

Innovative ideas – innovative solutions



HOF – innovation

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Success through innovation

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Dear Ladies and Gentlemen

the freeze-drying principle is based on various physical basic principles which, by definition, are not subject to change.

However, innovative and continual further developments of technologies around freeze-drying are necessary, in order to guarantee efficiency and safety in the manufacturing process of high-class products. Continual innovations and concepts are arising, particularly in the process technic area, plant safety and loading and unloading systems. As a machine manufacturer, we want to and have to react to these ever-increasing market requirements.

“HOFinsight” – versatile and informative

With the 1st issue of our new customer magazine HOFinsight, we would like to draw your attention to our innovations, solutions and developments.

With regard to product and plant safety, we are further working on the detection of silicone oil and on the life-cycle optimization of flexible hoses, in order to avoid any case of average. At the same time, we are conducting studies about alternative refrigerants to face the announcement of discontinuation of R404a.

HOF also further optimizes SynchroFreeze, which was developed as a controlled nucleation method.



In our loading and unloading systems segment, a successful concept has been realized in direct collaboration with one of our customers, which consists of a flanging machine working along the unloading area. Thanks to this system, we can save floor space and precious process times.

We are also pleased to announce that this year again, as in 2016, HOF ranks among the Top 100 most innovative companies in Germany.

We hope you are curious now and we look forward to answering your questions about the topics as listed above. We would like to invite you to our technical forum, which will now take place for the second time in November 2017. In this magazine, we will inform you about this event too.

We wish you a lot of success for the future and hope you will enjoy reading the first issue of “HOFinsight”.

Sincerely,
the Hof family



TOP 100-Innovator 2017

In 2017 HOF ranks once again among the innovation elite

Following the award in 2016, in 2017 HOF again was awarded with the TOP 100 label and thus ranks among the top 100 most innovative companies in Germany. During a festive support program, all award winners were honored by Mr. Ranga Yogeshwar, the mentor of this competition, with certificate and trophy. This time again, HOF could particularly score with its innovation management and its accompanying innovation successes. The label itself was awarded for the 24th time in Essen and honors the German innovation elite in different categories.

HOF SynchroFreeze for optimized freeze drying processes

In the pharmaceutical area, the controlled nucleation is a frequently discussed topic. “SynchroFreeze” is a development, well-established by HOF over the last years. Its aim is to provide the user with an additional tool to increase the quality of the pharmaceutical product and simultaneously ensure an efficient operation of the freeze-drying systems. SynchroFreeze is characterized by a conditioning phase, followed by cooling and vacuum-induced nucleation during the freezing process. In the conditioning phase, dissolved gases are withdrawn from the liquid product under partial vacuum, in order to prevent from strong gas bubble formation and swelling of the product in the subsequent freezing steps. The now largely degassed liquid is cooled and the nucleation is triggered by a further pressure drop at the desired freezing point in the lower millibar range (Figure 1).



Figure 1: Crystal growth after vacuum-induced nucleation

Product specifications matter

Studies on SynchroFreeze are carried out by different development teams. Application related adjustments of the freezing phase are described within first publications [1]. Conditioning times are different, depending on the product, liquid level and temperature. Moreover, the selection of the freezing point and the subsequent pressure adjustments offer further optimization potential even for difficult products.



Figure 2: Lyophilisate structures of a 5% saccharose solution, for comparison: left SynchroFreeze – right standard

In many application cases, a required supercooling can be set by means of the shelf temperature, by reducing the pressure level in the freeze-drying chamber at the same time. After completion of these steps, the product is liquid and put at the required supercooling level.

Optimization of the product structure

A further rapid pressure reduction enables a homogeneous freezing of the vials. The pressure reduction ensures the evaporation of the solvent contents on the liquid surface with local cooling, this triggers the freezing and crystallization process which progresses from the surface downward. Therefore, the adjustment of the chamber pressure enables a rapid and very efficient temperature change at the product surface. In many cases, the targeted application of SynchroFreeze allows the optimization of the product structure (Figure 2 and 3) as well as a significant reduction of the drying times. The larger structure of the lyophilisate simplifies the entry of the solvents and has a favorable effect for the reconstitution process.

