POLYOX Water-Soluble Resins NF
in Pharmaceutical Applications
An Introduction to POLYOX
Water-Soluble Resins

POLYOX™ Water-Soluble Resins, NF Grade are nonionic poly(ethylene oxide) polymers that meet all the specifications of the United States Pharmacopoeia—National Formulary. They are white, free-flowing hydrophilic powders supplied in a wide variety of molecular weight grades, ranging from one hundred thousand to seven million daltons or amu. They are essentially tasteless, colorless, nonionic, and non-caloric. This unusual combination of properties makes them useful in a surprisingly broad array of pharmaceutical formulations. They have a long history of successful applications in uses such as controlled release solid dose matrix systems, transdermal drug delivery systems, and mucosal bioadhesives.

Extremely Fast Hydration and Gel Formation
POLYOX Resins are among the fastest-hydrating water-soluble polymers used in pharmaceutical systems. They very quickly form hydrogels that initiate and regulate release of active ingredients. Systems using POLYOX Resins are often superior to others in approaching zero order release models.

Unusually Wide Range of Molecular Weights
With molecular weights ranging from 100,000 to 7,000,000, POLYOX Water-Soluble Resins offer exceptional formulating latitude. You can select from many different options to help control dosage size, matrix release profiles, and production methods while maintaining consistent flow properties and tablet performance.

Compliance With FDA and Other Regulatory Requirements
POLYOX Water-Soluble Resins, NF Grade comply with the USP polyethylene oxide NF monograph. These products meet the requirements of the Food Chemicals Codex, the International Codex Alimentarius, and the U.S. National Formulary (NF). These products have also been approved in drug products sold in all major European countries. Approval for use in Japan is under way and anticipated. The NF product family is listed in Table 1.
More Technical Assets to Help You Succeed Quickly

With an expanded technical staff and assets of The Dow Chemical Company, we can offer an unusually broad and synergistic body of excipient knowledge. Our strong team of technical individuals in several global locations is actively engaged in product development, technology development, and pharmaceutical applications support. So when you need help with technical issues involving excipient behavior, product selection, and formulation optimization, we can respond in surprisingly powerful ways.

Table 1 — POLYOX Water-Soluble Resins For Pharmaceutical Applications

<table>
<thead>
<tr>
<th>POLYOX Water-Soluble Resins, NF Grade</th>
<th>Approximate Molecular Weight</th>
<th>Viscosity Range at 25°C, cP</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>1/50</td>
</tr>
<tr>
<td>WSR N-40 NF</td>
<td>200,000</td>
<td>55 – 90</td>
<td>1/50</td>
</tr>
<tr>
<td>WSR N-750 NF</td>
<td>300,000</td>
<td>600 – 1,200</td>
<td>1/10</td>
</tr>
<tr>
<td>WSR-205 NF</td>
<td>600,000</td>
<td>4,500 – 8,800</td>
<td>2/2</td>
</tr>
<tr>
<td>WSR-1105 NF</td>
<td>900,000</td>
<td>8,800 – 17,600</td>
<td>2/2</td>
</tr>
<tr>
<td>WSR N-12K NF</td>
<td>1,000,000</td>
<td>400 – 800</td>
<td>1/10</td>
</tr>
<tr>
<td>WSR N-40K NF</td>
<td>2,000,000</td>
<td>2,000 – 4,000</td>
<td>3/10</td>
</tr>
<tr>
<td>WSR-301 NF</td>
<td>4,000,000</td>
<td>1,650 – 5,500</td>
<td>2/2</td>
</tr>
<tr>
<td>WSR Coagulant NF</td>
<td>5,000,000</td>
<td>5,500 – 7,500</td>
<td>2/2</td>
</tr>
<tr>
<td>WSR-303 NF</td>
<td>7,000,000</td>
<td>7,500 – 10,000</td>
<td>2/2</td>
</tr>
</tbody>
</table>

The physical property data listed are considered to be typical properties, not specifications.

