NiTech® Technology Application
Academic Crystallisation Examples

These slides summarise cases where NiTech® technology has been applied in academia for crystallisations.
Content

Academic Crystallisation Examples

• Continuous Crystallisation of β-L-Glutamic Acid

• Continuous and Simultaneous Paracetamol Synthesis and Crystallisation
Continuous Crystallisation of β-L-Glutamic Acid


Overview:
- A continuously seeded L-glutamic acid cooling crystallisation process, in a continuous oscillatory baffled crystalliser, was designed and operated to deliver control over polymorphic form.
- Different feed solution concentrations and seed loadings were examined.

Key Findings:
- Steady-state operation, based on particle size distribution and polymorphic form, was demonstrated consistently after two residence times.
- Where bulk supersaturation remained in the range 2–3, the polymorphic phase purity of the thermodynamically stable β polymorph was retained.
- A continuously seeded approach allowed robust processing for at least 10 h.
Continuous Crystallisation of β-L-Glutamic Acid

COBC setup for seeded crystallisations. Temperature zones are shown by colours. Operating conditions were 1 Hz, 30 mm amplitude, 30 g/min main flow and 20 g/min seed slurry flow.
Continuous and Simultaneous Paracetamol Synthesis and Crystallisation

M. Jiang & X. Ni, “Effects of water and temperature on reaction mechanism and crystal properties in a reactive crystallization of paracetamol,” Chemical Engineering & Processing: Process Intensification 131 (2018), 20–26
M. Jiang & X. Ni, “Reactive Crystallization of Paracetamol in a Continuous Oscillatory Baffled Reactor,” Accepted by Organic Process Research & Development 2019

Overview:
- Execute the synthesis and crystallisation of paracetamol as a single unit operation
- Optimised in batch to achieve successful simultaneous execution of continuous operation
- Crystallisation step optimised and reagents back-calculated to design continuous operation

Result:
Correct seeding allowed smooth and encrustation free operation to produce over 99.96% purity Form 1 paracetamol, following a cooling profile close to the solubility curve.
Continuous and Simultaneous Paracetamol Synthesis and Crystallisation
Continuous and Simultaneous Paracetamol Synthesis and Crystallisation

Illustrates close cooling control near the solubility curve and away from spontaneous nucleation.

Solubility, metastable zone, and crystallisation path were measured gravimetrically in a solvent ratio of acid/H2O = 1:9.

At 1 Hz and amplitudes of 26, 30 and 36 mm, respectively.

Open symbols indicate concentrations after crystallisation. Closed symbols indicate concentrations postreaction.
Continuous and Simultaneous Paracetamol Synthesis and Crystallisation

Crystal images

Narrow Distribution

Safer, Greener, Faster and Cheaper
Continuous and Simultaneous Paracetamol Synthesis and Crystallisation

Controllability of mean size from oscillation conditions
Continuous and Simultaneous Paracetamol Synthesis and Crystallisation

Concentration profiles at different points along a COBC:

- Flat trend lines illustrate steady state of solute concentration over time.
- The constant distances between trend lines indicate steady state along the length.
Continuous and Simultaneous Paracetamol Synthesis and Crystallisation

Size measurement for particles taken at sample points 2 and 3 at 15 w/w% seed loading. Trend lines show the steady state is achieved over time and the constant distance between trend lines illustrates the steady state with respect to space.