WHITE PAPER

Why- and how to Perform Batch Control During the Freeze Drying Process

Validation & Monitoring Solutions

06/21

Global Expertise with Local Reach

Validation & Monitoring Solutions

Table of Contents

Why Perform Batch Control of Freeze Drying Process? 3

How Costly is the Loss of a Freeze Drying Batch? 4

Why is it Important to Accurately Measure the Product Temperature? 5
- What Impacts the Product Temperature? 5

What Happens to the Product Temperature During Pre-freezing? 6

What Happens to the Product Temperature During Primary Drying? 7
- Why Monitor the Primary Drying Phase? 7

What Happens with the Product Temperature During Secondary Drying? 9
- How does the Secondary Drying Phase Eliminate Bound Water? 9
- When is the Secondary Drying Phase Over? 9

After all this, how does the Product Maintain its Condition? 9

How do You Safely Obtain the Product Temperature? 10

One Question Remains – What are the Best Tools for the Job? 11

Why Perform Batch Control of the Freeze Drying Process?

Almost half of all biological products produced within the pharmaceutical industry are freeze dried using vials as containers. An incredible scope that ensures millions of life-saving and quality-of-life drugs across the globe – making it immensely crucial to get the freeze drying process right.

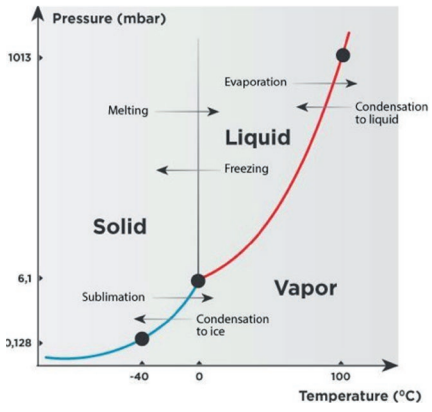
To ensure these drugs are safe for consumption, it is advised to perform batch control and monitoring of samples during the freeze drying process.

Monitoring and controlling the process through batch control by measuring the product temperature has two crucial purposes:

- Saving the batch if something unexpected happens – thereby ensuring the integrity of extremely expensive products
- Defining the end of the primary drying and optimizing the drying speed without jeopardizing the product

Measuring the product temperature therefore provides important information about the status of the product during the freeze drying process:

- **Pre-freezing**: Stabilizes the structure of the sample through freezing. The freezing speed is controlled to form the appropriate ice structure and crystals for sublimation
- **Primary Drying**: Through establishing a vacuum, ice will be converted directly into vapor without melting. This is also known as sublimation. This part of the process requires energy to be added to the product in order to compensate for the energy used by the sublimation process itself.
- **Secondary Drying**: As not all of the water within the product is frozen initially (intercellular water, bound water) and removed by sublimation, the secondary drying phase, also known as desorption, will remove this excess water.



Learn more about the Freeze Drying Theory and Process in our related White Paper

How Costly is the Loss of a Freeze Drying Batch?

Not only are the drugs that undergo freeze drying highly crucial for consumers, but the costs and impact of not properly monitoring and controlling the process correctly can be detrimental.

The Scale and Cost of a Freeze Drying Batch
Some freeze drying systems can operate with more than 100,000 vials at a time – all containing expensive and important biopharmaceutical drugs. A single batch can easily reach a worth of several million Euro or US Dollars – often greater than the cost of the freeze dryer itself.

How to Ensure the Safety of a Freeze Drying Batch
To reduce the risk of batch loss, accurately monitoring and controlling the process from start to finish ought to be in focus. There are two critical variables that affect the heat transfer, process efficiency and product quality, namely: chamber pressure and product temperature. By monitoring and controlling these parameters, the process can be optimized and adjusted to ensure a high quality batch. In this paper, we will be focusing on how to use product temperature to perform batch control.

