharmaceuticals

The organising committee for the CMAC-MIT International Symposium on Continuous Manufacturing of Pharmaceuticals has started to develop plans for a 2nd event to be held in Boston in 2016. This principal aim is to again bring together leading industry practitioners, academics and regulators to discuss progress made since the first event in 2014, building on the recommendations made in the whitepapers published in J Pharm Sci. The event will share case studies and practical examples and facilitate further discussion on key topics highlighted by the community.

A Joint International Doctoral Training Centre in Continuous Manufacturing and Crystallisation of Pharmaceuticals with NTU, Singapore

CMACs links with Nanyang Technological University (NTU) have led to establishing a joint doctoral training programme which commenced earlier this year. The first cohort has 6 students in place, 3 at Strathclyde and 3 at NTU and each student will have joint supervision from both universities and will have the experience of a 6 month international placement at their partnering institution.

Researcher Secondments

- Rebecca Halliwell, AZ Sweden
- Hosted Ridade Sayin from Purdue University
- Nazer Rajoub, GSK US
- Thomas McGlone, US trip

White papers

On 20th – 21st May 2014, CMAC co-hosted the first International Symposium on Continuous Manufacturing of Pharmaceuticals at MIT, US (https://iscmp.mit.edu). This prestigious event was attended by the world leaders in continuous processing, with pharmaceutical end users, suppliers, regulators and academics who discussed accelerating the adoption of continuous manufacturing for both small molecules and biological products and how global research groups are contributing towards the new technology and approaches.

Dr Clive Badman (CMAC Chair) was Cohost. The key outputs from the symposium were eight white papers. Alastair Florence, Craig Johnston, Jag Srai, Clive Badman, Jon-Paul Sherlock, Markus Krumme and the wider CMAC Network contributed to the papers entitled 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

Research Case Studies

Developing Workflows for Continuous Crystallisation

Academics:
Prof Alastair Florence (Strathclyde),
Prof Chris Rielly (Loughborough)
Prof Jan Sefcik (Strathclyde)

Researchers:
Dr Cameron Brown (Strathclyde)
Dr Pol MacFhionnghaile (Strathclyde)
Dr Thomas McGlone (Strathclyde)
Dr Anna Trybala (Loughborough)

Considerable time has been spent as part of the Phase II research campaign designing and implementing a workflow for continuous cooling crystallisation.

Below is the current version of the workflow for cooling crystallisation with the following qualifying statements:

- 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)

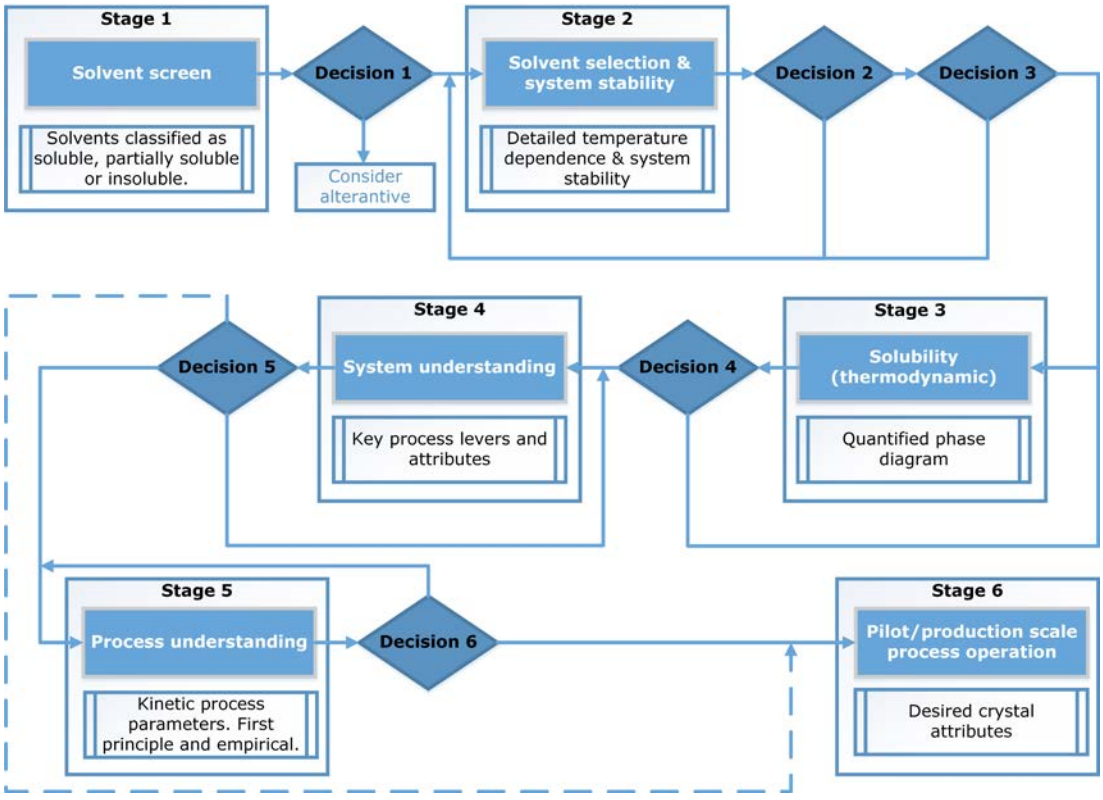


Figure 16. High level overview of the current cooling crystallisation workflow showing the six critical stages and the decision points for each.

The workflow is broken into 6 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: Solvent Screen

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. These are then scored based on dissolution class, cost and hazard. The top 5 – 10 candidates are carried forward to Stage 2.

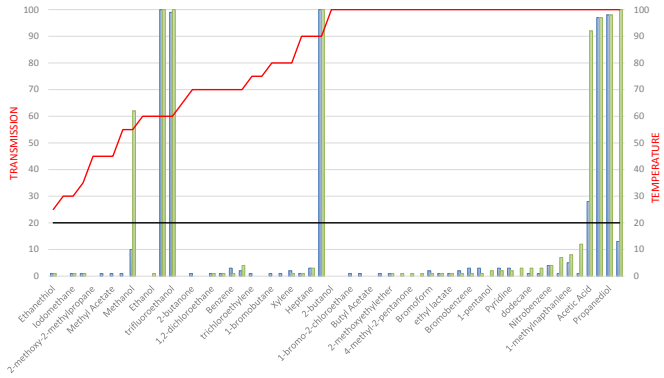


Figure 17. Typical output from the solvent screening stage.

Stage 2: Solvent Selection & System Stability

Of the reduced number of solvents carried forward from Stage 1, 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. When a solvent system is selected, the crystallised material is characterised both physically and chemically.

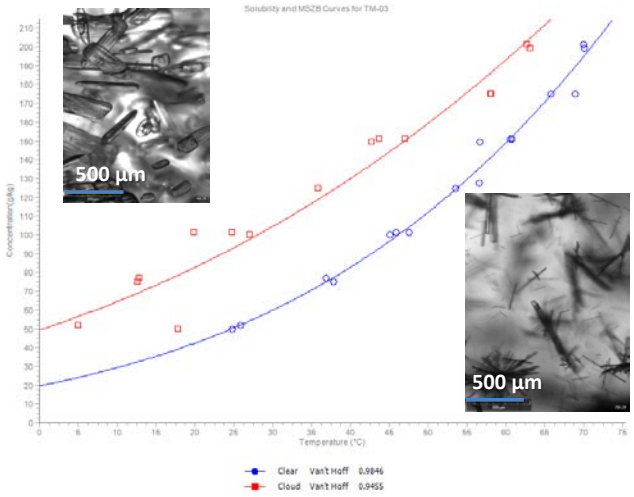


Figure 18. Typical output of an approximate phase diagram for Stage 2.

Stage 3: Solubility (thermodynamic)

With the selected solvent system from Stage 2, as 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.

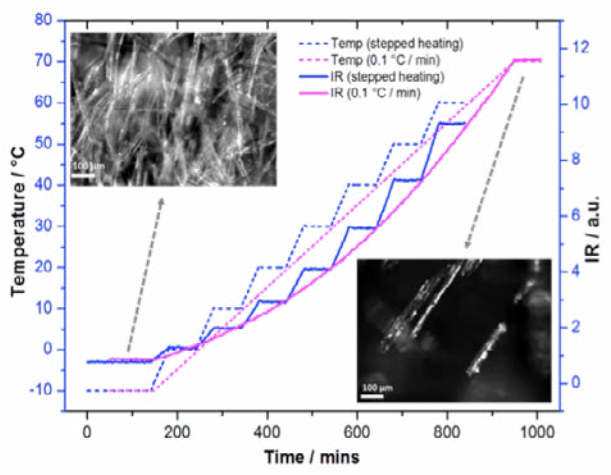


Figure 19. A specific, ramped heating profile is used to determine accurate temperature dependent solubility diagrams.

Stage 4: Process Understanding

The process conditions for a desired crystallisation are investigated with the primary objective being platform selection. A series of studies including single crystal growth in a flow cell, fouling propensity and secondary nucleation assessment are performed to inform the process design. Automated batch evaluation platforms including the Optimax and MF-OBC are used to determine MSZW under the harshest conditions (agitation, cooling rate) in addition to direct supersaturation control experiments to assess potential residence time.

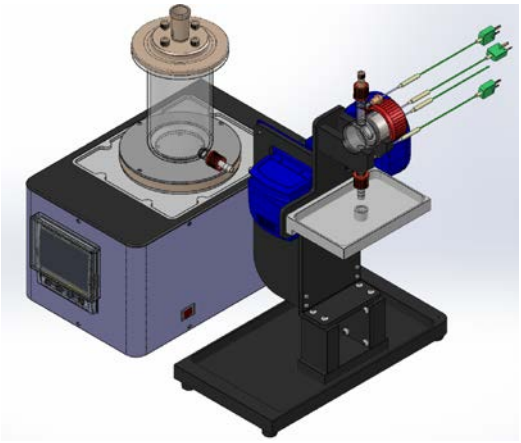


Figure 20. Image of the platform used to assess fouling propensity – 1 of the investigative process assessments in Stage 4.

Developing Workflows for Continuous Crystallisation

Stage 5: Parameter Estimation

While it is entirely feasible to proceed from Stage 4 to Stage 6 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 21. Typical process flow diagram from gCRYSTAL.

Stage 6: Pilot/production Scale Process Operation

From the detailed outputs of Stage 4 and 5, 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 22. Engineering diagram of a skid-mounted COBC – one of the process platforms utilised in Stage 6.

Research Case Studies

Rapid and Efficient Method of Solvent Screening of Organic Solvents

Academics:
Dr Andrea Johnston (Strathclyde)
Dr Blair Johnston (Strathclyde)
Prof Alastair Florence (Strathclyde)

Researchers:
Dr Thomas McGlone (Strathclyde)
Dr Anna Trybala (Loughborough)
Rjesh Gurung (Strathclyde)

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.

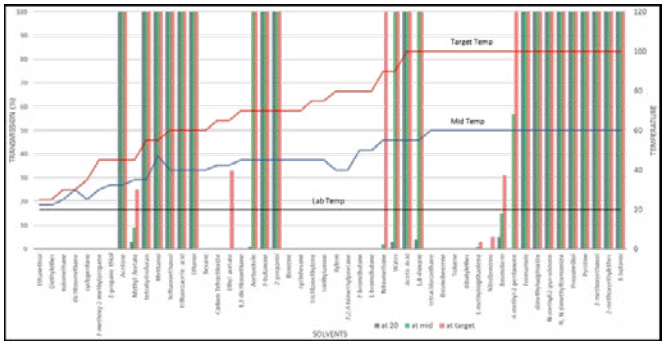


Figure 23. Experimental outcome for Paracetamol indicating the three outcomes: 1) Highly Soluble 2) Soluble 3) Completely Insoluble

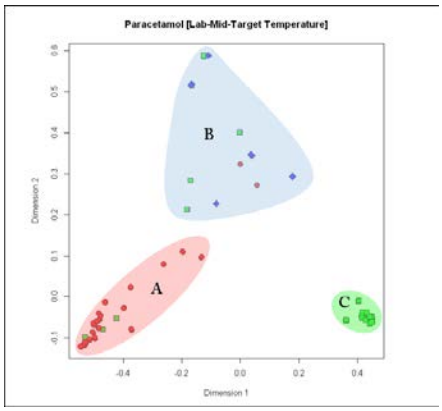


Figure 24. Multidimensional Scaling Plot in Random forest showing classification into three distinct zones of 'Completely Insoluble' indicated by Red circle, 'Highly Soluble' indicated by the Green circle and 'Soluble' indicated by the Blue circle.

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

From Molecule to Lab to Plant: Computer Aided Process Design

Academics:
Prof Alastair Florence (Strathclyde)
Dr Blair Johnston (Strathclyde)

Researchers:
Dr Cameron Brown (Strathclyde)
Dr Tomas Harrington (Cambridge)
Bruce Wareham (Strathclyde)

Computer Aided Process Design (CAPD) and simulation tools have been successfully implemented in the chemical and oil industries since the early 60s to accelerate development and optimise the design and operation of process. In recent years the use of process models in the pharmaceutical industry has increased dramatically and covers all aspects of the discovery and development processes - with the expectation of similar benefits as those seen in the chemical and oil industries. Through its current members and UK Research Partnership Investment Fund (RPIF) CMAC has recently expanded its CAPD capabilities in a number of areas in addition to the existing capabilities of Structure prediction (CCDC – Mercury and BIOVIA - Materials Studio) and crystallizer modelling (PSE - gCrystal).

