Theory 9

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Martin Christ
Osterode am Harz, Germany

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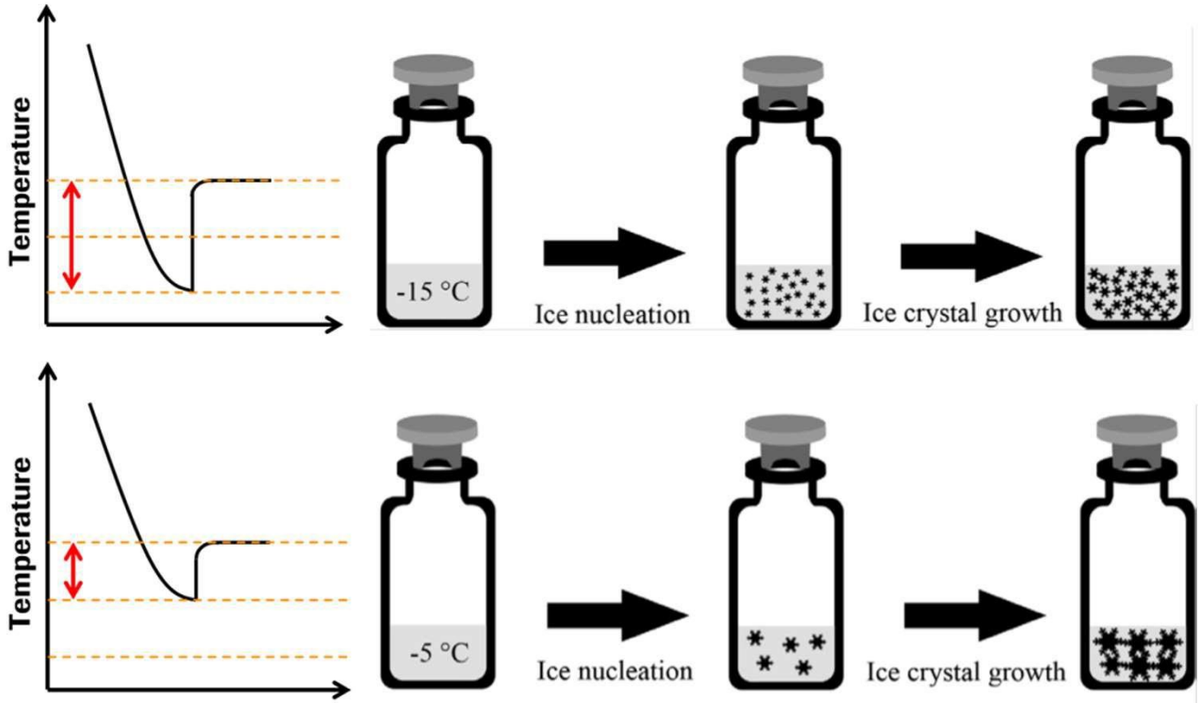
Controlled nucleation - General



Reprinted from: „Controlled ice nucleation in the field of freeze-drying: Fundamentals and technology review". R. Geidobler, G. Winter. 2013. 85(2). Copyright [2013] © Elsevier B.V., its licensors, and contributors

Low degree of supercooling

↓

Big dentritic ice crystals

↓

Product resistance R_p reduced

↓

Drying time reduced

Note:

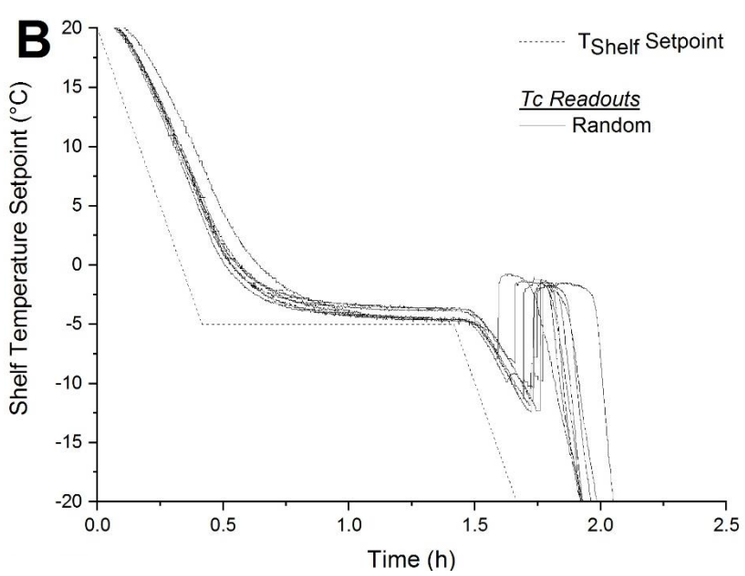
Drivers of the ice crystal size distribution are:

- Ice nucleation temperature[1] (T_N)
  - Aiming for highest technically feasible values
  - e.g., -5 °C to -10 °C
- Post-nucleation hold time[1,2]
  - Hold at -10 °C for 1h to 5h (caution! Prolonged time at freeze concentrated state)

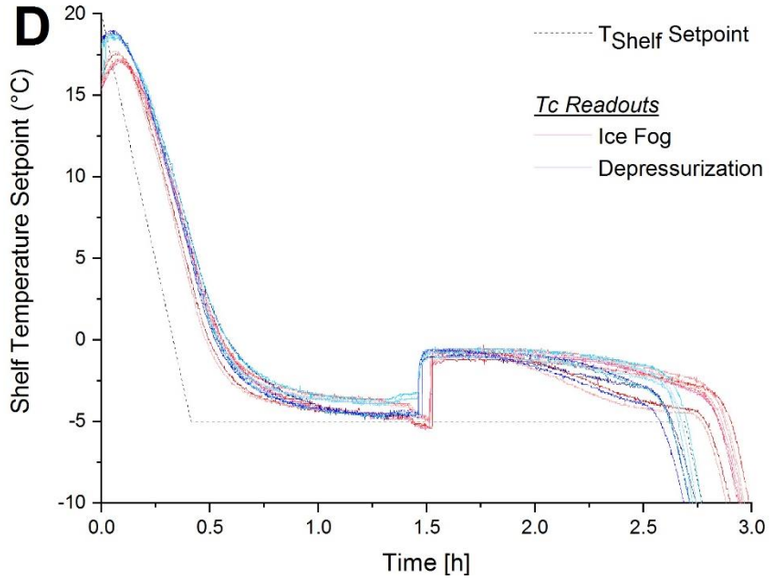
Caution! Different CN technologies (ref. following slides) may have different limitations

1 Oddone, Irene, et al. "Impact of vacuum-induced surface freezing on inter-and intra-vial heterogeneity." European Journal of Pharmaceutics and Biopharmaceutics 103 (2016): 167-178.
2 Wenzel, T., Gieseler, M. & Gieseler, H. Investigation of Two Different Pressure-Based Controlled Ice Nucleation Techniques in Freeze-Drying: The Integral Role of Shelf Temperature After Nucleation in Process Performance and Product Quality. J. Pharm. Sci. 109, 2746–2756 (2020).

