APPLICATION NOTE

Freeze Drying – Shelf Temperature Mapping

Validation & Monitoring Solutions

Pharmaceutical
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Why is Shelf Temperature Mapping Important?

Control of the shelf temperature is a primary process parameter and critical system function that has a direct impact on the quality of the product. Ensuring uniform temperature distribution across freeze dryer loading shelves, ensures consistent drying rates for all products. It is therefore crucial to adjust the sample's heat input to ensure a safe and optimal process temperature throughout the entire cycle.

Ensure Product Quality

In general, a sample temperature that is too high will ultimately result in a melt back – and low temperatures could unnecessarily prolong the process, resulting in wasted time and funds. In other words: the correct shelf heating can tremendously speed up the process, whereas even the slightest bit of overheating can destroy the product.

In this application note, we will present the guidelines and norms applicable for the shelf mapping of freeze dryers used for aseptic processing of health care products – as well as our own process recommendations to provide the best possible result.

Norms and Guidelines

The **ISO 13408-3 Norm** (Aseptic processing of health care products – Part 3: Lyophilization) describes in paragraph 8.4.11 how Shelf Temperature Distribution should be conducted:

- Shelf temperature distribution studies shall be performed to identify inter- and intra-shelf variations and shall demonstrate conformance to the specification
  - Ideally these studies should be performed with the chamber at atmospheric pressure and include a range of temperatures that take into account both the heating and cooling phases of the lyophilization cycle
- The number of temperature sensors used shall be specified

This norm does not provide a very precise description of the procedure and has already raised questions among freeze dryer operators and QA departments.

Shelf Temperature Mapping Challenges

Measuring surface temperature while a freeze dryer is operating is not exactly a walk in the park. Due to the high vacuum, you will discover high thermal resistance where most of the energy is transmitted by radiation, and close to none by convection. This makes the use of conventional contact sensors problematic unless they are designed specifically for that purpose.

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Recommended Measuring Equipment Requirements

- Non-conductive, minimally invasive, non-self-heating and flexible sensors with a single point measuring tip that can be in direct contact with the surface
- The temperature sensors should ideally be connected to wireless data loggers, as feeding the inside of the chamber with sensors from the outside using a traditional thermocouple system, may jeopardize the integrity of the vacuum sealed chamber
- The ideal wireless data logger system should use small, replaceable thermocouple sensors that provide direct contact with the shelf surface. This ensures good thermal contact and heat transfer, with minimal impact on the measurements
- The wireless data logger design should be small and ideally match the vials in both height and diameter. This would make it ideal for systems with automatic vial loading and unloading – which are commonly used during the manufacturing of pharmaceuticals
- The wireless data loggers must be able to operate within the temperature range of -60 to +60 °C and at pressures as low as 0.001hPa
- The wireless data loggers must be capable of working completely unattended for several days to cover the typical length of freeze-drying cycles – while also measuring, storing and displaying data in real time
- The wireless data loggers should ideally be able to measure both sample temperature as well as shelf temperature

How to Perform Shelf Temperature Mapping Correctly

Upon looking back at the ISO 13408-3 Norm, it becomes clear that it only provides little information on how to arrange your shelf mapping study. Therefore, we have conducted our own study to determine the Standard Operation Procedures (SOP'S) and best practices by asking operators and QA staff for their recommended approach.

We split our survey into 5 groups:

- **Measurement Distribution Pattern**
  - Number of measuring points and their positions on each shelf – and number of shelves
- **Shelf Loading Conditions**
  - Measurements on loaded shelves – or empty shelves
- **Chamber Conditions**
  - Measurements at Ambient Pressure – or under Vacuum
- **Temperature Range**
  - Fixed Temperature – or the range of the entire process
- **Temperature Accuracy**
  - Measuring Real Shelf Temperature – or Relative (and reproduceable) Temperature

Looking at the results, it was clear that there are many individual approaches, from minimal overviews to quite advanced theoretical considerations.

