Case Study: 100% Container Closure Integrity Inspection of Dual Chamber Freeze-Dried Cartridges

LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

D.I. Duncan

Introduction

A manufacturer of dual chamber freeze dried cartridges decided to implement 100% container closure integrity (CCI) inspection as part of the production process. This poster describes the implementation of a laser-based headspace inspection machine for CCI inspection and outlines the elements of a robust inspection process. Data is presented demonstrating: 1) the inspection of elevated headspace oxygen levels which are used to identify freeze dried cartridges that have leaked, and 2) the accuracy and precision of the cartridge headspace oxygen measurement at production line speeds.

Laser-based Headspace Analysis for 100% CCI Inspection

Conventional methods for container closure integrity analysis of sealed parenteral containers have specific limitations. The blue dye ingress test is destructive and is not suitable for 100% inspection. Vacuum decay and high voltage techniques are not able to identify all containers that have temporarily leaked – the container needs to be leaking at the time of inspection in order to be detected. On the other hand, a laser-based method for analyzing headspace pressure and gas composition can identify temporarily leaking containers as well as containers that are leaking due to sub-micron defects. The non-destructive nature of the measurement enables 100% analysis of product as well as the ability to monitor a single sample over time. For these reasons, analytical platforms based on this technique are increasingly being implemented for a quantitative physical container closure integrity test.

A Robust 100% CCI Inspection Process

Using laser-based frequency modulated spectroscopy (FMS), the headspace gas composition and pressure in a sealed parenteral container can be quantitatively determined. For pharmaceutical product with a modified headspace (something other than 1 atm of air), changes in the headspace gas composition and/or pressure are a clear marker for samples that have lost container closure integrity. A cartridge sealed under 1 atm of nitrogen that has suffered from a closure integrity failure will immediately begin to exchange gas with the outside air environment resulting in changes of the cartridge headspace conditions. A robust 100% CCI inspection process should a) detect these changes in the headspace conditions at production line speeds, and b) be sensitive to micron level defect sizes. Figure 1 shows how quickly headspace oxygen levels rise in an empty 1ml container that is initially purged with nitrogen. Elevated oxygen levels are clearly distinguishable from the initial low levels of oxygen demonstrating how leaking containers can be identified and rejected from the line on the basis of quantitative determination of the headspace oxygen levels.