Prediction of fluid properties:

Conductor like Screening Model for Real Solvents (COSMO-RS) is an ab initio quantum chemistry and thermodynamic method, and software, originally developed by Eckbert and Klamt. Using only the molecular structures of solvents and solutes, the model can be used to estimate activity coefficients required for solvent screening and solubility prediction. Models can also be used to construct multi-component phase diagrams and to predict a range of other physicochemical properties. COSMO-RS model data will be fused with data from other computational techniques in data workflows which underpin operational and control workflows allowing for informed decisions to be made before and during any “wet” laboratory processes. COSMO-RS is also being used to construct a CMAC solvent database to allow for simple, virtual solvent screening by all researchers involved in the project.

Related projects: Bruce Wareham and Dr Blair Johnston: Automated workflows for rational solvate and solvent system selection: in silico models for solubility predictions and quantitative structure - particle attribute relationships from molecular simulation and knowledge-based methods.

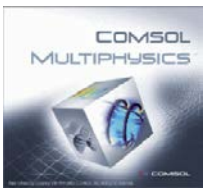
Scientific Computing & Modelling

Multiphysics simulations:

COMSOL Multiphysics allows for the modelling and simulation of complex systems through the layering and interaction of multiple physics interfaces:

- Computational fluid dynamics. Enables the modelling of most aspects of fluid flow, including: compressible, non-isothermal, non-Newtonian, two-phase and porous media flows. All in laminar and turbulent flow regimes.
- Mixers. Allows for simulations with rotating machinery acting upon fluids. This includes laminar and turbulent flow, incompressible and weakly compressible flow, as well as non-Newtonian flow. Simulations can be in 2D and 3D, time-dependent models that account for a full description of the rotation of the impeller, or through using the frozen-rotor approximation. Additional physics interfaces can include terms and equations to describe the effects of temperature, reacting species, and free surfaces on the fluid flow equations.
- Chemical reactions: Define material transport in dilute and concentrated solutions or mixtures through convection, diffusion, and ionic migration of any number of chemical species. These can be connected to definitions of reversible, irreversible, and equilibrium reaction kinetics that can be described by the Arrhenius equation, or any arbitrary rate law, where the effects of concentration and temperature on the kinetics can be included.
- Heat transfer: Tools to study the mechanisms of heat transfer – conduction, convection, and radiation. Can be readily interfaces other modules such as fluid dynamics and chemical reactions

Currently, COMSOL is being used to develop CFD models for the array of lab and pilot scale crystallizers within CMAC to serve as a comparison of each crystallizers mixing performance.
Related projects: Dr Cameron Brown – CharacterisatiIOn and ModelIIng of Crystallisers (COMIC)



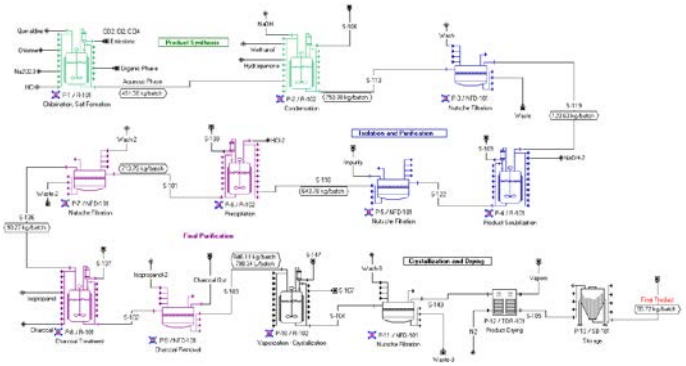
Stirred vessel mixing parameters:

With stirred vessel being commonplace in the chemical industry numerous models of their mixing patterns have been developed. Visimix turbulent provides an easy interface for calculation of these models based on classical approaches to hydrodynamics by Kolmogoroff, Hinze and Levich. This provides the necessary process parameters for analysis, scale-up and optimization of mixing vessels with a range of impeller types and configurations. Visimix turbulent is presently being used in conjunction with COMSOL multiphysics in developing comparison tools for crystallizer performance.
Related projects: Dr Cameron Brown – CharacterisatiIOn and ModelIIng of Crystallisers (COMIC)

Process flowsheeting and simulation:

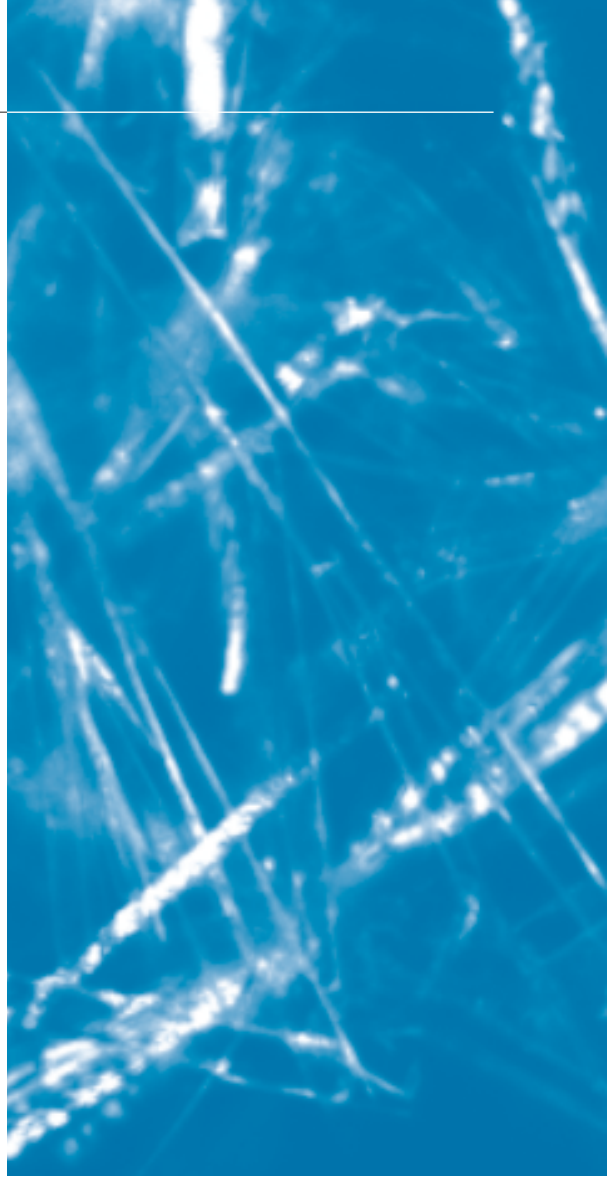
SuperPro Designer is a flowsheeting environment which facilitates the modelling, evaluation and optimization of integrated processes. With the combination of manufacturing and environmental models, SuperPro Designer provides an assessment of end-of-pipe treatment processes, project economics and environmental impact. With over 140 unit operations, equipment sizing and costing and batch scheduling, SuperPro Designer offers the opportunity to take data from current crystallizer modelling tools and extrapolate that to a full production facility. In turn, it can then be used to develop a series of future state supply network design scenarios, based on the emerging process technology options, in order to inform the business case for moving towards continuous processing. Presently, SuperPro Designer is being utilised to develop flowsheets for the existing and potential future production routes for paracetamol as part of the CMAC Phase II integration project.

SuperPro Designer



Research Case Studies

Solid State Selection Using a Novel Nucleator Coupled With Design of Experiment (DoE)



Academics:
Prof Jan Sefcik (Strathclyde)

Researchers:
Dr Pol MacFhionnghaile (Strathclyde)
Maria Briuglia (Strathclyde)
Thomas Kendall (Strathclyde)
John McGinty (Strathclyde)
Rachel Sheridan (Strathclyde)
Vaclav Svoboda (Strathclyde)

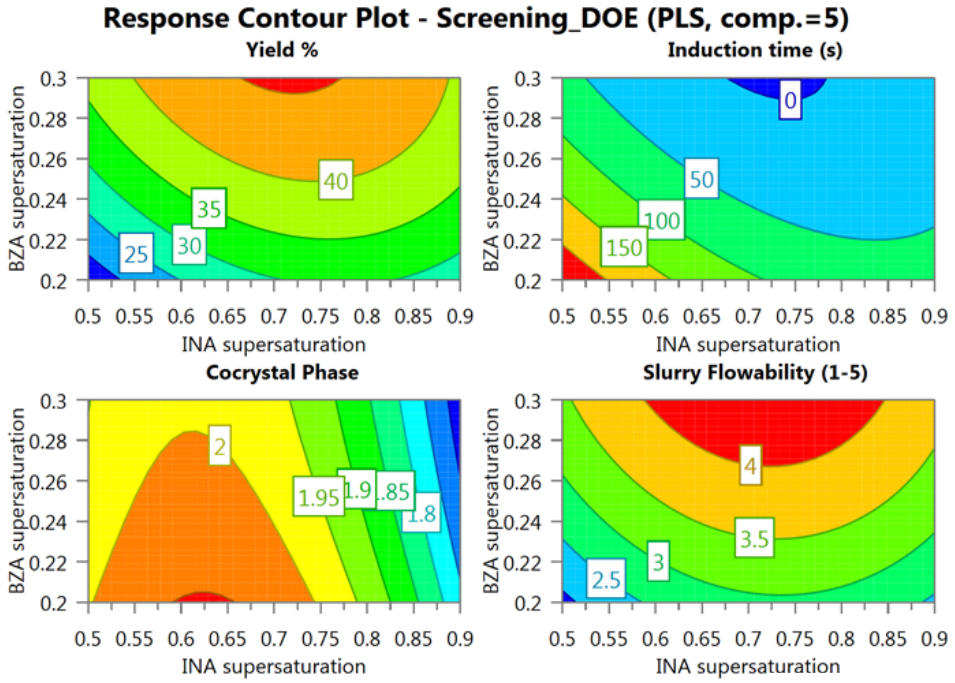
In the production of many materials solid state variation is recognised as a key issue. This is showcased by the strict stance the FDA has taken on polymorphism in manufacturing pharmaceuticals. The Sefcik group have used a Design of Experiments (DoE) based approach instead of a “trial by error” method to produce a selected co-crystal using continuous antisolvent crystallisation. The model molecular complex chosen was the 2:1 benzoic acid: isonicotinamide (BZA:INA) co-crystal[1]. This is a multicomponent crystallisation in where the INA in solution acts as an antisolvent to the BZA in its solution, and vice versa.

To reduce the complexity of the DoE the known parameters that vary crystallisation were streamlined. By keeping the experiment isothermal and using the tubular nucleator the temperature and mixing were kept constant. The solvent/antisolvent pairing was decided from results of bench screenings. The remaining variables were the solution concentration (saturation), the solvent/antisolvent composition, and the total flow rate.

The first attempt of running the process continuously used 164gkg^{-1} of benzoic acid in ethanol and 48.5gL^{-1} of isonicotimamide in water with each running with a mass flow rate of 50g/min. Although this system did crystallise, the 2:1 co-crystal the crystallisation rate was too great causing fouling and blockage to the tube. Because of this the DoE was revisited to reduce the crystallisation rate. Modified conditions of 110gL^{-1} of benzoic acid in ethanol and 48.5gL^{-1} of isonicotimamide in water were chosen as starting solutions and ran with total mass flow rate of 20g/min each. The system ran for 19 minutes without fouling. Characterisation by Powder X-Ray Diffraction, IR spectroscopy and Raman microscopy confirmed the product to be the 2:1 co-crystal. The particles were characterised as long needles using a Malvern Morphollogii.

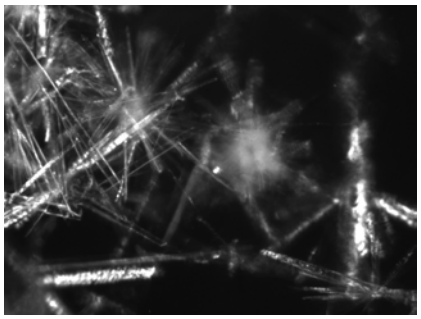
1.) Seaton, C.C., Parkin, A., Wilson, C.C., Blagden, N., 2008. Controlling the formation of benzoic acid: isonicotinamide molecular complexes. Cryst. Growth Des. 9, 47–56

Solution ratio 1:1

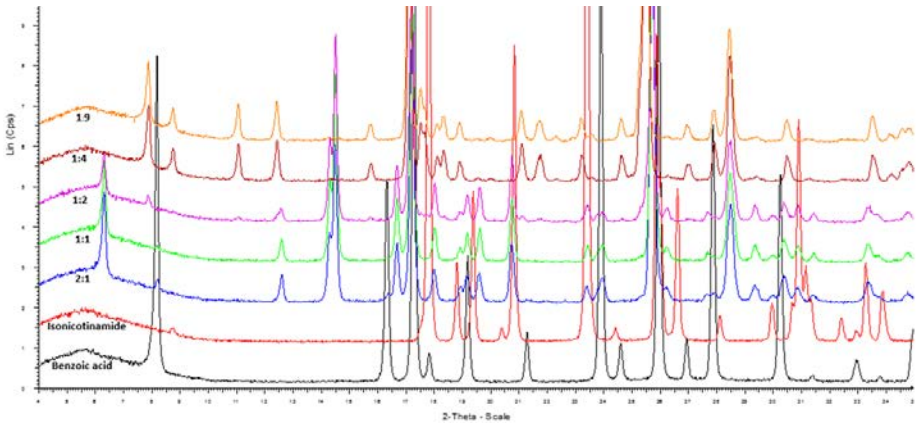


DoE response plots

Dried Particle



Particles in Solution



PXRD Patterns

Figure 25. EoE response plots, Particle images, and PRPD data of BZA:INA co-crystallisation

Research Case Studies

Improved Manufacture of a Melt-Cast Explosive

Academics:
Prof Colin R. Pulham (Edinburgh)

Researchers:
Paul L. Coster (Edinburgh)
Daniel Ward (Edinburgh)

The development of insensitive munitions that are less susceptible to accidental initiation and hence increase safety is an area of major interest. 2,4-dinitroanisole (DNAN) is a candidate material (that is attracting significant interest as a replacement for trinitrotoluene (TNT) in melt-cast formulations on account of the dramatic sensitivity improvements demonstrated during qualification testing. Several DNAN-based formulations are already in use, but there remain 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.

