Systematic freeze-drying

Fundamentals,
process management,
and applications

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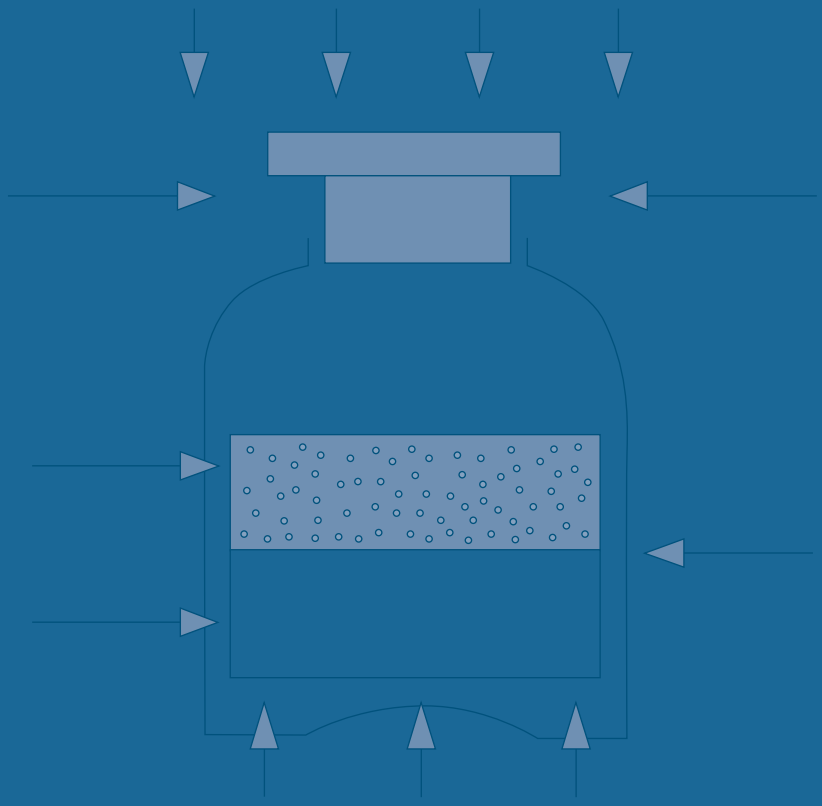

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While food products such as instant coffee make up the largest application by volume for freeze-drying,
biotech and pharma products such as vaccines
require machines and equipment that meet the highest quality

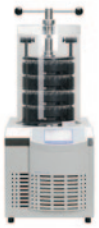
1 Introduction

Freeze-drying, or lyophilisation, is the most gentle method for drying materials. The underlying physical phenomenon of sublimation refers to the direct transition from a solid to a vapor state, bypassing the liquid state. The frozen product is thus dried under vacuum without thawing out. The method has a wide range of potential applications:

- Maintaining product characteristics
  of the original substances
  (e.g., pharmaceutical products, milk)
- Preserving the initial shape
  (e.g., taxidermy, archeological objects, flowers)
- Conditioning the material
  (e.g., freeze-dried fruits)
- Chemical analysis, sample preparation
  (e.g., trace organic testing
  in food products, sludge, and soils)

Freeze-drying is used for over 30 different categories of substances and materials, with the most important markets being the pharmaceutical and biotechnology fields, sample preparation in labs, and stabilizing food products.

In general, freeze-drying is divided into discontinuously and continuously operated systems. Discontinuously operated system are available on the market in versions from 2 kg to about 1 metric ton per batch.
Martin Christ has focused on this product group and is the only manufacturer worldwide of both series-production lab units and pilot freeze-dryers, up to large production lines.



Laboratory freeze-drying systems

- Ice condenser capacity from 2 to 24 kg
- Air-cooled chilling systems
- Wide range of accessories for a variety of applications
- Typically for drying pre-frozen products

Pilot freeze-drying systems

- Ice condenser capacity from 4 to 16 kg
- air or water cooled refrigeration systems
- Freezing and drying in the drying chamber on liquid-cooled shelves
- Insulator integration is possible

Production freeze-drying systems

- Ice condenser capacity from 20 to 500 kg
- Water-cooled chilling systems
- Freezing and drying in the drying chamber on liquid-cooled shelves
- Single or dual chamber systems
- Special customer-specific systems, with cleaning and sterilization
- Process integration with automated loading and unloading (LyoShuttle) and insulator integration

The historic use of freeze-drying under atmospheric conditions – by Eskimos, for example – is a legend.
In fact, this is a conventional "series circuit" of melting and evaporation processes. The latter occurs so rapidly that no visible liquid phase is formed.

2 Fundamentals

The principle of sublimation is explained below using the phase diagram for water. In practice, the process is nearly always used for aqueous systems, but in recent years the popularity of freeze-drying special solvent/water mixtures has increased.

In a phase diagram of a pure material, the three states of vapor, liquid, and solid are each bounded by a pressure and temperature function curve. Phase transitions occur at each of these curves. The phase diagram for water is explained in more detail in this example.
The vapor pressure curve (I) describes the phase transition of boiling/condensing. For example, it describes the boiling of water at 100 °C under atmospheric pressure. Lower pressure shifts the boiling point downwards (the principle of vacuum distillation), while higher pressure raises the boiling point (which is the reason that cooking times are faster in a pressure cooker).

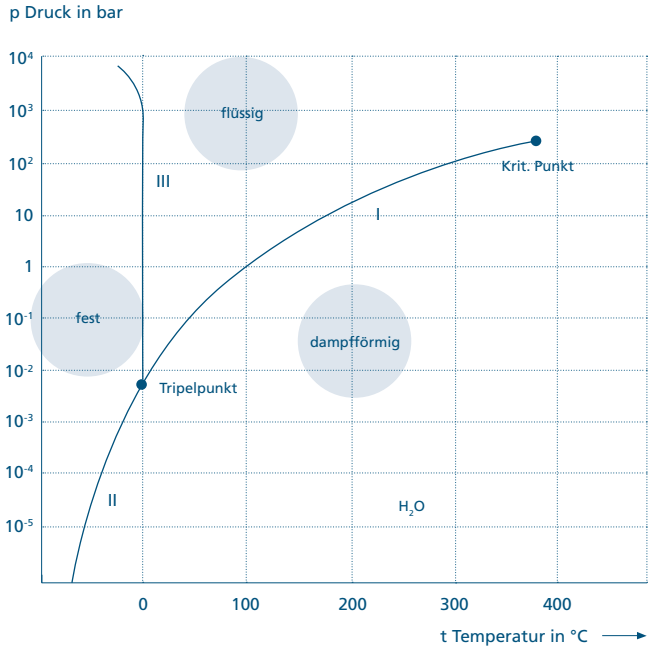


Figure 2.1 Phase diagram for water [1]

The sublimation pressure curve (II) describes the phase transition of sublimating, or desublimating/resublimating. The vapor transitions directly to the sold phase (ice). One example of this is the sublimation of CO_2 under atmospheric conditions.

The melt pressure curve (III) describes the transition between melting and freezing.

If the pressure is greater than 6.11 mbar, then H_2O passes through all three states (solid, liquid, vapor) when the temperature increases or decreases. Below this point, that is, if the pressure is less than 6.11 mbar, however, then H_2O passes directly from the solid to the vapor state. At precisely 6.11 mbar, at a temperature of 0.01 °C, the melt pressure curve, vapor pressure curve, and sublimation curve all meet at one point, the triple point. At this point, all three states occur simultaneously.
Above what is known as the critical point, at 373,95 °C and 220.64 bar, there is no clearly defined phase transition from the vapor phase to liquid.

All of the phase transitions are relevant for freeze-drying. The sublimation pressure curve is especially important here, as the sublimation from ice to vapor, as desired for freeze-drying, is possible only below the triple point. In practice, freeze-drying processes typically take place at temperatures from –20 °C to –40 °C.
The following table includes an excerpt of the sublimation pressure curve for water.

The units of measure typically used for conversion are:

°C	mbar	°C	mbar	°C	mbar	°C	mbar
0.01	6.110	–20	1.030	–40	0.120	–60	0.011
–1	5.620	–21	0.940	–41	0.110	–61	0.009
–2	5.170	–22	0.850	–42	0.100	–62	0.008
–3	4.760	–23	0.770	–43	0.090	–63	0.007
–4	4.370	–24	0.700	–44	0.080	–64	0.006
–5	4.020	–25	0.630	–45	0.070	–65	0.0054
–6	3.690	–26	0.570	–46	0.060	–66	0.0047
–7	3.380	–27	0.520	–47	0.055	–67	0.0041
–8	3.010	–28	0.470	–48	0.050	–68	0.0035
–9	2.840	–29	0.420	–49	0.045	–69	0.0030
–10	2.560	–30	0.370	–50	0.040	–70	0.0026
–11	2.380	–31	0.340	–51	0.035	–71	0.0023
–11	2.170	–32	0.310	–52	0.030	–72	0.0019
–13	1.980	–33	0.280	–53	0.025	–73	0.0017
–14	1.810	–34	0.250	–54	0.024	–74	0.0014
–15	1.650	–35	0.220	–55	0.021	–75	0.0012
–16	1.510	–36	0.200	–56	0.018	–76	0.0010

Pressure

1 mbar = 100 Pa = 1 hPa
1 Pa = 0.010 mbar

Temperature

$T = t + 273.15$
$t = T - 273.15$
$t_F = 1.8 \times t + 32$
$t = \frac{t_F - 32}{1.8}$

T = thermodynamic temperature K (Kelvin)
t = temperature in Celsius °C
t_F = temperature in Fahrenheit °F

A **freeze-dryer** or **lyophilisator** consists essentially of the receiver (product chamber), the separator for water vapor, (ice condensor), and a pump evacuation device (vacuum pump). There is a wide variety of technical solutions derived from this concept.

