LIGHTHOUSE

The Science of Pharmaceutical Manufacturing

Application Note **101**

Stopper “Pop-Up” and the Effects on Container Closure of Sterile Vials

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Introduction

Container closure integrity plays an important role in maintaining the stability and sterility of lyophilized products. The increased number of biological products coming to market and the need to extend product shelf life has driven the growth of lyophilization capacity worldwide. Lyophilization is a complex process that presents many manufacturing challenges one of which is maintaining and monitoring container closure integrity. Recent attention to package integrity issues can be seen in both the revised aseptic processing guidance from the regulatory agencies (for example, Annex 1 revisions to the European Guidelines for the Manufacture of Sterile Products) and an increasing number of package integrity related product recalls. Concerns over the number of customer complaints and the cost of investigations and recalls has motivated investment in container closure inspection systems by the industry as a means of building quality into manufacturing operations.

Prior to sealing finished vials at the end of secondary drying, a lyophilization chamber is backfilled to a gas pressure that is specified for the vial headspace. The specified headspace pressure varies from product to product. Typically, freeze dried products are stoppered at either full vacuum (0 mbar absolute pressure) or partial vacuum (typically 750 mbar absolute pressure). The vacuum level serves the practical purpose of helping to seat the stopper and to facilitate reconstitution. Once equilibrium is achieved, the gas pressure in the vial headspace matches the chamber pressure and the shelves are lowered to seat the stoppers into the vial. At this point the vial closure integrity is established but not considered complete until the aluminum overseal is applied. Once the shelves are raised, the seal integrity must be maintained for a period of time ranging from minutes to hours to possibly days before unloading and capping occur. It is possible during this time for stoppers to "pop-up" allowing gas ingress into the vial headspace. Stoppers can pop up due to a number of reasons including im-

proper seating during shelf lowering, out of specification stopper and/or vial flange dimensions, and stopper coatings.

If seal integrity is lost during this time period then the physical properties of the headspace (gas pressure and/or composition) will change as gas from the ambient environment outside the vial ingresses into the vial headspace. Two common situations serve to illustrate the point. If the vial is exposed to a nitrogen atmosphere, for example prior to unloading from the freeze dryer, then nitrogen gas will enter the headspace causing the pressure to rise. If the vial is exposed to an air atmosphere, either because the chamber was vented with sterile air or because the vial was exposed to room air prior to capping, then air will ingress into the vial causing both the pressure and the oxygen concentration to rise. The practical implications of lost seal integrity are threefold. First, the headspace pressure rises which may impact the ability to reconstitute the product and would likely result in a customer complaint. Second, if the product is oxygen sensitive then air ingress will result in oxygen exposure and potentially impact the product stability. Third, if container closure integrity is breached then sterility can no longer be assured.

In-process monitoring systems, based on laser absorption spectroscopy, now exist that can nondestructively monitor each vial for changes in the headspace gas composition and pressure. These systems are in routine use in the industry for inspecting container closure integrity in freeze dried product and, in particular, for addressing the stopper pop-up issue.

Measurement method

Laser absorption spectroscopy is a nondestructive method for monitoring pressure, oxygen

