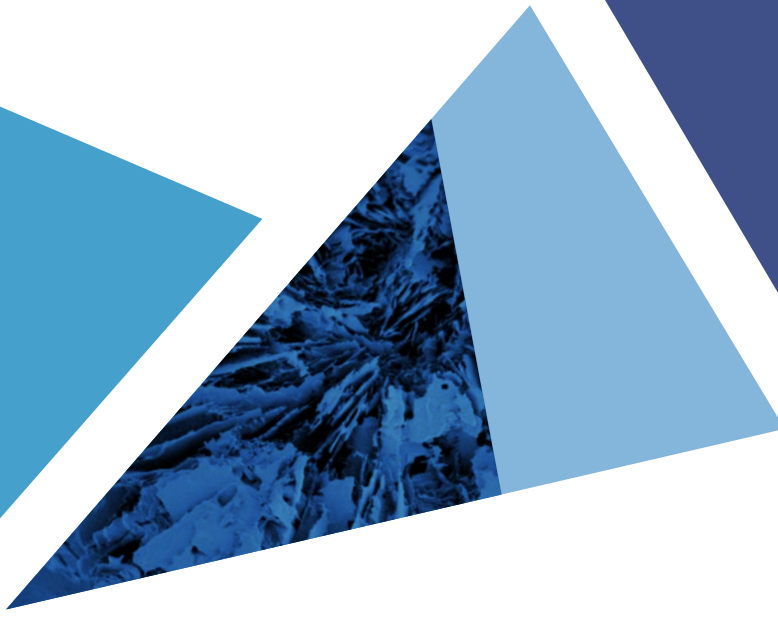
CMAC

FUTURE MANUFACTURING RESEARCH HUB

Annual Review

2018



EPSRC

Engineering and Physical Sciences Research Council

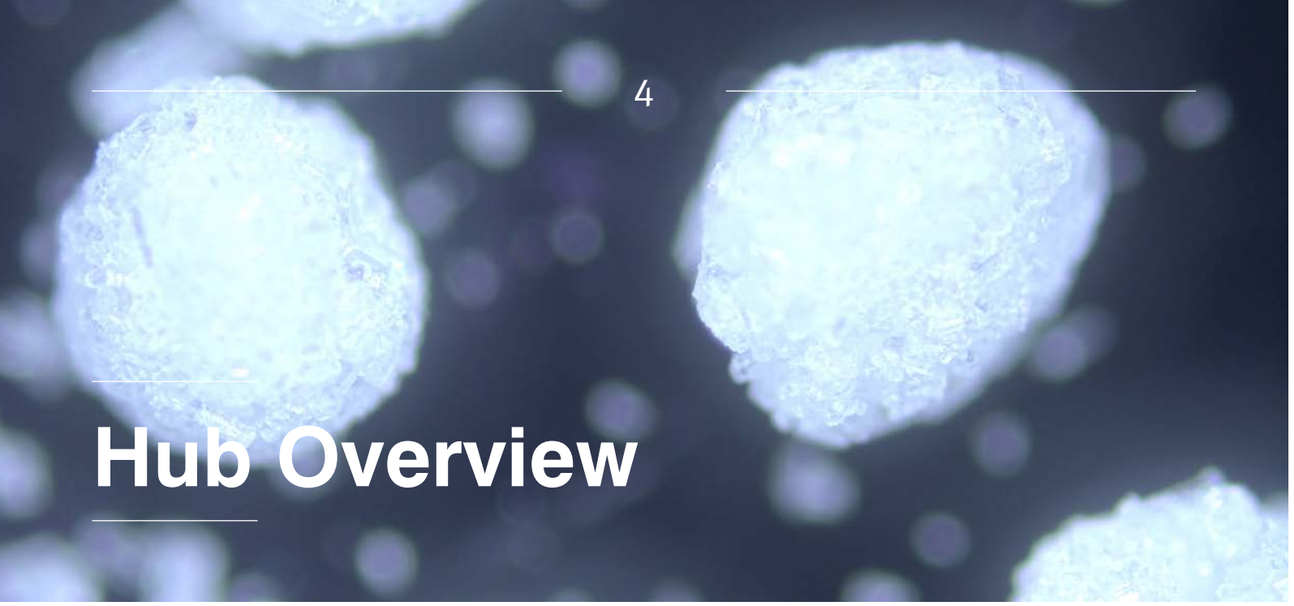
Contents

Opening Remarks

Welcome to the 2018 Annual Review for the EPSRC Future Continuous Manufacturing and Advanced Crystallisation Research Hub (CMAC). Our collaborative programme seeks to transform the way that medicines are developed and made and our growing portfolio of radical developments will accelerate the pace at which new chemical entities can be transformed into safe, effective, high quality and increasingly personalised products. The review highlights the significant progress that our manufacturing research program has made over the last 12 months in particular in developing Digital Twins for the predictive design of particles, products and processes and in the design and operation of modular, integrated Microfactory platforms to enable future supply chains. The development of digital design and digital manufacturing technologies underpins this progress, as highlighted in the recent government Made Smarter report, and so I am also delighted we are able to show how new EPSRC awards are also helping to extend this progress, specifically for the application of Artificial Intelligence and AR/VR technologies to continuous manufacturing. 2018 has also brought progress in developing our understanding and ability to control material properties to achieve improved manufacturability and performance. Examples and case studies are included that cover the vibrant program of research projects across CMAC partners as well as the steps being made to translate these into industry practice. In addition to our ambitious manufacturing research programme and technical translation activities, the review also reports on our ongoing training initiatives and the progress our talented trainees and researchers are making as well as the latest developments in CMAC's world class facilities.

The exciting developments across CMAC's scope have only been possible with the dedicated commitment to effective collaboration that all our academic, innovation and industry partners continue to share. I look forward to continuing to work with all my colleagues as we strive to place the UK at the forefront of advanced pharmaceutical manufacturing.

Professor Alastair Florence
Director



Hub Overview

The Future CMAC Hub is a world-class international hub for manufacturing research and training in continuous manufacturing and advanced crystallisation. Working in partnership with industry, its purpose is to transform current development and manufacturing processes into the medicine supply chain of the future.

Figure 1. CMAC vision and core areas of focus: research, facilities, skills and translation

CMAC's vision has been developed through close collaboration with industry and the support of our Tier 1 partners, GlaxoSmithKline, AstraZeneca, Novartis, Bayer, Takeda, Lilly, Pfizer and Roche and a wide range of technology companies. CMAC has already leveraged a £150m funding portfolio and currently comprises more than 120 staff and researchers, including academics, post docs, 50 PhD students and an experienced support team. In 2017, the EPSRC Future Manufacturing Research Hub was launched. This 7 year program, led from the University of Strathclyde, comprises academic investigators and research staff across 7 leading universities will deliver predictive design tools and novel integrated continuous processing platforms for the supply of next generation high performance personalised products.

CMAC

- Develops new solutions to company specific problems
- Delivers measurable successes that are of real benefit to society
- Creates commercial opportunities for start-ups and major global companies
- Produces a talent pipeline of highly skilled multi-disciplinary staff
- Influences policy, government, and regulators
- Understands and integrates with the broader supply chain context
- Collaborates with world class business and academia on an international basis

Research

CMAC's leading manufacturing research programme is funded by the EPSRC Manufacturing Research Hub programme. The University of Strathclyde is the hub with delivery achieved by a multidisciplinary and collaborative academic team at the UK universities of Bath, Cambridge, Imperial, Leeds, Loughborough and Sheffield. Research with impact has grown through new projects supported by EPSRC, InnovateUK, EU and industry. CMAC is a founding member of International Institute of Advanced Pharmaceutical Manufacturing (I2APM, www.i2apm.org) with partners C-SOPS (US) and RCPE (Austria). As part of the critical regulatory agenda CMAC and MIT organise a biennial conference with the FDA.

Training & Skills Development

CMAC has a unique Doctoral Training Centre, which operates across the partner universities, and is introducing the new Industrial PhD Programme that aligns with the Future CMAC Hub. CMAC also has joint doctoral training programmes in collaboration with NTU and as part of the NPL Scottish Hub. Training the next generation of scientists and engineers is vital to accelerating the adoption of continuous manufacturing. Additionally, a Master's programme in Advanced Pharmaceutical Manufacturing is delivered at Strathclyde. A key deliverable is the CMAC talent pipeline - see pages 22-23.

World Class Facilities

The £34M UK-RPIF scheme partnership established a world-class facility equipped with a comprehensive suite of continuous processing, process analysis, and characterisation equipment. The physical hub is within the new £89m Technology and Innovation Centre at Strathclyde opened by HM the Queen in July 2015. This provides open access approach across the established and evolving broad industry and academic community. In 2016, CMAC was the first ever academic winner of the Global International Society for Pharmaceutical Engineering (ISPE) Facility of the Year award.

Translation and Industry Engagement

CMAC has always benefited from strong industry engagement and leadership. An industry led membership organisation was created in 2011 and this has grown and developed over the years. The membership organisation operates under a pre-competitive, collaborative research and development model with senior level company support. The main industry partners (AstraZeneca, GSK, Novartis, Bayer, Lilly, Takeda, Roche and Pfizer) get an individual seat on the CMAC Board and an opportunity to influence the direction of future research and Hub activity. Integral to the CMAC ecosystem are the Tier 2 technology companies. These range from large companies, Siemens and PwC, to micro SMEs. This supportive environment helps translate research into equipment and products. In addition to CMAC members events, the Hub organises many open events for the broader industry landscape and collaborates with a wide range of additional companies locally, nationally and globally.

Hub Overview

Continuous Manufacturing and Advanced Crystallisation

Vision

To deliver predictive design tools, digital twins and novel integrated continuous processing platforms for the supply of next generation high performance personalised products.

The Future CMAC Hub will address the urgent need to translate new molecules into high-value products through rapid predictive development pathways and integrated continuous manufacturing systems, enabling more personalised, responsive and flexible product provision through digitalised supply chains. Building on the significant success of the EPSRC Centre for Innovative Manufacturing (CIM), and informed by extensive engagement with national and global industry, end-users, technology providers, international academic programmes and regulatory agencies, the industry-academic team has co-created an ambitious Future CMAC Hub Vision. The Hub will deliver new predictive tools and design approaches for products, processes and supply chains to enable the potential of Quality-by-Design (QbD) and Industry 4.0 initiatives to be fully realised by our partners. Whilst these regulatory and industry-driven initiatives have set out ambitious visions, the enabling tools do not yet exist. The Future CMAC Hub will deliver the tools and technologies for process industries to translate them into tangible benefit and enable a step-change in industry practice.

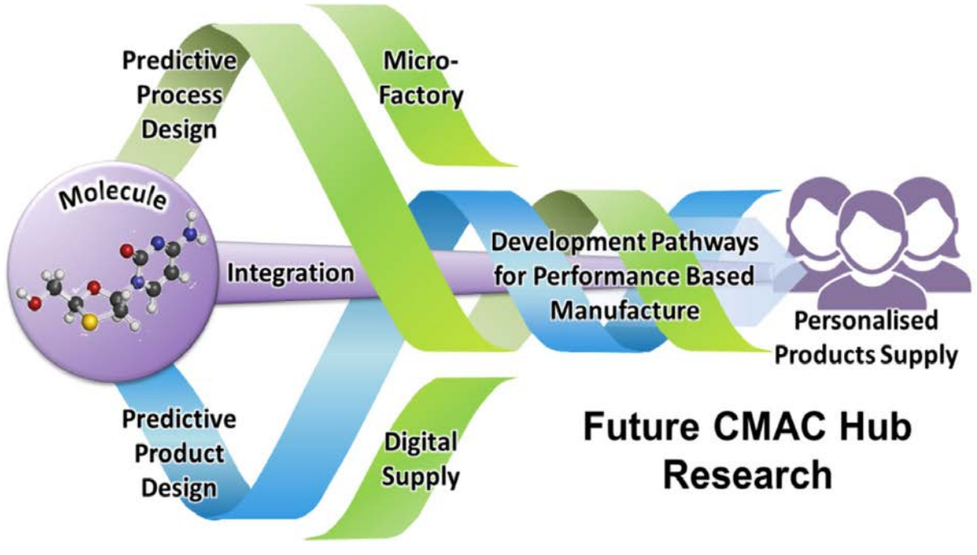


Figure 2: The Future CMAC Hub Research Program seeks to achieve closer integration of: prediction and experiment; drug product and process design, and primary and secondary processing

Academic Partners

University of Strathclyde Glasgow · University of Bath · University of Cambridge · Imperial College London · University of Leeds · Loughborough University · The University Of Sheffield.

Tier 1

GSK · AstraZeneca · Novartis · Bayer · Lilly · Takeda · Roche · Pfizer

Tier 2

Siemens · PwC · Mettler Toledo · PSE · CCDC · Perceptive Engineering Ltd · Britest · Sirius Analytical · Clairet Scientific Limited · NiTech Solutions · Technobis Crystallization Systems · Alconbury Weston Ltd · Booth Welsh Integrated Engineering Services · EDEM · Buchi · Snapdragon Chemistry · Blacktrace · Pion

Innovation Spokes

cpi · Cancer Research UK · NPL National Physical Laboratory · Diamond · rcpe research center pharmaceutical engineering · MMIP · Chemistry Growth Partnership · ReMediES · ADDOPT · Nanyang Technological University Singapore · KTN the Knowledge Transfer Network · Knowledge Centre Materials Chemistry · MHRA Regulating Medicines and Medical Devices · Scottish Enterprise

CMAC also works with a broad range of collaborators.

Hub Overview

Research Goals

CMAC's research focus will be to deliver novel manufacturing technology that will enable industry to deliver better products, quickly, economically and sustainably. This will meet the demand for reduced development time and costs and to exploit emerging opportunities driven by the urgent needs of patients and consumers for more personalised product performance.

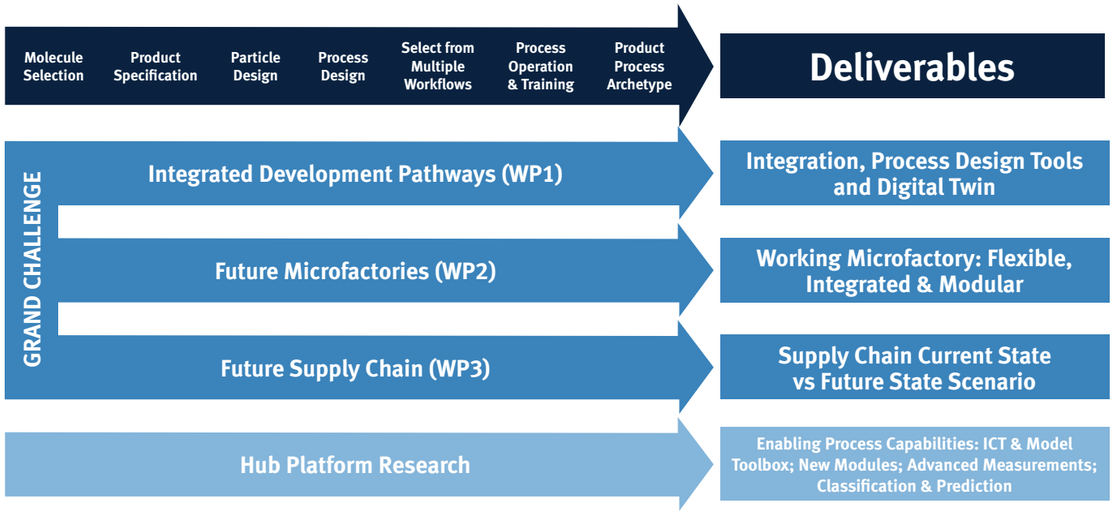


Figure 3: Rapid Performance Based Design and Continuous Manufacture of Particle Based Products

CMAC Partners

The Future CMAC Hub research programme is delivered by the seven partner universities with Strathclyde as the Hub and Bath, Cambridge, Imperial, Leeds, Loughborough and Sheffield as spokes. CMAC currently has over 125 people involved with over 70 researchers from the seven Future CMAC Hub partner universities and the 2 additional Universities (Glasgow and Heriot Watt) that have DTC researchers with CMAC.

CMAC has substantial industry engagement and support through 11 pharmaceutical, 5 chemical, 2 food and 19 technology companies (15 SMEs) as well as 12 key Innovation partners. (see page 7).

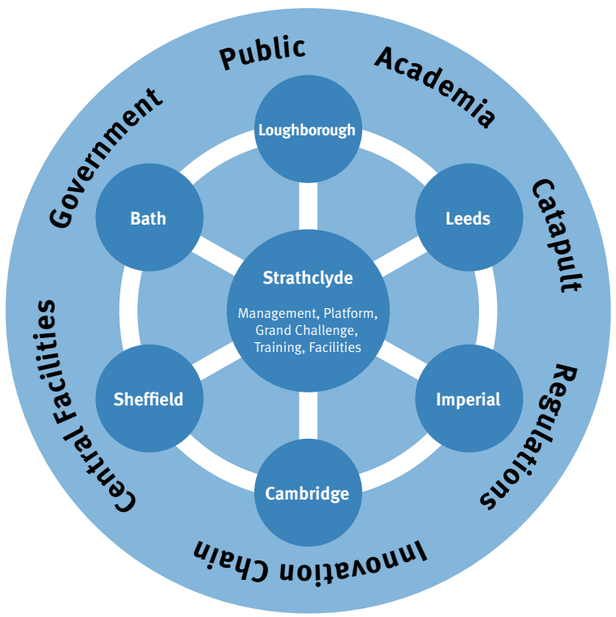


Figure 4: Hub and Spoke model

CMAC Portfolio

The entire CMAC research portfolio currently comproses over 80 projects. The projects and themes are shown in the diagram (figure 5). The research funding currently includes EPSRC, EU and Industry projects. The CMAC Future Manufacturing Research Hub Programme is the core of the CMAC Research Portfolio. Our Tier 1 partner companies support pre-competitive research through the CMAC membership structure and also collaborate with us on proprietary projects on a case by case basis.

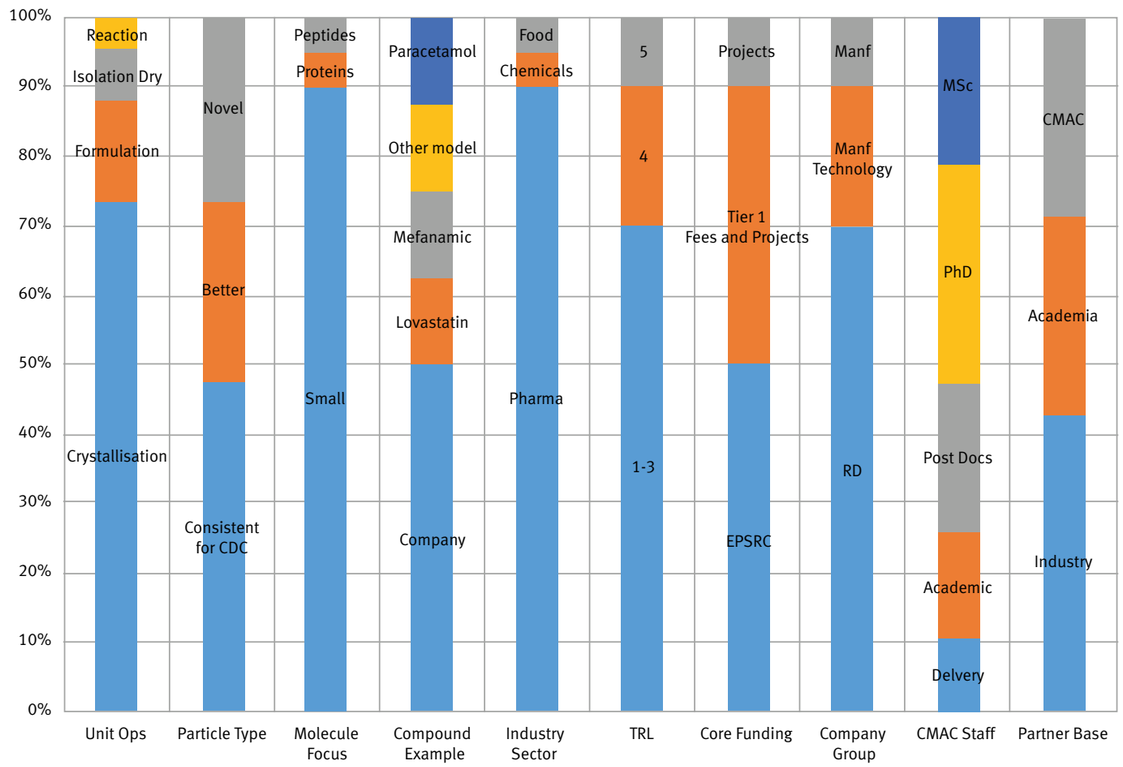


Figure 5: CMAC by the numbers. This shows the types of projects ongoing in CMAC as well as the funding, staff numbers and partner base.

