Freeze drying

Optimum vacuum solutions from a single source for your drying process

PFEIFFER VACUUM

Freeze drying

The optimal drying process for sensitive products

In the morning with coffee and cereal or getting vaccinated before the vacation – almost all of us have experienced lyophilized products. But what's behind the process of freeze drying and why does vacuum play a decisive role?

What is freeze drying?

Freeze drying, also called lyophilization, is a particularly gentle drying process and is, therefore, suitable for sensitive products. The material to be dried is initially frozen, and then dried in a vacuum chamber. In contrast to conventional vacuum drying, the primary drying takes place by sublimation. This requires a much deeper vacuum. The water or solvent is transitioned directly from the solid to the gaseous state. Meanwhile, the heat necessary for the phase change is provided, for example, via heating plates. Followed by optional secondary drying to further reduce the residual moisture content of the product. This is done by desorption of bound moisture. A low pressure and an increased heat supply promote the subsequent drying. The vapor is frozen by a cold desublimation trap, often called a condenser.

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Advantages

As with all drying processes, the main objective of freeze drying is to generally increase the storage-life of the product and, in part, also to reduce the weight, e.g., facilitate the transport. The advantage of freeze drying here is that the process runs at a very deep pressure and thus at low temperatures compared to other drying processes. This allows particularly heat-sensitive goods to be dried.

Applications

The main applications of freeze drying are in the food and pharmaceutical industries. But this gentle drying process is also used in many other areas. For example, for drying ceramic powders in ceramic production. Restoration of water-damaged books and documents can also be achieved by freeze drying.

Food – color and taste are preserved

In the food industry, high-quality fruits and coffee, for example, are freeze-dried as bulk material, largely preserving aroma and color. Due to the high throughput rates, the largest freeze-drying systems are used in these areas. A special feature here are the continuous drying systems often used in coffee drying, which are equipped with vacuum load locks.

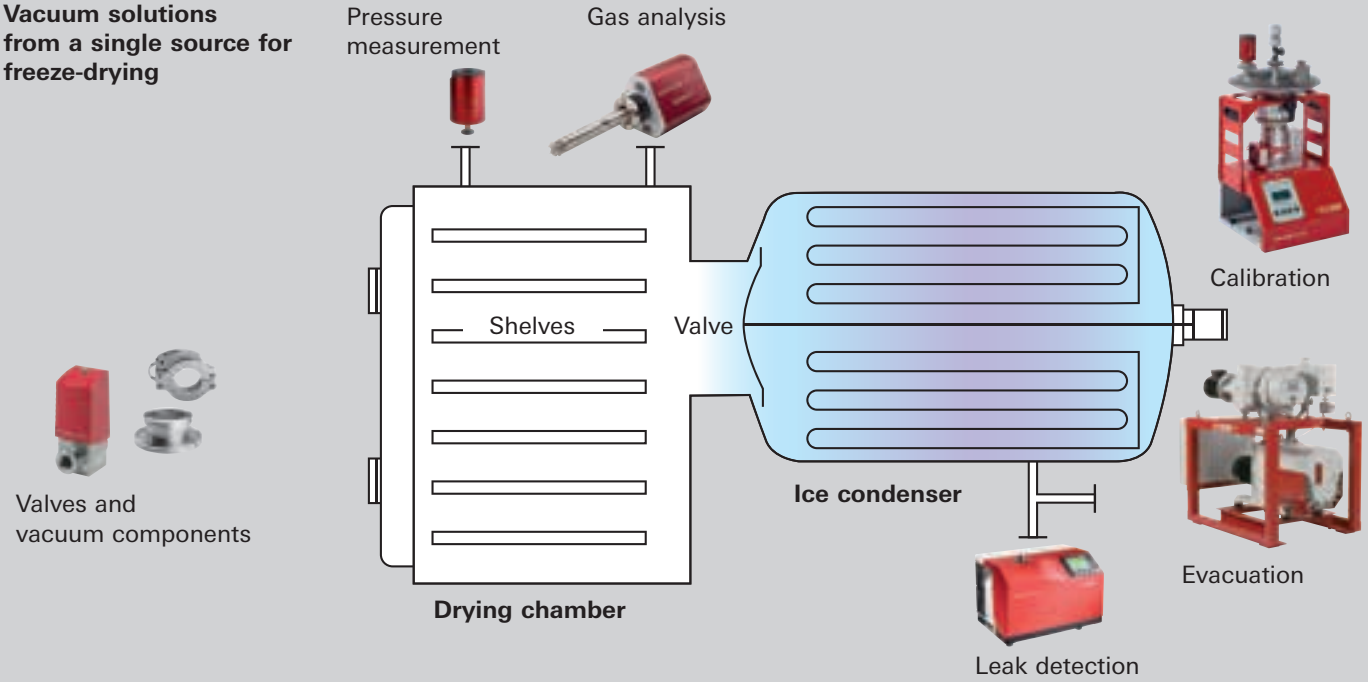
Pharmaceutical industry – high demands on purity and sterility

For pharmacy and biotechnology, freeze-dried substances include temperature-sensitive vaccines, antibiotics and bacteria. These are dried directly in glass vials or syringes for storage and can be dissolved in seconds, if required. When drying parenteral products, there are particularly high demands on the purity and sterility of the systems. Pfeiffer Vacuum supports this both with cleaning concepts for vacuum pumps as well as with products for monitoring the drying chamber.