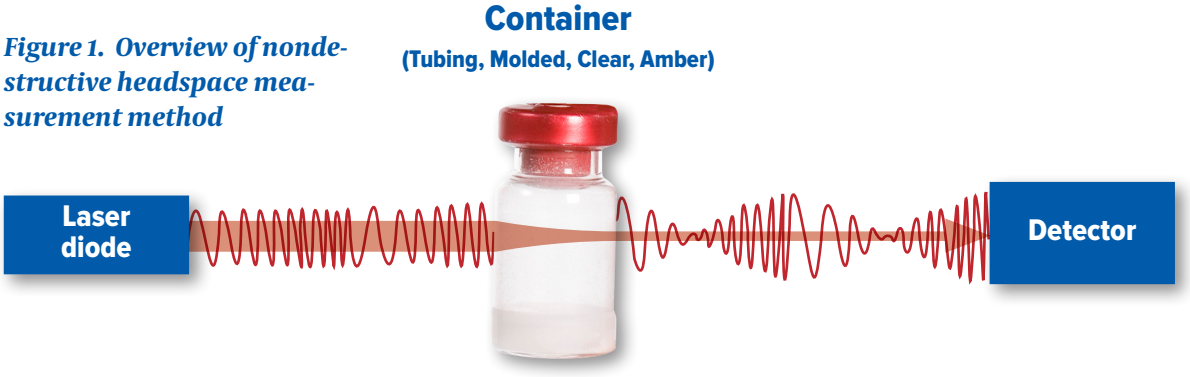

Figure 1. Overview of nondestructive headspace measurement method

and moisture in the headspace of parenteral containers. The method was first introduced to the pharmaceutical industry in the late 1990's and has been adopted and validated by companies around the world for both sterile development and manufacturing applications.

Container closure integrity in particular can be monitored nondestructively by headspace gas analysis. Changes in the gas pressure or gas composition are leak indicators. For vials stoppered under vacuum, a leak causes a rise in headspace pressure towards atmospheric levels. For vials stoppered at or near atmospheric pressure and exposed to air, a leak causes oxygen ingress into the vial headspace. The leak rates that result in pressure rise or oxygen ingress are dependent on vial volume and pressure differential. In general the headspace pressure and oxygen concentration of small volume parenterals (e.g. 3-10mL) packaged under vacuum rise more quickly than the headspace pressure and oxygen concentration of large volume parenterals packaged near atmosphere. Detectable changes in the headspace condition of a grossly leaking vial occur within minutes. A micro-leak (< 1 micron) will exhibit detectable changes in the headspace after a few hours to a few days depending on the initial headspace conditions. Both headspace pressure rise and oxygen ingress can be nondestructively monitored by laser absorption spectroscopy.

Systems for nondestructive headspace analysis using laser absorption spectroscopy are configured as shown in Figure 1. Laser light passes through the headspace of a vial and the laser wavelength is tuned to match the absorption wavelength of oxygen at 760 nanometers or moisture at 1400 nanometers. Oxygen con-

Figure 2. Headspace inspection systems incorporating the laser measurement technology

centration is proportional to the amplitude of the laser absorption signal and total gas pressure is proportional to the width of the laser absorption signal. Systems are calibrated using NIST traceable standards with known pressure and oxygen concentration.

In the case studies described below non-destructive headspace gas analysis systems from LIGHTHOUSE were used to monitor container closure integrity for commercial batches of lyophilized product. Systems, shown in Figure 2, can be configured for manual operation or in-line automated operation. Manually loaded systems are useful for conducting investigations or in-process monitoring of small (<5000) batches of containers. Automated systems are configured for 100% inspection applications when batch sizes are large.

Case study 1

The first case study involves an investigation of container closure integrity for an oxygen sensitive lyophilized product stoppered with a nitrogen headspace near atmospheric pressure (800 mbar). A number of vials from a commercial batch showed elevated levels of oxygen during routine QC analysis using a destructive oxygen analysis method. A decision was made

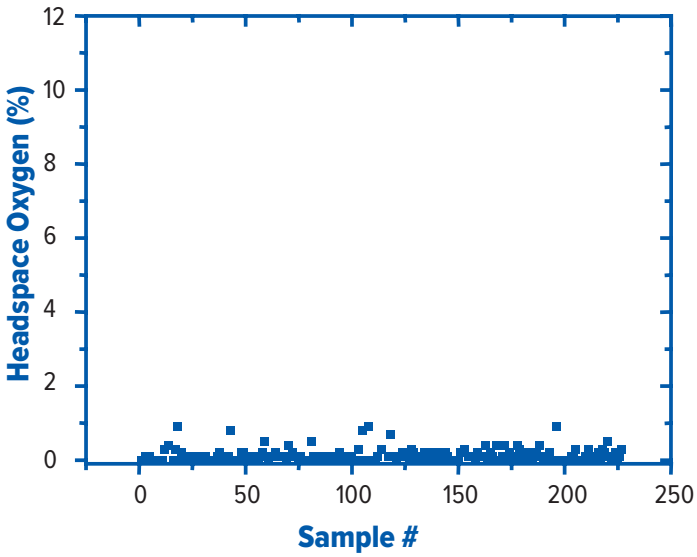

Figure 3. Headspace oxygen content of vials located in zones 4-6. Vials from this location in the freeze dryer showed no evidence of stopper pop up.

