Pharmaceutical Bulletin 1
Edition: May 31, 2011
Previous Editions: August 19, 2005 / December 1, 2008 / August 11, 2010

Polymers for Pharmaceutical Applications

Introduction

Lubrizol offers a versatile line of pharmaceutical ingredients that have been used in a wide range of applications. These functional ingredients have a proven track record of use in oral solid and liquid dosage forms, topical formulations, bioadhesive formulations and bulk laxatives.

Key product brands include Carbopol®* polymers, Pemulen™* polymers and Noveon®* polycarbophil. These polymers provide the following functionality in pharmaceutical applications:

- **Controlled release properties** in solid dosage forms. Carbopol® polymers are highly efficient gel matrix formers for controlling drug release in solid dosage forms. The polymers have demonstrated slower drug release rates at lower concentrations than other commercially available excipients, enabling overall formulation cost savings and smaller tablet sizes.
- **Bioadhesion** in buccal, intestinal, ophthalmic, nasal, vaginal and rectal applications. Noveon® AA-1 USP polycarbophil is the recognized industry standard for bioadhesion.
- **Rheology modification** at very low concentrations (less than 1%) to produce a wide range of viscosities and flow properties in lotions, creams and gels, oral suspensions, and in transdermal gel reservoirs.
- **Suspension of insoluble ingredients** in oral and topical liquids/semisolids.
- **Emulsification of** topical oil-in-water systems, even at elevated temperatures, with essentially no need for surfactants.

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

Product Descriptions

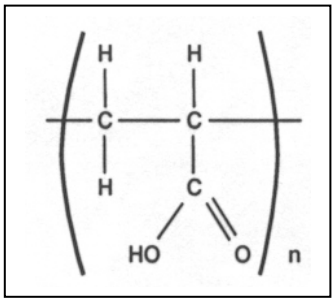
Carbopol® polymers, Pemulen™ polymers and Noveon® polycarbophil are high molecular weight, crosslinked, acrylic acid-based polymers. The main differences among the polymers are related to the crosslinker type and density, and presence of hydrophobic comonomers as summarized below.

- **Carbopol® homopolymers** are polymers of acrylic acid crosslinked with allyl sucrose or allylpentaerythritol.
- **Carbopol® copolymers** are polymers of acrylic acid and C10-C30 alkyl acrylate crosslinked with allyl pentaerythritol.
- **Carbopol® interpolymers** are carbomer homopolymers or copolymers that contain a block copolymer of polyethylene glycol and a long chain alkyl acid ester.
- **Pemulen™ polymers** are polymers of acrylic acid, modified by long chain (C10-C30) alkyl acrylates, and crosslinked with allylpentaerythritol.
- **Noveon® polycarbophil** is a polymer of acrylic acid crosslinked with divinyl glycol.

Typical Properties of Lubrizol's Pharmaceutical Polymers

Lubrizol's pharmaceutical polymers differ in performance, but their general properties are alike. Please refer to TDS-64, Typical Properties of Carbopol® Polymers for more information.

Lubrizol's pharmaceutical polymers are offered as fluffy, white powders. The products are water-swellable and form hydrogels in aqueous dispersions. The carboxyl groups provided by the acrylic acid backbone of the polymer are responsible for many of the product benefits. Carbopol® polymers have an average equivalent weight of 76 per carboxyl group. The general structure can be illustrated with the following diagram:



Carbopol® polymers, Pemulen™ polymers and Noveon® polycarbophil, are flocculated powders averaging 2 to 7 microns in diameter, as determined by Coulter Counter. They are produced from primary polymer particles of about 0.2 micron average diameter. The flocculated agglomerates cannot be broken down into the ultimate particle once produced. Each primary particle can be viewed as 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 linear polymers are soluble in a polar solvent, such as water. Crosslinked polymers swell in water up to 1,000 times their original volume (and ten times their original diameter) to form a gel when exposed to a pH environment above 4.0 - 6.0. Since the pKa of these polymers is 6.0 ± 0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative charges, which adds to the swelling of the polymer. Crosslinked polymers do not dissolve in water. The glass transition temperature of Carbopol® polymer is 105°C (221°F) in powder form. However, the glass transition temperature drops dramatically as the polymer comes into contact with water. The polymer chains start gyrating and the radius of gyration becomes bigger and bigger. Macroscopically, this phenomenon manifests itself as swelling.

