LIGHTHOUSE

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APPLICATION NOTE

Non-Invasive Headspace Analysis for Automated Media Fill Inspection

Background

Opportunities for improving and streamlining the media fill process are interesting for aseptic filling operations. In particular, the manual visual inspection process used to inspect media vials for signs of contamination after incubation is considered to be tedious and time consuming. Because the visual inspection is performed by operators, there is also risk for human error.

It is well-known that the inspection performance of human operators can vary (subjectivity) and that fatigue can affect performance. In addition, difficult-to-inspect containers such as molded or colored glass, or certain plastic containers, pose inspection challenges for operators. An inspection method that is analytical and automated should improve the media fill inspection and fit with the industry trend of removing human subjectivity and manual operations from the process.

HEADSPACE ANALYSIS FOR MEDIAFILL INSPECTION

Laser-Based Headspace Analysis has been demonstrated for detecting microbial growth in media-filled pharmaceutical containers. For detecting microbial growth, tunable diode laser absorption spectroscopy is used to measure the levels of headspace oxygen and carbon dioxide. Once aerobic microorganisms begin to grow after the lag phase and enter the exponential growth phase, there will be a significant consumption of oxygen in the sealed container as well as a corresponding production of carbon dioxide (1). Headspace analysis can accurately measure these changes in the headspace gas composition and can be used to detect contaminated media fill samples. The measurement itself is rapid and nondestructive, meaning that results are obtained immediately and the measured sample remains intact allowing for repeated measurements over time, if desired.

A microbial contamination study was performed by inoculating media vials with representative microorganisms and incubated for 14 days.
During the incubation period, the headspace oxygen and carbon dioxide levels in the sample vials were measured. Figure 1 plots the measured headspace oxygen and carbon dioxide levels over the 14 day incubation period in media vials inoculated with the mold *A. brasiliensis*. The results of three samples are plotted to indicate the spread between extreme high, medium, and low measurement results in the set of 20 vials. The dotted line indicates the start of exponential growth and it can be seen that the headspace oxygen in the inoculated vials decreases rapidly from near atmospheric levels (i.e. 18% atm) to zero in the first 75 hours of incubation. At the same time, the plot shows headspace carbon dioxide levels rising from zero to over 16% atm. These changes in headspace gas composition are easily detectable with laser-based headspace measurements – the standard deviations of the measurements are smaller than the value range of the data points plotted in the graph. It is also clear from the graph in Figure 1 that detectable changes in the headspace gas composition happened very early in the 14 day incubation period.

