SENTRY™ POLYOX™ Water Soluble Resins
Technical Information on Stability

Introduction
SENTRY™ POLYOX™ WSR resins consist of a family of high molecular weight polyethers with nominal molecular weights ranging from 100,000 to 7,000,000. These materials have many uses in the pharmaceutical industry, for example, in osmotic pump technology, hydrophilic matrix systems, abuse deterrence, gastroretentive systems, mucoadhesives, and hot melt extrusion formulations. In many of these applications, the properties that SENTRY™ POLYOX™ WSR polymers impart are dependent upon their molecular weights. Therefore, maintaining the proper molecular weight is important for prolonging the utility of the polymer. Polyethers can undergo chain cleavage via autooxidation, thus reducing the molecular weight of the polymer. The rate of autooxidation is affected by many environmental conditions, including temperature and humidity. Therefore, storage handling and stability are important considerations when using SENTRY™ POLYOX™ WSR polymers. The rate of autooxidation of the loose powder can be minimized through the addition of antioxidants and by controlling storage conditions.

Key Points
• BHT (butylated hydroxytoluene) and Vitamin E efficiently stabilize SENTRY™ POLYOX™ WSR powders. BHT is currently added into every premium grade that Dow manufactures.
• The stability of SENTRY™ POLYOX™ WSR grades is greatly improved by minimizing long term exposure of the polymer to high temperature, moisture, and oxygen.
• SENTRY™ POLYOX™ WSR in tablet form is more stable than SENTRY™ POLYOX™ WSR in powder form. Depending on the active ingredient type and/or formulation requirements, controlling the antioxidant concentration in the final formulation may improve tablet stability.

Antioxidants
Antioxidants can effectively terminate the free radicals generated during autooxidation and thereby reduce the rate of molecular weight loss. All SENTRY™ POLYOX™ WSR NF grades are supplied with a typical range of BHT content from 100 to 500 ppm (50 to 250 ppm for SENTRY™ POLYOX™ WSR N10 and N80 NF products), which is a safe and effective level of antioxidant for polyethers. Figure 1 shows the percent viscosity retained versus storage time for SENTRY™ POLYOX™ WSR 303 NF samples stored at ambient storage conditions. Solution viscosity is directly related to polymer molecular weight. The samples contain BHT at zero and 500 ppm, respectively. Note the significant improvement in polymer stability for the BHT-containing sample.

Figure 1: Effectiveness of BHT as Stabilizer For POLYOX WSR
Storage Temperature and Humidity

The rate of polyether autooxidation is a strong function of temperature and moisture. When powder material is stored at 25 °C and 60% relative humidity (RH), SENTRY™ POLYOX™ WSR N60K NF showed 87% viscosity retention in 18 months. This value decreased to 80% retention when the same batch of material was stored at 40 °C and 75% RH (Figure 2).

Many studies have shown that increases in temperature accelerate the autooxidation of SENTRY™ POLYOX™ WSR resins, but few point out the role humidity/moisture play. It was further identified that increases in relative humidity also accelerate SENTRY™ POLYOX™ WSR viscosity loss over time. The viscosity of SENTRY™ POLYOX™ WSR 303 NF was stable in storage conditions up to 60% RH (all at 25 °C) for 42 days. However, when stored in 75% RH conditions, it lost about 13% of its original viscosity (Figure 3).

Molecular Weight Effects

Polymer molecular weight (MW) also impacts the viscosity loss as a function of storage time (Figure 4). The number of chain cleavages taking place per unit time is independent of polymer molecular weight. However, each chain cleavage has a larger impact on the measured viscosity for a high molecular weight polymer than found for a low molecular weight grade.
In pharmaceutical applications, the polymer viscosity controls the drug release rate. In this case, it is important to realize that BHT is a volatile antioxidant and some pharmaceutical processing steps may cause BHT to sublime during processing. This is particularly true when using fluid bed techniques to process formulations containing SENTRY™ POLYOX™ WSR. Addition of BHT to the product after fluid bed processing will remedy this problem and can be accomplished by dry blending micronized BHT into the final granulation during lubricant addition.

Once formed into a compact, SENTRY™ POLYOX™ WSR polymers are stable under ambient storaged conditions as demonstrated by internal and external study results. For example, an internal study evaluated the change in Theophylline release profiles as a function of ambient storage time. The tablets were formed under direct compression conditions and have the following composition:

- 20% Theophylline
- 30% SENTRY™ POLYOX™ WSR Coagulant grade (MW ~ 5,000,000 daltons)
- 49.5% Avicel PH 102
- 0.5% Magnesium Stearate

After 2 years of ambient storage, the average release profile (n=6) remains the same as the initial release profile (Figure 5).

