



Aston
LyoSentinel™
Molecular
Sensor

Robustness
Reliability
Repeatability
Accuracy
Sensitivity
Cloud Ready

Application Note

Optimizing Lyophilization Using Miniature MS Lyophilization

Updated January 2022

Background

Lyophilization or freeze-drying is the process by which a solvent, typically water, is removed from a frozen solution by sublimation resulting in a porous structure (cake like) that can be easily re-hydrated. The low temperature of such a process makes it ideal for materials such as pharmaceuticals. The process is however costly due to, the low drying rate, the use of vacuum, and associated operating expenses.

The bulk of water vapor is removed during primary drying (bulk sublimation) and secondary drying (surface desorption) cycles at controlled temperatures to avoid irreversible product damages. Due to the thermal cycles and mechanical stress the trays and tubing of the freeze-dryer (FD) are subjected to, leaks can develop causing contamination of the vials (product). Furthermore, trace amounts of silicone oil used as a refrigerant can find its way into the product chamber hence compromising the sterility of the product. Another variation of silicone oil is also present in the rubber caps used to seal the vials.

Real time in-situ monitoring of the drying efficacy during primary and secondary drying cycles and tool diagnostics are therefore critical to:

1. Guaranteeing “safe” products as batches of thousands of vials are processed in a single run (Figure 1)
2. Maximizing the return on investment (ROI) of FD’s.

Mass spectrometry is a non-invasive multi-channel technique capable of performing measurements associated with all the tasks described above including:

1. Perform system leak checks.
2. Monitor water vapor for accurate endpoint detection at the end of primary and secondary drying cycles
3. Detect and monitor the evolution of known as well as previously unknown contaminants.
4. Detect and identify traces of silicone oil used as a heat transfer fluid in FDs.

Freeze-drying process control recipes are then concocted to:

1. Ensure good product quality.
2. Minimize and improve the reliability of the drying cycles.
3. Increase tool availability for FD duties.
4. Reduce product scrap by aborting FD cycles at the onset of air leaks and/or contaminants such as silicone oil.



Figure 1

Aston LyoSentinel Process Monitoring Features & Benefits

- Designed for lyophilization process monitoring
- Unique miniature high pressure mass spectrometer design
- Detect & Protect: Silicone oil detection and system protection
- Designed for standalone or integration operation.
- On board use cases –
 - Primary and secondary drying endpoint
 - Fast silicone oil detection
 - Baseline chamber health – leak and contaminates checking
 - Process transfer
 - User customizable
- Modular smart cradle docking system
- Edge device/ cloud-ready integration for Lyo system machine learning
- Field serviceable
- Endorsed by major pharma PAT professionals.
- 21CFR part 11 full compliance
- Real-time process monitoring

Aston LyoSentinel

Having gone through rigorous testing on laboratory and production FD tools, Atonarp's Aston LyoSentinel possesses unparalleled advantages in such applications. The device consists of a generic core unit outfitted with a front-end interface tailored for lyophilization. The AMS core platform is a miniature compact Mass Spec system featuring sensor and associated electronics, a pressure transducer, vacuum manifold, and vacuum pumps. A standalone sampling module is attached to the core platform upon installation. The module includes a dual sample path manifold outfitted with heater jackets, heater supplies and controller, and an optional sample pump.

The primary path features a patent pending membrane-based filter intended for monitoring the drying process and endpoint detection. The sample is drawn through a tubular membrane favoring water vapor and discriminating against silicone oils based on their permeation rates. The secondary path is intended for direct sample injection, through a computer controlled proportional valve, to detect traces of contaminants including silicone oils. Switching between paths is performed automatically under a preset duty cycle. Sub-second data update rates enable the user to optimize the duty cycle and hence protect the Mass Spec chamber from silicone oil build-up and other contaminants, e.g. oxygen prior to stoppering.

The proportional valve, operated in open loop control, is utilized to maintain a constant pressure in the Mass Spec chamber as measured by the pressure transducer. The Mass Spec system can operate continuously upon switching between the primary and secondary paths. The Mass Spec can be configured to scan different masses of interest under different ionization energy, sensitivity, resolution, and scan speed settings for each path. sensor and chamber walls that may occur during film.