From the survey, we were able to make the following conclusions:

- An entire shelf mapping process includes both ambient pressure and vacuum
- The typical temperature range is between -60 and +60 °C
- Products are placed on all shelves and occupy the complete shelf area
- Measuring real-time temperature is critical to find the maximum sublimation rate and avoid melt back

Based on this knowledge and the findings from our study, we have the following recommendations:

- There should be 5 measuring points per shelf – one in each corner and one in the center
- Measurements should take place on all shelves to allow you to measure the actual conditions and fully assess the safety margin for the complete load
- Measurements should take place on fully loaded (alternatively using a placebo product) as well as empty

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shelves. This is important because both scenarios provide vital information on how shelf configurations perform with and without a load
- While measuring, the chamber should be at ambient pressure during cooling phase temperatures – and under vacuum during heating phase temperatures. This is to reflect exactly how the freeze dryer is used in practice
- The shelf temperature settings during shelf mapping of the cooling phase should cover or exceed the entire range. All the way from ambient temperature down to the lowest freezing point (well below the Eutectic point) – for example, in decrements of 20 °C
- The shelf temperature settings during shelf mapping of the heating phase should similarly cover or exceed the entire range. All the way from the lowest freezing point to the highest acceptable temperature during secondary drying – for example, in increments of 20 °C
- Shelf temperature should be measured with the highest possible accuracy. This is crucial to steer the product towards optimal temperatures for fast sublimation while also ensuring the safety of the batch

Shelf Temperature Mapping Done Right – Example

For a pharmaceutical company that freeze dries a product in vials with:
- A freeze dryer with 10 shelves
- A collapse temperature of -15 °C
- A maximum allowed shelf temperature during secondary drying is +35 °C

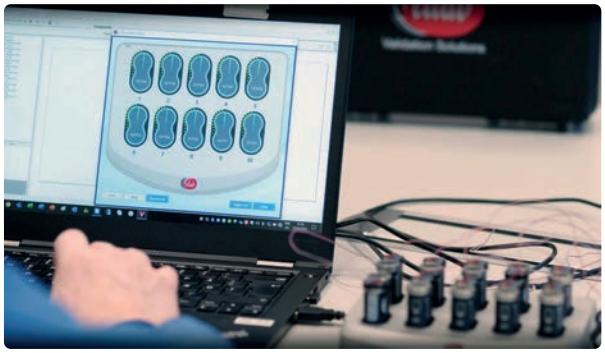
The shelf mapping steps would be the following:
- 50 loggers (10 x 5) measuring shelf temperature in all 4 corners and the center of all 10 shelves at +25 (ambient), 0 and -20 °C using atmospheric (ambient) pressure
- 50 loggers (10 x 5) measuring shelf temperature in all 4 corners and the center of all 10 shelves at -20, 0, +20 and +40 °C using vacuum

The temperature variations (gradient profile) across each shelf (inter) and between shelves (intra) at each temperature (total of 7 studies) will be calculated, and the data will be compared to the manufacturer specifications to determine a pass or fail.

The Ellab Solution

To handle shelf temperature mapping, batch control and validation of freeze dryers, Ellab has recently launched the TrackSense LyoPro wireless data logger system.

The LyoPro data loggers are uniquely designed for freeze drying, and come equipped with everything you need:
- Ultra-thin and replaceable thermocouple sensors
- Highly accurate measurements within the range of -60 to +60 °C
- Live- and stored data
- Ability to use over 100 data loggers in a single study
- Small loggers that fit the size of regular vials – but can also be adjusted to any vial size
- Software with on-site user calibration option
- And much, much more…



Contact Pucks for Shelf Measurements

Additionally, Ellab also offer a contact puck, the LyoPuck, that work along with the LyoPro data logger – allowing you to insert the sensor into a small device of stainless steel and PEEK that presses the measuring tip against the shelf in question. Doing so provides an accurate representation of the shelf temperature.
- Eliminates bulky and homemade alternatives
- Easily repeatable for consistent and accurate measurements
- Offers excellent performance at ambient conditions as well as during vacuum

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