Smart Freeze Drying

Basic principles, optimum procedures and applications

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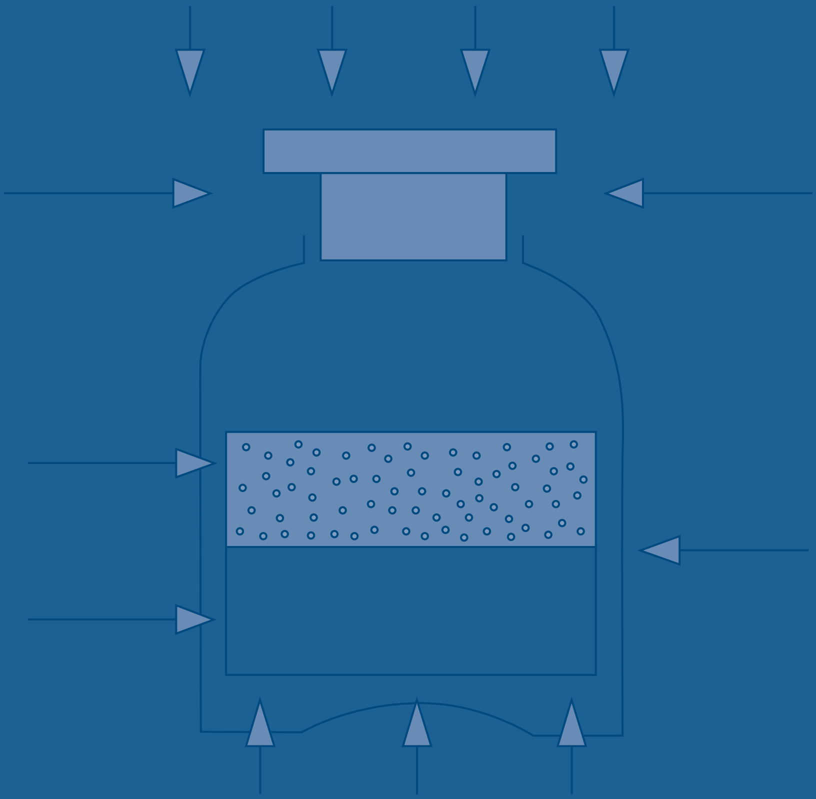

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The food industry accounts for the largest volumes of freeze-dried products, such as instant coffee, but biotechnology and pharmaceutical products, e. g. vaccines, require systems which meet the highest quality standards

1 Introduction

Freeze-drying or lyophilisation is an effective way of drying materials without harming them. It makes use of the physical phenomenon of sublimation, which involves the direct transition between the solid state and the gaseous state without passing through the liquid phase. To achieve this, the frozen product is dried under vacuum, without being allowed to thaw out. The process is suitable for a wide range of applications:

- for preserving the characteristics of the initial substance (e. g. pharmaceutical products, milk)
- or for preserving the initial form (e. g. taxidermy, or conserving archaeological finds or flowers)
- or conditioning materials (e. g. freeze-dried fruit in yoghurt)
- or chemical analyses (e. g. investigating trace organic substances in foodstuffs, slurries, soils)

Freeze drying is used for more than 30 categories of substances or materials. The most important markets are the pharmaceutical industry and biotechnology as well as the food industry.

In general, a distinction is made between freeze-driers used only in batch procedures, and continuously operating systems. Non-continuous systems are available to processes loads from 2 kg up to approximately 1000 kg. We specialise in this product group, and we are the only manufacturer worldwide to offer a complete range from laboratory bench-top systems and pilot freeze-dryers through to large-scale production machines:

Laboratory freeze-drying equipment

- Ice condenser capacity from 2 to 24 kg
- Mostly air-cooled refrigeration system
- Broad range of accessories for wide-range applications

Pilot freeze-drying systems

- Ice condenser capacity from 6 to 16 kg
- Air- or water-cooled refrigeration systems
- Freezing and drying in the drying chamber
- on liquid-controlled shelves

Production freeze-dryers

- Ice condenser capacity from 20 to > 1000 kg
- Water-cooled refrigeration systems
- Freezing and drying in the drying chamber on liquid-controlled shelves
- SIngle-or-double chamber systems
- Customized project engineering SIP/H_2O_2 disinfection, CIP, IQ/ OQ, …
- Process integration (loading systems, additional equipment)

Freeze drying under atmospheric conditions is widely believed to have been first developed by the aboriginal peoples living and hunting in the Arctic Circle, but this is a myth. In fact when they dry food it passes through a series of melting and evaporation processes, but the evaporation is so rapid that it is not possible to see any liquid phase forming.

2 Basic principles

The principle of sublimation can be explained with reference to a phase diagram (= vapour-pressure diagram). The process is usually carried out with aqueous systems, although in recent years freeze drying of solutions with special solvents have become increasingly important.

The vapour-pressure diagram shows the phase transition of the substance in a graph of pressure and temperature. For example, it shows the boiling point of water at precisely 100 °C at normal atmospheric pressure. At lower pressures, the boiling point is reduced (the principle on which vacuum distillation is based), and conversely, at higher pressures the boiling point is raised (which is the principle on which a pressure cooker operates).

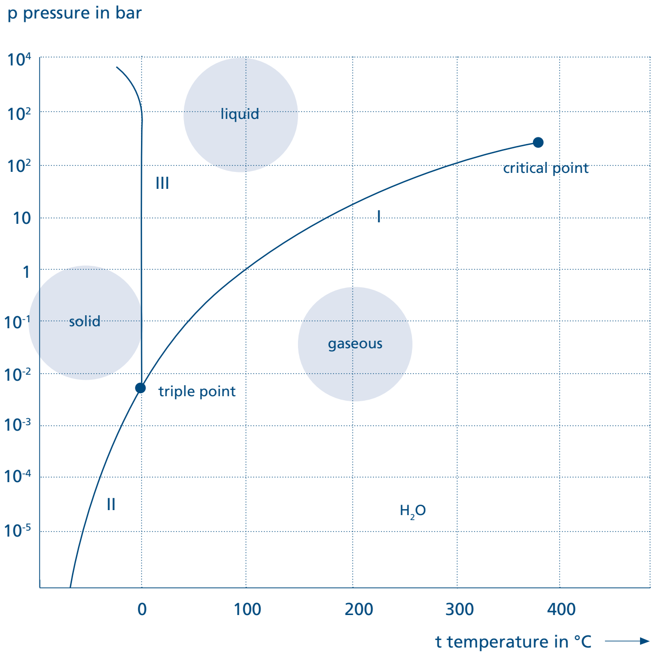


Figure 2.1 Phase diagram of water [1]

If the pressure is higher than 6.11 mbar, H_2O passes through all three states (solid, liquid, and gaseous) as the temperature increases or decreases. Below this point however, i. e. if the pressure is less than 6.11 mbar, it passes directly from the solid to the gaseous state. At exactly 6.11 mbar the melting-point curve, vapour-pressure curve and sublimation-pressure curve meet at the so-called triple point. At the triple point all three phases can coexist.

The following table contains values for part of the ice-pressure curve:

°C	≙ mbar	°C	≙ mbar	°C	≙ mbar	°C	≙ mbar
0	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
-17	1.370	-37	0.180	-57	0.016	-77	
-18	1.250	-38	0.160	-58	0.014	-78	
-19	1.140	-39	0.140	-59	0.012	-79	

For the conversion of units:

Pressure

1 mbar = 100 Pa = 1 h Pa
1 Pa = 0,010 mbar

Temperature

$T = t + 273$

$t = T - 273$

$t_F = 1.8 \text{ x } t + 32$

$$t = \frac{t_F - 32}{1.8}$$

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

Generally, a lyophilisator consists of a recipient (product chamber) in which the substance is placed, an ice condenser, and a vacuum pump. However, various technical developments have been made, and these are now incorporated in a wide range of available systems.

3 Freeze Dryer Design

The basic components of a freeze dryer are:

a) Vacuum drying chamber (see accessories catalogue)

b) Vacuum pump to extract air from the drying chamber (›gas pump‹)

c) Ice condenser operating at temperatures from - 55 °C to -105 °C (depending on the type of system) to extract water vapour from the chamber (›vapour pump‹)

d) Heated or unheated shelves for drying in dishes (see accessories catalogue)

e) Shelves with sealing device for drying in vials (see accessories catalogue)

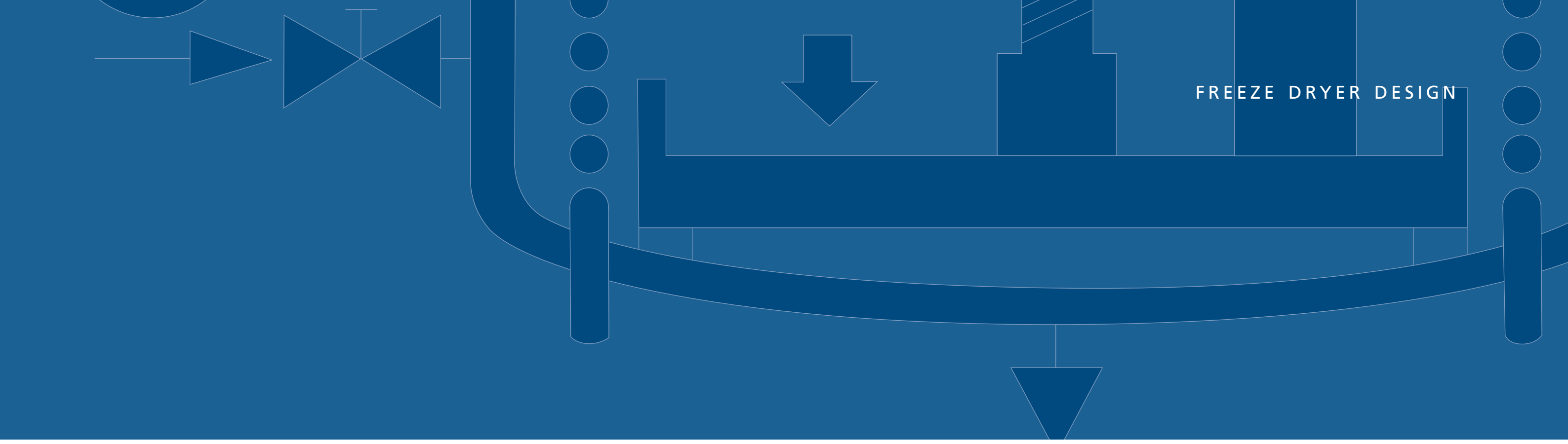
f) Rubber valves for the connection of round-bottomed flasks, wide-necked flasks, etc. (see accessories catalogue)

g) Manifolds for connection of round-bottomed flask, wide-necked flasks etc. (see accessories catalogue)

Figure 3.1 Freeze dryer with acrylic glass drying chamber (a) and rubber valves (f)

For both the laboratory freeze-dryers and the production-scale systems a distinction is made between single-chamber and double-chamber systems. Only the laboratory systems are presented here:

Figure 3.2 Freeze-dryer with sealing device for drying in vials (e) (placed inside during operations)



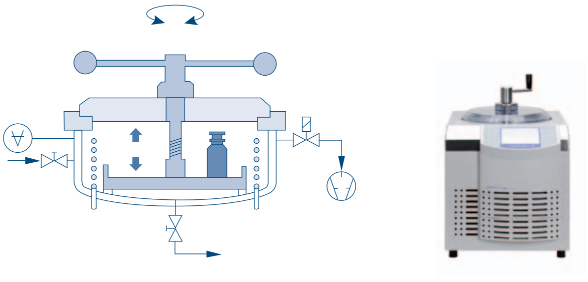


Figure 3.3 Laboratory system shown in single chamber operation

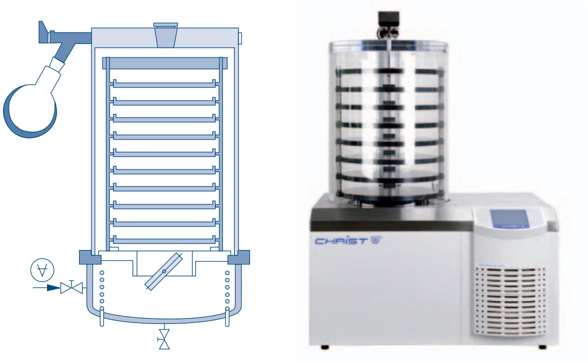


Figure 3.4 Laboratory system with two chambers

As shown in Figure 3.3, in the single-chamber system the freezing and then the drying of the product are carried out in the ice condenser. The freezing of the sample results from the low temperature of the ice condenser (-55 °C for the single-compressor system or -85 °C for the double-compressor system). The interior can then be cooled down to about -20 °C or -40 °C, respectively. Using a fan during the freezing phase proves to be very effective for transferring energy between the sample and the ice condenser (see Article no. 121423). During the primary drying phase it is necessary to introduce a moderate amount of energy to the frozen sample and this is provided from the heated shelf. The attachment unit shown in Figure 3.2 (see Article no. 121009) makes it possible after the completion of drying to close the injection vials under vacuum or inert gas, so that the freeze-dried sample is also vacuum-sealed.

