

Formulating Semisolid Products

Carbopol[®]* polymers, Pemulen[™]* polymers and Noveon[®]* polycarbophil are some of the most widely used excipients for thickening lotions, creams and gels. These polymers are also used to modify the rheology of water-based systems and to stabilize multi-phase systems such as emulsions and suspensions. Carbopol[®] polymers have enabled the formulation of topical pharmaceutical products for fifty years, and are widely used on a global basis.

The performance of the polymer in semisolid products is maximized when the macromolecule is fully swollen. The swelling provides rheology modification, suspending properties and emulsification to the topical formulation. Polymer swelling can be accomplished in several ways (neutralization or hydrogen bonding).

Carbopol[®] polymers, Pemulen[™] polymers and Noveon[®] polycarbophil, are polymers of acrylic acid, crosslinked with polyalkenyl ethers or divinyl glycol. Each polymer particle is a network structure of polymer chains interconnected by crosslinks. Without the crosslinks, the primary particle would be a collection of linear polymer chains, intertwined but not chemically bonded. These polymers swell in water up to 1,000 times their original volume (and ten times their original diameter) to form gels when neutralized. Since the pKa of these polymers is 6±0.5, the carboxylate groups on the polymer backbone ionize, resulting in electrostatic repulsion between the negative particles, which extends the molecule, adding to the swelling of the polymer.

Thickening by hydrogen bonding is recommended in cases where it is not feasible to increase the pH of the final formulation. For more details, see [Pharmaceutical Bulletin 5: "Neutralization Procedures"](#).

Lubrizol Advanced Materials, Inc. / 9911 Brecksville Road, Cleveland, Ohio 44141-3247 / TEL: 800.379.5389 or 216.447.5000

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Benefits of Carbopol® Polymers, Pemulen™ Polymers and Noveon® Polycarbophil in Topical Formulations

- Long history of safe and effective use in semi-solid formulations.
- Demonstrated to have low irritancy and non-sensitizing properties with repeated usage.
- Compatibility with most acidic, basic, and neutral drugs.
- Applications across a broad pH range (4.5 - 10.0).
- Excellent thickening and suspending agents in aqueous, anhydrous and hydroalcoholic systems. (Typical use levels in aqueous systems: 0.1 - 1.0% wt.)
- Consistent and reproducible properties due to their synthetic nature. Do not support microbial growth.
- Chemically stable and maintain formulation stability.
- Excellent dispersions can be formed without alternate heating and cooling cycles.
- No heat sensitivity compared to other thickening agents.
- Formulations can be sterilized by autoclaving or gamma radiation.
- Provide a non-greasy formulation, with no irritation.
- Function as primary emulsifiers (Pemulen™ polymers) or emulsification stabilizers (Carbopol® polymers).
- Possess shear thinning properties to facilitate extrusion from product packaging.
- Can increase bioavailability of the active pharmaceutical ingredient due to their bioadhesive properties.

Selecting the Right Polymers for Semisolid Applications

Table 1 can be used for general guidance in selecting the appropriate polymer for semisolid formulations.

Numerous enhancements have been made to the Carbopol® polymer family over time to address regulatory requirements, meet formulation demands and improve product handling during processing. For example, the solvent system used to synthesize the polymers has evolved. Specifically, the “traditional” polymers are synthesized in benzene and the “toxicologically preferred” polymers are synthesized in either ethyl acetate or a cosolvent mixture of ethyl acetate and cyclohexane. Additionally, Carbopol® ETD and Ultrez polymers provide greater versatility in formulating and processing with their improved ease of dispersion.