Everything from a single source

Pfeiffer Vacuum offers a comprehensive portfolio for freeze drying with vacuum pumps for evacuation, pressure gauges and calibration pumping stations, mass spectrometers for gas analysis for process monitoring, as well as leak detectors for the localization of leaks.

Vacuum solutions from a single source for freeze-drying



Freeze drying

Evacuation

The process

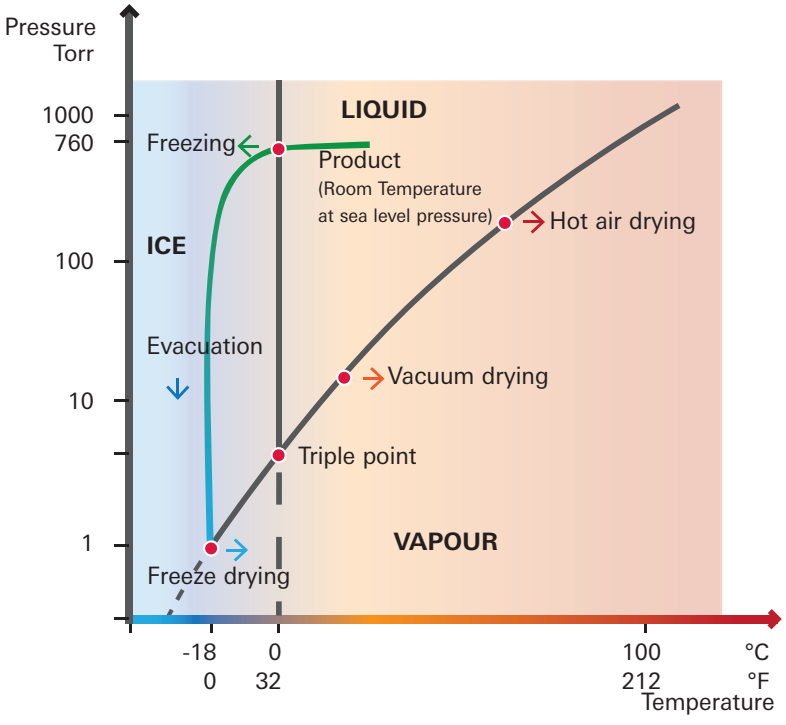
For the freeze-drying process, achieving a pressure below the triple point of the solvent used (e.g., water) is imperative. In addition, during evacuation, unwanted substances such as oxygen are removed from the drying chamber. While the working pressure for the duration of the primary drying is typically between 0.5 hPa and $1 \cdot 10^{-2}$ hPa, it can be up to $1 \cdot 10^{-3}$ hPa during secondary drying or also for the conditioning of the chamber.

Pump selection

The criteria for selecting the vacuum pumps include, in addition, to a sufficiently low final pressure, a high pumping speed to achieve the desired pump-down time, as well as reliability and long maintenance intervals.

Final pressure

For the final pressure, it should be noted that this value in the technical data of the vacuum pump corresponds to the value at which the vacuum pump no longer possesses any effective pumping speed. Therefore, the final pressure of the vacuum pump should be at least a decade below the desired working pressure. Due to its pumping effect, the ice condenser has a positive effect on the achievable pressure in the freeze dryer. This influence increases as the cooling surface temperature decreases. Our engineers will assist you competently in the selection of the right vacuum pump.



Pumping speed

One component of the specification of a freeze-dryer is usually the pump-down time to a defined pressure (usually 0.1 hPa). The nominal pumping speed of the vacuum pump is only an indication since it represents the maximum pumping speed in only one pressure point.