In the array shown in Figure 3.4 the rack with shelves is under an acrylic glass cover outside the ice condenser, so that this is referred to as a two-chamber system. The advantage of this is that it offers a much greater product capacity for the same footprint area. Furthermore, by separating the product chamber off from the ice condenser (by means of the intermediate valve shown in the sketch) it is possible to carry out a so-called pressure-increase test to determine the end of the drying process. This is explained on page 27. The disadvantage is that it requires additional handling of the samples, which have to be frozen externally in advance, e.g. in a refrigerator or freezer. After transfer to the freeze-drier, the acrylic chamber is put in place and the sublimation itself is started. All laboratory systems from Christ which are equipped with shelf temperature control can be operated either as a single-chamber or double-chamber system as required.

4 Procedures

4.1 Overview

Before loading a new product, it is important to remove any water from the previous batch that remains in the ice condenser chamber. When this has been done the outlet valve and the ventilation valve are closed. The product should only form a layer of 1–2 cm, because if it is too thick this will have a detrimental effect on the drying time.

As shown in Figure 4.1, the freeze-drying process can be controlled by the selection and alteration of only two master parameters in the system:

Figure 4.2 shows a record of the freeze-drying process for a ceramic suspension. Because it has a freezing point near 0 °C and no difficult product properties, this can be freeze-dried already at a pressure of 1 mbar and with a shelf temperature of + 40 °C. As the drying reaching completion, the temperature sensors in the 3 cm-thick layer of the suspension (yellow, green and blue lines) reach values close to the shelf temperature.

Before this, a ›mixed‹ temperature is measured combining the sublimation temperature and the temperature of the dried cake. The ice condenser temperature (black line) rises at the start of primary drying from - 83 °C to about - 70 °C, because large quantities of water vapour have to be frozen out. After about 20 hours this effect has declined to some extent so that the ice condenser again reaches a temperature of about - 85 °C.

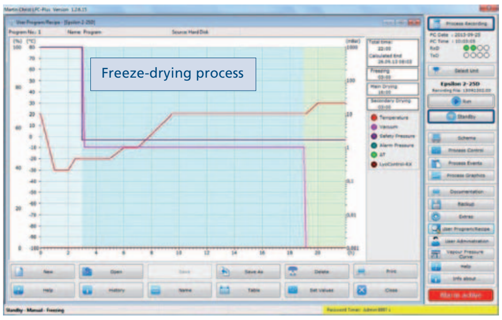


Figure 4.1 Vacuum and shelf temperature
Two key parameters of the system
· Vacuum p = f (FD-step)
· Shelf temp. T = f (process time)

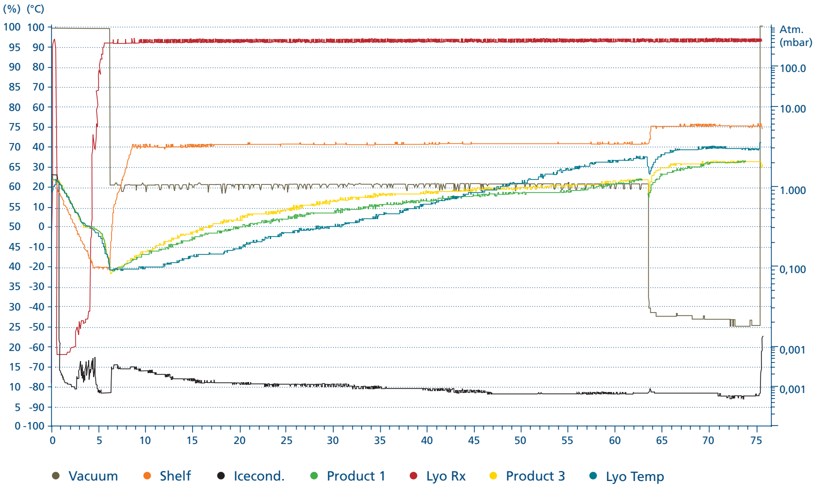
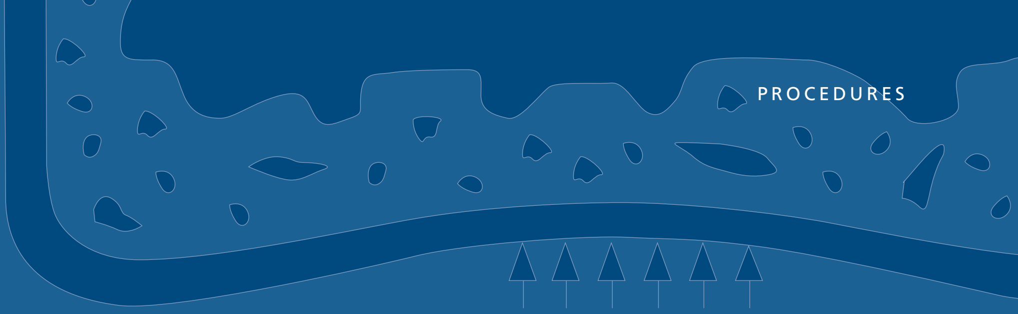


Figure 4.2 Process graph for the freeze-drying of a ceramic suspension



As a rule, the product is frozen under atmospheric conditions, analogous to a conventional freezer.

As already explained, the substance is frozen in small amounts in the ice condenser chamber (process inside) or separately in the laboratory in conventional freezer unit (process outside). A frozen product in round-bottomed flasks or wide-necked filter flasks is often preferred for drying because the flasks can be attached and removed separately, without affecting the drying process of the other flasks. As explained in Chapter 5.2, the time required for the drying is affected by the thickness of the layer, which can be considerably reduced by freezing under rotation rather than using conventional stationary freezing. The rotation leads to the formation of a uniform ice layer inside the glass vessel.

When freezing in a separate process it is advisable, particularly with small charges, to cool the shelf so as to avoid a partial melting during the evacuation process.

After the freezing, the system should then be taken through a warm-up / cool-down phase. The vacuum pump can warm up with the pressure control valve closed, and in this way improve its performance and its ability to withstand water vapour. At the same time the ice condenser is pre-cooled, so that it will be able to cope with the water vapour from the primary drying step. The preparation phase should take between 15 and 30 minutes.

In order to start the sublimation process, the pressure control valve to the vacuum pumps is opened so that the pressure drops. The primary drying is started.

The optional secondary drying involves reducing the pressure as low as possible in connection with a slightly elevated shelf temperature (both of these measures improve the desorption). This desorption phase is subject to different thermodynamic laws than the actual sublimation.

After the end of the process the drying chamber is aerated through a rubber valve or the ventilation valve. It is also possible to introduce nitrogen or an inert gas through the aeration valve. The system can then be switched off and the product taken out.

The ice condenser can be allowed to defrost at room temperature, or warm water can be used to speed up the process if necessary. The ice condenser chamber should not be more than half full of water. When defrosting the ice condenser in this way it is important to make sure that no water finds it way into the connecting pipes to the vacuum pump and the pressure gauge!

Condensation and defrosted water is drained off into a container through the drain valve. Before starting a new process any residual water in the system should be removed. The drain valve and aeration valve are then closed and the system can be loaded with the next batch.

The eutectic point is the point in a constitutional diagram at which an homogeneous eutectic alloy or mixture solidifies directly from liquid to solid state without forming a mix of phases.

4.2 Freezing

The freezing phase determines the microstructure formed by the solidified solution and thus also that of the dried product. A distinction is made between two different structures of frozen materials: the crystalline form is characterised by the presence of ice crystals with definite crystal boundaries. This is the case for most aqueous solutions with a low proportion of sugars or proteins. If the freezing is carried out slowly enough the mixture will separate out gradually until the final drop of liquid solidifies at the lowest possible temperature, the so-called eutectic temperature. In many cases the system does not keep to the thermodynamic equilibrium and the liquid becomes supercooled, possibly by as much as 10–20°C. Crystallisation can then be initiated suddenly by shaking or the introduction of a nucleus of crystallisation, and in this case the solid phase will not have a eutectic composition.

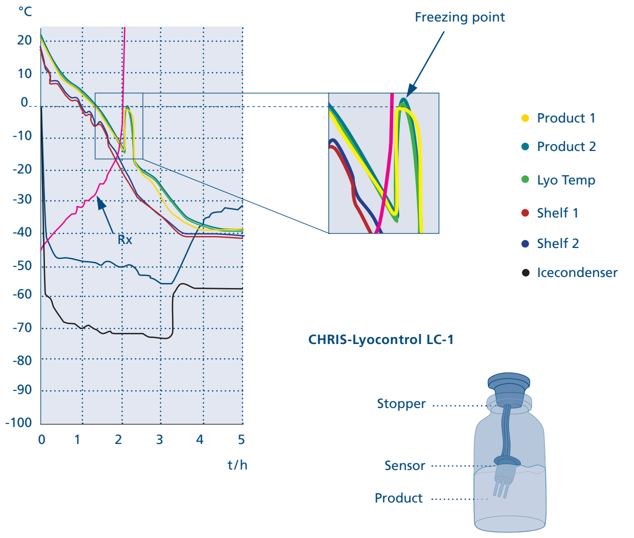


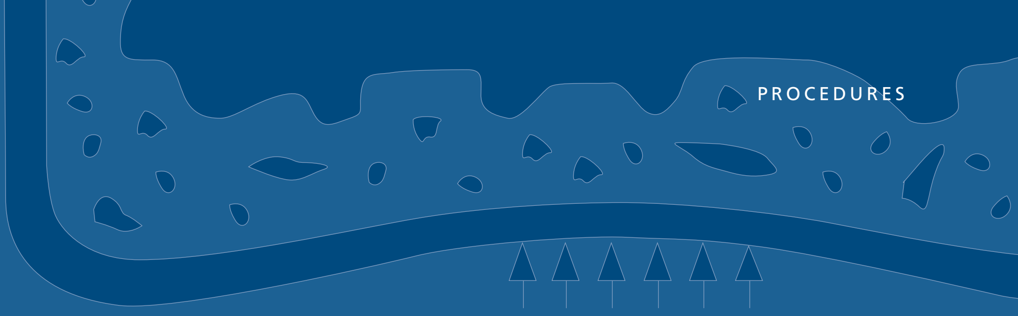
Figure 4.3 Determining the freezing point with CHRIST Lyocontrol

In contrast, amorphous substances do not have any crystal boundary, similar to a supercooled melt, e. g. window glass. Heating such a congealed solution does not lead to a sudden melting, but rather the material which has become softer begins to flow away. This is therefore referred to as the collapse temperature T_C. The glass transition temperature T_G refers to the solidification point from the liquid to the amorphous and is usually a few Kelvin lower than the collapse temperature.

