POLYOX™ Water Soluble Resins
Combining Flexibility with Consistency
POLYOX™ are nonionic poly (ethylene oxide) polymers that meet all the specifications of the United States Pharmacopoeia—National Formulary.

They are white to off-white, free-flowing hydrophilic powders supplied in a wide variety of viscosity grades corresponding to approximate molecular weight, 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, oral osmotic delivery systems, tablet binding, drug delivery systems, and mucosal bioadhesives.

**Particularly Fast Hydration and Gel Formation**

POLYOX™ polymers 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™ can facilitate release models approaching zero order in many instances.

**Great Thermoplastic Properties**

POLYOX™ extrudes particularly well and can easily be used in other types of heat treatments. Many abuse deterrent technologies take advantage of its distinctive thermo-mechanical properties combined with its hydration behavior in water.

**Formulation Flexibility Thanks to a Wide Range of Molecular Weights**

With molecular weights ranging from 100,000 to 7,000,000, POLYOX™ offers 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™ complies with the USP polyethylene oxide NF monograph. They also meet the requirements of the Food Chemicals Codex, the International Codex Alimentarius, and the U.S. National Formulary (NF). These polymers have also been approved in drug products sold in all major European countries as well as Japan. The NF product family is listed in Table 1.

* POLYOX™ for pharmaceutical applications = SENTRY™ POLYOX™ grades.
More Technical Assets to Help You Succeed Quickly

With an expanded technical staff and assets of The Dow Chemical Company, Dow Pharma & Food Solutions 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 powerful ways.

<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>
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</table>

The properties shown are typical but not to be construed as specifications. Data is based on results from internal studies. Model RVF.

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An Excellent Choice
for Controlled Release Systems

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, facilitating diffusion of the drug from the tablet core.

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

Experimental Procedure

Tablet formulations (caffeine, theophylline or riboflavin, POLYOX™, lactose and magnesium stearate) 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 II-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™ 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 in certain actives. 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 2 illustrates the effect of polymer concentration on release rate. Increasing polymer concentration raises the gel viscosity on the surface of the tablets, which retards the diffusion of the drug from the gel layer. Increasing the concentration, from 20 to 60 percent, of a relatively low molecular weight POLYOX™ results in a drug release profile very similar to that obtained from 20 percent of a high molecular weight POLYOX™. However, this concentration effect is seen only for low molecular weight polymer.

Figure 1: Effect of Molecular Weight of POLYOX™ on In Vitro Release Rate of Caffeine from a Matrix Tablet

Figure 2: Effect of Polymer Concentration and Molecular Weight on In Vitro Release Rate of Caffeine From a Matrix Tablet With POLYOX™ WSR-1105 NF and WSR-303 NF

The properties shown are typical but not to be construed as specifications. Data is based on results from internal studies.

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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 is 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™. 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™ swells greatly when hydrated, and the resulting gel layer does not erode readily. The polymer, therefore, is an excellent 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™ matrix tablets.

Figure 5 — In Vitro Release Rate of Water-Insoluble Actives from a POLYOX™ Matrix Tablet

![Graph showing release rates of different concentrations of actives from a POLYOX™ matrix tablet.]

5% Riboflavin, 10% POLYOX™ WSR-303 NF, 85% Lactose
20% Riboflavin, 20% POLYOX™ WSR-303 NF, 60% Lactose

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 6 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.

Figure 6 — Effect of pH on Release of Theophylline From Matrix Tablets Using POLYOX™

![Graph showing the effect of pH on theophylline release.]

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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 7 were generated by selectively separating a standard POLYOX™ 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™.

For customers with specific processing needs, Dow Pharma & Food Solutions offers fine and super fine particle grades for selected POLYOX™ products.

Figure 8 shows sample particle size distributions for POLYOX™ Coagulant NF, FP, and SFP grades. To illustrate their performance in a formulation, these materials were formulated with ketoprofen into 400 mg tablets consisting of 30% POLYOX™, 20% ketoprofen, 49.5% Microcrystalline Cellulose and 0.5% Mg Stearate.

