E-BOOK

MANUFACTURING STERILE PARENTERAL PHARMACEUTICALS:

How to Protect Oxygen Sensitive Formulations.

LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

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In-process monitoring of headspace oxygen levels in parenteral containers

INTRODUCTION

The need to monitor headspace oxygen levels in parenteral containers arises from the requirement to ensure the stability and potency of oxygen-sensitive product. Besides a loss of efficacy and reduction in shelf life, exposure of such products to oxygen can result in product discoloration, changes in dissolution rate and profile, and even toxicity or other pharmacological properties associated with negative side effects.

During the development of an oxygen-sensitive product, studies are performed that investigate the formulation's interaction with oxygen. End-of-shelf-life stability studies verify that the product indeed retains efficacy under specified headspace oxygen levels. Such studies allow for the specification of appropriate initial headspace oxygen levels in the primary packaging as well as insight into the oxygen permeation rate into the package during shelf life. Finally, headspace oxygen levels are often monitored during the filling process as an in-process control (IPC) of the purging system used to bring headspace oxygen levels below the required specification.

Conventional techniques, such as electrochemical methods or gas chromatography, are slow and/or destructive. This results in headspace oxygen analysis which is both time and resource intensive. In addition, it is difficult to implement the conventional headspace oxygen methods at- or in-line for immediate feedback about the filling process. The destructive nature of the measurement also means that these conventional methods cannot be utilized for 100% inspection of product.

LIGHTHOUSE platforms for rapid non-destructive headspace oxygen inspection can streamline the monitoring of purge performance on the filling line. The LIGHTHOUSE laser-based headspace method shines light through the headspace to measure headspace oxygen concentrations in finished product containers (Figure 1). Based on spectroscopic methods, the measurement is analytical, rapid and non-destructive. The automated PULSAR Headspace Inspection Machine and the benchtop FMS-Oxygen Headspace analyzer (Figure 2) enable the in- and at-line inspection of oxygen levels in sealed parenteral containers.

Figure 1: Non-destructive headspace analysis using a laser diode that shines through the headspace of a container.

IN-PROCESS MONITORING OF OXYGEN

The ability to make nondestructive headspace oxygen measurements enables immediate feedback to the filling process and 100% (or statistical) inspection of finished product.

As part of an experiment, in-line headspace oxygen analysis was performed while the nitrogen purge rate was adjusted during filling. The results of this in-line experiment are shown in Figure 3. Vials were filled initially with the nitrogen purge turned off and the figure shows the first vials in the filling run having atmospheric levels of oxygen.

The purge rate was then varied in real time as the vials were being filled. Turning the purge rate up to 7.0 standard liters per minute (SLPM) resulted in vials having headspace oxygen levels of approximately 3% atm. Further varying the purge rate demonstrated how the headspace oxygen levels change as a function of purge rate. The filling in this demonstration was performed at a line speed of 90 vials/min with the in-line headspace oxygen system giving immediate feedback about the headspace oxygen levels in each vial.

Figure 2: The LIGHTHOUSE Headspace Oxygen Inspection Systems. Left: Benchtop FMS-Oxygen Analyzer, Right: PULSAR Automated machine.

BENEFITS

- No destruction or disposal of valuable product
- Measurement method is robust and independent of operator
- Gives fast feedback on nitrogen purge performance during filling
- Enables efficient, accurate optimization and validation of the filling line
- Scalable for 100% product inspection and automated process monitoring

