Non-Destructive Monitoring of Oxygen in Pre-Filled Syringes

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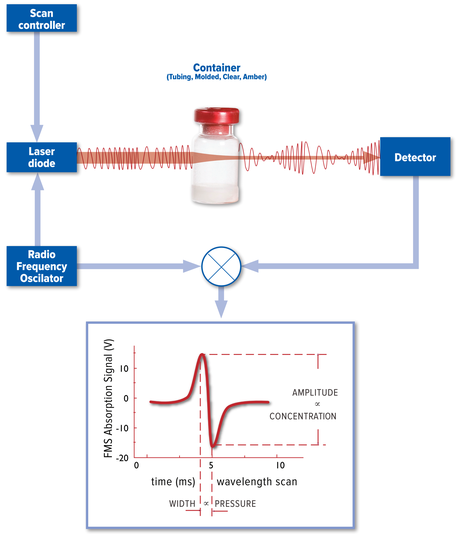
Introduction

Headspace oxygen is a critical parameter for controlling the stability of many liquid and lyophilized products. Monitoring headspace oxygen in syringes is particularly challenging due to the small volume and packaging configuration. Here we describe a nondestructive method for in-process monitoring of headspace oxygen in pre-filled syringes.

Method

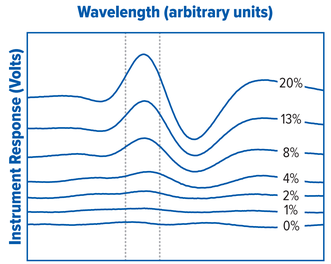
Six syringes (1.25cc) were filled with 0, 1, 2, 4, 8, and 20% oxygen with a balance of nitrogen to 1 atmosphere using certified gas mixtures (NIST traceable). One hundred oxygen measurements were made on each syringe. The results were compared with the known values to determine accuracy, precision, linearity, and measurement range for the method using guidelines from the USP 25 General Test <1225> .



Instrumentation

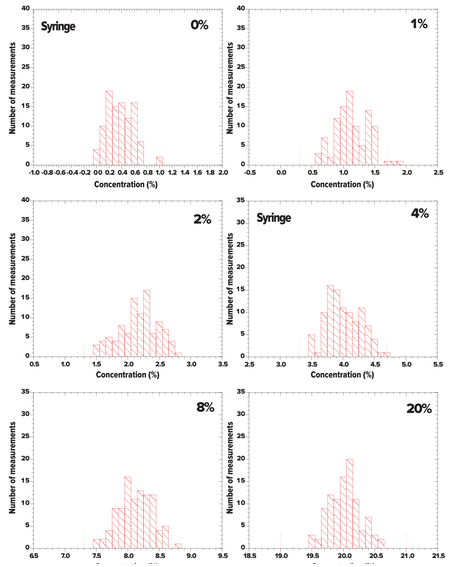
Headspace oxygen was measured using a Lighthouse FMS-760 Headspace Oxygen Analyzer.

The FMS-760 system measures the absorption of laser light by oxygen molecules in the container headspace. The absorption signal amplitude is dependent on the oxygen concentration. The laser absorption signal at varying oxygen concentrations is depicted below.



The laser measurement system (shown right) is comprised of a control unit and PC controller.

Validation data



Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value found using the method and the value that either is accepted as a conventional true value or is an accepted reference value. The table below shows a comparison of known oxygen to measured oxygen for N=100 measurements. The accuracy is stated as the absolute difference between the two.

ACTUAL	MEAN	ACCURACY
20	20.1	0.1
8.0	8.1	0.1
4.0	4.0	0.0
2.0	2.1	0.1
1.0	1.1	0.1
0.0	0.5	0.5

Precision

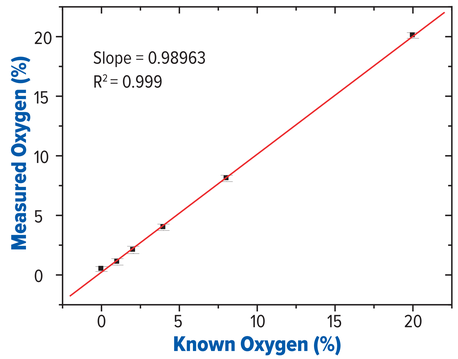
The precision of an analytical procedure expresses the closeness of agreement between a series of results obtained from the multiple sampling of the same homogeneous sample under the exact conditions required for performance of the method. This quantity is usually expressed in terms of the relative standard deviation measured during the multiple series of measurements. The table below presents the standard deviation and relative standard deviation for 100 separate measurements of each oxygen standard.

N= 100

MEAN	ST DEV	RSD
20.1	0.24	1.2
8.1	0.27	3.3
4.0	0.27	6.8
2.1	0.31	14.8
1.1	0.27	24.5
0.5	0.21	42.0

Linearity

The linearity of an analytical procedure is its ability to yield test results that are directly proportional to the concentration of an analyte in samples in a given range. Linearity is expressed in terms of the variance around the slope of the line (calculated using standard linear regression) from test results obtained via the analysis of samples containing varying concentrations of analyte.



Results

Accuracy: +/- 0.1%
Precision: +/- 0.25%

Linearity:
0.99 slope
0.999 linear correlation coefficient

Range of Measurement:
Present Study: 0 to 20%
Method Capability: 0 to 100%

Conclusion

The measurements demonstrate a novel method for non-destructive monitoring of oxygen in the headspace of pre-filled syringes. Validation of the FMS-760 system involves making a series of measurements on NIST traceable standards to assess performance including accuracy, precision, linearity and limit of detection. Among the many uses of these systems are leak detection of lyophilized product, process monitoring for oxygen sensitive liquid product, and container closure integrity studies.