

Excipients for Liquid and Semisolid Dosage Forms

Oral and Topical Applications



Introduction

Lubrizol LifeScience Polymers combines an in-depth understanding of functional polymer systems with a portfolio of specialty materials to deliver application-specific solutions to the medical device, pharmaceutical and healthcare industries. As a technology leader and a key provider of pharmaceutical polymers, Lubrizol is your custom solution development partner. Together, we help link science to life.

Lubrizol produces multiple grades of high molecular weight polymers for the pharmaceutical market. These specialty polymers, such as Carbopol® polymers and Noveon® polycarbophil, have been used successfully in commercial formulations for decades in a wide variety of medical applications.

Carbopol® and Pemulen® polymers and Noveon® Polycarbophil are high-molecular-weight polymers of acrylic acid, chemically cross-linked with polyalkenyl alcohols or divinyl glycol. These specialty polymers have been used successfully in commercial formulations that are designed for topical, oral suspension/solution, bioadhesive and oral care applications.

Lubrizol works with all relevant regulatory bodies to establish and maintain the global pharmacopeial status of its pharmaceutical ingredients. In addition, Lubrizol supports its pharmaceutical ingredients with Drug Master Files (DMFs) in the United States and Europe.



Key Benefits of Lubrizol Pharmaceutical Polymers

Versatile and Efficient

- At low usage levels, Lubrizol polymers provide highly effective rheology modification for aqueous, anhydrous and hydroalcoholic systems and improved stability for suspensions and emulsions:

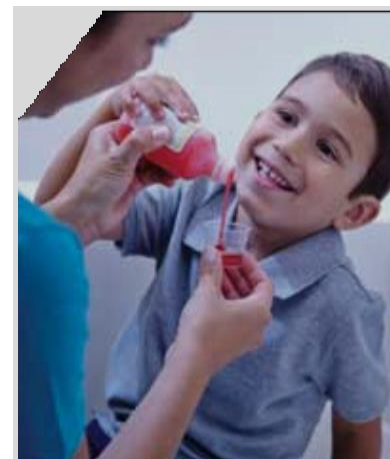


Table 1.

Application	Typical Usage Level (%)
Topical Gels, Lotions, Creams	0.5–3.0
Topical Emulsions	0.1–0.4
Oral Suspensions/Solutions	0.1–1.0

- Excellent bioadhesive characteristics: maximize contact with biological tissues; may result in lower active usage concentrations due to enhanced active pharmaceutical ingredient (API) bioavailability.
- Compatible with most acidic, basic and neutral drugs, and well-suited for applications across a broad pH range (4.0–10.0).

Multifunctional and Stable

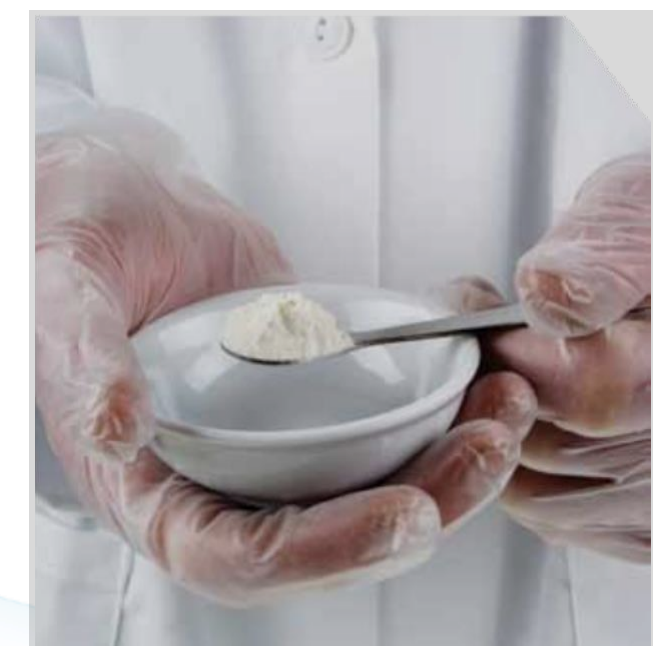
- Effective as primary emulsifiers or emulsion stabilizers for topical formulations.
- Thickening, suspending and emulsifying properties result in topical formulations that exhibit excellent aesthetics and skin feel.
- Polymers enable soft, silky and nonpilling skin feel, allowing for smooth application of API in medicated topicals. Carbopol polymers specifically allows formulations ranging from heavy-bodied gels to light creams to remain consistent, nonsticking and easily spreadable.
- Polymers provide a structural network for the permanent, stable suspension of nonsoluble active or inactive ingredients.
- Ideal for pouring, pumping, spreading and spraying applications due to the shear thinning effects of the polymer.
- Polymers in the dry powder state are chemically and thermally stable under typical storage and processing conditions.
- Temperature variations have a minimal impact on the viscosity of Carbopol polymer dispersions.
- Dispersions of Carbopol polymers are freeze-thaw stable and may be sterilized.
- Formulations such as those for “nonspill” pediatric products benefit from higher viscosity and yield values, even at low polymer concentrations.
- Taste-masking characteristics can reduce or eliminate the negative effects of bitter-tasting drugs.