The enabling Mass Spec sensor technology is a miniature array of quadrupole mass filters operating in parallel for high sensitivity. The sensor's small size (< 5 cc) and ability to operate at high pressures (mTorr) enable the use of a small vacuum chamber evacuated by small low-capacity vacuum pumps (Figure 3). Driven at 11 MHz, the sensor covers a 100 amu mass range and has low to sub-ppm sensitivity for dwell times ranging from 2 to 200 ms. Other advantages over conventional Mass Spec systems included:

1. The ability to probe strategic locations on the FD tool.
2. Generating quantitative measurements in the form of pressure and fractional concentrations.
3. Generating real time self-diagnostics for reliable maintenance-free operation.

FD Tool Qualification

Vacuum integrity is key for sterility and process performance. The high-pressure capability of the quadrupole array enables the AMS to monitor the vacuum pump-down for early detection of leaks

and/or contaminants. Real time assessment of the shape of pump-

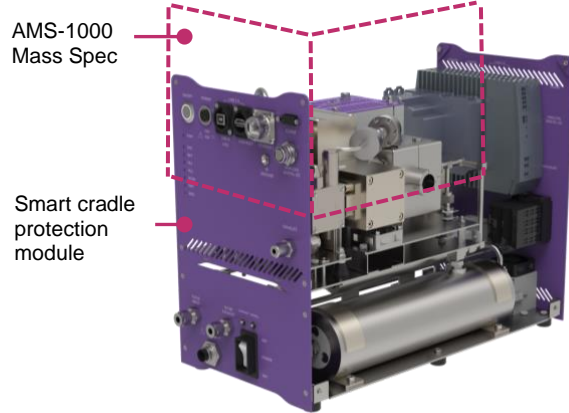


Figure 2 - Aston LyoSentinel



Figure 3 – Mass Spec sensor enclosed in a 1.33" CF manifold attached to a turbo pump

down curves indicates whether the tool will successfully reach its ultimate vacuum. In the case of leaks, these can be located using a Helium gas probe and activating the Helium Leak Mode. He leak detection is performed via the secondary path for high speed and sensitivity. As an integral component of the FD tool, the AMS is relied on for qualifying the FD tool for process.

FD Process Monitoring & Control

Monitoring the drying cycles is critical to carrying out the process at controlled temperatures and minimizing the time required by these steps. The extended dynamic range (up to six decades) of the Aston LyoSentinel enables accurate and reliable detection of the endpoint of the primary drying cycle, beyond which secondary drying starts. Figure 4 shows typical water vapor and nitrogen trends in select ion monitoring mode (SIM) during primary and secondary drying. For reliable endpoint detection, the ionization energy is lowered to 43 eV, hence eliminating interferences with moisture measurements at m/z 18 from doubly charged argon isotopes at m/z 36.

A major advantage of Mass Spec over other sensors, such as Pirani gauges, is the ability to measure much lower water vapor concentrations needed to monitor the endpoint of the secondary drying phase. Figure 5 shows the inability of the Pirani gauge to follow the drying process, including during a significant portion of the primary cycle below 50 °C/mTorr.

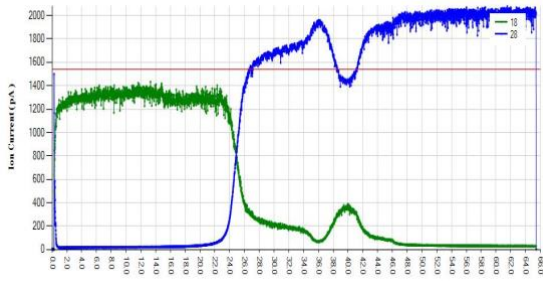


Figure 4 - Primary and secondary drying cycles as added N₂ replaces H₂O to control the ambient pressure & hence the ice temperature