Additional Benefits of Performing Batch Control
Monitoring the status of the product during the freeze drying process is also highly useful for:

- Scaling up a process
- Performing laboratory level validation cycles from a pilot to industrial plan
- Performing successful freeze drying cycles that avoid shrinkage, collapse, eutetic melt, excessive moisture levels in the final product, extended reconstitution time or ultimately loss of activity in the Active Pharmaceutical Ingredients (API)

Why is it Important to Accurately Measure the Product Temperature?

The most basic and frequently used method of batch control is the measuring of product temperature. Doing so helps avoid entering critical situations through automatic product temperature detection – as well as determining the endpoint of the primary drying phase in industrial freeze dryers.

What Impacts the Product Temperature?

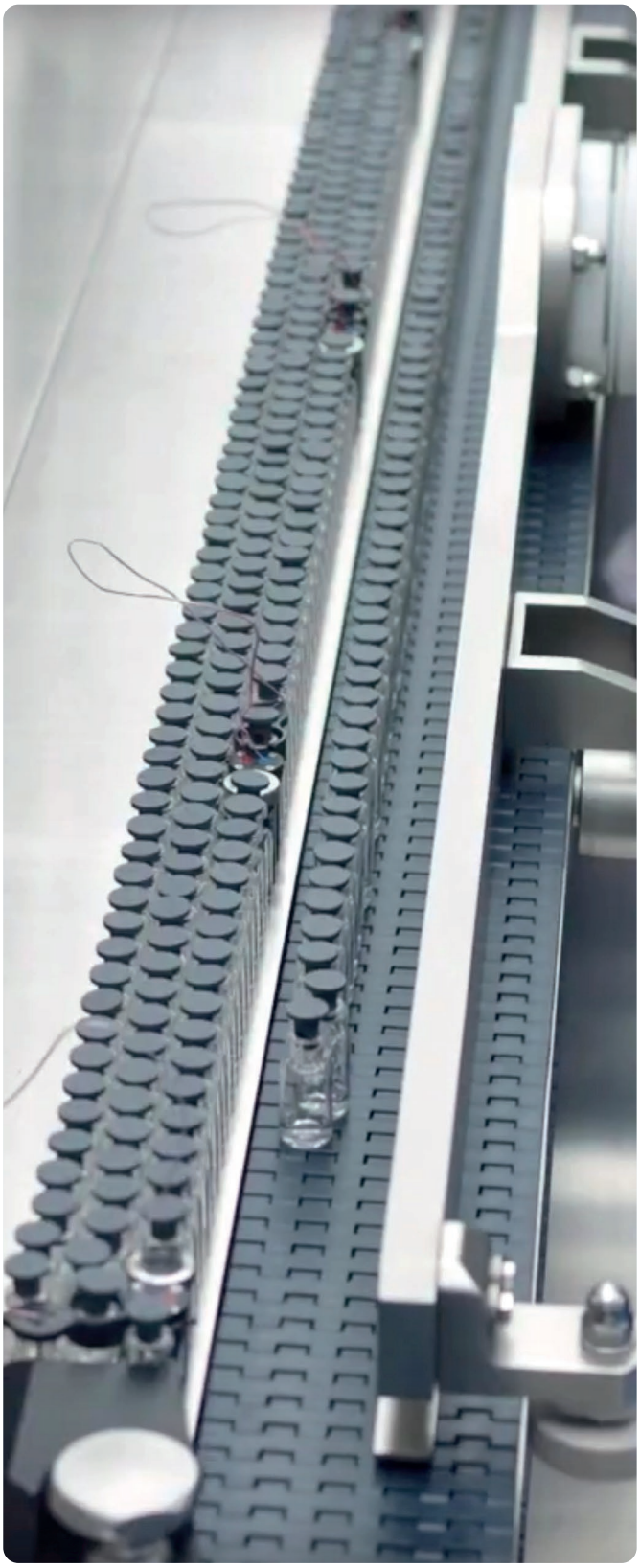
Theoretically, the product temperature is the result of a balance between the heat input from its surroundings (shelves) and the heat output activated by the self-cooling from the ice sublimation. In other words, the product temperature depends on:

- The properties of the product formulation
- Radiation and conduction heat provided by the shelves
- Chamber pressure
- Container type/material

Product temperature is therefore changed indirectly through the entire process, which is why it is so crucial to monitor and control this parameter throughout the freeze drying phases.