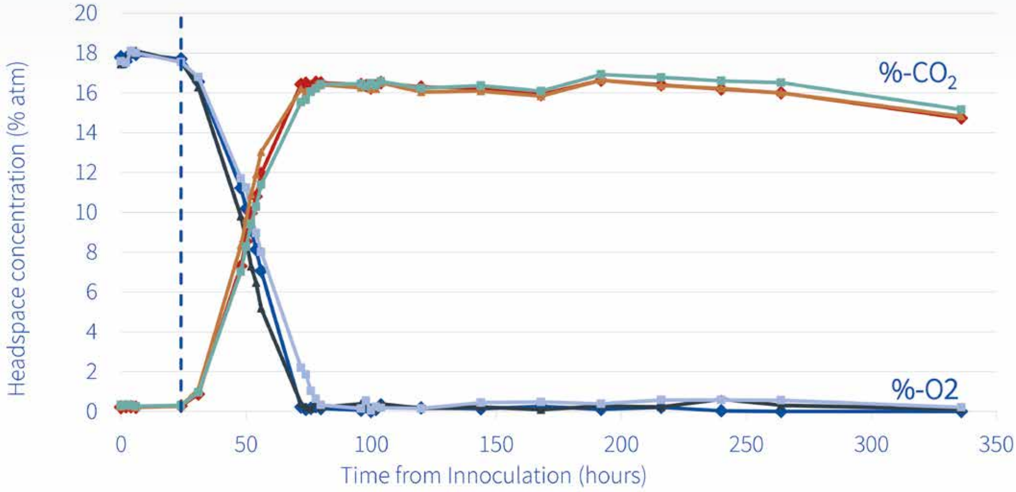

Figure 1

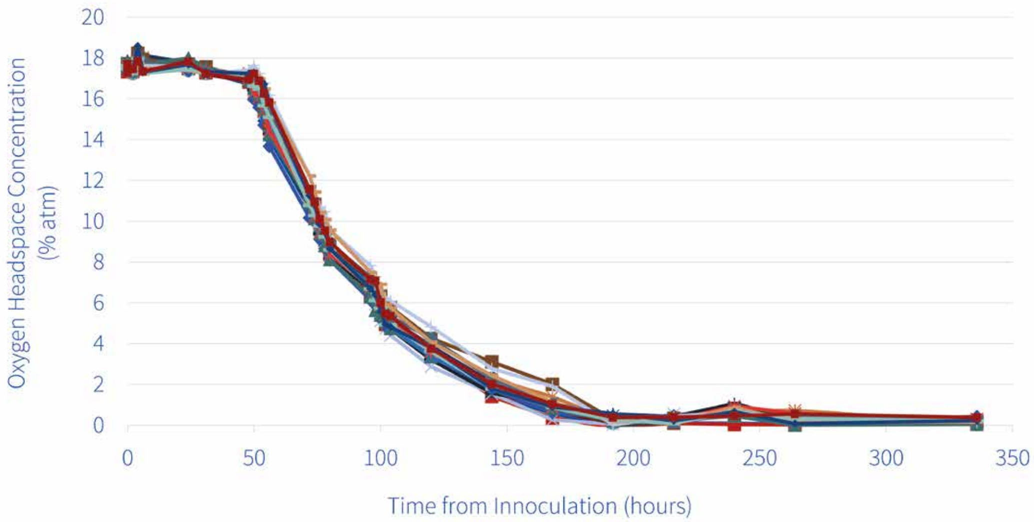

Figure 2

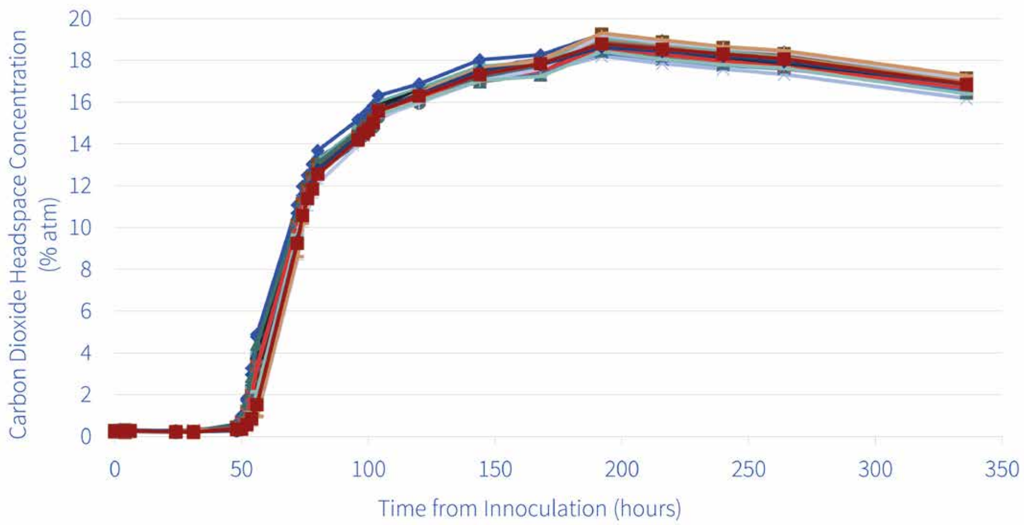

Figure 3

Figures 2 and 3 show the results from all twenty samples inoculated with the bacterium *S. aureus.* Again, the results show a drop of headspace oxygen levels (Figure 2) to zero during the 14 day incubation with a corresponding increase of headspace carbon dioxide (Figure 3). All 20 samples behaved identically, clearly demonstrating the consistency of the measured oxygen consumption and carbon dioxide production curves across the set of 20 contaminated samples. The dynamics of the headspace oxygen consumption and carbon dioxide production curves are dependent on the microorganism. Additional studies using headspace analysis have demonstrated the detection of more than 25 different microorganisms in media vials, including the standard compendial microorganisms as well as typical house isolates detected in sterile drug manufacturing facilities (2).

BENEFITS

Because headspace analysis can be automated at inspection speeds of several hundred vials per minute using existing headspace inspection machine platforms, a feasible application is automated media fill inspections as part of aseptic filling process validation. This represents an opportunity to replace the labor intensive human visual inspection process (a subjective method) with an automated analytical inspection for media fills. This change would improve the reliability of media fill inspection, reduce the total inspection time and required human labor, and would improve vial reconciliation and data integrity (see Table 1 summary).

MEDIA FILL INSPECTION METHOD	
HUMAN OPERATORS	LASER-BASED HEADSPACE ANALYSIS
Subject to human error	Quantitative analytical measurement
Slow, resource-intensive inspection	Fast automated machine inspection
Vial count done manually	Automated vial reconciliation
Some containers challenging to inspect	Challenging containers can be inspected
Difficult to validate	Can be validated as an analytical method

TABLE 1

REFERENCES

[1] Duncan, D.; Cundell, T.; Levac, L.; Veale, J.; Kuiper, S.; Rao, R. The Application of Nonvinvasive Headspace Analysis to Media Fill Inspection PDA J. Pharm.Sci. Technol. 2016, 70, 230–247.

[2] Brueckner, D. et al. 'Tunable diode laser absorption spectroscopy as method of choice for non-invasive and automated detection of microbial growth in media fills'. Talanta 167 (2017) 21-29.

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