MASS SPECTROMETRY

Reducing Cycle Times and Improving Yield in Lyophilization with In Situ Mass Spectrometers

Lyophilization, or freeze-drying, is a critical process used to stabilize sensitive pharmaceutical products for long-term storage. Despite its effectiveness, the process is traditionally slow and inefficient, relying heavily on historical knowledge and trial-and-error methods. This approach can lead to suboptimal cycle times and yields, making process development costly and time-consuming. In situ mass spectrometers, such as INFICON Transpector® CPX, offer a modern solution by providing real-time monitoring of residual moisture in the vacuum chamber, enabling more precise control of the lyophilization process. By continuously analyzing the composition of residual gases, mass spectrometers can significantly enhance process control, quality assurance, and regulatory compliance.

Experimental Setup of the Mass Spec

An experiment was performed to monitor the gas composition inside the process chamber during the lyophilization process using Transpector CPM 3, the precursor to Transpector CPX. The setup involved integrating the Transpector CPM 3 compact process monitor with a production freeze-dryer. An image of the setup is shown in Figure 1. Pressures during lyophilization can typically range from atmosphere to low mTorr values, which is several orders of magnitude above acceptable values for conventional mass spectrometers. Transpector CPM 3 is ideally suited for this application due to its specially designed orifice dosing system with differential pumping that ensures proper flow rate compatibility. Since the experiment concluded, INFICON introduced the next-generation Transpector CPX, which combines the features of the old model while improving detection capabilities and reducing the products footprint. This design allows the mass spectrometer to operate at all stages of the freeze-drying process for optimal performance.

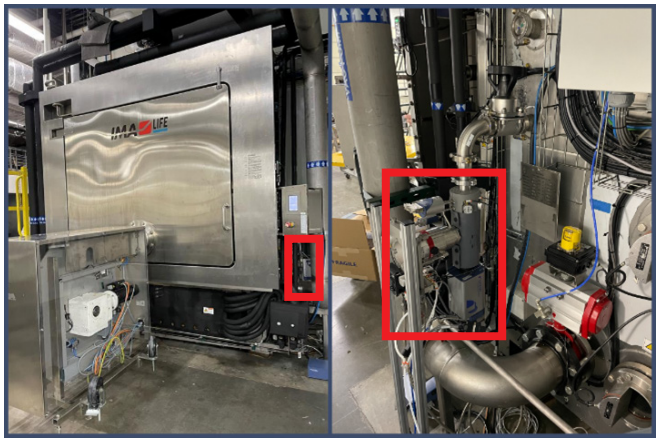

Figure 1. Transpector CPM 3 installation

Monitoring Lyophilization Steps

Freezing Step

The freezing step is the fastest and simplest part of the lyophilization process. The critical factor is ensuring that all moisture in the vacuum chamber and samples is completely frozen. Traditionally, the duration of this step is determined through trial and error. By using a mass spectrometer, the residual moisture in the air can be monitored, and the endpoint can be determined once the moisture signal stabilizes or passes a predetermined threshold. With the advanced analytic capabilities of the INFICON FabGuard® software suite, the water signal can be modified to show stability instead of the traditional drop in partial pressure due to the natural cryogenics in the chamber. Figure 2 details how the modified water signal could be used to predict when freezing is complete. This prediction is critical to optimizing cycle time and increasing product throughput.

