Current State of Scale-up in Freeze Drying:
Possibilities and Limitations

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The Concept of Freeze Drying

A General Introduction
What is "freeze drying“ ("lyophilization“)?

A (gentle) drying procedure to preserve delicate products where the solvent (water) is converted by freezing into the solid state (i.e. ice) and subsequently removed by sublimation using a high vacuum.

Why do people freeze dry? Multiple reasons, a few examples…

⇒ Solvents can impact (chemical) stability of the API.
⇒ Liquid dispersions, e.g. nanosuspensions, can show physical instabilities.

Advantages of freeze drying / a freeze dried product (examples):

⇒ Results in highly porous cake: original product (solution) can rapidly and completely be retained by adding the solvent ("reconstitution").
⇒ Improved chemical and physical stability of product → prolonged shelf life.

Disadvantages of freeze drying processes (examples):

⇒ Batch process: only a given number of vials per batch can be manufactured = limited production capabilities.
⇒ Expensive drying technology and time consuming process.
Basic requirements for freeze drying:

- **STEP 1**: Complete SOLIDIFICATION of the product by freezing
- **STEP 2**: Application of a VACUUM
- **STEP 3**: (Controlled) SUPPLY OF HEAT to the product
- **STEP 4**: Removal of water vapor from the atmosphere by DESUBLIMATION (deposition)
General Introduction 3

- General design of a freeze dryer (schematic):

1. Drying Chamber
2. Isolation Valve
3. Condenser
4. Differential Pressure Gauge
5. Shelf
6. Vent Valve
7. Door
Scale-up of Freeze Drying Cycles

What are Relevant Scales?
LABORATORY scale equipment:

- Corresponds to a total shelf area of about 0.1 m\(^2\) to 0.5 m\(^2\) (varies between US and EU).
- Equipment used for freeze drying of small amounts of material / limited numbers of vials (i.e. 50-1000 depending on vial size), development batches.
- Drying chamber and condenser can be designed SEPERATELY or COMBINED.
- The shelves can be heated and cooled, in some cases ONLY heated.
  - Desired: freezing of the product on the shelf by applying a controlled cooling rate.
  - Not desired: external freezing (uncontrolled) prior to loading.

Great differences in the pressure gauges:

- Capacitance Manometer (CM): expensive.
- Pirani gauge: standard.
- Thermocouple vacuum gauges: cheap, performance does not match a Pirani.

High radiation effects, doors usually consist of acrylic glass.

- Cheaper, lower equipment cost.
- Lightweight.
- Allows a user to "look" at the product.
Relevant Scales in Freeze Drying 2

- LABORATORY scale equipment (continued):

- **Very Simple Products**
  - NO SCALE-UP

- **High-End Developments**
  - SCALE-UP
Relevant Scales in Freeze Drying 3

- **PILOT scale equipment:**
  - Typical shelf area 0.5 m² to 5.0 m².
  - Frequently used for stability batches and material for clinical testing.
  - Used as an intermediate for cycle transfer to manufacturing scale.
  - Drying chamber and condenser are usually separate (EU).
  - Two design features are used (EU):
    - *Chamber and condenser connected by a spool piece.*
    - *Chamber “sits” on condenser (no spool).*
  - Shelves are always temperature-controlled.
  - Capacitance manometer (CM) for pressure control, at least in more recent equipment!
  - Radiation and atypical heat transfer effects are reduced.
  - Cleaning in Place (CIP) and Sterilization in Place (SIP).
  - Possibility for good instrumentation and accurate process monitoring, but often limited due to GMP environment.
Relevant Scales in Freeze Drying 4

- PILOT scale equipment (continued):

![Sample Thief](Image)

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Relevant Scales in Freeze Drying 5

- MANUFACTURING scale equipment:
  - Shelf area up to 50 m², 100,000 or more vials.
  - Drying chamber and condenser are separate, often stand-alone units. Distinguish between:
    - **Horizontal** design.
    - **Vertical** design.
  - Several powerful vacuum pumps.
  - Mostly plate condensers with high ice capacity.
  - CIP and SIP are standard.
  - More and more common: **automatic loading systems** without interaction by the user.
  - Few possibilities for process monitoring and optimization of cycle conditions due to conservative use of PAT and problems with integration of sensors in a sterile environment.
    - Sometimes, no process monitoring tools at all!
Principles of Scale-up

General Considerations & Sources of Variability
Points to consider:

⇒ The most important critical product parameter is the **product temperature at the ice sublimation interface**, \( T_p \).

⇒ The "**product temperature over time profile**" must be scaled / maintained during transfer of freeze drying cycles. \( T_p \) can only be **indirectly adjusted** by:
  • Adaptation of the "**shelf (inlet) temperature**".
  • Adaptation of the “**chamber pressure**”.