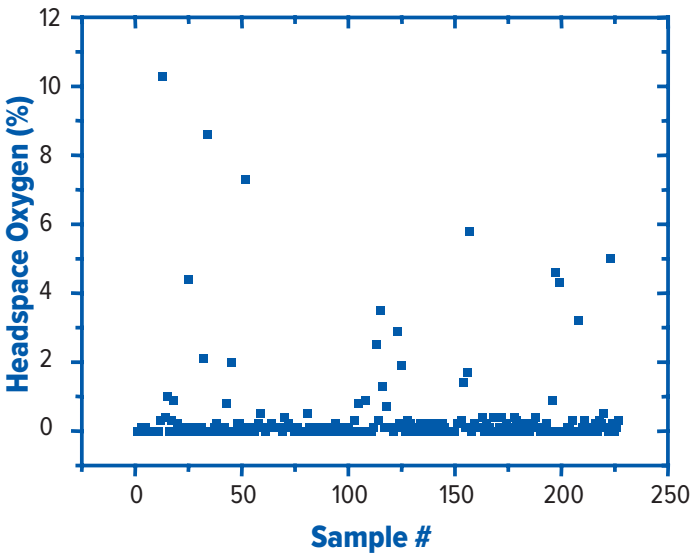

Figure 4. Headspace oxygen content of vials located in zones 1-3. Vials in these locations show air ingress due to stopper pop-up.

to test the entire batch using nondestructive headspace oxygen analysis.

A LIGHTHOUSE FMS-Oxygen Headspace Analyzer was used to test the entire batch for the presence of oxygen in the vial headspace. Vials with greater than 1% oxygen were to be rejected.

Figure 3 shows the headspace oxygen concentration in vials of freeze dried product that have maintained seal integrity. The headspace oxygen levels are all below 1%. Figure 4 shows a very different situation for a set of vials from the same batch of product. One difference between the two sample sets was their physical location inside the lyophilizer. In Figure 4 over 10% of the vials have lost seal integrity as evidenced by headspace oxygen levels ranging from 1.5% to 10%. It is believed that the root cause of the container closure integrity failures was due to stoppers not properly seated when the lyophilization chamber shelves were lowered. This allowed air to ingress at different rates resulting in oxygen concentrations over a broad range. The dependence of bad seal integrity on position in the freeze dryer allowed the manufacturer to troubleshoot mechanical stoppering issues at specific locations.

Case study 2

The second case study demonstrates a process development effort aimed at evaluating the container closure integrity of two different vial stopper combinations under actual in-process conditions. The same vial was evaluated with a grey butyl and a teflon coated stopper. The lyophilized product was specified to be stoppered at 414 torr (550 mbar) of nitrogen. The study evaluated each vial stopper combination for its ability to hold vacuum. The study used 1000 product filled vials (500 with each type of closure) distributed over 8 shelves (4 shelves with each type of closure).

Figure 5 shows the headspace pressure in vials of freeze dried product stoppered with a grey butyl elastomeric closure at 414 torr (550 mbar). All of

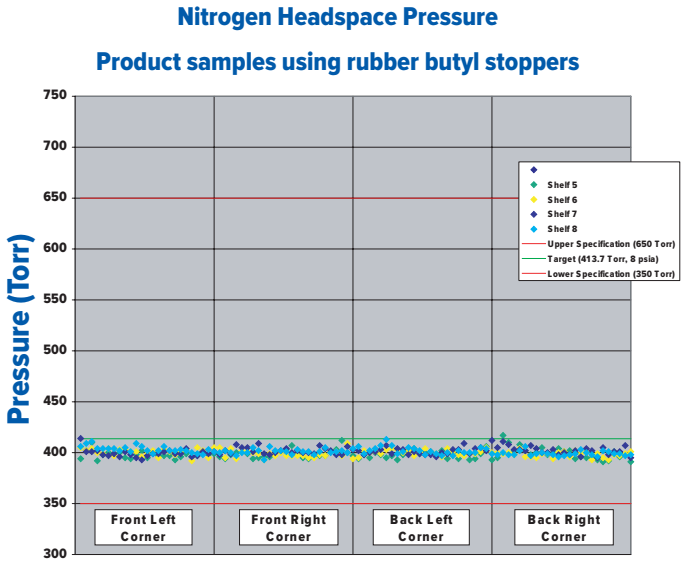

Figure 5, Headspace pressure in vials sealed with a grey butyl stopper. There is no evidence of stopper pop up on any shelf or in any location on a given shelf.