The molecular weight of these polymers is theoretically estimated to range from 700,000 to 3 or 4 billion. There are, however, no methods currently available to measure the actual molecular weight of a crosslinked (i.e. three-dimensional) polymer of this type. (See TDS-222, Molecular Weight of Carbopol® and Pemulen™ Polymers for more information.)

Product Grade and Types

Lubrizol's pharmaceutical grade polymers are all manufactured under cGMP standards and they are available in a broad variety of functional grades suitable for different dosage forms.

Numerous enhancements have been made to the polymers over time to address regulatory requirements, meet formulation demands and improve product 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.

Due to regulatory restrictions on the use of benzene in pharmaceutical formulations, Lubrizol recommends that carbomers polymerized in either ethyl acetate or a cosolvent mixture of ethyl acetate and cyclohexane be used for all new drug development projects.

Additionally, it may be desirable to substitute a benzene polymerized carbomer with a non-benzene polymerized carbomer in a pharmaceutical formulation. The substitute products are polymerized in either ethyl acetate or a cosolvent mixture of ethyl acetate and cyclohexane. Table 1 shows recommended substitutes for the benzene grade Carbopol® products based on viscosity criteria. It is important to note that substitute polymers are not identical and performance in a formulation may be different. 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.

Table 1

Recommended Substitutes for Benzene Grade Polymers

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 NF polymers

A product selection guide is provided in Table 2.

Table 2

Product Selection Guide

ORAL APPLICATIONS

			Application Type		
Product Trade Name	**Viscosity, cP (0.5 wt% at pH 7.5)**	**Residual Solvent**	**Solid Dosage**	**Suspensions**	**Bioadhesives**
Carbopol® Polymers					
71G NF	4,000 - 11,000	Ethyl acetate	●	●	●
971P NF	4,000 - 11,000	Ethyl acetate	●	●	●
974P NF	29,400 - 39,400	Ethyl acetate	●	●	●
934P NF	29,400 - 39,400	Benzene	●	●	●
Noveon® Polycarbophil USP					
	USP Absorption (g/g minimum)				
AA-1 USP	62	Ethyl acetate	●	●	●

TOPICAL APPLICATIONS

			Application Type			
Product Trade Name	**Viscosity, cP (0.5 wt% at pH 7.5)**	**Residual Solvent**	**Lotions**	**Creams**	**Gels**	**Bioadhesives**
Carbopol® Polymers						
71G NF	4,000 - 11,000	Ethyl acetate	●		●	●
971P NF	4,000 - 11,000	Ethyl acetate	●		●	●
974P NF	29,400 - 39,400	Ethyl acetate	●	●	●	●
980 NF	40,000 - 60,000	Cosolvent		●	●	●
981 NF	4,000 - 10,000	Cosolvent	●		●	●
5984 EP	30,500 - 39,400	Cosolvent	●	●	●	●
ETD 2020 NF	47,000 - 77,000[1]	Cosolvent	●	●	●	●
Ultrez 10 NF	45,000 - 65,000	Cosolvent	●	●	●	●
934 NF	30,500 - 39,400	Benzene	●	●	●	●
934P NF	29,400 - 39,400	Benzene	●	●	●	●
940 NF	40,000 - 60,000	Benzene		●	●	●
941 NF	4,000 - 10,000	Benzene	●		●	●
1342 NF	9,500 - 26,500[1]	Benzene	●	●	●	●
Pemulen™ Polymers						
TR-1 NF	10,000 - 26,500[1]	Cosolvent	●	●	●	●
TR-2 NF	4,500 - 13,500[1]	Cosolvent	●	●	●	●
Noveon® Polycarbophil USP						
	USP Absorption (g/g minimum)					
AA-1 USP	62	Ethyl acetate		●	●	●

[1] 1.0 wt%

Regulatory Overview

When Lubrizol's "traditional" polymers were originally proposed to the U.S. Pharmacopeia/National Formulary (USP/NF), mucilage viscosity and residual solvent levels differentiated the various compendial products. These traditional polymers were all polymerized in benzene solvent. Over time, Lubrizol has expanded its product offering to include products polymerized in more toxicologically preferred solvents such as ethyl acetate or a cosolvent mixture of ethyl acetate and cyclohexane.

