Use of an Oxygen Extractor to Minimize Oxidation of Compounded Preparations

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Abstract

A number of drugs are sensitive to the presence of oxygen, resulting in oxidative degradation and a shortened shelf-life. This is usually minimized by either the addition of antioxidants to the formulation or the replacement of headspace air with an inert gas, such as nitrogen. A new alternative is presented and involves the use of an oxygen extractor.

The purpose of this study was to demonstrate the effectiveness of the device in removing oxygen from drug vials. Aqueous epinephrine solutions were prepared from deoxygenated water. Twenty milliliters of the solution was filled into vials to which caps were affixed; some caps contained the oxygen extractor and others did not. The oxygen content of the headspace was analyzed and the appearance of the solutions was observed over a period of up to 19 days.

The results showed that the vials with the oxygen extractor remained clear for the 19 days' duration with essentially no oxygen present; whereas the vials without the unit discolored within 24 hours, turning to black, oily films in 15 days. This technology may provide compounding pharmacists with a method of packaging oxygen-sensitive preparations with enhanced stability.

Introduction

No organic drug is insensitive to oxygen. However, many are oxidized at a sufficiently slow rate to be considered stable. Other drugs related to the family of catechols, benzamides, thiazines, tetracyclines, etc. are oxygen sensitive and have limited shelf-life. Shelf-life extension is afforded by addition of oxygen scavengers (antioxidants), which are basically more oxygen avid than the drug. More recently, preservation of these drugs also includes the improvement of drug-container closures and drug processing under an inert gas. However, in essence, antioxidants are also life limited and common processing practices still allow 1% to 3% of oxygen in the inert processing gas.

Some extremely oxygen-sensitive drugs, which are essentially oxygen intolerant, require elaborate processing conditions and equipment with a tolerance limit of 200 ppm of oxygen. It is needless to elaborate on the investment required to achieve such standards and on the need for oxygen-resistant storage containers for these drugs.

Background

The basic concept of this technology is to remove oxygen via an electrochemical process that consists of applying a voltage available from a hearing-aid battery, or a button cell, to an electrochemical cell; reducing oxygen available within the drug vial and releasing oxygen at a counterelectrode, thereby effectively transferring oxygen out of the vial. The practical considerations underlying the implementation of such a concept are to provide: (a) an economical solution to the prevention of oxidative degradation of drugs in vials, (b) an oxygen-free environment in vials without the need to change the vial configuration and geometry, and (c) a means for oxygen elimination by incorporating only minor modifications to the existing conventional vial elastomeric closures.

Table 1. Extractor Useful Life.

Battery Q-value (mAhour)	Extractor Life (years)	Battery Size, mm (Diameter/Height)
50 - 60	1	5.8/3.6
110 - 120	2	7.8/3.6
210 – 220	4	7.8/5.3

The oxygen extractor has only two components, namely, a commercial battery (button cell) selected for the specific purpose to be accomplished, generally 5.8 to 11.6 mm in diameter and 3.6 to 5.3 mm high; and an electrochemical cell, which is a membrane fitted with two electrodes, about 0.2 mm thick. Structurally, once assembled, these two components can be less than 10 mm in diameter and less than 6 mm in elevation. On standby, the extractor is inactive. It becomes activated by closing the circuit between the battery and the cell, which can be accomplished by a variety of mechanical means, at any time before, during or after vial closure.

The most important variable affecting the extractor performance is the battery storage capacity. It will be used to extract oxygen from the initial air headspace in the vial and to remove the oxygen diffusing back into the vial, mainly through the elastomeric closure (stopper).

Miniature commercial batteries (button cells) have an oxygen extraction capacity of 10 to 50 cc of oxygen. This capability is adequate to maintain oxygen-free environments for one to four years for most elastomeric closures used for drug vials.

Oxygen-concentration levels can be achieved and maintained below 200 ppm, representing a thousandfold concentration decrease over air-filled vials and a hundredfold decrease over inert-gas-processed vials.

Extractor Life Expectancy

The life in hours of the extractor, T, can be estimated from the following correlation:

$$T = (6/R)(Q-V)$$

where R is the rate (cc/hour) of oxygen diffusion from the ambient air into the vial; Q is the battery storage capacity, in mil-

Table 2. Extractor Operating Time Required for a Twentyfold Reduction in Oxygen Concentration.

Gas Phase Volume (cc)	Extractor Characteristic K	Time to Achieve 1% Oxygen from Air
12	50	3.2 hours
0.7	50	11.3 minutes
12	121	1.3 hours

Table 3. Appearance of Epinephrine Solutions, at 60°C, in Absence and Presence of the Oxygen Extractor.

Time (Hours)	Visual Appearance of the Reference Solution without Extractor	Visual Appearance of the Vial with the Oxygen Extractor	Measure Oxygen %
0	Clear	Clear	NM
16	Faint yellow	Clear	1.9
45	Light yellow	Clear	0.4
88	Light yellow/brown	Clear	<0.1*
135	Golden brown	Clear	<0.1*
184	Dark golden brown	Clear	<0.1*
280	Dark amber brown	Clear	<0.1*
425	Oily film appears	Clear	NM
456	Black with oil film	Clear	NM

NM = not measured
* The sensor is inaccurate below 0.1%

liamphours; and V is the initial gas-phase volume of the vial, cm^3. For example, if the closure value R is 0.03 cc/day of oxygen, and V = 15 cc, the extractor's useful life can be estimated, as reported in Table 1, which also includes the size of the commercial batteries available to perform the extraction task.