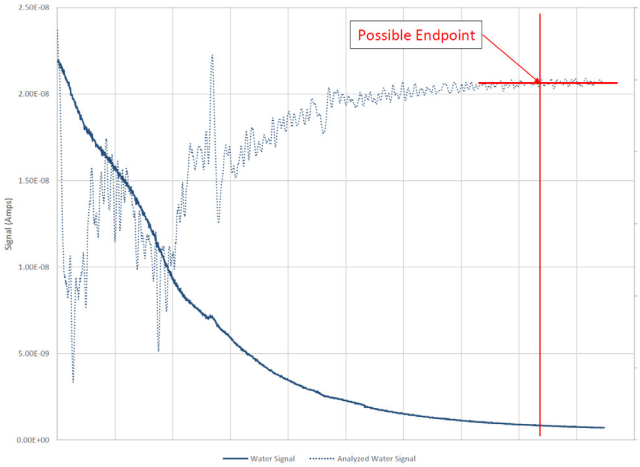

Figure 2. Lyophilization freezing step endpoint detection

Primary Drying Step

Once freezing is complete, the vacuum chamber will evacuate to a deep vacuum to prepare for sublimation. Once a deep vacuum is achieved, nitrogen is added to the vacuum chamber to achieve the vacuum level required for primary drying. A critical step of primary drying is to slowly increase the temperature in the vacuum chamber to achieve controlled sublimation of water. If the temperature is raised too quickly, the frozen water trapped inside the sample cake will rapidly sublimate, expelling the cake out of its container and all over the vacuum system. A mass spectrometer can monitor moisture levels, determining when moisture vaporizes and stabilizes, thus optimizing the temperature increments. Water vapor sublimes from the frozen product and fills the process chamber, accounting for the vast majority of the composition. The freeze-dryer injects nitrogen ballast to regulate the absolute chamber pressure around a target setpoint to be the operating pressure for primary drying. As the temperature continues to increase, the sublimation rate increases and less nitrogen is required to maintain the same vacuum level. Monitoring the partial pressure of nitrogen gives insight into the effectiveness of the temperature change and helps optimize when secondary drying can begin. Figure 3 identifies the temperature changes in primary drying and the resulting sublimation at that point.

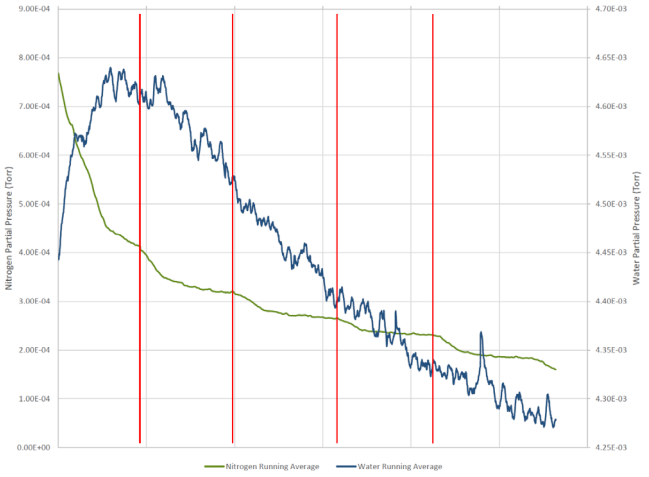

Figure 3. Primary drying with identified changes in temperature

Secondary Drying Step

The start of secondary drying involves pulling a deeper vacuum to ensure sublimation will occur throughout the vacuum chamber. This step accelerates the vaporization and removal of water throughout the vacuum system. The traditional method of determining if all water vapor has been removed from the vacuum system is by monitoring the rate of nitrogen supplied to the vacuum system. As the water vapor level decreases, the nitrogen flow rate will increase until all other gases stabilize. Once they stabilize, the nitrogen flow rate will stabilize as well. The issue with just monitoring the nitrogen flow rate is that it isn't possible to determine the actual states of all compounds in the vacuum system. An in situ mass spectrometer can monitor the entire step, determining when all moisture has been evacuated, potentially reducing process time and adding a quality measurement to ensure complete moisture removal. Figure 4 shows the entire secondary drying process and illustrates how there can be random water sublimation after the nitrogen slow rate has stabilized. Without a mass spectrometer, this would not have been possible and a potential quality risk may not have been found.

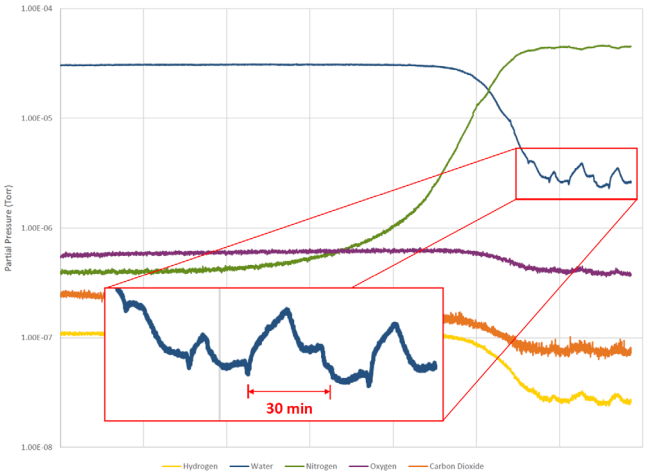

Figure 4. Water sublimation after nitrogen flow rate stabilized

Real-Time Contamination Detection

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. Compact, in situ mass spectrometers like Transpector CPX 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. This allows for immediate intervention and helps to maintain the integrity of both ongoing processes and the end product.

Conclusion

The integration of the INFICON Transpector CPX mass spectrometer into pharmaceutical lyophilization offers numerous advantages for process development and optimization by enabling precise detection and quantification of various volatile and non-volatile molecules in real time.

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