When the toxicologically preferred solvent products were first introduced, USP agreed that Lubrizol could utilize the same generic compendial name that was initially used for the benzene grade products. Since the traditional and toxicologically preferred solvent polymers have the identical raw materials and similar performance, only a product trade name change was needed, but not a compendial name change. The nomenclature difference between the compendial and product trade name has been a source of confusion because the NF Carbomer designation has historically applied to more than one Carbopol® product where chemical similarities exist (e.g. Carbomer 940 applied to Carbopol® 940 NF polymer and Carbopol® 980 NF polymer).

In order to minimize this confusion, umbrella monographs have been developed to separate Carbomer products that are manufactured without the use of benzene as a polymerization solvent. On January 1, 2006 the Carbomer Homopolymer monograph became effective in USP 29-NF 24. It is one of the umbrella monographs that separates the Carbomer products based on polymer structure and applies to homopolymer products that are not polymerized in benzene.

As noted in USP 29-NF 24, the monograph includes a delayed implementation date up to January 1, 2011. Prior to January 1, 2011 the current practice of labeling products as Carbomer 941, Carbomer 934P, Carbomer 934 or Carbomer 940 may be continued.

Additionally, the USP/NF compendial name "Carbomer Copolymer" applies to Pemulen™ polymers and "Carbomer Interpolymer" applies to Carbopol® Ultrez 10 NF polymer and Carbopol® ETD 2020 NF polymer. The Carbomer Homopolymer, Carbomer Copolymer and Carbomer Interpolymer monographs include sub-categories of Carbomers (Type A, Type B and Type C) which differ by viscosity range. The USP/NF compendial name "Polycarbophil" applies to Noveon® polycarbophil.

The European Pharmacopeia (Ph. Eur.) monograph name "Carbomers" covers various Carbopol® homopolymers. The Japanese Pharmaceutical Excipients (JPE) listing identifies Carbopol® homopolymers as "Carboxyvinyl Polymer".

The global regulatory status of Lubrizol's pharmaceutical grade polymers is summarized in Table 3.

Table 3

REGULATORY STATUS OF LUBRIZOL's PHARMACEUTICAL POLYMERS

Product Trade Name	Current USP/NF Monograph	Europe (Ph. Eur.)	Japan (JPE)[1]	U.S. Drug Master File
Carbopol® 934 NF Polymer	Carbomer 934	--	Carboxyvinyl Polymer	153
Carbopol® 934P NF Polymer	Carbomer 934P	--	Carboxyvinyl Polymer	153
Carbopol® 940 NF Polymer	Carbomer 940	--	Carboxyvinyl Polymer	153
Carbopol® 941 NF Polymer	Carbomer 941	--	Carboxyvinyl Polymer	153
Carbopol® 1342 NF Polymer	Carbomer 1342	--	--	7757
Carbopol® 71G NF Polymer	Carbomer Homopolymer Type A	Carbomers*	Carboxyvinyl Polymer	17095
Carbopol® 971P NF Polymer	Carbomer Homopolymer Type A	Carbomers*	Carboxyvinyl Polymer	7170
Carbopol® 974P NF Polymer	Carbomer Homopolymer Type B	Carbomers*	Carboxyvinyl Polymer	7170
Carbopol® 980 NF Polymer	Carbomer Homopolymer Type C	Carbomers*	Carboxyvinyl Polymer	10072
Carbopol® 981 NF Polymer	Carbomer Homopolymer Type A	Carbomers*	Carboxyvinyl Polymer	10071
Carbopol® ETD 2020 NF Polymer	Carbomer Interpolymer Type B			
Carbopol® Ultrez 10 NF Polymer	Carbomer Interpolymer Type A	--	--	12945
Pemulen™ TR-1 NF Polymer	Carbomer Copolymer Type B	--	--	7757
Pemulen™ TR-2 NF Polymer	Carbomer Copolymer Type A	--	--	7757
Noveon® AA-1 USP Polycarbophil	Polycarbophil	--	--	7618

* 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

Product Grade Summary

Oral/Mucosal Adhesive Grades

Select Carbopol® polymers and Noveon® AA-1 polycarbophil, USP are intended for oral and mucosal contact applications. The Carbopol® polymers which are recommended for oral and mucosal applications are designated by a "P" in the product trade name (i.e. Carbopol® 971P NF polymer).

Carbopol® 934P NF Polymer
(USP/NF Monograph: Carbomer 934P)

Carbopol® 934P NF polymer was designed especially for the pharmaceutical industry in the 1960s, as a high purity grade of Carbopol® 934 polymer. Some commercially available formulations contain Carbopol® 934P NF polymer, but this material is not recommended for new product development due to regulatory restrictions on benzene.