The processing of DNAN and its formulations involves crystallisation from the melt (mpt. 95 °C) and so research has focussed on controlling nucleation and crystallisation processes of both the melt and solid solutions. Previous work by the Edinburgh team has demonstrated that in the absence of any seeds of form-I, crystallisation from the melt results in the formation of the metastable form-II and that form-II is indefinitely metastable in the absence of form-I. The effects on crystallisation of dopant compounds in the range 5-10 mole% have been studied and certain compounds such as 2,4-dinitrotoluene have been shown to form solid solutions that suppress the temperature of the II-III transition to below 240 K when present at a level of 5 mole% and down to 210 K when present at a level of 10 mole%. Our current working hypothesis is that substitution of DNAN molecules with slightly smaller molecules results in slightly more space within the crystal structure of the solid solution thereby suppressing the disorder-order transition associated with the II-III conversion.

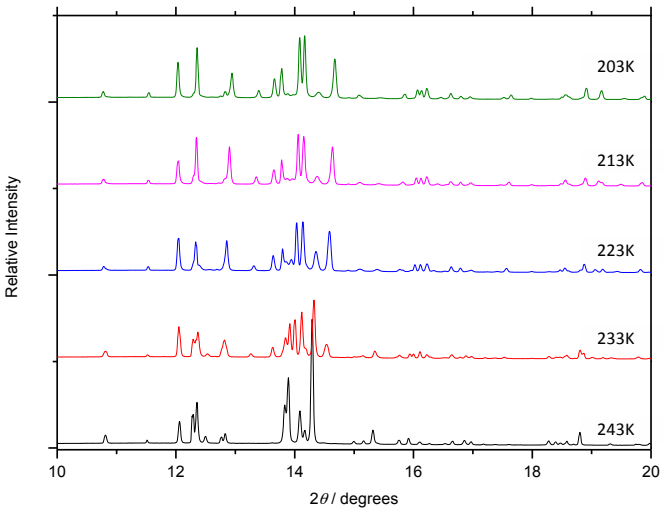


Figure 26. VT-XRPD for DNAN doped with 5 mole% dinitrotoluene

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.

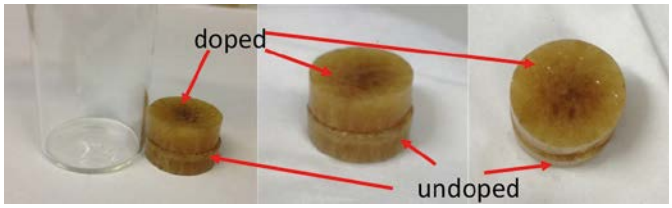


Figure 27: Images of doped (5 mole% dinitrotoluene) and undoped pellets of DNAN after thermal cycling, showing substantial expansion of undoped sample

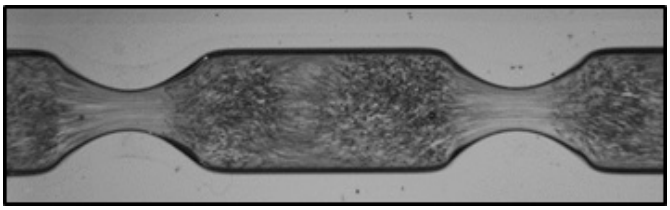
Our most recent exciting result shows that a new additive present at a level of 5 mole% completely inhibits the II-III transition over the entire operational temperature range. This has significant implications for the manufacture and processing of DNAN, as well as for the ultimate safety of DNAN-containing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

Research Case Studies

Platform Development – DN10

Academics:
Prof Alastair Florence (Strathclyde)

Researchers:
Stephanie Yerdelen (Strathclyde)
Dr Thomas McGlone (Strathclyde)



One of the key challenges in the next generation of continuous crystallisation via oscillatory flow is scale down. Although success has been demonstrated in the conventional 15 mm platform and Rattlesnake (69 mm) systems, these have required significant amounts of material for demonstration hence have been limited to generic compounds. To that end a 10 mm platform has been designed and developed in order to address scale down but in addition optimise the technology for continuous crystallisation.

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 fumecupboard includes a robust piston arrangement for oscillation at high frequency values, 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.

Research Case Studies

Continuous Crystallisation at Small Scales - Development of new platforms at University of Bath

Academics:
Prof Chick Wilson (Bath)

Researchers:
Dr Karen Robertson (Bath)
Kate Wittering (Bath)
Lauren Agnew (Bath)
Anneke Klapwijk (Bath)
Alex Cousen (Bath)

CMAC researchers at the University of Bath have been developing and commissioning a range of continuous crystallisation platforms. These are optimised for the assembly and manufacturing of target molecular materials at relatively small scales. These developments have encompassed a range of novel concepts, and have also benefitted from harnessing the best available technology solutions from both the upstream (flow chemistry) and downstream (flow processing) communities.

The platforms developed operate on a range of principles, from segmented tubular flow, through small scale cascade stirred tank reactors (cSTRs), to membrane-mediated continuous evaporative approaches. The platforms have been developed through both core CMAC Centre funding and the RPIF equipment award. They are being developed and commissioned with a view to deployment on a range of appropriate target materials across the CMAC consortium. The crystallisers in the Bath Continuous Crystallisation Laboratory (BCCL) form a part of the flexible approach to providing reconfigurable and fit-for-purpose platforms for continuous crystallisation across the scales, materials and process types the Centre and its industrial partners are tackling.

There is an understandable focus within CMAC research on the requirement to develop continuous crystallisation processes that scale-up to larger volumes of product. For many applications however, optimising small scale production of molecules, materials and particles - such as manufacturing of high value products - is an equally valuable challenge, and the work at Bath is addressing this. The designs of the three devices stem from different concepts of production thereby catering to a wide range of potential production pathways. A theme running through the three designs, however, is one of re-configurability, thus further maximising the accessibility of potential products.

Continuous segmented flow – the KRAIC

Image: KRAIC developed at Bath

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, and addresses in these configurations some of the traditional issues of continuous crystallisers, including blockages, sedimentation and the need to ensure consistent mixing. The KRAIC has been designed, constructed and developed within CMAC by the Bath group, principally by CMAC RA 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 other platforms within CMAC such as the COBC; the tubular flow in the KRAIC is of 3.2 mm diameter over a standard path length of up to 15 m which can be altered to suit the needs of the crystallisation process. The slugs created by the segmentation act as controlled reaction/crystallisation vessels moving steadily through the crystalliser, offering the required control for optimising product form and attributes. 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.

cSTR and continuous evaporative crystallisation (CMEC) platforms

With the focus on optimising crystallisation processes at small scale, 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.

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 of the way in which the membrane and flow paths of the sample solution is arranged in the CMEC device 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.

Research Case Studies

A Made to Order Processing Plant

Academics:
Dr Ian Houson (Strathclyde)
Prof Alastair Florence (Strathclyde)

Researchers:
Dr Humera Siddique (Strathclyde)

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 28) 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.

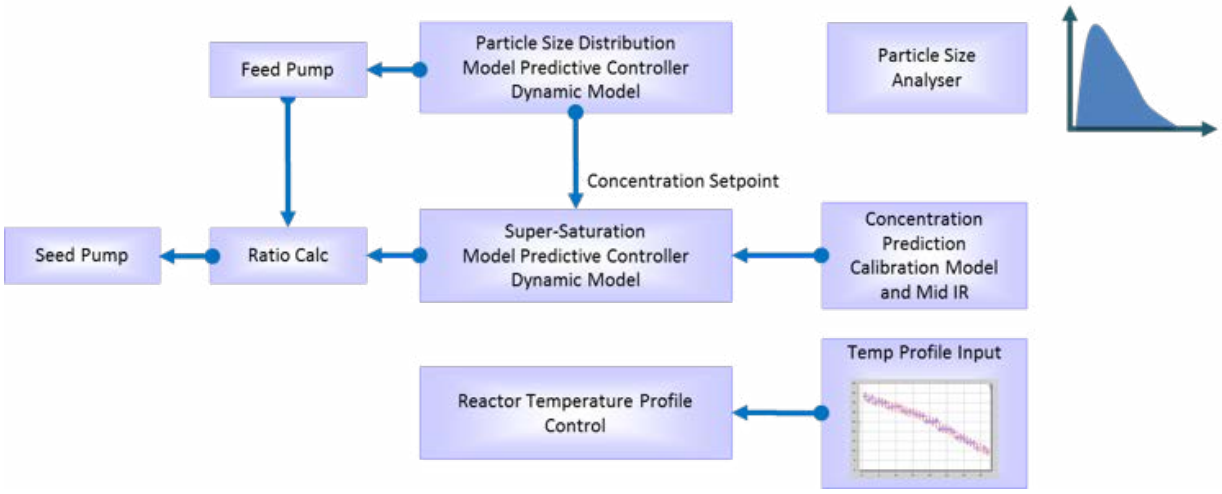


Figure 28. A control strategy for "Dial a Particle" in continuous crystallisation

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 29)
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 30)
6. Advanced process control capable of controlling available Crystallisation platforms

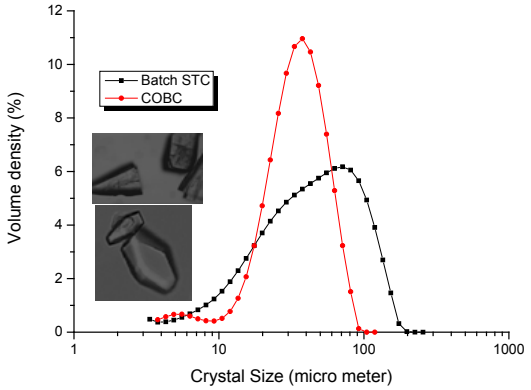


Figure 29: reduction in particle span in continuous crystallisation process

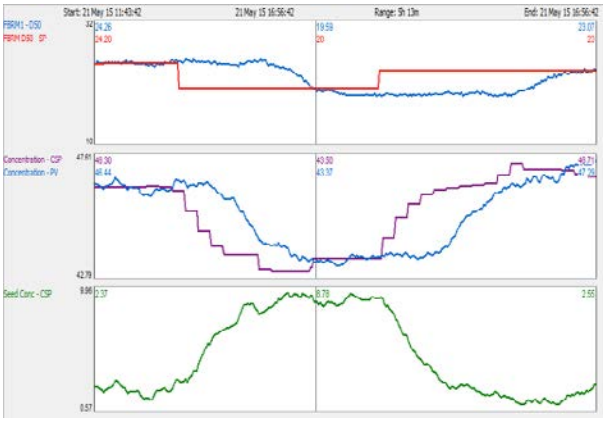


Figure 30: Dial a particle capability using model predictive control

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

Exquisite Particles: Towards predicting agglomeration in APIs

Academics:
Prof Alastair Florence
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.

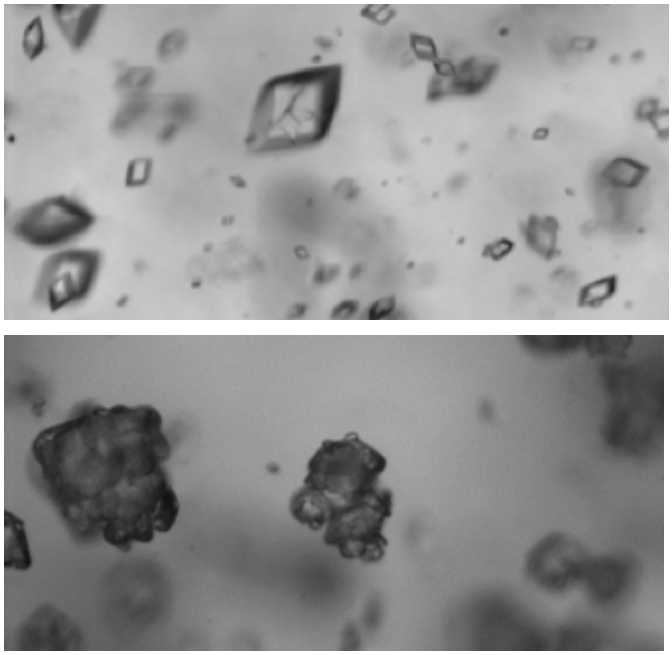


Figure 31. Unagglomerated (top) and heavily agglomerate (bottom) paracetamol crystals

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.