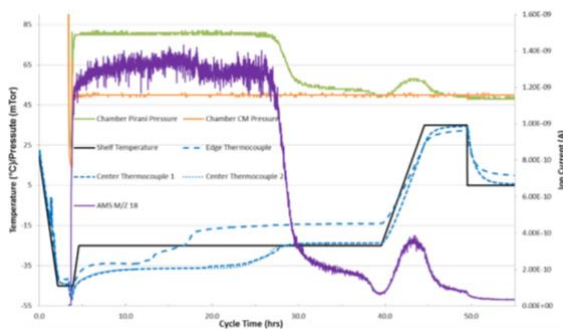


Figure 5 – Freeze drying of 5% w/v sucrose placebo
The performance of the AMS in quantifying the moisture concentrations, detecting the endpoint of the secondary drying phase, and determining the shape and timing of other observed features were verified to be in good agreement with the Karl Fisher titration gold standard and NIR spectroscopy.

Fault Detection Control

Silicone oil (polydimethylsiloxane) is used as a heat transfer fluid for temperature control of shelves inside the FD. Such a compound gets volatilized at freeze drying conditions (low pressure, moderate temperature). It is imperative to detect traces (ppm levels) of oil vapors in the chamber early during the process to avoid irreversible contamination and the waste of entire product batches.

The novel method introduced with the Aston LyoSentinel is to monitor the signature peaks for silicone oils at a lower frequency compared to that of the drying process via the filter. Figure 6 shows a monitoring trend deposited in a petri dish was placed inside an empty FD tool. The data is collected while switching between sampling paths with an arbitrary 10:1 duty cycle. The spikes correspond to oil signals through the secondary unfiltered path. Other signature peaks associated with oil from the rubber caps of the vials can also be monitored. of the silicone oil signature peak at m/z 73. For validation purposes, 0.8 mg of oil.

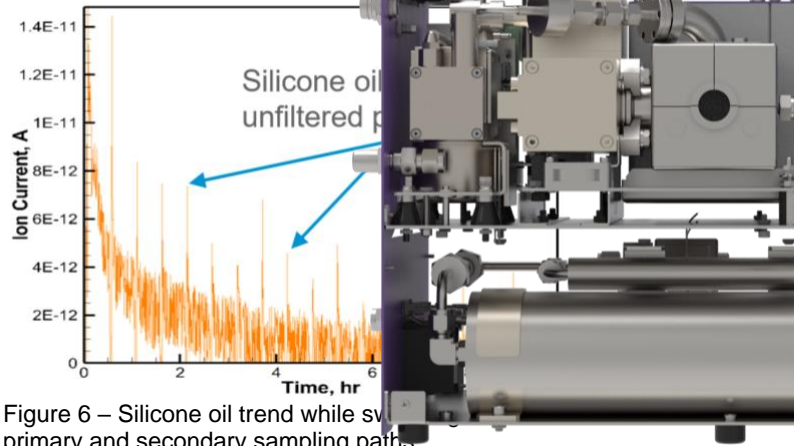


Figure 6 – Silicone oil trend while switching between primary and secondary sampling paths.

The Dual sampling path of the Aston LyoSentinel offers several advantages including:

1. Using the filtered primary path at a high sampling frequency to closely monitor the drying process.
2. Using the filtered path to protect the MS chamber and sensor from the accumulation of oil vapors over time and hence extend the lifetime and reliability of the device.
3. Using the secondary path at a lower sampling frequency to detect contamination.
4. Using the secondary path to enable high sensitivity (sub-ppm) for the detection of oil and other contaminants as longer dwell times can be used to monitor a limited number of signature peaks.
5. Deriving quantitative measurements of the size of the leaks as threshold indicators to FD tool user.

Modular AMS-1000 system with integrated roughing and turbo molecular pumps

Front panel control status and connection interface

Filter temperature control

Silicone oil filter module. Protects against saturation oil contamination whilst allowing trace amount detection.

Atonarp is advancing medical diagnostics, life sciences research, and industrial process control through next-generation digital molecular profiling. In-situ molecular profiling in advanced manufacturing means higher throughput, improved efficiency, and reduced waste. Real-time, quantitative diagnostic tests can improve outcomes and patient satisfaction at lower cost.

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Integrated Analog and Digital I/O Process control module

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