Hub Overview

CMAC Innovation Roadmap

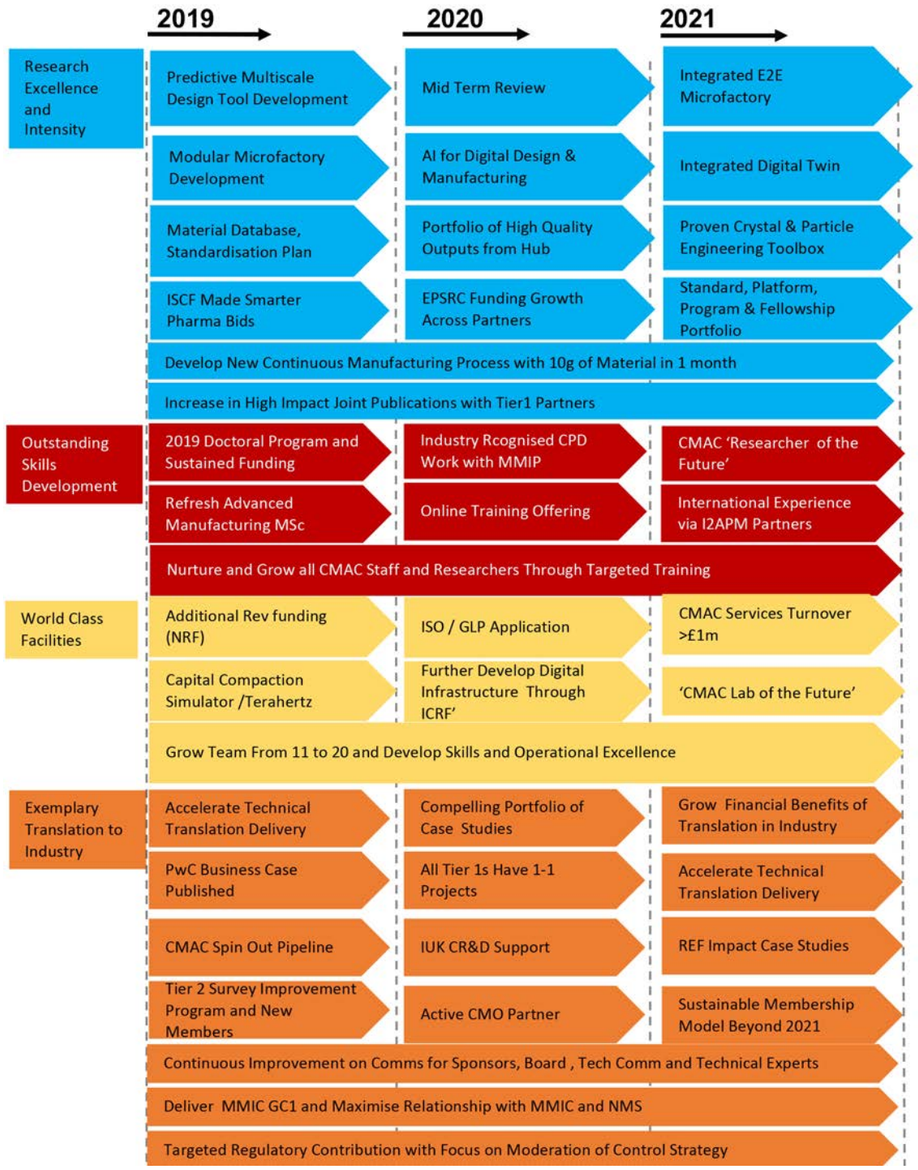


Figure 6: Innovation Roadmap (Rev1)

Why?

Optimised pharmaceutical and high-value chemical manufacturing operations across the value chain which

- Are economic, efficient, lean and world class
- Allow reduced time to market
- Are sustainable and wealth creating
- Deliver regulatory compliance

Benefits for patients

- Novel manufacturing technologies to address health needs
- Optimisation of processes that can be controlled or adapted for personalisation

High value products resulting from

- Understanding of 'better and novel particles'
- Insight into particle formation
- Impact in formulation and quality attributes

High level impact of manufacturing research produced through

- Multi-disciplinary expert collaborators
- Supportive governments
- Collaboration with companies
- Strong innovation network
- Strong UK Pharma base

Achieve in Future

- Leading Tier 1 and supply chain partners
- Peerless talent pool of PhD, MSc and post docs
- Impact of technology on new medicines and £1bn savings in manufacturing
- Process development with grams of material through modelling
- Grow world leading pre competitive £150m program
- Medicines Manufacturing Innovation Centre (MMIC) operational supporting Pathways to Impact

Benefits

- Improved manufacturing process and quality will benefit patients and producers driving CMAC sustainability
- Development of world class facilities will enable innovation across process and enhance to support manufacturing
- Focus on manufacturing translation will cement CMAC standing as leading International organisation influencing policy
- Production of Microfactories will enable future pharmaceutical manufacturing and create jobs
- MMIC will save time, save capital and de risk investment for pharmaceutical companies.

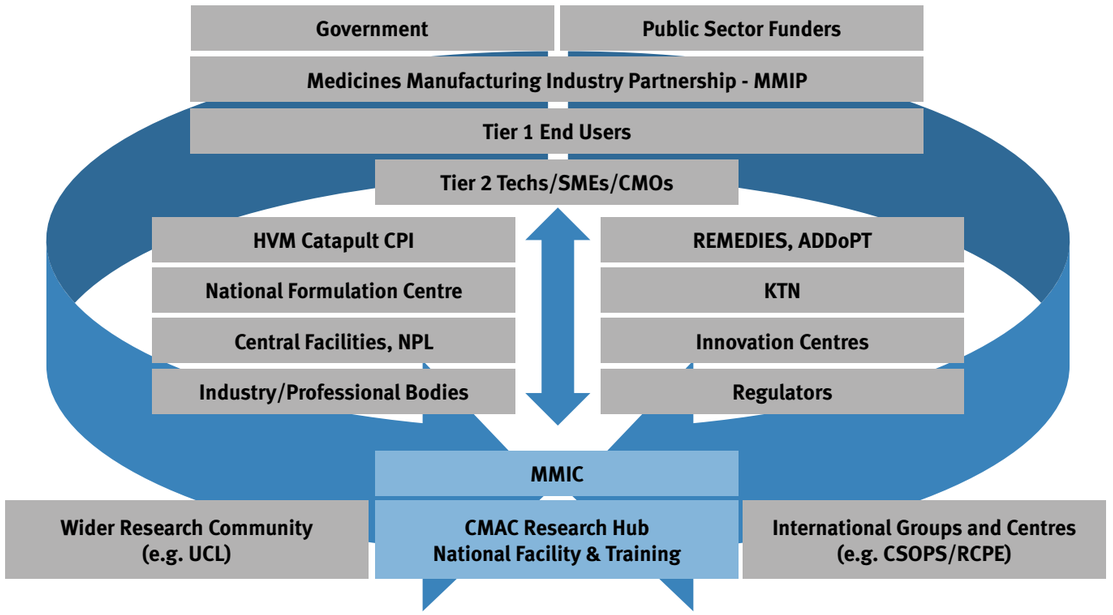


Figure 7: Innovation Landscape in UK

Hub Overview

Academic Engagement

- **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**

The Future CMAC Hub consists of seven academic partners, led from Strathclyde. Most of the researchers are based at those institutions. CMAC also has PhD researchers from Glasgow and Heriot Watt who are part of the CMAC EPSRC DTC (EP/K503289/1) that was aligned with the EPSRC Centre for Innovative manufacturing in Continuous Manufacturing and Crystallisation that preceded the Future CMAC Hub (see page 47 for more details on the DTC).

CMAC acts as a focus for the wider research community in the area of continuous manufacturing and advanced crystallisation. Outreach, engagement activities and collaborations are key to CMAC's growth and success. Since 2011, CMAC has engaged with the wider community, acting to influence policy, facilitate and support events, develop national expertise and establish the CMAC National Facility. CMAC holds an important position in the collaborative research and innovation landscape in the UK. Our work has included policy influence and strategy development in the area of continuous manufacturing and advanced crystallisation.

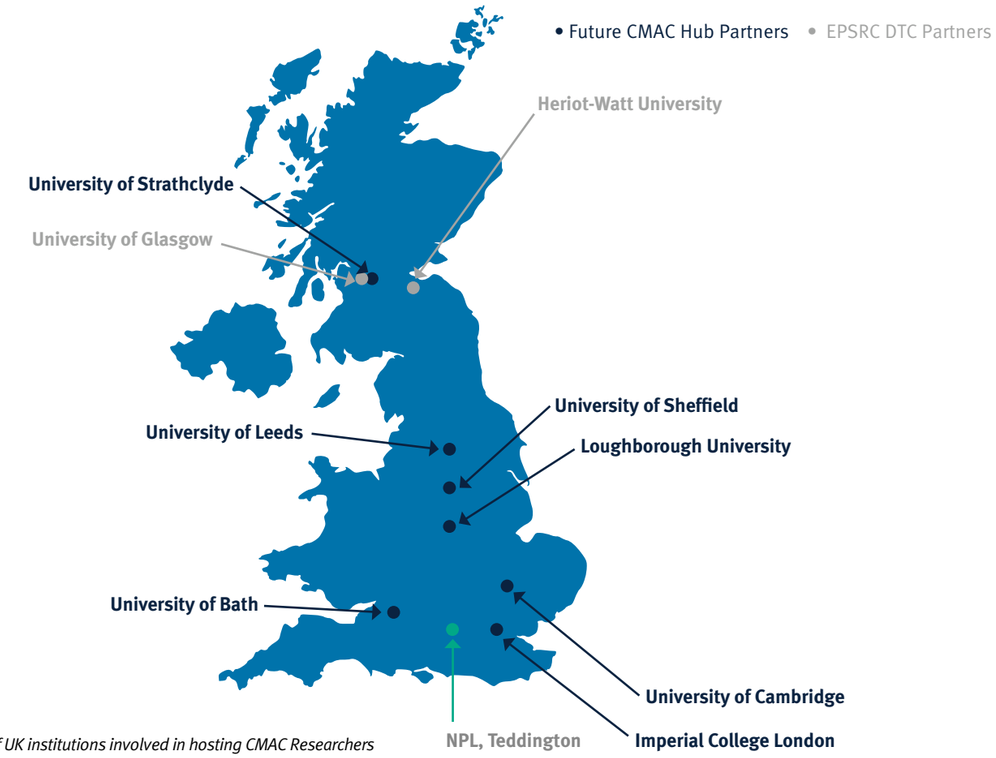


Figure 8: Map of UK institutions involved in hosting CMAC Researchers

The Hub has a number of projects that are part of the CMAC portfolio managed from Strathclyde, as well as being partners in aligned projects managed from other groups and Universities as shown in the figure 9. We have close links with the aligned projects summarised below. The CMAC Research Programme is summarised on page 24.

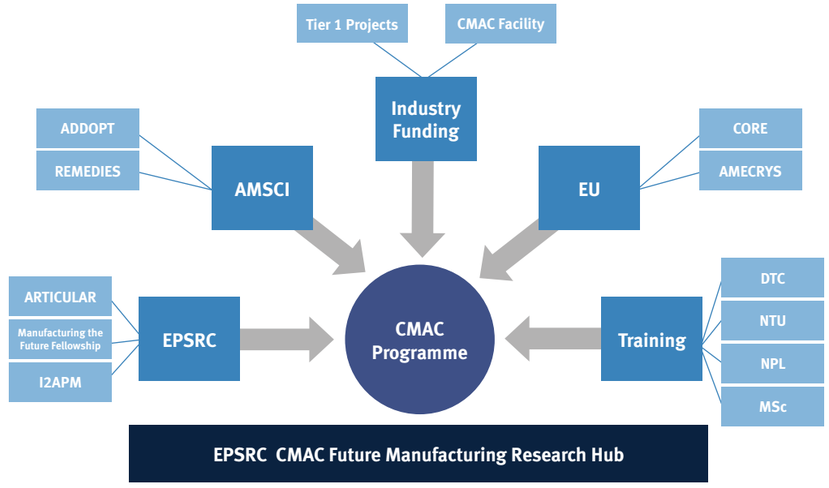


Figure 9: Map of funded projects

Aligned Projects

EPSRC

ARTICULAR: ARtificial inTelligence for Integrated ICT-enabled pharmaceUticaL mAnufactuRing is a £1.9m EPSRC project Led by Dr Blair Johnston (Strathclyde) that aligns with the CMAC Hub. This project will seek to develop novel machine learning approaches to learn from past and present manufacturing data, and create new knowledge that aids in crucial manufacturing decisions such as knowing the processes and operations to employ; the sensors and measurements to deploy to optimally deliver the product; and the potential process upsets and their future impact on the quality of the medicine manufactured. All of these data and the Artificial Intelligence (AI) "learning" will be made available via bespoke, personalisable Augmented Reality and Virtual Reality interfaces. Partners include Loughborough University, Glasgow School of Art, Arcinova, Booth Welsh, Cambridge Crystallographic Data Centre, Siemens plc, DAQRI, Perceptive Engineering Ltd.

"The School of Simulation and Visualisation (SimVis) is delighted to be continuing its successful collaborations with the University of Strathclyde and their world-class Future Manufacturing Hub at CMAC," Professor Paul Chapman, Head of GSA SimVis.

Dr Iain Oswald leads Pressure-Induced Nucleation for the Continuous Manufacture of supramolecular assemblies, with Prof Jan Sefcik and Prof Joop ter Horst as co-investigators. This project aligns with the Future CMAC Hub project, and seeks to develop a novel manufacturing methodology by which we are able to form new materials at high pressure and feed these into an industrial scale process. This project also has a post-doctoral and a PhD researcher based with CMAC at Strathclyde.

Prof Alastair Florence is a co-investigator on the Computationally Designed Templates for Exquisite Control of Polymorphic Form led from UCL by Prof Sally Price. There is a post-doctoral and a PhD researcher based with the CMAC team working on this project.

CMAC is a founding partner in I2APM. More details on this can be found on page 18.

EU

CMAC's Prof Joop ter Horst is part of the H2020 AMECRYS consortium (€335,500). AMECRYS aims at revolutionising the manufacture of biopharmaceuticals with innovative membrane crystallisation technology.

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

AMSCI

Refer to industry pages for AMSCI projects Remedies and ADDoPT on pages 56-57.

Joint International PhD Programme with NTU

Refer to pages 19 and 48.

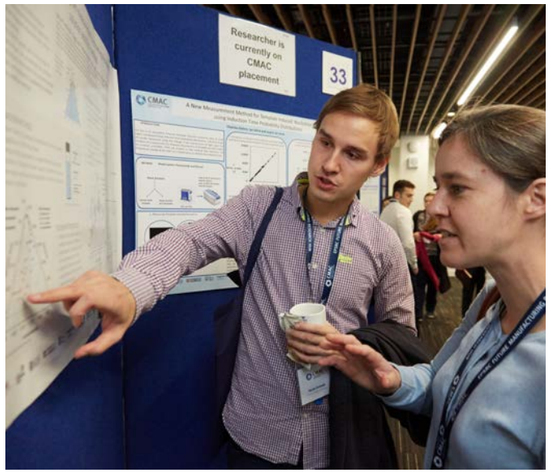
NPL

CMAC hosts 3 PhD students as part of NPL Scotland. This UK joint research collaboration is focused on pharmaceutical metrology in pharmaceutical innovation and manufacturing.

Hub 2018 Overview

CMAC Open Day 2018

The CMAC Open Day 2018 showcased the research outputs of the Future CMAC Hub through a packed programme of talks, posters, interactive demonstrations, a VR/AR demo and a tour that included a live demo of a prototype Lovastatin Microfactory and digital twin (see p32-34). Additionally, there were keynotes from Prof Marianthi Ierapetritou, Rutgers University and Prof Jon-Paul Sherlock, AstraZeneca and Chair of the CMAC Advisory Board. There were 260 delegates from 76 organisations in attendance including 22 exhibitors from technology companies.



Press and Media

18 December 2017 CMAC Welcomes Pfizer as Newest Partner. Link here.

26 February Siemens released a video of Alwyn Jones, Siemens UK & Ireland Head of Pharmaceutical & Life Sciences, in conversation with CMAC's Industry Director Craig Johnston. Link to video here.

26 March Chemistry World Article March 2018 "Solving the Crystal Maze" by Laura Fisher (26th March 2018) link here (subscribers only).

09 May Chemical Engineer Article May 2018 "Continuous crystallisation workflow enables high precision manufacturing of pharmaceuticals" link here.

15 June Strathclyde in Medicines Manufacturing Innovation Centre Full press release here.

22 June Looking back to look forward - ReMEDiES article.

25 June Accelerating the delivery of new drugs to patients - ARTICULAR announced.

03 July edition of Chemistry World "The Case for Lab Management Systems"

23 October Cambridge Crystallographic Data Centre (CCDC) has joined CMAC as a Tier 2 Member.

24 October EPSRC CMAC Future Manufacturing Research Hub – Microfactory and Digital Twin video.
CMAC is also active with a range of Tier 2s in their webinar programme (e.g. Siemens, Technobis and Mettler Toledo).