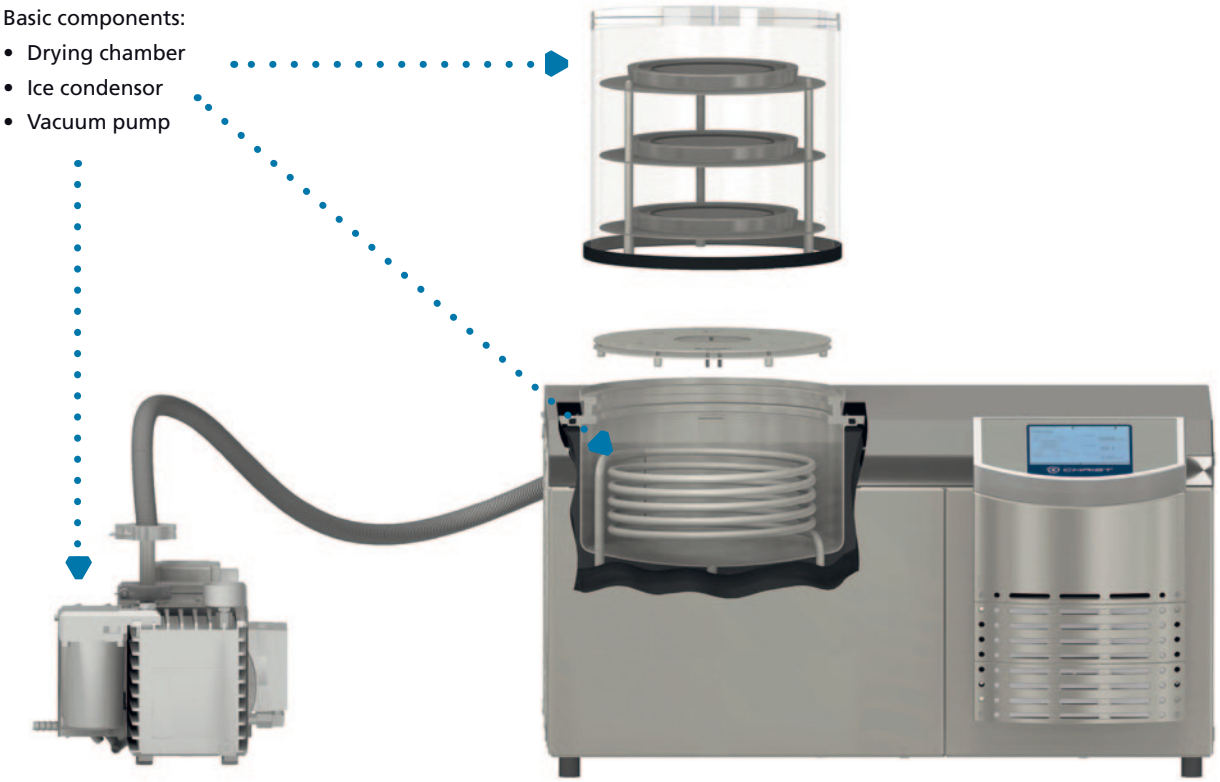
3 System structure

The basic components of a freeze-drying system are:

- Vacuum drying chamber
- Vacuum pump for evacuating air from the drying chamber (gas pump) and regulating the drying vacuum with a pressure control valve
- Ice condensor with temperatures from –55 °C to –105 °C (depending on the type of system) for resublimating the water vapor from the drying chamber (Vapor pump)

Extensive accessories can be added to the basic components, such as:

- Heated or unheated storage areas for drying in trays
- Shelves with closures for drying in bottles.
- Rubber valves for connecting round-bottom flasks, wide-mouth bottles, etc.
- Manifold for connecting round-bottom flasks, wide-mouth bottles, etc.
- Controller for operation and observation of process parameters



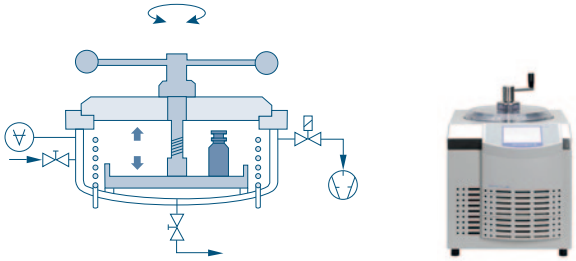


Figure 3.2 Lab system functioning as a single chamber system

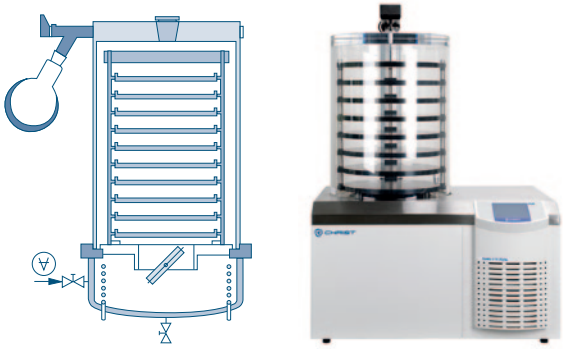


Figure 3.3 Lab system functioning as a dual chamber system

For both lab systems and commercial production freeze-drying systems, a distinction is made between single and dual chamber systems. The principle is presented here at the laboratory scale:

As shown in Figure 3.2, in the single chamber system, freezing and subsequent drying of the product are performed in the ice condenser chamber. The sample is frozen due to the low temperature of the ice condenser (–55 °C or –105 °C). The interior can be chilled down to about –20 °C or –40 °C. A significant improvement in cold transfer from the ice condenser to the sample can be achieved with the use of a fan during the freezing phase in a lab system. For larger freeze-dryers, shelves that can be chilled are used for freezing. The moderate energy input to the frozen sample required for primary drying is provided via the heated shelf on which the product sits. The closure device shown in Figure 3.2 can close vials once drying is completed under vacuum or inert gas, so that the freeze-dried sample is then addtiionally vacuum-sealed to some degree.

The arrangement of shelves under an acrylic glass receiver outside of the ice condenser, as shown in Figure 3.3, is referred to as the dual-chamber principle. Its advantage is its substantially larger product capacity, even when using the same basic system. By closing off the product chamber from the ice condenser chamber (see the intermediate valve in the sketch), a pressure rise test can also be used to determine when drying is complete. The disadvantage is additional handling of samples, which must be pre-frozen externally, for example in a freezer or a deep-freeze unit. Once they are transferred to the freeze-dryer and the acrylic chamber is in place, the actual primary drying is then started. All Christ lab systems with shelf temperature control capability can be run under the single or dual chamber principle, as desired.

4 Process management

4.1 Freeze-drying process flow sequence

Before the various process steps for freeze-drying are described in detail, this section is intended to provide an overview of the process flow sequence.

Prior to loading a new product, the freeze-drying system must be dry and any residual water from the previous run must be removed from the ice condenser chamber. The drain valve for emptying the ice condenser and the ventilation valve for venting the product chamber when the freeze-drying process is complete are then closed.

The product should not be more than 1–2 cm thick, as otherwise the drying time will be excessively long.

As shown in Figure 4.1, the freeze-drying process can be controlled by selecting and modifying just two master parameters for the device:
- the vacuum setting
- the shelf temperature

where both target values can be time-dependent curves.
As indicated above, the product is frozen in small amounts inside the ice condenser chamber (single chamber method) or separately in a deep-freeze unit in the lab area (dual chamber method)

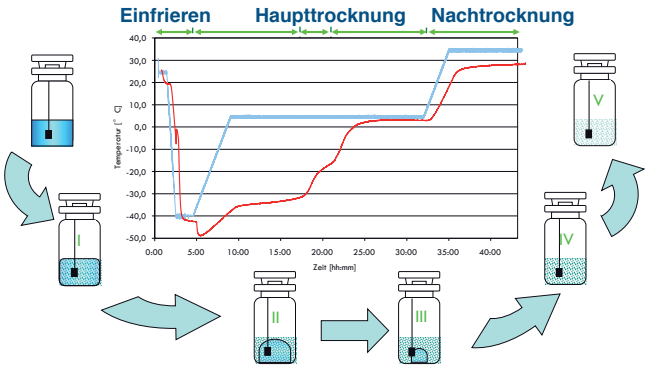


Figure 4.1 Vacuum and shelf temperature are the two master parameters for freeze-drying
· Vacuum p = f (GT-step)
· Shelf temp. T = f (process time)

As a rule, freezing takes place at atmospheric pressure, similar to a conventional freezer.

Drying the product in round-bottom flasks or closeable wide-mouth filters is popular and has the advantage of being able to place or remove these containers separately in the freeze-dryer without disturbing the drying process for the other bottles. As is explained in Chapter 5.2, the thickness that is so important for the drying time in this area of application can be significantly reduced by freezing under rotation, as opposed to conventional static freezing. Taking advantage of centrifugal force, a uniform ice layer is produced on the cylindrical wall of the glass container.

With separate freezing, it is helpful to pre-chill the shelves, especially for small volumes of product, in order to avoid partial thawing during transport to the freeze-dryer and evacuation.

In parallel with the freezing process, the device should run through what is called a warm-up / cool-down phase: the vacuum pump can then warm up by running against the closed pressure control valve, which improves its performance and its resistance to water vapor. At the same time, the ice condenser is pre-chilled in order to be able to separate out the water vapor produced in the next step, primary drying. The preparation phase should last between 15 and 30 minutes.

To start the sublimation process, the pressure control valve to the vacuum pump is opened, so that a vacuum is applied to the freeze-dryer. Primary drying is started.

During primary drying, the frozen water or solvent is removed as vapor from the product to be dried by means of sublimation. The vapor is transported out of the product due to the differential pressure and temperature in the chamber to the surface of the ice condenser, and is desublimated at the cold ice condenser.

Figure 4.2 shows a process graph for a ceramic suspension. Due to its freezing point near 0 °C and uncomplicated product properties, it can be freeze-dried using a fairly rough vacuum of 1 mbar, with a high energy input (shelf temperature +40 °C). The product temperature probes in the suspension (yellow, green, blue curves) reach values close to the shelf temperature when approaching the end of drying. Before this, a "mixed temperature" is measured, from the ice temperature and the temperature of the already dried cake. The ice condenser temperature (black curve) collapses from -83 °C to about -70 °C when primary drying starts, as large amounts of water vapor need to be desublimated. After about 20 hours, this quantity has dropped off enough that the ice condenser reaches about -85 °C again.

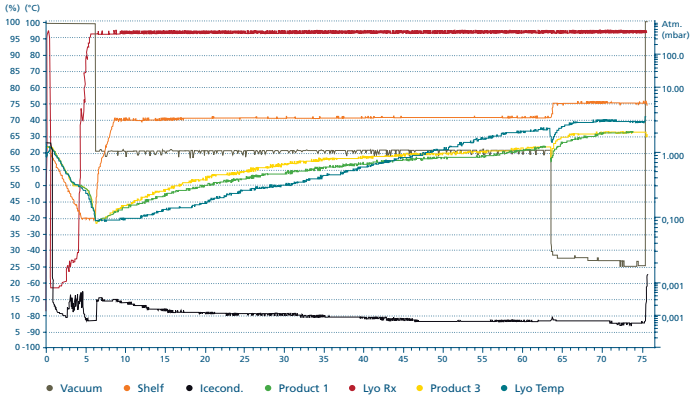


Figure 4.2 Process diagram for freeze-drying, using the example of a ceramic suspension (abscissa: time in hours)

Optional final drying involves lowering the vacuum to the most severe, lowest possible value in conjunction with increased shelf temperature. These two measures improve desorption. For this desorption step, other thermodynamic principles apply than those in the actual sublimation.
An increase in temperature and decrease in pressure have a positive effect on the residual moisture level that can be achieved.

When the process has ended, the drying chamber is vented via the ventilation valve. It is also possible to "vent" the system with nitrogen or another inert gas via the ventilation valve. The product can then be removed.

Subsequent thawing of the ice condenser takes place at room temperature, or most quickly by means of the hot gas defroster integrated in the freeze-dryer. The melt water is drained off via the drain valve and captured in a container.
Before starting a new process, residual water should be removed from the system. The drain and ventilation valves are closed again, and the system is loaded again.

The **eutectic point** refers to the point at which a homogeneous mixed phase transitions directly from the liquid to the solid state, so that no crystalline mixture consisting of different phases is produced.

4.2 Freezing

The freezing phase defines the microstructure of the solidified solution and thus also that of the product to be dried. Two fundamentally different structures of the frozen material are differentiated: crystalline structure and amorphous structure.

