Using 100% Headspace Inspection for Characterizing and Optimizing Parenteral Manufacturing Processes

LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

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Introduction

Laser-based headspace analysis provides a rapid nondestructive method for performing trace gas analysis in the headspace of sterile pharmaceutical vials, ampoules, bottles, and syringes. Industry case studies presented here illustrate the value of total headspace characterization for 100% of finished product. Insight is gained into both product quality and the efficiency of the sterile process itself; a correlation that is missed with standard development and validation studies. This additional insight can be used to optimise processes, identify manufacturing issues, and guarantee the quality of finished product with 100% inspection. Headspace parameters of interest in parenteral drug products include headspace oxygen concentrations, water vapor levels, and absolute nitrogen pressure. A primary application is 100% container closure integrity inspection of freeze dried vials. Other important applications include headspace oxygen monitoring on liquid filling lines for optimization and validation of nitrogen purging processes, and 100% moisture determination of finished freeze dried product supporting lyo cycle optimization and freeze dryer validation.

Headspace Oxygen Monitoring on a Pre-filled Syringe Filling Line

For a formulation that is oxygen sensitive, a filling process must be designed and optimized to ensure that headspace oxygen levels are below specification. Optimizing and validating the filling and purging process can be time-consuming when using traditional headspace oxygen analysis methods. These are slow and require being set up in a laboratory instead of at-line in the filling area. The portability and ease-of-use of a solid state laser-based Oxygen Analyzer allows for set up next to the filling line. In this way, immediate feedback is given with respect to the headspace oxygen levels in the container headspace. Parameters can be quickly optimized and validation data collected to demonstrate that the filling and purging process is working to specification. Figure 1 shows headspace oxygen data collected from syringes filled on a new pre-filled syringe line. This line is located in a new state-of-the-art parenteral facility and was in the process of being validated. The syringe was a 1 ml glass syringe purged with nitrogen before and during filling as well as at stoppering. The stopper was inserted to leave a headspace of approximately 5 mm. Headspace oxygen analysis performed on the syringes using a laser-based headspace system was used to optimize and monitor the purging process.

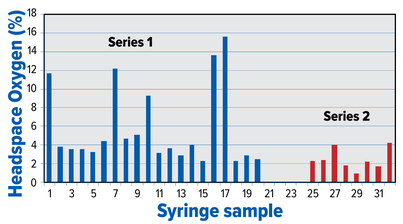

Figure 1. Measured headspace oxygen in syringes filled on a line being validated in a new parenteral manufacturing facility. An initial series of syringes showed a number of syringes having headspace oxygen levels above the 5% specification. A later series showed the optimized process producing syringes with average headspace oxygen levels of 3%.

100% Headspace Inspection to Determine Closure Integrity of Freeze Dried Vials

Here we describe an industry raised stopper case study involving a commercial batch of lyophilized product. The batch consisted of approximately 11,000 vials stoppered at 600 mbar of nitrogen. A suspected raised stopper issue resulted in product being put into quarantine and motivated the manufacturer to perform 100% laser-based headspace inspection of the batch a few weeks after production

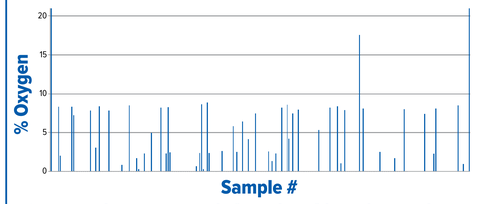

Figure 2. Headspace oxygen results for a subset of the product samples measured in a commercial lyo batch. It is clear from these results that a significant percentage (~ 25%) of the product vials has high oxygen content, presumably due to leaks that ingress air into the headspace. It is interesting to note that a large proportion of the high oxygen product samples have oxygen levels around 8% and that only one product sample contains near atmospheric oxygen levels.