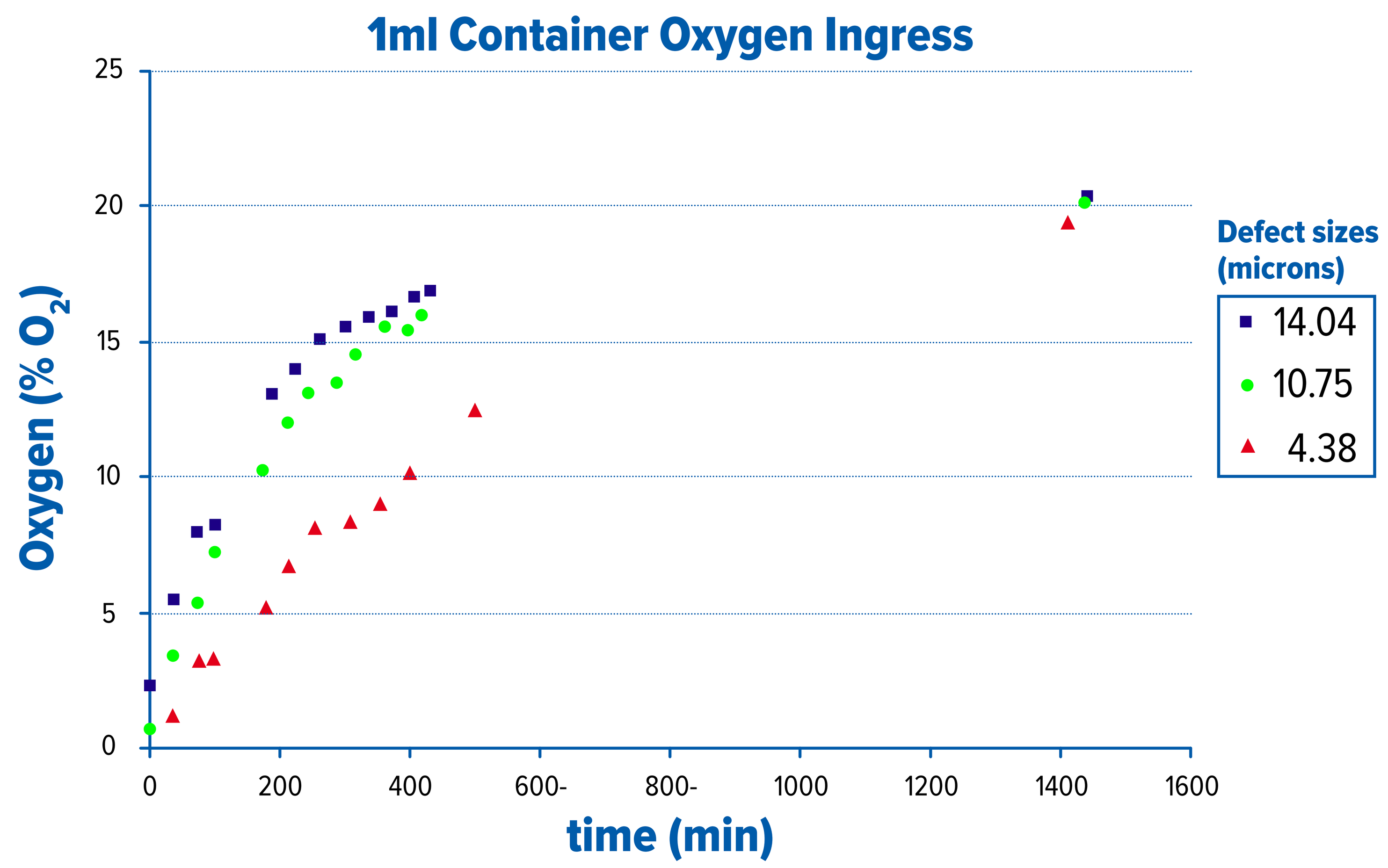

Figure 1: The rise in oxygen levels in purged 1ml containers as a function of time and defect size. Laser drilling was used to create known defects of certified sizes in the glass tubing barrel. After 24 hours, atmospheric levels of oxygen have been reached for all defect sizes due to the diffusion of air into the initial nitrogen headspace.

Headspace Inspection Machine Performance Data

A Headspace Oxygen Inspection Machine was configured for the inspection of the dual chamber freeze-dried cartridges (see Photo 1). The machine was configured with four FMS laser sensors to measure the headspace oxygen levels in the cartridges. A user-defined reject limit was configured that identifies cartridges that have lost container closure integrity. These cartridges are then automatically rejected from the line.

Photo 1 A close-up of the four oxygen sensor heads configured on a headspace inspection machine to inspect dual chamber freeze dried cartridges.

Table 1 gives a summary of the machine performance for the in-line headspace oxygen measurement. Certified NIST traceable oxygen standards were manufactured from empty cartridges. Because these standards were made from the actual cartridges, they could be run through the machine identically to product samples. Table 1 summarizes the results of machine measurements on a set of certified standards. The Table represents a full statistical overview of machine performance over the range of potential oxygen levels that could be found in the cartridge headspace.

ACTUAL OXYGEN (%)	MEASURED OXYGEN (%)	ERROR (%)	ST DEV (%)	MIN (%)	MAX (%)
20.00	19.18	-0.82	0.50	17.68	20.23
10.70	10.38	-0.32	0.56	9.03	11.44
8.01	7.70	-0.31	0.43	6.53	9.11
4.00	3.64	-0.36	0.44	2.65	4.78
2.00	1.81	-0.19	0.40	0.88	2.83
1.00	0.78	-0.22	0.40	0.00	1.59
0.00	0.07	0.07	0.13	0.00	0.50

Table 1: Summary of performance data generated by inspecting certified cartridge oxygen standards with the headspace inspection machine. The inspection measurements were performed at a line speed of 200 cartridges/min and the Table summarizes the results of 60 consecutive measurements of each standard.