(1) Model RVT.
A hydrophilic matrix tablet is a simple-to-formulate, yet effective sustained-release drug-delivery system in which a bio-active is uniformly distributed within a polymer matrix. The drug release mechanism is controlled by several variables in a dynamic process. Upon wetting of the tablet, the polymer on the tablet surface hydrates to form a gel layer. The drug diffuses from this surface gel layer, which expands with time into the interior of the tablet, allowing diffusion of the drug from the tablet core.

POLYOX Water-Soluble Resins are very hydrophilic polymers. They hydrate rapidly to form a gel layer on the tablet surface for the release of actives. Because POLYOX Resins are non-ionic, no interaction between drug and polymers is to be expected. The data presented here show how molecular weight and concentration of POLYOX Resins affect the release rate of a model water-soluble and water-insoluble drug in a matrix system.

**Experimental Procedure**

Tablet formulations (Table 2) were dry-blended in a double planetary mixer. Tablets were pressed with a single punch Carver Laboratory Press in a one-half inch diameter die with a compression force of one metric ton. Drug release data were obtained from uncoated tablets in a USP-specified dissolution apparatus, which was equipped with baskets. The dissolution medium was simulated gastric fluid (without pepsin) at 37°C. Rotation speed of the baskets was kept at 50 rpm. All data presented here represent an average of a minimum of three determinations. UV/visible spectroscopy was used to determine the concentration of the actives in the dissolution media.

**Results**

**Molecular Weight**

Figure 1 shows the effect of molecular weights of POLYOX Water-Soluble Resins on the release rate. Increasing the molecular weight while maintaining a constant polymer concentration can drastically reduce the release rates. The increased molecular weight leads to an increase in gel strength, which tends to decrease the diffusion of the drug; however, there is a maximum molecular weight beyond which no further change in release rate is affected. As can be seen, an increase in molecular weight from 5,000,000 to 7,000,000 does not appreciably alter the release rate for the water-soluble active, caffeine.

![Figure 1 — Effect of Molecular Weight of POLYOX Water-Soluble Resins on In Vitro Release Rate of Caffeine From a Matrix Tablet](image)

**Table 2 — Tablet Formulations**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>POLYOX Water-Soluble Resin NF</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>60</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Lactose</td>
<td>69</td>
<td>59</td>
<td>49</td>
<td>69</td>
<td>19</td>
<td>84</td>
<td>59</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

An Ideal Choice for Controlled Release Systems
Polymer Concentration

Figure 2 illustrates the effect of polymer concentration on release rate. Increasing polymer concentration increases the gel viscosity on the surface of the tablets, which will retard the diffusion of the drug from the gel layer. Increasing the concentration from 20 to 60 percent of a relatively low molecular weight POLYOX Water-Soluble Resin results in a drug release profile very similar to that obtained from 20 percent of a high molecular weight POLYOX Resin. However, this concentration effect is seen only for low molecular weight polymer. Figure 3 shows caffeine release from matrix tablets produced from POLYOX WSR-303 NF (7,000,000 molecular weight). When polymer concentration was changed from 10 to 60 percent in the formulation, no drastic changes in the release rate was observed. At a very low polymer concentration, the initial drug release is larger, but the rate of release is very similar to that obtained for higher polymer concentrations.
**Drug Loading**

Figure 4 summarizes matrix tablet release data obtained by changing the drug concentration of caffeine in POLYOX Water-Soluble Resins. Since diffusion is the primary kinetic factor in the release of water-soluble actives from matrix tablets, data were plotted using a Higuchi plot format to illustrate this point better. As can be seen, the lines are almost parallel, showing that very little change in the release rate takes place when the caffeine concentration is increased from 50 to 150 mg in 500-mg tablets.