What Happens to the Product Temperature During Pre-freezing?

Correctly measuring and controlling the sample temperature during freezing is of paramount importance. The freezing speed determines the ice morphology (crystal structure) which is essential for later success.



Slow Freezing and Fast Drying

In general, freezing at a low speed (<1 °C /minute) will typically create rather large ice crystals. And when combined with a relatively fast drying process, the final product ends up in a sort of 'flake' structure.

Fast Freezing and Slow Drying

Fast freezing, on the other hand, creates small ice crystals, and will typically result in a slower overall drying speed – resulting in a final product that is more granulated.

Collapse/Eutectic Temperature

It is also vital to understand that setting and monitoring the freezing speed during the freezing phase is not the only thing that is important - ensuring that an appropriate (low) initial temperature is reached before starting the drying process is also crucial. This barrier temperature is often referred to as the collapse or eutectic temperature and will depend on the sample composition. Some typical collapse temperatures are:

- Dextran at -9 °C
- Citrate Buffer at -40 °C
- Phosphate Buffer at -80 °C

Ensure a Consistent Speed

A general rule of thumb when freezing a sample in a vial is to ensure that the filling volume never exceeds the nominal volume by more than 50%. This is done by ensuring that the diameter of the vial is always twice the height of the filling depth. This will ultimately help avoid a decrease in the drying speed caused by a higher resistance being created by the longer path the vapor would have to travel to escape.

What Happens to the Product Temperature During Primary Drying?

Once the product has been frozen below the collapse temperature, the chamber is evacuated as vacuum is applied. This activates the sublimation whereby the ice in the product is converted directly into vapor.

Why Monitor the Primary Drying Phase?

The sublimation process will eventually continue until the product temperature arrives at a temperature close to the condenser temperature. Once there, it will have eliminated the difference in ice vapor pressure that is moving the vapor molecules.

To avoid this slow-down of the process, balanced heat is applied to the sample vial through the shelf that it is placed on. The idea here is to monitor the product temperature and adjust the shelf heating to the exact point where the product temperature is kept just below the collapse temperature. This would then continue all the way through the Primary Drying phase until all the ice is gone.

The limit definition for the Primary Drying sample temperature should include a safety margin from the eutectic point. This temperature should not be too low however, as this will extend the process time unnecessarily.

The Importance of Reliable Data

Primary Drying often makes up the bulk of the process. As the longest period of a freeze drying cycle, it is vital that the temperatures that are being measured from within the samples are reliable – making extremely accurate measurements and secure data storage crucial.

This table shows the Vapor Pressure of Ice at different temperatures. To illustrate how important it is for the sublimation speed to have accurate product temperature measurements, we can use this table.

Temp	Vapor Pressure			Temp	Vapor Pressure		
°C	Pa	µmHg	µbar	°C	Pa	µmHg	µbar
0	611.1	4584.4	6111	-42	10.22	76.6	102
-2	517.7	3883.6	5177	-44	8.10	60.8	81
-4	437.4	3281.6	4374	-46	6.39	48.0	64
-6	368.7	2765.9	3687	-48	5.03	37.7	50
-8	309.9	2325.1	3099	-50	3.94	29.5	39
-10	259.9	1949.4	2599	-52	3.07	23.0	31
-12	217.3	1630.0	2173	-54	2.38	17.9	24
-14	181.2	1359.1	1812	-56	1.84	13.8	18
-16	150.6	1130.1	1506	-58	1.41	10.6	14
-18	124.9	936.9	1249	-60	1.08	8.1	11
-20	103.2	774.4	1032	-62	0.82	6.2	8.2
-22	85.07	638.2	851	-64	0.62	4.7	6.2
-24	69.88	524.3	699	-66	0.47	3.5	4.7
-26	57.23	429.3	572	-68	0.35	2.6	3.5
-28	46.71	350.4	467	-70	0.26	2.0	2.6
-30	38.00	285.1	380	-72	0.19	1.5	1.9
-32	30.81	231.1	308	-74	0.14	1.1	1.4
-34	24.89	186.7	249	-76	0.10	0.8	1.0
-36	20.03	150.3	200	-78	0.08	0.6	0.8
-38	16.07	120.5	161	-80	0.05	0.4	0.5
-40	12.84	96.3	128	-82	0.04	0.3	0.4

