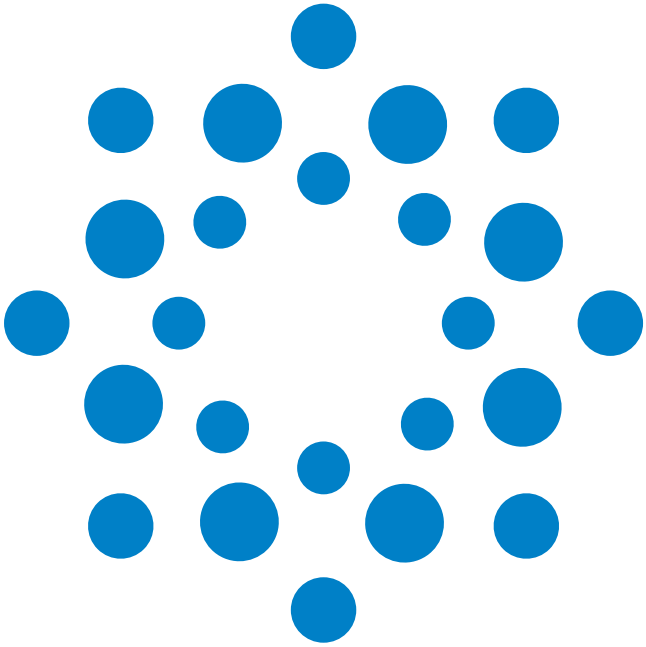
Where science
& creativity meet

POLYOX™ WATER SOLUBLE RESINS

Versatile hydrophilic polymers for advanced pharmaceutical applications



HYDROPHILIC POLYMERS FOR ADVANCED DRUG DELIVERY SOLUTIONS

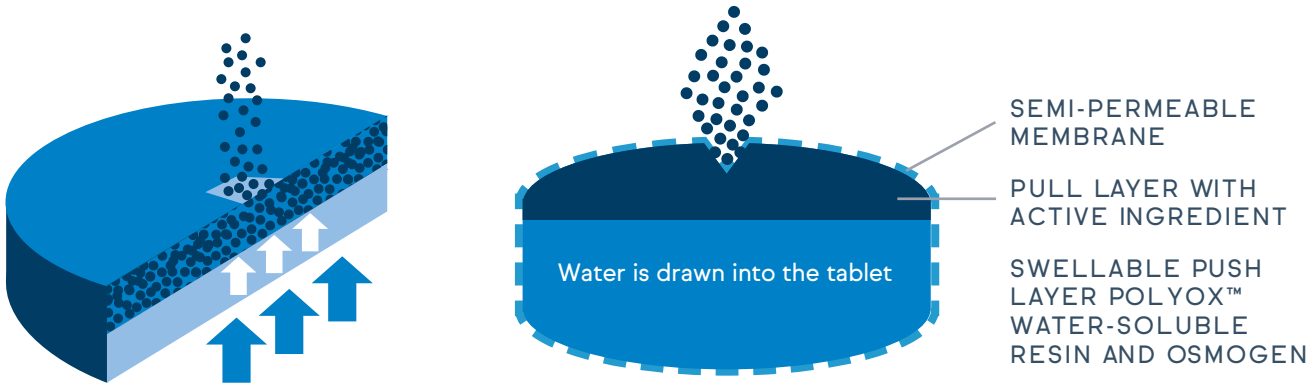
POLYOX™ water soluble resins (WSR) pharmaceutical NF grades possess a unique set of properties to facilitate the development of advanced drug delivery solutions.

As hydrophilic polymers, POLYOX™ WSR are available in a wide range of molecular weights and are supplied as white, free-flowing powders to suit a broad array of pharmaceutical applications including osmotic pump technologies, controlled-release matrix tablets, gastro-retentive dosages, and more.

Key applications

- **Osmotic pump technology**
- **Controlled-release matrix formulation**
- **Abuse deterrence**
- **Gastro-retentive formulation**
- **Hot-melt extrusion**

HYDROPHILIC POLYMERS FOR ADVANCED DRUG DELIVERY SOLUTIONS



Osmotic pump technology

Osmotic pump technology is a well-recognized method of producing reliable and reproducible controlled release drug delivery formulations showing clear advantages over other dosage forms including in-vivo robustness, near zero-order release, and less impact from variables like gastrointestinal motility or food effects.