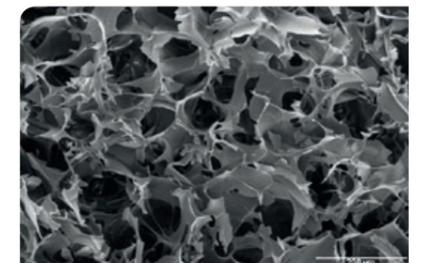


Figure 3: Scanning electron micrograph; product structure after application of SynchroFreeze during freezing and following freeze-drying. Micrograph by courtesy of IDT Biologika.

The high expectations put to the SynchroFreeze technology are confirmed by the product-specific test results. Furthermore, only limited plant modifications are necessary for the implementation.

[1] Allmendinger, A., et al. (2016). Controlled nucleation during freeze drying using vacuum-induced surface freezing. Data base no. 633018, www.researchdisclosure.com

HOF SynchroFreeze

- Synchronization of the the freezing process in the individual vials or product containers
- Conditioning of the product structure
- Improvement of the product homogeneity
- Reduction of required drying times
- Increase of the performance and reduction of the energy consumption

Very safe and markedly versatile ...

> HOF – loading and unloading systems



HOF's loading and unloading systems: successful innovations



Due to the long-term experience, HOF has become the suppliers of future-proof loading and unloading systems. Systems with all degrees of automation can be implemented in many ways, e.g. as an extension of existing freeze-dryers or integrated in newly developed production lines and be upgraded to be state-of-the-art. Through an intensive exchange between customers and HOF's experts, it is possible to achieve a 100% solution meeting each application requirement.

■ The demand for robot systems in the pharma sector shows a trend

The application areas of the robotic technologies extend from extraction systems in the bulk freeze drying sector, up to the fully automatic frame handling for individualized storage. The design in matters of function and size for the respective application is variable, so that a suitable solution can be offered.

HOF has already been implementing robot systems since 2006, amongst others for the extraction of bulk products. Furthermore it is possible to extend existing systems with robot systems or replace operator-assisted processes.

■ Your advantages

- High flexibility
- Space saving systems
- Improved performance



■ Combined HOF unloading system with superimposed sealing machine

A new and innovative system has been developed in collaboration with a renowned pharmaceutical company.

After the freeze-drying process, the vials are discharged via the HOF unloading system and are subsequently transported into the sealing machine along the unloading system. For this purpose, the system installed in the RABS (Restricted Access Barrier System) individually operates in front of the respective freeze-dryer.

■ Your advantages

- Spatially reduced RABS area
- Simplified product handling
- High performance
- Shorter processing times
- Reduced running costs

■ HOF SMART ACS – new developments currently under scrutiny

HOF has found innovative solutions to meet the ever growing requirements in the pharmaceutical area. In the field of loading and unloading systems, new developments have been continually strained in the past: in the sensor technology, hygienic designs, format parts, control system, visualization and system monitoring, in regard to "Industry 4.0". HOF has designed a test plant, especially for this purpose, in order to put in practice all new developments in a target-oriented way.

This test plant is installed in our facility in Mornshausen and can be used in the future to optimize further processes e.g. in regard of the control system technics.

Optimization of the product safety by means of a relief of the corrugated hoses

Among other components, stainless steel corrugated hoses also belong to the critical parts of a freeze-dryer. These flexible elements transport the silicone oil of the heat transfer system inside the chamber to and from the shelves and are subject to a very high stress level. Due to the fact that these flexible parts are under considerable strain and in combination with the long life time of a freeze-dryer, the corrugated hoses belong to the natural parts subject to wear.

It is very difficult to define change intervals and in case of damage, considerable breakdowns might happen. To counteract this, HOF has developed the so-called "relief shoe". The repeatedly occurring rated break points at the shelf connecting bends are supported by these "relief shoes" and the pressure of the movement is then derived to further hose spirals.

