Application Note

Silicone Oil Leakage - Detection in Freeze Dryer Systems

THE PROBLEM
Lyophilization, or freeze drying as it is more commonly known, is an important process used in the stabilization of delicate pharmaceutical products. This process requires that equipment be subjected to wide swings in both temperature and pressure. Over time these variations can lead to wear in the equipment that allows the leakage of heat transfer oils into the process chamber and subsequent contamination of the product undergoing lyophilization. Detection of these fluids is therefore a critical aspect of contamination control in the process.

BACKGROUND
Pharmaceuticals, in general, are relatively delicate chemicals that are at risk of decomposition under harsh processing and storage conditions. Furthermore, the thermal and chemical lability of many pharmaceuticals makes their stabilization for long term storage problematic.

For the above reasons, freeze drying (lyophilization) of pharmaceuticals has been widely adopted as a preferred stabilization process in pharmaceutical manufacturing. Lyophilization is, by far, the gentlest route for the conversion of the liquid formulations that are the typical end product of chemical manufacturing processes to stable and storable solid form. When properly freeze dried, pharmaceuticals can be stored at ambient temperature for up to two years without refrigeration. When needed, they can be completely reconstituted with water for injection within seconds. As the use of large, thermally labile molecular species increases in the pharmaceutical industry, it is expected that the use of freeze drying will increase significantly.

In freeze drying, the solvent in a solution (usually water) is removed from the product by sublimation. Sublimation is the phase transition by which a material goes direct from the solid phase to the gas phase without passing through an intermediate liquid state. The degree to which this direct phase transfer will occur is a function of the pressure and temperature of the solid. The phenomenon of sublimation is best illustrated by the phase diagram of a material, in our case water, shown in Figure 1. The phase diagram delineates the preferred physical state of water under differing conditions of temperature and pressure. Points at which a substance undergoes transition between the different phases are defined by the lines where one phase becomes another at the selected temperature and pressure. From the diagram it is seen that the sublimation of water occurs only below its triple point, at pressures of less than 6.13 mbar and temperatures below 0.0098 °C.

Obviously, the purity of any chemical compound being introduced into the human body is of paramount importance. One class of pharmaceutical, parenterals requires especially stringent purity specifications. Parenterals are introduced into the body non-orally, by means of injection, implantation, etc. Administration of these compounds thus by-passes the body’s normal defences against toxic materials and parenterals must be sterile, non-pyrogenic, free from insoluble contaminants and stable over reasonable storage periods. These stringent purity requirements for pharmaceuticals in general and parenterals in particular mean that the processes and equipment employed in their manufacture cannot expose the substrates to even minute levels of contaminants.

While lyophilization is relatively benign in terms of the impact of the process conditions substrate degradation, the process employs large swings in temperature and pressure that can be quite hard on the equipment. Temperatures can vary between -60 and 121 °C while the pressures range between 0.01 mbar and 2.45 bar. These temperature and pressure swings significantly stress the cooling system components in lyophilization equipment. The bending and stretching that these changes induce in the various pipes, etc. in piping of the cooling system produce stress and ultimately, micro cracks in the pipes that can allow cooling fluids to escape into the process chamber, contaminating the substrates.
Silicone oil is the dominant cooling/heating fluid used in freeze drying equipment. This oil circulates through the shelves in the freeze dryer and to an external exchanger that adjusts the temperature of the oil for heating/cooling purposes. These shelves move up and down during load/unload cycles, stoppering and CIP/SIP and this places mechanical stress on the tubes supplying the silicone oil to the shelves. As a freeze drying unit ages, the cycling of temperature and pressure and physical motion of the shelves can lead to the formation of small cracks through which the silicone oil can escape and contaminate the substrate being treated. Since these cracks are quite small, at least initially, their existence does not lead to any immediate malfunction in the unit and a number of batches of substrate can be contaminated before the leakage is detected. This note addresses contamination risks associated with the freeze drying process and the most effective means of minimizing the risk of lost product when these leaks occur.

**THE SOLUTION**

Product losses due to coolant contamination in freeze dryers are best minimized by employing an in situ detector for the presence of coolant vapors within the unit. Figure 2 compares the consequences of silicone oil contamination with and without some form of inline detection of the contaminant. Without such detection, traces of oil are eventually found through quality control checks after an unknown number of batches may have been contaminated. This uncertainty forces the rejection of all suspect batches. Conversely, if an oil leak is detected upon occurrence by an inline detector, only the batch in process is lost.

Mass spectrometry (MS) is a powerful detection tool for contaminants that should be applicable in environments such as freeze dryers. Quadrupole mass spectrometers (QMS) are widely used in a number of industries for inline contaminant detection and process control purposes.

