Perceptive Engineering discusses a two year collaborative R&D project it undertook to address challenges associated with the new generation of reactor systems used in production.

Introduction

A new generation of continuous small-scale reactors that will enable manufacturers of high-value, low volume products to move away from traditional batch processes, has recently come onto the market.

These micro reactors can be used in parallel, to achieve production scale-up without the associated chemical engineering problems. The major benefit of these reactors is the flexibility they offer, i.e., the ability to manufacture a number of products using a single reactor by rapidly adjusting the operating conditions, with little waste material generated during the transition.

Typical benefits of such systems include a waste reduction of 10-15%, energy reduction of 40-70% and solvent process inventory that can be as low as 10% of volume in an equivalent batch process.

Currently these reactors require high levels of manual intervention, to identify suitable operating conditions and adjust the process as needed to maintain final product quality. This can be challenging; the design of the reactors, and the ancillary equipment they require, often result in complex system interactions.

To exploit the full potential offered by these reactors, two distinct areas need to be addressed. Firstly, for existing products, improved automation is required during normal manufacturing, to better reject external disturbances such as feedstock variation, minimising wasted material and resources. Secondly, for new formulations, the ability to identify – and drive the process to – the operating conditions required for achieving on-spec products more rapidly, reducing development time and associated staff costs.

Finding a solution

Perceptive Engineering led a collaborative R&D project, in partnership with AstraZeneca, the Centre for Process Innovation Limited (CPI) and the EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC), based at the University of Strathclyde.

The two year project commenced in February 2013 and was part-funded by InnovateUK. With a title of Made-to-Order Product Properties (MOPPs), its principal aim was to address the challenges described above, applying advanced automation techniques to three of these novel reactor systems, to enable more precise control of product quality and optimise yield.

Perceptive Engineering Limited is based at Sci-Tech in Daresbury, one of the UK Government’s national science and innovation campuses. Drawing on their extensive experience in Advanced Monitoring and Model-Predictive Control, Perceptive designed and deployed software tools to simplify the development methodology used to determine process operating parameters. These software tools improve rapid prototyping, whilst examining multiple feasible operating regions for each product.

The final goal was to develop a control system that would simplify scale-up options for commercial manufacture, by achieving transferability between similar reactors.

Strategy

Two reactor types were used to demonstrate the benefits of advanced automation with process analytical technology (PAT) on two common processing stages in pharmaceutical and fine
chemical manufacture: a Corning® Advanced FlowTM reactor to represent the API reaction stage and both Cambridge Reactor Design’s Rattlesnake and Nitech’s DN15 continuous crystallisers, to represent the crystallisation stage of downstream processing.

These reactors were supplemented with ancillary units, process instruments and on-line PAT analysers that can be controlled remotely via Perceptive Engineering’s PharmaMV™ process automation software, in place of manual intervention. This software has been developed expressly for the pharmaceutical sector, but its functionality was extended to fully exploit the opportunities presented by the collaborative project, so ensure that the goals outlined above could be met. PharmaMV™ also provides the ability to monitor and operate the process remotely, which is of particular interest when the process is hazardous or needs to be operated in a controlled environment.

An intuitive Graphical User Interface was developed for each system, to allow easy adjustment of the process and the implementation of the proposed Model Predictive Control (MPC) scheme. MPC is a technology that has been successfully adapted by Perceptive from other process industries. Through the use of existing process and quality data, a model of the system’s behaviour and performance is constructed. This is then used to automatically adjust process conditions (flows, temperature profiles, feed ratios, etc) to maintain optimal product quality, such as particle size distribution and purity, whilst maximising yield and minimising energy consumption.

By using data extracted from on-line PAT measurements and spectra, the soft sensor capabilities within PharmaMV™ enabled the inference of intermediate and final product qualities. This technique significantly reduced the reliance on expensive off-line analysis. The additional benefit was the real-time inference of final product quality and properties, enabling far tighter and more responsive predictive control to be exercised.

Once the complete system was configured and the basic controller models identified, the entire setup was shown to be easily adaptable, to incorporate new products or changes in the desired properties of existing products.

Automatic real time diagnostics, for monitoring the quality and reliability of data from the analysers and for early detection of equipment fouling, formed part of the overall advanced solution, delivering a robust and self-contained processing unit.

Results
The results have been demonstrated on model compounds as well as products of true industrial interest and the project has shown a significant improvement in yield and in the ability to tightly control PSD.

We are now able to share the results from the CMAC continuous oscillatory baffled crystalliser (COBC) systems. Using lactose as the model compound, the following benefits were demonstrated:

- Increased yield: 26% higher yield (vs batch) in continuous crystallisation
- Consistent & higher product quality: two-fold reduction in span of PSD vs stirred tank reactor
- Process intensification: reduction in lactose crystallisation time from 16 hours to five hours
- Reduced resources: less operator intervention, less waste
- ‘Dial a Particle’: user-defined particle size characteristics, automatically delivered by MPC

The three demonstrator systems – the reactor and two crystallisers, complete with Perceptive Engineering’s Advanced Control and Monitoring platform – are now available to the wider industrial community through the CPI’s role as a national CATAPULT centre and CMAC’s status as an EPSRC national centre.

To learn more about this project, or about how PharmaMV™ can help your own processes meet or exceed their goals, please contact Perceptive Engineering.