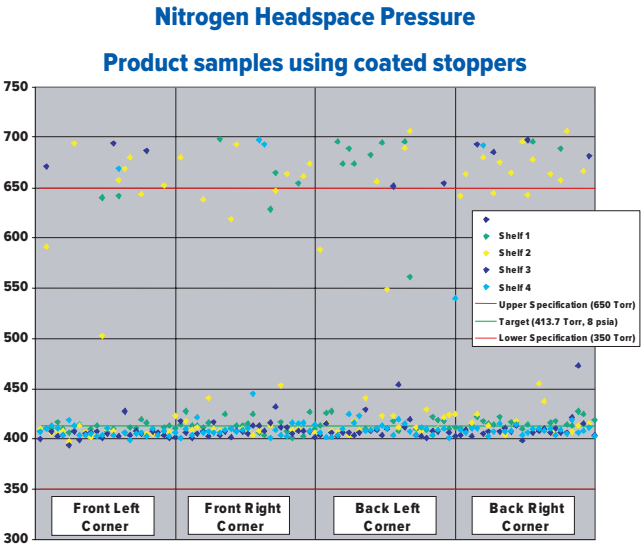

Figure 6, Headspace pressure in vials sealed with a teflon coated stopper. There is widespread evidence of stopper pop up on all shelves and in all locations on any given shelf.

these vials have maintained seal integrity. The headspace pressure levels are uniform and match the pressure set in the lyophilzation chamber prior to lowering the shelves. Figure 6 shows the headspace pressure in vials from the same batch that were stoppered using a teflon coated elastomer closure. Over 15% of these vials did not maintain seal integrity after removal from the lyophilization chamber. The gas ingress into these vials resulted in headspace pressures from 30 to 300 torr (40 to 400 mbar) above the target level.

The fact that bad seal integrity was not dependent on location in the freeze dryer pointed to an issue with the coated stopper closure system and/or an overall process issue. Further container closure studies using nondestructive headspace analysis allowed the manufacturer to optimize the stoppering process. Closure failures with the coated stopper were lowered from > 15% of the batch to < 1% with the optimized process. A headspace inspection machine was implemented for 100% final product inspection guaranteeing the detection and rejection of any residual vials that had lost container closure integrity.

Conclusion

Stopper pop-up resulting in loss of container closure integrity is not uncommon and impacts the stability, sterility and reconstitution of lyophilized product. Non-destructive headspace analysis is a powerful method for monitoring container closure integrity in finished vials of freeze dried product and for building quality into the manufacturing operation. Monitoring absolute pressure changes and/or oxygen ingress in the vial headspace serve as leak indicators. Manually loaded systems are valuable tools for small scale studies and investigations, and fully automated systems have been implemented and validated for 100% product inspection in commercial scale applications.

About Us

LIGHTHOUSE is the leading manufacturer and provider of optical, non-destructive headspace inspection systems for in-line, at-line, and R&D applications specific to the pharmaceutical industry. LIGHTHOUSE developed the non-destructive headspace inspection systems with funding from the Food and Drug Administration. We have over 100 laser based systems installed around the world at some of the world's leading pharmaceutical, biopharmaceutical and contracting manufacturing companies including: Amgen, Baxter, Bayer, Boehringer Ingelheim, BMS, DSM, Eli Lilly, Genentech, GlaxoSmithKline, Helvoet Pharma, Johnson & Johnson, Merck, Novartis, Patheon, Pfizer, Roche, Serum Institute of India, Sankyo, Sanofi-Aventis, West Pharmaceutical Services, and Wyeth.

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