The same batch of tablets were subjected to accelerated storage conditions (40 °C, 75% RH) for up to 6 months. Release profiles for tablets stored in accelerated conditions for 1 and 3 months were comparable to the release profile of tablets at time zero (Figure 6). An increase in Theophylline release rate was observed after 6 months accelerated storage, suggesting a slight decrease in the molecular weight of the SENTRY™ POLYOX™ WSR Coagulant NF resin. Since temperature has a significant effect on the autooxidation rate of polyethers, accelerated storage conditions are expected to affect the stability of the tablets more than ambient conditions.
Effects of Filler on Tablet Stability

The choice of filler is critical to the stability of a tablet containing SENTRY™ POLYOX™ WSR. The study below looked at the effects of filler on stability of POLYOX™ WSR 301 tablets formulated with Theophylline:

- 15% Theophylline
- 40% SENTRY™ POLYOX™ WSR 301 (MW ~ 4,000,000 Daltons)
- 44.5% Filler
- 0.5% Magnesium Stearate

The tablets were stored under accelerated conditions (40°C, 75% RH) for up to 3 months. Each month, samples of each formulation were run through dissolution testing. The data below demonstrate that the release rate of Theophylline from SENTRY™ POLYOX™ WSR 301 tablets increase over the storage time when certain sugars, like lactose (Figure 7) and mannitol (Figure 8), were used as fillers. There was no difference in release over time when dibasic calcium phosphate (Figure 9), microcrystalline cellulose (Figure 10) and Starch 1500 (Error! Reference source not found.) were used as fillers.
**Recommendations**

**Bulk Polymer**
- Refrigerated storage is recommended to prolong the life of POLYOX™. Re-test recommendations are based on ambient storage conditions, but keeping the product cool and dry has shown to decrease degradation rates.
- If stored for prolonged periods, retest product viscosity prior to use.

**Tablets**
Stability of SENTRY™ POLYOX™ WSR in tablet form is typically not a concern. If problems are seen:
- Ensure formulations are free of certain fillers, including lactose and mannitol, which may cause SENTRY™ POLYOX™ WSR instability.
- Ensure that adequate antioxidant concentration is present in the final product prior to tableting. Certain processing operations will reduce the BHT concentration in the final product more than other operations.
- Utilize product packaging or a tablet coating to minimize oxygen migration into the tablet if required.

<table>
<thead>
<tr>
<th>POLYOX® Water-Soluble Resins, NF Grade</th>
<th>Approximate Molecular Weight</th>
<th>5% Solution</th>
<th>Viscosity Range at 25°C, cP 2% Solution</th>
<th>1% Solution</th>
<th>Brookfield Viscometer, Model RVF, Spindle No./Speed, rpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSR N-10 NF</td>
<td>100,000</td>
<td>30-50</td>
<td></td>
<td>1/50(1)</td>
<td></td>
</tr>
<tr>
<td>WSR N-90 NF</td>
<td>200,000</td>
<td>55-90</td>
<td></td>
<td>1/50(1)</td>
<td></td>
</tr>
<tr>
<td>WSR N-750 NF</td>
<td>300,000</td>
<td>600-1,200</td>
<td></td>
<td>1/10</td>
<td></td>
</tr>
<tr>
<td>WSR 205 NF</td>
<td>600,000</td>
<td>4,500-8,500</td>
<td></td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>WSR 110 NF</td>
<td>800,000</td>
<td>8,800-17,500</td>
<td></td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>WSR N-12K NF</td>
<td>1,000,000</td>
<td>400-800</td>
<td></td>
<td>1/10</td>
<td></td>
</tr>
<tr>
<td>WSR N-80K NF</td>
<td>2,000,000</td>
<td>2,000-4,000</td>
<td></td>
<td>3/10</td>
<td></td>
</tr>
<tr>
<td>WSR 301 NF</td>
<td>4,000,000</td>
<td>1,600-5,500</td>
<td></td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>WSR Coagulant NF</td>
<td>5,000,000</td>
<td>5,600-7,500</td>
<td></td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>WSR 303 NF</td>
<td>7,000,000</td>
<td>7,500-10,000</td>
<td></td>
<td>2/2</td>
<td></td>
</tr>
</tbody>
</table>

Notice: No freedom from any patent owned by seller or others is to be inferred. Because use conditions and applicable laws may differ from one location to another and may change with time, Customer is responsible for determining whether products and the information in this document are appropriate for Customer’s use and for ensuring that Customer’s workplace and disposal practices are in compliance with applicable laws and other governmental enactments. Seller assumes no obligation or liability for the information in this document. NO WARRANTIES ARE GIVEN; ALL IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE ARE EXPRESSLY EXCLUDED.

---