Visiting Researchers

Visitor	Home Institution	CMAC Supervisor	Start date	End date	Programme	Project title
Stephen Messham	GSK	Kenneth Smith	04-June-2018	27-July-2018	Visiting Researcher	GSK breadth kaizen
Samy Peponnet	IUT Paul Sabatier Toulouse	Chris Price / Clarissa Forbes	15-Jan-2018	29-Jun-2018	BSc Student via Erasmus	Ultrasonic velocity measurements
Lucie Pedussaut	IUT Paul Sabatier Toulouse	Chris Price / Sara Ottoboni	15-Jan-2018	29-Jun-2018	BSc Student via Erasmus	Wettability and contact angle by Washburn capillary rise method
Natasha Rabaeijs	Strathclyde University Chemical Engineering	Chris Price / Nazer Rajoub	08-Jan-2018	25-Apr-2018	MEng CP18530	In house project
Claire MacLeod	AstraZeneca, Macclesfield	Chris Price	19-Feb-2018	23-Feb-2018	Visiting researcher	AZ proprietary
Simon Coleman	Alconbury Weston / UoS	Chris Price	08-Jan-2018	30-Sept-2018	KTP	Design and optimisation of the AWL CFD
Frederico da Conceição do Carmo Montes	Technical University of Denmark (Prof. Gürkan Sin)	Dr Alison Nordon	29-10-2018	21-12-2018	MSCA ESR in the ModLife ITN (http://www.modlife.eu)	In-silico process design and evaluation tool for pharmaceutical manufacturing
Christos Xiouras	Department of Chemical Engineering, KU Leuven	Prof Joop ter Horst	02-May-18	28-Jul-18	Visiting Researcher	Semi-continuous and continuous deracemization
Edwin Lucas	Radboud University	Prof Joop ter Horst	18-Feb-18	15-Jul-18	Erasmus Masters Student	Polarimetry for control of preferential crystallization processes
Jayjan Wuang	Hong Kong University of Science and Technology	Prof Joop ter Horst	15-Jun-18	31-Aug-18	Visiting Researcher	Process modelling of membrane crystallization
Francesco Civati	National University Ireland, Galway (COST action)	Prof Joop ter Horst	13-Aug-18	12-Oct-18	Visiting Researcher	Co-Crystallisation
Michael Giullot	Université catholique de Louvain (COST action)	Prof Joop ter Horst	28-Aug-18	27-Oct-18	Visiting Researcher	Ultrasound enhanced racemization
Shashank Bhandari	Otto-von-Guericke University Magdeburg, Germany	Prof Joop ter Horst	22-Oct-18	21-Dec-18	CORE ESR	Process modelling of deracemization processes

Hub 2018 Overview

Conferences

The CMAC community has attended worldwide conferences and events including AAPS, Achema 2018, at AFS FiltCon 2018, APM Forum, AstraZeneca Science Day, BACG, BCA Spring Meeting, Britest Day 2018, CCG Autumn meeting, ChemEngDay UK, Compaction Simulation Forum, Connected Everything, EPSRC Science for a Successful Nation, ISCMP 2018, Pharma Integrates, The Henry Royce Institute Community Conference - 'Shaping the Future of Royce', QbD Symposium, SCI Formulation Forum, and WCPT8 - 8th World Congress on Particle Technology.

Awards, Prizes & Esteem

CMAC was shortlisted as a finalist in the Contract Services and Outsourcing category in the CPhI Pharma Awards October 2018.

Professor Gavin Halbert (University of Strathclyde) received the Eminent Fellowship award of The Academy of Pharmaceutical Sciences of Great Britain.

Prof Sven L M Schroeder is an Editorial Board Member on the journal Crystals.

Prof Sven L M Schroeder is on the European Synchrotron Radiation Facility (ESRF), Scientific Advisory Committee 2018-2020.

Prof Alastair Florence gave a keynote at the 10th Symposium on Continuous Flow Reactor Technology for Industrial Applications.

Prof Alastair Florence was session leader at the 2018 ISPE Conference.

Prof Sven L M Schroeder gave a keynote talk at 18th European Conference on Applications of Surface and Interface Analysis (ECASIA), 15-20 Sep 2019.

Sara Ottoboni won the poster prize in division 1 at AFS FiltCon 2018

Carlos Moreno Leon won 2nd Poster Prize at BACG 2018

Journal Front Covers

Brown, C. J.; McGlone, T.; Yerdelen, S.; Srirambhatla, V.; Mabbott, F.; Gurung, R.; L. Briuglia, M.; Ahmed, B.; Polyzois, H.; McGinty, J.; Perciballi, F.; Fysikopoulos, D.; MacFhionnghaile, P.; Siddique, H.; Raval, V.; Harrington, T. S.; Vassileiou, A. D.; Robertson, M.; Prasad, E.; Johnston, A.; Johnston, B.; Nordon, A.; Srai, J. S.; Halbert, G.; ter Horst, J. H.; Price, C. J.; Rielly, C. D.; Sefcik, J.; Florence, A. J., Enabling precision manufacturing of active pharmaceutical ingredients: workflow for seeded cooling continuous crystallisations. Molecular Systems Design & Engineering 2018.

Bhardwaj, R. M.; Reutzel-Edens, S. M.; Johnston, B. F.; Florence, A. J., A random forest model for predicting crystal packing of olanzapine solvates. CrystEngComm 2018, 20, 3947-3950.

Case, D. H.; Srirambhatla, V. K.; Guo, R.; Watson, R. E.; Price, L. S.; Polyzois, H.; Cockcroft, J. K.; Florence, A. J.; Tocher, D. A.; Price, S. L., Successful Computationally Directed Templating of Metastable Pharmaceutical Polymorphs. Crystal Growth & Design 2018, 18, 5322-5331.

High Profile Visitors to CMAC National Facility

During 2018 the CMAC National Facility at University of Strathclyde had visits from Chancellor Philip Hammond on 6th September and a Ministerial visit by Ivan McKee (Minister for Trade, Investment & Innovation) and Sam Gyimah MP (joint Minister for Higher Education at the Department for Business, Energy and Industrial Strategy and the Department for Education) on 2nd August. UK/ Scottish Government ministers (Lord Duncan (Parliamentary Under Secretary of State for Scotland) and Paul Wheelhouse (the Scottish Government Minister for Business, Innovation and Energy) visited on 15th June. Other high profile visitors have included a delegation from Shangdong (including Deputy Secretary-General of Shandong Provincial People's Government) and the Scottish Chambers of Commerce; delegates from the Korean Federation of Science & Technology Societies; Debra Carr (DASA Innovation Partner – Scotland); delegates from the FIP World Pharmacy Conference; Pham Thanh Huyen (Vice Dean Hanoi University of Technology); British Pharmaceutical Industry Senior members and Prof Mustafa Ashmy, Dean of Pharma (Oman).

CMAC Public Outreach 2018

Explorathon 2018

CMAC and CORE delivered a series of activities for Explorathon 2018 – European Researchers Night, part of a European-wide Horizon2020 funded celebration of research, taking place across Scotland every September. This year CMAC outreach team part in the schools programme as well as Explorathon Extravaganza event held at the Riverside Museum, Glasgow.

The Explorathon Extravaganza at the Riverside museum brought together members of public with researchers from local Universities in Glasgow. The 'Crystal Builder' activities at the CMAC stall included: mirror molecules (to explain chirality of drug molecules and their effect on humans): tempered and un-tempered chocolate (to show the effect of different crystalline structures); marshmallow crystal builders (to allow kids to build different crystal systems); and lab analysis (use of USB microscope and acoustic levitator to demonstrate crystal analysis). Both adults and kids found the stall to be welcoming and the explanation from researchers on different activities and their work at CMAC & CORE to be "very clear and concise". Kids also found the marshmallow crystal builder activity to be "cool" and "helpful in understanding crystal structures".

CMAC Outreach Team Visit Lockerbie Primary School

CMAC Researchers visited Lockerbie Primary School during March 2018 in order to deliver the Crystal Builders Workshop to two P7 classes. The team carried out interactive activities with the pupils in order to explain continuous manufacturing (making medicines at CMAC), chirality (mirror molecules), and polymorphism (the crystal forms of chocolate). The students also discussed STEM careers in order to inform the pupils about opportunities available to chemistry/chemical engineering graduates in a variety of industries.

St Andrews RC Secondary School

In May 2018 CMAC hosted 53 pupils aged 12-14 and 6 teachers from St Andrews RC Secondary School, Carntyne. The pupils got the opportunity to look at crystals and their structure as well as learn about chirality. After which they received a demonstration on CMAC's 3D printing capabilities as well as pharmaceutical analysis. The pupils and teachers really enjoyed themselves and showed much interest.

Hub Overview

Internationalisation

I2APM

The International Institute for Advanced Pharmaceutical Manufacturing (I2APM) brings together world-leading academic expertise to deliver new end-to-end continuous manufacturing capabilities with the goal of advancing the science and technology of integrated primary and secondary continuous manufacturing of pharmaceutical products that will transform the global supply chain for medicines.

I2APM is a research and educational partnership between CMAC, the Center for Structured Organic Particulate Systems (C-SOPS) in the US and the Research Center Pharmaceutical Engineering (RCPE) in Austria. EPSRC SAVI funding has facilitated activities between CMAC and C-SOPS (Rutgers and Purdue).

Team, to date, have delivered international symposia, co exhibited at conferences and are putting together joint skills offerings

3rd International Symposium on Continuous Manufacturing of Pharmaceuticals
Implementation, Technology & Regulatory

Held in London, October 2018, this international high profile event brought together leaders in the field from across the globe including industry users, suppliers, regulators and academics to drive forward the acceleration of adoption of continuous manufacturing for both small and large molecules. The symposium provided a platform for varied groups with this common interest to collaborate together. This was an enormous opportunity to guide the way in which new technologies and new approaches in the pharmaceutical industry can transform quality, cost and service for the benefit of the patient. More than 300 delegates attended the event, with a Keynote from Dr Janet Woodcock, FDA.

Through the University of Strathclyde International Strategic Partnership Scheme, CMAC have Memorandum of Understanding agreements in place with NTU in Singapore and TU Graz.

CMAC and RCPE are escalating their existing engagements. They have joint marketing and exhibitor presence at major conferences such as Achema, Frankfurt and Pharma Integrates, London. They are exploring joint research funding opportunities and will be establishing an RCPE research activity at CMAC in early 2019.

CMAC are growing relationships across a number of European institutions with ITN Networks, Core and AMECRYS, thus allowing students from both these networks to work at Strathclyde and for Strathclyde students to work at various institutions.

CMAC NTU has a joint doctoral training programme established in 2014. the first tranche of studentships ended in 2018 with the second tranche half way through their studies. This scheme facilitates 6 month international placements with the partnering institutions. CMAC are further exploring Singaporean links and looking forward to increased engagement with the A-stars research facility in 2019.

NTU – Strathclyde Collaboration

The Collaboration between CMAC (Strathclyde) and SCBE (Nanyang Technological University - NTU) was initiated in 2012 and funded 5 PhD researchers in place across the University of Strathclyde and NTU Singapore. A Symposium event was hosted at Strathclyde by Strathclyde Principle Sir Jim McDonald and NTU President Professor Bertil Andersson in late 2016. Workshop Outputs included updating future research funding plans and scoping projects for future researcher exchanges. A researcher placement scheme is now in operation between the two Universities and the first two placements were completed in 2017 with more planned for the future. Two additional CMAC PhDs were recruited in October 2017 at Strathclyde as part of the continuing partnership between the two universities and are now in their second year.

RCPE – Strathclyde Collaboration

The Research Center Pharmaceutical Engineering (RCPE) and CMAC announced a new international partnership to accelerate progress in advanced manufacturing for pharmaceuticals late 2017. Combining their world-leading and complementary expertise and facilities this partnership provides a single-source platform for accessing new product and process design knowledge. Over the preceding months, RCPE and CMAC have had researcher secondments between organisations and various outreach and marketing activities at international conferences with further collaborations planned for 2019. Dr. Johannes Khinast, CEO and Scientific Director of RCPE commented, “The cooperation of both centres will deliver unmatched platform research scale and capabilities across drug substances and manufacturing technology that will benefit industrial partners.”

International Engagement

CSops – New Brunswick, USA

Rutgers, New Brunswick, USA

RCPE - Graz, Austria

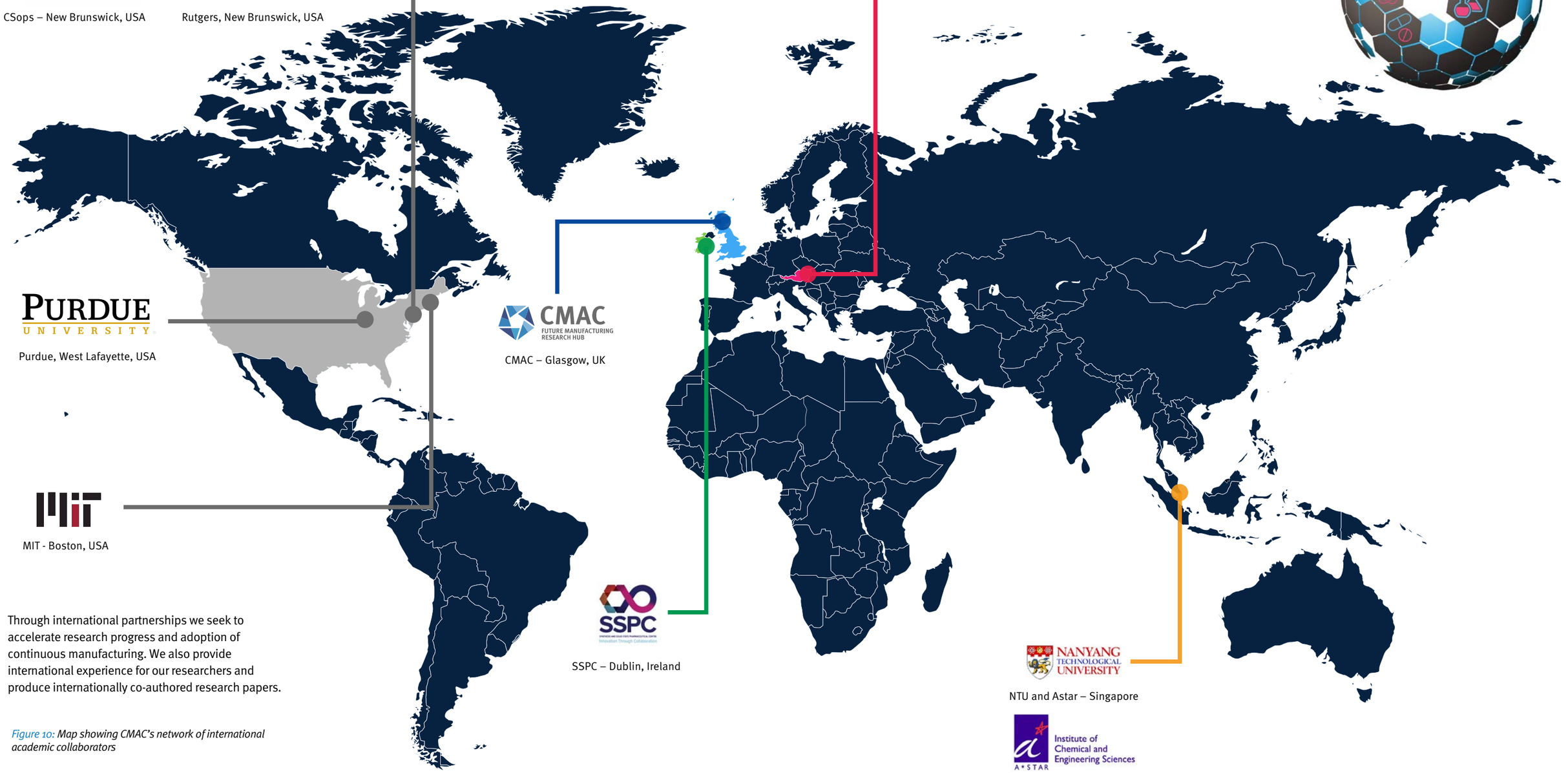
Purdue, West Lafayette, USA

CMAC – Glasgow, UK

MIT - Boston, USA

SSPC – Dublin, Ireland

NTU and Astar – Singapore



Through international partnerships we seek to accelerate research progress and adoption of continuous manufacturing. We also provide international experience for our researchers and produce internationally co-authored research papers.

Figure 10: Map showing CMAC's network of international academic collaborators

Hub Overview

Talent Pipeline

October 2011-December 2018

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

INPUT

96 PhD Researchers

56 Research Associates

Future CMAC Hub (Cambridge, Imperial, Sheffield, Strathclyde)
CIM Phase I (Bath, Cambridge, Glasgow x2, Strathclyde x3)
CIM Phase II (Cambridge, Loughborough x3, Strathclyde x6)
ADDoPT (Strathclyde)
COST (Strathclyde x2)
CPOSS (Strathclyde x2)
ICT CMAC (Loughborough, Strathclyde x7)
Manufacturing With Light (Edinburgh)
MOPP (Strathclyde)
Proprietary Projects (Strathclyde x10)
Remedies (Strathclyde)

42 Management & Support Staff

Future CMAC Hub (Strathclyde x4)
CIM (Strathclyde x6)
Industry Team (Strathclyde x4)
National Facility & Technical Staff (Strathclyde x11)
ICT CMAC (Strathclyde)

The success of CMAC in developing researchers has resulted in a two-way exchange between Academia and Industry. This is coupled with researchers who have used their multidisciplinary skills learned through the CMAC programme to gain prestigious places in industry. This talent pipeline is a key performance indicator for CMAC and highly valued by industry.

OUTPUT

PhDs

DTC Bath ⇢ GSK, UK
DTC Bath ⇢ AZ, UK x2
PhD Bath ⇢Johnson Matthey, UK
PhD Cambridge ⇢Industry
DTC Cambridge ⇢ Consultant
DTC Edinburgh ⇢ Nalas Engineering, USA
PhD Edinburgh ⇢ MOD
PhD Edinburgh ⇢ University of Edinburgh
DTC Glasgow ⇢ University of Glasgow
PhD Glasgow ⇢ University of Glasgow x2
DTC Heriot Watt ⇢ University of Strathclyde
PhD Heriot Watt ⇢ Solid Form Solutions, UK x2
DTC Loughborough ⇢ CMAC Strathclyde
DTC Loughborough ⇢ PSE
DTC Loughborough ⇢ Perceptive Engineering
PhD Loughborough ⇢ CMAC Strathclyde
DTC Strathclyde ⇢ Johnson Matthey
DTC Strathclyde ⇢ CMAC Strathclyde x5
DTC Strathclyde ⇢ Syngenta
PhD Strathclyde ⇢ Novartis
PhD Strathclyde ⇢ University of Strathclyde
PhD Strathclyde ⇢ CMAC Strathclyde
DTC Strathclyde ⇢ GSK, UK
PhD Strathclyde ⇢ Johnson Matthey
DTC Strathclyde ⇢ KTP Associate, University of Strathclyde
PhD Strathclyde ⇢ Mettler Toledo, Germany
PhD Strathclyde ⇢ MIT, US
PhD Strathclyde ⇢ science and engineering sector industry, Scotland

Research Associates

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

Staff

Assistant Centre Manager ⇢ iBioIC, UK
DTC Administrator ⇢ University of Strathclyde, UK x2
Laboratory Manager ⇢ City University of New York, US
Management Accountant ⇢ Freelance Accountant
National Facility Administrator ⇢ University of Strathclyde
Senior Technician ⇢ Macquarie University, Australia
Technician ⇢ PhD at University of Glasgow, UK
Technician ⇢ Pharmaceutical Industry, Ireland

Research

EPSRC CMAC Future Manufacturing Research Hub Programme

Vision

To deliver predictive design tools and novel integrated continuous processing platforms for the supply of next generation high performance personalised products.

CMAC is developing cutting edge design and modelling tools alongside integrated production and supply chain systems to address the future needs of patients, consumers and industry. Health systems worldwide are facing challenges to deliver better medicines to more people with tightening budgets and this programme addresses these via use of continuous manufacturing.

The idea behind this research programme is to take a molecule and use as little material as possible to rapidly design an end-to-end continuous manufacturing process to deliver the product. The resulting process design will be used to deliver a microfactory that can manufacture the product. The business case to support this innovative way of producing pharmaceutical products will be developed in parallel.

A partnership of world class researchers, from seven universities whose expertise spans multiple disciplines, will deliver the research programme.

Scope

The CMAC Future Manufacturing Research Hub Programme will deliver a platform research capability that benefits collaborators and industry partners, and will address the grand challenge: 'Rapid performance-based design and continuous manufacture of structured particulate products'.