Safe and Reliable

Carbopol and Pemulen polymers and Noveon Polycarbophil, as a class, have received extensive review and toxicological evaluation. The safety of these products is supported by a history of over 50 years of successful use in commercial pharmaceutical and cosmetic products*.

- Demonstrated to have low irritancy and nonsensitizing properties.
- NF grades manufactured under GMP conditions in ISO:9001-certified facilities.
- Synthetic nature results in consistent and reproducible properties.
- Polymers in the dry powder state do not support microbial growth.
- Polymers are not absorbed or metabolized in the body due to their high molecular weight (up to 3–4 billion).

*Additional information concerning the toxicological testing of Lubrizol polymers is included in the Toxicology Studies and Regulatory Information Bulletin at www.lubrizol.com/LifeSciencePolymers.



Recommended Polymers for Liquid and Semisolid Dosage Forms

A list of Lubrizol polymers that are recommended for use in liquid and semisolid dosage forms is included in Table 2.

Table 2. Lubrizol Polymers for Liquid and Semisolid Applications

Product Trade Name	Polymerization Solvent	Application Type					Viscosity Specification Ranges ¹		
		Lotions	Creams	Gels	Bioadhesives	Oral	% w/w	Minimum (Cp)	Maximum (Cp)
Carbopol® Polymers									
971P NF	Ethyl Acetate	*	-	*	*	*	0.5	4,000	11,000
974 P NF	Ethyl Acetate	*	*	*	*	*	0.5	29,400	39,400
980 NF	Cosolvent	-	*	*	*	-	0.5	40,000	60,000
981 NF	Cosolvent	*	-	*	*	-	0.5	4,000	10,000
5984 EP	Cosolvent	*	*	*	*	-	0.5	30,500	39,400
ETD 2020 NF	Cosolvent	*	*	*	*	-	1.0	47,000	77,000
Ultrez 10 NF	Cosolvent	*	*	*	*	-	0.5	45,000	65,000
934 NF ²	Benzene	*	*	*	*	-	0.5	30,500	39,400
934P NF ²	Benzene	*	*	*	*	*	0.5	29,400	39,400
940 NF ²	Benzene	-	*	*	*	-	0.5	40,000	60,000
941 NF ²	Benzene	*	-	*	*	-	0.5	4,000	10,000
1342 NF ²	Benzene	*	*	*	*	*	1.0	9,500	26,500
Pemulen™ Polymers									
TR-1 NF	Cosolvent	*	*	*	*	*	1.0	10,000	26,500
TR-2 NF	Cosolvent	*	*	*	*	*	1.0	4,500	13,500
Noveon® Polycarbophil USP									
AA-1 USP	Ethyl Acetate	-	*	*	*	*	0.2	2,000	12,000

¹Dispersion neutralized in water. Method information is included in the specification sheet for each product at www.lubrizol.com/pharmaceutical/literature/productspecifications.html.

²Due to regulatory restrictions on the use of benzene in pharmaceutical formulations, Lubrizol recommends the use of carbomers polymerized in toxicologically preferred solvents for all new drug development projects. A list of substitute products for benzene-grade Carbopol polymers is included below. Ingredient substitutions in existing pharmaceutical formulations should be verified to confirm compliance with key performance properties and regulatory requirements.

Polymer Functionality

Thickening Properties

Rheology Control Swelling and Thickening Characteristics

At low usage levels (0.1 to 3.0 wt%), Lubrizol polymers perform as highly efficient thickening agents. Polymer concentration, pH and the degree of hydrogen bonding can be modified to customize the rheological properties of the finished product for a wide range of applications.