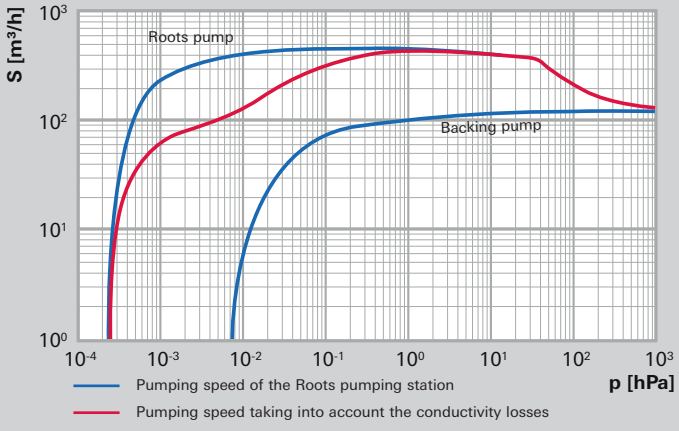
Design

Pfeiffer Vacuum assists you with the design and dimensioning of the vacuum system, taking into account the entire characteristic curve of the vacuum pump(s), and losses caused by pipes and leaks. Modern and specially developed calculation programs are used.

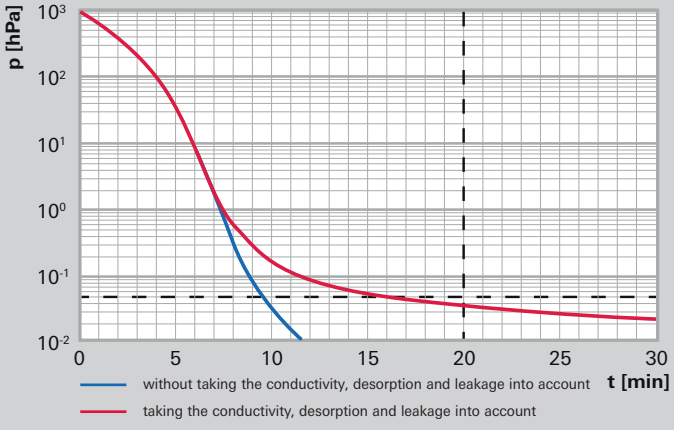
The pumping speed curves clearly illustrate the performance of the vacuum system over the entire pressure range. Achievable final pressure as well as the influence of the conductivity can be easily read off.

The evacuation curve shows whether the vacuum system reaches the target pressure within the required time.

Pumping speed curve of a Roots pumping station



Evacuation curve



Freeze drying

Evacuation

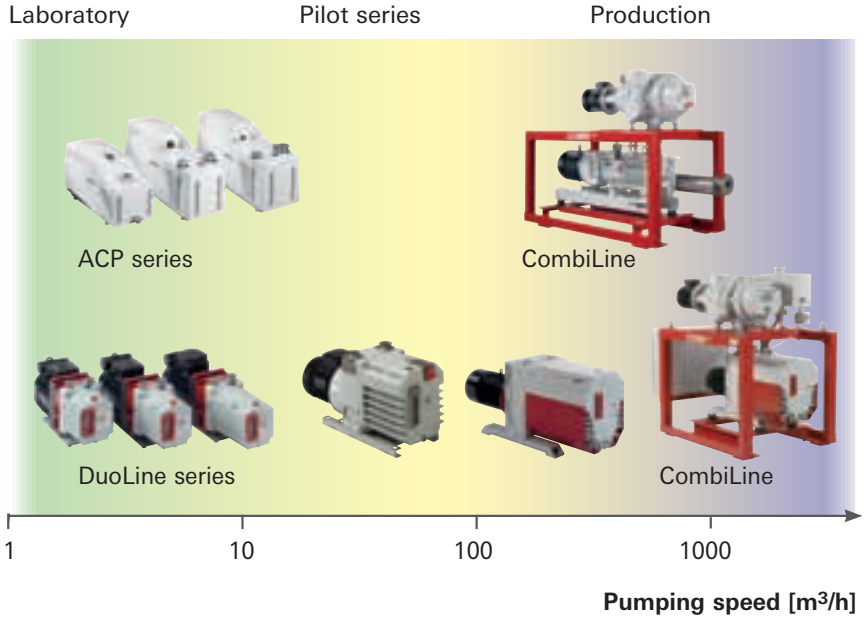
Laboratory and pilot systems

For the small and medium-sized laboratory and pilot freeze drying systems, oil-sealed, two-stage rotary vane pumps are the ones that are predominantly used. Due to their good final pressure, their robust construction and low investment costs, they have proven themselves for decades. This proven concept has been further developed in the compact pumps of the DuoLine. The option of a magnetic coupling between the motor and the pump ensures that oil leaks and unplanned downtime are a thing of the past.

Thanks to further developments in dry-sealing technologies such as multi-stage Roots pumps and scroll pumps, these types of pumps can also be used. A significant advantage is that the lubricant in this design does not come into direct contact with the pumped gases and vapors. This allows a longer oil change interval for dry-sealing pumps.

The multi-stage Roots pumps of the ACP series stand out with maintenance intervals of about 20,000 operating hours.