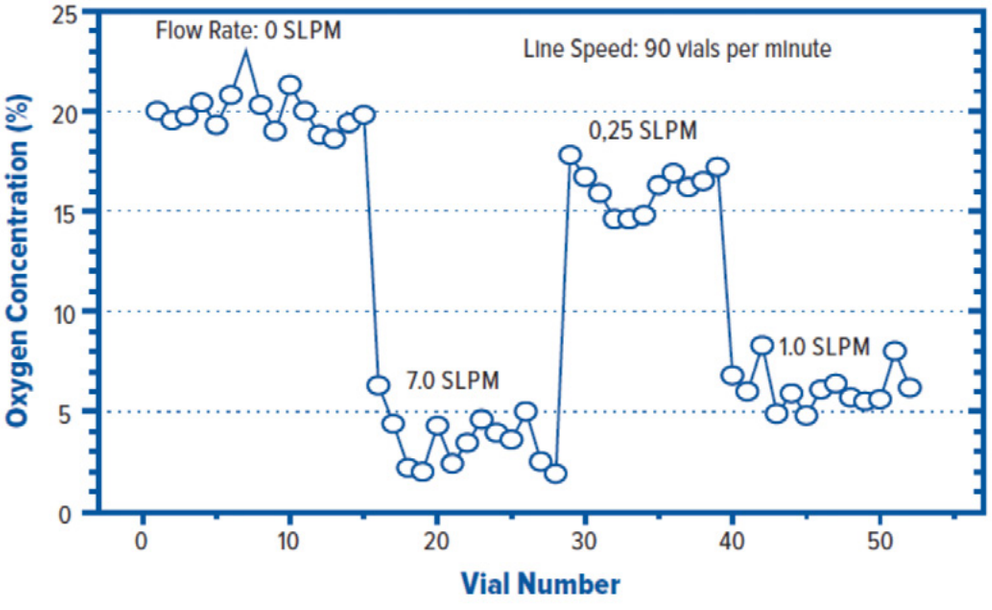


Figure 3: Automated headspace oxygen measurements performed while the nitrogen purge rate was adjusted in real time during filling.

Nitrogen purge optimization and validation of sterile liquid filling lines

INTRODUCTION

Sterile liquid filling lines are increasingly being implemented with nitrogen purge capability during filling. Large molecule biopharmaceuticals can be prone to oxidation and to prevent this from occurring, the headspace is often purged with an inert gas during filling to ensure a longer shelf life. Consistently producing containers with specified headspace oxygen conditions depends on a number of parameters and is not necessarily straightforward. The use of a fast and robust oxygen monitoring method can significantly streamline the set up and validation of a filling line. For these reasons, laser-based headspace analysis is often the method of choice for monitoring headspace oxygen levels during filling.

METHOD HIGHLIGHTS

The LIGHTHOUSE laser-based headspace method shines light through the headspace to measure headspace oxygen concentrations in finished product containers. Based on spectroscopic methods, the measurement is analytical, rapid, and non-destructive. These characteristics enable immediate feedback on the headspace oxygen levels in product containers during filling. This is especially useful during the set-up, optimization, and qualification of a filling line configured for nitrogen purging. Portable benchtop headspace oxygen analyzers can be implemented at-line to make immediate headspace oxygen measurements as a function of the various nitrogen purging parameters. Robust filling line performance qualification data can be collected efficiently saving both time and resource. Figure 1 shows the measured headspace oxygen in syringes filled and purged on a line being validated in a new parenteral manufacturing

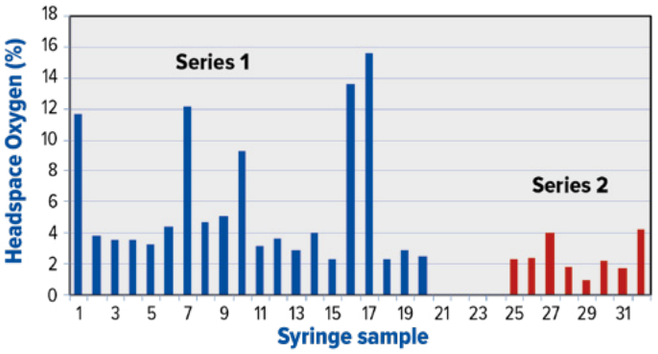


Figure 1: Measured headspace oxygen levels in syringes filled and purged on a line that is being validated in a new manufacturing facility.