▸ In the pharmaceutical industry amorphous matrices are preferred for embedding sensitive biomolecules because the active substance can be stabilised better. Conversely, crystalline products can be freeze-dried quicker and more easily because the grain boundaries favour the transport of water vapour.

▸ While the melting of a crystalline product during drying can lead to spattering and the risk of cross-contamination, with amorphous, honey-like substances there is at first ›only‹ a loss of structure. Although the product may not be impaired, any customer would object to being offered sticky crumbs. Many substances in the pharmaceutical sector have a longer shelf life if they are embedded in an amorphous matrix.

▸ The key aspect when determining the necessary shelf temperature and pressure during primary drying is the solidification temperature (= freezing point) of the material being dried. In addition to being dependent on the product in question, this is also dependent on the rate of freezing. As an example, the table in Figure 4.4 shows the wide range of eutectic points of microbiological culture media.



Sample	Eutectic Temperature/°C
Tab water	-1.0
Super pure water	0.0
UHT-Milk	-11.7
Skim-Milk	-11.0
Lactose 5 %	-1.0
Lactose 10 %	-2.0
mod. PC-med. (3 % NaCl)	-45.0
Litmus milk	-12.0
HGL	-12.0
BA bouillon	-29.0
Glucose bouillon	-6.5
Malt extract bouillon	-6.5
Yeast water	-1.5
YGC	-15.0
MRS bouillon	-20.0
M 17	-15.5
Basic medium streptococcus	-15.0

Figure 4.4 Eutectic point of various nutrient media [1]

The freezing point can be determined by means of

- the theoretical thermodynamic value (source: chemistry manuals, technical literature [e. g. VDI Thermal Atlas], references)
- Cryo-microscope
- DSC (Differential Scanning Calorimetry)
- measurement of temperature and resistance during the freezing phase

The electric resistance of the product being dried almost always rises dramatically with the transfer from the liquid to the solid state due to the reduced mobility of the ions and electrons. This means that by measuring the product temperature and electrical resistance at the same point it is possible to determine the freezing point.

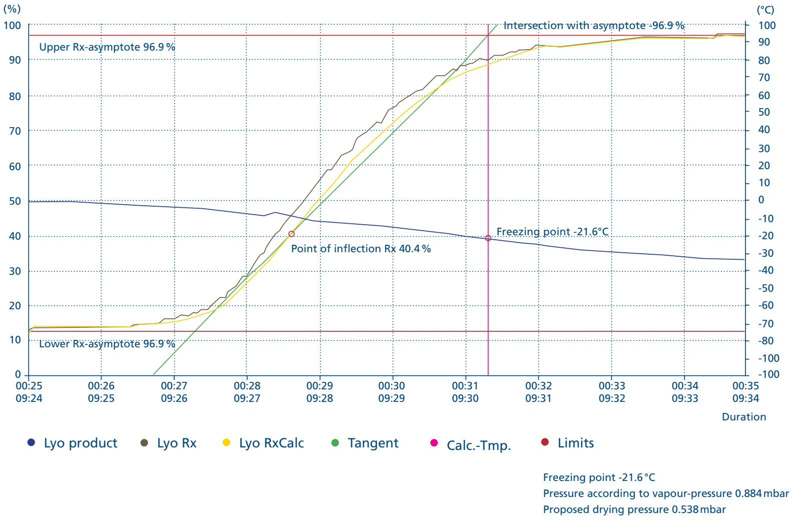


Figure 4.5 With a less rapid rate of increase of the Rx-value during solidification, the solidification point should be taken as the product temperature determined according to this figure.

Because there is usually a very abrupt rise in resistance, the intersection of the Rx- and T-curves can be taken as the freezing point with a very high level of accuracy. This has been confirmed by numerous measurements with various solutions.

> Amorphous substances – e. g. glass – have no crystalline boundary and behave like a frozen liquid. At the glass transition temperature T_G, the product starts to behave like elastic rubber and further begins to flow (collapse temperature T_C).

Figure 4.5 shows the determination of the eutectic point or more generally the freezing point. For a less steep rise of the Rx-value during the solidification then the solidification point should be taken as the product temperature at which the Lyocontrol resistance no longer changes.

The resistance is recorded as a percentage because it can vary over several orders of magnitude and the actual Ohm-value is not relevant for determining the freezing point. A further advantage of the Christ LyoControl system it the opportunity it offers to monitor the process. During primary drying the product can melt, leading to splattering, cross-contamination and possibly the loss of the batch, but this can be avoided by checking the Lyo-Rx level. The resistance can break down if the product is heated up too quickly. Figure 4.6 and Figure 4.7 show graphs for a non-sensitive product (resistance value always near 100 %) and for a very sensitive product which thawed out after only a few hours of primary drying.

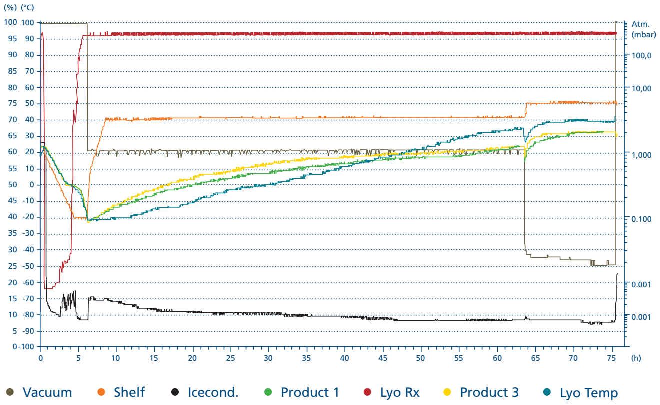


Figure 4.6 Plot of Lyo-Rx for a non-sensitive product

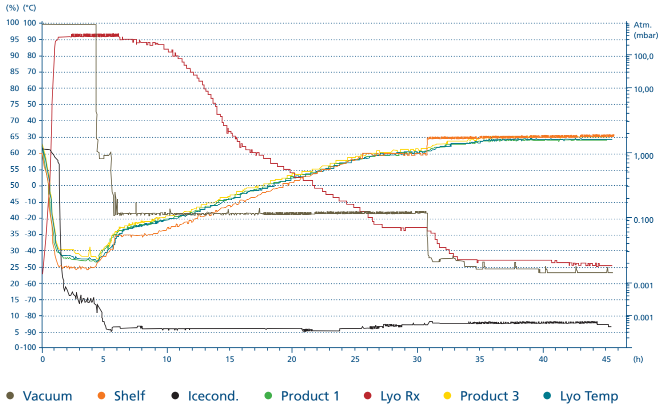
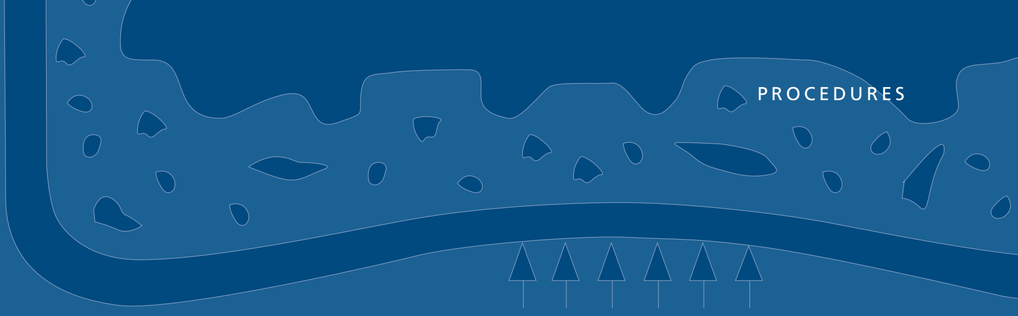


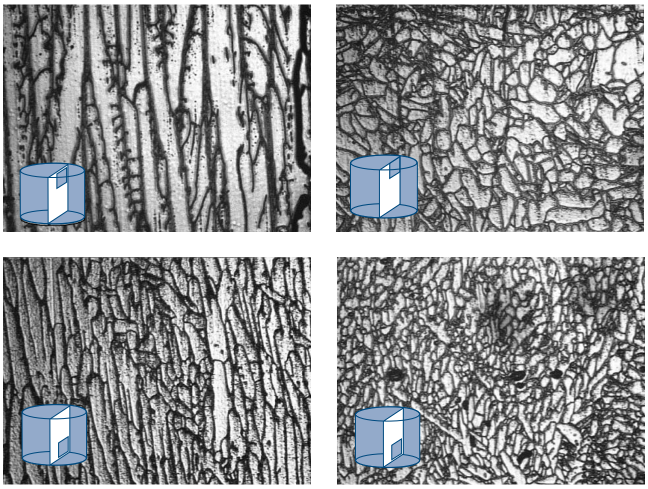
Figure 4.7 Plot of Lyo-Rx for a sensitive product which thaws out in the course of primary drying

With Christ pilot and production systems it is possible to specify an Rx minimum value in advance. Below this, the systems reverts to freezing mode, so that any of the product which has thawed out will be frozen again. The Lyo-Control System is able to accurately detect the freezing point of the solutions which solidify in a crystalline form, but is less good at reading off the collapse temperature of the amorphous substances used in the pharmaceutical sector. The rate of freezing has a considerable impact on the morphology of crystalline systems (see Figure 4.8).



Freezing too rapidly and to a too low temperature leads to a changed drying rate (lower pore diameter, crack-free surface structure)
–› longer primary drying

Crystal morphology (vertical cross-section) 10 % mannitol

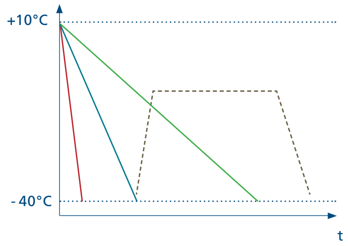


Crystal formation at -2 °C

Crystal formation at -8 °C

Figure 4.8 Crystal formation (vertical cross-section) when freezing 100% mannitol solution [3]

On the left a 10 % mannitol solution was slowly cooled to - 2 °C, and then crystallised out. The section on the right show the result of rapid cooling with crystallisation at -8 °C. Rapid freezing leads to a longer primary drying duration due to the lower pore diameter with fewer fissures in the surface structure. Slow freezing (classification see Figure 4.8) leads to so-called freezing concentration.



Fast freezing
(in liquid nitrogen LN_2, cooling rate approx. 50 °C / min)

Slow freezing
(cooling rate approx. 0.14 °C / min)

Moderate Freezing
(e. g.: cooling rate 1–1.5 °C / min)

›Annealing‹
(e. g.: cooling rate approx. 1.5 °C / min, 5 h storage at -10 °C)

Figure 4.9 Classification of possible cooling rates [4]

As an example, a sodium chloride solution forms two separate types of crystal during freezing, namely an NaCl-poor ice phase and a second, highly NaCl enriched phase. The last drop solidifies at the lowest possible temperature, the so-called eutectic temperature.

For practical purposes, a rate of reduction of temperature of 1–2 Kelvin per minute (moderate freezing) is best for avoiding freezing concentration on the one hand, while on the other hand allowing the formation of suitable crystal structures.

A starting material containing solvent, or a material with high salt concentration may thaw during the drying process (usually clearly visible because of foaming). It is then necessary to freeze the material to the lowest possible temperature, e. g. in liquid nitrogen.