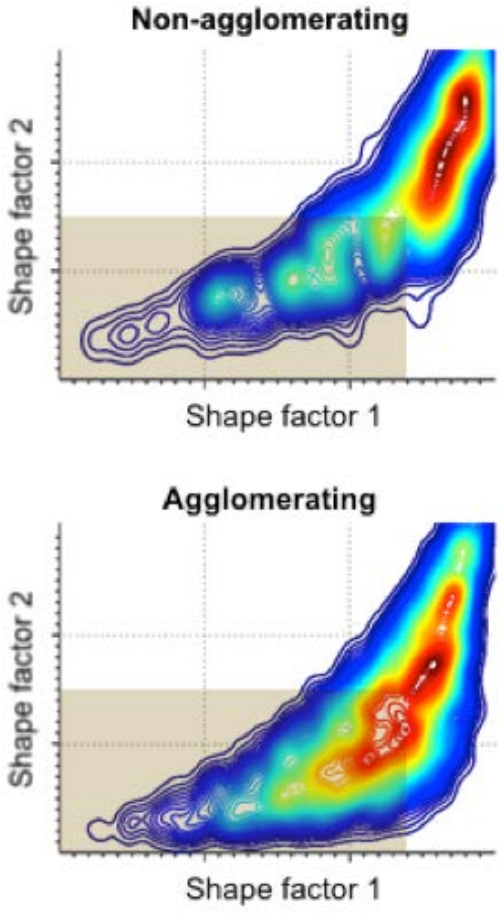


Figure 32. Population density plots of particle shape factors. Shaded area represents agglomerated particles

The Outcome

Agglomeration has been shown previously to be driven by a combination of physico-chemical and hydrodynamics 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.

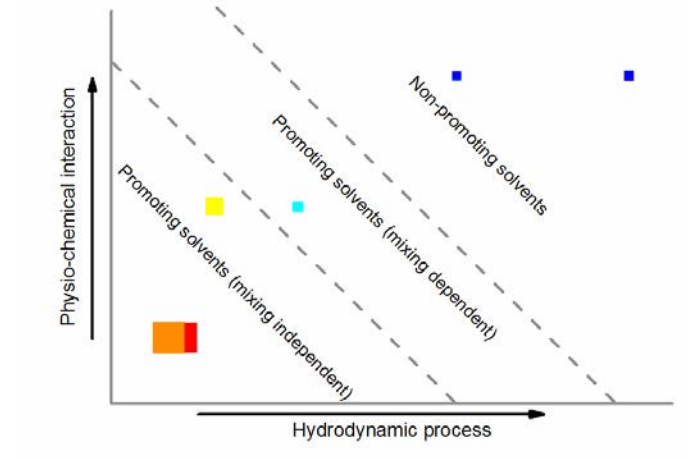


Figure 33. Conceivable solvent classification map. Symbols coloured based on shape factor 2 (red to blue – low shape factor 2 to high shape factor 2) and sized based on CED (larger symbol – higher CED)

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 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 characterize 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

Filtration and Drying

Academic:
Dr. Chris Price (Strathclyde)

Researcher:
Sara Ottoboni (Strathclyde)

Filtration is the second method used during drug production to guarantee high crystal purity. Academic literature has always focused on filtration performance, in particular pointing the attention on traditional filtration theory, where Darcy's law was considered the fundamental equation to explain slurry flow properties in relation to equipment characteristics. During the last decades new research was done to enrich Darcy's law in order to evaluate possible phenomena that deviate from the assumption related to this theory. Moreover, only recently some research has pointed our attention to correlate slurry chemical and physical properties with the traditional cake filtration theory, even if these investigations can only be considered as preliminary work. Furthermore, no research has previously been done to determine the role of washing solvent in impurity removal. This is a key process in the purification and isolation program because it gives us the chance to support the selection of optimal washing conditions and designing equipment to achieve this continuously.

Our continuous isolation research program therefore focuses on correlating the microscopical crystal, solvent and impurities properties with equipment parameters to create a "robust" and "efficient" method to determine impurity removal performance during a filtration process.

During a filtration process, a variety of parameters interact with the process performance and with the degree of crystal purity. Evaluating surface properties of crystals allows for modelling of their exact reactivity, the adsorption and dis-adsorption phenomena of these crystals to impurities or solvents.
Today, in the chemical industry, solvents are used in large quantities. In particular, in fine-chemical and pharmaceutical production, large amounts are used per mass of final products. Therefore, solvents define a major part of the environmental performance of a process and also impact on cost, safety and health issues. Traditional solvents are commonly toxic and non-recyclable. This means that pharmaceutical companies have costs related to purchasing, use and disposal of solvents. Green solvents offer numerous advantages, for instance ease of producing and recycling. The idea of "green" solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical production.

The continuous isolation research program is moreover focused on the assessment of filtration performance by using different filtration methods. In primis, batch and continuous filtration equipment are considered to estimate if continuous filtration can guarantee better impurity removal performance and better process consistency. Batch systems studied at CMAC are Biotage, Alconburny Weston and the GSK filtration robot. On the other hand, continuous filtration equipment investigated are the rotary drum filtration prototype and the supercritical CO_2 machinery. In addition, correlation between traditional cake formation, washing, drying and rotary filtration is taken into account. Moreover, the three systems evaluated in this program give us the possibility to shorten the drug manufacturing process, since these systems (Alconbury Weston, Supercritical CO_2 and rotary drum prototype) can simultaneously guarantee cake filtration, washing and possibly drying.

In summary, these parameters are fundamental to study a filtration process because they take into account microscopic and macroscopic properties in order to create a correlation of these phenomena that most of the time are viewed as distinct. The ultimate objective is to understand and to support the selection of optimal washing conditions and designing equipment to achieve this continuously.

Research Case Studies

Spray Drying

Academic:
Prof. Alastair Florence (Strathclyde)

Researcher:
Rebecca Halliwell (Strathclyde)

Process: Process automation – Spray dryer

To improve the understanding and impact that spray drying can have on the traditional formulation processes, an important focus for research is the aspect of process control, optimisation and automation.

Full process understanding can enable process modelling and critical particle responses to be characterised to gain a higher quality particle product. For each response to be optimised it would require research into the process factors which would need to be changed to gain the optimal response. This is to be investigated by researching the droplet behaviour and drying kinetics of a single droplet that will inform and indicate the behaviour of millions within the spray dryer. This will be achieved using the single-axis acoustic levitator to levitate droplets in controlled environmental conditions. If the full thermodynamic and kinetic behaviour of a single droplet can be understood then this will allow the optimisation of particle responses to be achieved easier through particle engineering.

The significance of process automation is development and improvement of the current laboratory spray dryer to gain quantitative control of the entire process. This will enable the increase of fundamental understanding and the ability to engineer particle properties to a higher degree. Perceptive Engineering, LTD has worked with CMAC to fully automate the Büchi spray dryer and have provided a software program that can control to a much higher degree of accuracy the process parameters. This will in turn increase the control and understanding of particle properties that will enable particle engineering by spray drying.

Co-processing of API and excipient – amorphous API – particle size and shape

The traditional purpose for drying in secondary processing of pharmaceuticals is to simply dry the filtered particles by different drying techniques prior to further processing that will combine the active and inert particles into a formulation. Spray drying in its most basic function will rapidly remove solvent but the technique if fully exploited can deliver different particle properties and formulations that can produce higher quality of particles for pharmaceutical products.

Spray drying can offer particle optimisation and an alternative method for particle formulations due to the different product and process parameters that can be varied. This optimisation can enable particle properties such as crystal form, size, polymorphic form, structure and shape to be considered and targeted to create an optimised formulated particle. This can be achieved by adapting the spray dryer to co-process an active compound with different inert excipients to create either composite particles or solid dispersions. These formulated particles can offer an increase in particle performance and an improvement in secondary manufacture of formulations.

Research Case Studies

Continuous Extrusion: Relationship between processing parameters, formulation and material properties

Academic:
Prof. Gavin Halbert (Strathclyde)

Researcher:
Laura Martinez-Marcos (Strathclyde)

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.

Hot Melt Extrusion (HME) – process and formulation

HME as a continuous pharmaceutical manufacturing process consists of pumping a blend of an Active Pharmaceutical Ingredient (API) and a pharmaceutical grade polymer that acts as carrier through a die into a shaped product. In a twin screw extruder, the HME process enables the transformation of an API from a crystalline to an amorphous form through the application of high temperatures and high mixing degree of the twin screws. It is known that the amorphous form at a molecular level enhances API solubility due to an increase in the molecules free mobility compared to the static arrangement in the crystalline form. Amorphous solid dispersions have an increased free energy and specific surface area that can lead to supersaturation of the system. Careful selection of the API and carrier must be performed due to the influence of their physicochemical properties on the later stability of the amorphous solid dispersion. Therefore, the application of HME is mainly focused towards the production of amorphous solid dispersions where an increase in API solubility with a possible impact in oral bioavailability is studied and observed.

Laura's research is assessing the relationship of processing parameters in HME on material properties of a solid dispersion formulation. A model drug molecule with an associated low solubility, a class II compound of the Biopharmaceutical

Classification system, in combination with a variety of polymer systems are investigated regarding their material properties, such as porosity and homogeneity, as a result of certain processing conditions. In addition, product performance indicators 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, Laura is investigating the use of ultrasound to increase the miscibility of polymer and API during the hot melt extrusion process.

Twin-screw granulation – Process parameters impacting flow ability properties of a Paracetamol formulation

The twin screw extruder setup can be modified to suit a granulation process. Twin-screw granulation is a continuous process where powder particles and a binding liquid are mixed leading to particle agglomeration and the formation of granules with suitable properties for powder processing, such as good powder flow or compression characteristics.
Laura's research is establishing relationships between process parameters, formulation compositions and granule characteristic that improve flowability of powders.

Research Case Studies

Formulation Considerations in Twin Screw Wet Granulation - A quality by design approach

Academic:
Prof. Gavin Halbert (Strathclyde)

Researcher:
Albarah Al-Afandi (Strathclyde)

In the form of the International Conference on Harmonisation quality guidelines, pharmaceutical regulators have increasingly emphasised the need for greater understanding of factors that may influence the final product quality, as well as the development of a comprehensive risk management strategy. These are the fundamentals of a Quality by Design approach, which seeks to pave the way for "building quality into the product" rather than the conventional method of "testing quality into the product". Hence, product development begins with the end-in-mind i.e. the target profile. Once the desired characteristics of the product profile are defined, then the attributes that are most critical to these characteristics are identified, monitored, and ultimately controlled.

Formulation and input materials play a significant role in the characteristics and performance of a product. Therefore, understanding the role of material attributes is paramount to controlling and ensuring quality. However, powders are notoriously difficult to characterise and a powder's behaviour within a system is difficult to predict. This is because powder performance is influenced by many powder attributes, such as particle size distribution, particle morphology, solubility and cohesion to name a few. Additionally, some powders may be particularly sensitive to the presence of other materials or environmental conditions such as temperature and humidity. The combination of these attributes and the complex relationship between them, dictates the flow and liquid penetration of a powder in many operations in the manufacturing process, including feeding, wet granulation and die-filling.

Hence, building a comprehensive knowledge space of input materials will enable the correct combination and specification of ingredients to be selected in the correct manufacturing conditions to meet the requirements of the target product profile. This approach will be applied to twin-screw wet granulation; a relatively new continuous platform that has gained interest over the past decade as an alternative to traditional wet granulation techniques. The role of particle size distribution of commonly used excipients within a typical blend is to be investigated. The effect of particle size on powder flow and wettability will be characterised so that the relationship to the granular output, and ultimately the solid dosage form, can be determined. From these results a design space can begin to form, from which formulation parameters can be derived for a desired product profile.

Research Case Studies

Personalised Medicines and 3D Printing

Academic:
Prof. Gavin Halbert (Strathclyde)

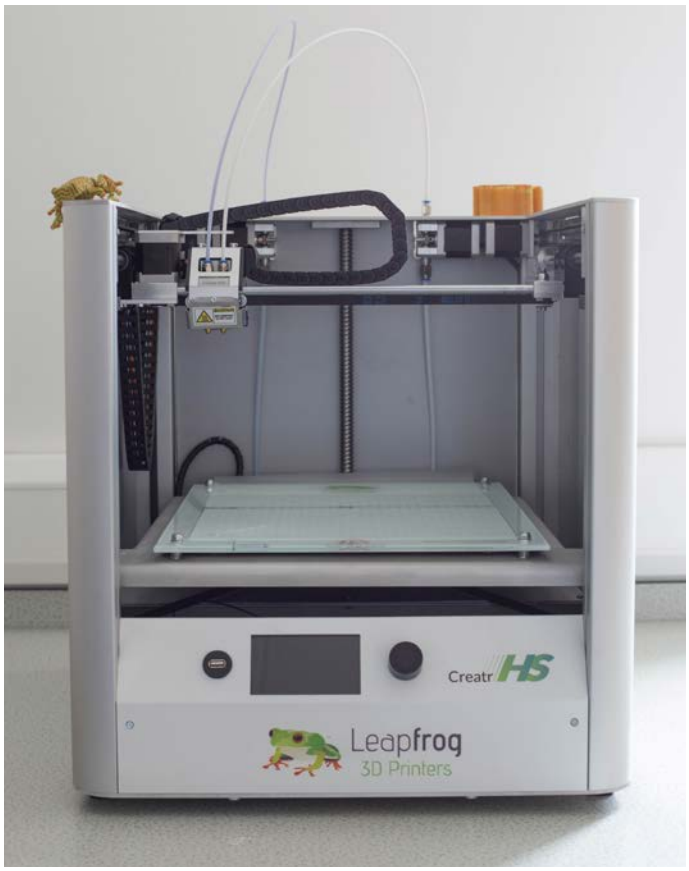
Researcher:
Elanor Brammer (Strathclyde)

Current tableting procedures, while useful for single dose medicines, are not practical for producing ranges of different doses quickly and in a cost effective manner. CMAC has the ability to combine continuous technology (hot-melt extrusion) with innovative manufacturing techniques (3D printing) to selectively produce oral doses for individual patients (personalised medicine).

