Supplementary material

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Freeze-drying in practice

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How to determine the reconstitution volume?

Note: Reconstitution volume ≠ Filling volume (solid content needs to be considered)

Two practical approaches:

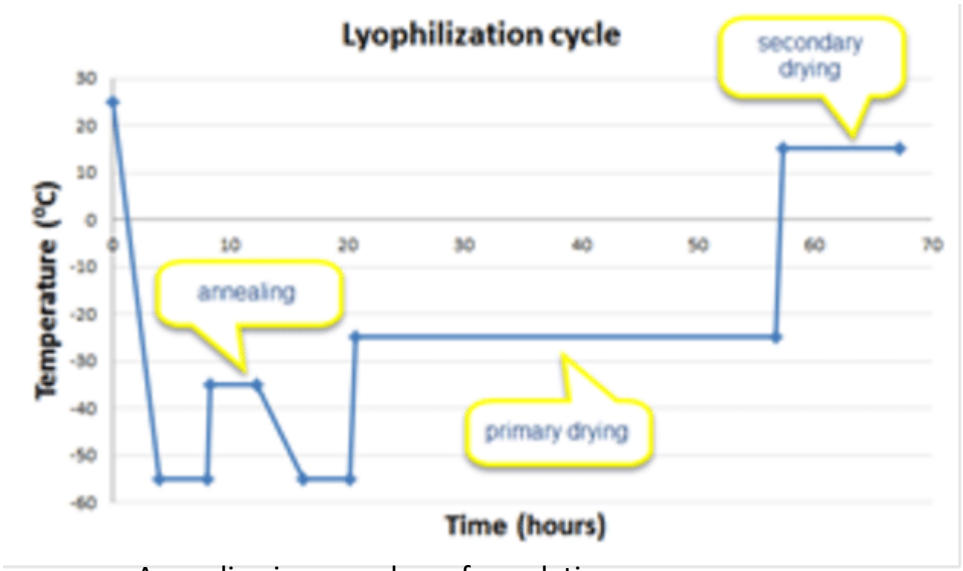
1. Measuring the loss on drying during freeze-drying
   - Weigh selected filled and semi-stoppered vials before and after freeze-drying
   - Mass difference can be accounted to water loss on drying
   - Mass loss can be converted to the reconstitution volume by division by density of water

2. Calculate the total amount of water that could be lost on drying
   - Determine the density of your formulated solution to be freeze-dried
   - Calculate the exact total solid content based on composition
   - Calculate the theoretically filled mass (by multiplication with formulation density)
   - Substract the total solid content from the theoretically filled mass
   - Calculated mass difference can be converted to the reconstitution volume by division by density of water

Freezing – Annealing/Thermal treatment

Annealing = hold step at **$T_s > T_g$‘** to allow for (complete) crystallization of potentially crystalline 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
- 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}
  - Allow for complete solidifcation afterwards again before starting with primary drying
    - Example annealing step for Mannitol/Glycine: T_s = - 20 °C for >= 2h



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.

Literature recommendation for design of DSC mesaurements: Pansare SK, Patel SM. Practical Considerations for Determination of Glass Transition Temperature of a Maximally Freeze Concentrated Solution. AAPS PharmSciTech. 2016;17(4):805–19.

Lyo cake appearance I

Typical cake defects

- **Collapse / Meltback:**
  - Collapse: Viscous flow resulting in loss of microstructure established by the freezing process
  - Meltback: poorly defined term mostly referring to melting of frozen matrix or collapse

Figure 1. Collapsed cake: total collapse (left) and partial collapse (center). The vial on the right shows no evidence of collapse.

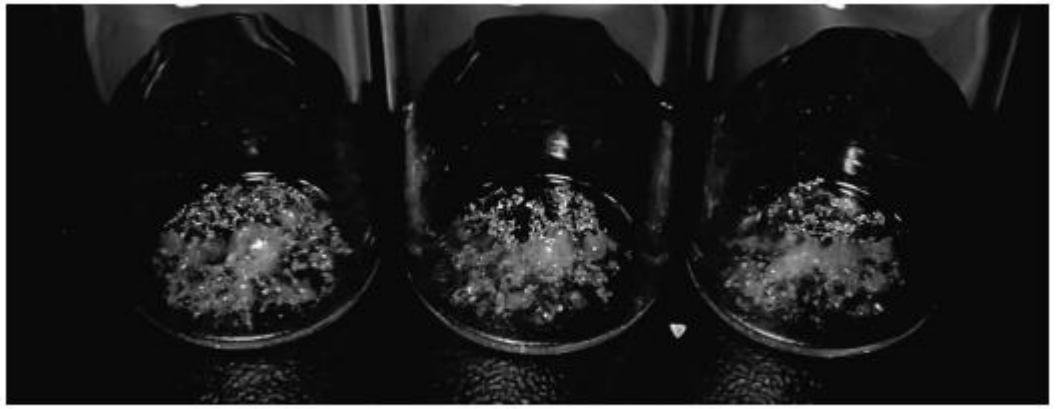


Figure 3. Meltback: could also be a form of collapsed cake.

Literature recommendation: Patel SM, Nail SL, Pikal MJ, Geidobler R, Winter G, Hawe A, et al. Lyophilized Drug Product Cake Appearance: What Is Acceptable? J Pharm Sci. 2017;106(7):1706–21.

Lyo cake appearance II

Typical cake defects

- **Lifted cake**
  - Potentially takes place during primary drying
  - May be caused by separation of the cake from the inner vial wall → low resistance path for water flow relative to flow through the partially dried solids

Figure 8. Lifted cake.

- **Cake shrinkage & cracked cake**
  - May be related to amount of unfrozen water in amorphous matrix
  - Unfrozen water content removed during (secondary) drying
  - Causes stress to build up in the cake due to volume contraction
  - Release of stress either by cake contraction or cracking

Figure 9. Cake shrinkage: this shrinkage is not associated with collapse.

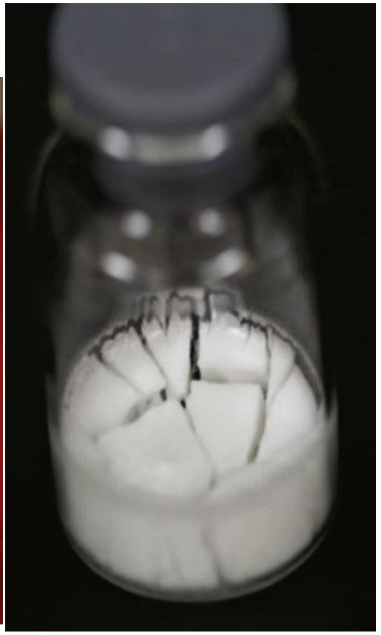


Figure 10. Cracked cake.

Literature recommendation: Patel SM, Nail SL, Pikal MJ, Geidobler R, Winter G, Hawe A, et al. Lyophilized Drug Product Cake Appearance: What Is Acceptable? J Pharm Sci. 2017;106(7):1706–21.

Lyo cake appearance III

Typical cake defects

- **Bubble/Foam formation**

Literature recommendation: Patel SM, Nail SL, Pikal MJ, Geidobler R, Winter G, Hawe A, et al. Lyophilized Drug Product Cake Appearance: What Is Acceptable? J Pharm Sci. 2017;106(7):1706–21.