Institution: Heriot Watt University

Unit of Assessment: 8 Chemistry

Title of case study: Baffled Reactors for Continuous Reaction and Crystallisation

1. Summary of the impact

Research at Heriot-Watt University (HWU) has led to the development of a new continuous oscillatory baffled reactor and crystalliser technology. This has direct economic and environmental impact in the chemical, pharmaceutical and food industries. Waste is substantially reduced, while the scale of the equipment and plant is dramatically decreased, reducing time to market, start-up and maintenance costs and on-going energy usage. The reactor/crystalliser was taken to market through a spinout, NiTech Solutions Ltd, with a peak of 16 employees in the REF period. Genzyme (now Sanofi) has implemented NiTech's technology for biopharmaceutical manufacture since 2007, with multi-100 ton production and sales of multi-£100M pa. The technology now underpins the larger-scale joint venture, the Continuous Manufacture and Crystallisation (CMAC) consortium, launched in 2010. CMAC has attracted over £60M investment, much of it from three major industrial partners, GSK, AstraZeneca and Novartis, with additional second-tier investors. CMAC is accelerating the introduction of new process-intensification technologies in the process industries.

2. Underpinning research

Traditional batch technologies for manufacture of fine chemicals are inherently inefficient due to the difficulties of consistently meeting product specifications. This incurs significant financial penalties and generates waste. The current norm is that for every 1 kg of active pharmaceutical ingredient (API) harvested, 50 to 200 kg of waste is produced. The typical raw material cost for a single batch of API is £1 to £5M. Many of these products (over 90% of pharmaceuticals and 80% of fine chemicals) are of crystalline form and involve a crystallisation step in their production cycle. The control of crystal purity, morphology and size distribution therefore has a significant impact on the efficiency and profitability of the overall production.

Research of Prof Xiongwei Ni at Heriot-Watt University has successfully addressed the underpinning physical principles that are responsible for these limitations of traditional batch reactors and crystallisers. The work was stimulated, in part, by the results of a 9-year EPSRC-funded project (part of which was carried out at HWU) 'Chemicals Behaving Badly'. This identified that the key to delivering consistent product specifications included the control of cooling (linear) profile and the attainment of uniform mixing. However, neither of these features is achievable in industrial batch systems, due to the facts that mixing becomes less efficient and the specific area per unit volume for heat transfer decreases dramatically with scale. This makes any controlled cooling profiles problematic to implement in any industrial production.

Ni's research has focused on understanding the science of achieving uniform mixing at all scales in plug flow under laminar flow conditions[1, 2] The continuous oscillatory baffled reactor and crystalliser technology developed as a result of this research combines both uniform mixing with precise temperature control, allowing any desired cooling profiles, e.g. linear, nonlinear, step function, parabolic, etc., to be achieved from lab to full scales. The applicability of the technology has been demonstrated for transport processes, reactions and crystallisation.[3, 4] Major patents have been filed on both apparatus and method.[5] The technology eliminates the two fundamental problems encountered in traditional industrial scale crystallisers identified above. It also enables kinetic reaction time to be executed at all scales, shrinking the space required. Unlike standard batch systems, laboratory monitoring tools have been shown to be capable of being implemented on industrial scales without modification, facilitating smooth, direct and fast transition from the laboratory to production. Knowledge gained in the laboratory can be applied directly in production, again unlike in traditional full-scale operations due to the effects of non-scalable mixing.

Trials with a large number of chemical, food and pharmaceutical compounds (>60) from various industrial companies have firmly reinforced that the technology delivers consistent product quality,

e.g. size distribution, morphology, yield and purity, with significant reductions (>90%) in process time, waste and unwanted products, as well as in energy, utility, plant size and inventory.[6] Continuous reaction and crystallisation are now identified as critical steps in process-intensification drives to improve manufacturing in the chemical and pharmaceutical industries, through more efficient use of reagents, solvents and energy while minimizing side reactions, unwanted products and waste materials.