Table 1
Polymer Selection Guide for Semisolid Formulations

Product Trade Name	Residual Solvent	Application Type					Pharmacopeia Monograph Compendial Name		
		Lotions	Creams	Gels	Bioadhesives	Oral Liquids/Semisolids	United States (USP/NF)	Europe (Ph. Eur.)	Japan (JPE) ¹
Carbopol® Polymers									
71G NF	Ethyl Acetate	•		•	•	•	Carbomer Homopolymer Type A	Carbomers*	Carboxyvinyl Polymer
971P NF	Ethyl Acetate	•		•	•	•	Carbomer Homopolymer Type A	Carbomers*	Carboxyvinyl Polymer
974P NF	Ethyl Acetate	•	•	•	•	•	Carbomer Homopolymer Type B	Carbomers*	Carboxyvinyl Polymer
980 NF	Cosolvent		•	•	•		Carbomer Homopolymer Type C	Carbomers*	Carboxyvinyl Polymer
981 NF	Cosolvent	•		•	•		Carbomer Homopolymer Type A	Carbomers*	Carboxyvinyl Polymer
5984 EP	Cosolvent	•	•	•	•		Carbomer Homopolymer Type B	Carbomers*	Carboxyvinyl Polymer
ETD 2020 NF	Cosolvent	•	•	•	•		Carbomer Interpolymer Type B		
Ultrez 10 NF	Cosolvent	•	•	•	•		Carbomer Interpolymer Type A		
934 NF	Benzene	•	•	•	•		Carbomer 934		Carboxyvinyl Polymer
934P NF	Benzene	•	•	•	•	•	Carbomer 934P		Carboxyvinyl Polymer
940 NF	Benzene		•	•	•		Carbomer 940		Carboxyvinyl Polymer
941 NF	Benzene	•		•	•		Carbomer 941		Carboxyvinyl Polymer
1342 NF	Benzene	•	•	•	•		Carbomer 1342		
Pemulen™ Polymers									
TR-1 NF	Cosolvent	•	•	•	•		Carbomer Copolymer Type B		
TR-2 NF	Cosolvent	•	•	•	•		Carbomer Copolymer Type A		
Noveon® Polycarbophil USP									
AA-1 USP	Ethyl Acetate		•	•	•	•	Polycarbophil		

* The Carbomers Monograph in the European Pharmacopeia stipulates that benzene is limited to 2 ppm.

¹ Based on customer request, Lubrizol certifies select lots of product against the JPE Carboxyvinyl Polymer Monograph

Table 2
Carbopol® Polymer Recommended Substitutes

The following table shows recommended substitutes for the benzene grade Carbopol® products based on viscosity criteria. The substitute products are polymerized in either ethyl acetate or a cosolvent mixture of ethyl acetate and cyclohexane. If a substitution is made in a pharmaceutical formulation, it is recommended that key performance properties be ascertained and regulatory considerations be taken into account. Depending on the desired dosage requirements, other Carbopol® polymers may be suitable alternatives.

Benzene Grade Carbopol® Polymers	Recommended Non-Benzene Carbopol® or Pemulen™ Polymers
Carbopol® 934 NF polymer	Carbopol® 5984 EP and Ultrez 10 NF polymers
Carbopol® 934P NF polymer	Carbopol® 974P NF polymer
Carbopol® 940 NF polymer	Carbopol® 980 NF and Ultrez 10 NF polymer
Carbopol® 941 NF polymer	Carbopol® 71G NF, 971P NF and 981 NF polymers
Carbopol® 1342 NF polymer	Pemulen™ TR-1 NF and TR-2 polymers

Formulating Topical Gels

Carbopol® polymers, Pemulen™ polymers and Noveon® polycarbophil are highly efficient thickeners, suspending aids, and emulsifying agents for topical formulations and oral liquids/semisolids. A key benefit of the polymers is their high efficiency at low usage levels (0.1 - 3 wt.%).

Carbopol® polymers can be used as rheology modifiers in anhydrous systems with or without neutralization. For more details, see [Pharmaceutical Bulletin 5: "Neutralization Procedures"](#).

Carbopol® Ultrez 10 NF polymer provides excellent versatility in processing for topical formulations. Its unique dispersion performance allows it to wet quickly, yet hydrate slowly. This minimizes agglomeration, which can be a problem if turbulent mixing is not available during dispersion. Compared with traditional Carbopol® polymers, Carbopol® Ultrez 10 NF polymer provides dispersions in water that are much lower in viscosity prior to neutralization which enables easier handling in mixing tanks and process lines. Once the polymer is neutralized, it is a highly efficient thickener.