The predominant crystalline form is characterized by the presence of ice crystals with clear crystal boundaries. This is the case for most aqueous solutions with low levels of sugars or proteins. If freezing is done sufficiently slowly, then the progressive separation of the phases will ensure that the last drop of liquid will freeze at the lowest possible temperature, known as the eutectic temperature. In practice, even at normal cooling rates, thermodynamic equilibrium is often lost and the liquid becomes supercooled. It then has a lower temperature at a given pressure than would be possible at thermodynamic equilibrium. The supercooling can be as much as 10 to 20 K. Agitation or inoculation with a seed then initiates spontaneous crystallization and releases enthalpy of fusion.
The release of enthalpy of fusion causes a spontaneous increase in temperature; see Figure 4.3.

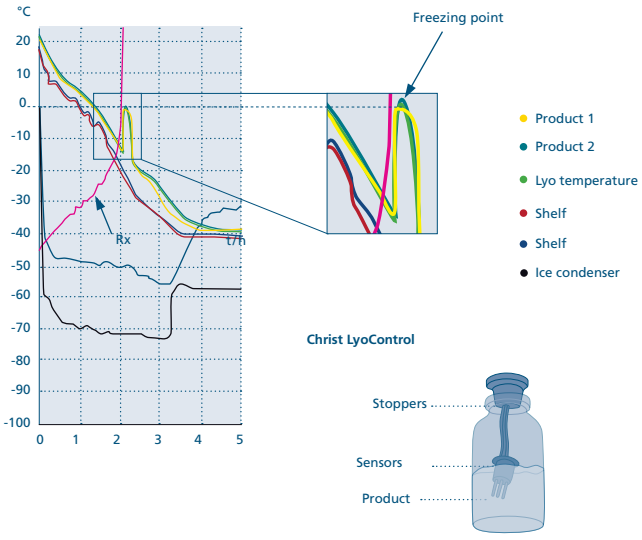


Figure 4.3 Determining the freezing point using Christ LyoControl

In contrast, amorphous substances are characterized by a lack of any crystal boundaries, similar to a supercooled melt, such as window glass. Heating up such a solidified solution also does not cause abrupt melting, but rather causes the softened material to flow away. This is therefore known as the collapse temperature, T_C. The solidification point from liquid to amorphous is referred to as the glass transition temperature T_G, and is typically a few Kelvin lower than the collapse temperature.

For pharmaceuticals, amorphous matrices are preferred for embedding sensitive biomolecules, as they are better able to stabilize the active substance. Crystalline products, in contrast, can be freeze-dried more easily and quickly, as the grain boundaries facilitate water vapor transport.

While melting the product in the crystalline range during drying can cause spatter, and thus cross-contamination, amorphous, honey-like substances initially demonstrate "only" a loss of structure. The product that has been frozen as glass begins to flow. Although the product may not yet be damaged, any customer would complain about collapsed, sticky crumbs. Many substances from the pharma sector demonstrate greater shelf stability when they are embedded in an amorphous matrix.

The significant aspect for defining the required freezing temperature on the shelf, and the working vacuum during primary drying, is determining the solidification point (= freezing point) of the material to be dried. This depends primarily on the product, but depends on the freezing speed as well.
The table in Figure 4.4 shows an example of the large bandwidth for microbiological culture media alone.

Sample	EP at °C
Tap water	-1.0
Ultrapure water	0.0
Ultrapasteurized milk	-11.7
Skim milk	-11.0
Lactose 5 %	-1.0
Lactose 10 %	-2.0
mod. PC med. (3 % NaCl)	-45,0
Litmus solution	-12.0
HGL	-12.0
BA bouillon	-29.0
Glucose bouillon	-6.5
Malt extract bouillon	-6.5
Yeast solution	-1.5
YGC	-15.0
MRS bouillon	-20.0
M 17	-15.5
Basic med. streptococci	-15.0

Figure 4.4 Solidification point (SP) of various culture media [1]

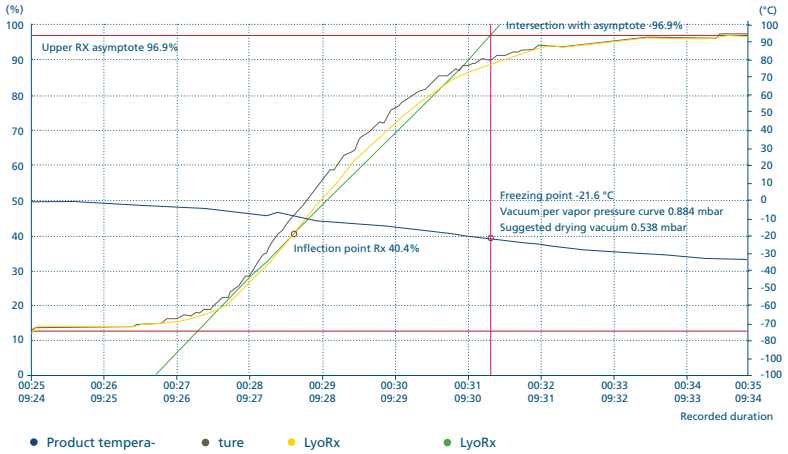


Figure 4.5 Graphic construction for determining the freezing point: For a flatter rise of the LyoRx value during solidification, to be on the safe side, the value for product temperature determined from this illustration should be considered to be the solidification or freezing point.

The freezing point can be determined

- using theoretical thermodynamic values (Source: chemical manuals, technical literature [e.g. VDI-Thermal Atlas], References)
- Cryomicroscope
- DSC (Differential Scanning Calorimetry)
- Measurement of temperature and resistance curves during the freezing phase

The electrical resistance of the product to be dried almost always rises steeply at the transition from liquid to the solid aggregate state. The reason for this is the reduction in motility of ions and electrons in solids. This phenomenon can be used to determine the freezing point by measuring the product temperature and the electrical resistance at the same point.

Due to the typically abrupt, very steep rise in resistance, the intersection of the resistance curve, LyoRx, and the temperature curve can be taken as the freezing point with a high degree of accuracy. LyoRx refers to the normalized logarithmic rise in the measured product resistance. Numerous measurements with solutions from practical experience have confirmed this.
For some substances, however, this method is of limited effectiveness.

Figure 4.5 shows the mathematically correct way to determine the freezing point in a graphic illustration. For a flatter, undefined rise in the LyoRx value during solidification, to be on the safe side, the product temperature at which the LyoControl resistance (LyoRx value) no longer changes should be taken as the solidification point.

Amorphous substances, such as glass, have no crystal boundaries and behave like solidified liquids. The glass transition temperature T_G is the temperature at which the brittle product becomes elastic and begins to flow away.

The resistance of a sample changes by several orders of magnitude during freezing. Because the concrete numerical value is not important when determining the freezing point, the measured resistance is normalized logarithmically on a linear percentage scale.

Determining the freezing point from the intersection of the resistance curve and the temperature curves is called LyoControl.

One advantage of the Christ LyoControl system is the potential for process control and monitoring. During primary drying, thawing of the product, commonly accompanied by spatter, cross-contamination, and potential loss of the batch, can be avoided by controlling the LyoRx level. Figures 4.6 and 4.7 show process logs for an insensitive product (LyoRx near 100%) and for a very sensitive product (LyoRx resistance value drops off abruptly from 95% to 25%) that thawed after a few hours in primary drying. Reasons that the resistance may collapse include a freeze-drying profile that is too aggressive (heating the shelves too rapidly).

Christ pilot and production systems provide the option of specifying a minimum LyoRx value. If the value falls below this limit, then the system switches to freezing mode to refreeze any thawed product. The LyoControl system can detect the freezing point of the largely crystalline freezing solutions very well. For amorphous substances used in pharma applications, the reading the collapse temperature is less accurate.

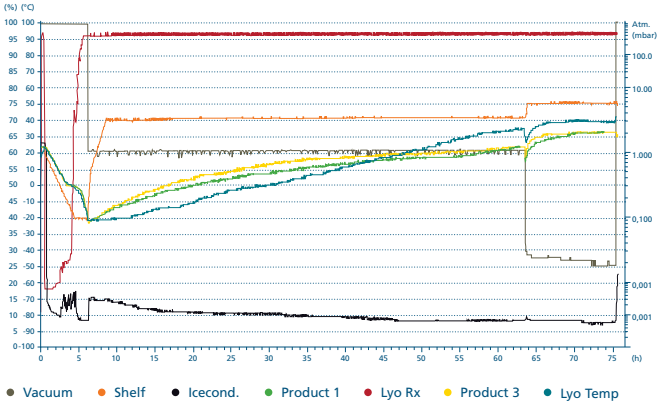


Figure 4.6 LyoRx curve for an insensitive product

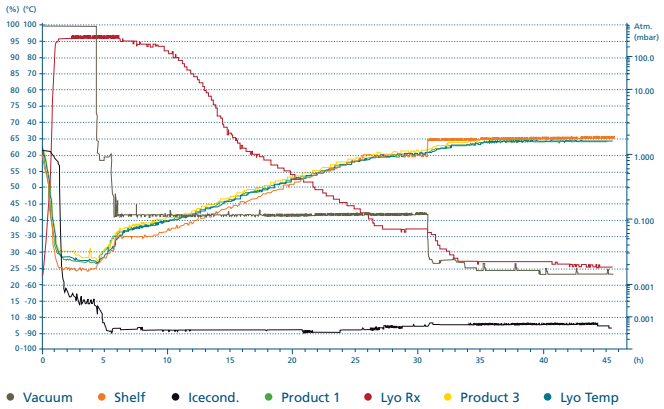
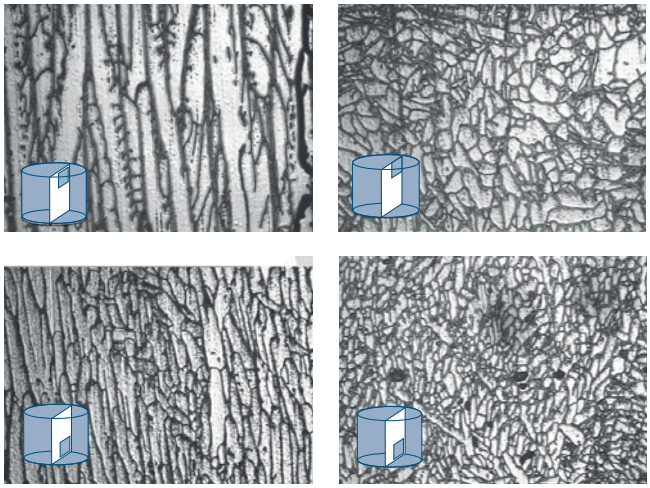


Figure 4.7 LyoRx curve for a sensitive product that has thawed during the course of primary drying

For crystalline systems, the speed of freezing has substantial effects on the system's morphology (see Figure 4.8).



Crystal formation at –2 °C

Crystal formation at –8 °C

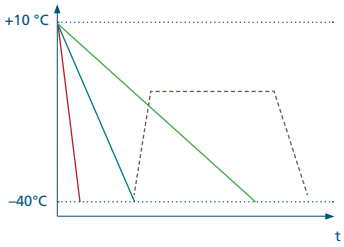
Figure 4.8 Crystal formation (vertical section) when freezing a 100% mannitol/water solution [3]

On the left, a mannitol solution is slowed cooled down to –2 °C and then crystallized. The sections on teh right show the result of a more rapid cooling, crystallizing out more rapidly at –8 °C. The rapid freezing leads to longer primary drying due to the smaller pore diameter and few cracks in the surface structure. On the other hand, slow freezing (see Figure 4.9 for classification) leads to what is known as freezing concentration.