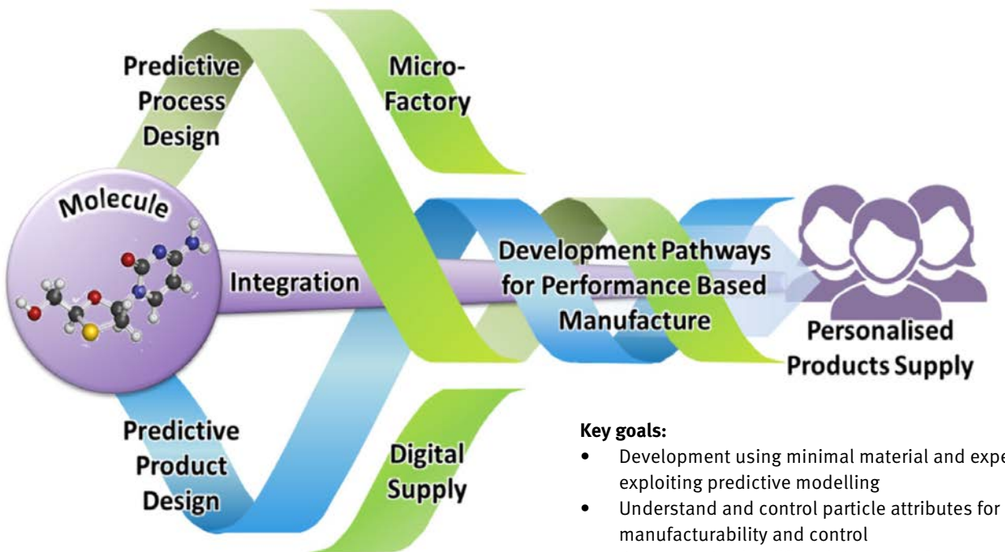


Figure 11: Future CMAC Hub Scope

Key goals:

- Development using minimal material and experiments exploiting predictive modelling
- Understand and control particle attributes for manufacturability and control
- Demonstrate simplified, integrated, flexible continuous process streams

Hub Platform Research

The Hub platform provides the underpinning operational framework, equipment capability and personnel to effectively support targeted research activity in a flexible way over the course of the project. Specific activities include:

- Process technology development
- Toolbox of novel ICT tools for continuous manufacturing
- Developing the science base: characterisation, classification and prediction
- Informing programme evolution
- Enhancing skills development and training

Hub Grand Challenge Research

This project will deliver a step-change in capability to bring functional high-value solid products rapidly to market, with a focus on pharmaceutical products. Small molecule systems of interest to industry and academic partners will be investigated. The work will inform development of radically new approaches for advanced predictive design and integrated manufacturing.

Three main work packages will deliver the project:

- Predictive Design & Digital Twin (WP1)
- Future Microfactories (WP2)
- Future Supply Chain (WP3)

The Future CMAC Hub will address the grand challenge: rapid performance based design and continuous manufacture of structured particle based products.

Research

Predictive Design & Digital Twin (WP1)

This work focuses on rapid, predictive design of products and processes. It will develop a new capability by integrating theoretical, modelling, experimental and ICT approaches. Predictive design approaches that combine crystal engineering, particle engineering and structure generation to produce final dosage forms with consistent and predictable performance will be targeted.

Future Microfactories (WP2)

Innovative flexible efficient production systems comprising integrated processing platforms are the goal of this work. At laboratory scale, prototype microfactories will be developed and operated based on the optimised process flowsheet identified using the integrated development pathways for each molecule of interest.

Future Supply Chain (WP3)

Future digital supply of personalised products and medicine is being investigated. We will develop new distributed manufacturing supply chain models that offer step changes in local volume flexibility and responsiveness, driving manufacturing closer to the point of need and personalisation. This will integrate technology capabilities emerging from WP1&2 and explore supply chain digitalisation opportunities that connect the digital factory through to the end consumer/patient.

Digital Twin

The CMAC digital combines model-based and data driven simulations of physical properties and transformations within integrated continuous processes. Data from small scale experiments/predictions are used to parameterise the models used to generate the digital twins.

The digital twins can be utilised and applied in a number of ways such as:

- To virtually design a full scale manufacturing process or individual unit ops within
- Enabling model-based experimentation to explore process conditions and determine optimal process outcomes
- Inform and prioritise “hands on” experimental approaches and key parameters to be evaluated as well as analysis of data and monitoring of systems
- Development of model-based-control systems
- Model based exploration of design changes and design optimisation for future implementations
- Evaluation of the impact of process on product

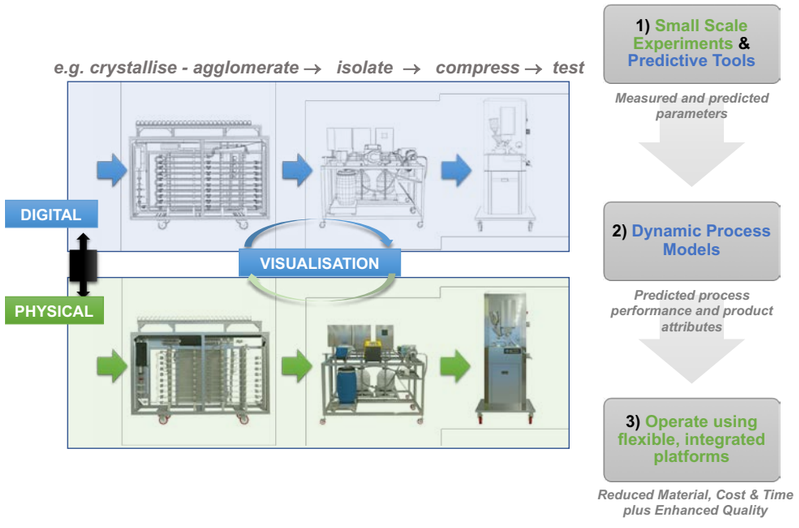


Figure 12: Schematic of the outputs of WP1: designed physical process and its digital twin

Future Microfactories for Performance Based Manufacture of Medicines

CMAC’s vision to transform medicines manufacturing requires development of innovative, modular, integrated continuous manufacturing processes for drug substance and drug product. The end-to-end modular lab scale Microfactories are being developed within the Hub to provide a rapid prototyping capability to control, measure and optimise critical transformations across multiple length-scales spanning crystal and particle engineering, structured product and dosage form generation and manage variable material properties and increased product complexity. Input from the Predictive Design & Digital Twin are used to design, build and operate flexible, integrated continuous manufacturing process chains at scale (kgs/day). A key deliverable is to enable simplified process chains targeting the processes and transformations that improve manufacturability of the drug into a dosage form suitable for good performance in the patient. By developing integrated continuous “direct to dose” approaches, we avoid multiple unit operations and scale up steps.

The Hub has three microfactory research projects ongoing:

Microfactory 1 (MF1) looks at product process archetypes that go from crystallisation through isolation and drying and then take dry powder into a hot melt extruder to combine the drug with polymer and then process the extruded drug polymer mixture via either 3D printing or injection moulding to produce a solid dosage form. The polymer is selected based on properties of the API and desired performance in vivo. MF1 looks at drugs which require particle properties that require drug to be suspended in polymer.

Microfactory 2 (MF2) looks at drugs which are poorly bioavailable and are aiming for formulation that improves this and builds on MF1 to deliver amorphous solid dispersions.

Microfactory 3 (MF3) addresses the challenges provided by drug compounds with difficult morphologies. An example of how this can be addressed is processing API with needle-like crystals by using a spherical agglomeration process to change the particle aspect ratio prior to isolation and drying, then using the dried powder for producing tablets by direct compression.

Product Process Archetypes

CMAC has identified scenarios that combine addressing challenging physical properties with specific continuous manufacturing chain processes. We have termed these scenarios product process archetypes (PPAs). We will target PPAs where integrated continuous processing will deliver benefits. Underpinning this is the idea that there are types of particle that will likely have an ideal type of continuous manufacturing process that delivers desired product performance. For example in MF3 “needle-like” crystals usually need to be processed in some way to give particles that are able to be handled easily and then formulated into products with desired performance.

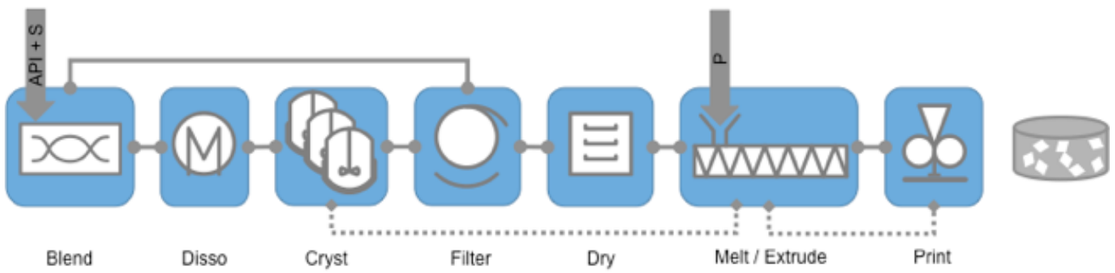


Figure 13: PPA1

PPA1 will deliver a Microfactory that combines crystallisation, isolation, extrusion and 3D-printing or injection moulding of a drug/polymer suspension, and fits with MF1. PPA2 is very similar to PPA1 but addresses API with challenging performance characteristics as per figure 14.

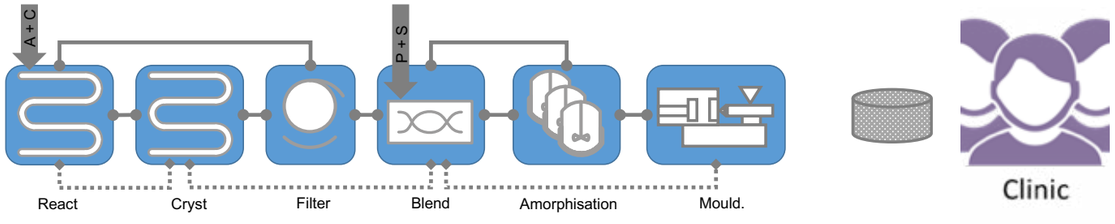


Figure 14: PPA2

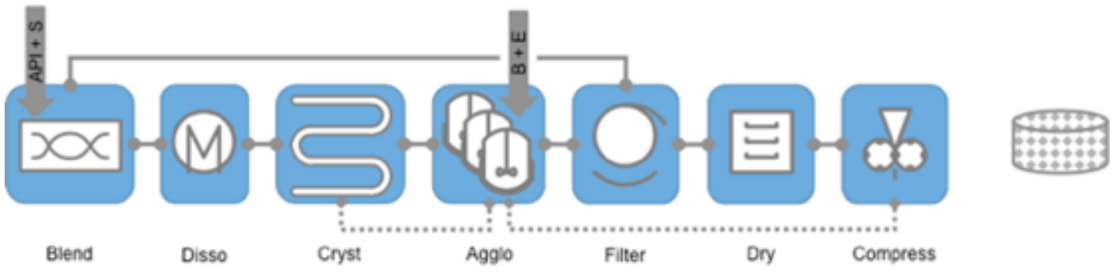


Figure 15: PPA3

PPA3 will deliver MF2 by combining continuous crystallisation, spherical agglomeration, and direct compression to produce the final dosage form and will address difficult morphology issues (e.g. needle like crystals).

Future Supply Chains Enabled by Continuous Manufacturing Technologies

Work Package 3 (WP3) looks at new supply network configuration design options and strategies aligned with emerging medicines manufacturing technologies, advanced production process control and analytics and data integration opportunities across the end-to-end supply chain enabled by ICT/digitalisation.

Product targets will be identified through assessment of market needs and where continuous manufacture will add greatest benefit. This work will assess customer demands and inform strategies for rapid re-formulation / redesign / customisation of products through deployment of flexible, reconfigurable, modular continuous manufacturing Microfactories.

Initial applications demonstrate the utility of the proposed approaches and strategies in accelerating the integration of emerging technologies in new redistributed manufacturing supply chain models. Emerging production and supply chain configurations enable new product sourcing and distribution paradigms, focused on targeting demand at differing scales in response to changing consumer or patient expectations (supply responsiveness, volume/variety flexibility and product personalisation). The further exploration utilises multi-layer modelling approach involving product demand and raw material sourcing data, detailed modelling of the supply chain model assisted with process simulation model.

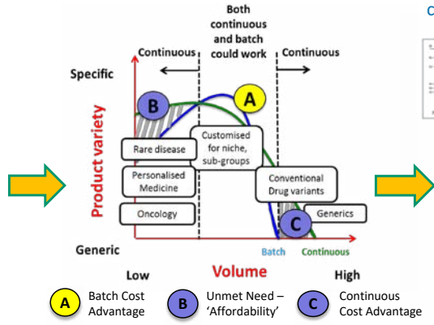
A multi-criteria technology assessment tool has been developed to provide rapid assessment of products and therapeutic areas where continuous manufacture will add greatest benefit based on a multi-dimensional analysis of key market and technical requirements. This work will assess customer demands and inform strategies for rapid re-formulation / redesign / customisation of products through the deployment of flexible, reconfigurable, modular continuous manufacturing MicroFactories in future digital supply chains.

Further work will address opportunities to maximize the impact of technology capabilities emerging from Digital Twins and Future Microfactories on supply network reconfiguration strategies. For selected product-process archetypes, we will also explore supply chain digitalisation opportunities that connect digital micro/continuous factory configuration scenarios with both upstream supplier sites and downstream distribution through to the end consumer/patient.

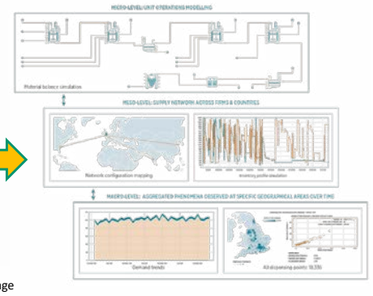
Conceptual analysis: identifying opportunities and challenges of batch to continuous

- **Patient centric supply, less managerial oversight and regulatory sanction**
- **Responsive production & distribution models, digitally enabled patient engagement**
- **Reduced capex and operating costs with Volume flexibility, more distributed mfg**
- **Process-control based quality and regulatory assurance**
- **Smaller patient groups, dynamic closed loop control, based on downstream**

Strategic targets identified through product category analysis and patient populations



Operational business case for specific products: quantification through supply chain analysis



Srai, J. S., Badman, C., Krumme, M., Futran, M., & Johnston, C. **2015**. **Future supply chains enabled by continuous processing – opportunities and challenges. 2014** MIT Symposium, Journal of Pharmaceutical Sciences, 104(3), 840–849.

Srai, J. S., Harrington, T.S., Alinaghian, L.S., Phillips, M.A. **2015**, ***Evaluating the potential for the continuous processing of pharmaceutical products – a supply network perspective.*** Chemical Engineering and Processing, 97, 248–258

Settanni, E., and Srai J.S., **2018**, **Towards a new approach to modelling pharmaceutical supply chains in a changing technological landscape.** Pharma Horizon, 2(1), 2018

Figure 16: Continuous manufacturing: business case for transformation

Research

Microfactory and Product Process Archetype 1 – Mefenamic Acid

Particle Size Distribution (PSD) control followed by extrusion + 3D printing or injection moulding of polymer-drug mixtures

The NSAID Mefenamic Acid exhibits variable exposure in man which is thought to be due to Active Pharmaceutical Ingredient (API)-size variability. Therefore key aspects of this microfactory development are to utilize advanced crystallisation methods to target consistent and close control over API size followed by a simple solid dispersion formulation. The simplified initial unit operation stream is shown below:

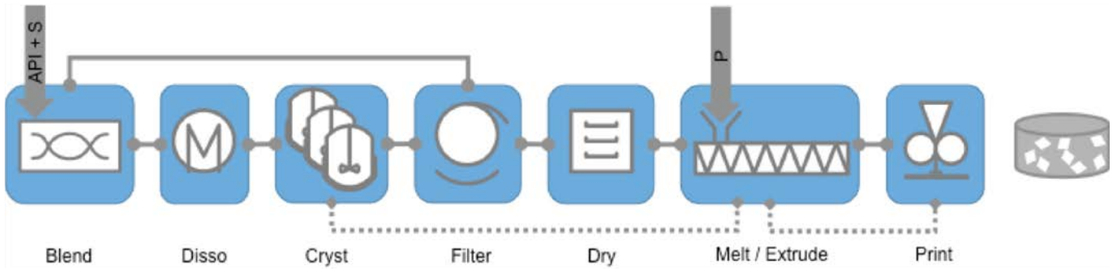


Figure 17: Simplified unit operation stream for Mefenamic Acid microfactory design

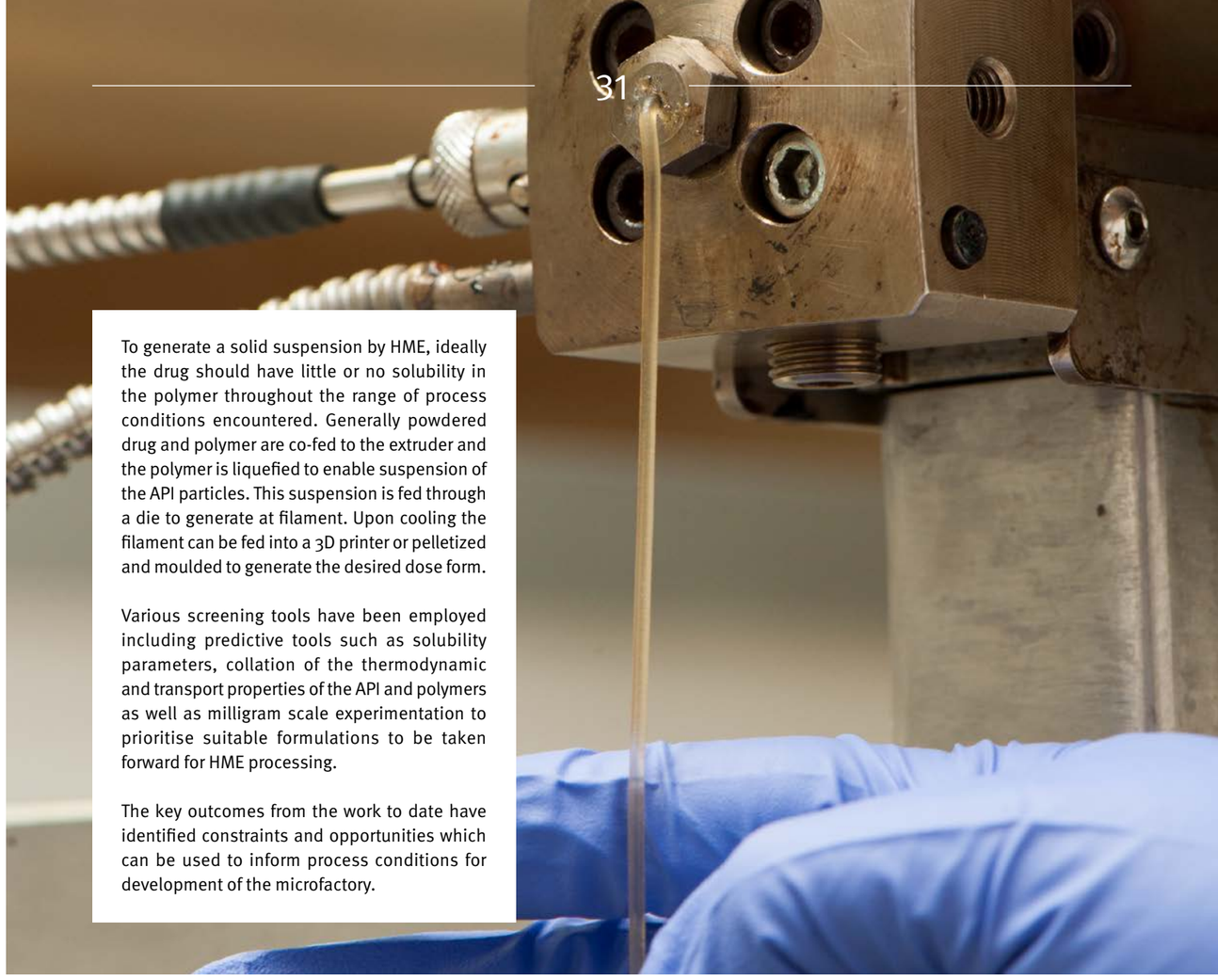
The defining unit operations are:

1. The crystallisation step targeting a particle size D90<42uM
2. The solid dispersion step, targeting a suspension of API crystals to achieve the required performance in a polymer matrix to enable production of a simplified (e.g. 2 component) dose by 3D-printing or injection moulding.