Formulating Topical Gels

Typical usage levels of Carbopol® polymers in topical aqueous or hydroalcoholic gels is 0.5% - 3 wt. %. General recommendations for formulation and processing appear below.

- Choice of Neutralizer** — Upon neutralization, Carbopol® polymer should form a salt that is swellable in the vehicle.
- pH** — The optimum pH range for a Carbopol® polymer is 4 - 10.
- Complexation with Other Ingredients** — Proteins, povidone, polyethylene glycol and polyethoxylated surfactants might form a complex with unneutralized Carbopol® polymers. In order to prevent the complexation, these ingredients should be added to the partially neutralized dispersion.
- Electrolytes, Metals** — Carbopol® polymers are sensitive to electrolytes, and preferably their level should be minimized. It is recommended to use the non ionized form of the API whenever possible. An increased level of Carbopol® polymer may be used to compensate for the effect of electrolytes on viscosity. Alternatively, a more salt tolerant grade of the polymer may be used such as Carbopol® ETD 2020 NF, Pemulen™ TR-1 NF or Pemulen™ TR-2 NF polymers. Additionally, deionized or distilled water should be used. Salts should be added after neutralization of the dispersion in order to reduce their impact on product viscosity. Multivalent cations (Ca²⁺, Mg²⁺, Fe³⁺, Al³⁺, etc.) should not be used with Carbopol® polymers.

Contamination with transition metals (Fe, Cu, etc.) causes a gradual reduction in viscosity. It is recommended to include EDTA in the formulation as a complexing agent. Processing in stainless steel or nonmetallic equipment will minimize the effect of metals.

5. **Dispersion Techniques** — Like many fine powders, traditional Carbopol® polymers, as well as Pemulen™ polymers and Noveon® polycarbophil, tend to agglomerate when improperly added to the solvent. Therefore, proper dispersion techniques must be followed to prevent excessively long mixing cycles, reduced viscosity and dispersion defects such as grainy texture, fluctuations in pH and viscosity and the formation of insoluble particles resembling “fish eyes.” If improper dispersion techniques are utilized, the surface of the agglomerated particles solvates to form a tough outer layer which prevents complete wetting of the interior polymer particles.

Carbopol® polymers can be dispersed by sifting the polymer into water, using an eductor or mechanical in-line powder disperser. For more details, see [Pharmaceutical Bulletin 4: “Dispersion Techniques for Lubrizol Pharmaceutical Polymers”](#).

6. **Incorporating Active Pharmaceutical Ingredients into Carbopol® Polymer Dispersions** - Carbopol® polymers, Pemulen™ polymers and Noveon® polycarbophil dispersions can be used as the vehicle in liquid and semisolid dosage forms. Other pharmaceutical ingredients are incorporated into the formulation via two different methods depending on the physical/chemical properties.

Insoluble Ingredients

Insoluble ingredients can be incorporated into the polymeric dispersion either before or after it is neutralized.

Soluble Ingredients

Soluble ingredients can be dissolved in the water used to make the polymeric dispersion. Some soluble ingredients are added to the final formulation to avoid compatibility issues (for example, electrolytes are added at the end).

7. **High Shear Mixing or Pumping** — Carbopol® polymers thicken by forming a gel matrix. High shear mixing, with colloid mills, homogenizers, etc., or high shear pumping can break down the polymer structure resulting in viscosity loss. If necessary, an in-line homogenizer can be used to minimize the homogenization time. Low shear pumps, such as reciprocating diaphragm or auger/gear pumps should be used.

Transparent Hydroalcoholic Gels

Ethanol or other alcohols (propylene glycol, isopropanol) can be used in hydroalcoholic gels to dissolve low solubility active pharmaceutical ingredients instead of using solubilizers such as PEG-40 hydrogenated castor oil, polysorbate 20, etc. The absence of a solubilizer greatly improves the aesthetics of the product as the stickiness and “rubbery” feel is virtually absent. Due to the large ethanol content, additional preservatives may not be required.

The viscosity of an aqueous gel is usually higher than the viscosity of a hydroalcoholic gel due to more hydrogen bonding. Viscosity of the hydroalcoholic gel can be adjusted by increasing the level of Carbopol® polymer.