If the starting material has a high solvent concentration or contains acidic material it cannot be dried without protective measures and special apparatus, e. g. additional LN_2 cooling traps to protect the vacuum pump (in case of doubt consult us). Alternatively, Vacuum Hybrid pumps (e. g. RC-6) can be used which are resistant to chemicals.

Sublimation in thermodynamics is when a substance transfers directly from the solid to the gaseous state without the intermediate formation of a liquid.

4.3 Primary drying and secondary drying

Following on from the necessary warm-up / cool-down phase already mentioned (warming up the vacuum pump and cooling the ice condenser) the pressure in the system is reduced to a specified working vacuum, and this is then generally maintained during the primary drying. As soon as the sublimation of the ice in the frozen material begins, heat energy is extracted from the material and it is therefore further cooled.

At the same time the stepwise increase of the shelf temperature supplies the necessary sublimation energy to the product.

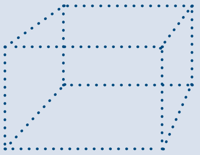
The duration of the freeze drying process can range from at least 12 hours for simple products through to several days for products which are more difficult to dry, such as a vaccine with a low solidification temperature. Drying voluminous archaeological finds may take weeks.

The vapour extracted when drying under vacuum freezes on the surfaces of the very cold ice condenser, so that the ice condenser effectively acts as a ›vapour pump‹. The vacuum pump serves only to extract the air from the drying chamber, but not to pump out the water vapour (›gas pump‹).

It is very important to select the correct pressure.
This can be explained with reference to the ideal gas law:

Ideal gas law

$p \times V = m \times R_m \times T = const.$

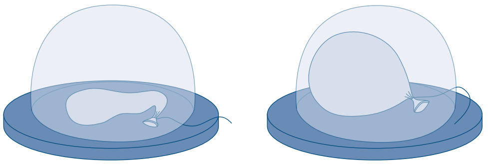


p = gas pressure [Pa], 10^5 Pa = 1 bar
V = volume [m^3]
m = mass [kg]
R_m = R / M, R = ideal gas constant = 8.314 J / mol x K,
M = mol mass [g / mol], M(H_2O) = 18 g / mol
T = temperature [K]

However, if the pressure is too low this is counterproductive:

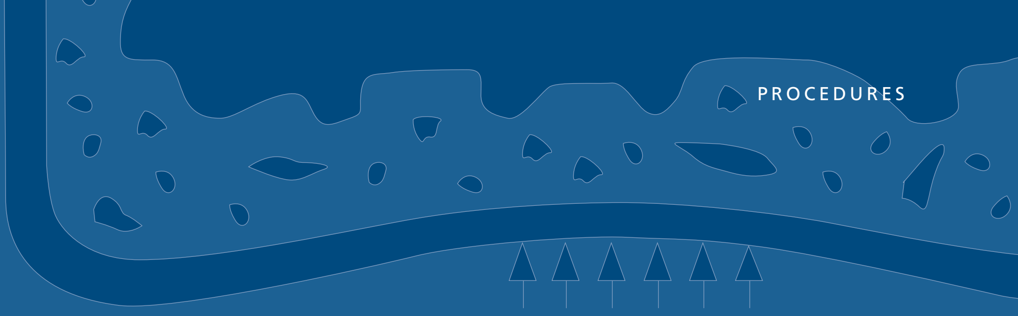
1.0 gram of ice at a pressure of

1.0 mbar produces 1 m^3 of water vapour
0.1 mbar produces 10 m^3 of water vapour
0.01 mbar produces 100 m^3 of water vapour



$P = 10^5$ Pa = 1bar $P = 10^4$ Pa = 0,1bar

A very low pressure would lead to the production of an enormous volume of water vapour, but not necessarily to a rapid reduction in the water content of the sample!



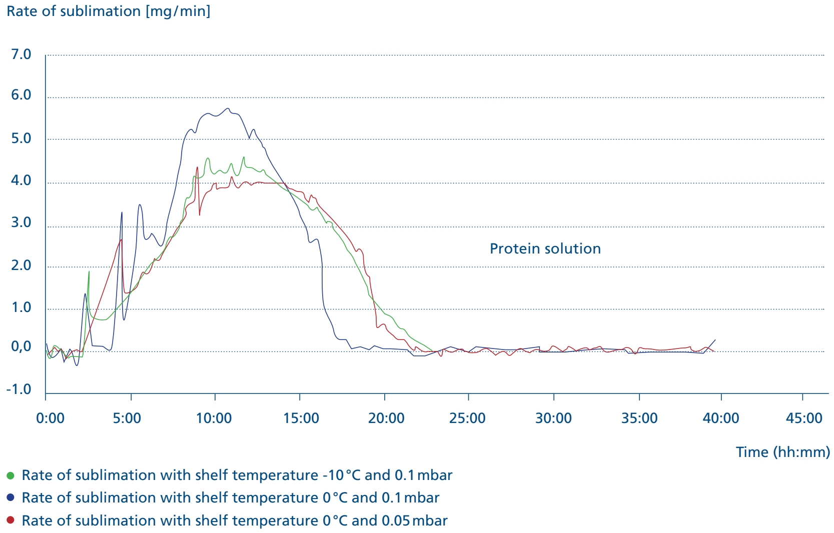


Figure 4.10 Influence of the working pressure on the rate of sublimation [5]

The longer drying times for very low pressures deduced from the vapour-pressure curve and the ideal gas law have been confirmed in many experiments. For example. Fig. 4.10 shows the rate of sublimation which can be achieved for various chamber pressures and shelf temperatures [This result was obtained using a Christ LyoBalance].

The comparison of the red and blue curves shows that even a slight increase in the pressure from 0.05 mbar to 0.1 mbar with the same energy supply can lead to a significant increase in the sublimation rate, with the result that the primary drying phase is about 4.5 hours shorter. This phenomenon is also used in industrial freeze drying. For example, when freeze drying ceramic suspensions, which have a freezing point near 0°C, a pressure of 2 to 4 mbar is used, that is near the triple point of water, but producers of vaccines operate at 0.04 to 0.12 mbar. This is because the freezing point of such solutions is often very low.

Another inhibiting factor in the pharmaceutical sector is the amorphous structure of the materials (no crystal boundaries for water vapour transport).

In view of the dominant influence of the apparatus vacuum on the product temperature, CHRIST has integrated a so-called safety-pressure function to protect the products. If the pressure in the drying chamber rises until it exceeds the safety pressure limit, then the energy supply to the shelf is interrupted and the sublimation process slows down. This prevents the product from melting and avoids the risk of cross-contamination and the alteration of the product properties. The safety temperature should be 5 °C below the melting point, i. e. between the drying temperature and the melting point:

Example

Eutectic temperature	t_{eu} = -10 °C
Drying temperature	t_{dry} = -20 °C
→ Drying vacuum	p_{dry} = 1.030 mbar
Safety temperature	t_{safe} = -15 °C
→ Safety vacuum	p_{safe} = 1.650 mbar

Figure 4.11 Freeze drier with safety pressure function

In larger units with liquid temperature control for the shelf it is possible to work with an additional alarm pressure. If the pressure in the drying chamber rises to a selected alarm value despite the energy supply being interrupted, the shelf is cooled down as quickly as possible to the freezing temperature. The alarm temperature should be about 3 °C below the melting point.

Example

Eutectic temperature	t_{eu} = -10°C
Drying temperature	t_{dry} = -20°C
→ Drying vacuum	p_{dry} = 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 Freeze dryer with additional alarm pressure function

Figure 4.13 Production unit with so-called liquid-controlled shelf temperature (with silicone oil) and alarm pressure function

The secondary drying is an option which can be used if the goal is to retain the minimum amount of residual moisture. This in fact involves the physical process of desorption, i. e. the removal of absorbed residual solvent. An ice phase should not longer be present. The secondary drying is carried out at the lowest possible final pressure in the system, as a rule supported by a raised shelf temperature (e. g. from +20 °C to +30 °C) in order to make it easier to outgas the thin layers of solvent molecules on the pore surfaces.

The lowest-possible final pressure in the drying chamber for the most effective desorption depends on the ice condenser temperature in accordance with the vapour-pressure curve over ice and the rating of the vacuum pump.

In order to be certain of avoiding a melting of the product during the drying, we recommend working at approx. 10 °C below the solidification temperature (eutectic point or glass-transition temperature). This approach is described in more detail on page 18.

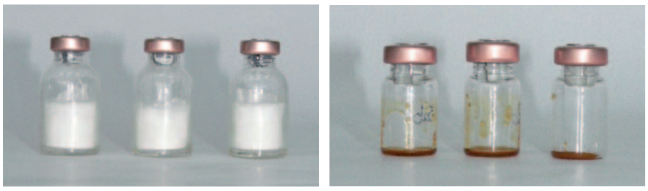


Figure 4.14 Properly dried product (left) and melted, splattered product (right)

Where efficiency and speed are key production factors, e. g. for active pharmaceutical substances, then the aim is usually to work as closely as possible to the solidification point (perhaps only 2 °C below this). These processes require good knowledge of the product and extensive pilot tests as preparation.

In order to start the sublimation process, the energy must be provided for the product in some form. Energy is received from the much warmer surroundings (direct contact heat) when drying in round-bottomed flask, wide-necked flasks, etc, or by ambient thermal radiation in the case of an unheated shelf, or directly from a temperature-controlled shelf.

Lyophilisation can be described mathematically as a complex heat and material transport problem. This can only be solved by making certain simplifications.

Figure 4.15 shows the temperature profile at a beaded-rim flask during primary drying.

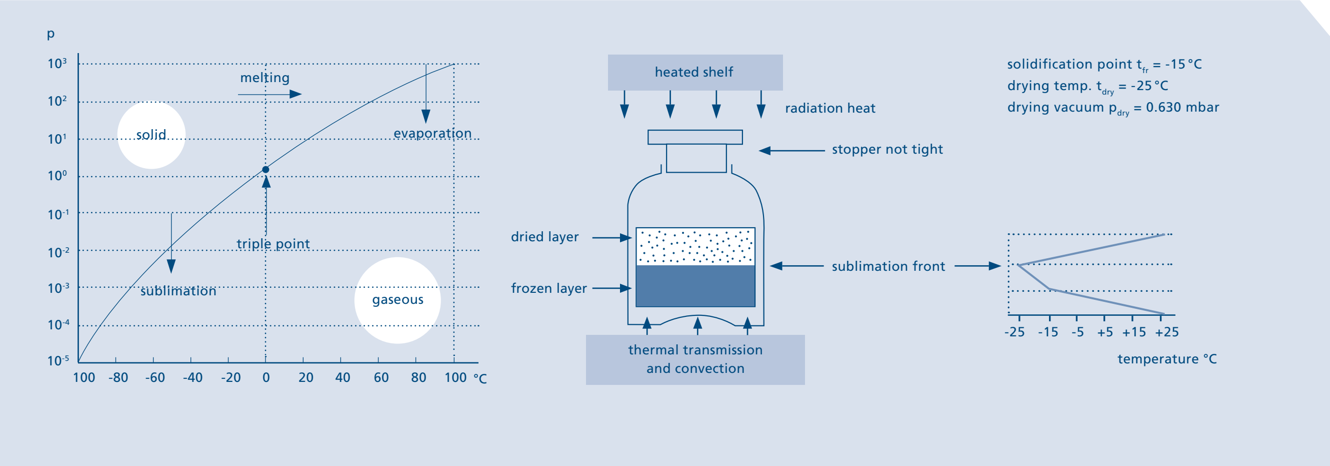


Figure 4.15 Temperature profile in a beaded-rim flask during primary drying

The thermal insulation provided by the vial material and the geometry of the base of the vials lead to a very high temperature drop from +25 °C on the shelf to -15 °C at the base of the vessel and the frozen product on it. The comparatively good thermal conductivity of the frozen solid leads to a lower temperature gradient from the flask base to the sublimation front. The heat transfer is given by the equation:

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

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

Q: heat quantity [J]

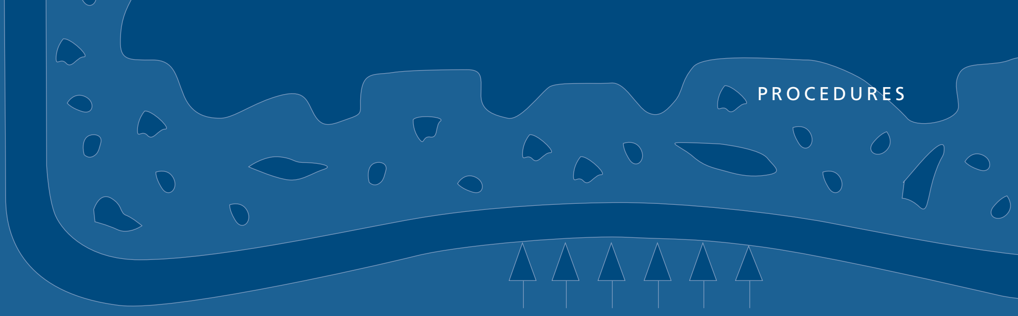
t: time [s]

k: heat transport resistance $[\frac{W}{m^2K}]$

A: cross-sectional area for the heat transport $[m^2]$

ΔT: temperature difference [K]

This provides a direct relation to the heat transported to the ice surface where it is required for sublimation. The ice temperature at the sublimation front is determined by the water vapour pressure curve of the material, which is ideally aqueous. The temperature gradient in the dried product cake above this is determined by the radiant heat and by the cooling effect of the water vapour flowing through it.



The situation in practice is illustrated in the following graphic.

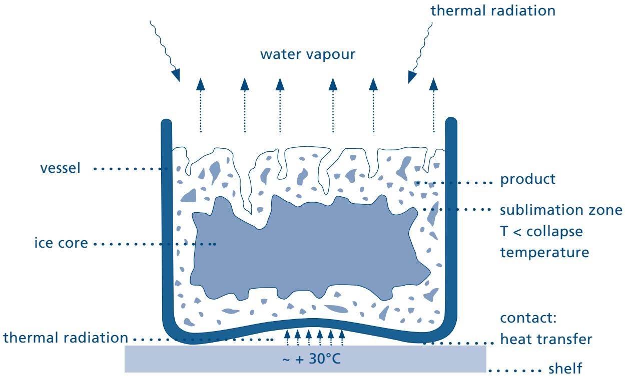


Figure 4.16 Freeze drying process in a product dish

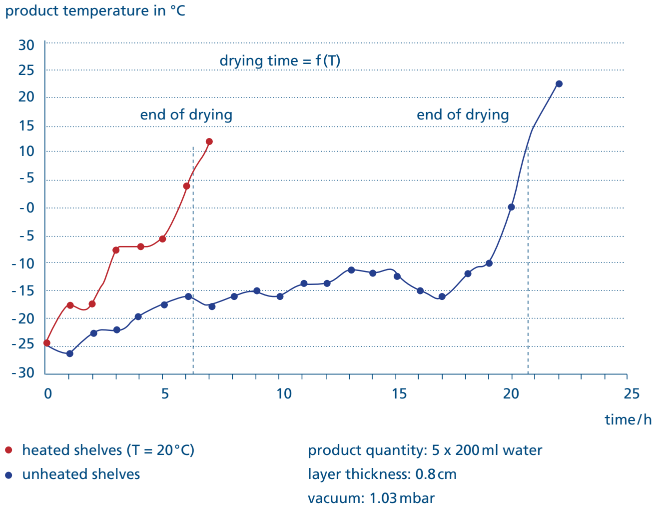


Figure 4.17 Influence of shelf heating on the drying rate (pure water) [6]

The second way to influence the speed is using the temperature-control of the shelf. Figure 4.17 presents the results of a laboratory drying experiment using pure water with and without shelf heating. In practical application the shelf temperature has less influence because the pressure will often be lower and normally a product matrix will impede the water vapour flow and reduce the rate of drying.

The freeze-drying of frozen liquids, slurries, suspensions etc. in dishes should be carried out in systems with heated shelves. But this is not necessary with materials in pieces or irregular forms, e. g. plants, fruits, archaeological finds, because the contact area for heat exchange would be in any case too small. As in the case of flask drying, the necessary energy here is provided by ambient thermal radiation through the transparent plexiglass hood. It is hardly possible to regulate the energy supply. If the product begins to melt (= too much radiation) then the hood or glass flask can be insulated, e. g. with aluminium foil.

The drying of a substance with a solids content of approx. 10 % is shown in figure 4.18.

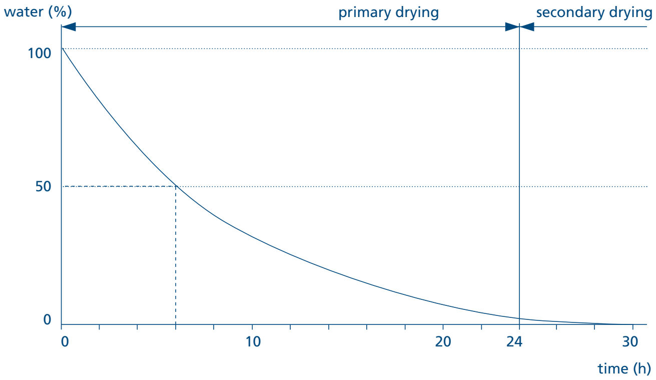
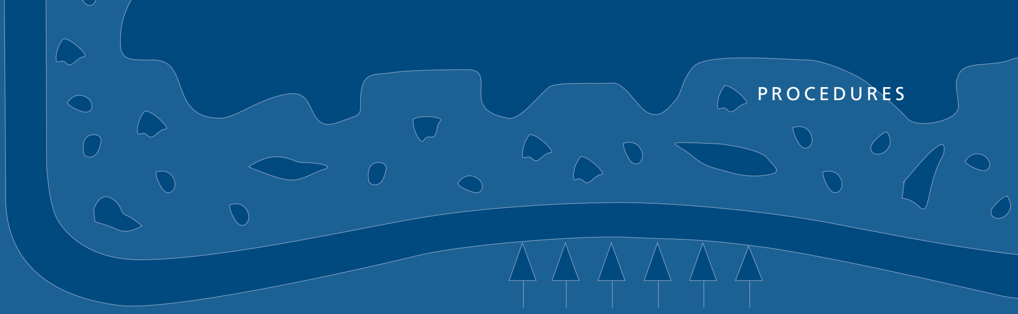


Figure 4.18 Asymptotic drying

In the first quarter of the primary drying accounts for 50 % of the water content, the next quarter for 50 % of the remaining water content, and so on until the drying curve asymptotically approaches the time axis. This is due to the fact that the sublimation level withdraws into the product and the water vapour then has to find its way through the dry layers and the resistance becomes increasingly greater. The drying process is determined mainly by the supply of sublimation heat and the rate of transport of water vapour. In order to increase the special thermal conductivity of the material to be dried and to generate the smallest possible volumes of water vapour, the drying should be carried out as near as possible to the solidification point (eutectic temperature or glass transition temperature).

The closer the pressure is to the solidification point according to the vapour-pressure curve over ice then the shorter is the primary drying time.

In summary, the product temperature during the drying is mainly determined by the vacuum level which is chosen, and less by the shelf temperature.



A **›virtual leak‹** is a phenomenon whereby liquid which has remained in a freeze drier from the previous drying process gradually evaporates, so that (as with a real leak) the pressure does not fall as low as would otherwise be possible.

5 Practical aspects

5.1 Warm up / cool down phase

With systems fitted with a pressure control valve, the opportunity should be used to warm up the vacuum pump. It is better for the working life of the vacuum pump if this is only subjected to the vapours after the operating temperature of the pump has been reached, to avoid condensation.

The vacuum pump can be started up during the freezing and the pressure control valve kept closed. The vacuum pump should be allowed to warm up for at least 15 minutes, or be switched on before the start of primary drying.
In some cases, it is possible that during the primary drying the pressure in the ice condenser chamber or in the drying chamber will drop (e.g. from 0.63 mbar to 0.47 mbar), even though the valve to the vacuum pump has been closed.
This is due to the pumping effect of the ice condensers (Cryo-Pumping Effect).

5.2 Shell-freezing and spin-freezing

If liquids are to be dried in flasks in a layer more than 1 cm thick, then we recommend using a shell- or spin-freezing arrangement (see Figure 5.2) in a cooling bath. The rotation spreads the liquid on the inner walls of the flask where it freezes. The freezing process produces a thinner layer and increases the potential area for sublimation, which considerably reduces the overall drying time.

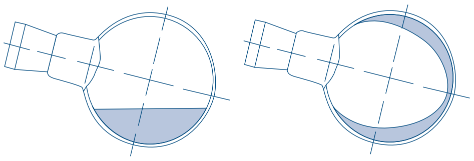


Figure 5.1 Shell-freezing in a round-bottomed flask

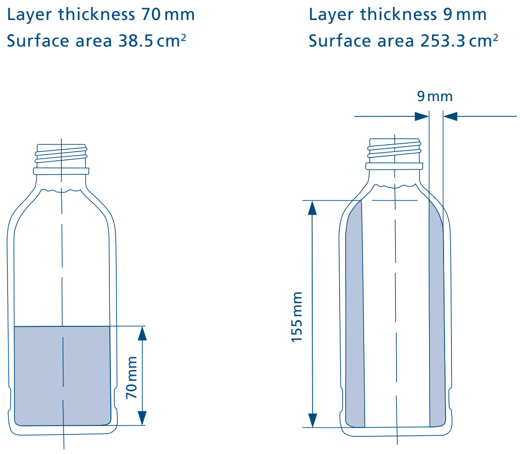


Figure 5.2 Spin-freezing in an infusion flask

As an example, if 250 ml of substance is introduced in a 500 ml blood plasma flask, the resultant layer would be approx. 70 mm thick. By rotating the flask in an upright position at approx. 1000 rpm, the frozen product liquid is spread evenly on the inner walls of the flask, so that the maximum thickness of the layer is approx. 9 mm.

The flask is rotated in a cooling bath. Spin freezing produces an even, homogeneous layer. Concentration increases, volume changes and the formation of varying crystals of the substances are largely excluded.

Figure 5.3 Cooling bath for freezing round-bottom flasks or wide-necked flasks under rotation (left) and drying flasks in a laboratory dryer (right)

5.3 Achievable pressure values

The vapour-pressure graph above ice – that is the relationship between ice temperature and the vapour pressure above this – has consequences for daily operations. With single-stage cooling systems (e. g. ALPHA 1–4, DELTA 1–24) the lowest possible pressure is ›only‹ 0.021 mbar, because the ice condenser has a temperature of -55 °C.

The attempt to reduce the pressure further, e. g. to 0.01 mbar, would be thwarted by the sublimation of ice from the ice condenser (›secondary vaporisation‹).

In comparison, the lowest possible pressures with a two-stage cooling system (e. g. GAMMA 2–16, EPSILON 2–6D) is limited by the final vacuum of the rotary vane pump which is usually used – this is about 0.005 mbar. The vapour pressure over the ice condenser at about -85 °C would be an order of magnitude lower, at 0.0005 mbar.

The theoretical values given here could only be achieved with a completely dry system. Any residual moisture, e. g. in an outlet, would increase the achievable final pressure as a result of secondary evaporation (›virtual leak‹).