To date, work has been carried out to screen potential formulations and assess the behaviour of the Mefenamic Acid in solid suspensions. The initial methodology selected for generation of the solid suspension has focused around hot melt extrusion (HME) as the mixing technology.

PAT/measurement work for the Hub Microfactory project

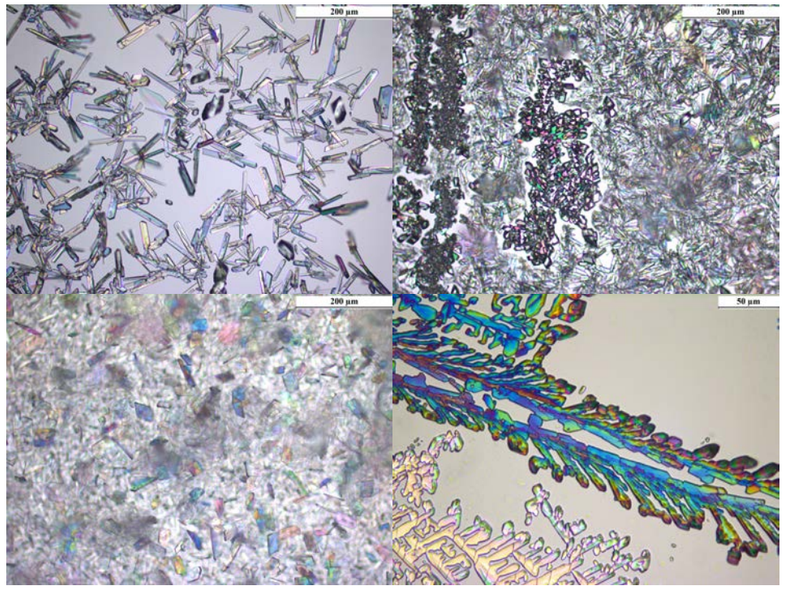
For Microfactory 1, multivariate analysis has been performed on terahertz Raman spectra of binary matrices of drug and polymer excipient acquired within the secondary processing facility. Principal component analysis (PCA) was applied to determine the temperatures at which the drug is amorphous and crystalline, to thus assign the drug solubilisation temperature for each drug/polymer composition. PAT research activities have included the development of protocols and workflows for spectral data acquisition and analysis within CMAC.



To generate a solid suspension by HME, ideally the drug should have little or no solubility in the polymer throughout the range of process conditions encountered. Generally powdered drug and polymer are co-fed to the extruder and the polymer is liquefied to enable suspension of the API particles. This suspension is fed through a die to generate at filament. Upon cooling the filament can be fed into a 3D printer or pelletized and moulded to generate the desired dose form.

Various screening tools have been employed including predictive tools such as solubility parameters, collation of the thermodynamic and transport properties of the API and polymers as well as milligram scale experimentation to prioritise suitable formulations to be taken forward for HME processing.

The key outcomes from the work to date have identified constraints and opportunities which can be used to inform process conditions for development of the microfactory.



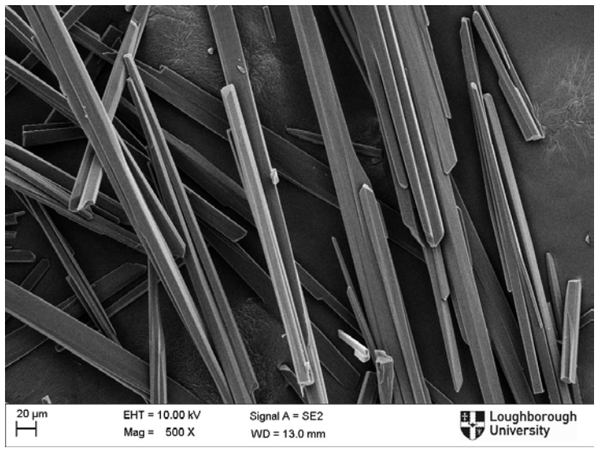
Mefenamic acid exhibits a relatively high vapour pressure which results in habit changes and crystal growth. Whilst this will limit operating at extreme conditions during extrusion it does present an opportunity to “lock the API” into a polymer matrix which may be useful in arresting these solid state changes.

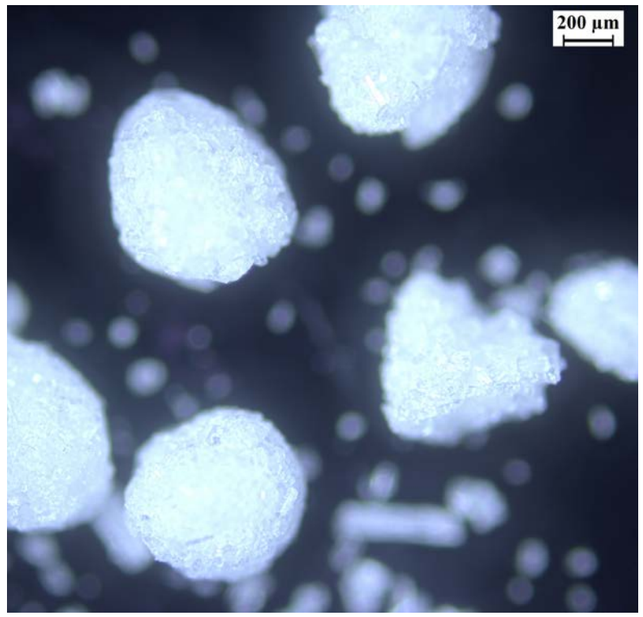
Research

Lovastatin Microfactory and Digital Twin Demonstrator

From August 2017, the Hub research team have been working full time on a project to deliver first a process design and digital twin (WP1), and then a microfactory (WP2) for Lovastatin as a model compound for crystals with a high aspect ratio needle-like morphology (MF3 / PPA 3 – see page 27-28). This microfactory has been designed to overcome the handling and manufacturability issues for compounds with a needle-like morphology due to properties such as poor flowability and low bulk density.

Lovastatin is the API in the product Mevacor, a statin for lowering cholesterol invented by Merck. It had $0.6 billion sales in 1999, but the patent expired in 2001. Tablets are sold in 20, 40 and 60 mg doses. Lovastatin is a high permeability, low solubility compound, typically synthesised by a fermentation process.





Over the past year the CMAC Hub team developed the end-to-end process for producing Lovastatin via continuous manufacturing from crystallisation to tablet. The outputs include a process design and digital twin of the process (WP1) and a prototype Lovastatin microfactory (WP2). Progress on these was demonstrated at the CMAC Open Day 2018.

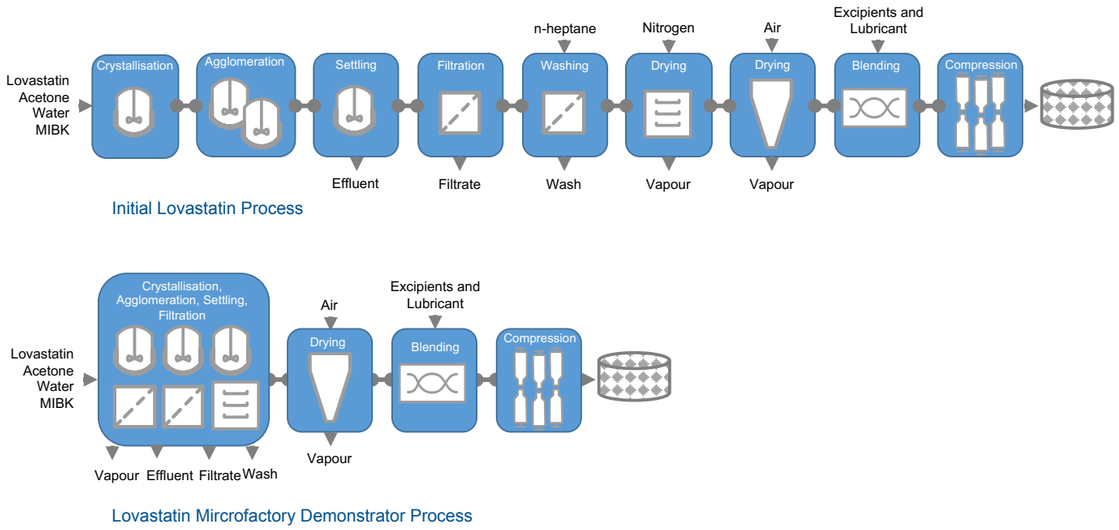


Figure 18: The intensification and integration achieved by our prototype Lovastatin MF2 demonstrator

This lab scale prototype Microfactory has been developed to combine and integrate continuous operations, which have for the first time enabled direct compression of lovastatin. This is in contrast to traditional approaches that would have required an additional wet granulation step prior to compression. The research team addressed challenges presented by needle-like morphology by introducing a spherical agglomeration stage into the process chain.

The physical process that was demonstrated at the CMAC Open Day 2018 integrates the crystallisation, spherical agglomeration, isolation and drying steps into a single unit operation that will feed into the secondary processing operations. Optimising scale, solvent selection and equipment from separate unit operations into an integrated process were important factors in creating the final Microfactory platform.

- Footprint 22.89m2
- Lovastatin flow 0.5-1.1g/min
- Tons per year 0.24-0.53 ton/yr
- Tablets per day (24hr) 3600-7920 tablets/day
- Worldwide production 17 ton/year in 2016/2017

Image: Lovastatin Microfactory demonstrator at CMAC Open Day 2018

Research

PAT/measurement work for the Hub Microfactory Project

Initial PAT research primarily focussed on in situ monitoring of the controlled isothermal antisolvent crystallisation process in which a solution of lovastatin dissolved in acetone/water was mixed with water as an antisolvent. Attenuated total reflectance (ATR) – UV visible spectrometry and ATR-mid infrared (MIR) spectrometry have been used for measurement of solute (Lovastatin) concentration and solvent composition (acetone/water ratio), respectively.

More recently, the antisolvent crystallisation process was adapted to be compatible with downstream processes (spherical agglomeration and filtration), and this became a new focus on monitoring the endpoint of the crystallisation process. MIR spectrometry was identified as a suitable technique for in situ monitoring of the composition of the continuous phase in a combined antisolvent crystallisation and spherical agglomeration process. Monitoring the kinetic nature of bridging liquid droplets during the process has been identified as a final challenge.

Further opportunities include investigations into the monitoring of the spherical agglomeration process, particularly by Raman spectrometry and/or acoustic emission. General activities concurrent with ongoing PAT/measurement work for the Hub microfactory project have included the development of protocols and workflows for spectral data acquisition and analysis within CMAC.

Lovastatin Digital Twin

The CMAC end-to-end process for manufacture of Lovastatin tablets and digital twin is being developed alongside the physical process. Currently, models for solubility, crystal growth and spherical agglomeration (SA) have been coupled to enable simulation of possible conditions of these integrated processes.

The models that have been used at each stage are:

Solvent Screen
- Cooling crystallisation digital workflow
- Anti-solvent digital workflow
- Solvent pairing, viscosity & miscibility
- Application of AI-enhanced COSMOtherm solubility predictions in CMAC
- SA bridging liquid selection

Crystal Growth
- Process optimisation for Crystal growth
- Computational Fluid Dynamics (CFD) models

Spherical Agglomeration
- Modified SA models

Compression
- Prediction of the properties of multicomponent tablets (excipients, lubricant, APIs) using parameters determined from pure component compression data.

Researchers from CMAC and ARTICULAR are working together on developing visualisation tools to support the digital twin for Lovastatin. These include AR and VR environments to interact with CMAC's rich data and more conventional dashboards that sit on top of the digital twin models. This work will then be expanded to cover the full end-to-end process and then applied to other APIs.

Solvent Selection

CMAC has the capability to undertake solvent selection for crystallisation process design through experimental and increasingly via predictive modelling approaches. The academic partners in CMAC have expertise in three key areas: (i) solubility measurement, (ii) solubility prediction using two approaches – COSMOtherm combined with Machine Learning (Strathclyde) and the group-contribution Statistical Associating Fluid Theory (SAFT) (Imperial College), (iii) rational model-based solvent design.

These complementary tools are being used together to assist solvent selection. Early work in the Hub project has been directed towards addressing solvent selection for crystallisation, with a recent focus on antisolvent crystallisation. In future this work will be expanded to investigate the requirements of other unit operations in an integrated end-to-end process to guide researchers in selecting suitable solvents for operations such as spherical agglomeration and filtration.

The CMAC Electronic Laboratory Notebook (ELN) and Data Management Policy have been a critical part of this effort. Together these tools ensure the collection, contextualisation and dissemination of data collected in solvent screening experiments by researchers so that it can be used to build and validate the predictive models being developed.

The solubility prediction models we have developed using these data have been developed into applications that are available within the CMAC ELN and gPROMS software. This allows researchers who are not specifically experts in predictive modelling to automatically generate predictions for APIs that are within model scope, comparing predictions to their experimental results or providing predictions that can help to plan experimental campaigns.

Our long term goal is to build a large enough library of data for a variety of APIs that will permit more general solvent selection predictions to become possible.

Research

Additive and Morphology Control

CMAC researchers across the Hub are undertaking research to develop a workflow that rapidly assesses the feasibility of using additive crystallisation to control the morphology of the particles formed and that is capable of being integrated into an end-to-end process to design a microfactory prototype.

Additives can be small molecules or polymers, that influence the crystallisation process but are not themselves incorporated in the final product. The additive workflow will sit alongside the existing cooling crystallisation and antisolvent crystallisation workflows that have been developed by CMAC so we can quickly assess which method is most suitable for a particular API.

The additive crystallisation workflow development will focus on rapid assessment of ability to control morphology, improving reproducibility, and operating at a scale that can integrate with other unit operations within an end-to-end process. It builds on previous work in CMAC that demonstrated the first polymer additive control of morphology in a continuous crystallisation process.

Additives can be used to engineer crystal growth by adsorbing onto, and inhibiting growth on, selected crystal faces. This results in different shaped crystals being produced under different conditions and with different additives. Optimising crystallisation conditions in such a multi-component environment represents a significant challenge in both academia and industry.

The Additive & Morphology research programme includes applying understanding and design of molecular interactions available from academic structural research in the selection of additives. A face indexing workflow has been developed and is being used to help predict how crystals will grow based on experimental measurements.

The predictive modelling aspect of the Additives & Morphology workflow element of CMAC digital design will, in the short term, be focused on particle attribute based models. Computational approaches to intermolecular interactions at the molecular level will target predictive design of additive-mediated primary particle control. This particle attribute based modelling work is being carried out in collaboration with the ADDoPT project. Process parameter models for additive-mediated crystallisations are a longer term goal.

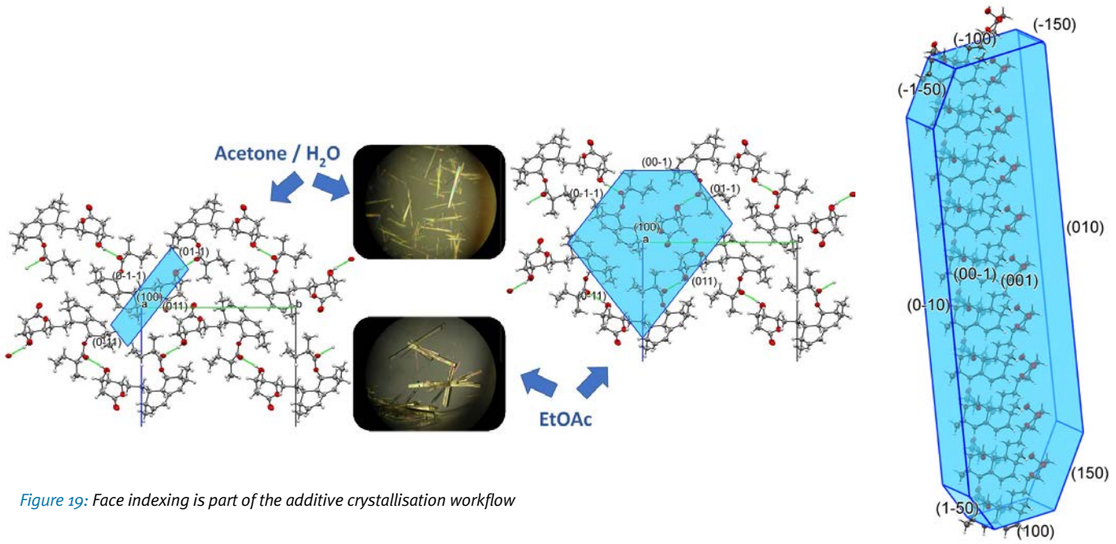
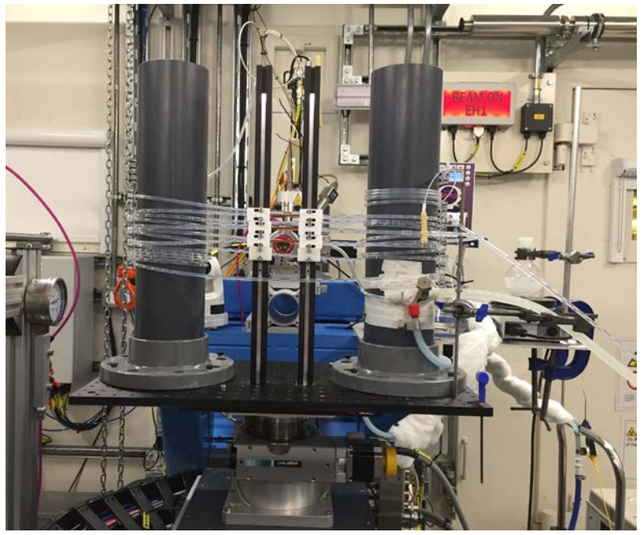


Figure 19: Face indexing is part of the additive crystallisation workflow

Advanced Measurements & Characterisation

Through its research team on the UK Science and Innovation Campus at Harwell (Oxfordshire) CMAC works seamlessly with the UK's central facilities – the Diamond synchrotron, the ISIS neutron source and the Central Laser Facility. The group is based in the Research Complex at Harwell, which is available as a 'research hotel' for all CMAC partners, for long and short term projects leveraging the advanced measurement facilities at Harwell.



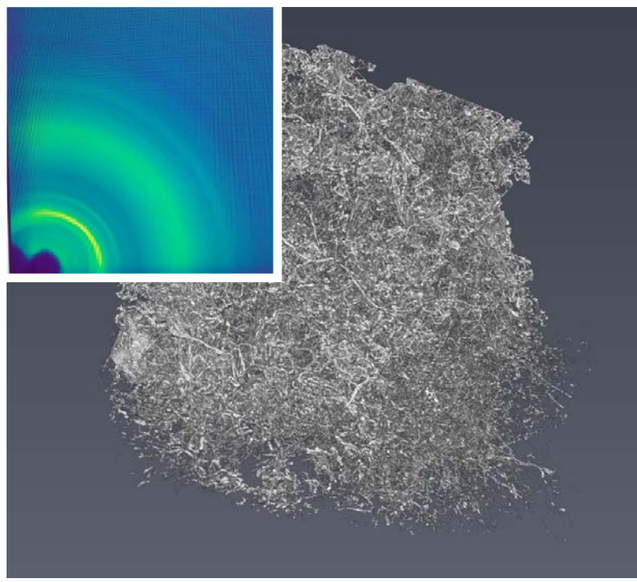
CMAC researchers from the University of Bath have developed time-resolved diffraction methods to follow the crystallisation of APIs in a continuous flow process. For example, the bespoke KRAIC-D segmented flow reactor was installed on the powder diffraction Beamline I11, where it was used to follow the complex phase transformations during carbamazepine crystallisation in real time. On the single-crystal diffraction Beamline I19, a larger-scale segmented flow set-up has been commissioned, which enabled the first in situ collection of single-crystal diffraction images from paracetamol crystals grown in flow at millisecond time resolution.

