RESIDUAL GAS ANALYSIS

Process Monitoring in Pharmaceutical Lyophilization

Freeze-drying is a manufacturing process that uses vacuum sublimation to stabilize food and pharmaceutical products prior to long-term storage. In many cases, the shelf life of freeze-dried materials is extended from hours or days to several months or years. Although highly effective, freeze-drying is slow and inefficient. Therefore, in the pharmaceutical domain, it is reserved for only the most sensitive materials. In these applications, high standards of stability, purity, and integrity of end-products are non-negotiable, making process development costly and time consuming. Residual gas analysis is a powerful tool that can be used to mitigate these pain points. Currently, many facilities rely on indirect measurement tools such as Pirani or capacitance manometers to monitor the freeze-drying process. While these gauges provide some insight into the overall pressure within the chamber, they often fall short in offering a comprehensive understanding of the gas composition or detecting trace contaminants. This lack of specificity can lead to undetected issues, potentially compromising product quality. The limitations of these traditional methods underscore the need for more advanced and direct analytical techniques to ensure optimal process control and product integrity. By continuously analyzing the composition of residual gases during freeze-drying, a residual gas analyzer (RGA) offers real-time insights into key process variables, including leak detection, endpoint determination, monitoring contaminants and leaks (O_2), sterilization/cleaning operations (H_2O_2), API/formulation decomposition and product meltback/collapse[1]. This in-depth understanding aids in quality control, process optimization, and regulatory compliance.

Experimental

The Transpector® CPM 3 compact process monitor is integrated with a research and development freeze-dryer (REVO® by Millrock Technologies Inc.) to monitor the gas composition inside of the process chamber during the freeze-drying process. An image of the setup is shown in Figure 1. Pressures during freeze-drying are typically on the order of 100 mTorr, several orders of magnitude above acceptable values for conventional RGAs. Transpector CPM 3 is ideally suited for this application due to a specially designed orifice dosing system with differential pumping that ensures proper flow rate compatibility. In addition, INFICON offers single pressure mass spectrometers, like Transpector SPS and Transpector APX, that are compatible with harsh chemistries.

Typical Process Pressure Range for Freeze Drying	Transpector CPM 3 Total Pressure Range
1e-2 Torr - 1 Torr	1e-8 Torr - 1.2 atm

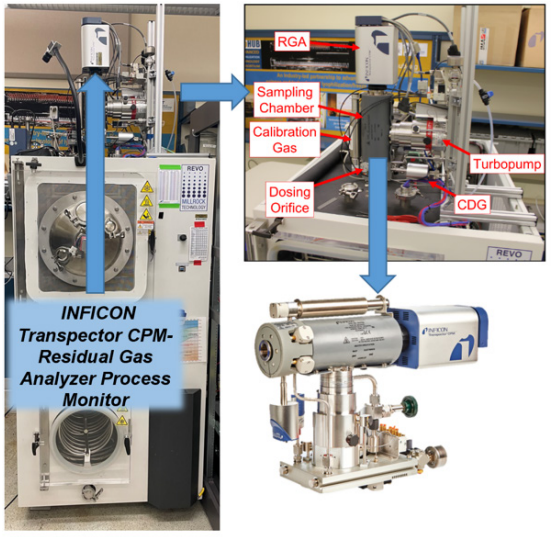

Figure 1: INFICON Transpector CPM 3 installed on Millrock REVO lyophilizer in the LyoHub Demonstration Facility at Purdue University.

Gas Composition Monitoring via Mass Spectrometry in Monoclonal Antibody Freeze-Drying

Monoclonal antibodies are proteins used to treat a variety of disorders, infections, and conditions. They are generally unstable in solution at room temperature and therefore administered as a freeze-dried dosage form. The measured gas composition during freeze-drying of a monoclonal antibody formulation is shown in Figure 2. During primary drying, water vapor (m/z=18) sublimes from the frozen product and fills the process chamber. In this case, the water accounts for roughly 90% of the total composition. The freeze-dryer injects nitrogen (m/z=28) ballast to regulate the absolute chamber pressure around a target setpoint of 100 mTorr. Near the beginning of the process where the sublimation rate is high, the nitrogen concentration is low. As the process continues, the sublimation rate decreases, and the freeze-dryer introduces more nitrogen to compensate for the load reduction. At the end of the cycle, all ice has been sublimed and the water vapor concentration decreases rapidly. According to Figure 2, argon (m/z=40) follows a similar trend to nitrogen. The nitrogen supply is derived from a liquid source that, due to their similar boiling points, also contains argon in trace quantities. The CO_2 (m/z=44) and O_2 (m/z=32) species trend with water vapor, suggesting they were dissolved in the water prior to freezing.

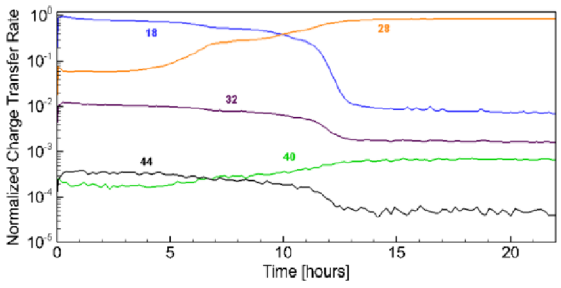

Figure 2: Residual gas analysis data for monoclonal antibody formulations[1]. Please see Table 1 for m/z ratios.