Freezing too low, too quickly causes the drying rate to change (lower pore diameter, crack-free surface structue)
and thus leads to longer primary drying.

Rapid freezing
(in liquid nitrogen LN_2,
Cooling speed
approx. 50 K/min)

Slow freezing
(Cooling speed
< 1 K/min)



Moderate freezing
(Cooling speed 1–1.5 K/min)

Tempering (annealing)
(Cooling speed about 1.5 K/min,
soak at -10 °C for 5 h)

Figure 4.9 Classification of potential freezing speeds [4]

The example used here is a sodium chloride solution that would divide into two types of crystals while freezing, namely a low-NaCl ice phase and a second phase with a very high concentration of NaCl. The last drop of liquid in the mixture solidifies at the lowest possible temperature, known as the eutectic temperature.
In practice, freezing speeds from 1 to 2 K per minute (moderate freezing) are used as an optimum to avoid freezing concentrations on one hand and to form suitable crystalline structures on the other.

For starting materials containing solvents, or a material with a high salt concentration, thawing may occur during the drying process. It is then necessary to freeze the material as deeply as possible, for example using liquid nitrogen.
An initial material with a high concentration of solvents, for example, or acidic material, cannot be dried without special protective measures. For these applications, there are specially designed freeze-dryers, for example with a lower ice condenser temperature and mechanical safeguards, such as an additional liquid nitrogencooling trap to protect the vacuum pump.

Sublimation, (from the Latin ›sublimis‹, located high in the air, elevated), refers to the thermodynamic process of direct transition of a substance from the solid to the gaseous state.

4.3 Primary drying and final drying

Now that the important step of freezing has been covered, we turn to the process steps of primary and final drying.

4.3.1 Vacuum

The previous chapters addressed the topic of freezing. Another important set of concepts in the freeze-drying process is the topic of vacuum.

Due to the nature of the machinery, the vacuum pump needs to warm up and the ice condenser needs to be pre-chilled in order to perform the sublimation at the selected working vacuum pressure. This working vacuum typically does not change during primary drying, and it determines the chamber pressure and the temperature at the sublimation front via the sublimation pressure curve. As soon as the sublimation of water vapor out of the frozen material has begun, heat is removed from the material (sublimation enthalpy), further chilling it.
The shelf temperature is selected to be 5 to 10 K higher than the product temperature at the sublimation front, as set by the chamber pressure. This temperature differential causes heat to flow from the shelf into the product. This heat flow transports the enthalpy required for sublimation to the sublimation front. Incrementally increasing the shelf temperature can accelerate the process.
Process times for freeze-drying range from at least 12 hours for simple products up to several days for products or substances that are difficult to dry or freeze. Drying large-scale archeological objects can take weeks.

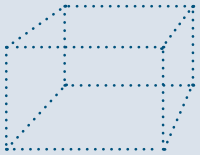
The water vapor produced under vacuum by freeze-drying is desublimated at the very cold ice condenser, which is why the ice condenser can also be referred to as the vapor pump. The sole job of the vacuum pump is to remove gases (air) from the drying chamber, but not to pump out the water vapor (gas pump).

A sensibly selected target value for the vacuum in the chamber is highly significant: the sublimation pressure curve substantially determines the temperature of the product and defines the volume of water vapor to be extracted.

The ideal gas law establishes a direct relationship between the pressure, the volume, and the temperature of a gas. At a constant temperature, the pressure and volume are inversely proportional. Lowering the pressure leads to an increase in volume of the gas.

Ideal gas law

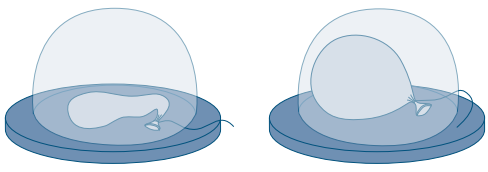
$p\ V = m\ R_m\ T$



p: Gas pressure [Pa], 10^5 Pa = 1 bar
V: Volume [m^3]
m: Mass [kg]
R_m: R/M, R = ideal gas constant R = 8.314 J/mol K, M: Molar mass [g/mol], M(H_2O) = 18 g/mol
T: Temperature [K]

Here is an example:
1 g water at a temperature of –55 °C has
the following volume as a function of pressure:

1.0 mbar means a volume of 1 m^3 of vapor
0.1 mbar means a volume of 10 m^3 of vapor
0.01 mbar means a volume of 100 m^3 of vapor



p = 10^5 Pa = 1bar p = 10^4 Pa = 0.1 bar

A very deep vacuum produces an enormous volume of vapor, but does not necessarily mean rapid reduction of the amount of water or solution in the sample.

4.3.2 The influence of vacuum on drying time

Due to the ideal gas law, and the relationship between pressure, volume, and temperature, the vacuum level selected directly affects the process time and the volume of vapor.

The example in the chart (Figure 4.10) shows the effect of various levels of vacuum on the sublimation speed.
This illustration shows the characteristic curve of sublimation speed over time during primary drying.
At the beginning of primary drying, the sublimation speed is zero, then during the first third it rises quickly, then drops to zero again at the end of primary drying, as all of the water has sublimated out of the product.

Comparing the red and blue curves, it is evident that even a slight increase in pressure from 0.05 mbar to 0.1 mbar, at the same shelf temperature, brings about a significant increase in sublimation speed, shortening the primary drying time by about 4.5 hours. Fundamentally, it has been found that a deeper vacuum and thus a lower product temperature (see the sublimation pressure curve on page 7) means that fewer molecules can move in the vapor space, and this leads to a general increase in drying time. This phenomenon is also familiar in the area of industrial freeze-drying: Ceramic suspensions, for example, are freeze-dried at a vacuum between 2 and 4 mbar due to a freezing point near 0 °C, that is, close to the triple point of water, while vaccine manufacturers must work with vacuum levels of 0.04 to 0.12 mbar. The reason is that the freezing point of such solutions is often very low.
As a result, the times required for primary drying are significantly longer.

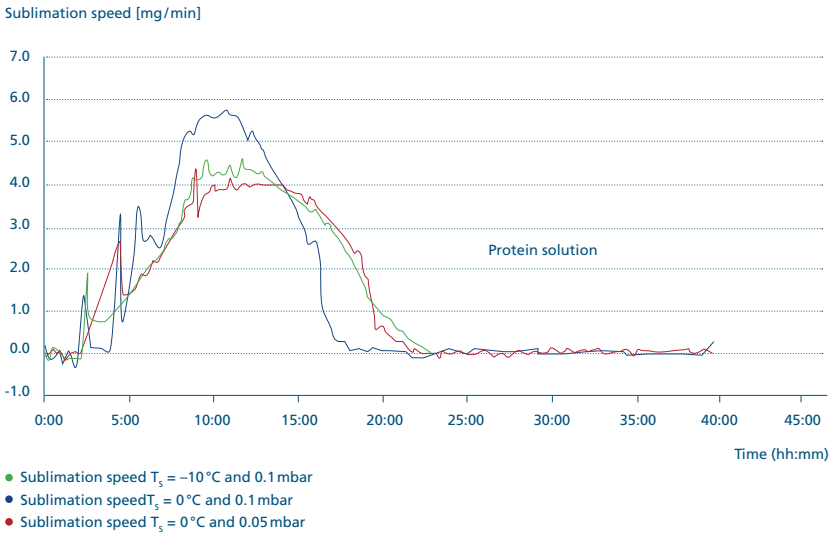


Figure 4.10 Influence of working pressure on the sublimation speed [5]

A sensibly selected target value for the vacuum is highly significant: the sublimation pressure curve substantially determines the temperature of the product. An initial estimate of the selected vacuum can be made from the solidification temperature, using the sublimation curve of the solvent used.

This point is illustrated in more detail using water as an example. For a selected drying temperature of –20 °C, the sublimation curve for water (page 7) yields a drying vacuum of 1.03 mbar. To reliably prevent the product from melting during drying, we recommend setting the corresponding vacuum about 10 K lower than the solidification temperature (eutectic point or glass transition point).

Knowing the dominant influence of the vacuum on the product temperature, Christ has integrated a safety pressure function in the freeze-dryer control system for shelf heaters: if the pressure in the drying chamber rises too severely, beyond the safety pressure limit that can be freely set in the recipe, then the power supply to the shelves is cut off and the sublimation process slows down. This prevents the product from melting and the risk of cross-contamination and changes to product properties.

The safety temperature should be 5 °C below the solidification point, that is, between the drying temperature and the melting point. To reliably prevent the product from melting during drying, we recommend setting the target value for the drying vacuum so that the product temperature is about 10 °C lower than the solidification temperature (eutectic point or glass transition point).

The vacuum can be calculated from the sublimation pressure curve of the product. For water, this "conversion" is already integrated in Christ freeze-dryers. For mixtures of solvent and water, the user must apply values from the literature, or experiments must be performed as described in Section 4.2.

Example for water

Solidification temperature t_{eu} = –10 °C
Drying temperature t_{tr} = –20 °C
–› Drying vacuum p_{dr} = 1.030 mbar
Safey temperature t_{safe} = -15 °C
–› Safety vacuum p_{safe} = 1.650 mbar

Figure 4.11 Procedure for determining the drying vacuum and safety vacuum from the sublimation pressure curve for water.

In large freeze-dryers with shelves with liquid temperature control, an alarm pressure can also be set. If the pressure in the drying chamber rises to the alarm setting despite the power supply being cut off, the shelves are chilled down to a lower temperature as quickly as possible. This alarm temperature should be about 3 K below the melting point.

Example for water

Solidification temperature t_{eu} = –10 °C
Drying temperature t_{tr} = –20 °C
–› Drying vacuum p_{dr} = 1.030 mbar
Safety temperature t_{safe} = -15 °C
–› Safety vacuum p_{safe} = 1.650 mbar
Alarm temperature t_{alarm} = –13 °C
–› Alarm vacuum p_{alarm} = 1.980 mbar

Figure 4.12 Procedure for selecting the alarm pressure function

In terms of efficiency and time savings, for example when producing active pharma components, the goal is to work as closely to the solidification point as possible (up to just 2 K lower). Such processes must be secured with good product knowledge and extensive testing at the pilot scale.

Freeze-drying can be described mathematically as a complex heat and material transport problem.
This model can be solved only by making simplifying assumptions.

4.3.3 Influence of energy input on process time

For the sublimation process, energy must be added to the product. For drying in round bottom flasks, large-mouth bottles, etc., this comes from the much warmer surrounding area via thermal conduction or convection. For unheated shelves, the energy input comes from thermal radiation from the surrounding area, while the energy input for temperature-controlled shelves comes mostly through thermal conduction from the heated shelves.

The influence of shelf temperature control is shown in Figure 4.13.