5.4 Determining the end of drying / PAT (Process Analytical Technologies)

The residual moisture in the substance being dried is mainly dependent on the temperature of the substance during the secondary drying and the final pressure achieved during secondary drying.

The end of the primary drying phase is reached when the product temperature and shelf temperature are approximately the same (temperature difference between shelf and product about 3 K to 5 K). If the absorbed water is to be removed from the product, it is then possible to proceed to the secondary drying phase.

A rough statement about the end of drying can be made on the basis of the pressure and the ice condenser temperature. Is the ice condenser not longer burdened, it reaches its final temperature of approx. -55 °C or -85 °C.

The pressure in the drying chamber falls in accordance with the ice condenser temperature.

Figure 5.4 shows an example of the placement of product temperature sensors. The drying is also at an end when sample temperature and shelf temperature are well into the positive range (15–20 °C) and do not differ from one another by more than 5 K. This indication is more reliable than the observation of pressure and ice condenser.

Figure 5.5 shows the extent to which the position of the sensor in the vial influences the recorded product temperature.

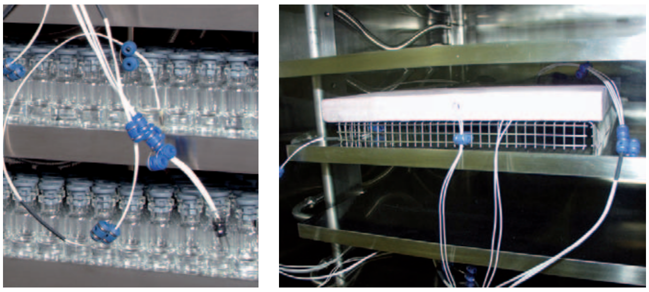


Figure 5.4 Product sensors in a 1 cm high beaded-rim flask filled with an active substance and in a spongy product

Figure 5.4.1 Wireless and batteryless temperature sensors are easy to handle and do not falsify the product temperature as wired probes do

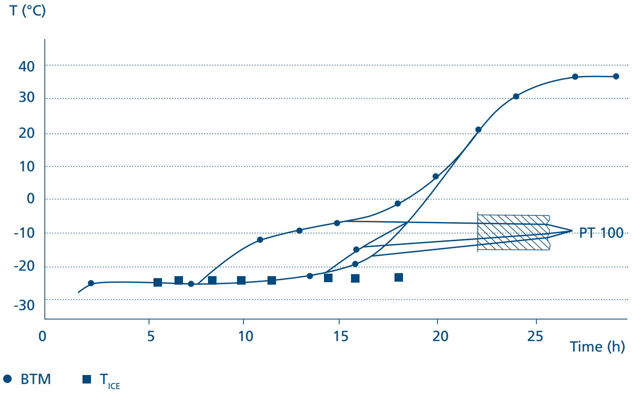


Figure 5.5 Influence of the positioning of a temperature sensor in the product [4]

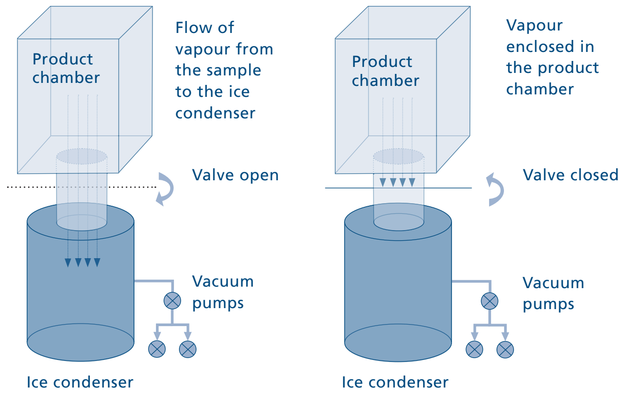


Figure 5.6 Principle of the pressure increase test

A sample can be assumed to dry from top to bottom, as a first approximation, and the upper of the three temperature sensors shows a rise in product temperature already after approx. 7 hours. Due to the cooling effect of the vapour from the sublimation boundary, the product temperature at the sensor takes approx. 20 hours to rise above 0°. The lowest of the three sensors shows the most correct value, because it is directly above the base of the vial or dish where the material will dry last. The box symbols in the graph show the product temperatures at the sublimation front determined using the relatively new, so-called barometric temperature process of measurement, a special process which operates with quickly opening and closing intermediate valves.

In contrast, the pressure increase tests, which have been in practical use for some time, operate with longer closing periods for the valve (see Figure 5.6). The principle is based on a separation of the product chamber from the ice condenser, so that the water vapour from the sublimation cannot escape. This results in an increase in pressure in the product chamber, which can be measured. But once the product is completely dry there will be little or no increase in the pressure.

This process is in wide practical use, wherever the freeze dryer is regularly operated with the same load (number and type of vials or dishes). The pressure increase test is frequently used as a criterion for switching automatically between primary and secondary drying as well as for recognising the end of the drying process.

With sensitive products, the valve must not be kept closed for very long, i. e. only for a few seconds, in order to prevent the frozen material from collapsing or melting.

The Christ LyoBalance is a unique tool for process development and optimization in pilot plants.

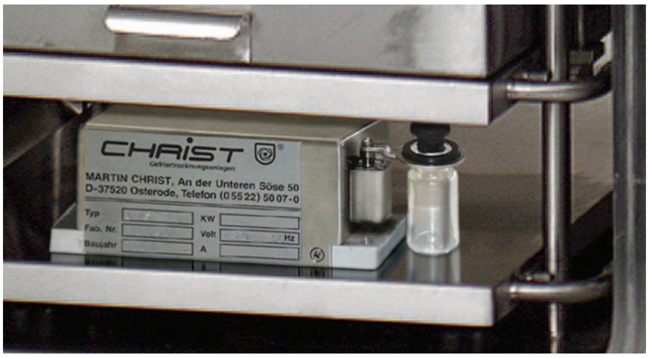


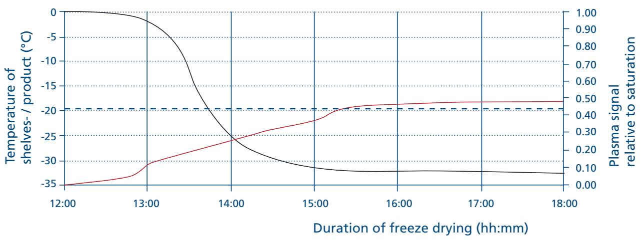
Figure 5.7 The microbalance from Christ for measuring vials and small dishes

The LyoBalance works on the principle of electromagnetic force compensation. At periodic intervals pre-selected by the customer, the LyoBalance lifts the vial and generates a weight reduction curve with an accuracy of 0.001 g, which indicates the completion of drying.

The drying process itself is not interrupted, and the balance can be placed at any position on the trays in the chamber. But the shelf where the balance is located cannot be used for sealing. Furthermore, the microbalance cannot be autoclaved. A dish is provided for the simulation of bulk-drying.

›Lyotrack‹, developed by Alcatel / Adixen, France – as mass spectroscopy – does not examine individual products but monitors the progress of drying indirectly. At a defined measuring point between the product chamber and ice condenser, a sample of the vapour flow is extracted and placed in a so-called ›Cold Plasma‹ using a special method. A spectrometric analysis of the radiation released provides the ratio of nitrogen to water vapour in the mixture on its way to the ice condenser at the time of measurement. The further the drying proceeds, the lower the proportion of water vapour becomes. Reference measurements in comparison with the LyoBalance show that the Lyotrack is so sensitive that it not only determines the end of the primary drying, but can also track the release of water vapour in secondary drying (desorption).

Plasma versus temperature sensor



Plasma versus microbalance

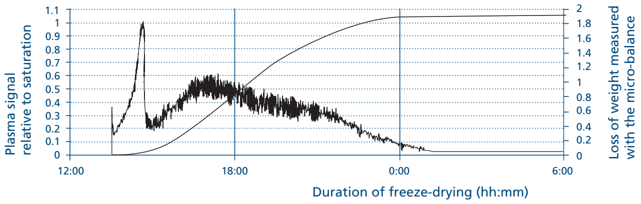


Figure 5.8 Spectroscopic measurement of the end of drying by recording the proportion of water vapour in the gas flow to the ice condenser (creating a ›cold plasma‹) [7]

The composition of the gas flow is also used in methods based on process monitoring with simultaneous measurement of the pressure using a Pirani gauge and with the capacitive sensor (comparative pressure measurement). Figure 5.9 shows both operational principles.

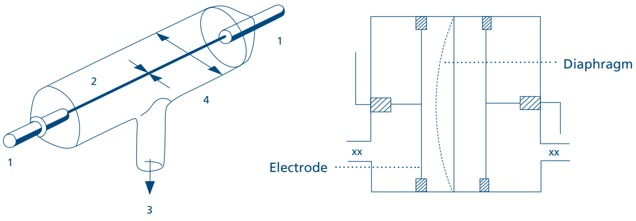


Figure 5.9 Principle of the pressure measurement with the Pirani gauge (left) and with a capacitive sensor (right)

The Pirani sensor consists of a single wire which loses heat depending on the pressure of the surrounding gas. The change of temperature of the wire alters its electric resistance and thus the current I flowing under a constant voltage V (I = V/R). The indirect relationship between current and pressure, I = f (pressure) is established by calibration. The heat loss also depends on the type of gas, and is higher if there is a large proportion of water vapour.

The capacitive sensor is based on the pressure-dependence of the deflection of the membrane of an electrical capacitor, which is not dependent on the composition of the medium.

Since the Pirani gauge readings are dependent on the type of gas, and in particular measurements are too high at the start of drying when a higher proportion of the mixture is water vapour, whereas the capacitive sensor measurements are independent of the nature of the gas, when the two measurement curves meet this indicates the end of the primary drying.

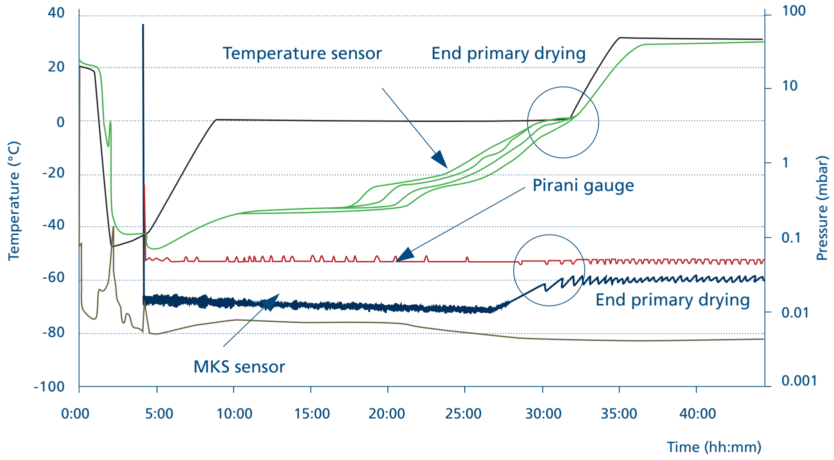
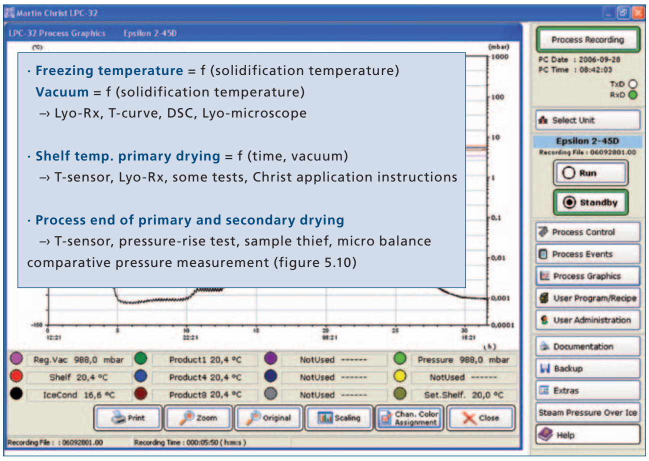


Figure 5.10 Pressure measurement with the Pirani gauge and with a capacitive sensor [5]

6 Summary of procedures

Figure 6.1 gives an overview of the master parameters for the design of a freeze drying cycle.