Figure 2 plots example in-line measurements made on product cartridges at a line speed of 200 cartridges/min. Cartridge oxygen standards containing elevated levels of oxygen were also included in the sample set to simulate leakers. The data shows how the headspace oxygen measurement easily distinguishes the standards with elevated oxygen levels from the product cartridges.

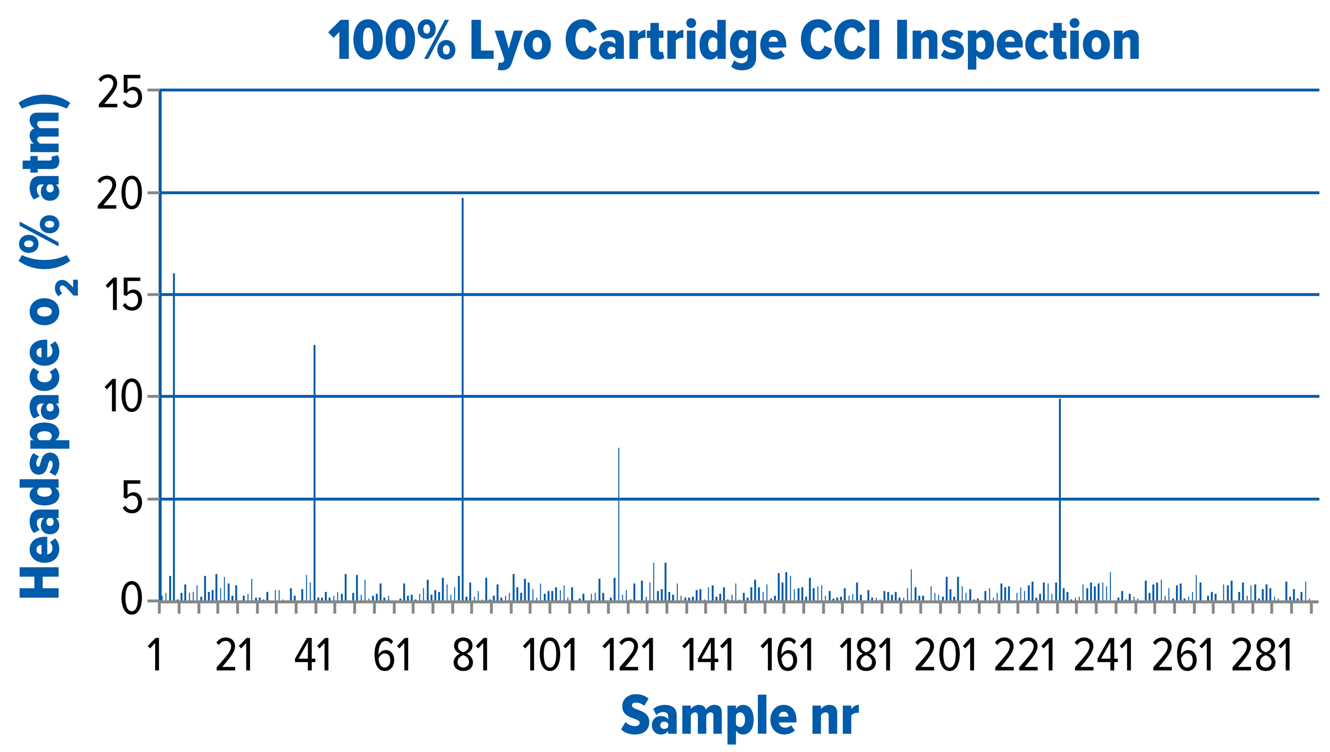

Figure 2: Plot of in-line headspace oxygen measurements of dual chamber lyo cartridges. Measurements of standards having elevated oxygen levels to simulate leaking cartridges have also been included in the plot.