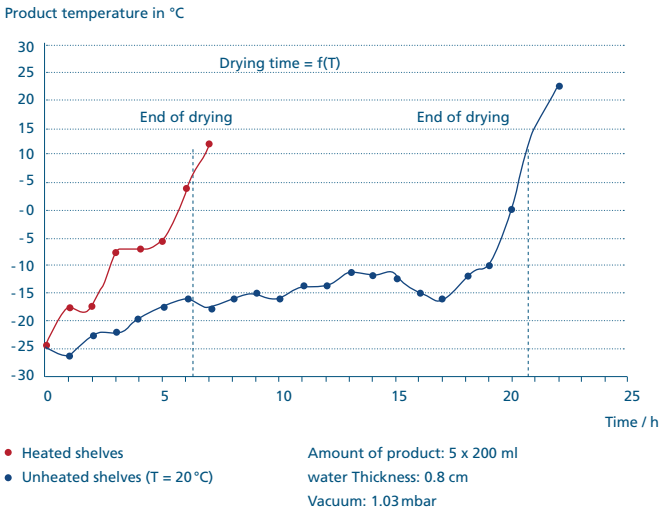


Figure 4.13 Influence of shelf temperature control on Drying speed (pure water) [6]

In a lab test with pure water, the influence of shelf temperature control was determined. The influence of shelf temperature observed in practice will be lower, as lower pressures are typically used. The product cake that is produced also creates resistance to the water vapor flow, causing the drying time to be longer.

Freeze-drying of frozen liquids, sludges, suspensions, etc. in dishes should be performed in systems with heated shelves. For fragmented or irregularly shaped materials such as plants, fruits, or archeological objects, however, shelf heating is unnecessary, as the contact surface for heat transfer is irregular or too small. As with flask drying, the required energy is provided in this case by ambient heat radiating through transparent Plexiglas covers. The energy input cannot really be controlled here, however. Only the case of product thawing (too much heat input) can be countered with insulation.

For freeze-drying in bottles, one other influencing factor is the insulating effect of the bottle material and the geometry of the hollow floor. The effects of these two factors can be seen in Figure 4.14.
On the right is the temperature profile along the vertical axis of a crimped-top vial during primary drying.

The heat flow to be transferred for sublimation can be increased by a good thermal transfer coefficient or greater temperature differential.
In the example in Figure 4.14, the (nearly) constant heat flow from the shelf to the sublimation front results in the temperature profile shown.

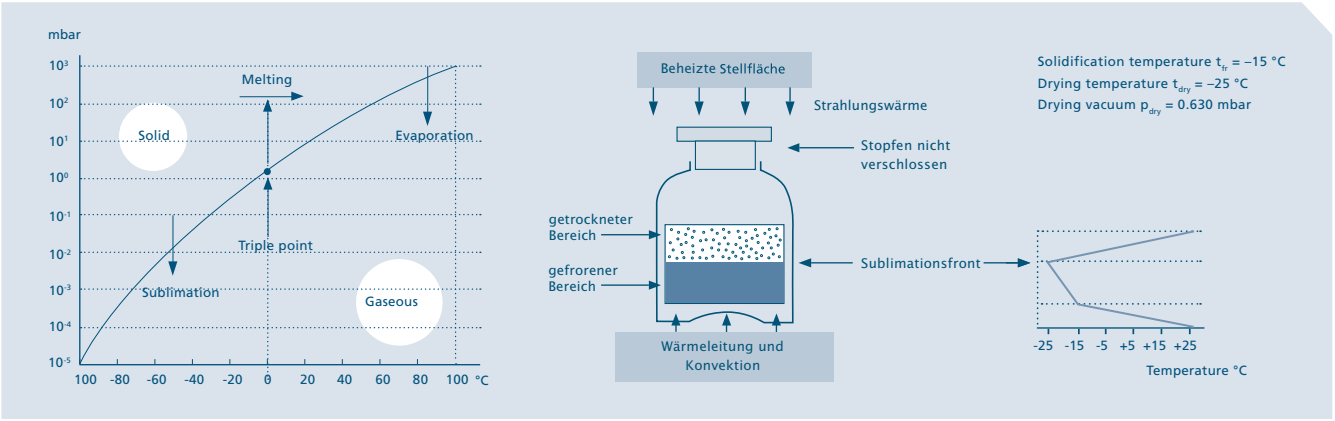


Figure 4.14 Simplifiedtemperature profile in a crimped-top vial during primary drying

The insulating effect of the bottle material and the geometry of the hollow floor of the vial in this example result in a very large temperature drop from +25 °C at the shelf to -15 °C at the base of the vial, where the frozen product is present. The relatively good thermal conductivity of the ice brings about a smaller temperature differential in the product from the base of the vial to the sublimation front further up. The following relationship applies to the thermal permeation:

the ice temperature is determined by the sublimation pressure curve. The temperature in the product cake above this is determined by the radiant heat input from above and by the cooling effect of the permeating water vapor flow.

$$\dot{Q} = k \cdot A \cdot \Delta T$$

$\dot{Q}$: heat flow [$W = \frac{J}{s}$]

k: Thermal transfer coefficient [$\frac{W}{m^2 K}$]

A: Cross-sectional area for heat transport [m^2]

ΔT: Driving temperature differential [K]

The situation in practice is shown in the following Figure 4.15.

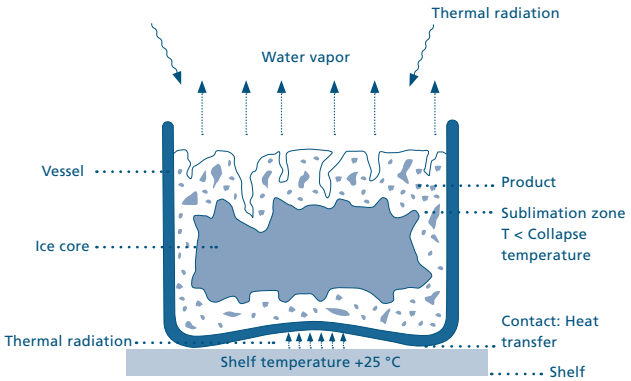


Figure 4.15 Mechanism of freeze-drying in a product dish or vial

The drying curve for primary and subsequent final drying of a substance with solid content is shown in Figure 4.16.

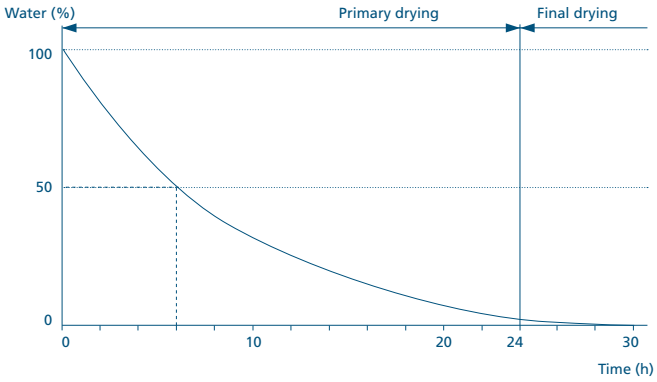


Figure 4.16 Asymptotic curve for drying

In the first quarter of primary drying, 50% of the water vapor is produced, then in the next quarter, again 50% of the remaining water content, etc., until the asymptotic drying curve approaches a low value. This typical drying curve occurs because the sublimation level in the product moves down and the water vapor must flow through the already dried layers. As drying progresses, the internal resistance becomes greater. The drying curve is largely determined by the sublimation heat input and the water vapor transport speed. In order to increase the thermal conductivity of the material to be dried, and to produce the smallest possible volume of vapor, drying should be done as close to the solidification point (eutectic temperature or glass transition temperature) as possible.

The closer the vacuum can approach the solidification point according to the sublimation pressure curve, the shorter the primary drying time.

In practice, the product temperature during drying is largely determined by the preselected vacuum, and less by the shelf temperature.

Final drying is an option that is used when minimal residual moisture is to be obtained. In the physical sense, it is a desorption process, that is, the removal of adsorptively bonded residual solvent. The ice phase should no longer be present. Final drying is performed at the lowest possible final pressure in the system, typically supported by an increased shelf temperature (e.g. from +20°C up to +30 °C), in order to facilitate removing the solvent molecules that are present only in thin layers on the surfaces of pores.

The term **'virtual leak'** describes the phenomenon that liquid remaining in the freeze-dryer from previous drying cycles can give the impression of a real leak. Due to continuous sublimation, the vacuum that is theoretically possible is never achieved.

5 Practical aspects

5.1 Preparation phase (warm up/cool down)

The opportunity to warm up the vacuum pump in a freeze-dryer should be used. It is beneficial to the service life of the vaccum pump if it is not loaded with condensable gases until the operating temperature of the pump has been reached. To do so, the vacuum pump can run with the pressure control valve closed during the freezing cycle. The vacuum pump should warm up for at least 15 minutes and be switched on prior to starting primary drying.

In some circumstances, it is possible for the vacuum in the ice condenser chamber or in the drying chamber to improve during primary drying (e.g., from 0.63 mbar to 0.47 mbar) even though the valve to the vacuum pump is closed. This is physically due to the pumping effect of the ice condenser (cryopumping effect).

5.2 Shell freezing and spin freezing

If liquids are to be dried in bottles in layers greater than 1 cm, then we recommend using a shell or spin-freezing device (see Figures 5.1 and 5.2) in a chilling bath for freezing. Due to centrifugal force, the liquid to be frozen climbs up the inside walls of the bottle and freezes solid. This freezing method reduces the layer thickness and thus increases the surface area available for sublimation, which substantially reduces overall drying time.

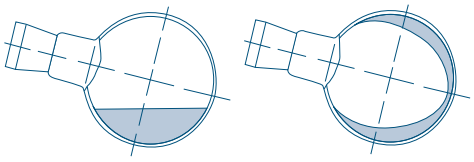


Figure 5.1 Shell freezing in round bottom flasks

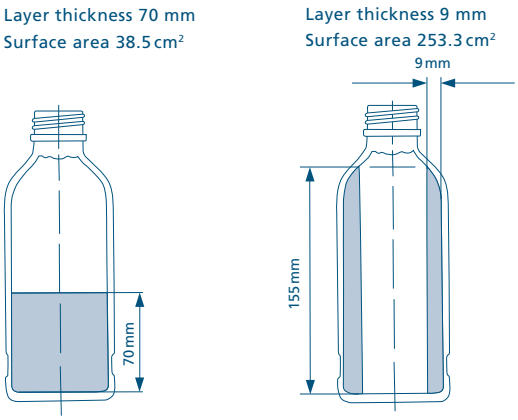


Figure 5.2 Spin freezing in infusion vials.

If 250 ml of substance is added to a 500 ml blood bottle, for example, as shown in Figure 5.2 , then the resulting layer thickness will be about 70 mm. By spinning the vertically oriented bottle, the liquid is distributed evenly over the inner wall by centrifugal force, resulting in a uniform layer thickness of about 9 mm.
The spinning takes place in a cooling bath. The use of the spin freezing method ensures homogenous and uniform freezing. Increased concentration, changes in volume, and variations in ice crystal formation in the substances are largely eliminated.

Figure 5.3 Cooling bath for freezing round bottom flasks or wide mouth bottles while spinning

5.3 Achievable vacuum levels

The sublimation pressure curve, that is, the relationship between the ice temperature and the sublimation pressure that it gives rise to, affects everyday applications:
In freeze-dryers with a single-stage refrigeration system, a temperature of –55 °C is typically achieved at the ice condenser. The target value for the vacuum in the chamber is typically a minimum of 0.021 mbar for water as a solvent; see the illustration, right. If a lower target value is set for the chamber pressure, there is a risk that the ice at the ice condenser will desublimate and flow toward the vacuum pump. This should be avoided in practice, as it could damage the vacuum pump and the water vapor or solvent could be pumped away by the vacuum pump.