3. References to the research (* = best indicates the quality of the underpinning research)

1.* Ni X and Pereira NE, Parameters affecting fluid dispersion in a continuous oscillatory baffled tube. *AIChemE Journal* **46**: 37-45 (2000). http://dx.doi.org/10.1002/aic.690460106

2. Ni X, Jian H and Fitch AW, Evaluation of turbulent integral length scale in an oscillatory baffled column using large-eddy simulation and digital particle image velocimetry. *Trans IChemE* **81**: 842-853 (2003). http://dx.doi.org/10.1205/026387603322482086

3. Ni X, Valentine A, Liao A, Sermage SBC, Thomson GB and Roberts KJ, On the crystal polymorphic forms of L-glutamic acid following temperature programmed crystallisation in a batch oscillatory baffled crystalliser. *Crystal Growth and Design* **4**: 1129-1135 (2004). http://dx.doi.org/10.1021/cg049827l

4.* Ni X and Liao A, Effects of cooling rate and solution concentration on solution crystallisation of L-glutamic acid in an oscillatory baffled crystalliser. *Crystal Growth and Design* **8**: 2875-2881 (2008). http://dx.doi.org/10.1021/cg7012039

5. Ni X, Laird I and Liao A, Improved apparatus and method for temperature controlled processes. EU patent WO 2007060412 A8 (22 November 2006).

6.* Lawton S, Steele G, Shering P, Zhao L, Laird I and Ni X, Continuous crystallisation of pharmaceuticals using a continuous oscillatory baffled crystalliser. *Organic Process Research & Development* **13**: 1357-1363 (2009). http://dx.doi.org/10.1021/op900237x

Research grants:

1998 – 2001 EPSRC GR/M31309/01 **£233,423** with Bonar Polymers Ltd and Professor David Sherrington of Chemistry, Strathclyde University on application of the oscillatory baffled reactor to continuous polymerisation processes

2000 – 2003 EPSRC GR/M63447/01 **£193,175** on fluid flow measurement using high resolution digital particle image velocimetry

2000 – 2002 **£36,000** Yorkshire Water on continuous coagulation using an oscillatory baffled Reactor

2003 – 2003 **£100,000** Department of Trade and Industry (DTI) and James Robinson Ltd on continuous production of a photochemical using oscillatory baffled reactor

2004 – 2005 **£50,000** SMART: Scotland Award on a feasibility study of continuous production of a family of nano particles using an oscillatory-baffled reactor

2005 – 2006 **£40,897** SMART: Scotland Award on a feasibility study of continuous crystallisation of l-glutamic acid using an oscillatory-baffled crystalliser

2009 – 2010 **£55,819** Technology Strategy Board (TSB) Award on achieving greater consistency in the modification of human recombinant proteins through scaleable continuous-production process technology

2009 – 2011 €**28,245** out of €958,429 from a FP7 Project on development of continuous oscillatory baffled reactor to enable the creation of graduated radar absorbing multi-layer structures

for wind turbine applications

2010 – 2014 **£148,384** two PhD studentship by the Scottish Founding Council on probing into how nucleation was generated without seeds in oscillatory baffled crystalliser while seeding was essential in traditional batch crystalliser

2012 – 2012 **£53,048** from Continuous Manufacturing and Crystallisation (CMAC) Industrial Consortium on the effect of seed size and quantity on crystal properties