The resulting drug release profiles are given in Figure 9. No significant dependence of drug release rate upon particle size distribution was observed. In many applications POLYOX™ grades can be selected based on the desired particle size for processing conditions with minimal changes in dissolution performance.
Conclusions

POLYOX™ is a family of highly versatile water-soluble polymers. Upon exposure to water or gastric juices, they hydrate and swell rapidly to form hydrogels with properties suitable for a controlled drug-delivery vehicle. Their utility is not limited to the hydrophilic matrix system that is the subject of this discussion. POLYOX™ has been successfully used in other drug-delivery systems, such as osmotic pumps. POLYOX™ polymers are available in a wide range of molecular weights, which helps the formulator to readily custom design to individual specifications.
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™ in water granulation. This work indicates that POLYOX™ 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

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

**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 fiability  
Granule morphology
Results

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

Figure 10 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 10 the orange data points represent 200,000 molecular weight polymer while the red 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.

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 11. The high molecular weight of POLYOX™ Resins would be expected to provide good granule strength.

In order to determine the impact of granulation solvent, a set of equivalent granulations was produced by water and ethanol. The release profiles for the resulting tablets are presented in Figure 12. 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

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POLYOX™ Offers Excellent Binding, Bioadhesion, and Melt Extrusion Properties

Beyond their role in controlled release matrix systems, POLYOX™ performs other valuable functions in pharmaceuticals. Often, a single POLYOX™ polymer can contribute several important properties in a single system.

**Direct Compression Tablet Binding**

POLYOX™ performs well as binders in economical direct compression systems. It often facilitates better flow and compaction properties than other binders. Its lubricity also assists tableting operations. This offers a system where a single excipient can offer both binding and rate-controlling properties.

**Mucosal Bioadhesives**

POLYOX™ offers a number of important properties for mucoadhesion—water solubility, hydrophilicity, high molecular weight, hydrogen bonding functionality, and good biocompatibility. POLYOX™ Polymers have a long linear chain structure which helps them form a strong interpenetrating network with mucus. Data indicate that molecular weights of 4,000,000 and higher have the highest level of adhesion.

**Osmotic Pump Technologies**

Osmotic pump technologies use osmotic pressure as the driving force for API delivery. In these formulations, POLYOX™ offers numerous advantages, including in vitro in vivo correlations, no food effect, narrow therapeutic window delivery, and effective low solubility drug delivery. POLYOX™ is a leading excipient for osmotic tablets.

High molecular weight POLYOX™ can be used interchangeably in a push-pull osmotic pump tablet. These polymers exhibit excellent swelling properties, improving control over drug release and approaching zero order release rates. Figure 13 demonstrates the benefits of a POLYOX™-based push layer in a push-pull osmotic pump tablet formulated with a poorly soluble drug. In comparison to an elementary osmotic tablet, incorporation of a POLYOX™ push layer increases the percent of nifedipine released and offers a zero-order release rate.

Low molecular weight POLYOX™ is commonly used as a dispersing agent that assists in the formation of a bi-layer tablet by improving compatibility between the layers. Suggested grades include POLYOX™ WSR N10 and POLYOX™ WSR N80.

**Experimental Parameters**(1)

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<th>Formulation</th>
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<tr>
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<tr>
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<tr>
<td>NaCl</td>
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<tr>
<td>Mg Stearate</td>
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<table>
<thead>
<tr>
<th>Push layer (mg)</th>
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</thead>
<tbody>
<tr>
<td>NaCl</td>
</tr>
<tr>
<td>PEO</td>
</tr>
<tr>
<td>Mg Stearate</td>
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</tbody>
</table>

Figure 13: Release rate of Nifedipine from push-pull and elementary osmotic pump tablets comprising various high-molecular weight grades of POLYOX™ as the push layer (1)

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Data is based on results from internal studies
**Melt Extrusion**

POLYOX™ polymers are thermoplastic polymers with a low melting point of ~ 65°C. They can be used in melt extrusion processes to prepare pharmaceutical dosage forms. During a melt extrusion process, a mixture of POLYOX™, drugs, and optional fillers or plasticizers is fed into an extruder. POLYOX™ 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. POLYOX™ offers excellent binding, bioadhesion, and melt-extrusion properties.

A twin screw extruder permits low temperature extrusion of both low and high molecular weight POLYOX™. 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™ with high, medium, and low molecular weights were used to prepare tablets containing riboflavin. The POLYOX™ 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™ 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 14).

![Figure 14 — Release Profiles of Riboflavin at 37°C in Distilled Water from Tablets (250 mg) Cut From Extruded Rod Containing 15% by Weight Riboflavin Dispersed in Three Different Grades of POLYOX™ or a Mixture of POLYOX™/Microcrystalline Cellulose (1:1) (1)](image-url)
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