Bends in both directions can be supported by means of double shoes at the chamber connections. Because of the restricted space situation, the connecting points of the pipe elbows at the shelves are supported by a dynamic single shoe.

Long-term tests have shown that the lifetime of the hoses could thereby be more than quadrupled. At the same time, the supporting elements are in conformity with the approved material classifications and are compatible with the common CIP systems. This could be verified in tests with elevated Riboflavin concentrations. In order to provide a benefit as big as possible concerning process safety, the elements were designed in a way, that the "relief shoes" can be generally retrofitted to existing machines.

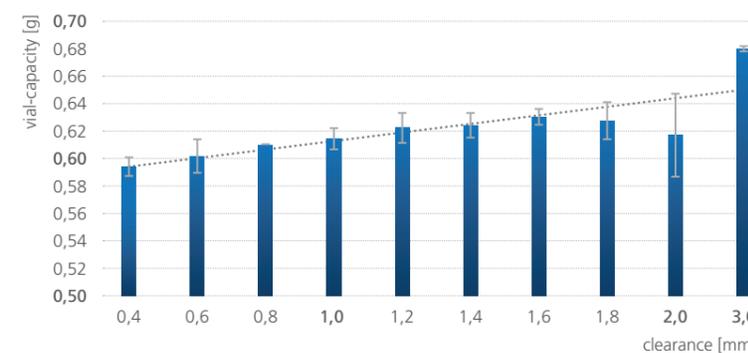
- without relief shoe
- using relief shoe (generation 1)
- using relief shoe (generation 2)



Container Closure Integrity

Because product protection and safety have an ever-growing priority, there are a lot of discussion topics about container closure integrity. It is frequently reported that vial sealing plugs are not correctly or not fully pushed in and therefore the vial sealing is not satisfactory. In many cases, the resulting gap size can be neutralized by the downstream crimping machine, but some uncertainty remains for the time span between opening the freeze-dryer and the actual crimping of the vials with the aluminum cap. These circumstances are usually directly associated with the freeze-drying machine. It must be admitted, that the handmade shelf area, as a welded construction, is certainly adjusted and ground a number of times, nevertheless a 100% flat surface cannot be reached.

The compliance with the specifications is confirmed by a corresponding certificate. However, major difficulties are met in this context due to variances in the used primary packaging material. Although these differences do range within the specified tolerances, over-sized vials impede the sealing of under-sized vials. In order to offer a better understanding of safety in this context, HOF is conducting a study on vacuum tightness with different packaging combinations. An integrity check is carried out at different time intervals on vials which are sealed under vacuum with defined gape-sizes. First tests showed that a gap size of up to 1,6 mm, even after a storing time under atmosphere, did not result in loss of vacuum. In order to cover a spectrum as wide as possible, we will go on with our checks, but we are confident that other packaging combinations will deliver similar results.



We will be pleased to keep you in the loop of our results.