The right vacuum pump for every freeze dryer



Product overview

Laboratory and pilot freeze dryer		Production freeze dryer			
DuoLine rotary vane pump	**ACP multi-stage Roots pump**	**HeptaDry screw pump**	**HenaLine rotary vane pump**	**OktaLine Roots pump**	**CombiLine Roots pumping station**
					
■ Pumping speed: 1.3 to 300 m^3/h ■ High operational safety thanks to integrated high-vacuum safety valve ■ Optionally available with wear-free magnetic coupling. As a result, extended maintenance intervals and no unplanned outages due to oil leaks.	■ Pumping speed: 15 to 40 m^3/h ■ Compact, dry-sealing pump concept ■ Universally applicable thanks to integrated frequency converter ■ Long maintenance intervals of approx. 20,000 operating hours	■ Pumping speed: 100 to 630 m^3/h ■ Dry-sealing ■ High pumping speed at atmospheric pressure reduces the pump-down time ■ Direct gas flow and optimized temperature profile minimizes deposits	■ Pumping speed: 25 to 760 m^3/h ■ Reliable and powerful rotary vane pump ■ Clean exhaust through integrated oil mist separator	■ Pumping speed: 145 to 27,400 m^3/h ■ Short pump-down time due to high compression ratio and overflow valve ■ Low operating costs due to air cooling ■ Optionally available with wear-free magnetic coupling. As a result, extended maintenance intervals and no unplanned outages due to oil leaks.	■ Pumping speed: 145 to 27,400 m^3/h ■ CombiLine stands for a large variety of Roots pumping stations with different backing pumps, graduations and accessories ■ Modular concept with DuoLine, HeptaLine and HenaLine ■ In addition to the standard range, customer-specific pumping stations can also be designed and constructed for individual requirements

Production systems

In the field of large production systems, in particular in the drying of pharmaceutical products, dry-sealing screw vacuum pumps are often used in combination with Roots pumps. The dry-sealing pumps have stood the test in these areas because of their good cleaning capability. Pfeiffer Vacuum offers special accessories for cleaning the rotors of process deposits for both the HeptaDry screw vacuum pumps and the OktaLine Roots pumps.

However, when drying fruits due to the low investment costs and depending on the chamber size in connection with Roots pumps, rotary vane pumps are predominantly used. The single-stage rotary vane pumps of the HenaLine are characterized by their robust construction and powerful oil mist separators.

Pfeiffer Vacuum offers the right solution for every freeze dryer with its wide range of pumping technologies and sizes.

Freeze drying

Vacuum pressure measurement and calibration

Vacuum pressure measurement

Accurate and repeatable pressure measurement in the drying chamber is essential for the development and control of freeze-drying processes. Due to the relevant pressure range in freeze-drying, two main technologies come into question: Pirani and capacitive vacuum gauges.

Pirani vacuum gauges

Pirani vacuum gauges measure the pressure indirectly via the pressure-dependent heat conductivity of gases. A common mode of operation is the heating of a wire to a constant temperature, whereby the required heat capacity is an indicator of the surrounding pressure. Pirani vacuum gauges can measure in the pressure range from atmospheric pressure to about $1 \cdot 10^{-4}$ hPa, whereby a meaningful accuracy can only be achieved in a much narrower range (about 10 hPa to $1 \cdot 10^{-3}$ hPa).

Use for comparative pressure measurement

The Pirani vacuum gauges are among the most cost-effective vacuum gauges with an electrical output signal. However, they are gas-dependent. The background is the different thermal conductivity of different gases. In freeze drying, it is common practice to take advantage of this gas type dependency. For example, a Pirani vacuum gauge calibrated for nitrogen or air shows a significantly higher pressure for water vapor. When simultaneously measuring a pressure signal from a gas-independent vacuum gauge (e.g., a capacitive vacuum gauge), by comparing the measured values it is indicative of the water vapor content in the drying chamber. Thus, adjusting the pressure signals from the Pirani and capacitive vacuum gauge is a helpful indicator for determining the end of primary drying. This procedure is also called comparative pressure measurement.

Thanks to their pulse technology, the innovative TPR 270 and TPR 271 vacuum gauges from Pfeiffer Vacuum offer better accuracy than conventional Pirani vacuum gauges. While the TPR 270 is ideal for all standard freeze-drying applications, the TPR 271 is ideal particularly for challenging applications.

