LIGHTHOUSE

The Science of Pharmaceutical Manufacturing

Application Note **102**

In-process monitoring of headspace oxygen levels in parenteral containers

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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. 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.

Unfortunately, existing analytical methods for monitoring oxygen in the headspace of parenteral containers are slow and/or destructive. This results in headspace oxygen inspection which is both time and resource intensive. Conventional destructive techniques, such as electrochemical methods or gas chromatography, are difficult to implement 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. Once the septum of the container is pierced to take a headspace sample, container integrity is compromised. Product is therefore destroyed and costs are incurred as a result of the destruction and disposal of analyzed samples.

LIGHTHOUSE platforms for rapid non-destructive headspace oxygen inspection can help streamline the monitoring of purge performance on the filling line. The automated VISTA Headspace Oxygen Inspection Machine and the benchtop FMS-Oxygen Headspace An-

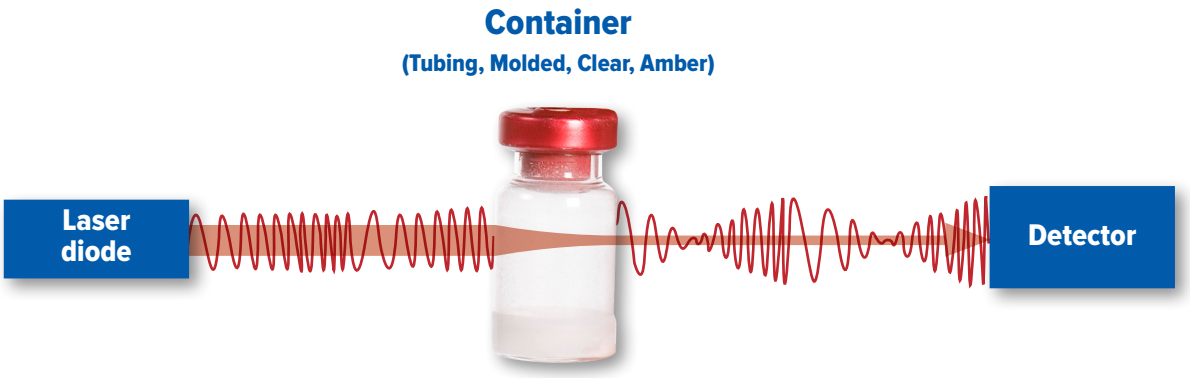
alyzer from LIGHTHOUSE enable rapid non-destructive inspection of oxygen levels in sealed parenteral containers. The robustness and easy operation of the platforms allow for in- or at-line implementation in the Production environment. The rapid non-destructive nature of the measurement allows for immediate feedback to the filling process, 100% inspection of containers, and there is no disposal of destroyed product.

The patented LIGHTHOUSE platforms utilize a high sensitivity detection technique known as Frequency Modulation Spectroscopy (FMS). Light from a near-infrared semiconductor laser is tuned to match the internal vibrational frequency of the oxygen molecule. Measuring the absorption of the laser light after it passes through the container headspace allows for the determination of headspace oxygen concentrations.

Experiments

The objective of the experiments was to demonstrate the correlation of the FMS rapid non-destructive technique for analyzing headspace oxygen levels with the most commonly used conventional destructive techniques for headspace oxygen inspection, and to demonstrate in-line oxygen monitoring with an automated inspection machine platform.

Sample sets with varying headspace oxygen levels were prepared in a variety of parenteral containers. These sample sets were inspected for headspace oxygen levels using a non-destruc-



The LIGHTHOUSE Laser-based Headspace Inspection Method

tive LIGHTHOUSE oxygen analyzer. One sample set was then analyzed with a conventional destructive electrochemical method. The second sample set was analyzed with a conventional destructive gas chromatography method. The correlation between the LIGHTHOUSE FMS technique and the destructive methods was then determined.