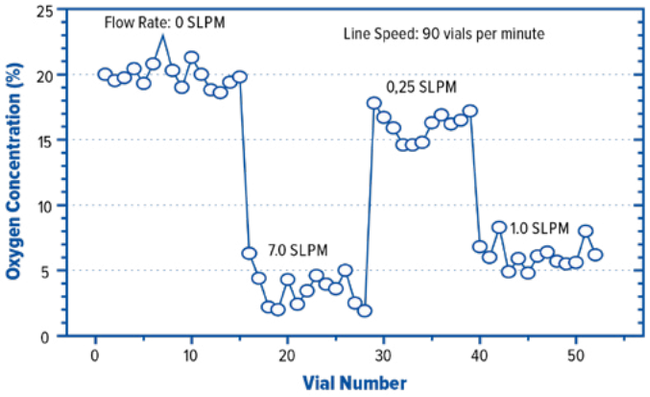


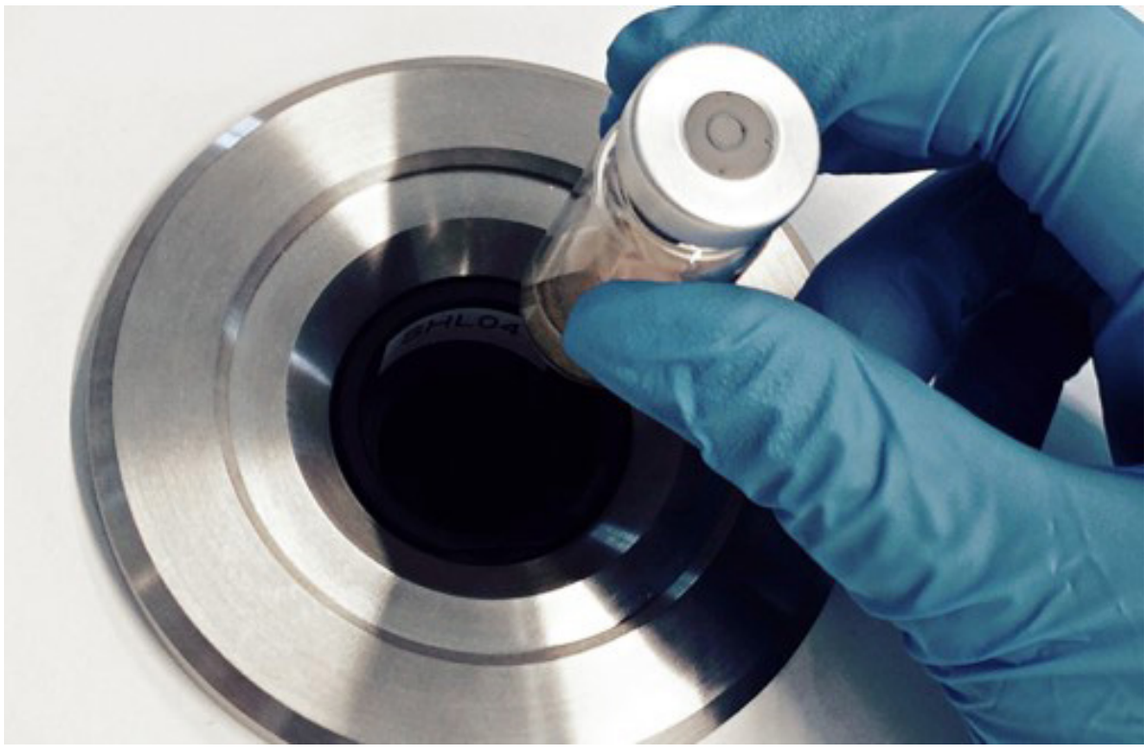
Figure 3: Automated headspace oxygen analysis performed while the nitrogen purging rate is adjusted during filling.

