

Lyophilization

**Freeze-drying for
sensitive products**





Figure 1: Medicines and vaccines are preserved by freeze-drying

Herbs, fruits and medicines have one thing in common: they can all be preserved by lyophilization. Freeze drying is an established process in many fields, particularly for preserving sensitive products and it often offers the most advantages compared to other drying processes. For many foods, such as freshly picked herbs or mushrooms, freeze-drying has become the standard method of preservation today. Lyophilization, however, is also used to preserve pharmaceutical products such as medicines and vaccines. This process requires a particularly deep vacuum. Unlike conventional vacuum drying, a freeze-dried product is produced by sublimation: ice passes directly into the gas phase. This means that the product is dried in a particularly gentle manner.

Freeze-drying is extensively used in the production of foodstuffs and pharmaceutical ingredients. Unsurprisingly, products such as these often tend to be sensitive to temperature or humidity. The best known is probably soluble coffee, often called 'instant coffee'. Here, coffee extract is processed by means of lyophilization in such a way that the consumer only has to dissolve the resulting powder in hot water. The powder can be kept in its packaging for years without being refrigerated.

A particularly deep vacuum is required for the lyophilization process.

Typical fields of application for freeze-drying

Freeze-drying retains the aroma and color of fruit. For example, it is possible to top pizzas with long-life mushroom slices that are in no way inferior to fresh vegetables. The long shelf life of herbs and spices is also a huge bonus. The essential oils contained in the herbs are also preserved as flavor carriers.

Lyophilization offers advantages in pharmaceutical production and biotechnology, especially for temperature-sensitive vaccines, antibiotics and bacteria. After processing, which is performed directly in vials or syringes, the preparations can be dissolved within seconds if required.

The importance of vacuum pumps for the process

But why does lyophilization have to take place in a vacuum? For the freeze-drying process, achieving a pressure below the triple point of the solvent used (e.g., water) is imperative. During evacuation, critical components of air such as oxygen are also removed from the drying chamber. While the working pressure for the duration of the main drying is typically between 0.5 hPa and $1 \cdot 10^{-2}$ hPa, it can be up to $1 \cdot 10^{-3}$ hPa during subsequent drying or also for the conditioning of the chamber. Such a vacuum requires powerful vacuum pumps that generate the desired final pressure safely and reliably. The criteria for selecting suitable vacuum pumps include, in addition to a sufficiently low final pressure, a high pumping speed to achieve the desired pump-down time. A long, low-maintenance operation of the pumps is also important, especially when used in production plants.

When specifying a freeze dryer, it is typically the pumping time to a defined pressure (usually 0.1 hPa) that is decisive. Ultimately, every user wants to plan how much time the process takes. The nominal pumping speed of the vacuum pump is only an indication since it represents the maximum pumping speed in only one pressure point.

As a provider of powerful vacuum systems, Pfeiffer Vacuum supports users in the design and dimensioning of vacuum systems. To deliver a perfectly fitting system with the right pump, the entire characteristic curve of the vacuum pump, losses caused by pipes and leaks are taken into account. The supplier uses the latest, specially developed calculation programs to achieve this. Pfeiffer Vacuum's broad portfolio includes vacuum pumps for evacuation, pressure gauges and calibration pumping stations, mass spectrometers for gas analysis for process monitoring, and leak detectors for locating leaks.

Systems for use in production

Production systems with screw pumps in combination with Roots pumps are mainly used in both, the pharmaceutical sector and in food production, –for example in coffee drying. The dry-sealing pumps are particularly popular with users because of their good cleaning capability. Pfeiffer Vacuum offers suitable accessories for cleaning the rotors of process deposits for both, the HeptaDry screw vacuum pumps, and the OktaLine Roots pumps.

Rotary vane pumps can be used if low investment costs are required –for example, when drying fruit. Depending on the chamber size, it is also a good idea to combine it with Roots pumps. Pfeiffer Vacuum recommends HenaLine single-stage rotary vane pumps for these applications: They offer a robust design and a powerful oil mist separator. Thanks to the wide range of pump technologies and sizes available from the supplier, the right solution is available for every freeze dryer.

Measurement technology for exact processes

For freeze-drying processes to run reliably and in a reproducible manner, it is essential to have the pressure measured accurately and repeatably in the drying chamber. Two technologies are used for the pressure range that prevails in lyophilization: Pirani and capacitive vacuum gauges. Pirani vacuum gauges measure the pressure indirectly via the

pressure-dependent heat conductivity of gases. A common mode of operation is to keep the filament at a constant temperature. The required heat power is an indicator of the surrounding pressure. Such vacuum gauges can measure in the range from atmospheric pressure to about $1 \cdot 10^{-4}$ hPa. However, a practicable accuracy can only be achieved in the much narrower range of about 10 to $1 \cdot 10^{-3}$ hPa. Advantages for use: Pirani vacuum gauges are among the most cost-effective vacuum gauges with an electrical output signal. However, they are dependent on the type of gas.