HOF R&D Lyo – for continuous development



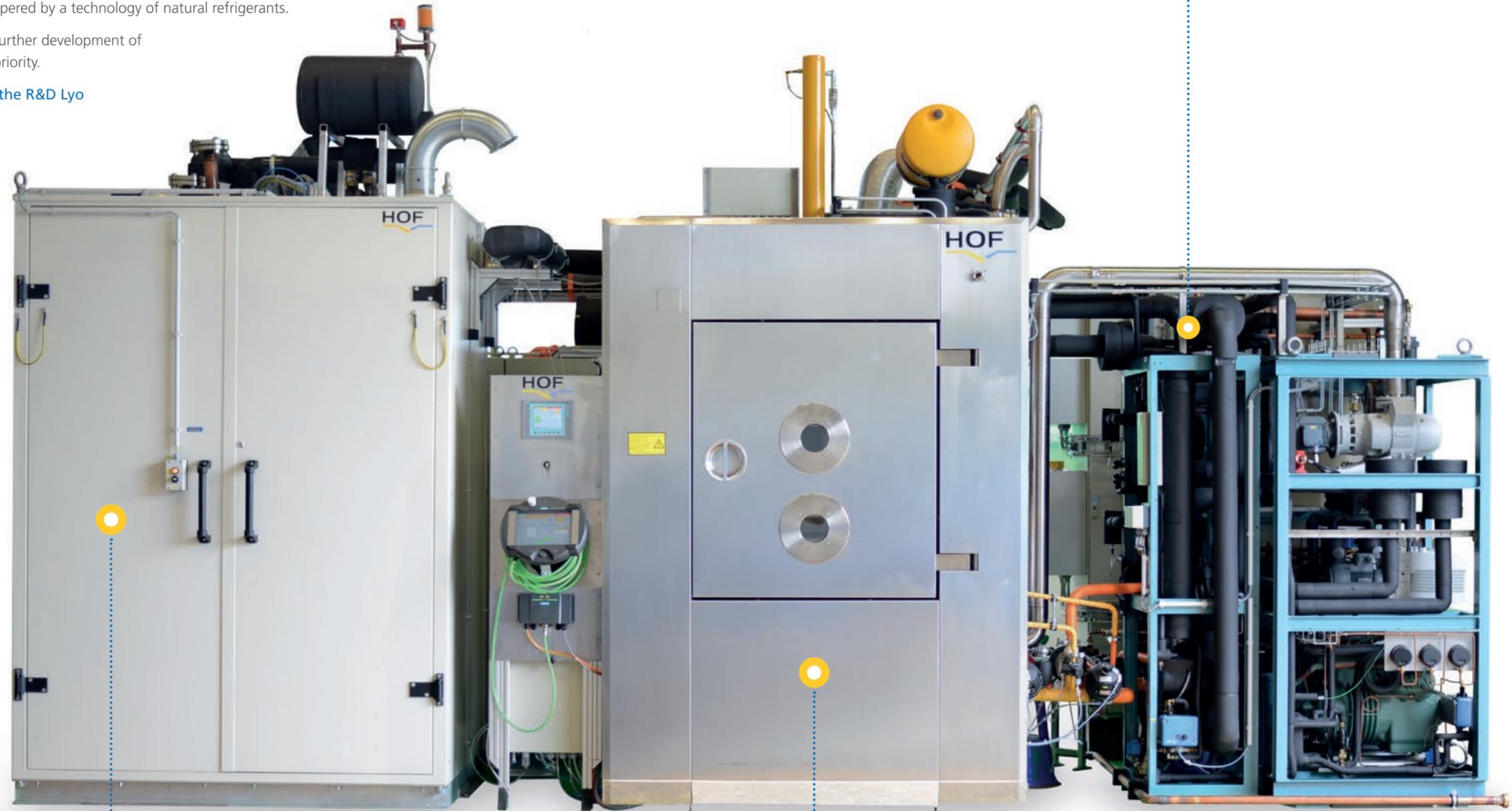
With the objective of advancing and testing innovations and technical developments, HOF has established a freeze-dryer for development purposes in its own factory. The so-called R&D Lyo has 5+1 shelves, 1,64 m² shelf area and a 28 kg ice capacity.

A special feature consists in 2 different refrigerating systems: on one side, the heat transfer system of the shelves is operated by conventional refrigeration, on the other side, the condenser is tempered by a technology of natural refrigerants.

Besides many other issues, the further development of both systems is currently a top priority.

[More information regarding the R&D Lyo on page 10](#)

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1 natural refrigerants

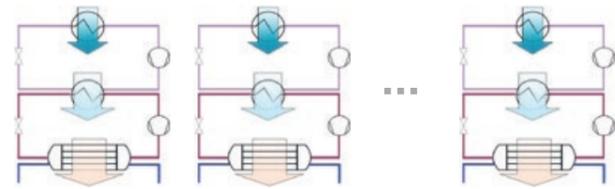
2 detection of silicone oil

3 conventional refrigeration technology

HOF R&D Lyo – for continuous development

1 Sustainability by means of natural refrigerants

According to the European F-gas regulation, the use of hydrofluorocarbons (HFCs) must be significantly reduced. Consequently, there are some restrictions in the use of conventional refrigerants. Alternatively, natural refrigerant can be used.

