Application Note

Lyophilization

Introduction

Lyophilization is a pharmaceutical-specific industry term for freeze drying, commonly used for pharma production. It is estimated that over half of injectable drugs undergo lyophilization, the practice of removing solvents, frequently water, from aqueous solutions or liquid pharmaceuticals, during the production process. There are three main steps in the lyophilization process:

1. The freezing process, during which the product is cooled down to below its triple point so that sublimation, rather than melting, occurs. This commonly occurs within a freeze dryer.
2. The primary drying step. The pressure is lowered and heat is added to encourage sublimation of the water.
3. A secondary drying process where additional drying occurs until the materials are dried somewhere between 1% and 5% residual moisture.

One of the benefits of lyophilization is an increased shelf life of the product. Some products can have a shelf life of 2-5 years. Additionally, the result of lyophilization is a densely packaged cape that can be more easily transported and reconstituted upon use.

Process Overview

A Residual Gas Analyzer (RGA), can be used to effectively detect contamination from cooling lines that use silicon-based oils. RGAs can also be used as an in situ air leak detection system to monitor process vacuum conditions. INFICON's Transpector® CPM tool is a self-contained system that includes a complete pumping package and inlet system providing an all-in-one process monitoring solution ideal for this application. RGAs can replace existing methods used for primary drying endpoint detection practices with a quicker specie-specific response, as well as chamber gas monitoring applications, which provide analysis of other gases in the system such as oxygen, nitrogen, carbon dioxide, and argon. RGAs are also useful to determine if product collapse or melt has occurred during the drying process. Silicon based oils are commonly used as the heat transfer or cooling fluid for the freezing step in lyophilization processes. Coolant leaks into the freeze drying chamber are an area of concern when ensuring product quality. If a product is contaminated, there are no steps to recover the product and it must be scrapped. RGAs can detect the presence of a coolant and identify a contamination event in real time.

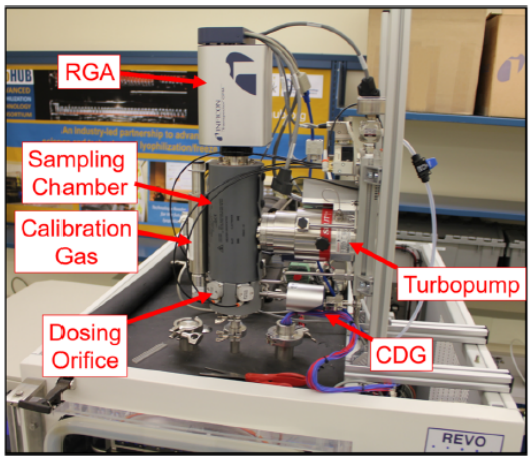
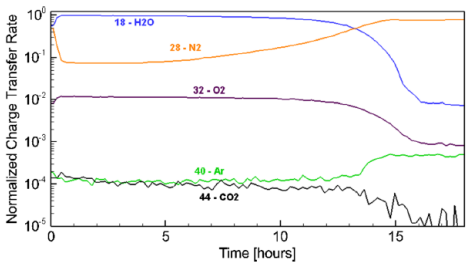


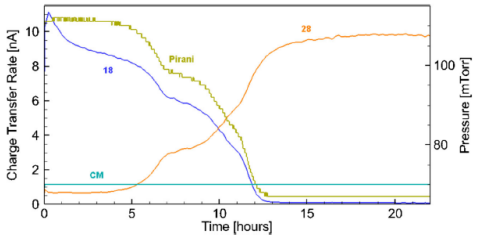
Photo credit: Liechty, E.T., Strongrich, A.D., Moussa, E.M. et al. In-Situ Molecular Vapor Composition Measurements During Lyophilization. Pharm Res 35, 115 (2018). https://doi.org/10.1007/s11095-018-2395-4

Application Description

RGAs are commonly used to confirm vacuum integrity in manufacturing processes that require low-pressure conditions. Both primary and secondary drying steps of lyophilization occur under vacuum and require proper sealing and low contaminants to ensure product quality. RGAs are useful tools for identifying air leaks that can lead to a pathway of contaminants to the process, whether those contaminants are constituents of air or microbial contamination from the ambient. In situ air leak detection provides value in decreased downtime during operational qualification of process equipment. RGAs can quickly identify air leak signatures or even act as an in situ helium leak detector and provide feedback to the operator in order to fix the source of the leak.



A commonly used method to determine the end-point in the primary drying phase is to use two vacuum gauges; one gas-dependent gauge and one gas-independent gauge (Vacuum Gauge Method). When the gas-dependent gauge agrees with the gas-independent gauge, it represents an environment that is mostly nitrogen. Nitrogen is the ballast gas, meaning that the water vapor in the system has been evacuated. In contrast, the RGA Method allows for a direct and faster measured response of the water vapor as well as the ballast gas. The RGA response to a change in water vapor is faster than the previously mentioned gauge method. Additionally, an RGA can monitor for contamination or impurities in the ballast gas that could affect product quality. The faster response time of an RGA leads to shorter cycle times for primary drying steps, which can increase product throughput.



The ultimate goal of any lyophilization process is to increase product stability and shelf life. Using an RGA to monitor the process - allows direct measurement of oxygen in the chamber, can have an impact on the shelf life of certain products in real time, can help determine product quality implications and identify quality issues in a process. Product collapse, or melt back happens when heating occurs too rapidly or at too high of a temperature. This phenomenon takes place when the product softens so much that it can no longer support its own structure. This is problematic because it can lead to an incomplete drying process, leading to poor product quality. RGAs can detect specific signatures that can infer that this phenomenon has occurred.

In pharmaceutical applications, cleanliness and sterility are critical requirements in the manufacturing process. A 0.22 micron filter between the RGA and process creates a sterile boundary that does not require the RGA to be subject to clean-in-place or sterilize-in-place requirements.

Conclusion

From all the testing performed with RGAs, it is evident that they are capable of fulfilling applications that the vacuum gauge method cannot. These applications include contamination detection and product collapse or melt back monitoring. Additionally, an RGA is a better tool for other applications, including air leak detection, primary drying endpoint detection, and chamber gas monitoring.

INFICON has a specific advantage over its competitors in that it provides a complete solution in the form of sensors and integration software used for process monitoring. It couples the in situ sensors with powerful integration software that can transform signals from the sensors into meaningful information that can be used to drive process decisions. INFICON also has a worldwide network of application experts that can work alongside their customers to implement a tailored solution to provide specific benefits to each customer's process. For many years these solutions have been successfully implemented for semiconductor applications, and its demonstrated benefits could also be transferred to pharma applications.

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