In freeze-drying, this gas type dependency is used: For example, a Pirani vacuum gauge calibrated for nitrogen or air shows a significantly

higher pressure for water vapor. If a pressure signal of a gas type-independent vacuum gauge is measured simultaneously (typically capacitive), the water vapor content in the drying chamber can be inferred by comparing the measured values. Adjusting the pressure signals from the Pirani–and capacitive vacuum gauges is a helpful indicator for determining the end of primary drying. The method is also called comparative pressure measurement.

Thanks to the pulse technology, the TPR 270 and TPR 271 vacuum gauges from Pfeiffer Vacuum offer better accuracy than conventional Pirani vacuum gauges. While the TPR 270 is suitable for all standard freeze-drying applications, the TPR 271 with its robust helix filament of platinum-rhodium and a stainless steel orifice is highly resistant to a variety of solvents and corrosive media.

Solutions for vapor-sterilizable freeze dryers

Capacitive vacuum gauges offer higher accuracy than Pirani vacuum gauges. The absolute pressure is determined via the deflection of a diaphragm, which is part of a condenser. The measured capacitance change is then a measure of the absolute pressure. For freeze-drying, capacitive vacuum gauges with a maximum measuring range of 1 hPa or 10 hPa offer the best accuracy. Pfeiffer Vacuum developed the CLR series of capacitive gauges specifically for steam-sterilizable

The wide range of pump technologies ensures the right solution for every freeze dryer.



Figure 2: Leak detector ASM 340

freeze dryers. It comprises three different models. These vacuum gauges are actively heated to 160 °C. This reduces the risk of condensation inside the gauge; furthermore, the electronics are not located in the immediate vicinity of the diaphragm and measuring chamber. This means they are not damaged by the hot vapor.

Calibration ensures product quality

In order to ensure the accuracy and repeatability of the pressure measurement and thus the process stability in the long term, it is necessary to regularly calibrate the vacuum gauges. The measuring signals may shift if the sensors become contaminated. Pfeiffer Vacuum offers both factory and DAkkS calibration of vacuum gauges. The calibration is carried out according to high quality standards and in compliance with the relevant ISO 3567. The test conditions and discrepancies recorded are documented in the calibration certificate issued.

If a customer has a large number of vacuum gauges in use, on-site calibration can be more cost-effective and easier. Pfeiffer Vacuum also offers suitable solutions for this purpose: the specially developed Basic and Pro calibration pumping stations. The systems incorporate an integrated turbo pumping station to provide the pressure necessary for accurate zero adjustment. A vacuum chamber in accordance with ISO 3567 ensures a homogeneous pressure distribution



Figure 3: For many foods, freeze-drying is the standard method of preservation

and a symmetrical arrangement of the vacuum gauges at the same height. Gas inlet and pump input are also located on an axis of symmetry. With these calibration systems and a corresponding reference vacuum gauge, the calibration can be carried out easily.

Quality assurance and process optimization

Mass spectrometers are used in freeze-drying for quality assurance and process optimization by means of Process Analytical Technology (PAT). They allow complete documentation of the production. With its proven mass spectrometer technology, the PrismaPro from Pfeiffer Vacuum represents an outstanding solution for detecting silicone oil leaks as they occur, thus protecting valuable batches from contamination. Thanks to its high flexibility, the mass spectrometer can also be used to monitor the water vapor concentration and other existing gases such as nitrogen and oxygen. By monitoring the water vapor content, the end point of the main and subsequent drying process can be determined much more accurately.

Locating leaks reliably

A good tightness of the drying system and the connected components is indispensable for achieving the necessary pressure for all freeze-drying processes. Particularly in the pharmaceutical sector, no microorganisms may enter the system during aseptic lyophilization. With its ASM 340 leak detector, Pfeiffer Vacuum also offers a powerful and universally applicable solution for this area of quality assurance. The compact and portable ASM 310 is the first choice if mobile use is desired, e.g., for service technicians.

Customized solutions for all applications

From conception to implementation, the experts at Pfeiffer Vacuum work closely with customers from a wide variety of areas ranging from pharmaceutical production to food production to develop customized solutions that are precisely tailored to the requirements of the respective application. Decades of experience in freeze drying and in-depth knowledge of the industry guarantee impressive solutions.



Figure 4: CLR gauge

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