Process

3D printing covers a wide range of techniques. In pharmaceuticals, the process can start with a powder feedstock, a paste feedstock or an extruded polymer filament (the latter known as fused filament fabrication - FFF). CMAC is currently focused on exploring its capability in the area of FFF. Designs are created using CAD drawing software and are capable of providing huge flexibility in size and shape of the manufactured tablet.

CMAC also has the added benefit of dual filament extrusion capability. This adds another dimension of flexibility to the process by allowing the extrusion of a placebo alongside a drug loaded filament to create complex tablet designs with different sections containing API.



Formulation

Personalised doses can be manufactured using FFF by varying the infill percentage of the tablet while keeping the tablet size the same. The void spaces can either be filled with a placebo, or left empty (although the latter presents tablets of varying density that could potentially float). Personalised doses can also be manufactured by changing the size of printed tablet, although there would be restrictions on maximum and minimum size.

Thermal stability could potentially be a problem with this process, meaning only APIs which do not degrade at high temperatures would be suitable.

Research Case Studies

Novel Dosage Forms

Academic:
Prof. Gavin Halbert (Strathclyde)

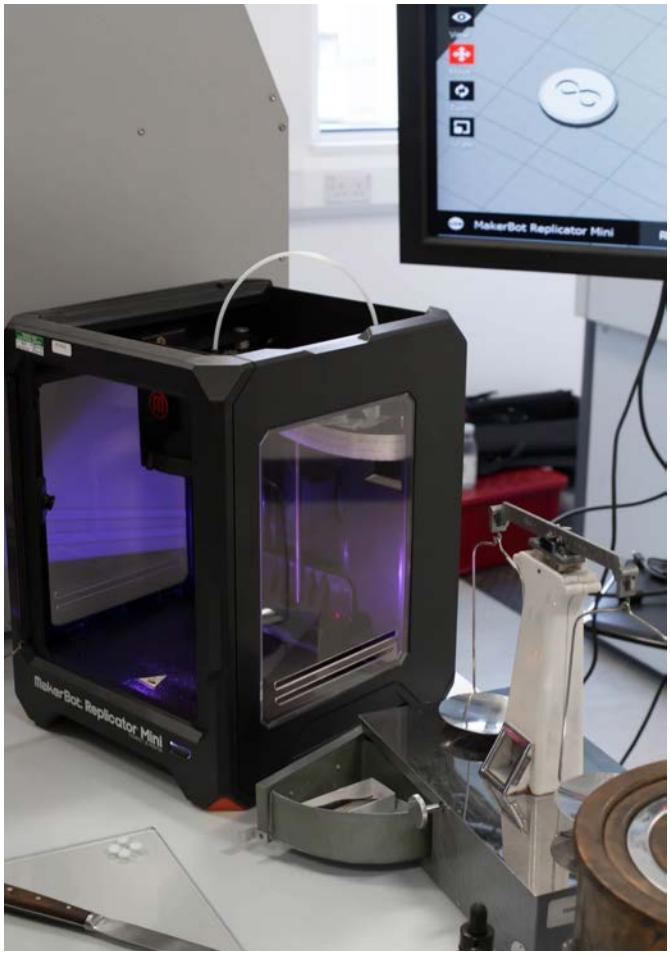
Researcher:
Alice Turner (Strathclyde)

Oral drug delivery systems make up 50% of the dosage forms currently on the market as they are relatively cheap to produce and allow patients to self-administer. However in reality not all drugs are ideally suited to oral formulation, with many drugs suffering from poor permeability and/or solubility. It is estimated 70% of drugs in development have poor solubility. Poor solubility leads to insufficient dissolution in the gastrointestinal fluid and thus intermittent and insufficient absorption of the drug into the systemic circulation. These drugs fall into what are known as Class II and Class IV of the Biopharmaceutical Classification System (Table 1). Class II is particularly interesting, making up 17% of the WHO list of essential medicines, as it has been found previously, if the solubility of the drug is improved, the bioavailability and thus therapeutic efficacy of this form of drug can be comparable to a class I drug. Table 1: The Biopharmaceutical Classification System.

	Highly Soluble	Poorly Soluble
Highly Permeable	Class I	Class II
Poorly Permeable	Class III	Class IV

Even a minute improvement to solubility can enhance a drug's bioavailability by increasing the overall dissolution rate. Solubility can be improved by primary processes such as salt formation, co-crystallisation, prodrug formation and polymorphism, but also by secondary processing of a drug molecule with excipients, such as polymers and compounds which can impart solubility on the molecule.

Alice's research will focus on increasing the solubility of a model BCS class II drug by creating novel formulations, with exceptionally high spatial resolution and therefore increased quality attributes combining injection moulding and 3D inkjet printing technology.



Injection moulding has been used within the plastics industry for a long time but its use in drug delivery formulation is relatively recent. It involves injection of polymers at high temperatures and pressures into cold metal moulds. These moulds then enable the hot polymer to set in the desired conformation. As a solvent free process, it is environmentally friendly and should be safer for patients. Pressure and heat applied during the process reduce the chance of microbial growth, improve patient safety and increase the chances of the product passing quality control tests. It also encourages interactions between the drug and the excipients to occur to increase the solubility of the drug through potential solid dispersion formation.

Inkjet printing has been developed for use in formulation with a view to rapid manufacture. Materials are added to a substrate in a liquid droplet form in a similar manner to how ink is added to paper. The droplet size can be as small as pico-litres allowing production of complex structures. Polymers and other excipients can be used in this manner to generate drug delivery systems by either solid free form fabrication or layered manufacturing, which involve manufacturing structures in a mould-less fashion by sticking slices of material together. Precise control of droplet size enables control of the dose however the "ink" formulation must have a viscosity which allows flow through the apparatus in a constant and consistent manner to achieve consistent dosage forms with the required distribution of drug and excipients.

Research Case Studies

Process Understanding Twin Screw Granulation

Academic:
Dr. Dimitrios Lamprou (Strathclyde)

Researcher:
Carlota Mendez (Strathclyde)

The main goal of the Pharmaceutical Industry is the manufacture of products with great levels of quality and consistency. For many years, this goal was achieved through operating in known ranges and times and the following testing of quality. However, the lack of understanding of the underlying mechanisms has produced systems are not flexible to slight variations associated with standard processing. To achieve this flexibility in the equipment, process control of the system which can counteract deviations when a uniform product is required. To successfully implement process control, a full understanding of the mechanisms behind the operation is required.

Continuous wet granulation using a Twin Screw Granulator (TSG) has already shown a remarkable potential to substitute traditional batch systems. This equipment is capable of overcoming the main disadvantages of other equipment available on the market. On an industrial scale, the TSG involves less operators and dramatically smaller facilities than those required for High Shear Batch Granulator or Fluid Bed Granulation systems. In addition, the amount of granulation liquid used is low and therefore, the footprint and the safety are more favourable. TSG can be used with the majority of APIs on the market, in an industrial or research and development setting. Furthermore, it allows the real time monitoring of granules and the development of more sophisticated control strategies than the commonly used 'End-Point'. However, the current process knowledge is not adequate to perform or design the process for operation in optimal conditions. Until now, no accurate model predicting either the attributes of the particles or the flow model within the equipment has been developed.

There are different approaches to improve the understanding of the process. One of the more complete methods is supplied by the FDA and summarised on the ICH Q8 guidance. This approach known as Quality by Design (QbD) ensures that the product quality objectives are defined from the beginning and all the design and development of the formulation and manufacturing processes accomplish these goals. In practice, the approach will use Process Analytical Technology (PAT) tools for acquisition of data, followed by characterisation and analysis of the acquired data in the search of a dynamic model which describes the system based on the theoretical granulation mechanisms. Based on one analogy with Chemical Engineering mass balances, population balance models are able to describe the characteristics properties in function of the process parameters. However, until now, there is no general equation which can describe the system without restrictions. Other typical approaches are based on fluid dynamics. For instance, Conceptual Flow Modelling uses concepts of traditional flow dynamic though the definition of the TSG as a non-ideal flow system. Increasing the knowledge as the particles behave within the TSG is especially useful in order to understand the interactions between them and to understand the performance of the equipment.

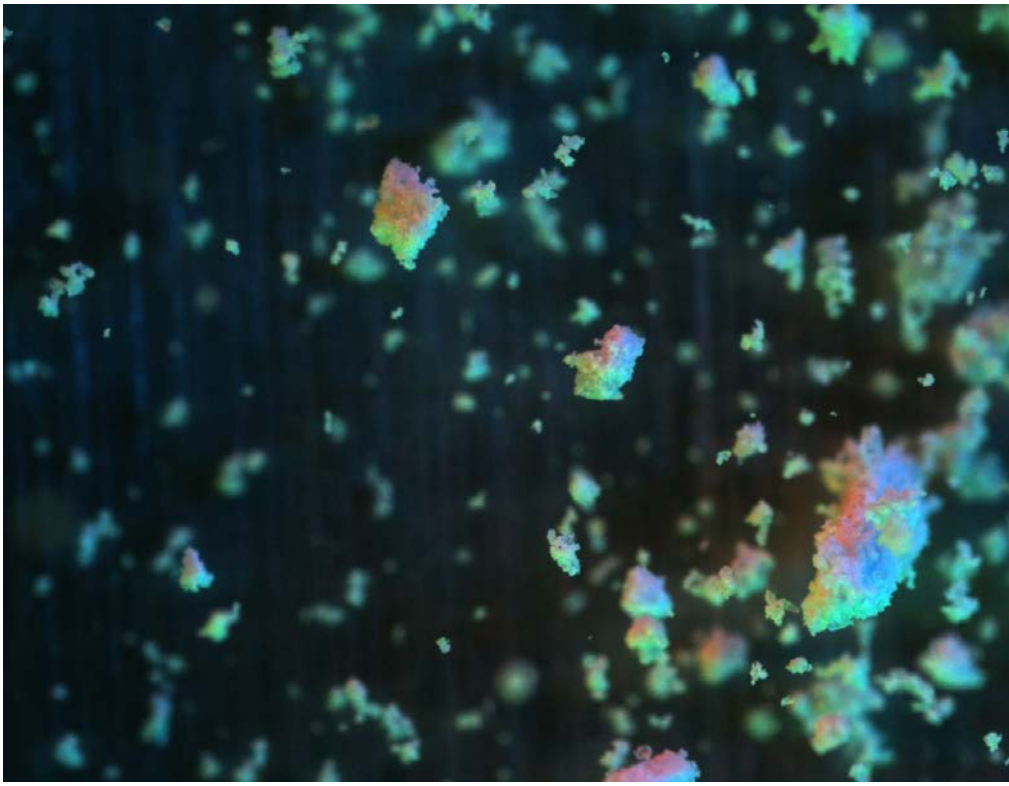
Theoretical mechanisms and Flow dynamics studies are complementary and they should be considered together. The collective effort to research both areas is the only way to obtain a satisfactory model with can supply the consistency and quality required for Pharmaceutical Products.

Research Case Studies

Process Analytical Technology in Twin Screw Wet Granulation

Academic:
Dr Alison Nordon (Strathclyde)

Researcher:
Jo Lothian (Strathclyde)



Granulation is a common unit operation for the manufacturing of solid dosage forms such as tablets and capsules. Granules are grains of agglomerated powder particles made from dry powder particles into larger permanent agglomerates. Granules produced for the pharmaceutical industry are generally composed of the desired amount of active pharmaceutical ingredient (API) and excipients. Granule particle size and particle size distribution are important parameters that not only help to improve powder flowability and material handling, they help prevent segregation, reduce the amount of dust produced during processing and can impact granule hygroscopicity, friability, bulk density, tablet weight variation, tabletabilty, tablet porosity and tablet dissolution rate. The desired properties allow for better tablet production.

Currently there are limited on-line particle size analysis tools available for real time analysis of continuous granulation. Sieve analysis is the most common particle sizing technique but it is tedious and time consuming. Another common but more expensive technique in comparison to sieve analysis is laser diffraction. Laser diffraction is much quicker than sieve analysis but the technique assumes that all particles are a sphere which is an issue for irregular shaped granules. Focus beam reflectance measurement (FBRM) has been used on-line for granule size analysis but the problem with FBRM is that is uses a chord length distribution (CLD) and the restoration of particle size distribution from CLD is not straightforward and requires many assumptions.

Jo's research focuses on extracting not only physical but chemical information from a process by the means of process analytical technologies. Jo is currently evaluating a high speed image analyser the Eyecon™ by Innopharma Labs for the use of real time particle size analysis for the continuous manufacturing of granules by means of a twin screw granulation process (TSG). The Eyecon™ is one of the newest particle analyzing technique, it gives information on the physical properties of granules such as particle size, number and morphology. The device uses novel technology in order to be able to capture high speed moving particles and for better edge detection. The camera circumference is covered in a ring of red green and blue LEDs. These lights give a 1µs, burst of light every second causing the particles to almost be frozen in time long enough for the camera to capture an image. From these images the subsequent D10, D50 and D90 values are calculated.

Research Case Studies

Supply Chain

Academics:
Prof Sir Mike Gregory (Cambridge)
Dr Jag Srai (Cambridge)
Prof Alex Duffy (Strathclyde)
Athanasios Rentizelas (Strathclyde)

Researchers:
Dr Tomas Harrington
Mark Philips
Georgi Aleksiev (Strathclyde)
Leda Todorova (Strathclyde)

Targeting a series of technology 'interventions' has enabled the potential for significant step changes across the pharmaceutical value chain - from early stage 'system discovery' and clinical trials, through to novel patient delivery models. This research strand explores future value network configurations which when aligned with disruptive shifts in technology may enable alternative routes to drug product production and the delivery of added value to the 'end-user'.

