# A Rapid and Nondestructive Method for Monitoring Oxygen in the Headspace of Parenteral Containers: Assessing Oxidative Degradation.

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## Introduction

Many of the active ingredients and excipients used to produce pharmaceuticals degrade in the presence of oxygen due to autoxidation processes. The initiation, chain propagation, and chain termination reactions are often multistep reactions with kinetics that have complicated dependencies on temperature, pH, light, and/or the presence of metal ion or other catalysts. Both the study of oxidative pathways and the study of a formulation's stability are necessary to set specifications for allowable levels of headspace oxygen. Although various methods to measure headspace oxygen concentrations exist, all of them are destructive in the sense that the container seals are broken, allowing only one measurement per sample. We evaluate a nondestructive method for monitoring oxygen trends in the headspace of 15cc vials. Three common antioxidants are used as model formulations: ascorbic acid, sodium ascorbate and sodium metabisulfite.

## Method

**Measurement Technique**

Heasdpace oxygen partial pressures were measured using a Lighthouse FMS-760 headspace oxygen analyzer.

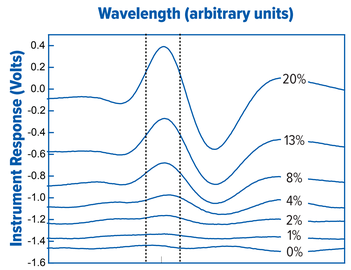
**Sample Set**

A total of 21 sample and standard vials were used in this study:
6 sodium ascorbate solution
6 ascorbic acid solution
1 sodium metabisulfite solution
2 control (water only)
6 oxygen concentration standards
Each solution contained 2g of antioxidant dissolved in 10cc of deionized distilled water.

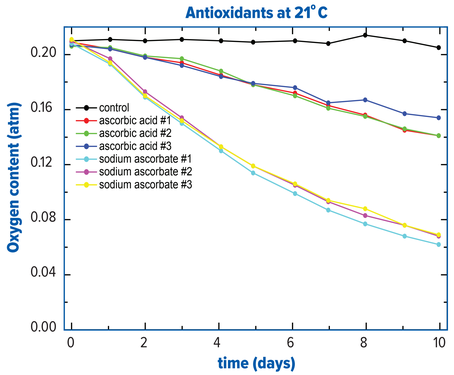
**Measurement Parameters**

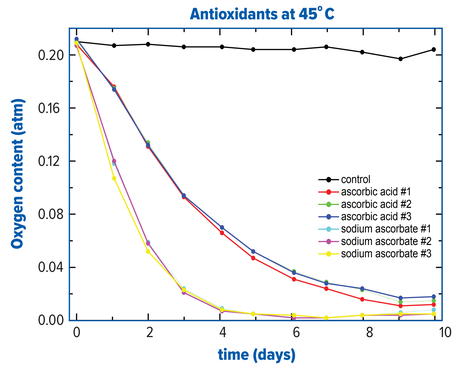
The headspace oxygen partial pressures of two sets of samples, one kept at room temperature and another at 45°C, were measured daily. As sodium metabisulfite auto-oxidizes more quickly, it was monitored continuously at room temperature for 15 hours.

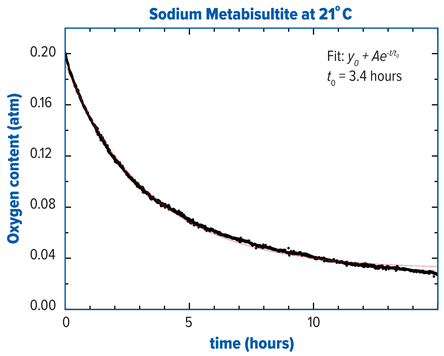
## Instrumentation

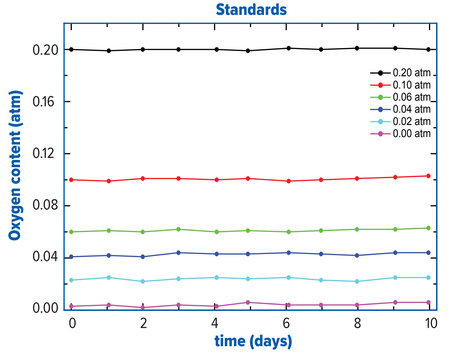




## Validation data




## Results

Our measured rates of oxygen consumption are:

| | |
|---|---|
| 0.04 day$^{-1}$ | ascorbic acid (21°C) |
| 0.11 day$^{-1}$ | sodium ascorbate (21°C) |
| 0.29 day$^{-1}$ | ascorbic acid (45°C) |
| 0.74 day$^{-1}$ | sodium ascorbate (45°C) |
| 7.00 day$^{-1}$ | sodium metabisulfite (21°C) |

These assume that oxygen is consumed at a single rate.

Qualitatively, one can notice that certain samples (e.g. sodium ascorbate #1 21°C) is consistently lower than the measurements from other vials of the same type. In a case where such deviation might be statistically significant, this information could be used by an investigator as reason to further scrutinize that particular vial.

The sodium metabisulfite data deviates slightly from exponential character, and is likely due to the details of the component initiation, chain propagation, and chain termination reactions.

## Conclusion

Frequency modulation absorption spectroscopy is useful in its ability to nondesctructively measure oxygen in the headspace of pharmaceutical vials. The ascorbate studies would have required 11 times the number of vials used in this study, as well as a larger number of oxygen standards, if any other technique were used. The sodium metabisulfite study would likely not be repeated with such high density of data points using a destructive technique, and would therefore not be able to show the deviation from exponential character. Nondestructive techniques such as FMS allow pharmaceutical formulators to better investigate product stability while reducing the amount of product that needs to be prepared and used. The time needed for analysis is also greatly reduced, increasing the efficiency of analytical activities.