Impact of Polymer Concentration and Type

Higher viscosities can be achieved at specific pH values by increasing the polymer concentration. This is particularly

effective when targeting the rheological properties of formulations with pH values of below 5 or greater than 9. Figure 1 provides an example of the effect of polymer concentration on viscosity at constant pH.

Lubrizol's use of different crosslinking materials and levels results in polymer types that exhibit different rheological characteristics. For example, polymers that are highly crosslinked as Carbopol 980 NF, 5984 EP, 974P NF, 934P NF, 940 NF and 934 NF exhibit very high viscosities. Alternatively, Carbopol 981 NF, 971P NF and 941 NF are lower in viscosity due to their lightly crosslinked structure.

Figure 1. Effect of Polymer Type and Concentration on the Viscosity at pH 6.0¹—Topical Products

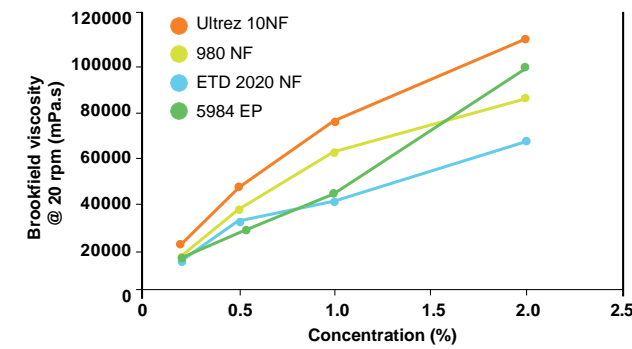
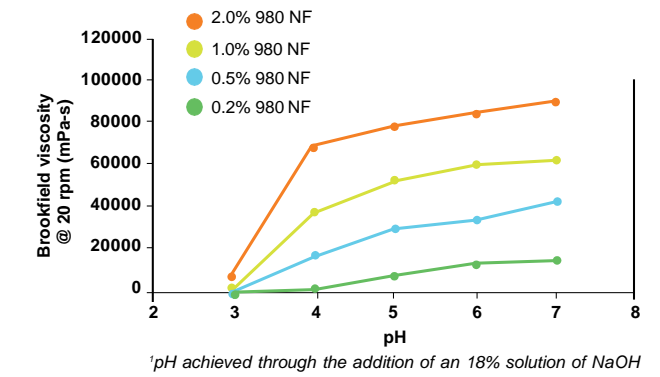


Figure 2. Effect of pH and Concentration on the Viscosity of Carbopol 980 NF Polymer Dispersion¹



Effect of pH on Properties

In aqueous systems, the primary mechanism for rheology modification is through pH adjustment. Polymer thickening is boosted via neutralization with bases (organic, inorganic, amino acids, etc.). Maximum viscosity is typically achieved at pH values of 6.0–7.0. Figure 2 illustrates the effect of pH on different concentrations of Carbopol 980 NF polymer dispersions.

Choice of Neutralizing Agent

A wide range of neutralizing agents can be used to achieve the target pH. Selection of a neutralizing agent is based upon the vehicle and intended characteristics of the finished product. Table 3 includes a list of the most commonly used neutralizers for aqueous systems. For hydroalcoholic systems, the choice of an effective neutralizer depends upon the level of alcohol in the system. Table 4 provides a list of recommended neutralizers for hydroalcoholic systems based upon the amount of alcohol present.

Additional information regarding the choice and use of a neutralizing agent can be found in the Bulletin: Thickening Properties and Neutralizing Carbopol and Pemulen Polymers in Aqueous and Hydroalcoholic Systems, data sheet at www.lubrizol.com/LifeSciencePolymers.

Table 3. Neutralizers for Aqueous Systems

Neutralizer/Amount	Neutralization Ratio (approximate amount per one part polymer) pH = 6–7
Sodium Hydroxide (18% solution)	2.30
Potassium Hydroxide (18% solution)	3.30
Ammonium Hydroxide (28% solution)	0.70
Triethanolamine	1.50
Tromethamine	1.30
Aminomethyl Propanol	0.95

Table 4. Neutralizers for Hydroalcoholic Systems

Hydroalcoholic Systems (up to alcohol %)	Neutralizer
20–30	Sodium Hydroxide or Potassium Hydroxide
60	Triethanolamine
60	Tromethamine
80	Aminomethyl Propanol

Hydrogen Bonding

For anhydrous systems or systems where pH adjustment is not feasible, formulation thickening can be enhanced through hydrogen bonding with hydroxyl donor coexcipients.