facility. An initial series of syringes analyzed at-line showed some samples having oxygen levels above the 5% specification. After optimization of the filling process, a later series showed syringes being produced with no outliers. It is also possible to implement 100% in-line oxygen monitoring of product on the filling line (Figure 2). Figure 3 shows the results of automated headspace oxygen measurements performed while the nitrogen purging rate was adjusted in real time during filling. The results show that the higher the purging rate in standard liters per minute (SLPM), the lower the oxygen levels in the finished product vials. Automated machine platforms can be implemented in-line after filling to measure the headspace oxygen levels in 100% of the product containers. Such a 100% oxygen monitoring implementation not only monitors the purging process but also guarantees that 100% of product is purged below specified headspace oxygen levels.

BENEFITS

- Laser-based headspace is analytical, rapid, and non-destructive
- Gives fast feedback on purge performance during filling
- Measurement method is robust and independent of operator
- Enables efficient, accurate optimization and validation of the filling line
- Scalable for 100% monitoring of product during filling

Figure 2: The LIGHTHOUSE automated PULSAR machine platform that can be implemented to perform 100% in-line oxygen monitoring.



WEBINAR

Protecting Oxygen Sensitive Formulations

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Manufacturing filling line nitrogen purge qualification.

Background:

- A client had an existing filling line and wanted to optimize the nitrogen purge process to decrease headspace oxygen levels to 2%.
- In addition, frequent line stoppages resulted in a need to identify and reject high oxygen vials that had lost the nitrogen headspace during the stoppage.
- A purging process qualification study was performed using rapid non-destructive headspace oxygen analysis in an at-line set-up with samples being measured immediately from the line.

Purge Qualification Study:

The existing filling line consisted of a pre-purge, and a post purge where nitrogen would be blown into the vials after filling of the product (Figure 1, right to left). As shown in the schematic there is a 'dead space' before stoppering occurs. This residence time before stoppering allowed nitrogen gas to escape.

The client was aiming to reduce the headspace oxygen to 2% but could do no better than 5% headspace oxygen because nitrogen was escaping before the vials were stoppered.

A suggestion, from the filling line manufacturer, was to introduce a Nitrogen Overlay System in the dead space (see Figure 1). However, the nitrogen 'tunnel' made the

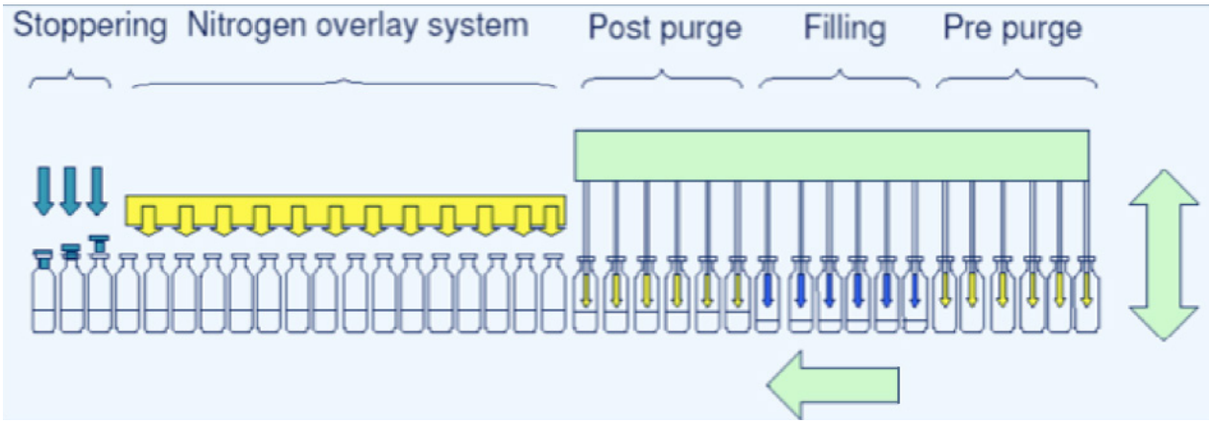

Figure 1: Filling line schematic illustrating the Nitrogen Overlay System in the 'dead space'.

situation worse and the headspace oxygen could not be purged lower than 7%. The Nitrogen Overlay System caused turbulent gas flow around the open vials, pulling air from around the vials into the headspace and preventing efficient purging.