Theory

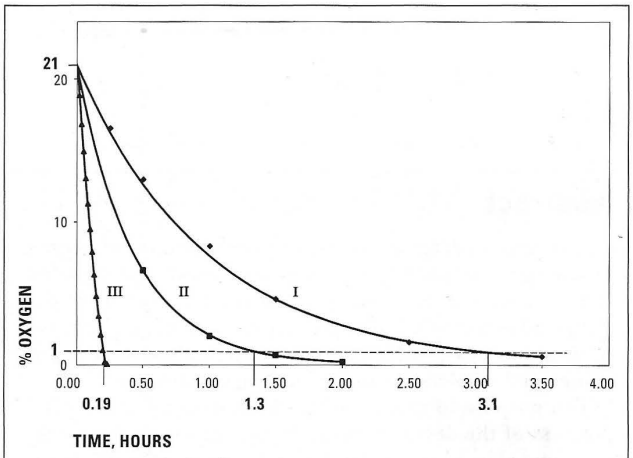
Since the rate of oxygen removal from the gas phase is proportional to the oxygen content, the oxygen pressure at any time t (hours) can be predicted from:

$$P_{O2} = P^{o}_{O2}\, e^{-kt} \qquad \text{Equation 1}$$

where P^{o}_{O2} is the original oxygen pressure in the vial and k is a system constant that depends on the initial gas volume, V cc, and a characteristic K of the extractor, such that k = K/V. The value of K depends principally on the active surface area of the extractor. Since the extractor current is also proportional to P_{O2}, the same type of relationship will hold for the battery current, namely:

$$I = I_o e^{-kt} \qquad \text{Equation 2}$$

where I_o is the initial extractor current for P^{o}_{O2}. These unique correlations suggest that measurements of the current become an indication of the level of oxygen depletion.



Conditions: I. Silver-oxide battery, model 76; V = 21 cc; K = 50
II. Silver-oxide battery, model 76: V = 21 cc; K = 212
III. Zn-Air battery, model 675; V = 0.71 cc; K = 50

Fig. 1. Extractor removing oxygen from containers.

Equations 1 and 2 are useful in predicting the time required to achieve a desired oxygen concentration level. For example, the time required to reduce the oxygen pressure from 0.21 to 0.01 atm, (or from 0.03 to 0.0015 atm) will be obtained from

$$t = (1/k)\ \text{Ln}\ 21 = 13.2\ (V/K), \text{ as illustrated in Table 2}$$

These calculated values compare favorably with the experimental results presented in Fig. 1.

Experiment

All experiments were conducted with an extractor assembly consisting of an electrochemical cell and a small battery. Electrical connections were made via a series-resistor placed between the battery anode and the electrochemical cell cathode. The extractor was attached to chambers sealed from the environment. In some instances, an oxygen sensor, (Microelectrodes, Inc., Bedford, NH) amperometric oxygen probe, model MI 730, and oxygen meter model OM-4 were placed in the gas chamber. The sensor is only accurate for oxygen concentrations above 0.1%. This experimental setup could be used to monitor battery current and oxygen concentration, simultaneously.

Experiments I and II of the figure were performed with a silver-oxide button cell, model 76 (11.6-mm diameter/5.35-mm height), with the same gas-phase volume, V = 21 cc, but different characteristics, K, of the extractor. Experiment III was performed with a model 675 zinc-air battery (11.6-mm diameter/5.35-mm height).

The oxygen concentration decreases predictably. Below 0.1%, the current progressively decreases to a "mainte-nance" current corresponding to the rate of diffusion of ambient oxygen into the chamber or vial. For a diffusion rate of 0.03 cc/day, the maintenance current is approximately 5 µA.

Oxygen Extraction from Drug Vials

Prototype extractors were used to determine their effectiveness in preventing oxidative degradation of epinephrine, which is known to be sensitive to oxygen. The rate of degradation was accentuated by using concentrated aqueous solutions (1:1250) at elevated temperature (60°C), in absence of any retardation agents, antioxidants or stabilizers. Epinephrine (as a bitartrate) solutions were prepared by using deoxygenated water and the system was assembled under a blanket of nitrogen. The 38-mL glass vials were filled with 20 mL of the solution, adjusted to a pH of 4. In the experiment reported in Table 3, the extractor included an oxygen probe, described previously.

Results

The reference solutions, without extractors, displayed a coloration within 24 hours, turning to black, oily films in 15 days; whereas the vial fitted with the extractor remained clear throughout the test duration, namely, 19 days. These stability results were confirmed by researchers at the University of Tennessee by measuring the epinephrine concentration over a period of 24 days.[1]

Conclusion

This technology allows removal of oxygen and maintenance of an essentially oxygen-free environment in containers, and is suitable for drug vials or any other application requiring the creation and maintenance of anaerobic environments. It can be applied to contained solids, liquids or solutions, including a variety of oxygen-sensitive products, such as cosmetics, food and beverages, chemicals, etc.

References

1. Wood G, Aksorntoae N, Thoma L. Evaluation of an oxygen extraction device in slowing epinephrine degradation. Presented at the Parenteral Drug Association Annual Meeting, Washington, DC, Fall 1998. ■

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