Product overview

Pirani		Capacitive		
TPR 270	**TPR 271**	**CMR 36x**	**CMR 37x**	**CLR**
				
■ Pulse Pirani principle ensures better accuracy[1)] ■ Gas-dependent measurement (may be used in conjunction with capacitive vacuum gauge for comparative pressure measurement)	■ Pulse Pirani principle ensures better accuracy[1)] ■ Gas-dependent measurement (may be used in conjunction with capacitive vacuum gauge for comparative pressure measurement) ■ Robust platinum rhodium-filament	■ Gas-independent measurement ■ Temperature-compensated measurement, without heating time ■ Sensor with ceramic technology – Highest temperature stability – Resistant to corrosive gases – Excellent lifetime – No plastic deformation	■ Gas-independent measurement ■ Temperature controlled to 45°C for high accuracy ■ Sensor with ceramic technology – Highest temperature stability – Resistant to corrosive gases – Excellent lifetime – No plastic deformation	■ Gas-independent measurement ■ Suitable for vapor sterilization ■ Temperature controlled to 160°C for highest accuracy and protection against condensation ■ Sensor with ceramic technology – Highest temperature stability – Resistant to corrosive gases – Excellent lifetime – No plastic deformation

[1)]Compared to conventional Pirani sensors

The helical shape and unique material properties of the platinum-rhodium filament provide an improved lifetime and resistance to solvent vapors.

Capacitive vacuum gauges

The capacitive vacuum gauges offer a far better accuracy than Pirani vacuum gauges. They are also independent of the type of gas. 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. Versions with heated diaphragms are more independent of changes in ambient temperature and, therefore, more accurate.

The measuring range of a capacitive vacuum gauge usually extends over four pressure decades. Accuracy is best for each of the upper decades, because at low pressure, the constant factors influencing the measurement inaccuracy are greatest. Therefore, for freeze-drying, capacitive vacuum gauges with a maximum measuring range of 1 hPa or 10 hPa offer the best performance.

Freeze drying

Vacuum pressure measurement and calibration

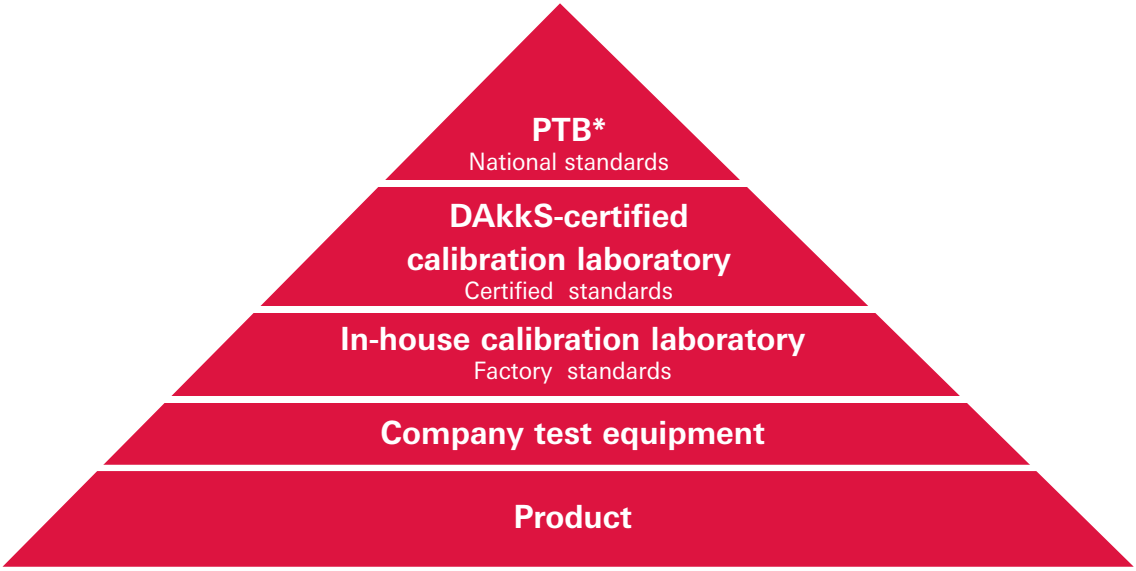
The solution for vapor-sterilizable freeze dryers

Based on decades of experience in the field of freeze drying and customer interviews, Pfeiffer Vacuum has developed the CLR series of capacitive vacuum gauges for vapor-sterilizable freeze dryers. The CLR vacuum gauges are actively heated to 160°C. On the one hand, this reduces the risk of condensation within the vacuum gauge. On the other hand, the electronics are not located in the immediate vicinity of the diaphragm and measuring chamber and are, therefore, not affected by the hot vapor. The 4-20 mA output signal enables interference-free further processing in the PLC. The CLR vacuum gauges are part of a large existing range of capacitive vacuum gauges, the CMR series.