Commonly Used Hydroxyl Donors:

- Polyols (glycerine, propylene glycol and polyethylene glycol)

- Sugar alcohols (mannitol, sorbitol)
- Select nonionic surfactants
- Polyethylene oxide

A comparison of Figures 3 and 4 demonstrates the effects of hydrogen bonding on viscosity for varying concentrations of Carbopol polymers in anhydrous and aqueous media.

Figure 3. Viscosity of Carbopol Polymer Dispersions in Glycerin as Prepared – Hydrogen Bonding

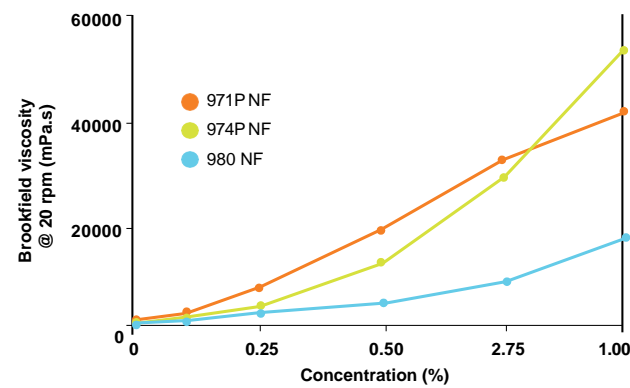
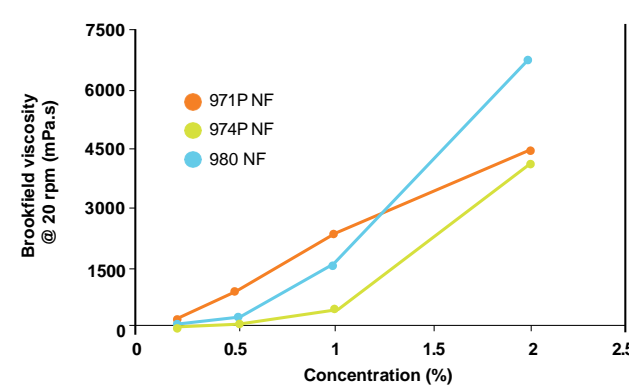


Figure 4. Viscosity of Carbopol Polymer Dispersions in Water as Prepared

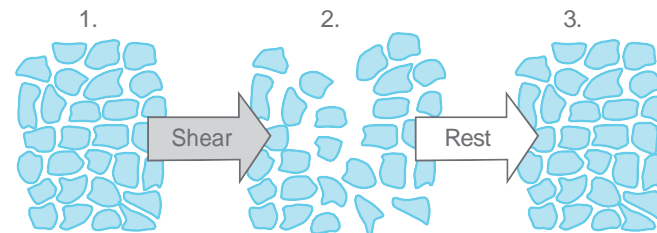


Viscoelastic Behavior

Shear Thinning – Pour, Pump, Spread and Spray

The viscoelastic behavior of Lubrizol Carbopol polymers is ideal for pouring, pumping, spreading and spraying applications.

1. Viscosity is high when the system is at rest.
2. The application of shear forces decreases viscosity and facilitates flow.
3. After shearing stops, the high viscosity of the original system is quickly restored.



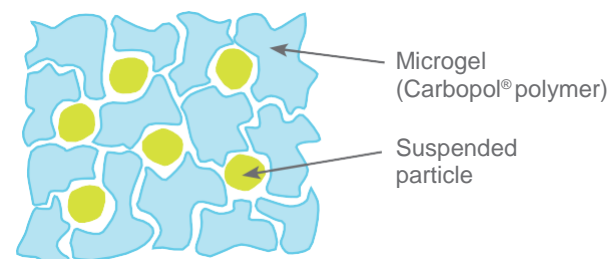
Suspension Stabilization

Yield Value vs. Viscosity

- Yield Value – The minimum amount of shear stress needed before flow begins.
- Viscosity – An expression of the resistance of a fluid to flow; the higher the viscosity, the greater the resistance.

