Antioxidant Use in POLYOX™ ER Matrices

APPLICATIONS DATA SUMMARY

- To improve stability of POLYOX™ water soluble resins butylated hydroxytoluene (BHT) is used as an antioxidant.
- POLYOX™ polymers intended for pharmaceutical use contain about 300-500 ppm (0.03-0.05% w/w) of BHT.
- It is recommended to add approximately 100-1000 ppm (0.01-0.10%) of BHT to the POLYOX™ tablet formulation.

STABILITY OF POLYOX™ POLYMERS

Polyethylene oxide (PEO) polymers, available commercially under the trade name of POLYOX™ water soluble resins (WSR), are novel materials with unique properties. They have found a number of uses in pharmaceutical applications, such as extended release (ER) matrices\(^1\), osmotic pumps, mucosal bio-adhesives, melt extrusion and gastro-retentive dosage forms.

POLYOX™ polymers are free flowing white crystalline powders with an average particle size of approximately 150 μm. They are non-ionic, highly swelling, thermoplastic and soluble in water and selected organic solvents.

POLYOX™ polymers are prone to degradation that occurs due to oxidation, leading to chain cleavage and reduction of viscosity during storage. Accordingly all POLYOX™ polymers intended for pharmaceutical use contain 300-500 ppm butylated hydroxyl toluene (BHT) as an antioxidant. The mechanism of PEO degradation is quite similar to that of hydrocarbon chains, but the presence of oxygen in the molecules strongly activates the process by increasing the labile nature of protons on α-carbon atoms.\(^3\)

Aliphatic ethers can react with oxidizing agents, such as oxygen and hydrogen peroxide to form hydroperoxides. These peroxides can further decompose in a variety of ways and result in chain scission. Polyethylene oxides are susceptible to degradation through similar oxidative intermediates.
Several auto-oxidative mechanisms of PEO degradation has been mentioned in the literature. The main mechanism is pyrolysis seen at higher temperatures that leads to a dramatic decrease in the molecular weight, and therefore, reduction of polymer effectiveness in extended release applications.\textsuperscript{3-10} The decomposition of PEO can be catalyzed by several metal ions, such as ferrous, cuprous, cupric and silver. Typically, lower valent ions are more effective catalysts.

High temperature speeds up the auto-oxidation of PEO and can impact POLYOX™ stability. The thermal oxidation of PEO is highly dependent on polymer molecular weight. The higher molecular weight POLYOX™ degrades more rapidly than the lower molecular weight polymer.\textsuperscript{11}

Degradation can be limited by the addition of antioxidants, removal of oxygen and other methods. One approach to improve polymer stability is to apply an oxygen barrier film coat onto the final dosage form.

**ANTIOXIDANTS**

The most widely used antioxidants can be classified broadly as chain terminators\textsuperscript{10} as they prevent or slow down chain initiation and propagation of free radical formation. Chain terminators are molecules, which form weak bonds to hydrogen atoms, such that they are attacked in the propagation steps. Importantly, however, they form stable radicals, which do not propagate chains. Such species include thiols, which donate a hydrogen atom and dimerize to form disulfides; and phenols, which donate a hydrogen atom followed by further oxidation to enones.

There are three main classes of antioxidants:\textsuperscript{12, 13}

1. Free radical scavengers: phenols [BHT, butylated hydroxyanisole (BHA), vitamin E, propyl gallate]
2. Reducing agents or oxygen scavengers (L-ascorbic acid)
3. Chelating agents [edetic acid (EDTA), citric acid, malic acid, fumaric acid]. Metal chelators function by forming complexes with, and sequestering, transition metal ions such as Cu\textsuperscript{2+} and Fe\textsuperscript{3+}, which catalyze oxidation.\textsuperscript{12}

Antioxidants are effective at very low concentrations.\textsuperscript{14} In solid dosage forms, an antioxidant is expected to function optimally when in intimate contact with the drug and/or reactive excipients to disrupt the chain process.\textsuperscript{10}

For PEO ER matrices, various antioxidants have been tested, e.g. EDTA, propyl gallate, BHA, ferrous sulfate, BHT, ascorbic acid.\textsuperscript{12, 13} The least degradation was observed in the presence of BHT or ascorbic acid.