Mass Spectra of Species Commonly Found in Freeze-Drying

m/z Ratio	Relative Abundance	Compound
18	1	H_2O
17	0.212	
16	0.009	
28	1	N_2
14	0.138	
32	1	O_2
16	0.218	
40	1	Ar
20	0.146	
44	1	CO_2
28	0.098	
16	0.096	
12	0.087	
45	0.01	
17	1	NH_3
16	0.801	
15	0.075	
14	0.022	
18	0.004	

Table 1: Mass Spectra of Species Commonly Found in Freeze-Drying

Optimizing Freeze-Drying Cycles for Organic Co-Solvents: Insights from Transpector CPM 3

Organic co-solvents are sometimes required for compounding or stabilizing complex freeze-dried systems. In many cases, the organic component often has a high saturated vapor pressure and low freezing point, making them difficult to freeze-dry using conventional cycles. The ability to monitor the concentrations of the individual systems is therefore highly desirable. Transpector CPM 3 provides this capability, allowing highly optimized cycles to be quickly and easily developed. Figure 3 contains the process data for a complex formulation of D-Mannitol dissolved in a 2-Butanol (m/z=45) and water co-solvent system. In this case, the 2-butanol has a higher vapor pressure than water and is completely removed prior to water vapor.

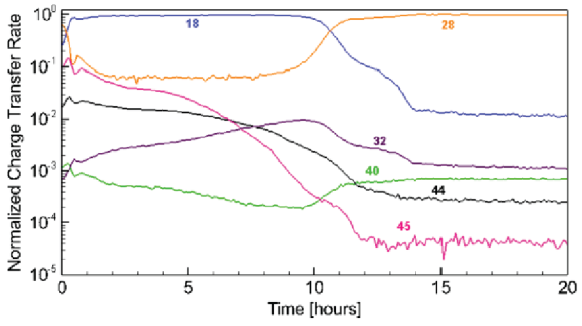

Figure 3: Residual gas analysis data for D-Mannitol in 2-Butanol and water[2].

Real-Time Contamination Detection in Pharmaceutical Lyophilization Using Residual Gas Analysis

In the field of pharmaceutical lyophilization, contamination detection is paramount for ensuring product quality and safety. Silicone-based oils are frequently used as heat transfer or cooling fluids during the freezing phase of the process. However, leaks of these coolants into the freeze-drying chamber pose a significant risk. Once a product is contaminated, it is irrecoverable and must be discarded, leading to significant financial loss and delays. RGAs offer an effective solution for this challenge by providing real-time detection capabilities. They can promptly identify the presence of coolants like silicon-based oils, thereby alerting operators to a contamination event as it occurs. See Figure 4 for an example of silicon oil spike detection. This allows for immediate intervention and helps to maintain the integrity of both the ongoing process and the end product.

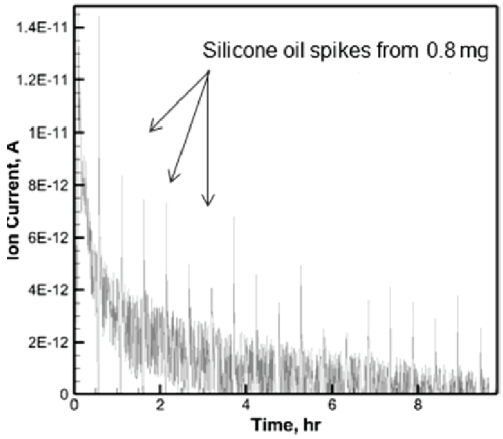

Figure 4: Silicon oil spikes[3].

Conclusion

The integration of the INFICON Transpector CPM 3 RGA into pharmaceutical freeze-drying offers numerous advantages for process development and optimization. By enabling precise detection and quantification of various volatile and non-volatile species, Transpector CPM 3 enhances process control, assures product quality, and confirms chamber integrity. The adaptability of this tool to complex formulations positions it as an indispensable asset in the modern pharmaceutical manufacturing landscape. Moreover, the non-intrusive nature of Transpector CPM 3 ensures that the process environment remains undisturbed, maintaining sterility—a paramount concern in pharmaceutical applications. Given these benefits, residual gas analysis stands as a cornerstone technology for advancing the state-of-the-art in pharmaceutical lyophilization.

For more information → inficon.com

[1]Connelly, J. P., & Welch, J. V. (1993). Monitor lyophilization with mass spectrometer gas analysis. PDA Journal of Pharmaceutical Science and Technology, 47(2), 70-75.

[2]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.

[3]Ganguly, A., Stewart, J., Rhoden, A., Volny, M., & Saad, N. (2018). Mass spectrometry in freeze-drying: Motivations for using a bespoke PAT for laboratory and production environment. European Journal of Pharmaceutics and Biopharmaceutics, 127, 298-308.

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