"Using advanced characterisation techniques, we aim to develop molecular level understanding of the systems at various stages of the workflows and end-to-end process design."

CMAC researchers from the University of Strathclyde are using phase-contrast X-ray imaging with sub-micrometer space resolution and sub-second time resolution to control and visualise phase transformations in continuous twin-screw extrusion process for API-polymer formulations. Their studies are underpinned by time resolved pair distribution function (PDF) measurements that allow correlation between structure at the molecular scale with mesoscopic and macroscopic information from the imaging studies. Amorphous drug-polymer systems were tracked in variable temperature experiments. The data allow a better understanding of the impact of process parameters on non-crystalline formulations.

CMAC researchers at the University of Leeds are carrying out in situ analysis of mixing, nucleation and crystal growth in continuous flow systems. For example, phase contrast X-ray tomography of glycine in an anti-solvent crystallisation process revealed the complex nature of the solid product, visualising the influence of the flow-field on product morphology.

Using in situ X-ray Raman scattering, X-ray photoelectron spectroscopy and time-dependent density functional theory it has been demonstrated that monitoring the 1s core level spectra of carbon, nitrogen and oxygen provides a powerful probe for monitoring local bond formation and breaking. This enables studies of nucleation from solution with unprecedented insight into molecular association processes in the metastable zone.



Facilities

World class facilities for pharmaceutical research

Vision:

To support a world class services for transforming medicines development and manufacture

Mission:

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

CMAC delivers world class research, training and services on a global scale supporting users from both academia and industry. Our advanced pharmaceutical manufacturing research facility is easily accessible by academics and businesses both in the UK and internationally.

CMAC has the additional benefit of co-locating multidisciplinary teams of academic and industry researchers within the state of the art Technology and Innovation Centre (TIC) at the University of Strathclyde. Contact the CMAC Team with your enquiries - see back cover for contact details.

The facility is equipped using £11.4 m funding awarded by the Higher Education Funding Council for England (HEFCE)'s UK Research Partnership Investment Fund (UKRPIF) and supported with £22.8M in industry and charity contributions. CMAC has a dedicated team offering services and consultation in the following areas;

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

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

- Modular skid-mounted crystallisation platforms (batch and continuous)
- Filtration and drying
- Secondary processing including spray drying, Hot Melt Extrusion (HME), granulation and tableting
- Process Analytical Technology (PAT) providing real time information and feedback
- Time of Flight Secondary Ion Mass Spectrometry (TOF-SIMS)
- Atomic force microscopy (AFM)
- Nuclear magnetic resonance (NMR) spectroscopy
- World class X-ray suite including single crystal, powder (crystalline & amorphous), Small Angle Scattering (SAXS) and Nano Computed Tomography (CT)

Laboratories, Equipment and Services

The laboratory footprint at TIC is over 2000m^2; designed to deliver a fully adaptable space for multi-phase batch and continuous primary processing. There is a dedicated, specialised support team within CMAC to offer services and assistance to research activity and industrial projects; analytical laboratories for advanced understanding of particulate formation and processing, and a secondary processing suite. Stores and ancillary areas have been constructed to complement the unique activities carried out in the laboratories to support the delivery of the research programme.

Primary Processing Laboratory

Our largest laboratory in TIC houses 12 multi-functional walk-in fume cupboards. These bespoke units are reconfigurable to meet the needs of current research and adaptable to meet future demands of the Hub programme. The fume hoods can be configured to accommodate a 3.8 m long process with pass through ports for PAT probes and fibres plus data communications to monitor and obtain real time data/control over processes.

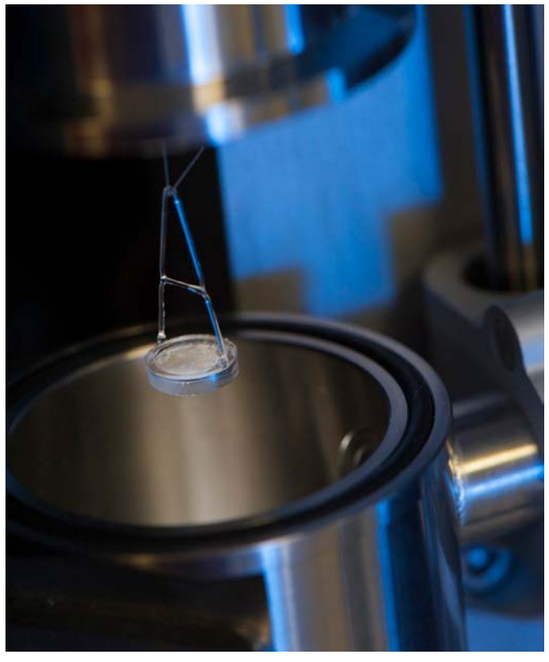
Facilities

Secondary Processing Suite

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

X-ray Analysis Suite

The world-class X-ray suite within CMAC can deliver a range of services from powder characterisation, fingerprinting, variable temperature and humidity measurements, and variable humidity measurements to unit cell determination and full structural solutions. CMAC, together with colleagues from BioNano and Physics at the University of Strathclyde, have purchased a Xenocs Small Angle X-ray Scattering (SAXS) instrument, which can be employed in the investigation of materials with larger intermolecular spacing for the determination of shape and alignment of particles. Our Nano-CT service offers a non-invasive technique for the three-dimensional structural characterisation of solids and can be applied to analyse samples with sizes › ca. 20 um.



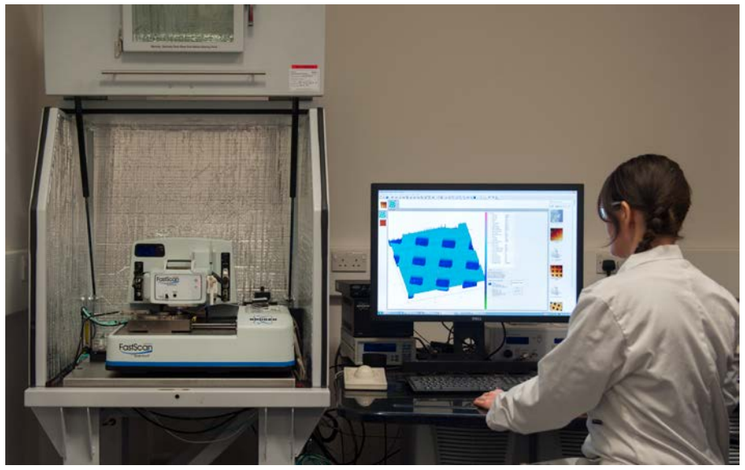
Materials Characterisation Laboratory

We have a wide range of advanced analytical equipment available at the facility and our dedicated technical team deliver services across multiple physical forms - powders, tablets, slurries etc. Highlights include: chemical analysis, gas and liquid chromatography and mass spectrometry in addition to physical methods such as porosity, density, surface area analyses, dynamic vapour sorption (DVS), inverse gas chromatography and powder and liquid rheometry. We house the latest technology in delivering innovative particle size and shape analysis. For advanced surface characterisation, we have a TOF-SIMS instrument*. This instrument, in addition to two AFM systems, allows a new level of nanoscale physical and chemical understanding with surface characterisation.

** additional funding from the Wolfson Foundation*

Microscopy Suite

The extensive optical and electron microscopy capability at CMAC is located within a vibration sensitive laboratory. This includes inverted optical microscopes, off-line IR and Raman instruments with surface mapping features plus a benchtop SEM. This service enables physical samples to be imaged and chemically analysed at the facility.



Facilities

Facilities at Spoke Institutions

Systematic analysis, characterisation and performance testing of materials produced though work on Integrated Development Pathways (WP1) and Future Microfactories (WP2) will be supported by utilising capabilities at the CMAC National Facility at Strathclyde and at the Spokes' facilities, including world class national capability in partners Diamond and NPL. The research will be translated though the planned MMIC project.

Innovation Spokes

Figure 20: MMIC

MMIC

The University of Strathclyde is a strategic partner in a new £56 million UK innovation centre, which will revolutionise the way medicines are manufactured. The world-first, industry-led Medicines Manufacturing Innovation Centre (MMIC) will offer pharma companies, from start-ups through to multinational organisations, a service to develop and adopt novel manufacturing techniques to adapt into their own manufacturing processes. The centre is to be located in Renfrewshire and will be operational in 2021. The project is led by the Centre for Process Innovation (CPI), in partnership with Strathclyde, the Medicines Manufacturing Industry Partnership (MMIP), and founding industry partners, AstraZeneca and GSK. The University is leading the work package of the development phase of a next generation continuous direct compression digital test bed and demonstrator.

Supported by Scottish Enterprise (£15 million), UK Research and Innovation, through Innovate UK (£13 million) GSK and AstraZeneca (£7 million each), the MMIC is one of the first projects across the UK to receive funding from the UK's Industrial Strategy Challenge Fund.

NPL

The National Physical Laboratory (NPL) is the UK's National Measurement Institute, and is a world-leading centre of excellence in developing and applying the most accurate measurement standards, science and technology available. NPL Scotland is a regional hub formed by the collaboration of strategic partners NPL and the University of Strathclyde. CMAC hosts 3 NPL Scotland PhD students who are doing research on pharmaceutical innovation and manufacturing metrologies supporting continuous manufacturing and crystallisation in the pharmaceutical sector. The researchers are co-hosted at the main NPL site at Teddington for part of their studies with access to the state of the art facilities there.

Diamond Light Source and Research Complex at Harwell

CMAC has access to the Research Complex at Harwell and Diamond Light Source on the Harwell Science and Innovation Campus, through academic spoke partners at University of Leeds. There are CMAC researchers from Universities of Leeds and Bath who are based at Harwell for some or all of their time. The facilities give capability to undertake advanced measurements at all length scales, for both surface and interface analysis, can use contrast agents and can undertake process studies: in situ / operando / in-line. The work is closely aligned with modelling and design through the ADDoPT programme.

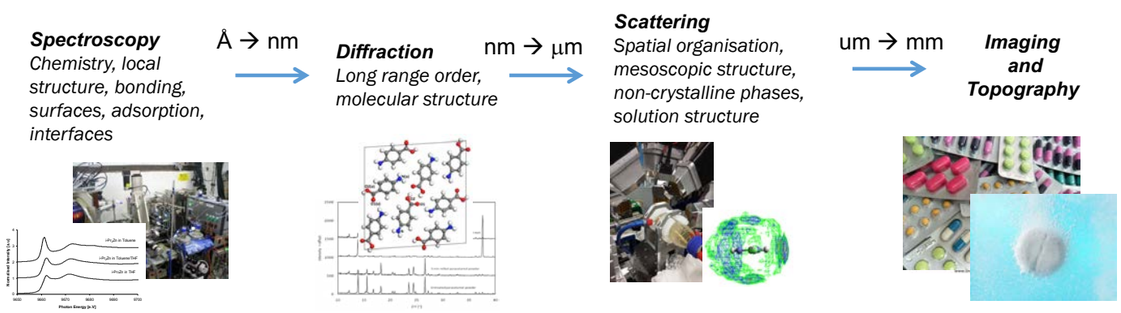


Figure 21: Capability to undertake advanced measurements at all length scales

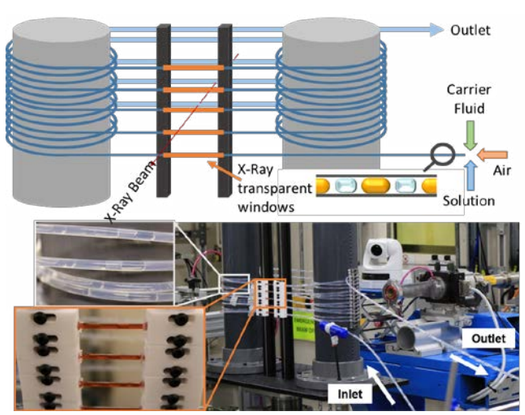


Figure 22: (a) KRAIC D developed at Bath and installed at Harwell (b) Harwell Science and Innovation Campus

Facilities

Academic Spokes

The Diamond at Sheffield

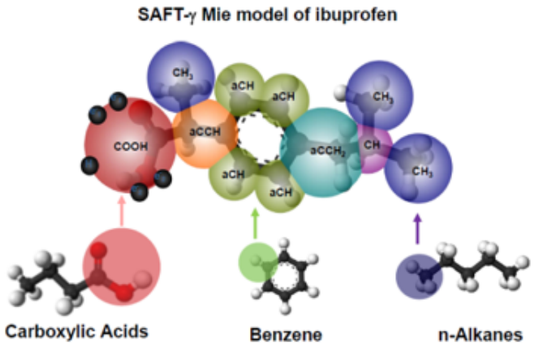
The University of Sheffield has a new state-of-the-art facility, The Diamond, which is a multi-disciplinary teaching space. It houses a Pilot Plant which tests integrated processes with simulations and control systems in a safe, product oriented environment, and a virtual and augmented reality lab which will be used to train researchers for the future.

Image: The Diamond at University of Sheffield

Imperial College London

Statistical Associating Fluid Theory (SAFT) is an advanced molecular thermodynamic model used to predict thermo-physical properties of fluids and complex mixtures developed at Imperial. This predictive approach can be applied to describe the solubility of complex molecules, such as active pharmaceutical ingredients (APIs), in solvents and solvent mixtures.

Figure 23: SAFT developed at Imperial



Loughborough University

The team at Loughborough are developing quality by control using intermittent / periodic flow crystallisation. This is model informed design of a continuous MSMPR platform development using periodic / intermittent flow to avoid transfer line blockage and control crystal size and shape by manipulating the residence time and supersaturation.

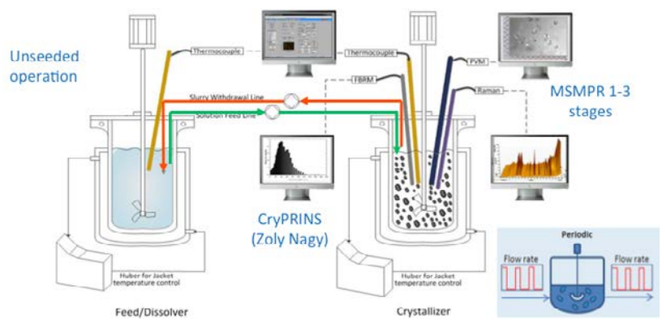


Figure 24: Periodic and intermittent crystallisation configuration at Loughborough

University of Bath

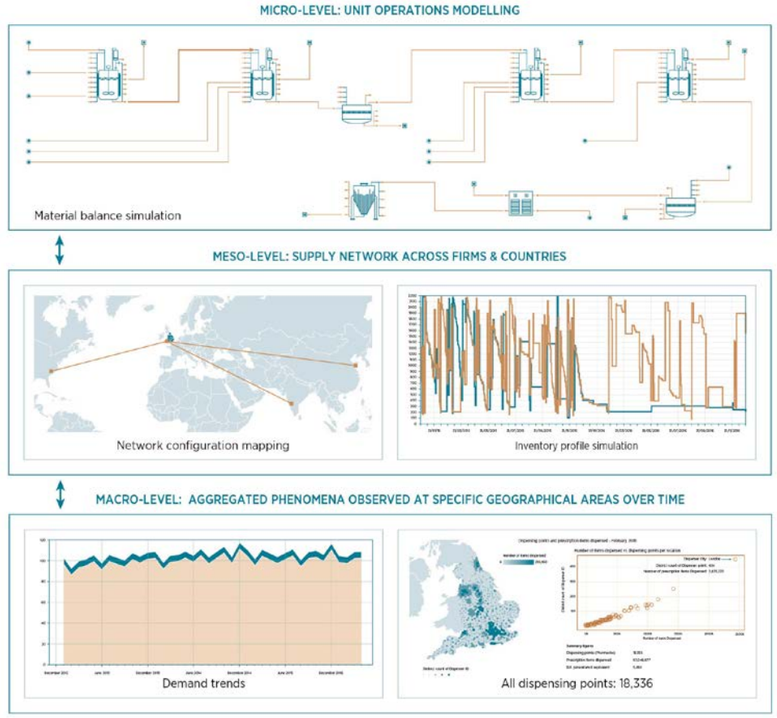
Researchers at Bath have been looking at Development and implementation of continuous crystallisation platforms at laboratory scale, including multi-component and confined environment crystallisation, and have deployed flow crystallisation at Diamond Light Source (Figure 27(a)).

Image: KRAIC platform developed at Bath

University of Cambridge

Researchers at IfM Cambridge will develop network reconfiguration strategies aligned with advanced production, process analytics and supply chain digitalisation, to accelerate integration with emerging technologies. This will drive new redistributed manufacturing supply chain models that offer local volume flexibility addressing drivers of manufacturing closer to the point of need and personalisation.

Figure 25: Digital supply chain mapping (https://www.ifm.eng.cam.ac.uk/insights/global-supply-chains/nextgensc/)



University of Leeds

Partners at Leeds are the main link into the facilities at Diamond Light Source at Harwell (Page 43), and with the ADDoPT project (Page 57).

Training

- **World-class training programme uniquely placed to address the interdisciplinary challenges in pharmaceutical manufacturing**
- **Delivering the next generation of highly skilled researchers and future workforce that will drive the transformation of continuous manufacturing**
- **“The demand for multidisciplinary talent is uniquely served by CMAC”**
  CMAC Industry Partners

A core focus area for CMAC is the Outstanding Training & Skills Development that aims to deliver interdisciplinary skilled researchers. The bespoke training programmes offered are aligned to the Hub research vision and informed by the needs of our Industry partners. CMAC graduates have progressed onto world-class academic, research and industrial positions; our talent pipeline illustrating our success can be found on page 22.

CMAC has a distinctive training programme on offer across all levels:

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

The CMAC doctoral training community has benefitted from a vibrant and dynamic ‘ecosystem’ of leading academic expertise across multiple disciplines, access to world-class facilities and contribution from leading industrial partners. Researchers are empowered through training and support to develop their skills, build collaborations and find innovative solutions within their research themes.

The Doctoral Training Centre in Continuous Manufacturing and Crystallisation

The CMAC Doctoral Training Centre (DTC) has established an innovative, world-class, multi-disciplinary doctoral training programme attracting high quality postgraduate students to become the future leaders in continuous manufacturing and crystallisation research. The uniquely qualified researcher cohorts produced are proving to be capable of transforming practice in pharmaceutical and speciality chemical manufacturing.

The CMAC DTC was launched in 2012 through an EPSRC award (£4.3m award, EP/K503289/1) supporting 38 students across 3 cohorts, with additional funds from Industry and partner universities. CMAC continued to train 15 more students in 2015-2016 with support from academic and industry partners. From October 2017 the CMAC DTC training programme was delivered to 10 CMAC PhDs supported through the Future CMAC Hub and aligned programmes.

By embedding the DTC within our Future CMAC Hub research programme, our students are exposed to:

- Relevant fundamentals across each discipline
- Current state-of-the-art knowledge including the challenges in continuous manufacturing and advanced crystallisation
- Existing research activities both within CMAC and international collaborations
- Unparalleled opportunities to engage in leading-edge research projects as part of a national interdisciplinary team

The CMAC DTC has been supported by a partnership that initially included three of the world’s largest pharmaceutical companies, AstraZeneca, GSK and Novartis, who delivered cash and significant in kind contributions. In 2015 Bayer joined CMAC followed in December 2016 by Lilly, Roche and Takeda, and finally by Pfizer in December 2017. All have indicated that the strength of the DTC talent pool was viewed as a real asset to joining CMAC.

To date 6 cohorts have completed their first year of training with 3 cohorts graduating and moving onto their next destinations, either University or Industry posts.

