Secondary nucleation

Rate Controlled Separation - Crystallization
Secondary nucleation agenda

1. Definitions
2. Mechanisms
3. Secondary nucleation rate
4. Applications
5. References
Classification of nucleation and growth mechanisms

Nucleation

- primary
  - homogeneous (HON) (from a clear liquid)
  - heterogeneous (HEN) on tiny foreign particles

- secondary
  - Contact
  - Shear
  - Breakage / Attrition

Growth

- Diffusion limited
- Integration limited
  - Rough growth
  - Surface nucleation
  - Spiral growth
Solubility, nucleation thresholds and metastable zone width

- Primary homogeneous nucleation threshold, HON
- Primary heterogeneous nucleation threshold, HEN
- Secondary nucleation Threshold, SN
- Growth line

Solubility curve

Temperature, $T$

Concentration, $c$

MSZW* for HON

MSZW* for SN

Primary homogeneous nucleation threshold, HON

Primary heterogeneous nucleation threshold, HEN

*Metastable zone width (MSZW)
Secondary nucleation – definition

- Secondary nucleation has been defined as: “nucleation which takes place only because of the prior presence of crystals of the material being crystallised” (so may be another polymorph or chiral compounds).

- Why is it important?
  - Seeded batch crystallization
    - If number of crystals shall be kept constant (growth only), secondary nucleation should be avoided
  - Continuous stirred tank crystallization (MSMPR)
    - Secondary nucleation required for a steady supply of new crystals
    - Secondary nucleation rate has to be controllable, given the process/geometry of the reactor, etc…

Mechanisms of secondary nucleation – tentative classifications

Mechanisms of secondary nucleation – rationalization

Origin of secondary nuclei: parent crystal
→ Mechanically-induced SN mechanisms
Possible situations:
• Parent crystal subjected to collision with impellers or vessel walls
• Parent crystal subjected to collision with others
• Dendrites from growth broken off

Origin of secondary nuclei: solution
→ Surface/fluid-induced SN mechanisms
Possible situations:
• Parent crystal subjected to fluid shear
• Clusters in the bulk nucleate when in contact with the parent crystal surface

Mechanically-induced SN mechanisms – Initial breeding, fragmentation, and attrition

These mechanisms can usually be studied separately from growth, and are only slightly dependent on $S$

- **Initial breeding**: can be reduced by washing
- **Fragmentation**: larger crystals are smashed into fragments due to mechanical collision (e.g. with magnetic stirring bar) and these crystalline fragments appear to be new nuclei
- **Attrition**: small pieces of larger crystals are broken off due to mechanical collisions (e.g., with impeller) and these small crystalline pieces appear to be new nuclei


Mechanically-induced SN mechanisms – Attrition

The same mechanism (attrition) can be described with population balance equations (PBE) in two ways:

1. Breakage rate (daughter distribution), \( B(x) \), + size dependent solubility, \( G(S,x) \).
2. Nucleation rate, \( J_S \), + size independent solubility, \( G(S) \).

\[
B(x) = \int_x^{\infty} b(\eta)g(x, \eta)f(\eta)d\eta \quad J_S = \int_{\eta_{\text{min}}}^{\infty} b(\eta)N_{F,\text{eff}}(S, \eta)f(\eta)d\eta \\
G(S, x) = k_g \left( S - \exp \left( \frac{\alpha}{x} \right) \right) \quad G(S) = k_g (S - 1)
\]
Surface/fluid-induced SN mechanisms

Contact nucleation:
External forces might be enough to “disturb” the clusters on the layer close to the parent crystal and they might evolve into nuclei.

In the example, this mechanism can be used to continuously produce nuclei.

Shear nucleation:
Fluid dynamic forces (shear) can induce clusters to nucleate and can transport them far away from the surface of the parent crystal.

In the example, a Taylor-Couette reactor. The vessel can be operated in laminar conditions, where the velocity gradient (shear) inside the reactor can be analytically calculated.


Secondary nucleation rate – functional dependency

The most general empirical expression for secondary nucleation rate can be written as:

\[ J_S = E_t(\theta)F_1(c)F_2(f) \]

where \( E_t \) and \( F_1 \) are generic functions and \( \theta \) represents the operating conditions (e.g. the stirring rate); \( F_1 \) accounts for the effect of concentration on the secondary nucleation, e.g. through the growth rate; \( F_2 \) is a functional of the particle size distribution, \( f \).

- A generic expression for any mechanism can be:

\[ J_S = K_{n,S}N_i^{j}M_T^{k}S^{h} \]

- A generic one for contact and attrition:

\[ J_S = K_{N}E_{c}f_{c}(c - c^{*})^{b} \]

- A specific one for attrition

\[ J_S = \int_{\eta_{\text{min}}}^{\infty} b(\theta, x)N_{F,\text{eff}}(S, x)f(x) \, dx \]

Enantiomer nucleation

According to the mechanism of secondary nucleation, one enantiomer or the other can be formed:

- mechanically-induced secondary nuclei should be the same as the parent crystal
- Surface/fluid-induced secondary nuclei have the same probability to be right- or left-handed.

Note: (1) “Supercooling” is another way to express supersaturation. (2) Conglomerate forming enantiomers have the same solubility


Secondary nucleation can be used to produce a desired polymorphic forms according to the mechanism.

For example, in the case of Glycine, secondary nuclei are produce by contact nucleation and according to the contact force, different polymorphic form are nucleated.

Note: similar behaviour to enantiomers, but different polymorphic forms have different solubilities.
Continuous crystallization (MSMPR)

Population balance for an MSMPR:

\[
\frac{d(fG)}{dL} + \frac{f}{\tau} = 0
\]

And the solution of the steady state number density distribution is

\[
f = f_0 \exp\left(-\frac{L}{G\tau}\right)
\]

With boundary conditions of

\[
f_0 = \frac{J_S}{G}
\]

Secondary nucleation, \(J_S\), and growth kinetics, \(G\), can be calculated directly from intercept and from the slope of the steady state population, respectively.

Plug flow crystallization / baffle crystallization – the absence of attrition

Reactors without stirrers are used for special applications. In these cases, we would like to avoid, or at least minimize, secondary nucleation, while operating in supersaturated solutions.

In the examples: an Air-Lift crystallizer (left) and an Oscillatory Flow Crystallizer (right).

References

References