1 mbar = 750.1 microns | 1 micron = 0.1333 Pa | 1 Pa = 7.5006 microns

1 mbar = 100 Pa | 1 micron = 0.0013 mbar | 1 Pa = 0.01 mbar

Example 1 – Adjusting Product/Shelf Temperature to Change the Sublimation Speed

A product with a eutectic temperature of -30 °C is freeze dried in a setup with a condenser temperature of -50 °C. As the sublimation speed is directly proportional to the Ice Vapor Pressure difference between product temperature and condenser temperature, the relative speed in this case would be 38 – 3.94 = **34.06 (ideal situation)**.

However, getting too close to the eutectic temperature could result in product loss (melting).

Instead, the shelf temperature should be adjusted to get a sample temperature of – 34 °C. Now the relative sublimation speed is 24.89 –3.94 = **20.95 (a whole 38.5 % slower than ideal)** with just a 4 °C decrease in product temperature.

If you instead decided to operate more aggressively with a -32 °C product temperature, the relative sublimation speed would now be 30.81–3.94 = **26.9, which is 28.3 % faster** than at -34 °C.

Example 2 – Adjusting Condenser Temperature to Change the Sublimation Speed

By decreasing the condenser temperature, it is also possible to increase the sublimation speed, although the difference would be marginal.

A) A product temperature of -32 °C and a condenser temperature of -50 °C, provides a relative sublimation speed of 30.81–3.94 = **26.9**,
B) A product temperature of -32 °C and a condenser temperature of -60 °C, provides a relative sublimation speed of 30.81 – 1.08 = **29.73 (or just 10.5 % faster than A)**

In conclusion, the product temperature should be as close as possible to the eutectic temperature in order to get the maximum sublimation speed, as just a relatively small change makes a huge impact.

The condenser temperature should always be lower than the product temperature, however, changing the condenser temperature to increase the sublimation speed is not always necessary as it might only serve to add additional costs.

How to Tell the Primary Drying Phase is Over
If you observe a difference in the product temperature compared to the shelf temperature, the Primary Drying is still running. Other indicators that point to the Primary Drying phase being over, could be that the condenser temperature has returned to its original low temperature as almost no vapor arrives.

Alternatively, measuring the chamber pressure (vacuum) returning to its original level, would also indicate that the movement of vapor molecules has decreased substantially.

What Happens with the Product Temperature During Secondary Drying?

When the Primary Drying phase is over, the sample is not yet completely dry. Left-over water that was never frozen in the first place will still be present in the sample. This is referred to as residual moisture or "bound" water.

Using Secondary Drying to Increase Shelf Life
The amount of bound water left in the sample after the primary drying could be as high as 2-5%. However, if a sample requires a long shelf life in storage, this percentage must come down to well below 1%.

This is achieved during Secondary Drying, sometimes referred to as Desorption, where cautions about keeping the sample temperature below the collapse temperature (eutectic point) are left behind.

How does the Secondary Drying Phase Eliminate Bound Water?

The removal of water is controlled and optimized by increasing the shelf to its maximum allowed temperature. This is typically defined by the sample composition. As many biological products contain proteins, the usual maximum temperature is denaturating of +42 °C.

Next up, the pressure in the chamber is lowered to its absolute minimum (highest vacuum) to drive the final vapor molecules out and away from the product.

When is the Secondary Drying Phase Over?

As with Primary Drying, monitoring the product temperature and eventually comparing it to the shelf temperature will indicate when Secondary Drying is complete.