The lowest target value for the vacuum in dual-stage chilling systems, in contrast, is limited by the final vacuum of the rotary vane pump that is typically used, that is, to about 0.005 mbar. The sublimation pressure above the ice condenser, which has a temperature of about –85 °C, is initially a power of ten lower, that is, 0.0005 mbar. This prevents desublimation at the ice condenser.

The theoretical values given here can be achieved only in completely dry devices. The example given here for the least target values apply to water as the solvent. For other solvents, such as organics, lower temperatures are required at the ice condenser in order to achieve desublimation of the solvents at the ice condenser. There are special freeze-dryers for use with solvents, with ice condenser temperatures of -105 °C and special materials particularly suitable for use with solvents.

°C	mbar	°C	mbar	°C	mbar	°C	mbar
0.01	6.110	–20	1.030	–40	0.120	–60	0.011
–1	5.620	–21	0.940	–41	0.110	–61	0.009
–2	5.170	–22	0.850	–42	0.100	–62	0.008
–3	4.760	–23	0.770	–43	0.090	–63	0.007
–4	4.370	–24	0.700	–44	0.080	–64	0.006
–5	4.020	–25	0.630	–45	0.070	–65	0.0054
–6	3.690	–26	0.570	–46	0.060	–66	0.0047
–7	3.380	–27	0.520	–47	0.055	–67	0.0041
–8	3.010	–28	0.470	–48	0.050	–68	0.0035
–9	2.840	–29	0.420	–49	0.045	–69	0.0030
–10	2.560	–30	0.370	–50	0.040	–70	0.0026
–11	2.380	–31	0.340	–51	0.035	–71	0.0023
–11	2.170	–32	0.310	–52	0.030	–72	0.0019
–13	1.980	–33	0.280	–53	0.025	–73	0.0017
–14	1.810	–34	0.250	–54	0.024	–74	0.0014
–15	1.650	–35	0.220	–55	0.021	–75	0.0012
–16	1.510	–36	0.200	–56	0.018	–76	0.0010

Sublimation pressure curve for water

5.4 PAT tools for measuring product temperature

The residual moisture content of the product to be dried depends essentially on the product temperature during final drying, and on the final vacuum achieved during final drying.

The end of the primary drying phase is reached when the product temperature and the shelf temperature are approximately equal. In practice, the temperature differential between the shelf and the product is about 3 K to 5 K. If the adsorptively bound water is to be removed from the product, then a transition to the final drying phase can be made.

The product temperature can be measured by wired product temperature probes (Figure 5.4) or wireless product temperature probes (Figure 5.5).

Figure 5.4 shows an example of placement of wired product temperature probes.

Figure 5.4 Product probe in a crimped top vial filled with an active agent to about 1 cm depth, and in a sponge-like product

Figure 5.5 Wireless product probes with no battery are user-friendly and do not affect the product temperature

A rough estimate of the end of drying can be made using the vacuum and the ice condenser temperature. The ice condenser is then no longer under load, and reaches the final temperature. The pressure in the drying chamber drops according to the ice condenser temperature.

The end of drying is reached when the temperature of the samples and shelves are significantly positive (15 to 20 °C) and deviate from each other by no more than 5 K. This index is more reliable than observation of the vacuum and ice condenser.

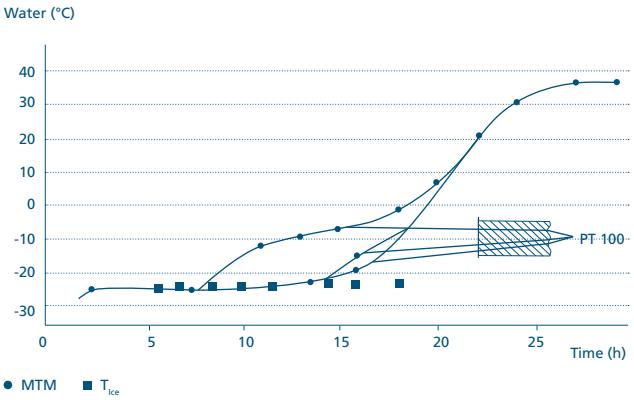


Figure 5.6 Effect of the position of a temperature probe in the product [4]

Figure 5.6 shows the significant effect that the position of the temperature probe in the vial has on the recorded product temperature.

Because the samples, as a first approximation, dry out from the top to the bottom, the highest of the three temperature probe positions in Figure 5.6 indicates a temperature rise after just about 7 hours. Because the sensor is cooled by the water vapor flowing from the sublimation boundary surfaces located below it, the product temperature does not rise above the 0 °C limit until about 20 hours later. The lowest of the three probes shows the most correct value, as the material just above the floor of the vial or dish dries last. The product temperature indicated by square symbols at the sublimation front was determined by means of the manometric temperature measurement method MTMplus.

Pressure rise test

For the pressure rise test, as proven in practical applications, the intermediate valve (see Figure 5.7) is closed for a longer period of time. The principle is based on separating the product chamber from the ice condenser, so that the sublimated water vapor cannot flow out. The result is more or less great rise that is measured in the pressure chamber. For a completely dried product, in contrast, the vacuum is not degraded, or only to a very slight degree.

The method is common practice at production scale. A prerequisite is that the freeze-dryer must always have the same load (number and type of vials or dishes). The pressure rise test is used in drying recipes as an automatic switchover criterion between primary and final drying, and for detecting the end of the process.

For sensitive products, the length of time that the intermediate valve is closed must be short, that is, a few seconds, in order to prevent the frozen material from collapsing or melting.

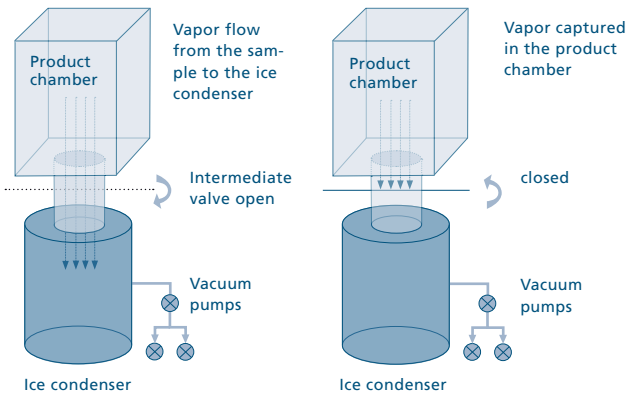


Figure 5.7 Principle of the pressure rise test

Manometric temperature measurement

In contrast to the use of sensors in selected vials for measuring the product temperature, manometric temperature measurement (MTM) is a non-invasive technology. A characteristic product temperature for the entire batch, and other significant parameters, are determined during freeze-drying, particularly during primary drying.

For the MTM measurement, the product chamber must be disconnected from the ice condenser for a timespan of typically 20 to 30 seconds. The ongoing sublimation and heating of the chamber (from the shelf heaters) causes the pressure in the product chamber to rise. The pressure at the sublimation front, along with other process parameters, can be determined from the time curve of the pressure rise using a physical model ("MTM" equation from Pikal [19]) by means of a mathematical method (nonlinear regression analysis). A characteristic product temperature can be calculated from this pressure, using the familiar sublimation pressure curve for the solvent used. The underlying physical models can also be used to calculate additional parameters.

For the static MTM measurement, the product chamber is usually cut off from the ice condenser for a fixed period of time. This means that there is a risk, especially at the beginning of primary drying, of an unallowable rise in pressure and therefore in temperature. With the dynamic MTM measurement developed by Christ (MTMplus), the pressure and temperature at the sublimation front are calculated during the measurement, that is, while the intermediate valve is closed. Because the iterative calculation convergence quickly, especially at the beginning of primary drying, the amount of time that the product chamber is cut off from the ice condenser can be significantly reduced to a few seconds, e.g. 5 to 10 seconds. At the same time, optimization of the calculation means that the fast closing of the intermediate valve that is usually required is unnecessary, which is advantageous particularly for larger freeze-dryers.

LyoBalance
For process development and optimization in pilot systems, LyoBalance from Christ is a unique tool.

Figure 5.8 Microscale from Christ for measuring vials and small dishes

This microscale uses the functional principle of electromagnetic force compensation. At intervals that the operator can select, the LyoBalance raises the vial periodically. The loss of mass, that is, the amount of sublimated solvent, can be used to determine the sublimation performance and the end of drying. The drying process as such is not disturbed, and the scale can be placed at any position on the shelves in the chamber.

Comparative pressure measurement
The comparative pressure measurement uses two different vacuum measurement probes to determine the end of drying.

Based on a change in the vapor composition, the process monitoring system simultaneously measures the vacuum using the Pirani and the capacitive measurement probe (comparative pressure measurement). Figure 5.9 shows both functional principles.

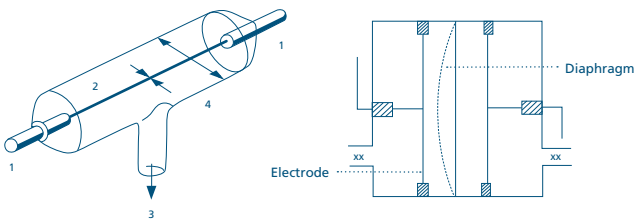


Figure 5.9 Principle of pressure measurement using the Pirani probe (left)

The measurement principle of the Pirani sensor is based on the fact that heat dissipation from the internal heating wire to the surrounding area depends on the pressure. This heat output affects the electrical resistance of teh wire and the current I that flows at a constant applied voltage U ($I = U/R$). Of course, the indirect relationship I = f(vacuum) must be established by calibrating the probe.
The calibration depends on the type of gas, as different gases and solvent vapors influence the heat transfer in different ways, and even the partial pressure of the vapor influences the pressure measurement. Typically, calibration is based on air with no water vapor content.
The capacitive probe is based on the deflection of the membrane of an electrical condenser as a function of pressure, which does not depend on the composition of the medium.

Because the Pirani probe measurement depends on the type of gas, and specifically measures too low a vacuum when the water vapor content is high at the beginning of drying, while the capacitive probe works independently of the type of gas, the end of primary drying is indicated by the two measurement curves approaching each other. See also Figure 5.10.

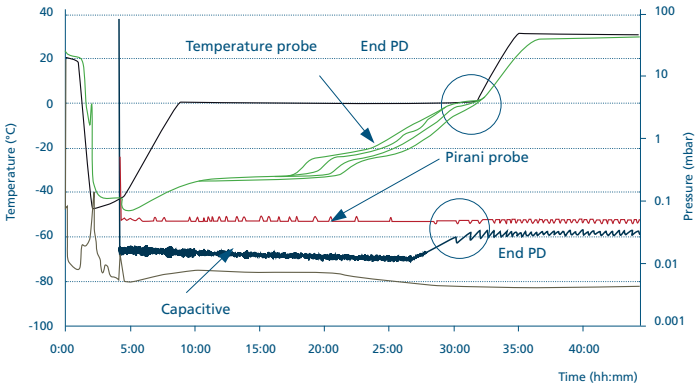


Figure 5.10 Determining end of drying with the Pirani probe and a capacitive sensor [5]

LyoCoN

As mentioned in Section 4.2, freezing is an important process step, so it makes sense to provide the user with a helpful tool. Due to thermodynamic constraints, freezing the same product in many vials is a stochastic process, not a simultaneous process. The different chilling times lead to different crystal structures and ultimately to inhomogeneity of the drying results. The LyoCoN method developed by Christ, which is based on the ice fog principle, triggers solidification abruptly by simultaneously injecting each vial with an ice crystal. A special feature of LyoCoN is that the ice fog is not generated externally, but instead comes from the product itself. The ice crystals previously formed on the cold ice condenser are transported into the evacuated individual vials in the form of a microscopic ice fog.

