Continuous crystallisation

Alastair Florence is talking at 1230 on Thursday 6 June on 'Development of a continuous crystallisation in an oscillatory baffled reactor'

How is continuous flow changing the pharmaceutical industry?
There's a big driver to explore the opportunities that continuous flow offers over traditional batch manufacturing approaches: reducing time to market, reducing cost of quality, reducing variability and overall reduction in total manufacturing time. The traditional approach of batch manufacturing inherently involves a lot of inventory in the system, holding up material as you pass it through - operating a process at steady state as part of a continuous operation has some advantages that include reduced variation and improved quality. These are key challenges expressed as technical problems statements from GSK, AZ and Novartis

Continuous opens up some really interesting opportunities by focusing on the chemistry to exploit that workflow: different solvents, better yields, reduced impurities, reducing the need for solvent swaps or other costly and time-consuming steps in the process. There are some challenges to have the technology to support work-up, continuous extraction, distillation, absorption processes and so on. Moving to crystallisation, one of the big drivers within our centre is to be able to deliver really exquisite control over the nucleation and growth steps of crystallisation to optimise yield and purity but also deliver shape, form and size control. If you can improve that level of control you start to be able to avoid or streamline downstream processing steps.

How do you do crystallisation with continuous flow?
With traditional industrial crystallisation in batch, you're trying to get uniformity and the aim is to get purity and yield and the right polymorphic form and particle shape. Now there's been tremendous progress in real-time feedback control for batch crystallisation processes to allow you to control, in the pot, the trajectory through the phase diagram to maximise yield and maintain control over the nucleation and growth processes. But one of the challenges of doing that at scale is the development process - there are big challenges in scalability going from a 10ml to a 1 litre to a 100 litre to a 5000 litre reaction vessel, which is not a linear process. So continuous offers some benefits in scalability - some of the technologies we are exploring offer very efficient heat and mass transfer; you've got much larger specific surface area for heat transfer. So you can in principle get much better control over the process.

In a batch process, we change the conditions continually over time and we mix it to try and get an even distribution of molecules. In a continuous operation, we ideally keep the conditions constant at any given location but they change over distance. In the tubular-type reactor we move from a position of constant high temperature to one of constant low temperature and so the molecular experience through that reactor is similar to applying a cooling profile to a large batch vessel. Combined with the advantages of efficient heat transfer and the uniformity of mass transfer this in principle allow much tighter and better control over the formation of the particle.

Is this technology being used by pharmaceutical companies or is it still under development?
There's been significant investment across the pharmaceutical industry in continuous manufacturing and companies have been able to demonstrate the benefits in a range of projects especially around hazardous chemistry and secondary operations. There are several examples of continuous

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API processes. There are a number of areas where improved understanding, de-risking and optimisation of technology is still required. Using flow for crystallisation is an obvious choice if you have rapid kinetics, potentially explosive or hazardous materials, because there are safety benefits as well.

What are the barriers holding back industry from using continuous flow?
One of the big challenges is the existing capital infrastructure - when a new product comes along, there is a pressing case to use existing under-utilised facilities rather than investing in new equipment. And so part of the need for further work is to really be able to demonstrate the benefits.

Is a continuous crystallisation process able to deliver the purity, yield and particle control requirements to at least the same degree as a batch process? What benefits do you get if you are able to daisy-chain your operations together in a continuous operation? How does that impact on your responsiveness to changing market needs from development phase through clinical trials, which is notoriously difficult to predict the supply and demand of materials, and what scale will the ultimate market of that be?

Continuous operation for large volume commodity chemicals has been around for some time, but for pharma the traditional batch mode has delivered. With changing business models, the patent cliff, the need for greater efficiencies and the desire to deliver enhanced quality, there's a different challenge for continuous to produce a larger variety of small-volume, high-value products that may have differing market needs. Another barrier is that traditional development is done in batch - researchers use beakers and stirring plates for example. As we move to continuous we need ensure we are able to generate the thermodynamic and kinetic data required to to deliver a robust and reliable process.

How easy is it for researchers to use continuous flow equipment?
During my presentation I'll be talking about some of my work on oscillatory baffled reactors with a 15mm internal diameter and a total volume of 4-5 litres - we need around 10kg of material as a minimum to allow us to start to develop and test the process. But we're also looking at other systems that we're operating, maybe 2-4mm diameters, that allow us to start working with smaller amounts of material. One of the drivers for our research programme is the aim of taking a molecule, understanding its physical properties and being able to ask if it is best suited to batch or continuous. If it's suited to continuous, which of the available options and technology platforms is it best suited to? We also have a broad range of equipment and are working with technology companies to test and develop new equipment is a key part of our ethos.