⇒ The **influence of process- and equipment-related differences** needs to be evaluated and compensated.

⇒ **Laboratory, pilot and manufacturing freeze dryers** need to be characterized as accurately as possible to derive relevant **differences**. Such differences / limitations must already be considered during cycle development in the laboratory (Design Space).

⇒ The **product** should be the **limiting factor** for the optimal process conditions, **NOT** the freeze dryer.

⇒ The **robustness of a cycle** should be characterized by “robustness testing“ protocols in laboratory to **assess of consequences of cycle deviations**.
Possible sources of variability:

- Different heat transfer ($dQ/dt$) from the shelves to the product.
- Shelf temperature variability due to differences in mass flow rate.
- Different design of the shelves with regard to:
  - Thickness of the stainless steel.
  - Fluid flow direction and/or distribution.
- Changes in the "edge-to-center-vial" ratio.
- Changes in the vial heat transfer coefficient ($K_v$).
- Reduced heat transfer by radiation in pilot/production equipment. Note:
  - Laboratory equipment: acrylic doors.
  - Pilot/manufacturing: polished stainless steel.
- Differences in mass transfer of the batch in primary drying due to differences in the freeze dryer design and setup:
  - Differences in length/diameter of the spool (duct) between chamber and condenser.
  - Different types and positions of isolation valves.
  - Condenser temperature, condenser design and condenser capacity.
Possible sources of variability (continued):

⇒ Increase in product resistance ($R_p$) caused by different freezing behavior:
  - Controlled vs. uncontrolled nucleation.
  - Differences in freezing affects both primary and secondary drying performance!

⇒ Variations in process control systems in different freeze dryers:
  - Temperature control (thermocouples in the laboratory, resistance temperature detectors or nothing in production).
  - Pressure gauges and their corresponding location.
  - Comparative pressure measurements, innovative PAT.
Possibilities and Limitations in the Assessment of Critical Parameters for Scale-up

Example #1: Heat Transfer by Radiation
Radiation effects impose batch heterogeneity:

- Heat flow into the product is a function of direct conduction (A), gas conduction (B) and radiative heat transfer (C).

- Radiation from chamber door and walls leads to atypical heat transfer to the product = "edge" vials dry (much) faster and at (much) higher temperatures.

- Heterogeneity between edge and center vials is more pronounced in laboratory scale than in manufacturing scale freeze dryers:
  - Number of edge vials reduced due to shelf size.
  - Atypical radiation effects are reduced due to polished stainless steel environment.
Estimation of radiation effects by emissivity measurements:

- The extent of heat emission per time is dependent on the temperature and the emissivity of the surface (Stefan-Boltzmann Equation):

\[
\frac{dQ_r}{dt} = A_v \varepsilon (T_2^4 - T_1^4)
\]

- Effects of atypical radiation are more significant at high temperature gradients between cold vials and warm chamber door or walls.

- Emissivity is dependent on the surface characteristics:
  - Glass, acrylic door, etc. (ca. 0.95).
  - Stainless steel (ca. 0.2 for polished, ca. 0.6 for unpolished surface).

- Emissivity of chamber walls and door of freeze dryers can be measured by wireless handheld infrared thermometers.
Possibilities and Limitations in the Assessment of Critical Parameters for Scale-up

Example #2: Freeze Dryer Performance Testing (Under Load)
Sublimation test protocols using pure water:

- Evaluation of the “load capacity of the freeze dryer” (sublimation tests with water in bottomless trays with a thin plastic foil between ice and shelves).

Example for a sublimation test in TRAYS:

- Fill plastic-lined tray (garbage bag) with water (e.g. 1 cm fill depth).
- Freeze to -40°C; apply vacuum and vary shelf temperature and chamber pressure for simulation of various mass flow rates.

Example for a sublimation test in VIALS:

- Use desired vial system, 1 shelf load, ca. 50% fill with pure water, weigh each single vial, leave outermost row of vials empty (dummy vials for radiation shielding).
- Use thermocouples in selected vials.
- Freeze to -40°C; apply vacuum and ramp fast (1°C/min) to target temperature (e.g. -10°C).
- Wait until ca. 30% to 50% of the total mass have been removed.
Performance Tests (Under Load) 2

- Sublimation test protocols using pure water:

  Example for a sublimation test in VIALS (continued):
  - Re-weigh vials and calculate mass difference and mass flow over time.
  - Use calculated $\frac{dm}{dt}$ and steady state heat and mass transfer equations to predict $K_v$.

  $$\frac{dm}{dt} = A_v \cdot K_v \cdot (T_s - T_b)$$

  ⇒ Determination of the minimum obtainable chamber pressure and the minimum required condenser temperature for various sublimation rates.
  ⇒ Indications for “CHOKED FLOW“, i.e. limitations of mass transfer through the spool piece between drying chamber and condenser.
  ⇒ Accuracy of the shelf fluid control and differences regarding shelf surface temperature, especially at high mass flow rates and fast ramp rates (relevant for crystalline formulations).
  ⇒ Indications for a possible condenser overload situation.
  ⇒ Results from operational qualification (lab and pilot / production) should be (ideally) available prior to the development of the freeze drying cycle.
Sublimation tests, case studies:

⇒ Example of sublimation tests in TRAYS to evaluate the system performance of a laboratory and pilot scale freeze dryer (0.5 m² Lyostar II vs. 3.3 m² Lyomax 3).