Controlled nucleation – Process view



Uncontrolled ice nucleation



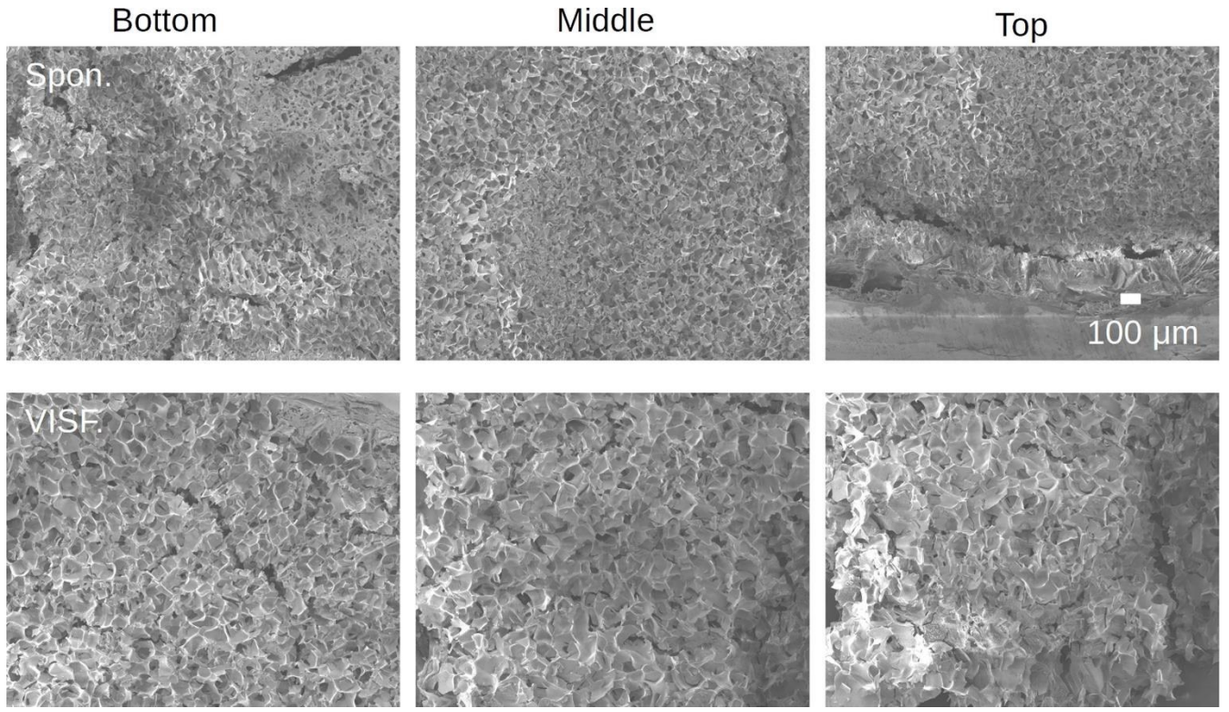
Controlled ice nucleation

Example video of the ControLyo® (= depressurization) technology:
https://youtu.be/_gCBwwTNapQ?si=VTTqnKmmTXluTGbM

Reprinted from: Gitter JH, Geidobler R, Presser I, Winter G. A Comparison of Controlled Ice Nucleation Techniques for Freeze-Drying of a Therapeutic Antibody. *J Pharm Sci*. **2018**;107(11):2748–54. © 2018 American Pharmacists Association®.

Controlled Nucleation – what to expect?

- Reduction in primary drying duration due to reduced R_p because of larger pores/ice crystals [1] (impairs also lower T_p)[2]
- Increases residual moisture content in lyophilizate due to reduced SSA
- Increased intra- and inter-vial product homogeneity[3]
- Adds another element of control and predictability to the FD process (QbD)
- Impact on CQA: controversial

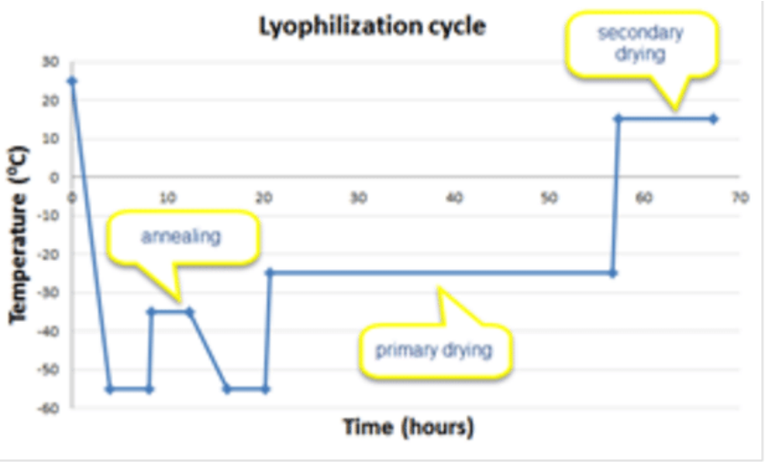


Reprinted: **1** Arsiccio et al. Impact of controlled vacuum induced surface freezing on the freeze drying of human plasma. Int. J. Pharm. 582 (2020), 119290 © 2020 Published by Elsevier B.V.
2 Scutellà et al. Determination of the dried product resistance variability and its influence on the product temperature in pharmaceutical freeze-drying. Eur. J. Pharm. Biopharm. 128 (2018)
3 Arsiccio et al. Vacuum induced surface freezing as an effective method for improved inter- and intra-vial product homogeneity. Eur. J. Pharm. Biopharm. 128 (2018)