Properties of commonly used antioxidants are summarized in Table 1.\textsuperscript{10, 14-17}

\textsuperscript{3-10}
Table 1. The Most Commonly Used Antioxidants in Pharmaceutical Dosage Forms

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>Solubility in water (mg/mL)</th>
<th>Solubility in alcohol (mg/mL)</th>
<th>Usage concentration (% w/w)</th>
<th>Sensitivity</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHT</td>
<td>Insoluble</td>
<td>Freely soluble</td>
<td>0.005 - 0.020</td>
<td>Light, heat, humidity; can turn yellow</td>
<td>H-atom donor</td>
</tr>
<tr>
<td>BHA</td>
<td>Insoluble</td>
<td>Freely soluble</td>
<td>0.005 - 0.020</td>
<td>Light, especially with metals</td>
<td>H-atom donor</td>
</tr>
<tr>
<td>Ascorbic acid (Vitamin C)</td>
<td>333</td>
<td>20</td>
<td>0.020 - 0.500</td>
<td>Light; discolours on oxidation; can increase the rate of metal-catalyzed oxidation</td>
<td>reducing agent</td>
</tr>
<tr>
<td>Alpha tocopherol (Vitamin E)</td>
<td>Insoluble</td>
<td>Freely soluble</td>
<td>0.050 - 0.075</td>
<td>Light, heat, alkali, Fe, Ag; β, γ, δ better as an antioxidant than α</td>
<td>H-atom donor</td>
</tr>
<tr>
<td>EDTA</td>
<td>2</td>
<td>Insoluble</td>
<td>0.005 - 0.100</td>
<td>Unstable above 150°C</td>
<td>Chelator</td>
</tr>
<tr>
<td>Propyl gallate</td>
<td>1</td>
<td>333</td>
<td>0.050 - 0.100</td>
<td>Light; darkens with Fe</td>
<td>H-atom donor</td>
</tr>
</tbody>
</table>

The most popular antioxidants used with POLYOX are BHT and Vitamin E.

**Butylated Hydroxytoluene**

BHT (C_{15}H_{24}O) is a white crystalline powder with 220.34 molecular weight; 71°C melting point. Figure 1 shows the chemical structure of BHT.

*Figure 1. Chemical Structure of BHT*

![Chemical Structure of BHT](image)

BHT is a lipophilic (fat soluble), water-insoluble organic compound that is primarily used as an antioxidant food additive (E321), as well as in pharmaceutical and cosmetic applications.

BHT can be sourced from Merisol (Antioxidants LLC, USA), Rhein Chemie (Germany) and other companies. For optimal dispersion and efficacy, it is generally recommended to use micronized BHT.

While POLYOX™ polymers intended for pharmaceutical use contain about 300-500 ppm (0.03-0.05% w/w) of BHT, it is also recommended to add approximately 100-1000 ppm (0.01-0.10%) of BHT to the POLYOX™ tablet formulation.
As BHT is a volatile material (vapour pressure at 20°C = 1.33 Pa and at 100°C = 266.6 Pa), pharmaceutical processing with heating (above 60°C temperatures) such as fluid bed granulation may cause it to sublime. Addition of BHT to the product after fluid bed processing will remedy this problem and can be accomplished by dry blending the antioxidant into the final granulation during lubricant addition.

**Vitamin E**

An alternative antioxidant to BHT that can be used in POLYOX™ tablet formulations is vitamin E.

Vitamin E BHT (C_{29}H_{50}O_{2}) is available either as a practically odourless, clear colourless or yellow viscous oil. It is practically insoluble in water; freely soluble in acetone, ethanol, ether and vegetable oils.

Most commercially available products are used as a source of vitamin E, rather than as an antioxidant in pharmaceutical formulations. Individual manufacturers should be consulted for specific information on their products.

Vitamin E can be added to POLYOX™ formulations as an oxidative stabilizer at approximately 500 - 1000 ppm (0.05-0.10% w/w). To achieve uniform mixing of vitamin E into the polymer powder, the antioxidant should be dissolved in a small amount of isopropyl alcohol, before mixing it with the POLYOX™.
REFERENCES


Physicians’ Desk Reference, 2000, 54TH EDITION, Medical Economics Company Montvale, NJ, U.S.A.

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