Calibration

In order to ensure the accuracy and repeatability of the pressure measurement and thus the process stability in the long term, it is essential to regularly calibrate the vacuum gauges. The measuring signals can shift due to the contamination of the sensors through particles or condensate as well as due to long-term aging. Therefore, calibration is an integral part of quality assurance in which the measuring signals of the measurement instruments are compared with

Hierarchy of the calibration chain (decreasing accuracy)



*Physikalisch-Technische Bundesanstalt
(National Metrology Institute of Germany)

a reference vacuum gauge. The reference vacuum gauge must have been calibrated by a certified laboratory (e.g., DAkks [*Deutsche Akkreditierungsstelle GmbH = German accreditation agency*] certified in Germany, NIST certified in the U.S.) and can be traced back to a national standard.

Factory and DAkkS calibration

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 ISO 3567. The test conditions and discrepancies recorded are documented in the calibration certificate issued.

Pfeiffer Vacuum calibration systems

When using a large number of vacuum gauges, a calibration directly in-house can be more cost-efficient than an external calibration. For this purpose, Pfeiffer Vacuum offers specially developed calibration pumping stations with the Basic and Pro models. These systems incorporate an integrated turbopumping station to provide the pressure necessary for accurate zero adjustment. A vacuum chamber in accordance with ISO 3567 ensures a homogeneous pressure distribution and ensures 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 the Pfeiffer Vacuum calibration systems and a corresponding reference vacuum gauge, the calibration can be carried out easily, particularly for the pressure range relevant for freeze drying.

Product overview

Calibration system Basic	Calibration system Pro
	
■ Compact system with up to 6 flange connections for vacuum gauges	■ Mobile system with up to 8 flange connections for vacuum gauges

- Calibration range 1,013 – 10^{-4} hPa
- Easy to use
- Recipient according to ISO/TS 3567 standard
- For static and dynamic calibration
- Customized solutions available
- DAkkS reference vacuum gauges optionally available

Freeze drying

Silicone oil detection and process monitoring with mass spectrometry

Quality assurance and process optimization

The mass spectrometer is a very effective process analytical technology (PAT) tool for freeze drying. It is used both for quality assurance and for process optimization and allows a complete documentation of production. The two main areas of application are described below.

Silicone oil detection – the problem

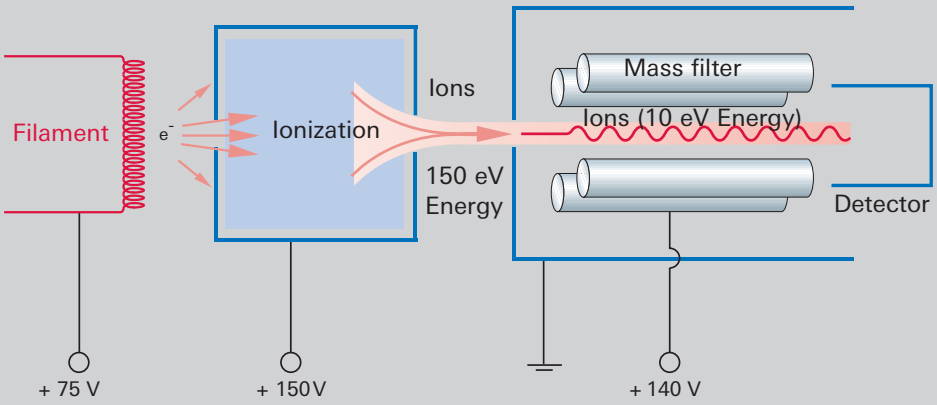
The shelves of production freeze dryers are predominantly tempered with silicone oil. The circulation of the heat transfer fluid is sealed from the drying chamber. However, the corrugated tube supply and discharge lines for the silicone oil are particularly subject to high stress. Temperature and pressure fluctuations as well as mechanical stress during the positioning of the adjusting plates cause leaks over time. Due to the initially small amounts of silicone oil, several batches can already be contaminated before the leak is detected. In addition, it is difficult to determine from which batch the silicone oil leakage has already occurred and must, therefore, be discarded. This can prevent high follow-up costs.

Mass spectrometry – the solution

In order to counteract this problem effectively, it is necessary to detect the silicone oil leakage already at the time of formation and thus being able to save valuable batches from contamination. The PrismaPro from Pfeiffer Vacuum with the proven mass spectrometer technology provides an excellent solution for this, and also offers valuable additional options for process monitoring.

Mass spectrometry – fundamental principles

In the mass spectrometer, electrons are emitted in a filament which ionize gas molecules. These are separated by a mass filter, which allows only ions with a certain charge/weight ratio to pass by means of electric fields. These ions are then neutralized in the detector and generate a current signal. This can be optionally enhanced by the so-called secondary electron multiplier (SEM) for better sensitivity.