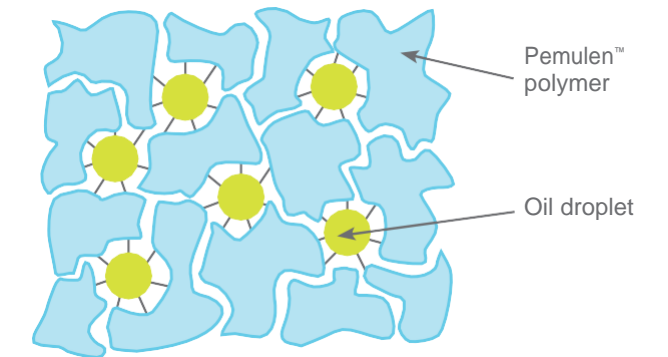
While viscosity can only slow down the rate of settling, a high yield value is crucial to the successful formation of permanent suspensions.

The high yield values of Carbopol polymers enable the formation of permanent, stable suspensions at significantly low polymer concentrations. The polymers swell when hydrated and neutralized, forming a colloidal dispersion. The swollen, closely packed microgels hold solid particles within the gel structure and result in the formation of a robust suspension.



Emulsion Stabilization – Pemulen Polymers

Pemulen polymers are carbomer copolymers of acrylic acid and a long-chain alkyl methacrylate crosslinked with allyl ethers of pentaerythritol. A combination of large hydrophilic and small lipophilic regions within the polymer matrix facilitates the formation of stable oil/water emulsions through steric and associative stabilization mechanisms.



- The hydrophilic portion of the polymer forms a gel network around the oil droplets.
- The hydrophobic portion functions as an anchor for the oil phase.

Pemulen Polymers vs. Traditional Surfactants

- Formulation flexibility: largely independent of oil type(s), hydrophilic-lipophilic balance (HLB) values and oil levels.
- Highly efficient: Typically used at concentrations of 0.10–0.40 wt% to achieve emulsion stabilization. If necessary, viscosity can be adjusted with Carbopol polymers.
- Use of a surfactant is not required; however, the polymer may be combined with low amounts of surfactant to achieve a smaller droplet size and whiter, brighter appearance.
- Increased viscosity and yield values with polymer use result in improved emulsion stability.
- Finished formulations benefit from shear thinning rheological properties.

The Skin Contact Advantage

Ions present in the skin trigger the release of oil droplets contained within the emulsion. The oil droplets coalesce to form a lipophilic film on the surface of the skin. In the absence of surfactants, this film cannot be re-emulsified or washed off. This property of Pemulen polymers is particularly advantageous when used in the formulation of sunscreen products.

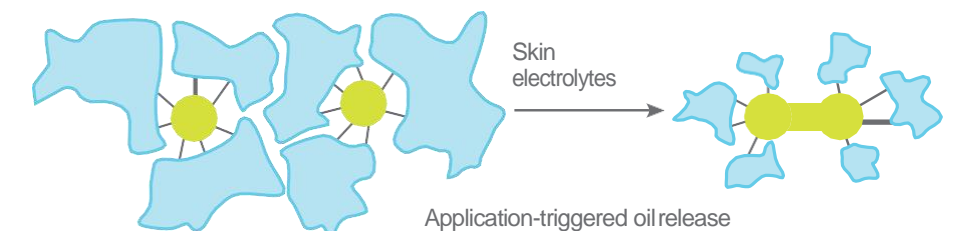


Table 5. Specifications and typical properties of Pemulen polymers in product formulations.

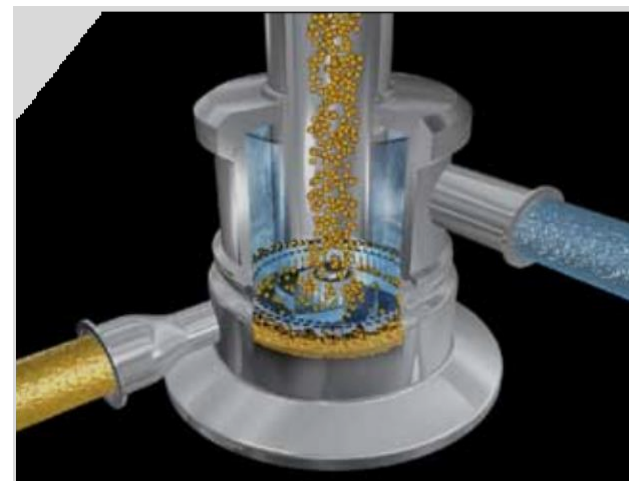
Pemulen™ Polymers	TR-1 NF	TR-2 NF
USP/NF Monograph	Carbomer Copolymer Type B	Carbomer Copolymer Type A
Typical Oil Levels	Up to 20%–30%	Up to 50%
Typical Use Level (wt%)	0.20–0.40	0.15–0.30
pH Formulating Range	4–8	4–8
Viscosity (mPa.s) pH 7.3–7.8		
0.2 wt% emulsion	6,500–15,500	1,700–4,500
1.0 wt% dispersion	10,000–26,500	4,500–13,500