The solution was an extended post purge arm (Figure 2, right to left). Post purge was done closer to the stoppering, reducing the residence time and allowing less nitrogen to escape.

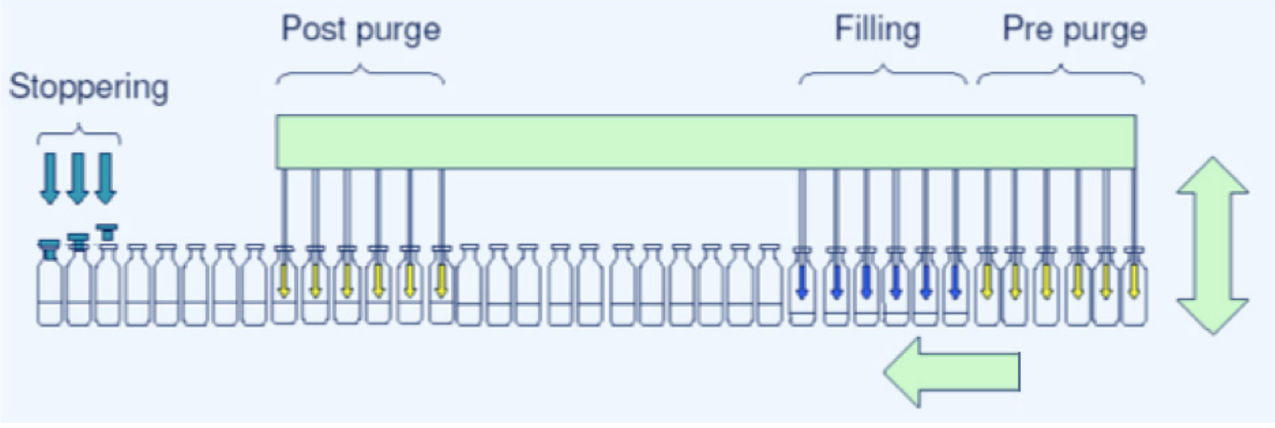

Figure 2: Filling line schematic including an extended post purge arm to purge closer to the stoppering.

The extended post purge arm allowed the client to achieve the targeted 2% headspace oxygen. Figure 3 shows the measured headspace oxygen levels as a function of the residence time.

