Primary and Secondary Crystal Nucleation

New approaches to measure nucleation rates

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Introduction

Primary and Secondary Crystal Nucleation

- Nucleation
  - Primary (clear supersaturated solution)
    - Homogeneous
  - Secondary (induced by already present crystals)
    - Heterogeneous

- Supersaturation
  - Precipitation
  - Batch crystallization
  - Continuous crystallization
Challenges in Controlling Primary Nucleation

Primary Nucleation is the start-up process of crystallisation

- Primary Nucleation is a stochastic process
- Metastable Zone Width (MSZW) is also a stochastic property and it depends on several factors (e.g., cooling rate, volume…)
- Relations between nucleation and MSZW are unclear

Aim: Understanding primary nucleation within the MSZW
Challenges in Controlling Secondary Nucleation

Secondary Nucleation influences the crystal size distribution (CSD)

- Difficult prediction and control
- Currently it is not possible to incorporate secondary nucleation in a quantitatively predictive way in process design or product quality control

**Aim:** Develop a systematic method for secondary nucleation assessment
Single Nucleus Mechanism

Clear Solution  Single Nucleus  Final Suspension

PRIMARY NUCLEATION  SECONDARY NUCLEATION

Kadam / Crystal Growth and Design 2011, 11, 1271-1277
System Understanding

Part 1: System Understanding in 3 ml volume

1. Metastable Zone Width Determination (MSZW)
2. Identification of condition for seeding in the MSZW
3. Single Crystal Seeding for Secondary Nucleation Rate Measurements
4. Identification of Secondary Nucleation Threshold

Part 2: Scale-up of the developed method

Isonicotinamide in Ethanol
Part 1: System Understanding in 3 ml volume

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Part 2: Scale-up of the developed method

Isonicotinamide in Ethanol
1. MSZW Method

Crystalline (3 ml Volume, magnetic stirring)
1. MSZW Results

![Graph showing the relationship between concentration (C) and temperature (T) with two curves representing clear points and cloud points.](image)
Part 1: System Understanding in 3 ml volume

1. Metastable Zone Width Determination (MSZW)
2. Identification of conditions for seeding within the MSZW:
   2.1. Induction time measurements
      2.1.1. Primary Nucleation Rate
      2.1.2. Determination of working window for seeding
3. Single Crystal Seeding for Secondary Nucleation Rate Measurements
4. Identification of Secondary Nucleation Threshold

Part 2: Scale-up of the developed method

Isonicotinamide in Ethanol
2. Identification of conditions for seeding within the MSZW
2.1. Induction time Measurements Method

Induction time = \( t_n - t_0 = 46.1 - 38.4 = 7.7 \text{ min} \)
2.1. Induction time Measurements Results
2.1.1. Primary Nucleation Rate

Probability Distribution of Induction Time Measurements

\[ P(t) = 1 - \exp(-JV(t - t_g)) \]

Nucleation Rate \( J \) at different \( S \)
2.1.2. Determination of working window for seeding
Part 1: System Understanding in 3 ml volume

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Part 2: Scale-up of the developed method

Isonicotinamide in Ethanol
3. Seeding Method

Under saturated solution

Supersaturated solution

$T_s = 25^\circ C$

$t'$

$t_0$

$t_n$
3. Calibration Suspension Density

Number $N$ of particles determined by Crystalline software versus suspension density $N_p$

$N_p \times 10^3$ [#/ml]

$N$ [#]

50 μm monodisperse polymer particles
3. Seeding Results

$N_p \times 10^{-3}$ [#/ml]

Seeded experiment

Unseeded experiment

$t-t_0$ [min]
3. Seeding Results

Secondary Nucleation Rate $B$

$B = \frac{\text{Slope of suspension density in time}}{\text{[#/ml.min]}}$

$B = 12.8 \times 10^3 \text{#/ml.min}$
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Isonicotinamide in Ethanol
4. Secondary Nucleation Threshold

Seeds size: 3-6 mm$^2$
Crystallization Design Workflow

Stage 1
Prior Knowledge
Existing data on compound collected

Stage 2
Solvent Screen
Solvents classified as high or low solubility

Stage 3
Solvent Selection
Detailed temperature dependence & stability

Stage 4
PAT selection and calibration
Calibrated PAT and detailed solubility curve

Stage 5
System Understanding
Key crystallisation behaviour and attributes

Stage 6
Process Understanding
Kinetic process parameters: First principle and empirical

Stage 7
Proof of Concept Crystallisation
Desired crystal attributes: Purity, polymorphic form, CSD, habit

Decision 1
Solvants with suitable properties for cooling crystallisation?

Decision 2
System stable & temperature dependent solubility suitable?

Decision 3
Measurement capability on/off line suitable?

Decision 4
Suitable continuous platform identified?

Decision 5
Reliable process model?

Decision 6
Desired product attributes achieved consistently?
System Understanding

Stage 5

Key crystallisation behaviour and attributes

Metastable Zone Width
Choose Supersaturation S
Measure Induction Times at Selected S
Single Crystal Seeds Preparation
Measure Secondary Nucleation Rates at Selected S
Secondary Nucleation Threshold
System Understanding

Part 1: System Understanding in 3 ml volume

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Part 2: Scale-up of the developed method

Isonicotinamide in Ethanol
Secondary Nucleation in 100 ml

C = 66 mg/ml
Secondary Nucleation Thresholds

$C = 66 \text{ mg/ml}$

$\% \text{ Seeds Loading} = 0.5\% \text{ w/w}$

Seeds size = $125 \mu\text{m} < x < 250 \mu\text{m}$
Secondary Nucleation Thresholds

MSZW [°C]

Secondary Nucleation Threshold

- 3 ml
- 700 ml
- 100 ml

- 700 rpm
- 200 rpm
- 200 rpm
Conclusions

- A meticulous and reproducible seeding procedure for secondary nucleation assessment has been developed providing a systematic workflow for secondary nucleation determination.

- The method have been applied at different volume of crystallisers and seeds loading obtaining successfull results for secondary nucleation rate calculation.

- When different crystalliser layouts are used, it is necessary to count how volume, stirrer type, used probes can affect the nucleation rate measurements.
Acknowledgement