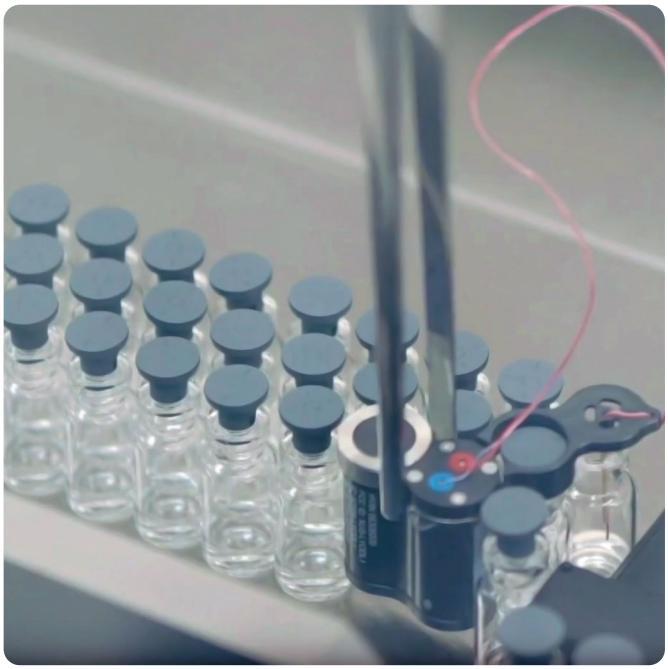
After all this, how does the Product Maintain its Condition?

To maintain the relatively low moisture content obtained during the Primary and Secondary Drying phases, it is essential that vials are closed before being exposed to the atmosphere outside of the freeze-drying chamber.

Sealing Vital Products Through Stoppering
To seal the vial, freeze dryers have a stoppering arrangement that presses the shelves together. Thereby pushing the rubber stopper down into the vial to seal it. It is therefore essential that the temperature sensor within the sample, is positioned in a way that it is not damaged and can be reused.

How do You Safely Obtain the Product Temperature?

Throughout this paper, the critical parameter required to perform accurate batch controls was product temperature. But how does one properly measure this without risking the integrity of the chamber and ruining the product?



Ensuring a Sealed and Leak-free Process

Wireless data loggers can safely be placed inside of the freeze dryer, thereby allowing for a complete seal of the process. These data loggers come equipped with sensors that can be used to measure the product temperature.

Sensor Placement and Impact

The temperature sensors should ideally be tiny, thereby having next to no impact on the measurements, especially when positioned inside of the vial/sample.

The goal is to place the tip of the sensor just above the bottom center of the vial, as this location will hold the last quantity of ice before sublimation is complete. Another reason for the placement is that the product will always dry from the top down.

Place the monitored vials in the four corners and the middle of the shelf, as these locations often suffer from edge vial effects that cause the vials to dry differently than the rest of the batch. It is therefore important to monitor and control these.

The vials containing the measuring devices are not fully representative of the entire batch, as these conduct more heat and will therefore typically dry faster than the rest of the batch. Due to this, it is important to add some drying time to ensure that the ice in the entire product batch has been completely removed. How much additional time should be added highly depends on sample characteristics.

One Question Remains – What are the Best Tools for the Job?

What are the Temperature Measurements for?

Temperature sensors are used to collect information about the product temperature as a function of the chamber pressure and shelf temperature – serving as an indirect method of determining when sublimation is complete.

Additionally, live temperature measurements allow operators to act and adjust the temperature or vacuum on the fly to avoid the loss of batch.

With products as important as life-saving and quality of life drugs, there is little room for error. The loss of batch is not an option, and the quality and safety of the drugs can never be compromised. Which is why Ellab developed TrackSense® LyoPro to solve all the usual headaches associated with batch control, while also providing industry-leading accuracy and secure data collection.