While evidence exists that continuous processing delivers financial benefits (mainly for single-purpose plants), studies have largely been focused at production and plant level with the business case, in each case, lacking any formal end-to-end supply network assessment. For continuous crystallisation-based technology interventions to become more generally accepted within the sector, the business case for transformation and the resultant impact across the entire value chain needs to be better understood and quantified. In addition, critical linkages to emerging continuous process technologies both upstream (e.g. in synthesis and work-up) and downstream (e.g. filtration, drying, secondary processing) from crystallisation must also be considered.

The approach presented here forms the basis of this on-going research agenda, providing a link between continuous crystallisation technology options and future product iterations - assessing value chain reconfiguration opportunities, which may result from a continuous technology intervention. Rather than just focus on individual unit operations, the approach assesses pharmaceutical end-to-end (E2E) supply chain benefits (time-to-patient; quality; inventory; enhanced volume flexibility; customisation etc.) that breakthroughs in the area of continuous crystallisation may enable.

Assessing Value Network Reconfiguration Opportunities

The systematic approach developed as part of this research at Cambridge extends prior work on industrial systems analysis and supply chain mapping techniques, and may be summarised as follows:

- **Pre-screening** (barriers, opportunities, target markets and candidates)

Individual drug products are assessed at this pre-screening stage, in the context of new continuous capabilities and technology interventions that may create opportunities with respect to new markets (e.g. products previously considered uneconomical to serve in terms of batch processing or new chemical entities for initial assessment) as well as established market segments (e.g. more established, generic products in reaction to future trends and changing markets).

- **Current state mapping** (supply networks, unit operations)

This activity involves mapping the 'current state' for the candidate, in terms of e.g. unit operations and the supply network.

The first mapping exercise scopes out unit operations where an existing batch (or new) production process may be 'pre-disposed' to a series of continuous technologies (in terms of current state and future potential) - namely - synthesis, purification (e.g. work-up, crystallisation, extraction), isolation (e.g. filtration, centrifugation, drying crystallisation), formulation (e.g. mixing, blending, milling, spray-drying, extrusion granulation, drying, compression) and packaging. An E2E network performance analysis is then used to define overall system metrics in order to re-examine these semi-independent sub-systems challenging the current state configuration design parameters and trade-offs being made.

- **Future state models and scenarios**

An initial assessment of future/alternative processing models may then be conducted where alternative chemical process scenario analyses consider opportunities for more flow-through continuous processing. These scenarios are then evaluated in terms of the 'delta' or relative benefits against key system level operational benefits that might emerge from continuous processing. This step in the process generates 'the delta' or potential step change possibilities in the key metric(s) or impact variable under consideration.

The figure below sets out impact variables for 3 CMAC case studies in terms of cycle time vs. inventory for primary/secondary processing. In assessing specific continuous interventions and the potential scale of opportunities across the E2E supply chain, significant reductions of up to 50%, in terms of cycle time (starting materials to packed product) may be achievable.

- **Building the business case for transformation**

Finally, the approach integrates business context/viability and technology readiness inputs (from supporting technology roadmaps) in order to evaluate value network reconfiguration opportunities and develop a case for transformation.

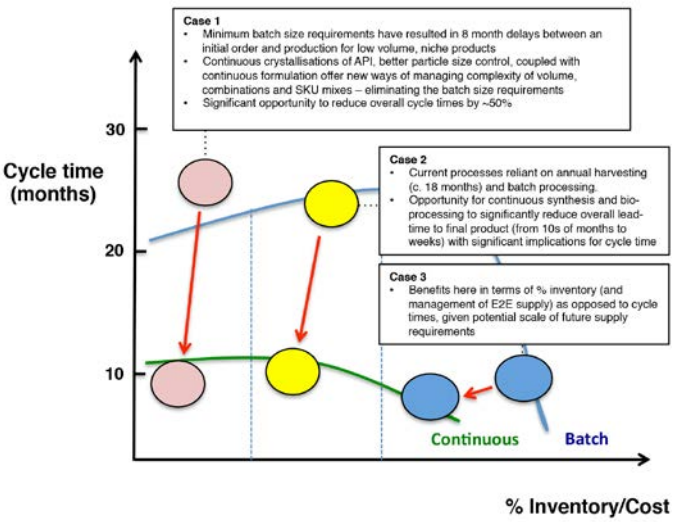


Figure 34. Primary/secondary continuous processing – specific benefits for 3 CMAC case studies in terms of improved cycle time

On-going Research Agenda

Ten diverse pharmaceutical products will form the focus of this on-going study (e.g. Metformin, Paracetamol, Piroxicam, Caramazepine, Carvedilol, Albendazole, Fenofibrate, Lactose, Budesonide and Ibuprofen) – in order to provide the basis for exploring alternative product-process supply network options and value chain implications arising from a technology intervention. The case studies were chosen as they represent products at different stages of their product life cycle, have dissimilar product volume and pack complexity profiles, and varying transformation challenges if an alternative process, value network and/or business case is implemented.

Research Case Studies

Sensor and Measurement Modelling

Academics:
Dr Tony Mulholland (Strathclyde)
Prof Massimiliano Vasile (Strathclyde)
Prof Jan Sefcik (Strathclyde)

Researcher:
Dr Okpeafoh Stephen Agimelen (Strathclyde)

The Challenge

One of the major challenges of the ICT-CMAC project is to extract as much useful information from measured data on a continuous process as possible, in a real-time manner, to allow intelligent decision making. The extraction of this information from different measurement streams often requires the application of complex mathematical/numerical models.

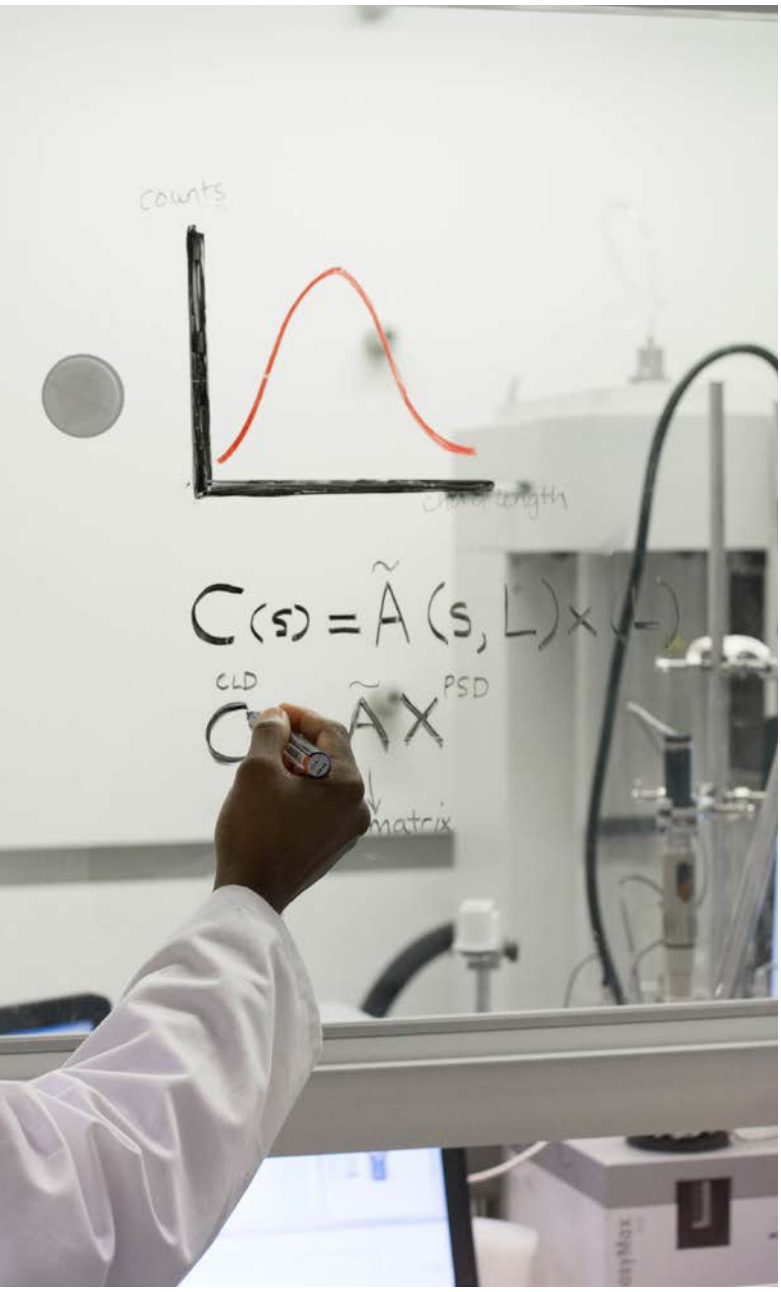
One such model is the inversion method developed by ICT-CMAC Work Package 2 to calculate particle morphology from experimentally measured data. Stephen Agimelen, Tony Mulholland and Jan Sefcik have developed a model which has been supplemented by inputs from other ICT-CMAC Work Package researchers.

Initially working with measured chord length distributions (CLD) data obtained with the Focussed Beam Reflectance Measurement (FBRM) sensor to calculate a representative aspect ratio (which quantifies the shape of the particles) for the particles in a slurry, the algorithm was then improved by combining CLD data with images obtained with the Particle Vision and Measurement sensor. This is because the inverse problem of estimating the particle size distribution (PSD) for a given aspect ratio from the CLD data is ill-posed as there are multiple possible PSD and aspect ratios that could be derived from the same CLD; this necessitated the addition of supplementary image data to improve the results. The images were processed to evaluate the range of aspect ratios present in the images, which in turn improves the accuracy of the algorithm by constraining the search space for aspect ratio. Successful results have been obtained from this model when applied to polystyrene microspheres (as a control sample), cellobiose octaacetate (COA) and glycine. We reported in the last Annual Review that the initial algorithm to invert CLD data was under review for publication; this paper is now fully published and the second paper detailing the process to improve the algorithm using image data is currently under review.

The third measurement modality to further improve the algorithm is the incorporation of laser diffraction measurements, using data from the Malvern Mastersizer. The incorporation of laser diffraction data to the inversion algorithm will serve two main purposes:

1. To improve the degree of accuracy of aspect ratio estimated from the images. This is because the aspect ratio estimated from images contains some degree of variation as the objects in the images are not always in focus. The improved aspect ratio estimate will help to further constrain the search space for the inversion algorithm.

2. To constrain the width of the PSD obtained from the CLD data. This is because of possible chord concatenation in the CLD data. This is a phenomenon whereby chords from two different particles are counted as belonging to the same particle due to the close proximity of the two particles. There could also be chord splitting; a phenomenon whereby a single chord from a particle is counted as two separate chords due to poor optical reflectance of the particle.



Methods for combining image data

With the initial CLD inversion model, a nonlinear least-squares minimisation was carried out using the Levenberg-Marquardt method to obtain the possible original particle aspect ratios. Then, PVM images were processed to obtain particle shape descriptors and therefore a distribution of the aspect ratios present in the images.

In the first approach (Method 1), all the particles in a slurry are assigned the same representative aspect ratio, and the PSD is estimated at this aspect ratio. This aspect ratio is estimated from the mean shape descriptor obtained from the images. However, for elongated particles, there is also a possibility that different particles with the same length could have different thickness. This possibility is taken into account in the second approach (Method 2) in which a distribution of aspect ratios is assigned to particles of the same length. The distribution of aspect ratios is obtained from the individual shape descriptors of the objects in the images.

Research Outcomes

Figure 35 shows examples of estimated PSD by the two different methods for glycine. The symbols in Fig. 35(a) are the measured CLD for the glycine sample while the solid line (in Fig. 35(a)) is the estimated CLD for the same sample. Figure 35(b) shows the estimated PSD by the two methods for the glycine sample. There is good agreement between the PSD obtained by the two methods in this case because of the near uniform distribution of aspect ratios (as a function of particle lengths) for the sample.

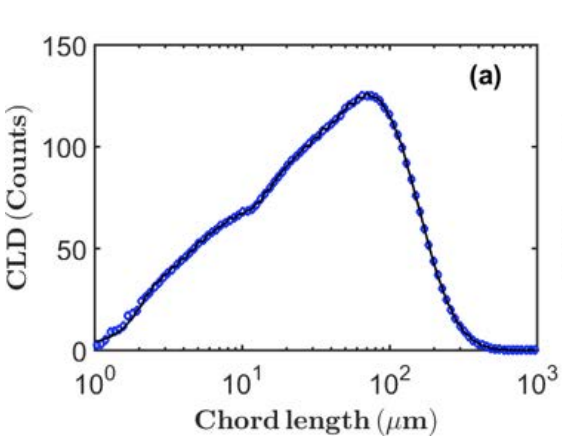


Figure 35(a)

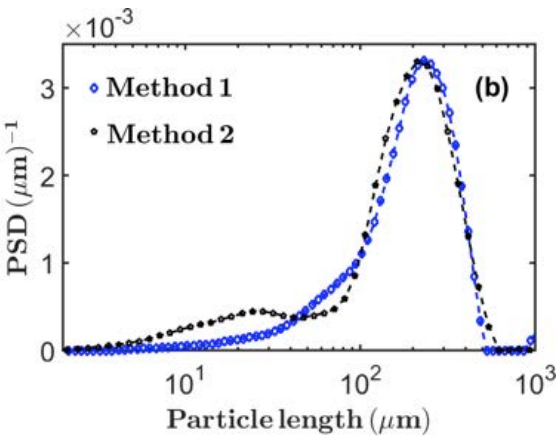


Figure 35(b)

Research Case Studies

Intelligent Support Platform

Academics:
Dr Craig Michie (Strathclyde)
Dr Robert Atkinson (Strathclyde)

Researcher:
Dr Christos Tachtatzis (Strathclyde)

The Challenge

To develop a method of identifying fouling/encrustation in real-time during process operation, to distinguish crystal growth in the bulk solution and crystalliser walls, to measure nucleation induction time in bulk solution and crystalliser surfaces, to allow quantification of the degree of fouling and allow mitigative action to be taken.