Side note: Freezing – Annealing/Thermal treatment

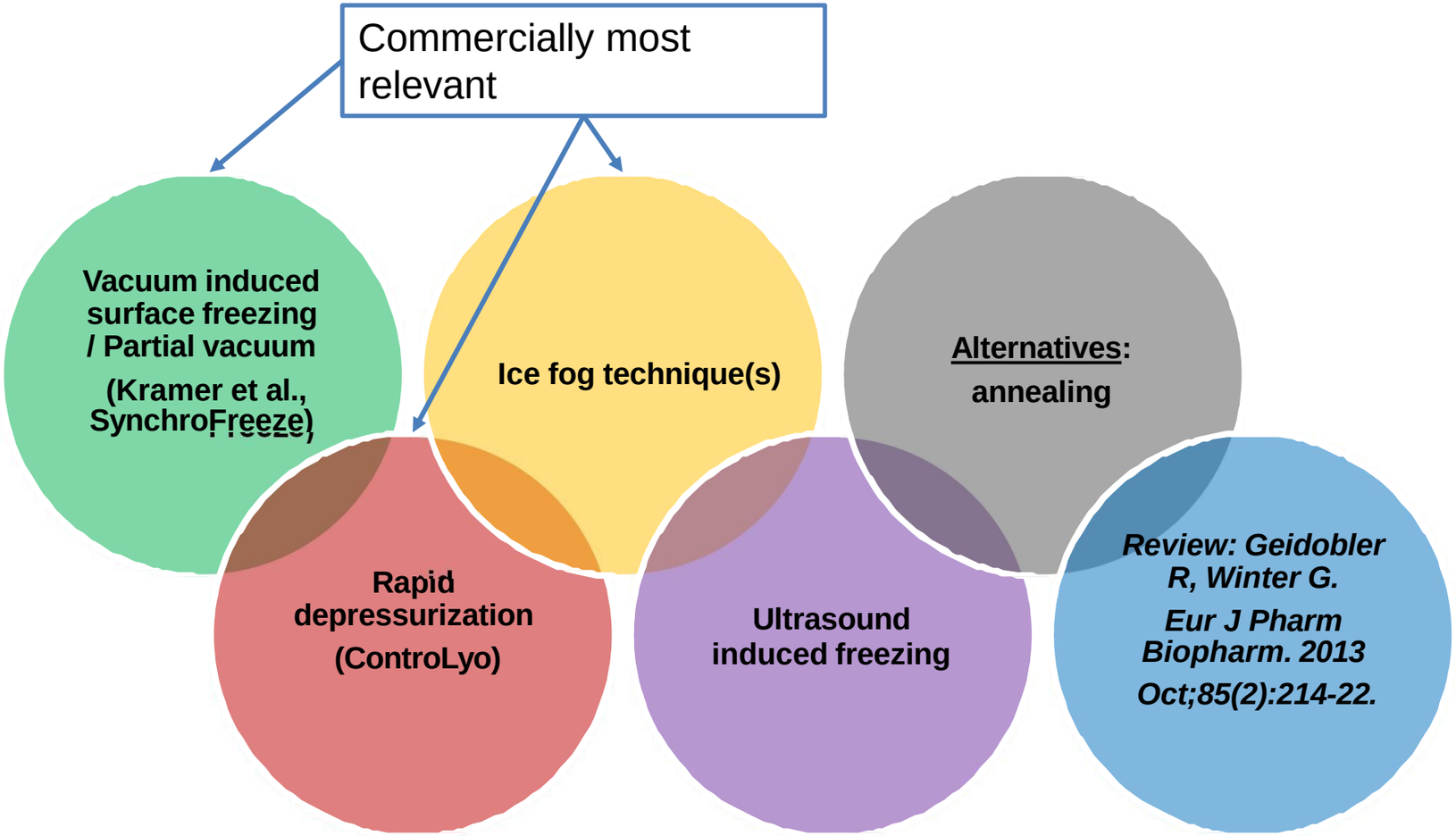
Annealing = hold step at $\mathbf{T_s > T_g'}$ to allow for ice crystal growth and/or (complete) crystallization of crystallizing formulation components