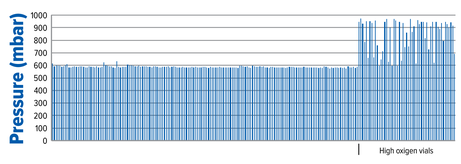

Figure 3. The measured headspace pressures give additional insight into the container closure issues in the batch. The headspace pressures of the high oxygen content vials are plotted on the righthand side of the plot. It is now clear that the high oxygen content vials have lost vacuum relative to the specified stoppering pressure of 600 mbar with a large proportion of the defective vials showing headspace pressures near one atmosphere

The data in Figure 4 correlates the headspace oxygen and headspace pressure measurements in the defective samples and identifies three categories of leaking vials: **Category 1 – Temporary gross leaker:** From Figure 4 it can be seen that vials having 8% headspace oxygen levels also have headspace pressures near one atmosphere. Raised stoppers in these vials caused gross leaks from the freeze dryer to the capping machine. Due to the gross leaks, 400 mbar of air (corresponding to 8% oxygen) quickly ingressed into the product vials. The capping process stopped the leaks sealing these vials under headspace conditions of 8% oxygen and one atmosphere. **Category 2 – Permanent leaker:** One vial in Figure 4 can be seen to have near atmospheric oxygen AND pressure levels. This vial was also leaking coming out of the freeze dryer. In contrast to the vials described in Category 1, the capping process did NOT stop the leak in this vial. After an initial ingress of 400 mbar of air into the headspace, this vial continued to ingress air after capping resulting in atmospheric oxygen levels. **Category 3 – Temporary partial leaker:** The remaining defective vials have oxygen levels between 0.5% up to 8% and headspace pressures between 600 mbar up to one atmosphere. The raised stoppers in these vials resulted in smaller leaks. Between the freeze dryer and the capping machine, these vials ingressed some amount of air partially raising the headspace pressures above 600 mbar. The leaks were stopped by the capping process sealing the vials under a range of partially elevated headspace oxygen and pressure levels.

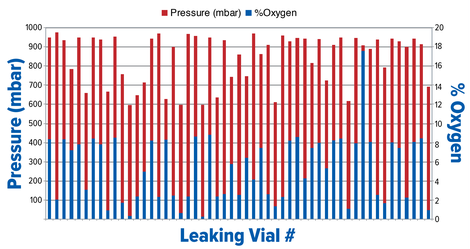

Figure 4. The correlation between the headspace oxygen and headspace pressure measurements in the defective vials is plotted in this Figure and provides the deepest insight into the closure integrity issue of this particular batch.

100% Headspace Moisture Determination of Freeze Dried Product

A commercial freeze drying cycle was used to manufacture a clinical batch of lyophilized product in a pilot freeze dryer. To gain insight into the drying efficiency, 100% headspace moisture inspection was performed on the batch using a laser-based headspace inspection system. When the headspace moisture measurements showed inhomogenous drying of the batch, the manufacturer adjusted parameters of the lyo cycle to achieve more consistent drying.

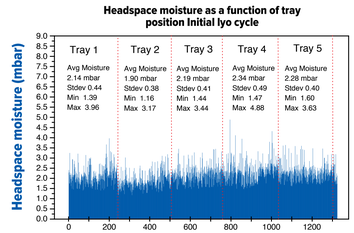

Figure 5. Headspace moisture values as a function of tray position are plotted for the samples from the initial lyo phlization cycle. It is clear that the drying efficiency for this lyo cycle depends on location within the freeze dryer. For example, average headspace moisture values and standard deviations across the tray show that the samples in Tray 2 dried more efficiently than the samples in Tray 4.

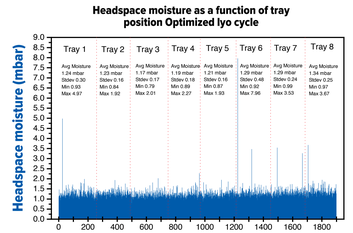

Figure 6. Headspace moisture as a function of tray position for the optimized lyo cycle shows more consistent drying across the freeze dryer shelf. Average headspace moisture values are also lower indicating better drying when compared to the initial cycle. It should be noted that even for this improved lyo cycle there are some vials (6 out of 1898) that have elevated levels of moisture content. The trays containing these 'wet' samples are easily identified by the high standard deviations across those trays (Trays 1, 6, 7, and 8).

Conclusions

In summary, the laser based headspace inspection case studies presented here show that performing headspace analysis for 100% of finished product can be an extremely powerful analytical tool for characterising sterile manufacturing processes and for guaranteeing the quality of finished product with respect to closure integrity and stability against oxygen and/or moisture. As a rapid nondestructive in-process analytical method, laser-based headspace inspection offers unprecedented insight into the various stages of aseptic processing showing where processes are under control and also where processes are at a greater risk for going out of control. `This scientific knowledge is invaluable to those persons responsible for maintaining and improving sterile manufacturing processes.