<table>
<thead>
<tr>
<th>run #</th>
<th>product</th>
<th># of trays</th>
<th>$T_{shelf}$ setpoint ($1^{st}/2^{nd}$ drying)</th>
<th>$P_c$ setpoint</th>
<th>$1^{st}/2^{nd}$ drying time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pure water</td>
<td>3’ / 4’</td>
<td>0°C</td>
<td>100 mTorr</td>
<td>3 hrs</td>
</tr>
<tr>
<td>2</td>
<td>pure water</td>
<td>3’ / 4’</td>
<td>20°C</td>
<td>150 mTorr</td>
<td>3 hrs</td>
</tr>
<tr>
<td>3</td>
<td>pure water</td>
<td>3’ / 4’</td>
<td>40°C</td>
<td>200 mTorr</td>
<td>3 hrs</td>
</tr>
<tr>
<td>4</td>
<td>pure water</td>
<td>3’ / 4’</td>
<td>40°C / 40°C</td>
<td>500 mTorr</td>
<td>3 hrs</td>
</tr>
<tr>
<td>5</td>
<td>mannitol 5%</td>
<td>3’ / 4’</td>
<td>20°C / 40°C</td>
<td>150 mTorr</td>
<td>33 hrs / 5 hrs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>run #</th>
<th>avg. velocity</th>
<th>avg. velocity</th>
<th>avg. mass flux</th>
<th>avg. mass flux</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lyostar II</td>
<td>Lyomax 3</td>
<td>Lyostar II</td>
<td>Lyomax 3</td>
</tr>
<tr>
<td>1</td>
<td>110 m/sec</td>
<td>32 m/sec</td>
<td>0.56 kg hr⁻¹ m⁻²</td>
<td>0.68 kg hr⁻¹ m⁻²</td>
</tr>
<tr>
<td>2</td>
<td>108 m/sec</td>
<td>41 m/sec</td>
<td>1.17 kg hr⁻¹ m⁻²</td>
<td>1.29 kg hr⁻¹ m⁻²</td>
</tr>
<tr>
<td>3</td>
<td>105 m/sec</td>
<td>79 m/sec</td>
<td>1.31 kg hr⁻¹ m⁻²</td>
<td>1.55 kg hr⁻¹ m⁻²</td>
</tr>
<tr>
<td>4</td>
<td>51 m/sec</td>
<td>24 m/sec</td>
<td>1.34 kg hr⁻¹ m⁻²</td>
<td>2.00 kg hr⁻¹ m⁻²</td>
</tr>
</tbody>
</table>

*: pseudo steady state not fully accomplished

Performance Tests (Under Load) 4

- Sublimation tests, case studies (continued):
  - Example of VIAL sublimation tests (SGD EasyLyo vial, $P_c$: 50 mTorr, $T_s$: -5°C).

Sublimation tests, literature example. Development of “choked flow”:

⇒ Choked flow situation, 0.5 m² Lyostar II, laboratory scale freeze dryer.

Possibilities and Limitations in the Assessment of Critical Parameters for Scale-up

Example #3: Shelf Temperature Control
Beware of differences in the course of the fluid flow!

- Course and direction of the heat transfer fluid transport through the shelf and the thickness of the steel layer can change between different scales.

- The fluid temperature across the shelf and the temperature difference between fluid and shelf surface can vary significantly. Measurements under load conditions are imperative for operational qualification.

Simple and informative - Shelf temperature mapping:

- Attachment of insulated adhesive thermocouples at different positions of the shelf surface and determination of the temperature difference between heat transfer fluid and shelf surface. If possible, at different load conditions (e.g. various cooling rates, amounts of product, etc.).

- Example (cf. schematic): temperature gradient between fluid inlet temperature and shelf surface temperature during fastest possible cooling without load (!):

Shelf mapping experiments are integral in any scale of equipment!