Controlled release systems

A hydrophilic matrix tablet is a simple-to-formulate, yet effective controlled release drug delivery system in which a bioactive 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. At the same time, the polymer slowly dissolves into the surrounding aqueous environment, causing erosion of the tablet, which also facilitates active release.

Abuse deterrent technology

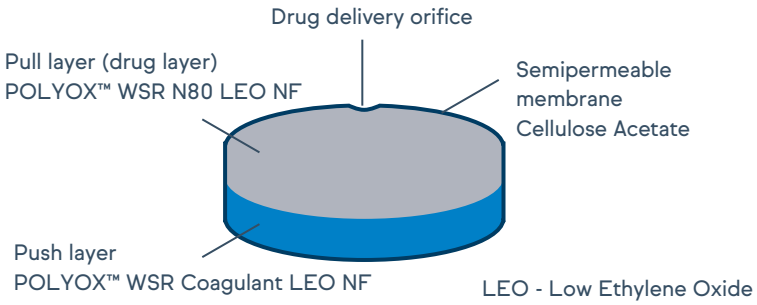
Abuse deterrent formulations can reduce deliberate and unintentional misuse of drug products. Various mechanisms, including crush resistance and gelling, are incorporated into drug agents for this reason. POLYOX™ WSR is one of the most common deterring agent used in abuse-deterrent formulations. The thermoplasticity and gelling behavior of POLYOX™ WSR makes them successful candidates for discouraging abuse. Heat treatment of high molecular weight POLYOX™ WSR makes tablets difficult to crush, while also creating a highly viscous gel upon exposure to water to help deter injection.

OSMOTIC PUMP TECHNOLOGY

Osmotic pump technology (OPT)

Osmotic pumps are a very reliable technology for controlled drug delivery. Osmotic pressure is used as the driving force for API release. POLYOX™ WSR polymers are the leading excipient for osmotic pump tablets due to their high swelling and non-ionic properties. In a push-pull tablet dimensionally constrained by the semipermeable membrane, POLYOX™ WSR hydrates upon contact with water, expanding and pushing the drug layer through the delivery orifice.

Figure 1 demonstrates the benefits of the POLYOX™ WSR push layer in a push-pull osmotic pump (PPOP) tablet containing a poorly soluble API. In comparison to an elementary osmotic tablet, incorporation of a push layer increases the total nifedipine delivered to the patient and offers a near zero order release rate. Low molecular weight POLYOX™ WSR are effectively used in the drug layer as a dispersing agent which assists the bilayer tablet formation and improves compatibility between the bilayers. Because POLYOX™ WSR are non-ionic, interactions between the API and an excipient are less likely. Suggested pull layer grades include POLYOX™ WSR N80 and POLYOX™ WSR N10.



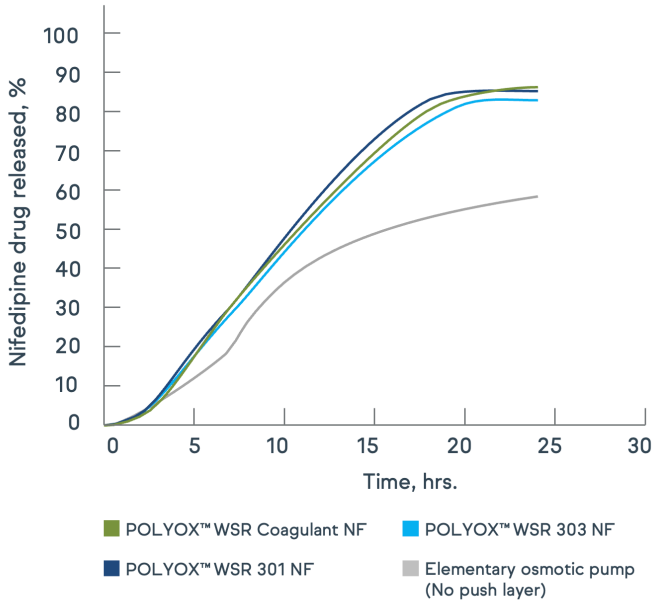


Figure 1: Comparison of Nifedipine release rate in push-pull tablets containing three high-molecular weight POLYOX™ WSR grades in the push layer to an elementary osmotic pump tablet without a push layer

POLYMER PROPERTIES

- POLYOX™ WSR are free flowing powders with a broad particle size distribution ranging from a few microns to several hundred microns in diameter, with average particle size approximately 150 microns.
- POLYOX™ WSR are soluble in water and select organic solvents.
- POLYOX™ WSR are stable under a wider range of pH conditions.
- POLYOX™ WSR are also highly crystalline, contain silica as a flow aid, and BHT as an antioxidant.