Benefits of Carbopol ETD and Ultrez Polymers

- Processing versatility: Carbopol Ultrez 10NF and Carbopol ETD 2020 NF polymers can be added directly to water without screening or the use of an eductor.
- Unique performance characteristics enable the polymers to wet quickly, yet hydrate slowly.
- Use minimizes particle agglomeration when turbulent mixing is not available for dispersion.
- Facilitate processing and handling: compared with traditional Carbopol polymers, Carbopol ETD and Ultrez polymers produce dispersions that are much lower in viscosity prior to neutralization.
- Upon neutralization, the polymers become highly efficient formulation thickeners.

Processing Considerations and Best Practices

Courtesy of Ytron Process Technology GmbH & Company and Quadro Engineering Corporation



Dispersion Preparation

The dispersion technique employed depends upon the size of the batch, the polymer concentration and the manufacturing equipment that is available.

Table 6.

Approximate Batch Size	Traditional Carbopol® Polymer Concentration (%w/w)	Recommended Equipment
Small-Medium Several hundred milliliters to several hundred liters	Up to ~2%	Coarse sieve or 20 mesh screen; a mixer with a conventional open-blade impeller
Large Tens of hundreds of liters	Up to ~3%	Eductor or flocculent disperser
Large – Continuous Production Tens of hundreds of liters	Up to ~3%	Mechanical in-line powder disperser

Processing Recommendations

- Use a stainless steel screen, eductor or mechanical disperser to add the polymer to the aqueous phase to facilitate the formation of a uniform, stable dispersion.
- When possible, add the polymer at the beginning of the manufacturing process and neutralize at the end.
- Use water at room temperature to disperse traditional polymers.
- For best results, disperse the polymer in water that does not contain salts or alkalis. The presence or addition of electrolytes will significantly reduce the viscosity of the dispersion.
- After dispersion, allow time for complete polymer hydration while mixing at a slow rate.
- Uniformly disperse the polymer to avoid agglomeration. Dispersions that are not properly prepared may exhibit a grainy or nonuniform appearance, viscosity variation and/or formulation instability.
- Neutralizers should be gradually introduced to allow for pH equilibration. The gradual introduction of the neutralizer will optimize the viscosity consistency and stability of the formulation.
- Some ingredient incompatibilities can be circumvented through adjustments in the order of addition (e.g., electrolytes added after pH adjustment).

Refer to the Bulletin: Dispersion Techniques for Lubrizol Pharmaceutical Polymers at www.lubrizol.com/LifeSciencePolymers for additional information concerning the preparation of Lubrizol polymer dispersions.



Emulsion Preparation

An indirect method of dispersion is recommended for emulsion preparation:

- Predisperse the polymer in the nonpolar (oil) phase before adding the aqueous phase.
- The polymers readily disperse in most oils.
- Once the oil dispersion is mixed with the aqueous phase, neutralize with a suitable base.

Active Pharmaceutical Ingredient (API) Addition

Incorporating an active pharmaceutical ingredient (API) into Carbopol polymer dispersions depends upon the physical/chemical properties of the API:

- **Insoluble ingredients:** can be added before or after the pH adjustment of the polymeric dispersion.
- **Soluble ingredients:** can be dissolved in the water used to prepare the polymeric dispersion. It may be beneficial to add some soluble ingredients to the final formulation in order to avoid compatibility issues (e.g., electrolytes are commonly added during the final phase of the dispersion preparation).

