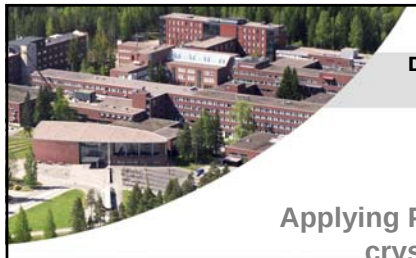

Department of Chemical Technology

Applying PAT in reactive crystallization

Docent Marjatta Louhi-Kultanen

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HELSINKI DRUG RESEARCH 2008

Contents

Reactive crystallization

Driving force of crystallization: supersaturation

Process Analytical Technology (PAT) applied in:

- *Inline* process monitoring based on ATR FTIR and Raman spectroscopy
- Process control of semi-batch precipitation based on Proportional-Integral-Derivative (PID) feedback control

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Background

Main aims :

– to control

- crystal purity
- crystal morphology
- crystal size distribution
- polymorphism

in crystallization processes of pharmaceutical compounds

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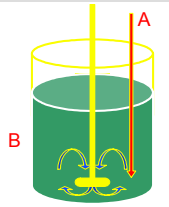
Reactive crystallization

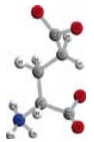
Operation of precipitation is usually a semi-batch process, i.e. one or two reactants are added to the reactor continuously

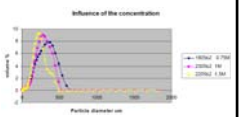
Reactive crystallization

$$A + B \rightarrow C\downarrow + D$$

where *A, B* reactants
C sparingle soluble solute
D forming solute having high solubility



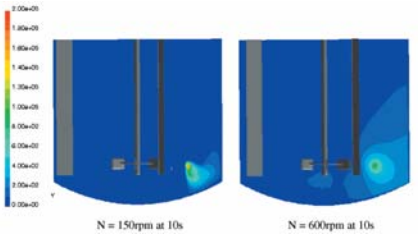




Model compound *L*-glutamic acid (at LUT, 1-liter crystallizer):

Na - glu (*aq*) + ½ H_2SO_4 (*aq*) ↔
H- L- glu (s) + ½ Na_2SO_4 (*aq*)

Factors affecting reactive crystallization



Supersaturation at different mixing intensities (CFD simulation)

Wei et al. 2001

- Reactant concentrations
- Reactant feeding
  - Present work: controlled pumping flow rate of reactant
- Mixing system
- Reaction kinetics

vs.

Crystallization kinetics

Driving force of crystallization: Supersaturation

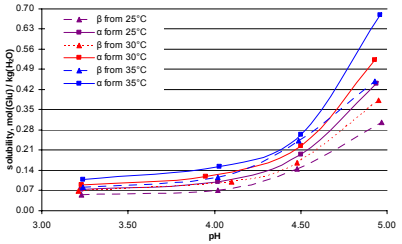
The amount of solute required to make a saturated solution for a given condition is called solubility.

Supersaturation:

$$\Delta c = c - c^*$$

Inline/Insitu concentration measurement of saturated solution

Solubility of L-glutamic acid in water



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Concentration measurement of supersaturated solution

Methods:

- **ATR FTIR spectroscopy**
  - **streng in solid-liquid suspensions: back-reflective method → crystals do not disturb measurement, multi-variate models are required**
- **Raman spectroscopy**
  - **can be used for highly concentrated solutions in some cases (carbamatzepine)**
- **pH (base – acid compound systems)**
- UV spectrophotometry
- ultrasonic measurement
- solution density
- electronic conductivity (electrolytes)
- refractometric measurement (sugar industry)
- etc.

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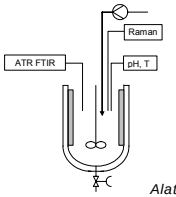
Applying PAT

A. ***Inline*** **process monitoring**

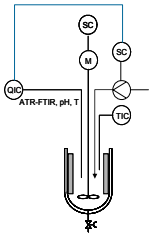
- concentration measurements of most of the solutes with ATR FTIR
- polymorphs with Raman
- determining supersaturation course based on ATR FTIR and thermodynamic model
- constant feed rate of reactants



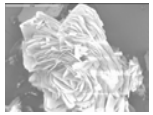
Alatalo et al. 2008

B. Feedback process control (Proportional-Integral-Derivative, PID)

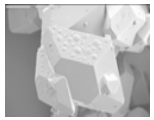
- controlled reactant feeding rate based on determined concentration of glutamate ion with ATR FTIR
- ongoing: comparison of different control policies



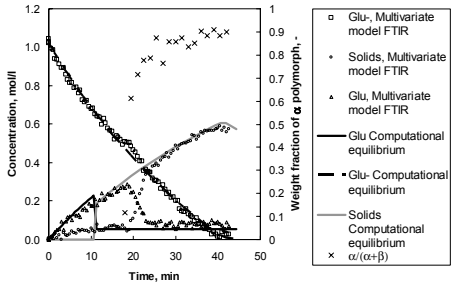
Inline process monitoring of semi-batch reactive crystallization using *L*-glutamic acid



β form



α form



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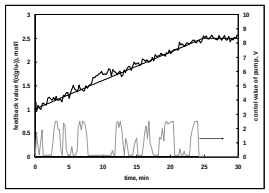
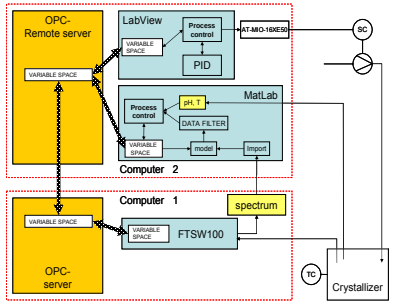
Alatalo et al. 2008

Process control of reactive crystallization

PID controller implemented for semi-batch precipitation: concentration control of glutamate ion (too high fluctuations in *L*-glutamic acid concentrations)





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Summary

- *Inline* ATR FTIR can be used to determine concentrations of various species in *L*-glutamic acid reactive crystallization operating in semi-batch mode
- *Inline* Raman spectroscopy can be used to monitor *L*-glutamic acid polymorphic composition in solid phase during processing
- Reactive crystallization is not easy to control: in fast growing crystal systems supersaturation can be difficult to control on PID basis
- Aims in future work: to create new control policies for reactive crystallization, to improve reproducibility

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