For in-line experiments with the automated headspace oxygen inspection platform, two experimental setups were used. The first setup involved implementing an automated headspace oxygen platform directly after filling of an oxygen-sensitive product. The purging rate of the nitrogen purge system was then varied as vials were filled, and the effects on the headsapce oxygen levels were monitored in real-time. The second in-line setup involved manufacturing headspace oxygen standards using certified gas mixtures. The certified oxygen vial standards were then run continuously through the automated headspace oxygen platform to produce statistical data demonstrating the accuracy and precision of the in-line oxygen measurement.

The LIGHTHOUSE Headspace Oxygen Inspection systems.

Results

The results of the analysis of the first sample set are shown in Figure 1. Samples of a liquid product filled in 10 ml ampoules and having a range of headspace oxygen levels were produced by varying the purge rate on the filling line. The table lists the average oxygen levels from ten non-destructive LIGHTHOUSE measurements along with the standard deviations and relative standard deviations of these ten measurements. The LIGHTHOUSE results are then compared to the one destructive measurement made by the electrochemical method. The comparison shows a very good correlation between the two measurement techniques. Unfortunately, it is not possible to determine the precision of the electrochemical technique as the sample is destroyed by the measurement. Similar correlation experiments were

SAMPLE	ELECTROCHEMICAL % OXYGEN MEASUREMENT	LIGHTHOUSE % OXYGEN MEASUREMENT	LIGHTHOUSE STD DEV	LIGHTHOUSE RSD
8A	2,5	2,3	0,05	2,2
8B	2,8	2,9	0,09	3,1
9A	12,4	12,0	0,12	1,0
9B	12,4	12,6	0,09	0,7
10A	5,5	5,5	0,09	1,6
10B	5,6	5,3	0,08	1,5
11A	5,4	5,5	0,08	1,5
11B	4,4	5,0	0,14	2,8
12A	2,8	2,6	0,1	3,8
12B	2,9	2,6	0,09	3,5
13A	12,3	12,1	0,09	0,7
13B	analysis failed	12,3	0,11	0,9

Figure 1. Results from headspace oxygen measurements performed first with the LIGHTHOUSE technique (total of 10 non-destructive measurements) and then with a destructive electrochemical technique. Experiments comparing the LIGHTHOUSE technique to gas chromatography also resulted in similar correlations.

also performed using gas chromatography as the destructive method.

The results of the first in-line experiment are shown in Figure 2. Vials were filled initially with the nitrogen purge turned off and the figure shows the first vials in the 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%. 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.

The results of the second in-line experiment are shown in Figure 3. The figure plots in-line measurements made on a set of certified oxygen standards. The set of standards was cycled continuously through the automated headspace oxygen measurement system at a speed of 300 vials per minute so that each standard was measured 100 times. The histograms in Figure 3 are plots of the 100 measurements for each standard. The histogram results give a complete statistical picture of the machine performance with the peak average of the distribution related to the accuracy of the measurement and the width of the distribution related to the measurement-to-measure-