The fouling indicator was developed as part of the ICT CMAC project, fusing expertise in statistical analysis and machine learning from the Centre for Intelligent Dynamic Communications (CIDCOM) in the Electronic and Electrical Engineering Department at Strathclyde with domain knowledge in CMAC.

The Technology

Simple, low-cost imaging equipment was chosen deliberately to establish the possible performance bounds of the measurement system and associated algorithms.

Christos Tachtatzis, a senior postdoctoral researcher, worked with DTC student Rachel Sheridan on a Moving Fluid Oscillatory Baffled Crystalliser (MFOBC) rig, as shown in Figure 36. The MFOBC platform was chosen as the demonstrator platform that mimics the operation of a continuous plug-flow crystalliser. L-Glutamic Acid (LGA) was used as the test compound under which the algorithms were developed.

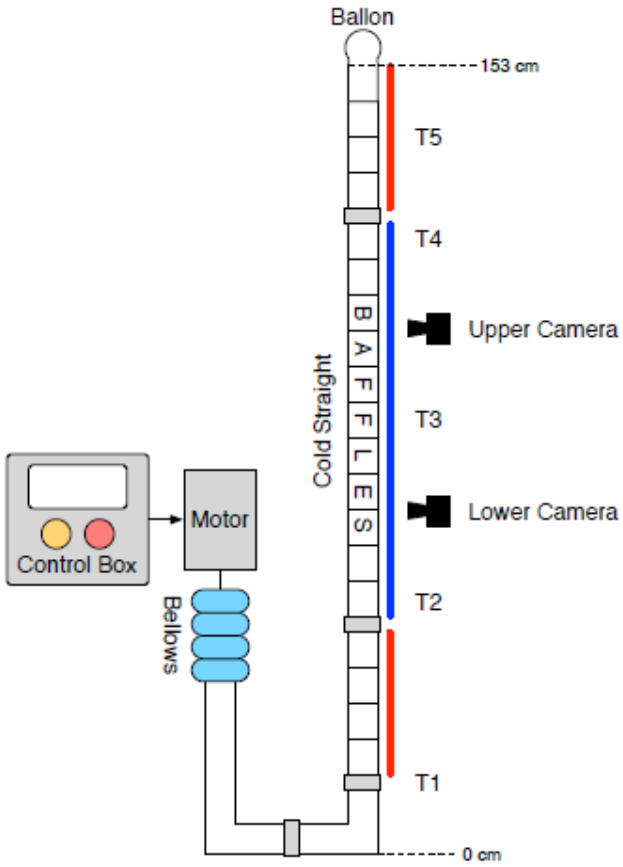


Figure 36. MFOBC experimental setup.

The monitoring and image analysis approach developed can be used to analyse data collected from any experimental setup where real-time images of vessel walls are available, under batch or continuous, isothermal or non-isothermal conditions.

The Method

A stable measurement environment, i.e. a measurement chamber with consistent lighting was set up, and images of the nucleation and crystallisation processes were taken at regular intervals.

On each image, regions with crystals reflect light resulting in proportional pixel intensities. Fouled regions have higher intensities as these pixels are closer to the camera and reflect more light. Statistical analysis tools were developed to identify regions with crystal near the wall. When crystals are attached on the crystalliser walls, the pixel intensity is consistently high for a consecutive number of frames. When crystals are detached from the wall, pixel intensity drops and pixel regions are classified as bulk. This means that crystals in bulk solution can be distinguished from those on the wall. The numbers of pixels that contain crystals on the crystalliser wall provides a fouling indicator and give an instantaneous measurement of the degree of fouling.

Nucleation induction time can also be estimated by analysing the time series of pixels classified in the bulk and on the crystalliser walls using Bayesian Online Change Point Detection. This method was applied to the crystallisation process here as it provides a method of estimating induction time that is agnostic to compound, experimental setup and conditions and type of sensor (PAT) used for monitoring.

Research Outcomes

Using Chebyshev's inequality to define the outlier pixel intensities and therefore identify pixels near the crystalliser surface, these pixels were then monitored for a number of frames to distinguish those that stayed at a high intensity (fouled) to those that changed (non-fouled). After running images through the classification algorithm the results were then visualised, as demonstrated in Figure 37.

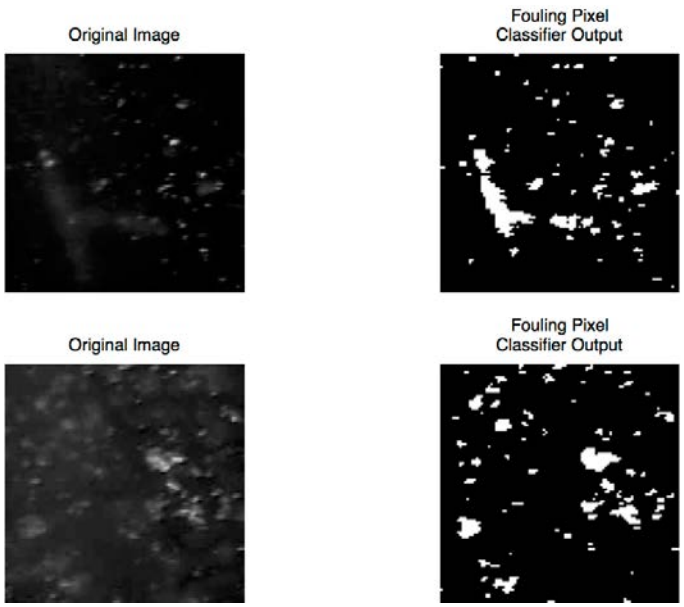


Figure 37. Example outputs from the fouling pixel classifier.

The Bayesian Online Change Point detection algorithm was applied to FBRM and turbidity measurements that were taken simultaneously from the MFOBC experiments while the image capture process was also running. This meant that three different types of measurement streams were available to validate the algorithm. For processing the image data to obtain induction times, Mean Grey Intensity (MGI) statistics were used. Figure 38 shows the results from the FBRM and turbidity measurements, and Figure 39 shows the results obtained using the MGI on different sizes of image area.

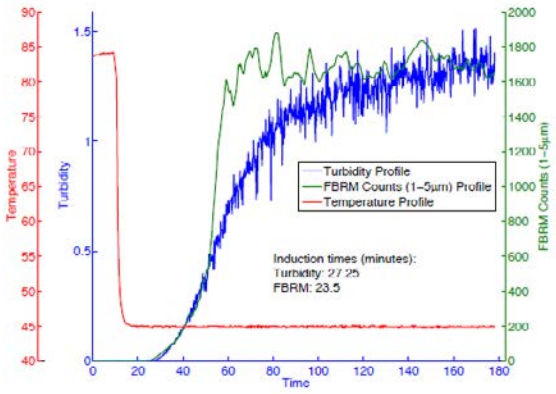


Figure 38. Results of induction time monitoring using turbidity and FBRM measurements using Bayesian online change point detection.

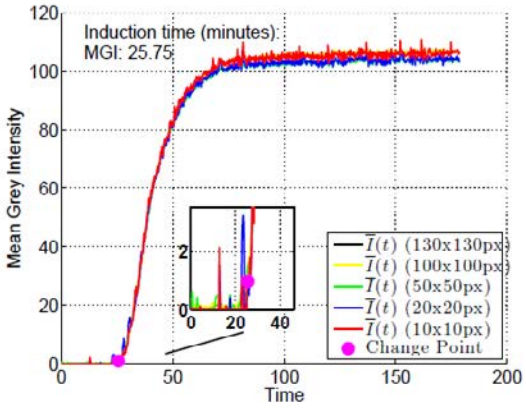


Figure 39. Results of induction time monitoring using the MGI of images.

The fouling and induction time monitor have been packaged as a Graphical User Interface (GUI) to allow application to a range of processes within the CMAC consortium.

Personnel

Prof Ivan Andonovic (ICT CMAC project PI), Dr Christos Tachtatzis, Dr Craig Michie, Dr Robert Atkinson, Prof Jan Sefcik, Dr Alison Cleary

Research Case Studies

Plant-Wide Modelling and Control

Academics:
Prof Chris Rielly (Loughborough)
Prof Zoltan Nagy (Loughborough)

Researcher:
Qinglin Su (Loughborough)

The Challenge

Part of the challenge of the ICT CMAC project is to develop suitable modelling and control strategies for a continuous crystallisation platform and associated secondary manufacturing processes. Work Package 4, led by Prof Chris Rielly and Prof Zoltan Nagy at Loughborough University is addressing the issue by developing a series of mathematical models that can be implemented based on the types of process used. To date, models have included continuous flow cascaded mixed-suspension mixed-product removal (MSMPR) crystallisers, periodic flow cascaded MSMPR crystallisers, tubular loop crystallisers, multi-segment multi-addition plug flow crystallisers, continuous mixing blenders, and dry granulation.

The Technology

Process models are built using Process Systems Enterprise gSOLIDS and gCRYSTAL software, and Matlab where appropriate. A combination of population balance modelling and experimental validation is used to develop the final models. Process design and optimisation are also routinely applied to achieve better product quality. The models will then be further combined to formulate a complete and integrated plant-wide process model, and robustness of the model to experimental and measurement variations will be carried out. Corresponding advanced model-based adaptive control technologies will also be proposed.

The Method

Recently Qinglin Su (postdoctoral researcher in Work Package 4) has been working together with ICT CMAC Work Package 2 and 3 colleagues in order to develop a 2D population balance model with an aim to have a better understanding of crystal size and shape evolution during crystallisation and to design appropriate control strategies to obtain quality products (Figure 40). The model will be applied together with in situ PVM and FBRM tools for model parameter estimation and validation purposes.

By using PVM and FBRM as the core PAT measurement tools to aid the model development, the modelling tools developed as part of Work Package 2 (Sensor and measurement modelling) with input from Work Package 3 (Intelligent support platform) can be utilised to inform the population balance models of Work Package 4. Work package 2 inversion models were developed initially to use FBRM, and then to incorporate data from simultaneously acquired PVM images that have been processed to extract aspect ratio information.

Recent work also focused on the development of the plant-wide modelling and control of a pharmaceutical dry granulation process, consisting unit operations of feeder, blender, roller compactor, milling, and screen (Figures 41 and 42). The model was based on the Process Systems Enterprise gSOLIDS software, with a customised and innovative milling model. Future work would implement advanced model-based predictive control strategies to this process through gO:MATLAB software.

Research Outcomes

Recently, a high resolution finite-volume method has been applied to a 2D population balance model in Matlab to simulate the evolution of particle size and shape in a seeded cooling crystallisation process. The in situ detection of particle shape using PVM imagines by Work Package 3 is progressing well and will be further combined with the FBRM inversion algorithm by Work Package 2 to infer the crystal size and shape. The final integration of the three work packages is promising.

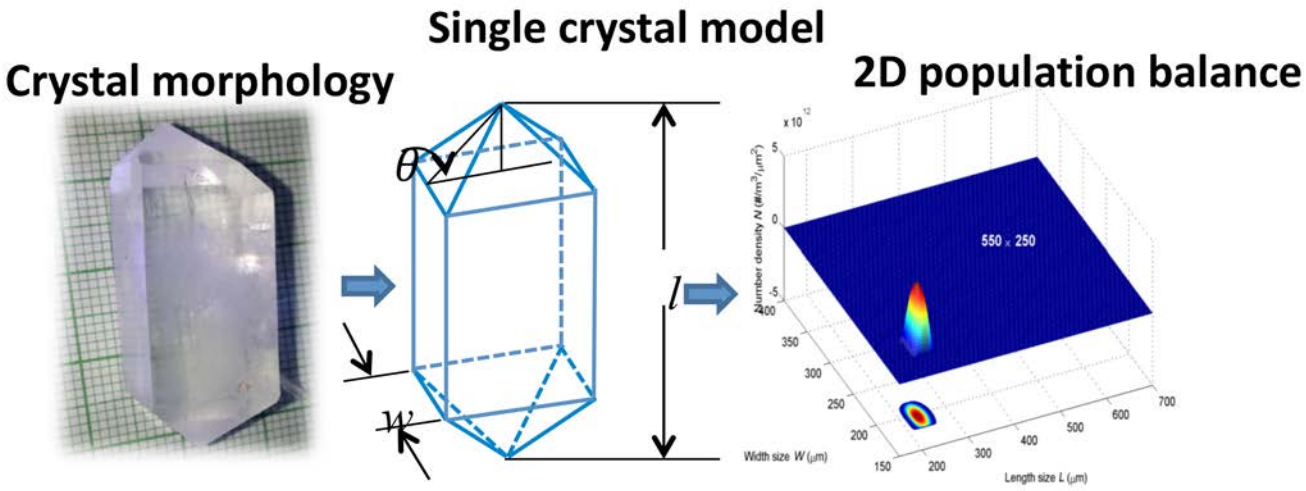


Figure 40. The work carried out by ICT CMAC Work Package 4 in collaboration with Work Packages 2 and 3.