- Mainly used in formulations with crystalline bulking agents (e.g., Mannitol or Glycine)
- Allows for crystallization of potentially crystalline excipients in the freezing step and prevents crystallization during (primary) drying and has been shown to increase chemical stability
- Only partial crystallization of potentially crystalline excipients may impair product stability after lyo
- But also used for amorphous formulations to reduce product resistance Rp to eventually shorten primary drying
- Literature recommendation (Tang, Pikal, Pharm. Res., 2004):
  - Apply regular freezing procedure
  - Allow for complete solidifaction by hold times of 1-2h
  - Bring product temperature to 10 °C – 20 °C above T_g', but well below T_{eu}, e.g., to -10 to -15 °C for 3-5h
  - Allow for complete solidifcation afterwards again before starting with primary drying



Annealing in amorphous formulations:
Luthra SA, Hodge IM, Pikal MJ. Investigation of the Impact of Annealing on Global Molecular Mobility in Glasses: Optimization for Stabilization of Amorphous Pharmaceuticals. J Pharm Sci. 2008;97(9):3865–82.
T. Kharatyan et al. Quantitative Analysis of Glassy Relaxation and Ostwald Ripening during Annealing Using Freeze-Drying Microscopy. Pharmaceutics. 2022;14(6), 1176.

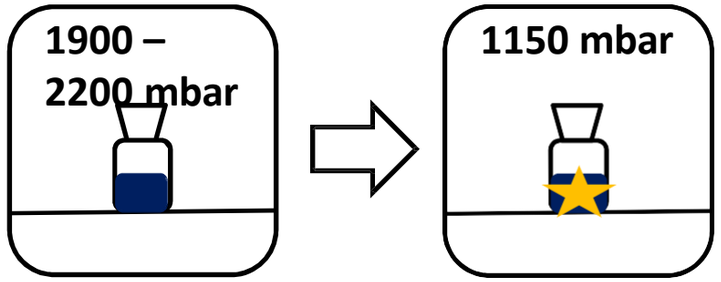
Controlled Nucleation - Methods



Controlled Nucleation – Commercialized Methods

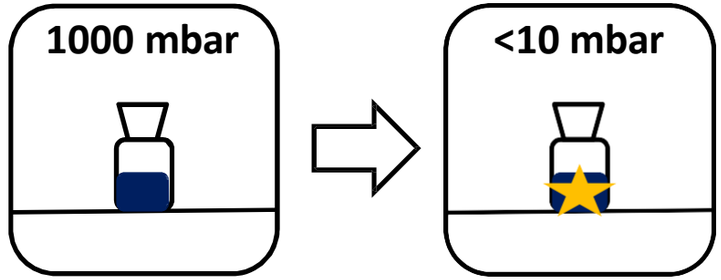
Depressurization

ATS Scientific Products ControLyo®



Partial Vacuum (VISF)