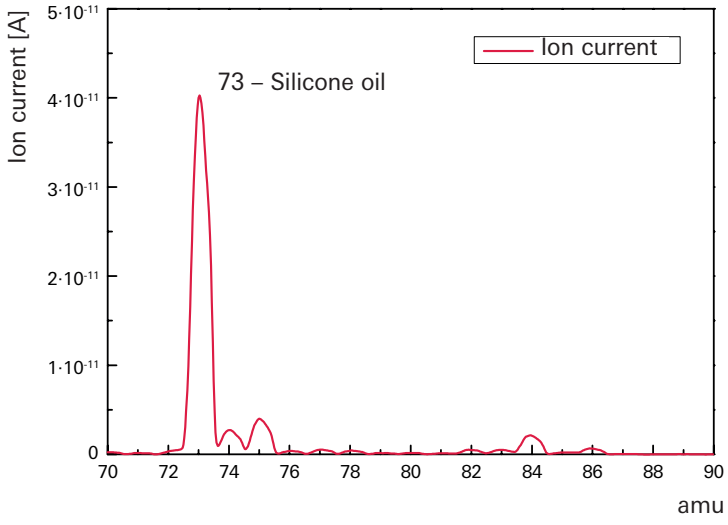
Functioning of a mass spectrometer

Pressure range

Conventional mass spectrometers are operated in a high vacuum of about $1 \cdot 10^{-6}$ hPa. This has the advantage that the contamination of the filament by the entry of silicone oil is significantly lower than in miniaturized mass spectrometers, which are operated at a comparatively high pressure.

Detection in seconds

Extensive tests have shown that the relevant silicone oils can be detected with a mass spectrometer, particularly on the atomic mass unit 73. The response time depends on the installation situation and the size of the chamber, but ranges from a few seconds. When a SEM is used, the detection limit is in the ppm range. So even the smallest silicone oil leaks can be detected in a very short time.



Measuring silicone oil with PrismaPro

Freeze drying

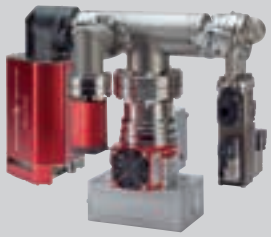
Silicone oil detection and process monitoring with mass spectrometry

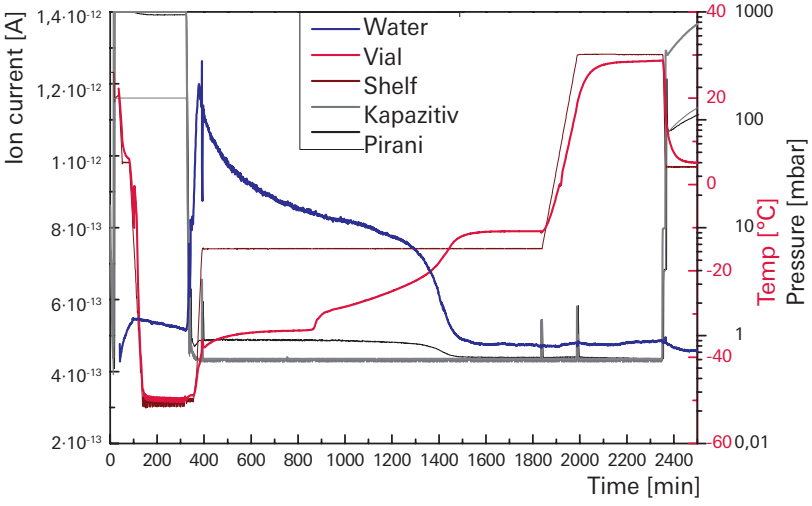
Process monitoring and end point determination

Due to its high flexibility, the mass spectrometer can also be used to monitor the water vapor concentration as well as other existing gases (e.g., nitrogen, oxygen). By monitoring the water vapor content, the end point of the main and subsequent drying process can be determined much more accurately than is possible with the help of comparative pressure measurement, for example. This provides new opportunities for optimization, particularly, in the development of freeze-drying processes.

Pfeiffer Vacuum works closely with the manufacturers of freeze-drying systems when integrating the mass spectrometer into the production system. Pfeiffer Vacuum delivers the complete mass spectrometer system including turbopumping station, measuring technology and control valve and provides support for integration into the controller of the freeze dryer. Pfeiffer Vacuum offers both manual systems for use on laboratory equipment, as well automated units for integration into production freeze dryers.