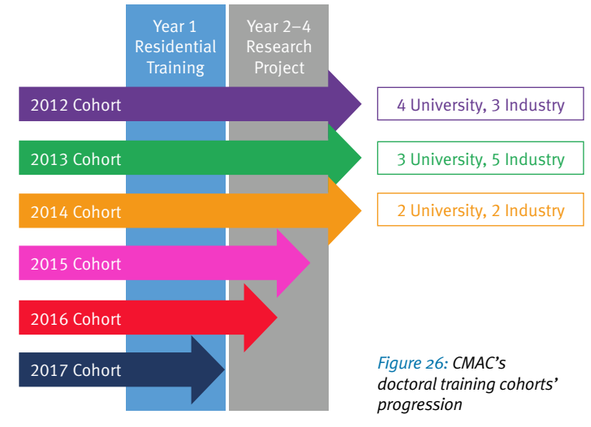


Figure 26: CMAC’s doctoral training cohorts’ progression

Training

CMAC Industrial PhD Programme

CMAC is continuing its success in doctoral training through the introduction of the new Industrial PhD Programme. This programme will build on the established mechanisms from our multi-institutional Doctoral Training Centre, which is recognised by global industry as a world leading Doctoral Training Centre for medicines manufacturing, and deliver the next generation of highly skilled doctoral researchers required to innovate across the medicines supply chain and lead scientific and industrial transformation.

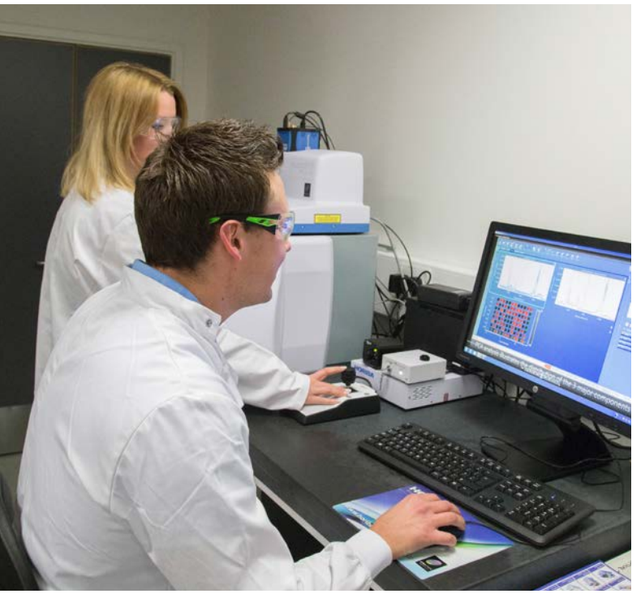
The Industrial PhD programme will be aligned with the CMAC Future Manufacturing Research Hub that will deliver training in advanced manufacturing, materials and measurement science, and modelling and data science. Studentships will be co-funded from the 7 academic institutions of the Hub (Bath, Cambridge, Imperial, Leeds, Loughborough, Sheffield and Strathclyde) and our Tier 1 industrial partners. Each cohort will consist of 10 studentships with the first due to start in October 2019.

Figure 27: Vision of CMAC Industrial PhD Programme

Pharmaceutical Innovative Manufacturing Metrologies (PIMMs): NPL

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

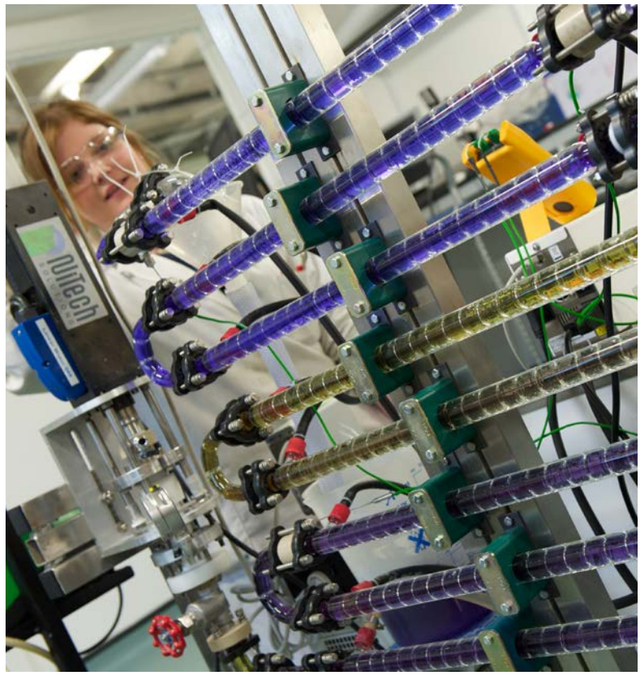
Research projects in Metrology for Pharmaceutical Manufacturing, Measurement of Surfaces and Big Data Management are being explored by PhD researchers in the PIMMS collaboration as part of the NPL Scottish Hub at University of Strathclyde.



Collaborative International PhD Programme

A Collaborative International PhD Programme was initiated as part of an EPSRC Global Engagements award in 2012/2013. CMAC 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, established a joint doctoral training programme which commenced in October 2014. The partnership's first cohort consisted of 5 students; 3 based at the University of Strathclyde and 2 at NTU, and several of these students have now completed their PhDs. The partnership was extended to support a further cohort in 2017 of 2 students 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. The researchers participate in an exchange programme during their PhD studies with plans for collaborative projects and joint publications.



MSc in Advanced Pharmaceutical Manufacturing

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

Students undertake the following compulsory classes:

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

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**

CMAC has always benefited from strong industry engagement and leadership. An industry led membership organisation was created in 2011 and this has grown and developed over the years. The membership organisation operates under a pre-competitive, collaborative research and development model with senior level company support. The main industry partners (AstraZeneca, GSK, Novartis, Bayer, Lilly, Takeda, Roche and Pfizer) get an individual seat on the CMAC Board and an opportunity to influence the direction of future research and Hub activity.

Integral to the CMAC ecosystem are the Tier 2 technology companies. These range from large companies, Siemens and PwC, to micro SMEs. This supportive environment helps translate research into equipment and products. In addition to CMAC members the Hub organises many open events for the broader industry landscape and collaborates with a wide range of additional companies locally, nationally and globally.

CMAC at Achema

Figure 28: The meeting in numbers

108,000 visitors to conference, 500 journalists

500 delegates visited stand

2000 hits - Linkedin blog

100 delegates at Siemens sponsored whisky tasting

CMAC had a joint stand with strategic partners, RCPE at the recent ACHEMA conference, Frankfurt, Germany. We had over 500 visitors to the stand making some excellent new contacts as well as meeting established collaborators and friends. Siemens generously sponsored a whisky tasting on the flow chemistry stand and dinner with CMAC and RCPE collaborators which provided an excellent social and networking opportunity leading to the development of exciting new projects.

The joint stand in the new Flow Chemistry Pavillion deepens our relationship with RCPE and builds on recent researcher exchanges including:-

- RCPE to CMAC: Professor Heidi Gruber-Woelfler and Dr Thomas Forgber (2019)
- CMAC to RCPE: Dr Vaclav Svoboda and Sarah-Jane Wood

Technical Committee

CMAC sincerely thank the Technical Committee for all their time and effort over the year as well the invaluable scientific discussions with the researchers. Phil Shering has stepped down as chair of the Technical Committee after 7 fantastic years and the new chair is Dr Chris Burcham, Lilly. Phil has worked tirelessly to ensure the technical relevance of CMAC's research as well as helping integrate new Tier 1 companies. The chair formally reports to the Board as well as leading technical input to strategy reviews. A list of the technical committee members can be found on page 59. The Technical Committee is made up of industrial scientists from each of the Tier 1 companies who help ensure the industrial relevance of the research and deliver meaningful, translatable impact. The main focus areas for the Technical Committee are: to provide feedback and steer on new PhD projects through industry problem statements, select and steer the core projects (see previous page), coordinate industrial placements for PhD researchers (see below), mentor group attendees and 1:1 confidential projects (see page 51) as well as support new funding bids and disseminate existing CMAC collaborative projects within their own companies.

Image: 5 Stage MSMPR Running a Cooling and Anti-solvent Crystallisation

1:1 Proprietary Projects (confidential projects usually in live Pharma compounds)

Working on both launched and developmental pharmaceutical compounds, the projects have delivered immediate impact from CMAC's academic research into live projects. Highlights from the year include:

- Comparison of the different material attributes and operability of a commercial API when crystallised in 2 different continuous crystallisers where each crystalliser was run for at least 3 days.
- Continuous manufacture of 3 different batches at 100's g scale, each with different, tightly defined range of specifications.
- Investigation of the impact of continuous mixing during a reactive salt formation
- Joint development of the 5-stage MSMPR system (see image to left)

Changes on the CMAC Industry Board

Dr Clive Badman, OBE formally stepped down after 7 years as the chair of the CMAC industry board. He has been a driving force in developing CMAC from a collaborative project to the reality it is today with over 130 staff and researchers with a £150million funding and project portfolio. As a token of our thanks, Clive was presented with a bottle of continuously distilled whisky as well as some 3-D printed examples of CMAC tablets and a continuous reactor at the 30th CMAC board meeting held at the Small-Volume Continuous (SVC) manufacturing plant Lilly plant in Kinsale, Ireland. We would like to thank Clive very much indeed for all of his time effort and highly valued input and wish him all the best in the future.

Dr Jon-Paul Sherlock, AstraZeneca has taken over as the new chair of the board and we look forward to working closely with him and seeing where he will take us in the coming years!

Another change is that Sean Bermingham, PSE steps down after 2 years and is replaced by David Lovett, Perceptive Engineering as the Tier 2 representative. We would like to thank Sean for the significant value he has added to CMAC since its inception.

Image: Dr Jon-Paul Sherlock Delivering the Keynote Address at the 2018 CMAC Open Day

Industry & Knowledge Exchange

Core Projects (Pre-competitive higher TRL projects)

The Technical Committee have funded four applied research projects to deliver outputs that will be directly implemented into the companies. These projects work at higher Technology Readiness Levels (TRLs) and are focused on building on some of the more fundamental EPSRC research within the Hub to focus on utilising the research in an industrial environment; whether that be through implementing workflows, new techniques employed in industrial labs or targeted at specific industrial challenges.

Project Title	PDRA Researcher	Academic	Industry Steering-Team
Investigation of Nucelation Rates in Different Anti-solvent Systems	Dr Lennart Ramakers, Dr John McGinty	Prof Jan Sefcik, Strathclyde	**Mei Lee** (GSK) Helen Wheatcroft (AZ) Guillaume Levillain (Bayer) Wolfgang Beckmann (Bayer, now retired)
Development and Testing of a Novel Scale-down Continuous Filter	Dr Nazer Rajoub	Dr Chris Price, Strathclyde	**Charles Papageorgiou** (Takeda) Julien Douillet (GSK) Manuel Konrath (Roche) Alex Heller (Lilly) Jan Cornevin (Novartis)
In-line Monitoring and control of a Counter-Current Liquid-Liquid Extractor	Dr Zied Hosni	Dr Brahim Benyahia, Loughborough	**Tim Braden** (Lilliy) Steven Guinness (Pfizer) Anna Parsons (AZ)
Impurity Effects and Rejection Efficiency During Crystallisations	Dr Stephanie Urwin, Dr Stephanie Yerdelen	Prof Joop Ter Horst, Strathclyde	Ivan Marziano (Pfizer) Guillaume Levillain (Bayer) Jeremy Merrit (Lilly) Ruairi O'Medhra (Novartis)

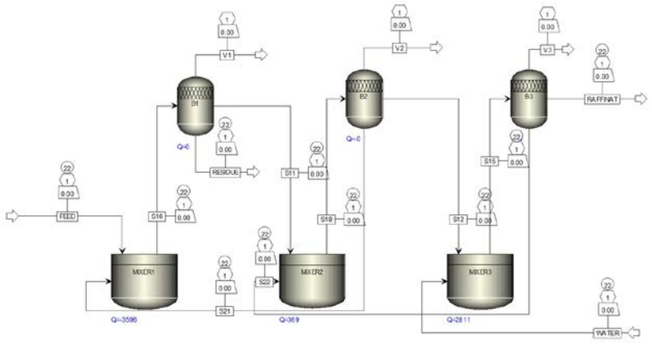


Figure 29: Aspen Schematic for Predictive Design of ccLLE Process

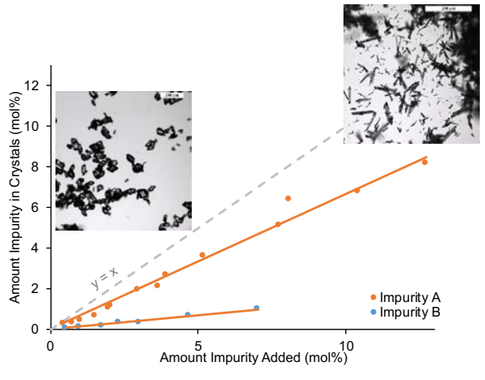
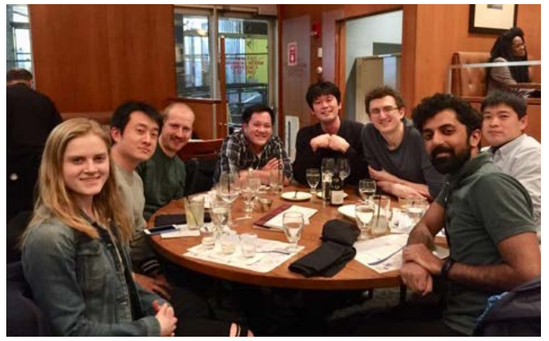


Figure 30: Diagram showing impact and rejection of impurities during a cooling crystallisation



PhD Researcher Industrial placements

The placement programme continues to grow from strength to strength delivering some real impact and benefits with 8 researchers on placement within the Tier companies for ~ 3 months each in 2017/18 programme (table below), and 12 arranged for 2018/19.

Image: Bilal Ahmed on placement with the Crystallisation team at Takeda, Boston

Researcher	Industrial Host	Project
Alex Cousen	Dr Guillaume Levillain, Bayer, Wuppertal, Germany	Enhanced Separation of Pharmaceutical Enantiomers by Co-crystallisation
Ravi Parekh	Dr Johan Rommelgas, Dr Mike Quayle, AZ, Mölndhal, Sweden. Sean Clifford, Gavin Reynolds, AZ, Macclesfield, UK	Development and Implementation of Monitoring and Control for a Twin Screw Granulation
Carlota Mendez	Dr Richard Elkes, Dr Lee Gorringe, GSK, Ware, UK.	Use of CAMES Particles for Process Understanding in Twin-Screw Granulation
Sara Ottoboni	Dr Marcello Bosco and Dr Manuel Konrath, Roche, Switzerland	Investigation of Approaches for Scale-up and Down of Filtration Models
Alice Turner	Dr Liz Meehan, AZ, Macclesfield, UK.	Characterisation of Excipients and Linking Materials properties to Drug Formulation Performance
Bilal Ahmed	Dr Charles Papageorgiou and Dr Yihui Yang, Takeda, Boston USA	Application of Ultrasound for Seed Generation in a Crystallisation
Vaclav Svoboda	Dr Steve Myers, Tim Braden, Lilly, Indianapolis, USA	Investigation of the Use of In-Line Milling for control of PSD in a Continuous Crystallisation
Bruce Wareham	Dr Thoralf Hartwig, GSK, Stevenage, UK.	Implementation of Machine Learning to Improve Solubility Prediction

Quote from Industrial Supervisor in the area of Continuous Particle Size Contol

"The student brought in his own expertise with regards to crystallization modeling and particle breakage modeling. He was well trained on laboratory procedures and experimentation in addition to the numerical modeling....

This work, done effectively in a short period of time, will be the basis for a core particle size control strategy in our continuous manufacturing platform. This methodology offers a superior particle size control in a shorter timeframe than traditional approaches. It is expected to save significantly on operator time and equipment use. The student is clearly a very intelligent scientist and possess a very strong work ethic. The combination resulted in extremely valuable contributions in the short project duration. The achievements were beyond expectations."

Industry & Knowledge Exchange

Tier 2 Partners

The seventeen tier 2 members have supported the CMAC academic and industrial partners via supply of innovative and new: papers, case studies, application notes, software, control, equipment, design, advice, equipment trials, and workshops. Networking events such as the Open Day have brought together industrialists, academics and researchers to present their work, technology, challenges, and to explore how we can collaborate moving forward.

CMAC has hosted and facilitated face-to-face industrial and academic sessions, workshops and training sessions with the companies including the DTC summer school, and made a large number of business-to-business and academic introductions in 2017/2018, a number of which have resulted in new collaborations. Tier 2 members have been integral to the Hub and research support and collaborative projects such as ICT-CMAC, Remedies, ADDOPT and Articular.

Figure 31: Tier 2 technology companies

Images: Tier 2s exhibition and microfactory demonstrations at the CMAC Open Day 2018.

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

Industry & Knowledge Exchange

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

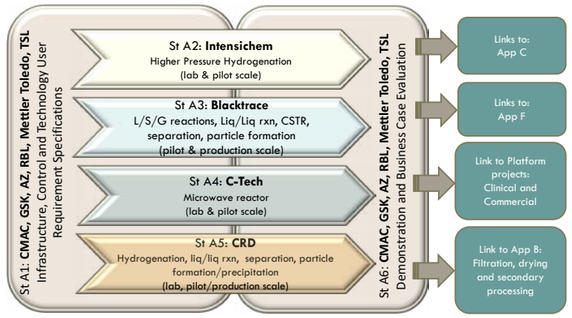
The £23m REMEDIES project completed this year it is part of the Advanced Manufacturing Supply Chain Initiative (AMSCI) programme working with 22 partners to improve the global competitiveness of UK advanced manufacturing supply chains via funding research and development, skills training and capital investment to achieve world-class standards and encourage major new suppliers to locate 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 sought to address these challenges.

CMAC led workstream (App) "A" – Active Pharmaceutical Ingredients and Registered Starting Materials and was technical lead on workstream (App) " B" – Primary to Secondary Formulation.

OVERVIEW

App A objectives:

- The development of mobile continuous process equipment capable of a range of chemistries with open access.
- Identifying and exploiting suitable technologies for continuous processing for specific applications.
- Creating an asset network for use by CMOs and primes.