Mixing Guidelines

- Use a sufficient amount of time and mixing to ensure that the polymer is completely hydrated prior to adding other formulation components.
- Excessive/improper mixing during dispersion may result in air entrapment, viscosity variation and/or formulation instability. Air entrapment can be minimized by using a variable-drive motor. Once the Carbopol polymer has been dispersed, air entrapment can be minimized by repositioning the impeller and reducing the mixing speed. Allow the acid dispersion to stand to release entrapped air bubbles.
- Moderate agitation is recommended.
- Any necessary high-intensity mixing should be completed prior to neutralization.
- Avoid high shear mixing with Waring blenders or rotor-stator homogenizers. Such mixing can damage the polymer and result in permanent loss of functionality.
- If persistent foam is generated, it can be broken by partially collapsing the polymer with the addition of a very low level of acid before neutralizing the dispersion with a suitable base. Hydrochloric or phosphoric acids are effective at 0.5% of the weight of the polymer used.



Equipment Cleaning

Manufacturing equipment should be promptly cleaned after processing carbomer dispersions.

- Gelled residue may be removed by powerwashing with warm water.
- If an excessive gel layer has formed, it may be collapsed using a dilute solution of salt (5% w/v).
- Any dry residue that remains on equipment after processing

may be soaked for 10–30 minutes using warm (~65°C) dilute alkaline solutions and then removed with pressure washing.

- Recommended detergent solutions:
 - 2% solution of P3-cosa®CIP 95 (Ecolab GmbH & Co. OHG)
 - 0.2% solution of Extran® AP12 (EMD – Merck KGaA)

Storage and Handling Recommendations

Dry Powder Polymer

Chemical Stability

Carbopol polymer powders are chemically very stable under normal storage conditions. Studies indicate that the chemical properties of the material do not change significantly over a five-year period.

Moisture Effect

In terms of physical stability in a powder state, the moisture content (also referred to as loss on drying, or LOD) increases with storage time due to the hygroscopic nature of Carbopol polymers. A change in the moisture content of the polymer does not affect its chemical stability; however, it does affect the material's ability to meet the LOD specification. The material

should be periodically retested to ensure conformance with the loss on drying specification.

Carbopol Polymers, Pemulen polymeric emulsifiers and Noveon AA-1 polycarbophil are hygroscopic products. They are supplied with moisture content of less than 2 percent as determined by loss on drying testing. Moisture pickup does not affect the efficiency of polymers, but polymers containing high levels of moisture are more difficult to disperse and weigh accurately. Therefore, containers of Carbopol and Pemulen polymers must be tightly closed and stored out of contact with water.

Thermal Stability

The polymers are thermally stable under normal conditions. When exposed to excessive temperatures above the glass transition temperature (~105°C), the dry polymers become sintered. Depending on the temperature and duration of exposure, the dry polymer may become discolored. Sintered polymers are more difficult to disperse and slower to gel in liquid formulations.

Polymer Dispersions

Oxidation Stability

Lubrizol polymers are not subject to hydrolysis or oxidation under normal conditions. The viscosity of liquid formulations can decrease as a result of a reaction with oxygen. This reaction is catalyzed by UV light or trace levels of metals that may be present in the water. Chelating agents, UV absorbers, and pH adjustments can be used to minimize degradation.

Control of Microbial Growth

The polymers will not support mold or bacterial growth, but will not suppress it. For prolonged storage, use of an appropriate preservative is recommended.

Electrolyte and Cationic Effects

Use of electrolytes or cationics as co-ingredients with Carbopol polymers may lower viscosity, reduce clarity and contribute to the precipitation of a formulation. The incorporation of multivalent vs. monovalent ions can increase the severity of these effects. Figure 5 demonstrates the typical effect of sodium chloride on Carbopol polymer viscosity. In general, lightly crosslinked Carbopol polymers perform better than highly crosslinked Carbopol polymers in electrolyte systems.

Recommendations to minimize cationic or electrolyte co-ingredient effects:

- Increase the Carbopol polymer concentration.
- Select a different grade of Carbopol polymer.
- Reduce the amount of electrolytes or cationics used in the formulation.
- Add electrolytes or cationics after pH is adjusted.
- Use cationics with a lower charge density and higher molecular weight.

Microbial Growth

Carbopol polymers, Pemulen polymeric emulsifiers and Noveon AA-1 Polycarbophil do not support bacteria, mold or fungus growth in powder form.

Dust Precautions

Based on the physical characteristics of Lubrizol powders, routine safety precautions should be taken to prevent potentially explosive dusting.

Figure 5: Effect of Salt on Viscosity of 1.0% Carbopol 971P NF Polymer Dispersions at pH 6.0