**Drug Solubility**

Release of insoluble actives from hydrophilic matrix systems occurs through a diffusion-erosion mechanism. POLYOX Water-Soluble Resins swell greatly when hydrated, and the resulting gel layer does not erode readily. The polymer, therefore, is an ideal vehicle for insoluble drugs in matrix tablets. Figure 5 illustrates how drug-delivery profiles of water-insoluble actives can be manipulated with polymer and drug concentration in POLYOX Resin matrix tablets.
Figure 6 — Particle Size Effect on Riboflavin Release From Matrix Tablets Using POLYOX Water-Soluble Resins

Particle Size

Particle size can play a role in matrix tablet performance by influencing the initial rate of hydration and gel layer formation. The data in Figure 6 were generated by selectively separating a standard POLYOX WSR sample into 5 different particle size fractions. Tablets were produced from each fraction and drug release rates were measured. The data indicate some variation in release rate as a function of particle size with the smaller particles producing slower initial release rates. Interestingly, extreme drug dumping is not seen even when using the very large particle size fraction due to the rapid swelling characteristics of POLYOX WSR.

Figure 7 — Effect of pH on Release of Theophylline From Matrix Tablets Using POLYOX Water-Soluble Resins

pH

When used in oral applications, POLYOX WSR systems do not show a strong pH response due to their nonionic nature. The data in Figure 7 show release profiles collected at different pH values for a theophylline matrix system. As expected, the release rate does not vary as a function of pH.

Conclusions

POLYOX Water-Soluble Resins NF are highly versatile water-soluble polymers. Upon exposure to water or gastric juices, they hydrate and swell rapidly to form hydrogels with properties ideally suited for a controlled drug-delivery vehicle. Their utility is not limited to the hydrophilic matrix system that is the subject of this discussion. POLYOX Water-Soluble Resins NF have been successfully used in other drug-delivery systems, such as osmotic pumps. The polymers are available in a wide range of molecular weights, which enables the formulator to readily custom design to individual specifications.
Water Granulation With POLYOX Water-Soluble Resins NF

As environmental and manufacturing concerns limit the use of organic solvents as granulating liquids, water is increasingly preferred as a granulating solvent. The following study explores the performance of POLYOX Water-Soluble Resins in water granulation. This work indicates that POLYOX Resins can offer several important features in water granulation, including:

● Ability to be water granulated in a high shear unit.
● In addition to acting as a hydrophilic matrix or swelling agent, ability to also act as binders during granulation, eliminating the need for special binders.
● Readily release water during drying, leading to short drying times.

Experimental Parameters

Granulator
High Shear Granulator equipped with chopper and impeller
Chopper Speed ....................3045 rpm
Impeller Speed ................... 450 rpm

Fluid Bed Dryer
Inlet Temperature ..................60°C
Outlet Temperature ..............40°C
Air Volume............................280 CFM
Drying Time..........................15 – 45 minutes

Processing Variables
Water Concentration
Water Addition Rate
Polymer Molecular Weight

Responses
Mean Particle Size
Granule Friability
Granule Morphology

Results

The initial set of experiments was carried out using 100% POLYOX Water-Soluble Resin. This enabled evaluation of the polymer under various process conditions and is relevant to formulations containing high polymer and low drug loadings.

Figure 8 shows the median particle size developed as a function of water addition rate and concentration. The data indicate that particle size is inversely related to the water addition rate. Because no wet mashing was used in this study, rapid water addition limits the time for particle growth, leading to a smaller median particle size. The median particle size was found to be directly related to the final water concentration used in the granulation. Ten percent water was found to be sufficient for many granulations.

In Figure 8 the purple data points represent 200,000 molecular weight polymer while the blue data points represent 4,000,000 molecular weight polymer. The polymer molecular weight did not have a significant impact on particle growth, as seen for the runs consisting of 10% water and an addition rate of 60 mL/min.

Figure 8 — Median Particle Size
The granules could be dried in the fluid bed to less than one percent moisture in about 15 minutes. Because no binder was added to the granulating liquid, additional work was performed to test the susceptibility of the dried granules to attrition. Because aggressive fluidization is known to cause attrition of friable granules, granules dried to less than one percent moisture were mixed in the fluid bed for an additional 45 minutes. No significant attrition was detected, indicating the product will withstand normal handling.