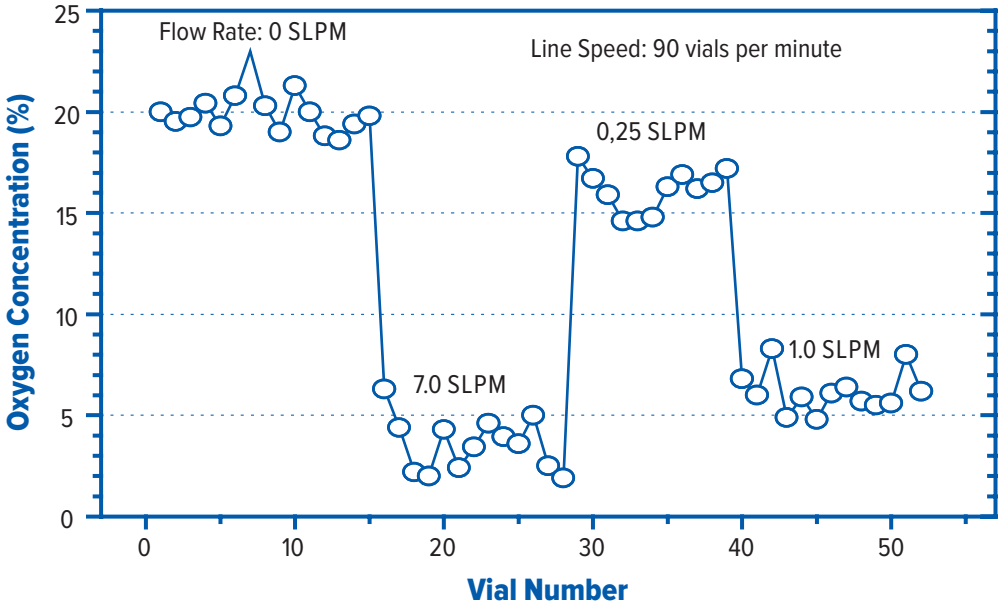


Figure 2. Results of automated headspace oxygen measurements performed while the nitrogen purge rate was adjusted in real time during filling.

ment precision. The results in Figure 3 show that at a line speed of 300 vials per minute, the platform can distinguish between 0% and 2% oxygen in the headspace. Further experiments demonstrated that better sensitivity can be achieved by lowering the line speed.

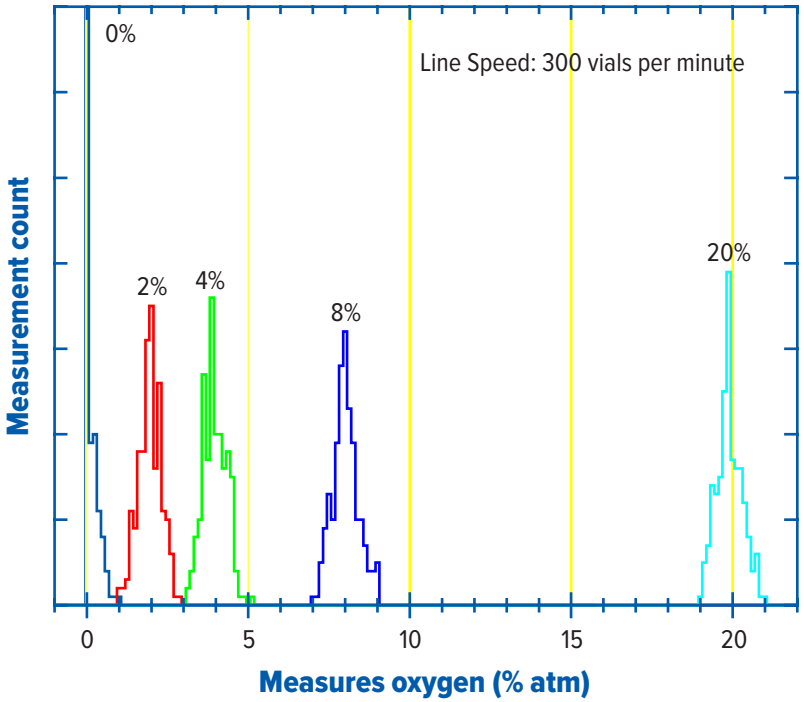


Figure 3.
Results of automated headspace oxygen measurements made on known oxygen standards of 0, 2, 4, 8, and 20% oxygen. The histograms plot the results of 100 separate measurements on each standard at a line speed of 300 vials/minute and demonstrate the accuracy and precision of oxygen monitoring in this experiment.

Conclusions

LIGHTHOUSE platforms are able to measure headspace oxygen levels in sealed parental containers in a rapid and non-destructive manner. Comparative experiments demonstrate that the LIGHTHOUSE technique correlates well with the conventional destructive methods used for IPC of headspace oxygen levels during the filling process. Automated machines have now been implemented, validated, and registered with regulatory authorities for in-line headspace oxygen monitoring in facilities around the world. The advantages of a rapid non-destructive technique include the following:

- Fast feedback on purge performance during filling
- Scalable for 100% inspection of product and automated process monitoring guaranteeing quality
- Measurements independent of operator expertise
- Efficient and accurate optimization and validation of nitrogen purging systems
- No waste disposal of destroyed product
- Low ongoing consumable costs

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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