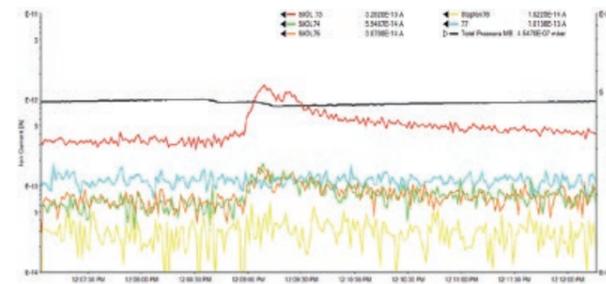


Nevertheless, one natural refrigerant alone cannot reach the required temperatures in the condenser. That is the reason why HOF already launched a cascade system in 2007, in which ethane (R-170) and propene (R-1270) are used. This cascade system consisting of 2 separate circuits, forms an individual module, which can be combined with further modules, for redundancy purposes or to improve the performance. Because ethane and propene are combustible hydrocarbons (group A3), the cooling devices are designed according to the ATEX guidelines. Depending on the building concept it is also possible to waive the ATEX requirement if gas detection systems are used.

2 Product safety by means of silicone oil detection

Any leak of silicone oil in the drying chamber means product losses and production losses. In case a leakage is visually assessed, it is in many cases no longer possible to trace back when the silicone oil leak occurred for the first time and we must cast doubt on the quality of many product batches.

Mass spectrometry enables to detect the smallest quantities of silicone oil in the drying chamber, so that any contamination can be immediately identified. Depending on the production concept and on the process requirements, cyclical or continual measurements are made. Currently, we are testing different detection systems at our R&D Lyo, while the limits of the actual method are also checked. At the same time, we are testing the



implementation of this technology in existing automatization concepts. By means of a defined additional metering of different types of silicone oil, it is possible to clearly identify the corresponding masses. In parallel, optimal test conditions can be observed.

3 Alternatives in the field of conventional refrigeration technology

To achieve the objectives of the F-gas regulation, there is a step-wise reduction of the HFC quantities which are allowed in the EU. A scarcity of available conventional refrigerants is arising. The limit value for the scarcity is fixed at a GWP_{100} *-value of ≥ 2.500 . Among those also R-404A ($GWP_{100} = 3.922$) and R-507 ($GWP_{100} = 3.985$) are listed.

Sure, up to the 1st of January 2030, these refrigerants can be implemented in low-temperature areas but already now, there are shortages in the availability and the prices are considerably rising. Consequently, HOF is using the R&D Lyo to check the readiness for use and efficiency of diverse alternative refrigerants in order to enable the offering and usage of alternatives in

the field of conventional refrigerating technology. Basic condition for this is a technically flawless application, without any elaborate system modifications. Up to now, two alternative refrigerants could meet all criteria, they are now standing in the final testing phase.



* The GWP_{100} -value describes the global warming potential of a refrigerant over a period of 100 years.



HOF's technical forum 2017:

"Always think ahead"

Our 2nd technical forum will take place on the 16th of November 2017. We will welcome our guests with varied lectures, current developments and interesting guest speakers from the freeze-drying sector, as well as presentations of our company departments.

This time again, you will get the opportunity to exchange information with HOF experts and other users.



16th of November 2017

Welcome Hotel Marburg

The event will take place at the Welcome Hotel in Marburg.

Further information and details about lecture contents will be published on time.



Retrospective of the 1st HOF's technical forum of 2014

"Gained in praxis, for the praxis"



On the occasion of the 25th anniversary, HOF Sonderanlagenbau held its 1st technical forum. During the symposium, notable experts from fields of research and industries reported on their recent research results and innovative fields of application in the manufacturing process.

More than 100 attendees came to our site in order to exchange experiences.



Here, you can watch the video about the event:

www.hof-sonderanlagen.de/en/the-1st-hof-technical-forum.html



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