- **Freezing temperature** = f (solidification temperature)
  Vacuum = f (solidification temperature)
  → Lyo-Rx, T-curve, DSC, Lyo-microscope
- **Shelf temp. primary drying** = f (time, vacuum)
  → T-sensor, Lyo-Rx, some tests, Christ application instructions
- **Process end of primary and secondary drying**
  → T-sensor, pressure-rise test, sample thief, micro balance
  comparative pressure measurement (figure 5.10)

Reg.Vac 988,0 mbar
Shelf 20,4 °C
IceCond 16,6 °C
Product1 20,4 °C
Product4 20,4 °C
Product8 20,4 °C
NotUsed ------
NotUsed ------
NotUsed ------
Pressure 988,0 mbar
NotUsed ------
Set.Shelf. 20,0 °C

PC Date : 2006-09-28
PC Time : 08:42:03

Epsilon 2-45D
Recording File : 06092801.00

Recording File : : 06092801.00
Recording Time : 000:05:50 (h:m:s)

Figure 6.1 Key relationships for the freeze-drying

A key factor is the solidification temperature of the product in question. As an approximation, it is possible to record the cooling temperature in the freeze dryer. At the freezing point, the curve will have a plateau, i.e. the product only cools further when the last liquid drop has solidified (Gibbs' phase rule). Alternatively, the solidification temperature can generally be determined reliably with the Lyocontrol. However, this process is less accurate when used with amorphous structures. When such substances are being handled, for example in the pharmaceutical industry, then it is better to use other procedures such as differential scanning calorimetry (DSC) or cryo-microscopy.

The temperature of the frozen product before the start of sublimation should be approx. 10 °C below the solidification temperature. The pressure value for the 10 °C lower value should be chosen using the ice pressure curve.

During the primary and secondary drying, the shelf is heated to provide the necessary energy, but the shelf temperature profile can as a rule only be determined empirically.

Figure 6.2 shows how the rate of sublimation depends on both, the pressure and the shelf temperature.

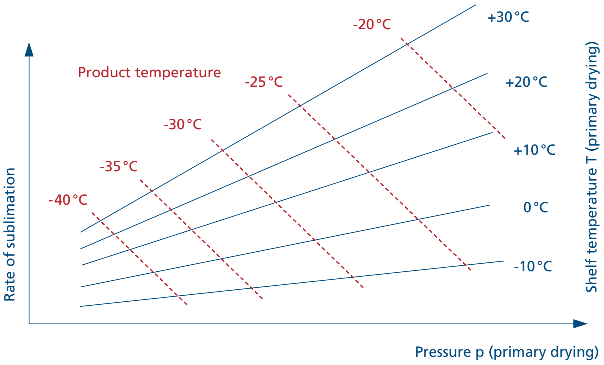


Figure 6.2 Dependence of the rate of sublimation on pressure p and the shelf temperature T with the corresponding isotherms of the product temperature [19]

This figure only applies for a time point t, because the array of curves changes with the development of a dried, porous layer (increasing pressure loss for vapour flow). The determination of the suitable temperature profile of the shelf heating involves a very complex thermodynamic heat and material transport problem. In this case, some empirical tests with temperature sensors and Lyocontrol are preferable to time-consuming theoretical calculations. Christ provides recommendations for product applications on its web site (www.martinchrist.de) and in the following part of this brochure.

The end of the primary drying process can be determined by a temperature sensor, the pressure rise test or the micro-balance. In order to determine the end of secondary drying, the pressure rise test is a suitably sensitive process and is preferable because the product temperature no longer changes and the balance is not always sensitive enough for measurements during desorption. Alternatively the detection of the residual water vapour in the chamber is a suitable method (Lyotrack by Adixen). Of course it is also possible to use manipulators or sampling equipment to take samples during the process for the chemical analysis of the residual moisture content.

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It is very difficult to model the processes involved in freeze-drying, because the transport of heat energy and mass involve very complex phenomena.

Algae

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
-35 °C, freezing in LN_2 is convenient	-15 to -25 °C	wide-necked flasks, dishes	A and C	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ → ice pressure curve = 0.630 – 0.220 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-10 °C / 4 h, 0 °C / 4 h, +10 °C / 4 h, +20 °C / 12–24 h	6–24 h	not necessary

Special features

- watery material (not de-watered or pre-treated), straggly consistency
- very hygroscopic
- fresh water and sea-water species have different freezing points

Short description of market

Uses of the freeze-dried products / Typical users

- Food industry (inclusion as flavour carrier, protein-rich)
- Cosmetics

* Comments	
Process A ("inside")	(Freezing and) drying in the ice condenser chamber
Process B ("outside")	Freezing separate (e. g. refrigerator), drying outside the ice condenser, e. g. with plexiglass hood
Process C	Freezing (on liquid-cooled shelves) and drying outside the ice condensers, e. g. with plexiglass hood or steel chamber (like EPSILON-systems)
EPSILON	system with rectangular product chamber, front loader

It is usually advisable to carry out optimization tests with a product first. Some examples of applications follow to offer a basis for this.

Books, archaeological finds

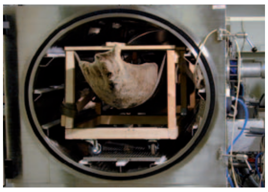
e. g. wood, textiles, leather

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
books: freezing in the deep freezer at -10 °C, arch. finds: -30 °C	approx. 0 °C to -3 °C	steel cabinet / chamber, plexiglass tubes	B or C (tempered stainless steel tubes)	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ –› ice pressure curve = 2.560–1.980 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-30 °C / 10 h, increase by 5 °C every 10 h, if shelf heating is not possible, infrared heating may be possible (no reports available). Do not dry too much, books are then placed in the climate chamber	t = 3–8 days per object, (for archaeological finds also some weeks) end of drying by measuring pressure increase or weight loss	for books no secondary drying

Freeze-dryer for book drying with 2 refrigeration units and heated shelves



Special dryer for archaeological finds, here treating a Viking boat

Special features

- Books must stand vertically (rack), because otherwise water vapour cannot escape
- Heat transport also possible in ›safe‹, operate close to the eutectic point!
- Heating is bad for books (deformation due to uneven drying because the book is only warm at the bottom), infrared heating would be possible (heater at the back of the cabinet)
- As far as possible, objects should be of similar size so that they dry at the same rate (for example arch files)
- No temperature profile necessary and not possible without heated shelf
- Other application in a vacuum cabinet (pharmaceutical industry):
- Aventis Pharma, Frankfurt freeze dries Erlenmeyer flasks in such cabinets with heated shelves, giving even heat transfer!

Uses of the freeze-dried products
Restoration, for example: wet planning permission documents after a flood

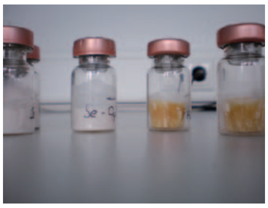
Typical users
Libraries, museums, public authorities

Bacteria, viruses, fungi, vaccines

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
-50 °C and below	-40 °C and lower	beaded-rim flasks, vials, ampoules, dishes	A or EPSILON (process C) in the production range	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ –› ice pressure curve = 0.040 mbar and below

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-50 °C / 5 h, increase every 5 h by 5 °C (4 or 5 times), then reduce to time interval to 3 h and 1.5 h, Lyocontrol highly recommended	24–48 h	only in exceptional cases



Various bacteria cultures under vacuum in tightly-sealed injection vials

Special features

- In laboratories: Disinfection and gas sterilisation possible: Ethylene oxide (highly toxic, outdated), paraformaldehyde, H_2O_2 , (increasingly common)
- Chemically-resistant CHRIST systems can be provided
- Disinfection / decontamination: Liquid cleaning (alcohol, etc.), germs may still be present, special cleaning agents are recommended for plexiglass (e. g. Incidur)
- It is usually necessary to steam-sterilise systems for production purposes
- Sterilisation: with steam > 121 °C, complete elimination of germs
- Operating in accordance with GMP (Good Manufacturing Practices) and FDA (Food and Drug Administration) requirements

Uses of the freeze-dried products

- For human and veterinary vaccination
- Ampoules are sealed under vacuum
- Vials are closed under vacuum or N_2-atmosphere using special accessories
- (pressure of 800 mbar avoids excessive air diffusion into the closed vial in storage and is enough to keep the sample sterile)

Plants, fish

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
freezer: -35 °C, eutectic range can only be determined after homogenization	to -15 °C	see books, large chambers	B	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ → ice pressure curve = 0.630 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying	Duration of secondary drying
not applicable, see books	1 d to 1 week (depending on object dimensions)	minimal	3 h–10 h

Freeze-dried fish with a protective surface coating

Flower seeds after freeze drying

Special features

- No temperature-profile required
- Fish: remove fish entrails in order to reduce the layer thickness
- Flowers: hang upside down in holders
- Note: tissue (bodily fluids) of aquatic animals contains $CaCl_2$ and so the freezing points are very low
- Specialist publication ›Restoration‹ available from us

Short description of market

Uses of the freeze-dried products

- Fish: anglers, works of art, teaching demonstrations
- Plants with very high water content (aquatic plants) for decoration purposes

Typical users

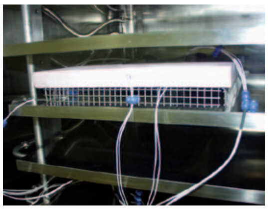
- Fish: taxidermists, anglers
- Flowers: Garden centres, biological institutes, generally smaller companies

Collagen, tissue samples, thymus

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
pre-cooled in LN_2 or on the shelf Collagen: -45 °C	Collagen: about -35 °C, Tissue samples: -56 °C (contain $CaCl_2$)	special dishes, Special formats (L x W, indentation)	A and C	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ → ice pressure curve = 0.070 mbar to 0.0047 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-30°C / 5 h, increasing first by 5 °C every 5 h (5–6 x), then reduce the time interval to 2 h	36 h	necessary to remove capillary water, lowest pressure of pump (10^{-3} mbar)



Collagen plate during test drying

Special features

- Rate of refrigeration ≥ 1 °C / min
- Avoid damage to cell walls with non-freezing mixture (cryo protectants, displace water in the cell wall and prevent denaturation)
- Only heat moderately so that cells do not defrost and burst

Short description of market

Uses of the freeze-dried products

- Collagen for skin cosmetics (moisturiser, cell rejuvenation)
- Cell tissue, bone, arteries, scalp tissue, or aorta valves for transplantation can be lyophilised

Typical users

- Doctors, clinics, increasingly also beauty farms

Fruits, vegetables, meat

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
fruits, vegetables: -35 °C; meat: -40 °C	-25 °C	dishes	B	$T_{ICE} = T_{EP}$ -10 °C (= -35 °C) $p_{HT} = f(T_{ICE})$ –› ice pressure curve = 0.220 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying	Duration of secondary drying
fruits, vegetables: 0 °C / 4 h, 10 °C / 4 h, 20 °C / 16–24 h) meat: -10 °C / 4 h, 0 °C / 4 h, +10 °C / 4 h, +20 °C / 12–24 h	24–36 h	a question of cost, not usually needed	optional