Production freeze dryer from OPTIMA pharma GmbH
Courtesy of OPTIMA pharma GmbH

Individual components	Laboratory and pilot freeze dryer	Production freeze dryer
PrismaPro	**HiCube RGA**	**Automated systems for operation on production FD**
		
■ Compact dimensions and high performance ■ Simple system integration through a variety of interfaces ■ High measuring speed, stability and resolution ■ Best availability through two filaments ■ Smallest detectable partial pressure of 1 $\cdot 10^{-14}$ hPa	■ Complete system with integrated turbopumping station ■ Manual gas inlet system allows measurement at any pressure range in the freeze dryer ■ Filament protection through pressure monitoring	■ Ideal complete system for batch monitoring ■ Controllable gas inlet system allows measurement at every pressure range in the freeze dryer ■ Completely automated operation possible due to control via the PLC of the freeze dryer ■ Filament protection through pressure monitoring



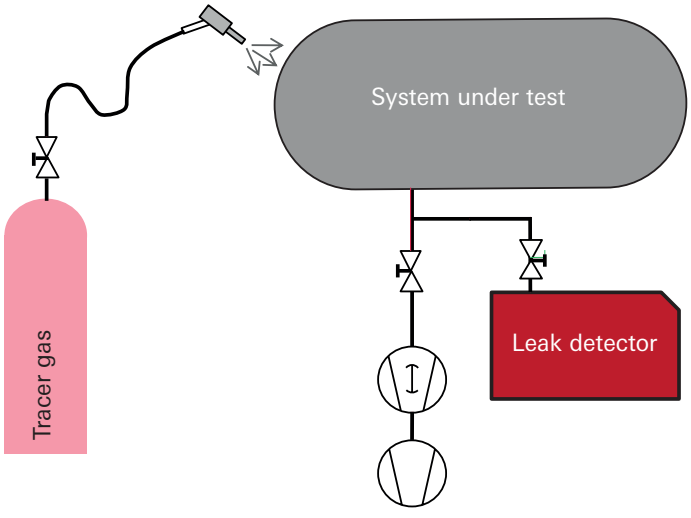
Monitoring a freeze-drying process. The PrismaPro mass spectrometer allows monitoring of process gases in near real time. The water vapor concentration can be displayed in much better resolution than would be possible with comparative pressure measurement.
This measurement was performed through the kind support of OPTIMA pharma GmbH.

Freeze drying

Leak detection

Special requirements for pharmaceuticals

A good tightness of the drying system and the connected components is indispensable for achieving the necessary pressure for all freeze-drying processes. Special requirements apply to the aseptic freeze drying of pharmaceuticals, preventing the entry of microorganisms into the system. In this range, integral leakage rates < $2 \cdot 10^{-2}$ hPa·l/s are considered safe, while the trend is moving more toward dense systems. The integral leak test is usually carried out through the pressure rise method. In doing so, the system is evacuated to a defined pressure value. After that, all valves are closed. The pressure increase as a function of time yields then the integral leakage rate. It should be noted that internal leaks, desorption of surfaces as well as evaporation or sublimation also cause a pressure increase and may falsify the result through that. Therefore, an empty, clean and dry chamber is a requirement for accurate detection of the leakage rate.



Leak detector in partial flow to the existing vacuum system for large systems

Localization of leaks

If the leak rate exceeds the desired threshold, it is important to locate and correct the leakages. Their high detection sensitivity, short test time and easy operation make helium leak detectors ideal for localizing leaks. With this method, the freeze-drying system is evacuated. From the outside, helium is sprayed locally on sealing points, weld seams and other potential leaks by using a spray gun. In the event of a leak, the helium flows into the evacuated vacuum chamber and is detected and sucked in by the leak detector. In order to realize short response times, the leak detector is used in large systems in partial flow to the existing vacuum system (see the leak detection diagram).

Ideal solution by Pfeiffer Vacuum

With the ASM 340, Pfeiffer Vacuum offers a powerful and universally applicable leak detector. The compact and portable ASM 310 is the first choice for mobile use, e.g., for service technicians.

Product overview

ASM 340	ASM 310
	
■ Fastest response time thanks to high helium pumping speed ■ Easy handling, intuitive menu navigation and big color touchscreen ■ Fastest operational readiness in its class	■ Dry pump system, fore-vacuum pumping speed 1.7 m^3/h ■ Ultralight, only 21 kg and portable ■ Clever design with extensible handle ■ Removable control panel ■ SD card for data storage

VACUUM SOLUTIONS FROM A SINGLE SOURCE

Pfeiffer Vacuum stands for innovative and custom vacuum solutions worldwide, technological perfection, competent advice and reliable service.

COMPLETE RANGE OF PRODUCTS

From a single component to complex systems:
We are the only supplier of vacuum technology that provides a complete product portfolio.

COMPETENCE IN THEORY AND PRACTICE

Benefit from our know-how and our portfolio of training opportunities!
We support you with your plant layout and provide first-class on-site service worldwide.

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Pfeiffer Vacuum GmbH
Germany
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