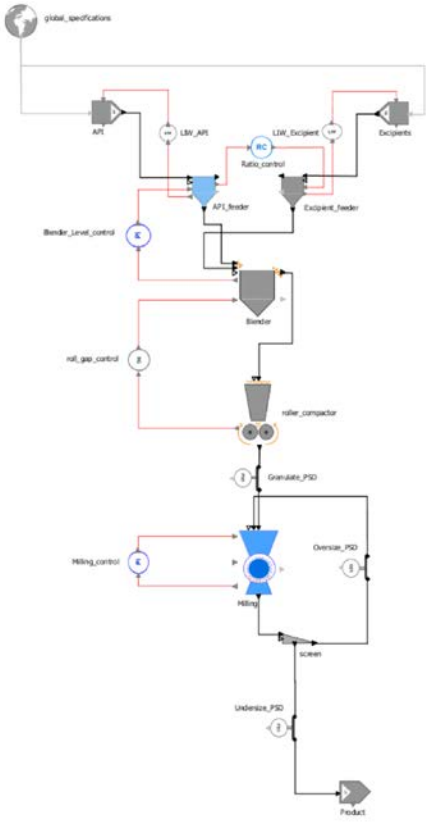


Figure 41. The dry granulation process model

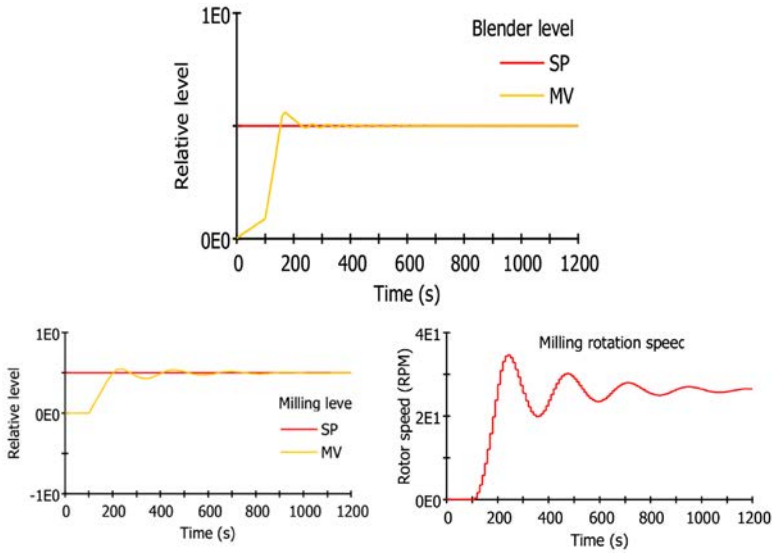


Figure 42. The dry granulation process model has been developed to a state where the blender level can be controlled (SP=setpoint and MV=manipulated variation for controller) and the milling level can be controlled by altering the speed of the rotor.

Research Case Studies

People and Processes

Academics:
Dr Blair Johnston (Strathclyde)

Researchers:
Dr Murray Robertson (Strathclyde)

The Challenge

Implementing a versatile, effective and easy to use system to manage, store and catalogue academic research data is being addressed by Murray Robertson and Blair Johnston as part of the ICT-CMAC project. Working with Biovia (Accelrys), a comprehensive Electronic Laboratory Notebook (ELN) system has been developed to meet the needs of CMAC researchers both present and future.

The Technology

Core to the ELN system is the integrated data environment in which it operates, and our system provides a complete link for the user from data acquisition to final experimental reporting and write-up, incorporating a series of selectable data analysis tools and modelling with novel algorithms, automated workflow components, and vital metadata tagging for data curation. Novel algorithms that are developed as part of the ICT-CMAC project will be integrated to the ELN environment as the project progresses.

The ELN system is now operational in the new labs in the Technology and Innovation Centre, and all experimental work carried out in TIC will be ELN-compatible. The ELN can also be accessed via a web interface from outside the lab or University network.

The Method

Figure 43 shows the high-level architecture of the complete system. Pipeline Pilot is a graphical, reconfigurable workflow automation software that has been fully integrated with the ELN system, thus allowing common processes, calculations, visualisations and reports to be generated quickly and easily in a standardised manner. Efficiency is therefore improved, and error-prone calculations can be automated.

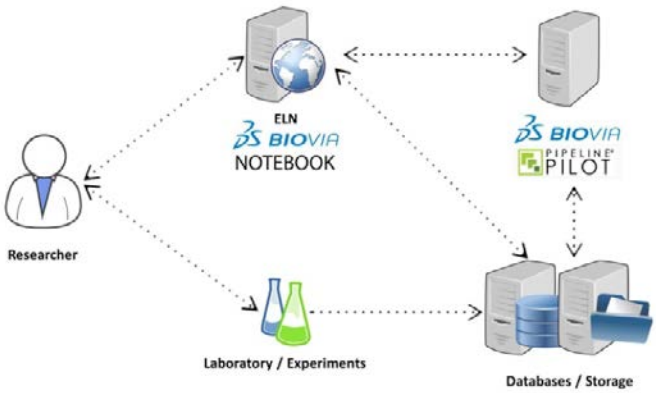


Figure 43. ELN link structure.

Within an ELN experiment a researcher will be able to upload their experimental output. This will them be processed and reported back into the ELN in an appropriate form (table, chart, data file). Standard meta tags are automatically generated and a copy of the data saved to a file server where the data and file naming is standardised to aid future machine reading and processing.

Access and sharing options are configurable, meaning that confidential data can be kept secure, but publicly funded research data can be made available according to the funder's requirements.

Centre Structure

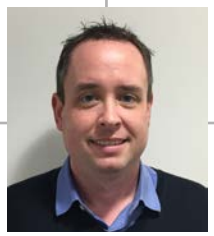
Management and Support Team

Industry Director
Craig Johnston

Centre Director
Alastair Florence

Academic DTC
Jan Sefcik

Technical Project Manager
Ian Houson



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Project Manager CMAC Technology Companies
Stewart Mitchell

Centre Manager
Andrea Johnston

Assistant Centre Manager
Helen Feilden

Management Accountant
Tim Faehnrich

Modern Apprentice
Rebecca O'Hare

International Collaboration Coordinator
Claire Ordoyno

Centre Administrator
Lorna Gray

DTC Administrator
Jacqueline Brown

Administrative Assistant
Rebekah Russell

Centre Structure | Meet the Teams

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

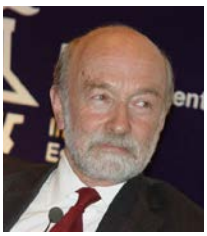
Professor Zoltan K Nagy

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

Professor David Watson

Professor Alex Duffy

Dr Athanasios Rentizelas

Dr Brahim Benyahia

Dr Chris Price

Dr Dimitrios Lamprou

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Researchers:

- Dr Thomas McGlone, Senior Research Associate, Developing workflows for continuous crystallisation
- Dr Cameron Brown, Senior Research Associate, Constructing Exquisite Particles (growth, transport, fouling and controlling agglomeration), and Phase II Activities
- Dr Humera Siddique, Research Associate on Innovate funded projects, Made to order process plants (Perceptive Engineering, CPI and AstraZeneca) and Development of an innovative modular system for continuous chemical processing (Syrris, GSK and AMRI)
- Dr Huaiyu Yang, Research Associate, Quick Win Projects
- Francesca Perciballi, PhD Researcher, Continuous formation of optimised particles for formulation and processing.
- Vishal Raval, Centre Platform Technician/PhD Researcher, Integrated lab scale continuous manufacturing of Pharmaceutical products
- Dr Muhammad Tariq Islam, Research Associate, REMEDIES AppB
- Dr Vijay Srirambhatla, Research Associate, CPOSS
- Rebecca Halliwell, DTC Researcher, Lab scale continuous crystallisers for control of pharmaceutical olymorphs and critical particle attributes.
- Fraser Mabbott, DTC Researcher, The exquisite particle – Understanding fouling.
- Rajesh Gurung, DTC Researcher, Development and Testing of a Synthetic Design Approach for Continuous Crystallisation Process Design
- Stephanie Yerdelen, DTC Researcher, Lab-scale Equipment For Continuous Crystallisation Towards Control Of Various Particle Attributes
- Bilal Ahmed, DTC Researcher, Lab-scale equipment for continuous crystallisation for control of particle attributes: seed production via slurry media milling approaches
- Sebastion Davidson, Joint International PhD Researcher, Multi-component crystallisation in COBC

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E-mail: Joop.terHorst@strath.ac.uk

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Researchers:

- Dr Murray Robertson, ICT-CMAC Research Associate, Work package 5 People and Processes
- Bruce Wareham, DTC Researcher, Automated workflows for rational solvate and solvent system selection: in silico models for solubility predictions and quantitative structure.

Co-Investigator: Professor Lee Cronin

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Researchers:

- Sergio Martin, DTC Researcher, Coupling molecular synthesis with continuous crystallisation in organic and inorganic synthesis

Co-Investigator: Professor Gavin Halbert

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Researchers:

- Dr Elke Prasad, Research Associate, Surface dissolution imaging
- Laura Martinez-Marcos, DTC Researcher, Continuous twin screw extrusion processing: Relationship of processing parameters, formulation and material properties
- Elanor Brammer, DTC Researcher, Personalised medicines and 3D printing
- Albarah Al-Afandi, DTC Researcher, Formulation considerations in twin screw wet granulation – A Quality by Design approach
- Alice Turner, DTC Researcher, Novel dosage forms

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Researchers:
- Dr Anna Trybala, Research Associate, Optimization of continuous MSMPR crystallization
- Qinglin Su, Research Associate, ICT CMAC
- Keddon Powell, PhD Researcher, Improving continuous crystallisation using process analytical technologies
- Iyke Onyemelukwe, DTC Researcher, Comparative investigation of continuous crystallisation approaches using process analytical technology
- Emmanuel Kimuli, DTC Researcher, Coupled CFD/PBE modelling of continuous crystallisation
- Dimitrios Fysikopoulos, DTC Researcher, Comparative investigation of continuous crystallisation approaches using process analytical technology
- Louisa Ejim, DTC Researcher, Novel Polymeric Helicoidal Meso-scale Oscillatory Baffled Reactors

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- Hannah McLachlan, PhD Researcher, Investigations into parameters affecting purity in OBC and STC
- Juliet Adelakun, DTC Researcher, Characterisation of profiles and steady states in a continuous oscillatory
- baffled crystalliser (COBC) using cooling crystallisation process
- Guillermo Jimeno Millor, DTC Researcher, Continuous Crystallisation under pressure in a continuous oscillatory baffled crystalliser
- Meifen Jiang, DTC Researcher, Characterisation of A Reactive Crystallisation

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- Alasdair Mackenzie, PhD Researcher, Crystallisation using laser-induced nucleation for polymorph control
- Fraser Keir, DTC Researcher, Combined experimental and computational studies of nucleation and crystallisation processes under continuous and non-ambient conditions
- Daniel Ward, DTC Researcher, Continuous crystallisation of energetic materials
- Adam Michalchuk, DTC Researcher, Applications of resonant acoustic mixing for the processing of powders and particles

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Researchers:
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Researcher: Dr Jag Srai
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E-mail: jss46@cam.ac.uk

Researchers:
- Dr Tomás Harrington, Research Associate, Manufacturing operations and supply chain management challenges in continuous manufacturing
- Mark Phillips, DTC Researcher, Exploring supply network reconfiguration opportunities arising from more continuous processing in pharma

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Researchers:
- Dr Pól MacFhionnghaile, Research Associate, Continuous nucleation and seed generation
- Rachel Sheridan,PhD Researcher, Understanding and mitigation of fouling in continuous crystallisation
- John McGinty, DTC Researcher, Development of continuous nucleation processes: salt crystallisation
- Maria Briuglia, DTC Researcher, Development of laboratory test bed for assessing effects of flow conditions on agglomeration/deagglomeration and attrition/breakage in continuous crystallisation
- Thomas Kendall, DTC Researcher, Laser induced nucleation in continuous crystallisation
- Vaclav Svoboda, DTC Researcher, Scale down of modular test bed for continuous crystallisation process development: continuous mixing, nucleation/seeding and solution/slurry transfer

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Researchers:
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- Anneke Klapwijk, DTC Researcher, Inducing layered solid-forms and controlling crystalline defects in multicomponent continuous crystallisation
- Lauren Agnew, DTC Researcher, Multicomponent templating approaches to polymorph selection, elusive form discovery and crystallisation
- Alex Cousen, DTC Researcher, Scale-up, yield, purity and selectivity in continuous production of micronized API's

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Researcher:
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Researcher:
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Researcher:
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Associated Investigator: Dr Dimitrios Lamprou
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Researcher:
- Carlota Mendez, DTC Researcher, Process understanding twin screw granulation

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/TSB Members		
Dr Karen Brakspear	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.

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

The last year has seen tremendous progress for CMAC. The manufacturing research is now having direct business benefit and industry is recruiting talented CMAC alumni. A key highlight was the move of the hub into TIC building at University of Strathclyde with world class facilities for engaging industry, suppliers and academics. I have also been encouraged by the outputs from all of the university partners. CMAC has also established itself as an internationally leading group and is working collaboratively across skills, research, common language and appropriate regulatory areas. Bayer Health Care joining as Tier 1 member is a very welcome addition and they bring much expertise and energy to the developing program."

Dr Clive Badman OBE, GSK, CMAC chair

EPSRC
Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

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