To manufacture transparent hydroalcoholic gels based on Carbopol® polymer, the ethanolic solution should be added to the hydrogel (Carbopol polymer pre-dispersed in water) using a slowly moving anchor mixer. Also, to reduce air entrapment in the final product, the ethanol solution should be degassed prior to addition as the solubility of air in ethanol is quite high. Degassing of the alcoholic solution is best done by filtering through a glass filter under reduced pressure.

Neutralization of hydroalcoholic gels with Carbopol[®] polymer can be accomplished using different bases. The amine salt of Carbopol[®] polymer must be swellable in the solvent system. If it is not, it will precipitate and no thickening will occur. Triethanolamine can be used in hydroalcoholic gels with up to 50% alcohol. A higher alcohol level requires more alcohol soluble amines, such as tetrahydroxypropyl ethylenediamine, PEG 15 Cocamine, diisopropylamine, amino methyl propanol or tromethamine. For more details, see [Pharmaceutical TDS 237: "Neutralizing Carbopol and Pemulen Polymers in Aqueous and Hydroalcoholic Systems"](#)

Formulating Creams and Lotions

Carbopol[®] polymers can be used to stabilize creams and lotions. In contrast, Pemulen[™] polymers can both stabilize and emulsify (function as primary emulsifiers) oil-in-water emulsions. These emulsifiers have a small lipophilic portion in addition to a large hydrophilic portion. The lipophilic portion adsorbs at the oil-water interface, and the hydrophilic portion swells in the water forming a gel network around oil droplets to provide exceptional emulsion stability to a broad range of oils.

See [Pharmaceutical Bulletin 8: "Emulsification Properties"](#) for more information on using Pemulen[™] polymers to emulsify your topical creams or lotions.

Formulating Topical Emulsions

Typical usage levels of Pemulen[™] polymers in topical emulsions is 0.1% - 0.4 wt.%. As described in [Bulletin 8: "Emulsification Properties"](#), more Pemulen[™] polymer is not necessarily better. The viscosity of the external phase can be increased by using Carbopol[®] polymer in addition to Pemulen[™] polymer. General recommendations for formulation and processing appear below.

1. **pH** — The optimum pH range for an emulsion using Pemulen[™] polymeric emulsifiers is 4-8. A pH above or below this range may cause an unstable emulsion.
2. **High Shear Mixing or Pumping** — Pemulen[™] polymers stabilize the emulsion by forming a gel around the oil droplet. High shear mixing, with colloid mills, homogenizers, etc., or high shear pumping can break down the polymer structure resulting in viscosity loss and emulsion instability. If necessary, an in-line homogenizer can be used to minimize the homogenization time. Low shear pumps, such as reciprocating diaphragm or auger/gear pumps should be used.
3. **Electrolytes, Metals** — Pemulen[™] polymers are sensitive to electrolytes, and preferably their level should be minimized. It is recommended to use the non ionized form of the API whenever possible. Additionally, deionized or distilled water should be used. Salts should be added after neutralization of the dispersion in order to reduce their impact on product viscosity. Multivalent cations (Ca²⁺, Mg²⁺, Fe³⁺, Al³⁺, etc.) should not be used with Pemulen[™] polymers because they will break the emulsion.

Contamination with transition metals (Fe, Cu, etc.) causes a gradual reduction in viscosity and emulsion instability. It is recommended to include EDTA in the formulation as a complexing agent. Processing in stainless steel or nonmetallic equipment will minimize the effect of metals.

4. **Droplet Size** — Pemulen[™] polymers can produce extremely stable macro emulsions, even at large average oil droplet sizes (approaching 1 - 2 millimeters diameter). For aesthetic reasons, it is often desirable to produce small particle size emulsions having a high degree of whiteness, opacity and creamy appearance. The droplet size of the oil phase can be reduced by increasing the mixing time, using moderate shear agitation when the emulsion is made, or by the use of a liquid nonionic surfactant (HLB 8-12) at 0.1 - 0.4 wt. %.
5. **Emulsification Method** — Both a direct and indirect method could be used to create an emulsion with Pemulen[™] polymers.

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