LyoCam

Because process times can extend over several hours, observation of drying is virtually impossible. On the other hand, process incidents that last only seconds or minutes can make the difference between a good or bad result. With the LyoCam, integrated in the LPCplus process visualization system, the product can be recorded and documented continuously in every program segment.

6 Summary of process management

Figure 6.1 shows a summary of the master parameters for the design of a freeze-drying recipe and its primary dependencies.

- **Freezing temperature** = f (solidification temperature)
  Vacuum = f (solidification temperature)
  –› Lyo-Rx, T-curve, DSC, Lyo-Microscope

- **Shelf temp. Primary drying** = f (time, vacuum)
  –› T probes, Lyo-Rx, some tests, Christ application tips

- **Process end for primary and final drying**
  –› T probes, pressure rise test, sampler,
  weighing cell, comparative pressure measurement (Figure 5.9)

Figure 6.1 Essential relationships for freeze-drying

The solidification temperature of the product is highly important. It can be measured provisionally by recording the temperature of the cooling curve in the freeze-dryer. At the freezing point, the curve will have a plateau, that is, the product will not cool down any further until the last drop of liquid has solidified. Alternatively, the reliable LyoControl method can be used to determine the freezing point; see Section 4.2. The method is slightly less accurate when amorphous structures are present. For such formulations used in the pharmaceutical field, tools such as Differential Scanning Calorimetry (DSC) or cryo-microscopy should be used.

The freezing temperature, that is, the temperature of the frozen product prior to the start of sublimation, should be set to about 10 K below the solidification temperature. According to the sublimation curve, the vacuum should be selected according to the value that is 10 K lower.

The profile for shelf temperature, which is needed for heat input as an energy supplier, rises during primary and final drying and can generally only be determined empirically. Figure 6.2 demonstrates the dependence of the sublimation speed on both the vacuum and the shelf temperature.

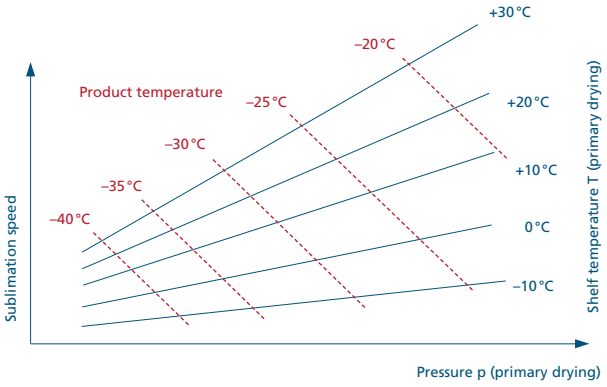


Figure 6.2 Dependency of the sublimation speed on the pressure p and the shelf temperature T with the correspondin isothermals for product temperature [19]

This illustration applies only at a particular point in time t, as the location of the family of curves changes when a dried, porous layer has been formed (increasing pressure loss). Determining a suitable temperature profile for shelf heating is based on an extremely complex thermodynamic heat and material transport problem. Some empirical tests with temperature probes and LyoControl are better than extensive theoretical considerations here. Christ has product-based suggestions available on the Internet (application area at www.martinchrist.de and the next pages of this application brochure) for a first attempt.

The end of the primary drying process can be determined using the temperature probe or the load cell; see Section 5.4. To determine the end of final drying, the sensitive method of the pressure rise test should be used, as the product temperature will no longer change and the sensitivity of the load cell is not always sufficient for measuring during desorption. Fundamentally, natural samples can be gathered during the process, by means of what are known as manipulators or samplers, for chemical analysis of the residual moisture content.

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It is very difficult to map freeze-drying processes in a process model as they involve complex heat and material transport processes.

Algae

Process engineering (overview)

Freezing	Solidification range, solidification point SP	Vessel for the FD	Method A / B	Vacuum primary drying
–35 °C, freezing favorable in LN2	–15 to –25 °C	Wide mouth bottles, dishes	A	$T_{Ice} = T_{SP} - 10\,°C$ $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
–10 °C / 4 h, 0 °C / 4 h, +10 °C / 4 h, +20 °C / 12–24 h	6–24 h	not necessary

Process engineering (special features)

- aqueous material (not previously dewatered or pretreated), shaggy consistency
- severely hygroscopic
- different SP's depending on the type of fresh or salt water algae

Brief description of the market

Field of application of the freeze-dried products / Industry of FD users

- Food products industry (added as flavor enhancer, high protein content)
- Cosmetics

* Explanation	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

It is generally more efficient to run several optimization tests with the
- product in question. These application examples are inten-

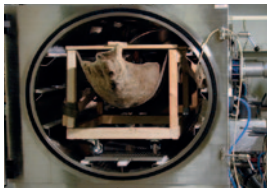
Books, archeological objects

e.g., wood, textile, leather

Process engineering (overview)

Freezing	Eutectic range	Vessel for the FD	Method A / B	Vacuum primary drying
Books: Freezing in the deep freeze at –10 °C. Arch. objects –30 °C	approx. 0 °C to –3 °C	Steel cabinet / chamber, Plexiglas tubes	B	$T_{Ice} = T_{SP} - 10$ °C $p_{HT} = f(T_{Ice})$ → Ice pressure curve = 2.560–1.980 mbar

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
–30 °C / 10 h, increase by 5 °C every 10 h, but heating via the shelves is often not possible	t = 3–8 days, depending on the object (up to several weeks for archeological objects), end of drying via pressure rise measurement, barometer on the cabinet	No final drying for books



Special dryers for archeological objects, loaded here with a Viking dugout canoe

Process engineering (special features)

- Books must be standing upright (on a frame), as otherwise it is not possible to transport the vapor away
- Heat transfer possible and successful in the 'safe' as well, working near the eutectic point.
- Heating is damaging to books (deformation due to uneven drying), infrared heating could be possible (with a lamp on the back side of the cabinet)
- Objects of identical size when possible for uniform drying, for example, folders

Field of application of the freeze-dried products

- Recovery, restoration,
  Ex.: soaked building permits
  at public agencies after water damage

Industry of FD users

- Libraries, museums, public agencies

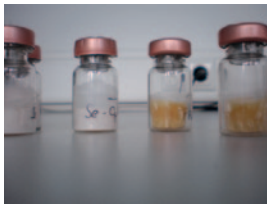
* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Bacteria, viruses, fungi, vaccines

Process engineering (overview)

Freezing	Solidification range, solidification point SP	Vessel for the FD	Method A / B	Vacuum primary drying
–50 °C and lower	–40 °C and lower	Crimped top bottles, vials, ampules, dishes	A or Epsilon in production areas	$T_{Ice} = T_{SP} - 10$ °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
–50 °C / 5 h, increase by 5 °C every 5 h at first (4–5 x), then reduce time intervals incrementally to 3 h and 1.5 h; LyoControl is highly recom-	24–48 h	only in exceptional cases (can be reduced)



Various bacteria cultures in vacuum-sealed and crimped top bottles

Process engineering (special features)

- Lab systems:
  Disinfection (H_2O_2) and gas sterilization (possible)
- Disinfection / decontamination:
  Liquid cleaning (alcohol, etc.), germs may still be present afterward Special cleaners are recommended for Plexiglas
- Systems in production areas usually must be able to be steam sterilized
- Sterilization: with steam > 121 °C, complete germ reduction
- Work according to GMP (Good Manufacturing Practices) and FDA (Food and Drug Administration) requirements is common

Area of application of freeze-dried products

- For human and animal vaccines
- Ampules are closed under vacuum with melter
- Vials are closed under vacuum or N_2 atmosphere using special closure device (accessory) (vacuum of 800 mbar) prevent excess air diffusion into the closed vial during storage and is sufficient to keep the sample sterile

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Flowers, fish

Process engineering (overview)

Freezing	Eutectic range	Vessel for the FD	Method A / B	Vacuum primary drying
Deep freezer –35 °C, eutectic range is difficult to determine (possibly after homogenization)	to –15 °C	see books, large-volume chambers	B	$T_{Ice} = T_{SP} - 10$ °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying	Duration of final drying
Not used, see books	1 d to 1 week (depending on dimensions of object)	minimal	3 h–10 h

Freeze-dried fish subsequently painted with preservative varnish

Process engineering (special features)

- No temperature profile required
- Fish: Remove innards to reduce layer thickness
- Flowers: are hung upside-down in racks
- Note: tissue (bodily fluid) contains $CaCl_2$, so so that organisms resist the cold, so therefore the freezing point is rather low

Brief description of the market

Flower seeds after freeze-drying

Field of application of the freeze-dried products

- Fish: Anglers, art objects, display materials (schools)
- Flowers: high water content, succulent varieties (water plants) for decorative purposes

Industry of FD users

- Fish: Conservators, anglers,
- Flowers: nurseries, biological institutes, generally smaller companies

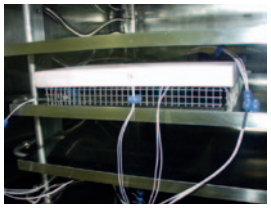
* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

collagen, tissue samples, thymus

Process engineering (overview)

Freezing	Solidification range, Solidification point T_{SP}	Vessel for the FD	Method A / B	Vacuum primary drying
pre-chilled inLN2 or on the shelf collagen: –45 °C	collagen: around –35 °C, Tissue samples: –56 °C (containing $CaCl_2$)	special dishes, special formats (L x W, cavities)	A	$T_{Ice} = T_{FP} –10$ °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve = 0.070 mbar to

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
–30°C / 5 h, increase by 5 °C every 5 h at first (5–6 x), then reduce time intervals to 2 h	36 h	needed in order to remove capillary water, Final vacuum of the pump (to $1*10^{-3}$ mbar)



Collagen tray during sample drying

Process engineering (special features)

- Cooling speed ≥ 1 °C / min
- Prevent damage to cell walls with anti-freeze agents (displace water in the cell wall and prevent denaturing)
- Heat moderately to avoid thawing (cells burst!)