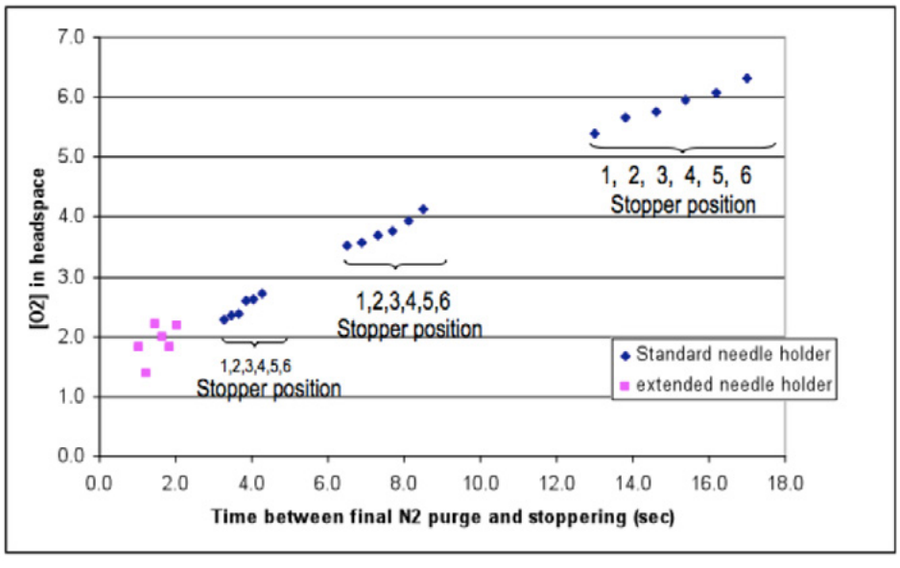

Figure 3: Headspace oxygen levels as a function of the residence time, comparing the filling process using a standard needle holder with using an extended post purge arm. The targeted 2% headspace oxygen is achieved using the post purge arm (extended needle holder).

Conclusion:

Use of the at-line headspace oxygen analyzer during the purge qualification study enabled:

- Efficient purge optimization and validation.
- Optimal purge performance at ~2% headspace oxygen.
- Validation of a software solution to reject a fixed number of vials after a line stoppage.
- Ultimately, a significant reduction in production downtime.

Manufacturing departments filling oxygen-sensitive formulations benefit greatly from using LIGHTHOUSE FMS-Oxygen Headspace Analyzers. At-line configurations give operators the ability to quickly and accurately determine headspace oxygen levels. This in turn streamlines filling line optimization and qualification during set-up and enables in-process control measurements during routine production.

Nitrogen purging process development for oxygen sensitive formulations in pre-filled syringes

Background:

- A new biological product, in pre-filled glass syringes, had demonstrated oxygen sensitivity in stability studies.
- Therefore, the headspace was purged with nitrogen during filling, and the client wanted to validate the batch production process and assess the nitrogen purge efficiency.
- As part of their manufacturing control strategy, the client decided to generate as much data as possible before commercial launch by performing a 100% inspection on the engineering batches using non-destructive headspace oxygen analysis.

Case

The product was launched in 1ml glass pre-filled syringes with two filling volumes: 0.5 mL and 1.0 mL. The product specification was to have less than 5% of oxygen in the headspace after filling. During scale-up, 100% headspace oxygen inspection was carried out on engineering batches to assess the nitrogen purge efficiency. A total of approximately 80,000 syringes were inspected. The results of this study are summarized in Table 1.

Table 1: Results of 100% headspace oxygen inspection on the pre-filled syringe engineering batches.

Filling volume	1.0 mL	0.5 mL
No. syringes inspected	~ 50.000	~ 30.000
Out of specification	0	300 (10-15% headspace oxygen)

For the approximately 50,000 syringes with a 1 mL fill, headspace oxygen inspection revealed that all syringes were below the specified 5% oxygen level. 100% rapid non-destructive oxygen headspace analysis provided the client with science-based data that demonstrated the nitrogen purging and filling process worked and is robust.

For the approximately 30,000 syringes with a 0.5 mL fill, the outcome was different. Again, headspace oxygen analysis was performed on the complete engineering batch. This time however, about 300 syringes were found to have headspace oxygen levels between 10-15% - well above the 5% specification. A root cause investigation was initiated by the client to determine whether the increased headspace oxygen levels were caused by the filling process or due to a container closure integrity issue. The root cause investigation discovered that the increased levels of oxygen were the result of a process issue, namely foaming in the headspace as the filling needle was withdrawn from the syringe. Adjustments made by the filling line supplier took care of the issue, and improved performance was confirmed by further studies using headspace oxygen analysis. Resolving the process issue resulted in an improved purging process and consistent product quality, which in turn enabled the validation of a robust filling process.

Conclusions

- Rapid and non-destructive 100% headspace inspection can be used to generate statistical product and process data of finished product.
- Analysis of engineering batches gave deep insight into process issues that needed to be resolved before validation.
- The statistical process and product data generated ultimately demonstrated the robustness of the improved production process for the syringe filling line described here.

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