LyoPro – Qualification, Validation, Monitoring and Batch Control all in one

The TrackSense LyoPro wireless data logger is as versatile as high-end measuring equipment comes. LyoPro comes equipped with an ultra-thin replaceable thermocouple sensor that can be placed in the vials for the product temperature – or stuck on the shelves or put in contact pucks to measure shelf temperature.

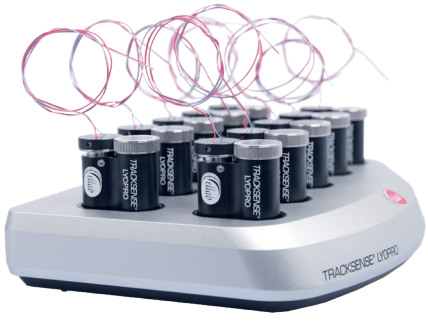
These thin sensors have next to no impact on the product temperature and therefore provide highly accurate measurements – unlike thicker stainless-steel sensors or transmitters that have an increased impact on the sample and therefore less reliable readings.

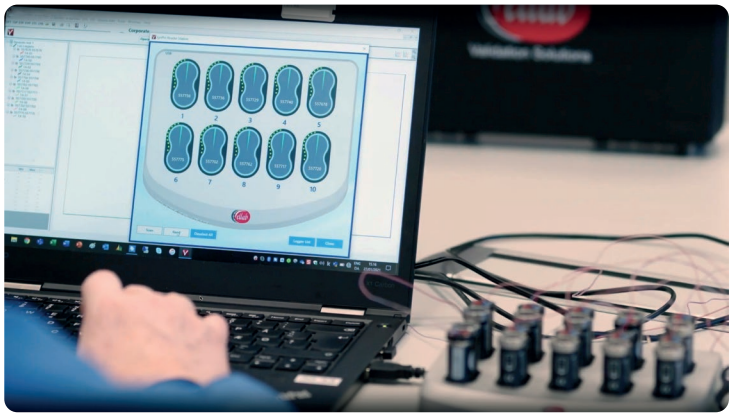
Uniquely Designed for Freeze Drying

Having been designed specifically for the freeze drying process, LyoPro comes with a wide range of features that makes using it within the crucial process a whole lot easier:

- LyoPro comes equipped with special stoppers that keep the sensor fixed at the desired measuring point throughout the entire process. These stoppers also make future measurements easily repeatable and keeps the thermocouples from being damaged during stoppering
- The ultra-thin replaceable thermocouple has next to no impact on sampling
- An optional buffer vial can be placed between the sample vial and LyoPro to eliminate any potential heat conduction from the logger
- LyoPro transmits real time data throughout the entire process, but also stores all samples on its large internal battery operated memory.
- Over 100 LyoPro data loggers can be used simultaneously for a single study – eliminating data gaps
- Just to name a few…

Learn more about TrackSense LyoPro in our related Product Spotlight





Data Analysis, Data Integrity and FDA Compliance

The ValSuite® software which runs LyoPro and all other Ellab hardware, is fully FDA 21 CFR Part11 compliant. Data is collected and saved using a quick and safe proprietary transmission protocol. ValSuite is the perfect software for batch control and documentation – and here's why:

- Fully compliant user reports in accordance with current standards and norms
- Can be integrated in small- as well as large-scale IT systems
- Data integrity through audit trails, electronic signatures, advanced access/user management and Windows security option
- On-screen statistical calculations, limit alarms, heat maps and graphs
- Live view of the process
- And much, much more…

User-Calibration

ValSuite also offers user-calibrations that can be performed on-site using oil baths/dry blocks and the Ellab Temperature Standard. Allowing effortless pre- and post-calibrations of all LyoPro thermocouple sensors – thereby eliminating the need for returning equipment to the factory.

Online Technical/Application Support

The Lyophilization Validation experts at Ellab are pleased to provide online technical/application consultancy for any assistance related to the validation and batch control of Lyophilizes. Ellab also conducts frequent training courses on various pharmaceutical validation services, including validation of the freeze drying process. We welcome everyone to participate in our training courses.

© Ellab A/S 2021