Freeze-dried tropical fruits ›Arillen‹

External freezing of truffles in a freezer

A wide range of foodstuffs can be freeze-dried

Special features

- Meat is diced with a side length of about 1 cm
- The packaging for freeze-dried products must be impermeable to air, water vapour and gases

Additional information

- Freeze drying is viable if the price is more than Euro 10 / kg (market price)
- Freeze-drying plants have an amortisation period of at least ten years
- Doubling the capacity reduces specific production costs by 10 to 20 percent
- A freeze dried product has ten times the aroma intensity of the same amount of fresh product

Uses of the freeze-dried products

- Fruits: Baby food, milk industry (adding aroma to milk products),
- Vegetables: Kitchen herbs
- Meat: only as flavour carrier (deep-frozen granules, or ground in a mill)

Typical users

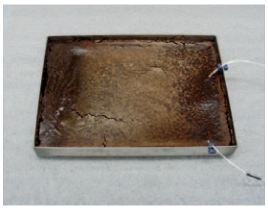
- Food industry
- Drying specialists

Gelatine

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
-25 to -30 °C	below -20 °C	dishes	A	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ → ice pressure curve = less than 0.370 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
sensitive, stepwise warming needed -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 with tendencies of form surface skin

Special features

- Viscous material, can form skin, affecting process
- Hygroscopic
- The resultant cake is ground

Short description of market

Uses of the freeze-dried products / Typical users
Intermediate products for the pharmaceutical industry (carrier, filler), foodstuffs sector (binding agent)

Royal jelly, honey

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
process A or C, pre-cooled shelf, shock freezing usually at -40 °C	to -40 °C	dishes	A, C	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ –› ice pressure curve = to 0.040 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-30 °C / 5 h, first increase by 5 °C every 5 hours (5 to 6 x), then reduce the interval to 2 hours	24–36 h	as appropriate

Special features

- Product is very hygroscopic, must be packed quickly
- Substances containing aroma additives and sugar tend to form skin during the drying process

Short description of market

Uses of the freeze-dried products
Drugs, food additives

Typical users
Pharmaceutical companies, private companies

Ceramic powders

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
to -20°C, separately or in system	below -10 °C (that is 0 to -10 °C)	dishes or modules	A	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ → ice pressure curve = 1.030 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-10 °C / 4 h, 0°C / 4 h, +10 °C / 4 h, +20 °C / 12–24 h, stepwise, rapid drying possible up to +80 °C	2–24 h	no

Cylinder from porous special ceramics (not a finished product)

Special features

Initial material is ceramic powder and binding agent (coating grains), this binder is preserved by freeze-drying, it would be broken up by thermal drying)

Short description of market

Uses of the freeze-dried products /
Typical users

- Use as ceramic base structure for compound materials
- Small-scale (Lab): KFA Jülich (Inst. For Materials Testing), BAM, Berlin

Sewage sludge, soil samples

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
at about -35 °C	-25 °C	dishes, with sieves to hold back very fine silt particles	A, B, C possible	$T_{ICE} = T_{EP} - 10\,°C$ (= -35 °C) $p_{HT} = f(T_{ICE})$ –› ice pressure curve = to 0.220 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying	Duration of secondary drying
0 °C / 6 h, 30 °C / 18 h	slurry: 24 h soils: 24–36 h	not necessary	not applicable

Lab freeze-drier for up to 4 litres of slurry or soil samples

Special features

- Material of dishes: Aluminium (less rigid) or stainless steel, can be teflon-coated for heavy-metal analysis
- Product sieve for fine-grained soils
- German standard DIN 38414/22 (Sample preparation) gives details of effective working pressure, safe pressure, the pressure control valve, the heatable shelf and sample preparation)

Short description of market

Uses of the freeze-dried products

- Analytical laboratories, environmental departments of industrial companies
- Assessing soil contamination levels

Typical users

Environmental offices, analytical laboratories, sewage treatment plant, water management associations

Microbiological products, fermented products

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

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
200–500 ml spin freezing (in vertical flasks, with corresponding cooling baths	-13 to -35 °C	5–500 ml flasks, dishes (albumin)	A and C, EPSILON systems (Soletemp.)	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ –› ice pressure curve = to 0.770–0.070 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying	Duration of secondary drying
-30 °C / 5 h, increase temperature initially by 5 °C every 5 h (e.g. 3 x), then reduce the time interval to 2 h	24 h (at 1 cm)	not at max. vacuum; set for residual moisture content of 2–5 %, (customer expertise)	2–4 h

Freeze-dryer with temperature-regulated shelf and system for closing flasks under vacuum

Special features

- LyoControl recommended for freezing process,
- Max. product temperature 30 °C (denaturation above 37 °C),
- Close under vacuum, but risk of air diffusion internally (better to close in an N_2 atmosphere)

Short description of market

Uses of the freeze-dried products
Blood derivatives for injection purposes, now used instead of full plasma transfusions (blood substitute = saline solution and plasma components dissolved in bi-distilled water; allows faster uptake of key components)

Typical users
Red Cross, pharmaceutical companies

Milk products

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
Shell-freezing (round-bottomed flask) Spin-freezing (cylindrical flasks), minimum -25 °C	-13 °C (cow's milk)	dishes, round-bottomed flask, wide-necked flasks	B, possibly C	$T_{ICE} = T_{EP}$ -10 °C (= -23 °C) $p_{HT} = f(T_{ICE})$ –› ice pressure curve = 0.770 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
0 °C / 5 h, then increase to between +25 and +30 °C	24 h	not necessary

Drink yoghurt and freeze-dried yoghurt

Drying yoghurt in stainless steel trays

Special features

- non-sensitive product,
- Single-chamber systems highly suited for production applications

Short description of market

Uses of the freeze-dried products
Mare's milk (health food, valuable vitamins), goat's milk, camel milk (Emirates), mother's milk

Typical users
Mare's milk farms, pharmacists who wish to supply to wider areas (frozen then not possible, therefore freeze-dried); mare's milk goes off very easily if not freeze dried

Nucleic acids, peptides

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
to -40 °C	to -30 °C	nucleic acids: flasks peptides: dishes, flasks, vials, ampoules	A (nucleic acids) A and B (peptides)	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ → ice pressure curve = 0.120 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-30 °C / 5 h, increase temperature by 5 °C every 5 h (5–6 x), then reduce the time interval to 2 h, more rapid heating often possible if no problems are encountered	24–36 h	as required

Freeze-dried peptides in injection vials

Special features

- Material is hygroscopic
- In production plant with automatic cleaning (CIP), steam sterilisation in some cases

Short description of market

Uses of the freeze-dried products/
Typical users
Pharmaceutical companies (additives)

Organic solvent

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
first evaporate solvent with RVC	below -50 °C possible	dishes in part also flask drying (particularly ACN-water mix)	A	corresponding to the fixed point (Ice pressure curve for water not applicable)

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
$T_{Fp.}$ -10 °C, note: avoid partial defrosting if the pore structure of the sample is important	must be determined experimentally for a wide range of substances (see below)	depends on product

Laboratory system for flask drying from solvent

Rack with sieve cover for drying from solvent (avoidance of cross-contamination)

Special features

- Examine vapour-pressure curve of the solvent, Ice pressure curve for water is often not applicable
- An indication of the drying time relative to water (1 cm layer of ice in 24 h) is given by comparing the vapour pressure or better sublimation pressure of the substance with that of H_2O
- Check state of system (rubber seals, acrylic doors/hoods)
- With processes A and C, freeze-drying systems can also be used for vacuum drying or conditioning processes (creating a ›product foam‹). At a low pressure, careful increase of the heating temperature causes a controlled boiling process.

Short description of market

Uses for the freeze-dried products

- Special market, preparation processes in the pharmaceutical industry, extracting natural substances
- Solvents with high-boiling points can also be used (the key is the solubility of the relevant substances)

Typical users

Chemical and pharmaceutical industry, growing markets for special applications

Comments

A special presentation is available on this with details of applications

Vegetable materials

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
-10 °C (sometimes down to -40 °C) A and C, freezer cabinet, rarely with LN_2	-10 °C (in some cases to -30 °C)	dishes, shelves	A and B	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ –› ice pressure curve = 1.030–0.120 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-10 to -15 °C / 5 h, increasing by 5 °C every 5 h (5–6 x), then reduce time interval to 2 hours	36 h	case by case

Shock freezing of plant pollen in a laboratory freeze-dryer with LN_2

As necessary

- Vegetable material is usually not sensitive
- Pay attention to heat transfer,
  area of contact with shelf may be rather small,
  plexiglass hoods are suitable for this
  and allow heat radiation
- Such chambers can be made to order

Short description of market

Uses of freeze-dried products

- Storage (instead of large, expensive freezers)
- Structural investigation of tissue, membranes
- Analysis of contents (followed by extraction)

Typical users

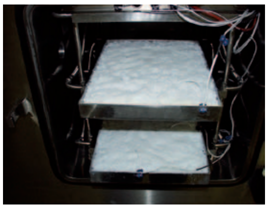
- University institutes
- Agricultural chemistry

Polymers, Tensides

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
down to -40 °C	-2 to -30 °C	dishes	A	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ –› ice pressure curve = 2.170–0.120 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-30 °C / 5 h, increase by 5 °C every 5 hours (5–6 x), then reduce interval to 2 hours	36 h	as necessary, with slight residual moisture



Drying polymers

Special features

- Note, solvent may still be contained (lowered solidification temperature), but is usually evaporated before
- Special conditions: aggressive starter components create HS^-, stainless steel 1.4571 is not fully resistant)
- Viscous, honey-like solutions

Short description of market

Uses of the freeze-dried products / Typical users

- Quality control
- Also used on an industrial scale

Urine/faeces, residue analysis

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
-40 °C	-30 °C	in flasks and dishes	A and B	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ –› ice pressure curve = 0.120 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
-30 °C / 5 h, increase by 5 °C every 5 hours (e.g. 5–6 x), then reduce the time interval to 2 h	36–48 h	as necessary

Special features

- Products tend to defrost and foam
- Products are very hygroscopic, and should be packed directly (bag, glass containers)
- Products are virtually odour-free after freeze-drying

Short description of market

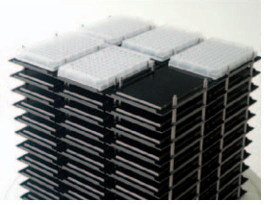
Uses of the freeze-dried products
Medical analysis of residues

Aqueous solution with small amounts of other solvents or salt

Procedure (Overview)

Freezing	Solidification range, Solidification point	Container for FD	Process A / B / C *	Vacuum primary drying
to -30°C, on occasions to -40°C	-2 to -30 °C	dishes, vials, flasks, microtitre plates	mainly B, occasionally A (if there are signs of thawing due to the proportion of solvent)	$T_{ICE} = T_{EP}$ -10 °C $p_{HT} = f(T_{ICE})$ –› ice pressure curve = 2.170–0.120 mbar

Temp. of the shelves during primary drying (T_{SF}/t)	Duration of primary drying	Vacuum for secondary drying
Products mostly not sensitive, Product can be heated from the $T_{Fp.}$ (freezing point) -10 °C to 20 °C in 24 h (Lyocontrol may be appropriate to optimise the drying time)	24 h	usually unnecessary



Special rack for freeze-drying of microtitre plates

Special features

none, standard application

Short description of market

Uses of the freeze-dried products / Typical users

- broad range of laboratory applications
- A slight decline to be expected in favour of vacuum concentration

CHRIST

01 / 2015 VN

Martin Christ
Freeze Drying Systems

An der Unteren Söse 50
37520 Osterode am Harz

Phone +49 (0) 55 22 50 07 0
Fax +49 (0) 55 22 50 07 12

info@martinchrist.de
www.martinchrist.de