Brief description of the market

Field of application of the freeze-dried products

- collagen for cosmetics, sits between epidermis and subcutaneous tissue (moisturizer, cell renewal)
- Tissue for transplants (bones, veins, scalp aortic valves) are available in lyophilized form

Industry of FD users

- Physicians clinics, beauty treatment spas, increasing applications

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Fruits, vegetables, meat

Process engineering (overview)

Freezing	Eutectic range	Vessel for the FD	Method A / B	Vacuum primary drying
Fruits, vegetables –35 °C; meat: –40 °C	–25 °C	Dishes	B	$T_{Ice} = T_{EP} –10 °C$ (= -35 °C) $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying	Duration of final drying
Fruits, vegetables: 0 °C / 4 h, 10 °C / 4 h, 20 °C / 16–24 h) Meat: –10 °C / 4 h, 0 °C / 4h, +10 °C / 4 h, +20 °C / 12–24 h	24–36 h	Cost question, normally not available	optional

Freeze-dried tropical fruits ('arils')

External freezing of truffles in a freezer

Various food products that are also freeze-dried

Process engineering (special features)

- Meat is cut up to an edge length of about 1 cm (in pieces)
- Packaging for freeze-dried products must be air, vapor, and gas-tight

Additional information

- if the price per kilogram is > 10 euros (market price), then freeze-drying is interesting,
- Amortization period for freeze-drying systems is at least ten years
- Doubling capacity (throughput) means reduction of 10 to 20 percent in specific production costs
- 1/10 of the amount of the fresh product has the same flavor intensity when freeze-dried

Field of application of the freeze-dried products

- Fruits: baby food, dairy industry (flavoring of dairy products),
- Vegetables: Culinary herbs
- Meat: only as a flavor enhancer (granulated, ground in grinders when freeze-dried)

Industry of FD users

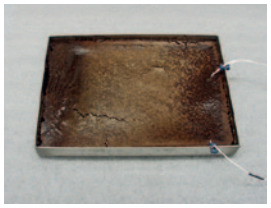
- Food products industry
- Contract drying

Gelatins

Process engineering (overview)

Freezing	Solidification range, solidification point SP	Vessel for the FD	Method A / B	Vacuum primary drying
–25 to -30 °C	less than –20 °C	Dishes	A	$T_{Ice} = T_{SP} - 10$ °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
sensitive, incremental heating is absolutely necessary –10 °C / 4 h, 0 °C / 4 h, +10 °C / 4 h, +20 °C / 12–24 h	24–48 h	No



Freeze-drying of lecithin that tends to form skin

Process engineering (special features)

- Viscous material, may form a skin and critical for the process
- Hygroscopic
- The resulting cake is then pulverized

Brief description of the market

Area of application of the freeze-dried products / Industry of FD users

- Intermediate product for the pharmaceutical industry (substrate, filler), food products industry (binders)

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Royal jelly, honey

Process engineering (overview)

Freezing	Solidification range, Solidification point SP	Vessel for the FD	Method A / B	Vacuum primary drying
Per methods A and C, pre-chilled shelves, sudden freezing, typically to -40 °C	to -40 °C	Dishes	A	$T_{Ice} = T_{EP}$ -10 °C (= -35 °C) $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
-30 °C / 5 h, increase by 5 °C every 5 h at first (5 to 6 x), then reduce time intervals to 2 h	24–36 h	Case by case

Process engineering (special features)

- For production scale, single chamber systems are suitable
- Product is highly hygroscopic, package quickly
- Flavorings and sugary substances tend to form skins during the drying process

Brief description of the market

Field of application of the freeze-dried products

- Medications, nutritional supplements, and restorative remedies

Industry of FD users

- Pharmaceutical companies, individuals

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Ceramic powders

Process engineering (overview)

Freezing	Solidification range, solidification point SP	Vessel for the FD	Method A / B	Vacuum primary drying
to –20°C, separately or in the system	less than –10 °C (that is, 0 to –10 °C)	Dishes or molds	A	$T_{Ice} = T_{SP}$ –10 °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
–10 °C / 4 h, 0 °C / 4 h, +10 °C / 4 h, +20 °C / 12–24 h, incrementally, rapid heating possible, up to +80 °C	2–24 h	No

Cylinder made of special porous ceramic (intermediate stage, not a finished product)

Process engineering (special features)

- Initial material is ceramic powder and binder

Brief description of the market

Field of application of the freeze-dried products /

- *Industry of FD users*
- Used as a ceramic base structure, for example, for compound materials

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Sewage sludge, soil samples

Process engineering (overview)

Freezing	Solidification range ('solidification point')	Vessel for the FD	Method B	Vacuum primary drying
at about –35 °C	–25 °C	Dishes with screens to retain very fine silt particles	B	$T_{Ice} = T_{EP} -10$ °C (= -35 °C) $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying	Duration of final drying
0 °C / 6 h, 30 °C / 18 h	Sludge: 24 h Soil: 24–36 h	not necessary	not applicable

Process engineering (special features)

- Material of the dishes: Al (greater deformation) or stainless steel, possibly Teflon-coated for heavy metals
- Use product screens with finely-grained soils
- DIN 38414/22 (Sample preparation) contains information on cost-effective working pressure, safety pressure, the necessity of a pressure control valve, heatable shelves, and general sample preparation)

Brief description of the market

Field of application of the freeze-dried products

- Analysis labs, industrial environmental departments
- Evaluation of contaminants

Industry of FD users

- Environmental agencies, analysis labs, sewage treatment plants, water utilities

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Microbiological products, fermented products

e.g. proteins, enzymes, blood serum, blood plasma, other blood products (albumin, fibrinogen, factors 8 and 9)

Process engineering (overview)

Freezing	Solidification range ('solidification point')	Vessel for the FD	Method A / B	Vacuum primary drying
200–500 ml spin freezing (in vertically immersed flasks, with appropriate cooling baths	–13 to –35 °C	5–500 ml flasks, dishes (albumin)	A Epsilon systems Base temperature	$T_{Ice} = T_{SP} - 10$ °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying	Duration of final drying
–30°C / 5 h, increase by 5 °C every 5 h at first (e.g. 3x), then reduce time intervals to 2 h	24 h (at 1 cm)	not at max. vacuum; set so that residual moisture is 2-5% (customer expertise)	2–4 h

Process engineering (special features)

- Freezing process: LyoControl recommended,
- max. product temperature 30 °C (denaturing at max. 37 °C),
- Seal under vacuum, but risk of inward air diffusion (better closure after N_2 gas immersion, see photo)

Brief description of the market

Field of application of the freeze-dried products

- Blood derivates for injection purposes

Industry of FD users

- Red Cross, pharma companies

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Dairy products

Process engineering (overview)

Freezing	Solidification range ('solidification point')	Vessel for the FD	Method A / B	Vacuum primary drying
Shell freezing (round bottom flasks) Spin freezing (cylindrical bottles), minimum –25 °C	–13 °C (cow's milk)	Dishes, Round-bottom flasks, Wide-neck bottles	B	$T_{Ice} = T_{SP} -10\,°C = -23$ $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
0 °C / 5 h, then increase to +25 to +30 °C	24 h	Final drying not required

Yogurt in liquid form and freeze-dried

Drying yogurt in stainless steel dishes

Process engineering (special features)

- none, insensitive product,
- Single chamber system can be used very well in production areas

Brief description of the market

Field of application of the freeze-dried products

- Mare's milk (remedy, valuable vitamins), goat's milk, camel's milk (Emirates), breast milk

Industry of FD users

- Mare's milk farms, pharmacies that wish to supply to a wider range

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Nucleic acids, peptides

Process engineering (overview)

Freezing	Solidification range, solidification point SP	Vessel for the FD	Method A / B	Vacuum primary drying
to –40 °C	to –30 °C	Nucleic acids: flasks Peptides: dishes, flasks, vials, ampules	A (nucleic acids) A and B (peptides)	$T_{Ice} = T_{SP} - 10$ °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
–30 °C / 5 h, increase by 5 °C every 5 h at first (5–6 x), then reduce time intervals to 2 h, often uncomplicated drying progression, that is, rapid heating is posisble	24–36 h	Case by case

Freeze-dried peptides in crimped top vials

Process engineering (special features)

- Hygroscopic material
- For production area, systems with automated cleaning (CIP), able to be steam sterilized in some cases

Brief description of the market

Area of application of the freeze-dried products / Industry of FD users

- Pharmaceuticals (additive, less active agent)

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Organic solvents

Process engineering (overview)

Freezing	Solidification range ('solidification point')	Vessel for the FD	Method A / B	Vacuum primary drying
evaporate solvents first with RVC	below –50 °C is possible	Dishes Sometimes flask drying (especially for ACN-water mixtures)	B	Depends on product

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
$T_{Fp.}$ –10 °C, Caution: avoid partial thawing if pore structure of the sample is important	Can only be determined experimentally for the wide variety of different substances (see below)	Depends on product

Process engineering (special features)

- Use the sublimation pressure curve for the solvent betrachten, sublimation pressure curve for water is not applicable

Brief description of the market

Field of application of the freeze-dried products

- Specialty market, preparation processes for the pharma industry, natural material extraction

Industry of FD users

- Chemical and pharma industries, market for specialty applications is growing

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
Method B Dual chamber method	Freezing separately (e.g., in a freezer), drying outside of the ice condenser, e.g. with Plexiglas cover
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Plant material

Process engineering (overview)

Freezing	Solidification range ('solidification point')	Vessel for the FD	Method A / B	Vacuum primary drying
–10 °C (to -40 °C in some cases) A, deep freezer, rarely LN2	–10 °C (to -30 °C in some cases)	Dishes, racks	A and B	$T_{Ice} = T_{SP} - 10\,°C$ $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
–10 to -15 °C / 5 h, increase by 5 °C every 5 h at first (5–6 x), then reduce time intervals to 2 h	36 h	Case by case

Shock-freezing of plant pollen in a lab freeze-dryer using LN_2

Process engineering (special features)

- Plant materials are usually insensitive
- Use caution with heat transfer, shelves transfer heat relatively poorly due to small surface area, Plexiglas covers work well due to radiant heat
- Such chambers can be built as needed

Brief description of the application

Field of application of the freeze-dried products

- Storage instead of expensive freezers that take up a lot of space
- Structural analysis of tissues, membranes
- Ingredient analysis (followed by extraction)

Industry of FD users

- Institutes of higher education
- Agricultural chemistry

* Explanations	
Method A Single-chamber method	(Freezing and) drying within the ice condenser chamber
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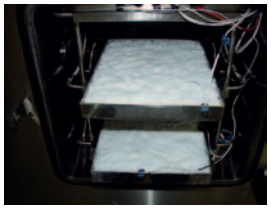
Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Polymers, tensides

Process engineering (overview)

Freezing	Solidification range ('solidification point')	Vessel for the FD	Method A / B	Vacuum primary drying
to -40 °C	–2 to –30 °C	Dishes	A	$T_{Ice} = T_{SP} - 10$ °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
-30 °C / 5 h, increase by 5 °C every 5 h at first (5 to 6 x), then reduce time intervals to 2 h	36 h	Case by case, for lower residual moisture



Drying polymers

Process engineering (special features)

- Caution, solvent may still be present (lowering the solidification point), but usually they will have previously evaporated
- Special conditions: aggressive starter components produce HS^-, Stainless steel 1.4571 is only somewhat resistant
- Viscous, honey-like solutions

Brief description of the market

Field of application of the freeze-dried products / Industry of FD users

- Quality control
- Application at production scale as well

* Explanations	
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Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

Urine / stool, residue analysis

Process engineering (overview)

Freezing	Solidification range ('solidification point')	Vessel for the FD	Method A / B	Vacuum primary drying
–40 °C	–30 °C	in flasks and dishes	A and B	$T_{Ice} = T_{SP}$ –10 °C $p_{HT} = f(T_{Ice})$ → Sublimation pressure curve

Temp. of the shelf during primary drying (T_{Sh} / t)	Duration of primary drying	Vacuum final drying
–30 °C / 5 h, increase by 5 °C every 5 h at first (e.g. 5–6 x), then reduce time intervals to 2 h	36–48 h	Case by case

Process engineering (special features)

- Products tend to thaw and foam up
- Products are severely hygroscopic and must be packaged immediately (bags, jars)
- Products have little to no odor after FD

Brief description of the market

Field of application of the freeze-dried products

- Residue analysis in the medical field

* Explanations	
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Epsilon	System with rectangular product chamber and shelves with liquid temperature control, front loader

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