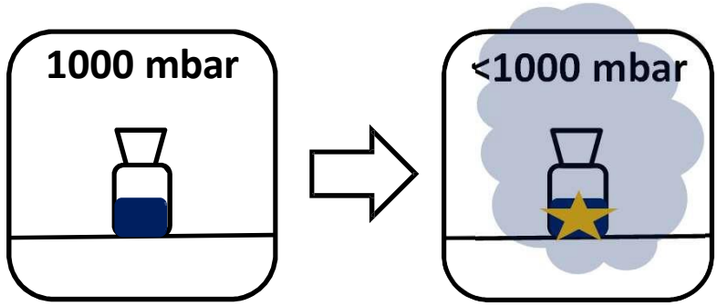
HOF SynchroFreeze™



Ice Fog

Linde/IMA VERISEQ®, Martin

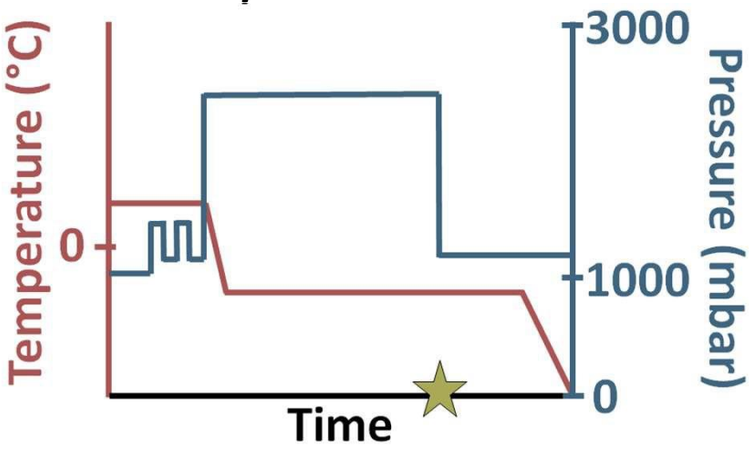
Christ LyoCoN, Millrock



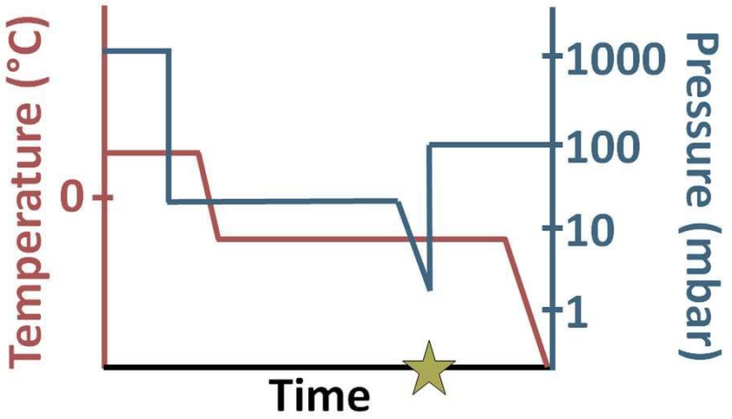
FreezeBooster®, GEA LYOSPARK®,…

Controlled Nucleation – Modes of operation

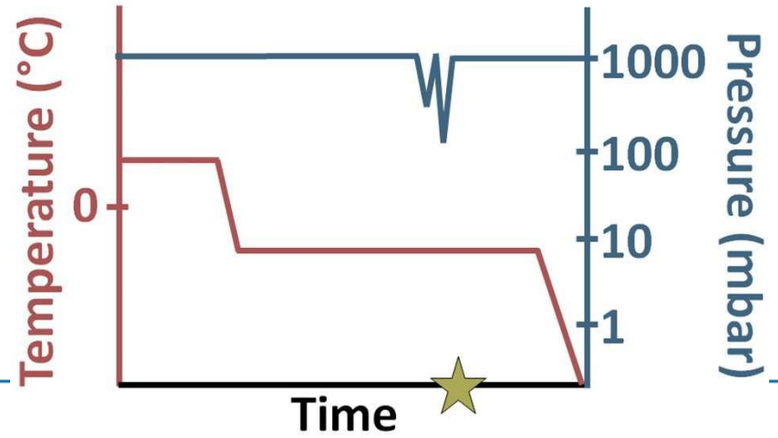
Depressurization



Partial Vacuum



Ice Fog



Nucleation event

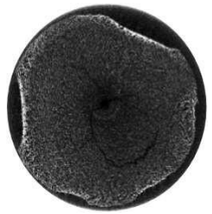
Controlled Nucleation - Limitations

Several publications investigated the Comparability and Limitations of CN methods

Findings from J. Luoma, A. Allmendinger et al., Processes, 2020, 8(11), 1439 are summarized in the following:

- Robustness testing for formulation and vial configuration revealed
  - Depressurization method struggled with 2cc vials
  - Partial vacuum method struggled with formulation with very high total solid content

- Nucleation at the same temperature resulted in comparable solid state properties like residual moisture and specific surface area, which directly relates to stability behavior dependent on the molecule studied



- Specific example showed that macroscopic structure (top layer) may be different between nucleation techniques, which may impact drying behavior, and is currently further studied

Controlled Nucleation - Take-home message

- Each technology has limitations
  - Depending on vial format and formulation you may need to nucleate at lower temperatures to ensure robust nucleation, which triggers formulation and configuration dependent process development
  - If operating conditions result in microcollapse, comparability between material produced with the different CIN technologies is not guaranteed
- Each technology has different installation and operation requirements like availability, location and size of ports or availability of liquid nitrogen
- If you are working in R&D, always keep the aspect of scalability in mind when developing a process with CN