Certain requirements must be met by any QMS unit used in pharmaceutical manufacturing applications. The detector must be capable of untended, automated operation over prolonged periods of time with minimal maintenance. In operation, it should have sufficient versatility to reliably monitor the freeze drying chamber, not only for contaminant silicone oil signatures, but also for process states such as drying end-point detection. The QMS system should be easily integrated into the manufacturing site’s product management system (PMS) without the need for validation of software/setup revisions. Obviously, for the application under consideration in this note, the QMS system should have sufficient flexibility to fulfill any unique requirements present in pharmaceutical production equipment for freeze drying/sterilization procedures.

Figure 3 shows a mass spectrometer system ideally suited to this application, the MKS Vision 2000P high performance quadrupole mass spectrometer. The Vision 2000P QMS has a mass range of either 1-100 or 1-200 atomic mass units.
(AMU) and a detection limit of 0.5 ppm for silicone oils. The Vision 2000 is can be implemented in SCADA/PMS solutions using the MV2 ASCII protocols. (The unit has customized hardware interfaces (GEMÜ valve adaptors) that allow sterilization of the system with no risk for backstreaming of any contamination. The Vision 2000P has a heated inlet that minimizes background levels and enables reliable end-point detection. Sensors within the unit provide for fail safe operation that protects the equipment and QMS. The unit can be automatically calibrated.

An evaluation of the Vision 2000P QMS in this application has been performed in simulation tests that were conducted at GEA Lyophil in Hürth, Germany. The Vision 2000P was integrated into a dedicated tool for leak detection and process control within freeze drying units, the GEA LYOPLUS™ System (Figure 4 shows the LYOPLUS unit; a system schematic of the LYOPLUS showing the integration of the Vision 2000P is presented in Figure 5).

This test showed that, when analyzed by the QMS, KT5 oil exhibited its largest characteristic peak in the mass spectrum at an m/e (mass/charge) value (this measure is sometimes referred to as the atomic mass unit, AMU) of 73. As well, the electron impact ionization employed in the Vision 2000P produced additional ion fragments from the KT5 oil exhibiting strong peaks at m/e values of 71 and 75. Figure 6 shows the QMS response in tests for the detection of KT5 in a freeze dryer with 40 m² of shelf area. The Vision 2000P exhibits rapid response to contamination by silicone oil with full scale response seen within 20 seconds of introduction of the contaminant.

Table 1 - Detection limit as a function of dryer size

Table 1 shows the results of similar tests that were conducted on actual production freeze dryer units. These freeze dryers were in-service units installed either at GEA Lyophil or at other manufacturing units at European production sites of multinational pharmaceutical companies. The shelf area in the chambers varied between 0.1 and 44 m² while the dryer chamber volume varied between 0.08 and 12.2 m³. KT5 detection limits in these tests correlated inversely with dryer volume, maintaining a constant ratio of 0.2 mg/m³ between the detection limit and the chamber volume.

The Vision 2000P can also be used for end-point detection in the freeze drying process. Figure 7 shows the results of a test to determine the characteristics of the QMS moisture signal in the freeze drying process. The QMS trace for moisture shows that the bulk of the drying process is complete by about the half-way point in the procedure, under conditions of moderate pressure and temperature. Additional increases in temperature and reductions in pressure produce further drying albeit at a reduced rate. It is easily seen from this diagram how the user can employ Vision 2000P data for enhanced process design and control.
CONCLUSION

The rapid and reliable detection of silicone oil leakage in a freeze drying apparatus is critically important for the prevention of product loss in pharmaceutical manufacturing. We have shown that the MKS Vision 2000P High Performance Quadrupole Mass Spectrometer is an excellent tool for this application, detecting these oils during the primary and secondary phase and after the drying process. The Vision 2000P is able to detect all of the various silicone-based oils that are commonly used in freeze drying operations and maintenance. The response of the Vision 2000P to the presence of silicone oil vapors is both rapid and reliable. The system is effective over a wide variety of common industrial freeze dryer configurations with a specific detection limit for Bayer KT5 silicone oil of 0.2 mg/m³ of dryer chamber volume. This specific detection limit was shown to be constant over dryer chamber volumes ranging between 0.08 and 12.2 m³.

The Vision 2000P is an effective tool for pre-process chamber qualification and chamber leak testing. It is also a sensitive drying process monitor. Water concentrations can be monitored for optimizing the process and verification of the endpoint.

REFERENCE MATERIAL

MKS Publication:
Vision 2000P datasheet

Figure 6 - Vision 2000P QMS detection and response time characteristics for Bayer KT5 silicone oil contamination in a freeze dryer with 40 m² of shelf area. The graph shows the response of the characteristic peaks at m/e = 71, 73 and 75.

Figure 7 - Endpoint monitoring by using the Vision 2000P to measure chamber moisture

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