4. Details of the impact

NiTech Solutions Ltd was spun off from Heriot-Watt University in Dec 2004, aided by a SMART award from Scottish Enterprise, with plug-flow crystallisation and reaction as the key technologies for chemical, pharmaceutical and food industries. A second SMART award on continuous crystallisation supported Dr Anting Liao, Xiongwei Ni's ex-PhD student from HWU, to be employed at NiTech to carry out the designed trials. Excellent results were generated; for example, consistent crystal morphology/size distribution/enhanced yield, significantly reduced process time and waste, and elimination of the use of milling machines. An example of the impact of the technology is the continuous crystallisation of one of the AstraZeneca's blockbuster drug ingredients. In their operation in traditional crystallisers, it takes 9 hours and 40 minutes for the crystallisation step; the filtration rate is poor because of uneven sizes of crystals generated due to the difficulties, identified above, of controlling the crystallisation environment. In order to obtain the required size a milling machine is used as one of the key downstream unit operations. When applying NiTech continuous crystallising technology, the overall process was shown to take only 12 minutes with uniform sizes, enhanced filtration rates (which eliminate the use of the milling machine) and significant savings in capital and operational costs (see ref [6] above).

Another leading example is the production of a biopharmaceutical drug in Genzyme (now Sanofi). In less than two years from conception in 2005, full production was commissioned at the Haverhill site in April 2007 after successful trials and design at NiTech as well as the certification of the process by the FDA. NiTech technology was used to launch production of a new active pharmaceutical ingredient (API) via a three-phase reaction on the scale of multi-hundred tons p.a. with a value of multi-£100M p.a. The reaction is approximately 40 times faster than a batch process, with good flexibility to control throughput. The reactor was able to fit into a small footprint in an existing building, avoiding the traditional alternative of two large pressure reactors and a new building. There was a resultant saving of several million pounds in capital expenditure and approximately four times faster construction. Simplicity of operation and reduced maintenance costs have been sustained. Product quality is higher, with the ability to continuously monitor and control the reaction leading to a zero reject rate for this reaction step, all contributing to a competitive commercial advantage. Quoting a Senior Manager of Genzyme:

"This is believed to be the largest scale continuous manufacturing plant for a patented API in the world. Importantly, we were able to supply the market many months earlier than would have been the case with conventional batch processing. This was one of the best investment decisions that I have made! "

[Text removed for publication]

NiTech has filed key patents on continuous crystallisation, worked with a large number of chemical, food and pharmaceutical companies on continuous crystallisation, including seven out of the top ten global pharma giants and two out of the top three global food companies on edible oils. It has received investments over £3M and employed more than 16 people.

Following discussions between NiTech, GSK, and members of the ScotCHEM research pooling and Chemical Sciences Scotland industry-academia collaborative initiatives on how to further

exploit this technology, a joint demonstration project was established in mid-2009. GSK provided 'model' crystallisation process and materials. Outstanding results were obtained in these trials. It was seen as an opportunity for Scotland to take the lead in meeting the challenges facing chemical manufacturing globally. This led to continuous crystallisation being the platform technology in the GSK-led Continuous Manufacture and Crystallisation (CMAC) consortium. CMAC was established in 2010 with £1M cash injection and £1M in kind each from GSK, AstraZeneca and Novartis as the tier-one members, plus £250k from tier two members including Fujifilm, Genzyme, Croda, Syngenta, Evonik, NiTech itself and others. In 2010/11, NiTech changed its business model to become an integrator and facilitator, focussing on collaboration with an engineering company rather than manufacturing the reactors itself. It is a critical part of CMAC, indeed, according to a member of the Board

"*NiTech's technology is the technology that started it all off*".

CMAC has now grown into a >£60M consortium with research grants from EPSRC Centre for Innovative Manufacturing (£9.1M), ESPRC DTC (£6.9M), Scottish Funding Council (£1.5M), TSB (1.75M), EPSRC ICT Platform (£4M), EU (£0.5M), and EPSRC RPIF (£34M). CMAC is now the largest and the most comprehensive centre in the world on continuous crystallisation. It is focused on helping industry to evaluate and trial leading edge process solutions against their requirements and to accelerate the introduction of new process-intensification technologies to meet wider industry needs.

5. Sources to corroborate the impact

A senior manager with technical responsibilities, Genzyme.

A member of the Board of NiTech Solutions.

A member of the Board of Chemical Sciences Scotland.

A senior manager in Investigational Materials Supply, GlaxoSmithKline.

www.nitechsolutions.co.uk