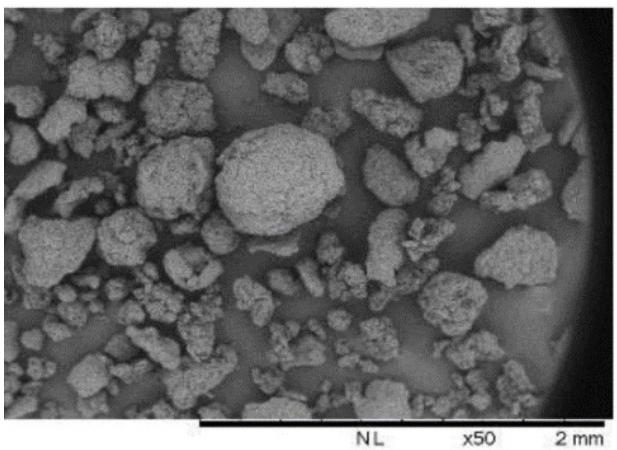


Figure 2: POLYOX™ Scanning Electron Microscope Image

MATRIX TABLET SYSTEMS

POLYOX™ WSR are a viable and robust solution for matrix tablet formulations

Effects of Molecular Weight and Concentration

Figure 3 highlights the effects of POLYOX™ WSR molecular weight on the release rate in a matrix tablet. 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 decreases drug diffusion. In addition, increased molecular weight reduces the rate of erosion, which slows down the drug release rate, especially for low-water soluble drugs. However, there is often a maximum molecular weight beyond which no further change in release rate is observed.

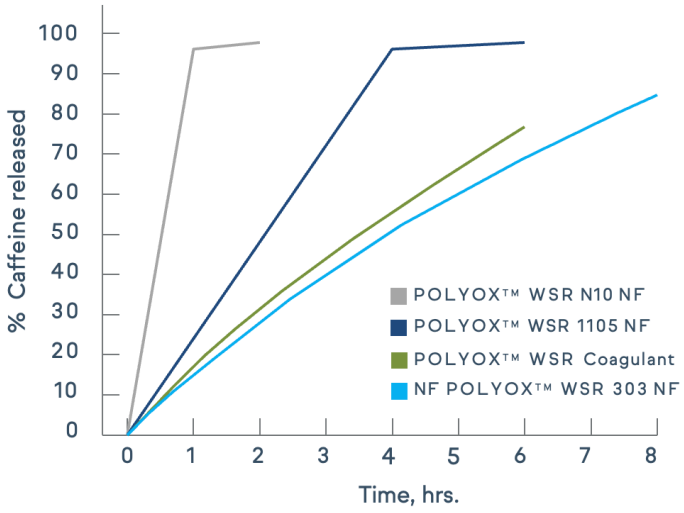


Figure 3: Effect of POLYOX™ WSR Molecular Weight on *In Vitro* Release Rate of Caffeine

Figure 4 illustrates the effects of polymer concentration on release rate. Increasing polymer concentration raises the gel viscosity on the surface of the tablets and slows down the erosion rate of the matrix, both of which will retard the drug release rate. Increasing the concentration from 20 to 60 percent of a relatively low molecular weight, POLYOX™ WSR results in a drug release profile very similar to that obtained from 20 percent of a high molecular weight POLYOX™ WSR. However, this effect of increasing concentration is one of the most drastic for lower molecular weight polymers.

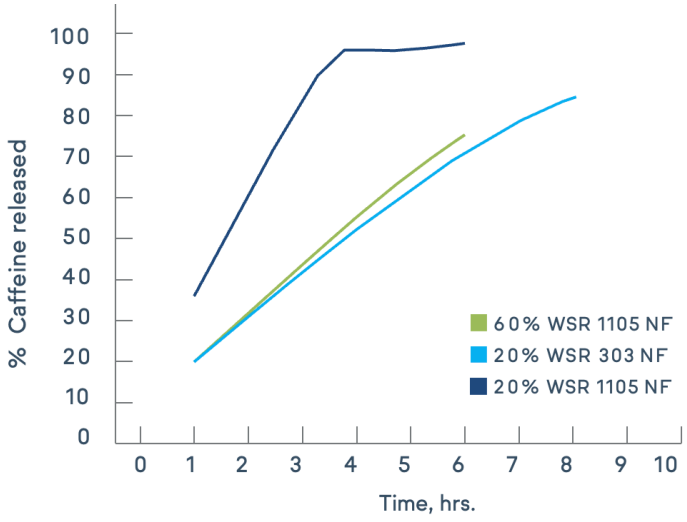


Figure 4: Effect of Polymer Concentration and Molecular Weight on In Vitro Release Rate of Caffeine from a Matrix Tablet with POLYOX™ WSR 1105 NF and WSR 303 NF