Possibilities and Limitations in the Assessment of Critical Parameters for Scale-up

Example #4: Differences in Product Freezing
Differences in Product Freezing

The obstacle of different product freezing:

⇒ Typically, higher extent of supercooling under GMP conditions = more and smaller ice crystals are formed upon nucleation:
  • Smaller pores = elevated product resistance ($R_p$).
  • Elevated $R_p$ = higher product temperature during primary drying.
⇒ Supercooling in the laboratory: ca. -10°C to -15°C.
⇒ Supercooling in manufacturing: ca. -20°C to < -40°C.
⇒ The extent of supercooling might be evaluated by using:
  • Thermal probes, attached to the outer side of the vial (laboratory scale).
  • SEM, SSA, embedment of cake in polymer (laboratory and manufacturing scale).
  • Video capture of freezing (lab and manufacturing).
⇒ Variations in nucleation temperatures can be compensated by:
  • Annealing (limited efficiency).
  • Laboratory experiments in a GMP environment (impractical).
  • Controlled nucleation techniques.
Possibilities and Limitations in the Assessment of Critical Parameters for Scale-up

Example #5: Condenser Performance & Pressure Gauges
Condenser Performance & Pressure Gauges

Condenser type, capacity and performance:

⇒ Types of condenser: PLATE or COIL.
⇒ Minimum achievable condenser temperature: typically -70°C to -85°C.
⇒ The condenser must be able to desublime and distribute large amounts of ice in a short time interval, especially in manufacturing scale. If condenser performance is insufficient:
  • *Condenser overload* situation (temperature of the condenser increases to ≥ -40°C).
    ❖ Loss of pressure control in the chamber.
  • *Condenser capacity limitation* (uneven distribution of ice).
    ❖ Ice growth towards spool, restriction of mass flow rate.

A sometimes neglected factor - The type of pressure gauge:

⇒ Types: Capacitance Manometer, Pirani, Thermocouple Vacuum Gauge.
⇒ Many laboratory and some manufacturing dryers use *Pirani pressure sensors* to control chamber pressure = correction to absolute pressure necessary.
⇒ *Commercial dryers are programmed for larger pressure tolerances* to accommodate possible deviations during manufacturing (ca. ± 20mTorr).
Use of Partial Loads and Placebo During Scale-up

Introducing “Home Made” Problems...
Partial Loads

- **Definition:**
  Use of a reduced number of vials, either by using only few shelves or by using only a part of the total area of each shelf.

- **Partial loads - Where most (economically) relevant?**
  - In practice, mostly applied in lab scale!
  - Relevance: scale-up from pilot scale to manufacturing scale.

- **What is the benefit of partial loads?**
  - Reduced financial risk, along with limited availability of (expensive) API.

- **The biggest problem(s):**
  - Use of the results of runs with partial loads for the evaluation of freeze dryer performance is LIMITED, specifically when partially loading a shelf:
    - Smaller "cooling effect" of the shelf fluid by sublimation might result in higher drying rates (relative to a full load).
    - Beware of a lack of sensitivity in endpoint detection (premature endpoint detection).
  - Positioning of the partial load must be carefully chosen!
Placebo

- Implementation of placebo
  - Runs with full or partial loads of a placebo formulation can be employed for qualification, scale-up and technical batches.
  - For scale-up, a full load with a placebo formulation or with a mixture of placebo and API product vials can be performed.

- Placebo characteristics
  - The placebo used should have the identical formulation composition, except that the API has been replaced by a model substance. Ideally, the placebo formulation has similar physicochemical characteristics (crystallization, collapse temperature, etc.).
  - Use of a placebo formulation is helpful for formulations with LOW drug content, but becomes dramatically complex for a HIGH drug load.
    - For high concentrated protein formulations, the API (protein) is typically exchanged by a sample protein (e.g. BSA, HSA).
    - Thermal analysis by DSC and Freeze Dry Microscopy might reveal similar or overlapping results for the critical formulation temperature.
    - Beware of viscosity and water re-adsorption differences between API and model.
  - Caution: placebo tends to dry at different mass flow rates!
The Value of Having PAT Tools in Place

From Laboratory to Production…
Example: Scale-up from 0.5 m² to 20 m² using enhanced PAT tools.
Example: Scale-up from 0.5 m² to 20 m² using enhanced PAT tools.
Summary & Conclusion
Summary & Conclusion

- Scale-up of freeze drying cycles requires the following considerations:

  ⇒ Exact characterization of the freeze dryers used on different scales and relevant process parameters is essential to resolve scale-up issues and to shorten scale-up times.

  ⇒ The process should be limited by the characteristics of the formulation, i.e. the collapse temperature. The process should not be limited by the freeze dryer on the specific scale.

  ⇒ Variations and alterations of the product due to changes of atypical radiation, supercooling and other parameters need to be avoided by adaption of the process conditions.

  ⇒ Experiments with partial loads or well characterized placebo formulations may save time and money IF the experiments have a sound scientific basis.

  ⇒ Robustness testing and determination of a Design Space during the development phase seems beneficial for subsequent adjustments and optimization on manufacturing scale.

  ⇒ Information which is collected in the laboratory should be scaled to manufacturing by using at least one PAT tool which can be applied in manufacturing scale!