CASE STUDY

SITUATION

Crystallization affects every aspect of process chemistry, including process transfers, filtration, impurity purging, drying, and particle size measurements. To produce desired crystal size distributions with specific compounds, chemists must obtain accurate values for the concentrations, temperatures, solubility levels and other crystallization parameters for those compounds.

These values define the metastable zone width (MSZW), the range of reaction conditions that support crystallization. Due to the frequent occurrence of crystallization processes throughout process development, the accuracy and precision of these values, and the time and effort involved in acquiring them impact overall product yield, development time and cost.

OBJECTIVE

Manual analysis of crystallization reaction conditions using turbidity meters is a common method of obtaining values for MSZW parameters. However, this is a time-consuming process that yields imprecise values. Process chemists at Pfizer wished to reduce the time required to obtain MSZW parameters and increase the precision of parameter measurements.

ACTION

Advantage Series™ 4100 Process Scale-up Reactor from Argonaut Technologies controls reaction vessel heating and cooling, agitation, additions, and pressure. The Advantage Series 4100 connects to a variety of analytical instruments and can be programmed to automatically identify and respond to specific reaction termination conditions with quenching, cooling, additions or other steps.

For this MSZW determination study, an Advantage Series 4100 was connected to a Lasentec® FBRM® focused beam reflectance measurement instrument. The FBRM instrument provides real-time particle size and concentration readouts.

Using the particle count value as a stage termination condition, Pfizer researchers programmed the Advantage Series 4100 to reduce the crystallization reaction solution concentration at the onset of crystallization (Figure 1). This automated step eliminated unnecessary cooling and heating time, reduced the risk of self-seeding, and produced a single, synchronized data file for further analysis (Figure 2). Data files from crystallization experiments included elapsed time, temperature, agitation rate and additions controlled by the Advantage Series 4100, plus simultaneous particle count and cord length data from the Lasentec FBRM probe. Researchers used the data from these files to determine the MSZW of their compound of interest.

Figure 1. MSZW reaction parameter determination without (B) and without (A) Advantage Series 4100 Process Scale-up Reactor fitted with FBRM probe. Programmed stage termination based on real-time particle count feedback eliminated reaction parameter exploration cycles through non-informative parameter ranges.
RESULT

The integrated, automated Advantage Series 4100 fitted with a Lasentec FBRM instrument allowed Pfizer process chemists to determine MSZW within 1.5 days. This represents a significant improvement over a non-integrated manual method, which requires 5 working days to make MSZW determinations.

Rapid determination of crystallization MSZW boosts process chemistry productivity by reducing crystallization process times, recording precise reaction, and eliminating manual data management and analysis steps.

APPLIED TECHNOLOGIES

- Advantage Series 4100 Process Scale-up Reactor 300 and 1000 mL jacketed glass reactors
- Lasentec FBRM probe
- Serial communications interface from Lasentec to Advantage Series 4100
- Temperature gradient

ACKNOWLEDGEMENTS

This case study is based upon results presented by Peter Rose, et al. of Pfizer during the Argonaut Technologies Power User Conference in August 2001. Rose uses an Advantage Series 4100 Process Scale-up Reactor equipped with a Lasentec FBRM probe.

Figure 2. Parameter exploration cycles without (A) and with (B) Advantage Series 4100 fitted with FBRM probe. Over the course of a MSZW determination, programmed stage termination, automated reaction condition control and integrated synchronized data collection saves days of work, reducing a week-long process to less than two days.