Application Note

Crystallization Process Improvement

Return on Investment

Crystallization Improvements of a Diastereomeric Kinetic Resolution through Understanding of Secondary Nucleation

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Problem Statement

The isolation of high purity single enantiomers from solution via crystallization is a commonly utilized approach in high value chemicals industries. In this example, crystallization of a diastereomeric kinetic resolution (Figure 1) was studied as part of a continuous process improvement initiative. The isolated intermediate was occasionally failing optical purity specs, and often exhibited long filtration and drying times. Excessive secondary nucleation occurred during the crystallization, the temperature at which this occurred (T_N) was identified as the critical response variable (Figure 2).

Scientific Approach

ParticleTrack™ (FBRM) was used to systematically estimate T_N at a 1 L scale under different process conditions. Shear rate at the impeller tip and seed loading were identified as the critical variables that influenced T_N, and subsequently influenced optical purity and filterability.

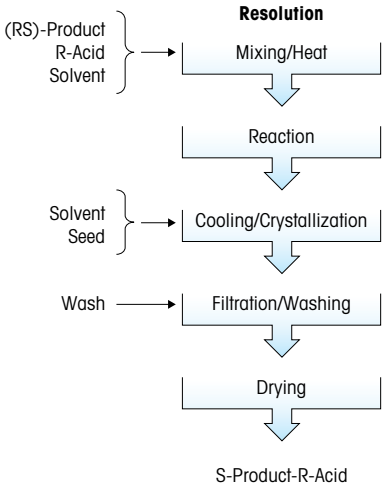

Figure 1. Block flow diagram of the resolution process

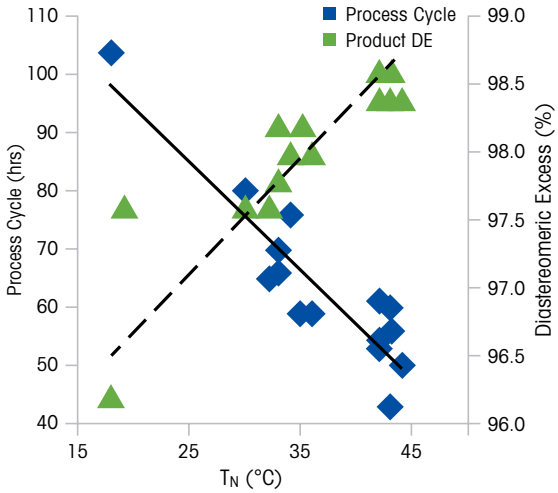

Figure 2. Process cycle time and product Diastereomeric Excess (DE) purity versus T_N

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In Figure 3, ParticleTrack (FBRM) was used to measure how different combinations of impeller speed and seed loading chosen as part of a DOE impacted the nucleation temperature, crystallization kinetics, and overall cycle time of the process.

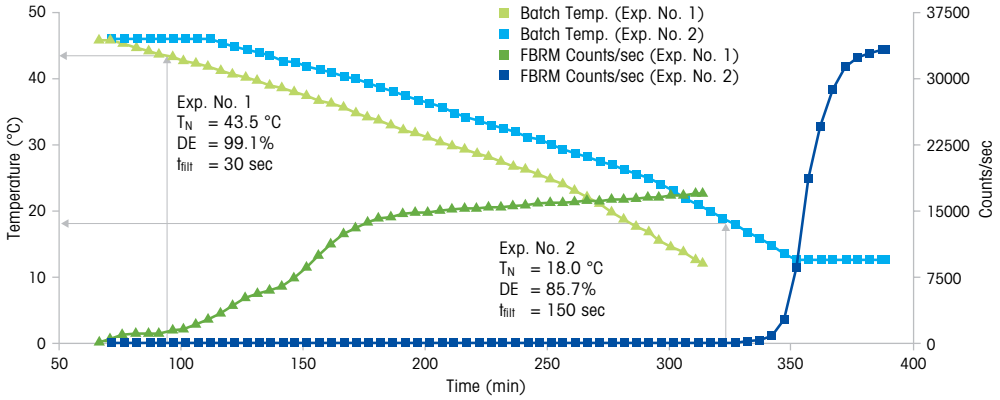

Figure 3. Crystallization profiles for two experiments using different seeding and agitation conditions

Return on Investment

The results of this experimental study provided scientists with the process understanding they needed to develop a new process that was scaled back up to manufacturing. In Table 1, a comparison between the old and new optimized process is made, indicating the following improvements in product quality and process efficiency:

- 66% reduction in centrifugation time
- Elimination of the need for manual filter discharge
- Reduction of failed batches from 3/18 to 0/39

Parameter	Original Process	New Process
Secondary nucleation	Average: 37 °C	Average: 44 °C
Induction temperature	Range: 26 °C to 43 °C	Range: 42 °C to 45 °C
Centrifugation time	Average: 7.5 h; Range: 3 h to 12 h	Average: 2.2 h; Range: 1 h to 4 h
Manual discharge of centrifuge required	Yes	No
No. of failed batches/no. of batches in 2006 campaign	3/18	0/39

Table 1. Process validation at contract manufacturer in 2006

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