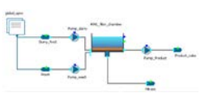


App A partner organisations:

APP B – CONNECTING TECHNOLOGY PLATFORMS

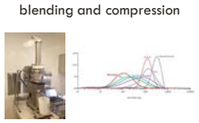
Continuous drug substance filtration

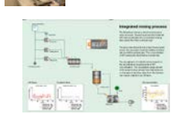
- AWL lab scale prototype
- Continuous washing, filtration and drying



Continuous direct compression

- GEA CDC50 test rig, PAT enabled
- Continuous feeding, blending and compression





Hot melt extrusion/3D printing

- 16mm twin screw extruder at Univ of Strathclyde, PAT enabled
- Potential to direct couple HME and 3DP

Full project report at www.remediesproject.com

Figure 32: Overview of REMEDIES App A & B

ADDOPT: Advanced Digital Design Transforming Pharmaceutical Development and Manufacture

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

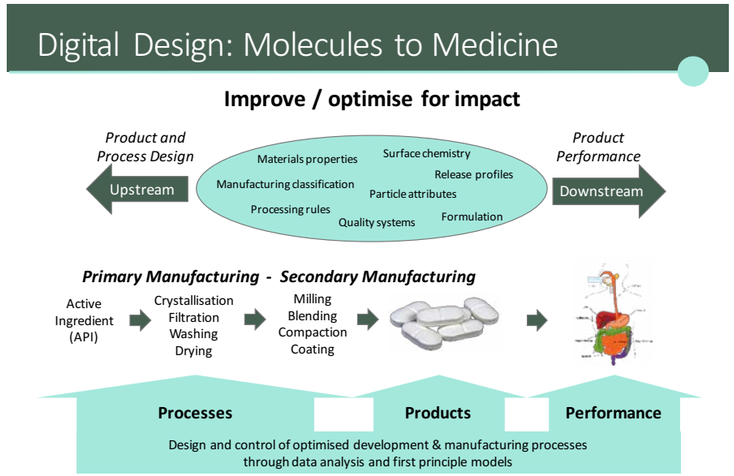


Figure 33: ADDoPT project overview

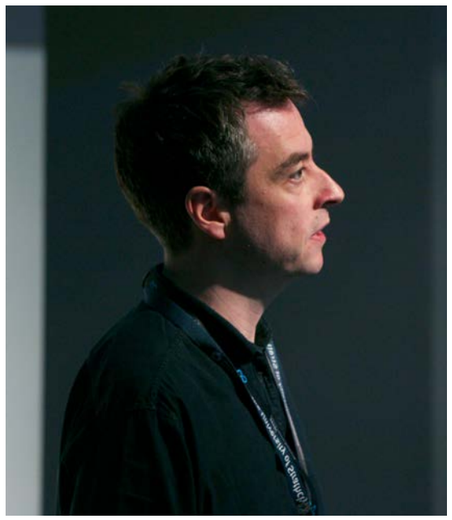


Image: Dr Blair Johnston, CMAC's technical lead in the ADDoPT Project

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

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

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

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

Appendix

Hub Structure 2018

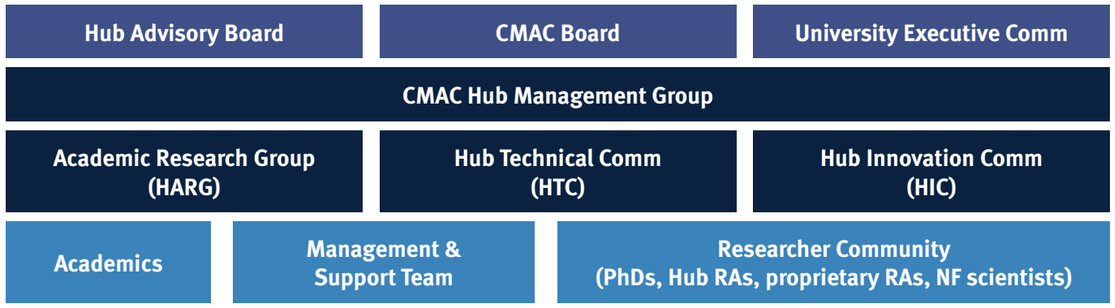


Figure 34: CMAC Governance Structure

Hub Advisory Board

Name	Organisation
Dr Clive Badman	University of Strathclyde
Dr Neil Baker	Pfizer
Dr Sean Bermingham	PSE
Professor Alastair Florence	CMAC, University of Strathclyde
Dr Malcolm Hannaby	Innovate UK
Professor Ian Gilmore	NPL
Miss Lorna Gray	CMAC, University of Strathclyde
Professor Richard Hague	University of Nottingham
Dr Sophie Walton	CPI
Dr Andrea Johnston	CMAC, University of Strathclyde
Mr Craig Johnston	CMAC, University of Strathclyde
Mr Ewan Norton	MHRA
Ms Jo Pisani	PwC
Dr Amy Robertson	AZ
Dr Walkiria Schlindwein	De Montfort University
Professor Nilay Shah	Imperial College London
Professor Sarah Sharples	University of Nottingham
Professor Paul Sharratt	ICES
Dr Nigel Westwood	CRUK
Dr Charlotte Wiles	Chemtrix
Ms Stephanie Williams	EPSRC
Dr Aaron Cole	Merck, Sharp and Dohme

CMAC Industry Board

Name	Organisation
Dr Jon Paul Sherlock (Chair)	AZ
Dr Phil Dell' Orco	GSK
Mr Phil Shering	AZ
Dr Markus Krumme	Novartis
Dr Olaf Queckenberg	Bayer
Dr Charles Papageorgiou	Takeda
Dr Sarah O'Keefe	Lilly
Dr Liam Tully	Pfizer
Dr Brian Chekal	Pfizer
Dr Pirmin Hidber	Roche
Professor Alastair Florence	CMAC
Mr Craig Johnston	CMAC
Professor Graham Wren	University of Strathclyde
Dr David Lovett	Perceptive Engineering
Dr Christopher Burcham	Lilly
Dr Jan-Olav Henck	Bayer

Hub Academic Research Group

Professor Alastair Florence, University of Strathclyde (Chair)
Representatives from AZ, Bayer, GSK, Lilly, Novartis, Pfizer, Roche, Takeda & Tier 2 Partners
Mr Craig Johnston, CMAC
Dr Ian Houson, CMAC
Dr Stewart Mitchell, CMAC

Professor Claire Adjiman, Imperial College London
Professor Amparo Galindo, Imperial College London
Dr Sara Febra, Imperial College London
Professor George Jackson, Imperial College London
Dr Suela Jonuzaj, Imperial College London

Dr Brahim Benyahia, Loughborough University
Dr Wei Li, Loughborough University
Professor Chris D. Rielly, Loughborough University

Professor Chick C. Wilson, University of Bath
Dr Lauren Hatcher, University of Bath

Dr Parminder Kaur Heer, University of Cambridge
Dr Ettore Settanni, University of Cambridge
Dr Jag S. Srai, University of Cambridge

Dr Thokozile Kathyola, University of Leeds
Dr Anuradha Pallipurath, University of Leeds
Professor Kevin Roberts, University of Leeds
Professor Sven Schroeder, University of Leeds

Dr Omid Arjmandi-Tash, University of Sheffield
Dr Rachel Smith, University of Sheffield
Professor Jim Litster, University of Sheffield

Dr Ali Anwar, University of Strathclyde
Dr Cameron Brown, University of Strathclyde
Dr Magdalene Chong, University of Strathclyde
Miss Helen Feilden, University of Strathclyde
Professor Gavin Halbert, University of Strathclyde
Dr Tariq Islam, University of Strathclyde
Professor Joop ter Horst, University of Strathclyde
Dr Andrea Johnston, University of Strathclyde
Dr Blair Johnston, University of Strathclyde
Dr Hikaru Jolliffe, University of Strathclyde
Mr Corin Mack, University of Strathclyde
Dr Alison Nordon, University of Strathclyde
Dr Sara Ottoboni, University of Strathclyde
Dr Chris Price, University of Strathclyde
Dr Elke Prasad, University of Strathclyde
Dr John Robertson, University of Strathclyde
Dr Murray Robertson, University of Strathclyde
Professor Jan Sefcik, University of Strathclyde

Technical Committee

Company	Members
AZ	Dr Amy Robertson Mr Phil Shering Dr Helen Wheatcroft
Bayer	Dr Guido Wegener
GSK	Dr Mei Lee Dr Robert Dennehy
Lilly	Dr Chris Burcham Mr Tim Braden
Novartis	Dr Berthold Schenkel Dr Ruairi O'Meahdra
Pfizer	Dr Kevin Girard Dr Paul Meenan Dr David Walker
Roche	Dr Pirmin Hidber Dr Marcello Bosco
Takeda	Dr Charles Papageorgiou Dr Justin Quon

Appendix

Hub Structure 2018

Management Team

Job Title	Name
Director	Professor Alastair
Industry Director	Mr Craig Johnston
EPSRC Hub Research Manager	Dr Andrea Johnston

Industry Team

Job Title	Name
Industry Director	Mr Craig Johnston
Tier 1 Technical Project Manager	Dr Ian Houson
Tier 2 Project Manager	Dr Stewart Mitchell
Tier 1 Coordinator	Ms Rebekah Russell

National Facility Team

Job Title	Name
Technical Project Manager	Dr Kenneth Smith
Business Development Manager	Dr Claire MacDonald
Technical Operations Manager	Dr Thomas McGlone
CMAC National Facility Administrator	Ms Mashaal Malik
Senior Instrument Scientist	Dr Humera Siddique
Senior Continuous Processing and Analysis Engineer	Mr Vishal Raval
X-Ray Facility Research Technician	Dr Alan Martin
Physical Analysis Research Technician	Dr Deborah Bowering
Physical Analysis Research Technician	Dr Monika Warzecha (Dr Lennart Ramakers)
Chemical Analysis Technician	Ms Laura Harvey

Administrative and Support Team

Job Title	Name
EPSRC Hub Research Manager	Dr Andrea Johnston
EPSRC Hub Training & Outreach Manager	Ms Helen Feilden
Training Co-ordinator	Dr Rebecca Halliwell
Hub Administrator	Ms Lorna Gray
CMAC Operational Coordinator	Mrs Morell Kerr
Assistant Hub Administrator	Ms Rebecca O'Hare

Researcher Teams 2018

EPSRC Future CMAC Hub

University of Strathclyde

Professor Alastair Florence Group

Research Fellows
Dr Cameron Brown
Dr John Robertson

Research Associates
Ali Anwar
Dr Zied Hosni
Dr Muhammad Tariq Islam
Dr Hikaru Jolliffe
Dr Ebenezer Ojo
Dr Iyke Onyemelukwe
Dr Nazer Rajoub
Lennart Ramakers
Dr Vijay Srirambhatla
Dr Stephanie Yerdelen

PhD Researchers
Bilal Ahmed
Sebastion Davidson
Frederik Doerr
Hector Polyzois
Michael Devlin
John Mahon
Jenna Johnston
Siya Nakapraves

Dr Yi-Chieh (Claudia) Chen Group

PhD Researchers
Carla Ferreira

Professor Alex Duffy Group

PhD Researchers
Leda Todorova-Aleksiev

Professor Gavin Halbert Group

Research Associates
Dr Elke Prasad

PhD Researchers
Elanor Brammer
Albarah Al-Afandi
Sarahjane Wood
Eleonora Paladino
Ecaterina Bordos

Professor Joop H. ter Horst Group

Early Stage Researchers
Dr Maria Briuglia
Maxime Charpentier
Johannes Hoffman
Raghunath Venkatraman

PhD Researchers
Andrew Dunn
Olayinka Olalere
Carlos Moreno Leon
Corin Mack
Jose Luis Capdevila Echeverria

Dr Blair Johnston Group

Research Fellow
Dr Murray Robertson

Research Associate
Dr Antony Vassileiou

PhD Researchers
Michael Chrubasik
Laura Straughair

Dr Alison Nordon Group

Research Associate
Magdalene Chong

PhD Researcher
Nura Salah Aldeen Ahmed

Dr Iain Oswald Group

Research Associates
Dr Martin Ward

PhD Researchers
Suse Bebiano
Lloyd Farquhar

Dr Chris Price Group

PhD Researchers
Clarissa Forbes
Georgia Sanxaridou
Muhid Shahid

Professor Jan Sefcik Group

Research Associate
Sara Ottoboni

PhD Researchers
David McKechnie
Andrew Cashmore
Russell Miller

Spokes

University of Bath

Professor Chick Wilson Group

Research Associate
Dr Lauren Hatcher

PhD Researchers
Ruth Lunt
Lois Wayment
Pollyanna Payne

University of Cambridge

Dr Jagjit Singh Srai Group

Research Associates
Dr Parminder Kaur Aulakh
Dr Ettore Settanni

Imperial College London

Professor Claire S. Adjiman Group

Research Associates
Dr Sara Febra
Dr Suela Jonuzaj

PhD Researcher
Oliver Watson

University of Leeds

Professor Sven Schroeder

Research Associates
Dr Thokozile Kathyola
Dr Anuradha Pallipurath

PhD Researcher
Gunjan Das

Professor Kevin Roberts

Loughborough University

Professor Chris Rielly Group

Research Associate
Dr Wei Li

PhD Researcher
Zhuang Sun

Dr Brahim Benyahia

University of Sheffield

Professor Jim Litster Group

Research Associate
Dr Omid Arjmandi-Tash

PhD Researcher
Jon Tew

Dr Rachel Smith

EPSRC CMAC DTC Universities

Professor Xiongwei Ni, Heriot-Watt University

PhD Researcher
Francisca Navarro Fuentes

Dr Ross Forgan, University of Glasgow

PhD Researcher
Sarah Griffin

Publications in 2018

1. Pitt, K.; Peña, R.; Tew, J. D.; Pal, K.; Smith, R.; Nagy, Z. K.; Litster, J. D., Particle design via spherical agglomeration: A critical review of controlling parameters, rate processes and modelling. Powder Technology 2017.
2. Ahmed, B.; Brown, C. J.; McGlone, T.; Bowering, D. L.; Sefcik, J.; Florence, A. J., Engineering of acetaminophen particle attributes using a wet milling crystallisation platform. International journal of pharmaceutics 2019, 554, 201-211.
3. Bhardwaj, R. M.; Reutzel-Edens, S. M.; Johnston, B. F.; Florence, A. J., A random forest model for predicting crystal packing of olanzapine solvates. CrystEngComm 2018, 20, 3947-3950.
4. Bouvart, N.; Palix, R.-M.; Arkhipov, S. G.; Tumanov, I. A.; Michalchuk, A. A. L.; Boldyreva, E. V., Polymorphism of chlorpropamide on liquid-assisted mechanical treatment: choice of liquid and type of mechanical treatment matter. CrystEngComm 2018.
5. Brown, C. J.; McGlone, T.; Yerdelen, S.; Srirambhatla, V.; Mabbott, F.; Gurung, R.; L. Briuglia, M.; Ahmed, B.; Polyzois, H.; McGinty, J.; Perciballi, F.; Fysikopoulos, D.; MacFhionnghaile, P.; Siddique, H.; Raval, V.; Harrington, T. S.; Vassileiou, A. D.; Robertson, M.; Prasad, E.; Johnston, A.; Johnston, B.; Nordon, A.; Srai, J. S.; Halbert, G.; ter Horst, J. H.; Price, C. J.; Rielly, C. D.; Sefcik, J.; Florence, A. J., Enabling precision manufacturing of active pharmaceutical ingredients: workflow for seeded cooling continuous crystallisations. Molecular Systems Design & Engineering 2018.
6. Burcham, C. L.; Florence, A. J.; Johnson, M. D., Continuous Manufacturing in Pharmaceutical Process Development and Manufacturing. Annual Review of Chemical and Biomolecular Engineering 2018, 9, 253-281.
7. Case, D. H.; Srirambhatla, V. K.; Guo, R.; Watson, R. E.; Price, L. S.; Polyzois, H.; Cockcroft, J. K.; Florence, A. J.; Tocher, D. A.; Price, S. L., Successful Computationally Directed Templating of Metastable Pharmaceutical Polymorphs. Crystal Growth & Design 2018, 18, 5322-5331.
8. Doerr, F. J. S.; Oswald, I. D. H.; Florence, A. J., Quantitative investigation of particle formation of a model pharmaceutical formulation using single droplet evaporation experiments and X-ray tomography. Advanced Powder Technology 2018.
9. Forbes, C.; Nguyen, T.T.H; O'Leary, R.L.; Price, C.J., Elucidating the mechanism of paracetamol sonocrystallization for product purity enhancement. Proceedings of Meetings on Acoustics, 2018 32, ICU2017 - 287. https://asa.scitation.org/doi/abs/10.1121/2.0000739
10. Hatcher, L.; CCDC 1829765: Experimental Crystal Structure Determination, 2018, DOI: "https://dx.doi.org/10.5517/ccdc.csd.cc1zfop3" \t "_blank" 10.5517/ccdc.csd.cc1zfop3
11. Jiang, M.; Ni, X.-W., Effects of water and temperature on reaction mechanism and crystal properties in a reactive crystallization of paracetamol. Chemical Engineering and Processing - Process Intensification 2018, 131, 20-26.
12. McLaughlin, A,M.; Robertson, J.; Ni, X., Material characterisation and parameter effects on bulk solid dissolution rate of paracetamol in a stirred tank vessel using an in situ UV-ATR probe. International Journal of Engineering Research & Science. 2018, 4(1):10-20.
13. Michalchuk, A. A. L.; Hope, K. S.; Kennedy, S. R.; Blanco, M.; Boldyreva, E.; Pulham, C. R., Ball-Free Mechanochemistry: In Situ Real-Time Monitoring of Pharmaceutical Co-Crystal Synthesis by Resonant Acoustic Mixing. Chemical Communications 2018.
14. Neugebauer, P.; Cardona, J.; Besenhard, M. O.; Peter, A.; Gruber-Woelfler, H.; Tachtatzis, C.; Cleary, A.; Andonovic, I.; Sefcik, J.; Khinast, J. G., Crystal Shape Modification via Cycles of Growth and Dissolution in a Tubular Crystallizer. Crystal Growth & Design 2018.
15. Onyemelukwe, I. I.; Benyahia, B.; Reis, N. M.; Nagy, Z. K.; Rielly, C. D., The heat transfer characteristics of a mesoscale continuous oscillatory flow crystalliser with smooth periodic constrictions. International Journal of Heat and Mass Transfer 2018, 123, 1109-1119.
16. Onyemelukwe, I.I.; Parsons, A.R.; Wheatcroft, H.P.; Robertson, A.; Nagy, Z.K.; Rielly, C.D. The role of residence time distribution in the continuous steady-state MSMPR crystallization of glycine. Crystal Growth & Design 2018, DOI: 10.1021/acs.cgd.8b00853.
17. Ottoboni, S.; Chrubasik, M.; Mir Bruce, L.; Nguyen, T. T. H.; Robertson, M.; Johnston, B.; Oswald, I. D. H.; Florence, A.; Price, C., Impact of Paracetamol Impurities on Face Properties: Investigating the Surface of Single Crystals Using TOF-SIMS. Crystal Growth & Design 2018, 18, 2750-2758.
18. Ottoboni, S.; Price, C. J.; Steven, C.; Meehan, E.; Barton, A.; Firth, P.; Mitchell, A.; Tahir, F., Development of a Novel Continuous Filtration Unit for Pharmaceutical Process Development and Manufacturing. Journal of pharmaceutical sciences 2018.
19. Steendam, R. R. E.; ter Horst, J. H., Scaling Up Temperature Cycling-Induced Deracemization by Suppressing Nonstereoselective Processes. Crystal Growth & Design 2018, 18, 3008-3015.

Closing Remarks

Progess in the programme has been outstanding and the latest developments are showing great promise in bringing more rational and reliable approaches to design of continuous processes."

Paul Sharratt, Chair CMAC Advisory Board and Astar

The pharmaceutical industry is dealing with significant change as demands from patients, payers and healthcare systems drive increased complexity in the design, development, manufacturing and supply of future medicines. CMAC, with 8 Tier 1 Pharma companies and a thriving Tier 2 community, has been built on pre-competitive, industry led collaboration and is delivering an ambitious and impactful research programme. Ensuring CMAC delivers research excellence and intensity and outstanding skills development, whilst establishing world class facilities and promoting exemplary translation to industry, is critical to sustainable success and a focus for the industry partners. The environment is changing with the formation of UKRI, the emergence of MMIC and targeted funding through ISCF and CMAC is well positioned to continue to be provide a clear and influential voice in this new ecosystem."

Dr Jon-Paul Sherlock, AstraZeneca, CMAC Chair

CMAC
FUTURE MANUFACTURING RESEARCH HUB

Prof Alastair Florence, Director
e: alastair.florence@strath.ac.uk
t: +44 (0)141 548 4877

Craig Johnston, Industry Director
e: craig.johnston.101@strath.ac.uk
t: +44 (0)141 548 2240

Dr Andrea Johnston, Programme Manager
e: andrea.johnston@strath.ac.uk
t: +44 (0)141 548 4506

CMAC National Facility
e: national-facility@cmac.ac.uk
t: +44 (0)141 444 7102

General Enquiries
e: info@cmac.ac.uk

www.cmac.ac.uk