APPLIED MATERIALS®

Monitor Control Optimise

Batch to Continuous Crystallisation

Make to Order Process Platform

INTRODUCTION

There are many reasons to run crystallisation in a continuous rather than batch mode. Continuous crystallisation enables better control of crystal size distribution because operation is maintained at a controlled steady state and offers a narrow residence time distribution. Higher yields can be achieved using controlled recycle. Wider volume ratios of solvent to anti-solvent are possible. Difficulties with scaling up from development to commercial production scale are addressed by scale –out rather than up.

These are some of the advantages that continuous crystallisers have over batch.

In light of this, a new generation of continuous small scale crystallisers have recently come onto the market, allowing manufacturers to move away from the traditional batch manufacturing processes.

Typical benefits of such systems include waste reduction of 10-15%, energy reduction of 40-70%and solvent hold up that is the order of 10% of the equivalent batch process. A further, major, benefit of these reactors is their ability to manufacture a number of products using a single reactor by rapidly adjusting the operating conditions.

THE PROBLEM

Whichever form of crystalliser, to achieve an effective crystallisation it is important to control seeding and crystal growth to achieve the desired crystal characteristics whilst maximising yield and throughput. Currently the new crystallisers are operated in a staff- intensive fashion, with manual operation to identify suitable operating conditions and adjustments made to the process during operation.

There is a need to automate the operation of the process to achieve precise control of crystal properties whilst rejecting external disturbances such as feed material variation. There is also a desire to identify new operating conditions required for new products, in a less time-consuming manner. Put simply, end users require a complete solution capable of producing crystallised product with precise properties, right first time, with minimal waste and wide flexibility.

THE OBJECTIVES

Develop a flexible automation system for a Continuous Oscillatory Flow Reactors utilising standard equipment, a flexible analytical platform and where possible transferable “Plug & Play” features.

Design and develop a software platform capable of rapid re-configuration to enable COBR’s achieve flexible manufacturing.

Provide an intuitive User Interface to enable an automated generation of meta stable zones for new formulations with minimal operator intervention.

Provide supervisory diagnostics capable of detecting fouling or undesirable process conditions that impact the effectiveness of the crystalliser.

Deliver a demonstration unit with the ability to produce crystals with desirable properties, reject raw material inconsistency and minimise waste relative to batch.

PERCEPTIVE ENGINEERING | an Applied Materials company

EPSRC
Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

cpi   AstraZeneca

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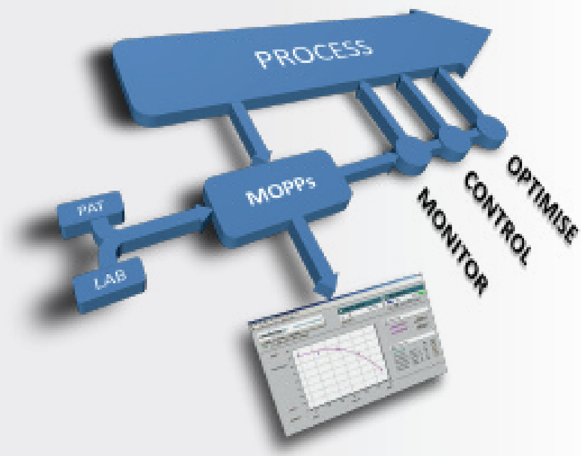
THE STRATEGY

Instrument two Continuous Oscillatory Flow Reactors (from CRD Ltd and Nitech Ltd) with standard temperature, flow and pressure sensors, positioned to give the appropriate measurement points for effective control.

Through model based control and monitoring techniques, generate a dynamic process model capable of control to precisely attain the desired product parameters. Included within the system is a software platform to interface with the variety of analytical devices and provide the necessary calibration parameters for each device.

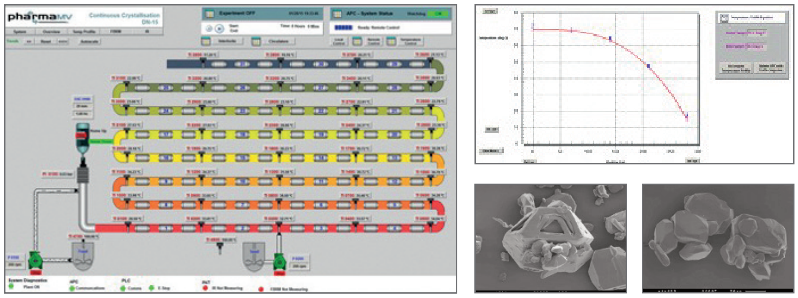
Through control of the temperature profile along the reactor there is should be the potential to both improve conversion and control particle size distribution, but also the option to manufacture more that one product in the same reactor in a sequential planned process. This is a multivariable control challenge which offers huge potential, but which has not been exploited successfully anywhere in the world.



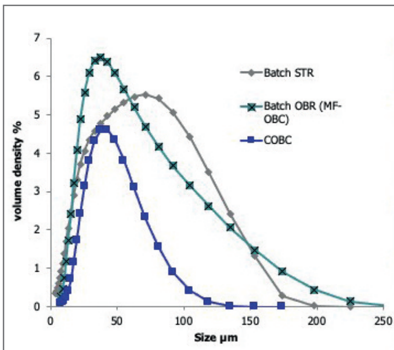
The system was designed and developed to fit into the existing PerceptiveAPC robust industrial automation platform, building on the Advanced Process Control functionality with an integrated ability to develop calibration models using both spectral and process data.

THE RESULTS

An intuitive Graphical User Interface was developed for each system to allow easy adjustment of the process and the implementation of the Model Predictive Controllers. These controllers automatically adjust the process conditions (Flows, temperature profiles, feed ratios etc) to maintain optimal product properties (yield, concentration etc.). These properties are derived from calibration models based upon measurements from the PAT instrumentation.



Once the complete system has been configured and the basic controller models identified, the entire setup is easily adapted to incorporate new products or changes in the desired properties of existing products.



Crystalliser	Residence time	RPM/Reo
STR	2.5	500
MF-OBC	2.5	300
COBC	2.5	300

Crystalliser	Mean particle size	Yield %
STR	71.2	27.9
MF-OBC	37.6	31.2
COBC	37.6	37.3

The results have been demonstrated on both model compounds and products of true industrial interest and have shown a significant improvement in yield and ability to control PSD. The complete COBR with PAT enhanced automation is currently being demonstrated at the Centre for Innovative Manufacturing and Crystallisation at the University of Strathclyde.

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