Figure 5 shows caffeine release from matrix tablets produced from POLYOX™ WSR 303 NF. When polymer concentration increased from 10 to 60 percent in the formulation, less dramatic changes in the release rate were 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.

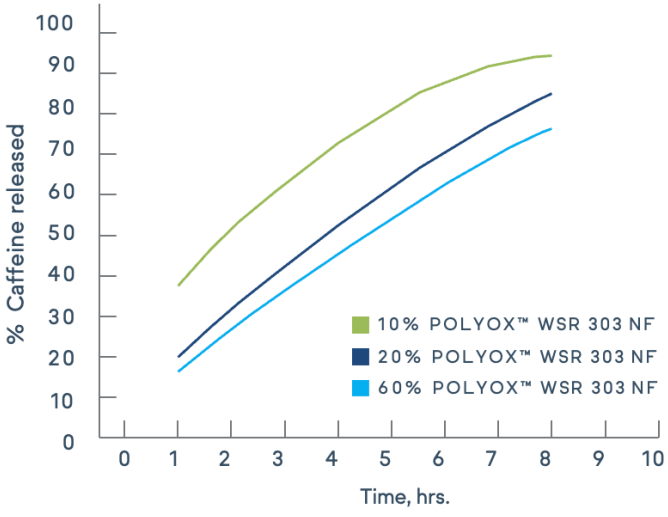


Figure 5: Effects of Polymer Concentration on *In Vitro* Release Rate of Caffeine from a Matrix Tablet with POLYOX™ WSR-303 NF

Note: The properties shown are typical, but not to be construed as specifications; data is based on results from internal studies.

POLYOX™ WATER SOLUBLE RESINS

Versatile and Reliable Choice for Use in Controlled Release Systems

- Reproducible hydration and swelling for use in osmotic pump technologies
- Consistent hydration and gel formation for use in hydrophilic matrices minimizes burst
- Wide range of polymer molecular weights ranging from 100,000 to 7,000,000 enhancing formulation flexibility
- Excellent flow, compressibility and lubricity for direct compression extended-release applications
- Thermoplastic, highly crystalline with low-melting temperature for hot-melt extrusion and melt granulation

PRODUCT RECOMMENDATIONS

Applications	Benefits & Features	Grade Considerations
Osmotic Pump Technology	Zero-order release, clinical robustness and little to no food effect	Low MW POLYOX™ (N10/N80) for drug layer High MW POLYOX™ (301/Coagulant/303) for push layer
CR Matrix Tablets	Rapid hydrogel formation, excellent tablet binding and lubrication properties	High MW POLYOX™ (N60K up to 303)
Abuse Deterrence	Thermoplasticity and gelling behavior help harden tablets and increase the viscosity of liquid to prevent drug injection	High MW POLYOX™ (N12K up to 303)
Mucoadhesive Delivery Systems	Adheres well to mucosal membranes	Mid and High MW POLYOX™ (205 up to 303)
Hot-Melt Extrusion	Highly thermoplastic in nature, POLYOX™ polymers extrude very well	Lower MW POLYOX™ will be easier to extrude. To extrude high MW POLYOX™, a small amount of low MW POLYOX™ should be added to reduce melt viscosity

POLYOX™ WSR Grades	Approximate Molecular Weight	Osmotic Pump Tablets	Oral Thin Films	Melt Extrusion	Abuse Deterrence	Controlled Release Matrix	Muco-adhesive	Gastro-Retentive Tablet
N10	100,000	*	*	*				
N80	200,000	*	*	*				
N750	300,000		*	*				
205	600,000			*			*	
1105	900,000			*			*	
N12K	1,000,000			*	*		*	
N60K	2,000,000			*	*	*	*	*
301	4,000,000	*		*	*	*	*	*
Coagulant	5,000,000	*		*	*	*	*	*
303	7,000,000	*		*	*	*	*	*

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