Examination of the final granules by SEM indicates that the agglomeration leads to polymer bridging between particles as seen in Figure 9. The high molecular weight of POLYOX Resins would be expected to provide good granule strength.

In order to compare granulation prepared via water and ethanol routes, a set of equivalent granulations was produced by these two approaches. The release profiles for the two tableted products are presented in Figure 10. Drug release from the water granulation is very similar to that seen for the ethanol granulation.

Conclusions

- POLYOX Water-Soluble Resins can be granulated using 100% water.
- The average particle size is dependent on the rate of water addition.
- POLYOX Resins are effective binders.
- Drug release from a water granulation is very similar to that of an alcohol granulation.
Beyond their role in controlled release matrix systems, POLYOX Water-Soluble Resins perform other valuable functions in pharmaceuticals. Often, a single POLYOX Resin can contribute several important properties in a single system.

**Direct Compression Tablet Binding**

POLYOX Resins perform well as binders in economical direct compression systems. They often provide better flow and compaction properties than other binders. And their lubricity also assists tableting operations. This provides a system where a single excipient can provide both binding and rate-controlling properties.

**Mucosal Bioadhesives**

POLYOX Water-Soluble Resins offer a number of important properties for mucoadhesion—water solubility, hydrophilicity, high molecular weight, hydrogen bonding functionality, and good biocompatibility. These resins have a long linear chain structure which allows them to form a strong interpenetrating network with mucus. Data indicate that molecular weights of 4,000,000 and higher have the highest level of adhesion.

**Using POLYOX Water-Soluble Resins NF in Controlled-Release Dosages by Melt Extrusion**

POLYOX Water-Soluble Resins are thermoplastic polymers with a low melting point of ~68°C. They can be used in melt extrusion processes to prepare pharmaceutical dosage forms. During a melt extrusion process, a mixture of POLYOX Resin, drugs, and optional fillers or plasticizers is fed into an extruder. The POLYOX Resin and other low melting point components are melted inside the extruder, and the molten mixture is extruded through a die mounted at the front of the device. The extrudate can be further processed into familiar shapes of tablets, caplets, or pellets.
A twin screw extruder allows low temperature extrusion of both low and high molecular weight POLYOX Resins. A small amount of vitamin E is often added to the mixture as an antioxidant to stabilize the solid dosage form. Various plasticizers such as water and glycerin can be added to reduce the melt viscosity. Solid and liquid ingredients can be added separately to the extruder and mixed in situ during the extrusion process.

As an example of a pharmaceutical solid dosage form produced by a melt extrusion process, three different grades of POLYOX Resin with high, medium, and low molecular weights were used to prepare tablets containing riboflavin. The POLYOX Resin powder was pre-mixed with riboflavin and vitamin E in a blender. The mixture was then fed into a twin screw extruder fitted with a rod die. By using different grades of POLYOX Resin and adding different amounts of microcrystalline cellulose, the tablets cut from extruded rods achieved sustained-release profiles ranging from 3 h to 24 h by in vitro dissolution tests using USP Method II at 37°C and 100 rpm in 900 mL distilled water (Figure 11).
For more information, complete literature, and product samples, you can reach a Dow representative at the following numbers:

From the United States and Canada:
call 1-800-447-4369
fax 1-989-832-1465

In Europe:
toll-free +800 3 694 6367
Phone: 32-3-450-2240
Fax: 32-3-450-2815

In Latin America:
Phone: 55-11-5188-9222
Fax: 55-11-5188-9749

In the Pacific:
Phone: 800-7776-7776
Fax: 603-7958-5598

In China:
Phone: 800-600-0015
Fax: 603-7958-5598

†Toll free from Austria (00), Belgium (00), Denmark (00), Finland (990), France (00), Germany (00), Hungary (00), Ireland (00), Italy (00), Netherlands (00), Norway (00), Portugal (00), Spain (00), Sweden (00), Switzerland (00) and the United Kingdom (00).

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Published August 2004

Printed in U.S.A.  Trademark of The Dow Chemical Company  Form No. 326-00013-0804 AMS