Carbopol® 971P NF and Carbopol® 71G NF Polymers
(USP/NF Monograph: Carbomer Homopolymer Type A)

Carbopol® 971P NF polymer is polymerized in ethyl acetate and is similar to Carbopol® 941 polymer (polymerized in benzene). Carbopol® 971P NF polymer was introduced specifically for use in oral and mucosal contact applications such as controlled release tablets, oral suspensions and bioadhesives. It is lightly crosslinked and therefore tends to be more efficient in controlling drug release than Carbopol® 974P NF polymer which is highly crosslinked. Typical usage levels in tablets for achieving extended release characteristics are 3 - 10 wt.%, depending on the drug properties, co-excipients and processing parameters.

Carbopol® 971P NF polymer also provides thickening, suspending and emulsion stabilizing properties to low viscosity systems for topical applications.

Carbopol® 71G NF polymer is a granular form of Carbopol® 971P NF polymer which is ideal for use in direct compression for tablets. It is the same chemical with no additives and improved flow properties.

Carbopol® 974P NF Polymer
(USP/NF Monograph: Carbomer Homopolymer Type B)

Carbopol® 974P NF polymer was introduced specifically for use in oral and mucoadhesive contact applications such as controlled release tablets, oral suspensions and bioadhesives. In addition, Carbopol® 974P NF polymer provides thickening, suspending and emulsion stabilizing properties to high viscosity systems for topical applications.

Noveon® AA-1 Polycarbophil, USP
(USP/NF Monograph: Polycarbophil)

For bioadhesive applications, Noveon® AA-1 polycarbophil, USP is the industry standard and has been extensively formulated in a variety of drug delivery systems for mucosal applications. Buccal, intestinal, nasal, vaginal and rectal bioadhesive products can all be formulated with Noveon® AA-1 polycarbophil.

Topical Grades

Carbopol® 941 NF Polymer (USP/NF Monograph: Carbomer 941)
Carbopol® 981 NF Polymer (USP/NF Monograph: Carbomer Homopolymer Type A)

Carbopol® 941 NF polymer and its cosolvent polymerized alternative, Carbopol® 981 NF polymer, have the ability to stabilize low viscosity suspensions. The gels produced with these polymers have excellent clarity. In ionic systems, they perform better than most of the other Carbopol® polymers. Carbopol® 941 NF and 981 NF polymers produce higher viscosities than Carbopol® 934 NF, 940 NF or 980 NF polymers at concentrations below 0.1% in aqueous systems; and at concentrations below 1.5% in solvent systems. If the hydrogen bonding thickening mechanism is used, Carbopol® 941 NF and 981 NF polymers may be more effective than the other Carbopol® polymers.

Carbopol® 1342 NF Polymer
(USP/NF Monograph: Carbomer 1342)

Carbopol® 1342 NF polymer provides pseudoplastic rheology which is highly effective in formulating pourable products containing suspended ingredients; or in making stable emulsions. Carbopol® 1342 NF polymer contains a long chain alkyl acrylate, a lipophilic modification to its backbone, giving it a compatibility advantage over other Carbopol® polymers in thickening and imparting yield value to ionic systems.

Carbopol® 934 NF Polymer
(USP/NF Monograph: Carbomer 934)

Carbopol® 934 NF polymer is very effective in high viscosity formulations such as gels, emulsions and suspensions.

Carbopol® 934 NF polymer provides permanent stability. In aqueous systems, Carbopol® 934 NF polymer provides short flow and quick recovery, properties which are of interest in topical applications.

Carbopol® 940 NF Polymer (USP/NF Monograph: Carbomer 940)
Carbopol® 980 NF Polymer (USP/NF Monograph: Carbomer Homopolymer Type C)

Carbopol® 940 NF polymer and Carbopol® 980 NF polymer, its cosolvent alternative, form sparkling clear water or hydroalcoholic gels. They are also the most efficient thickeners of all the Carbopol® polymers, and have extremely short flow properties (non-drip) suitable for spray-on applications.

Carbopol® ETD 2020 NF Polymer
(USP/NF Monograph: Carbomer Interpolymer Type B)

Carbopol® ETD 2020 NF polymer is an "easy-to-disperse" copolymer processed in a toxicologically preferred cosolvent system. It delivers excellent thickening efficiency and suspending capability, long viscous flow and sparkling clarity in gel systems.

Carbopol® ETD 2020 NF polymer is specifically designed to produce aqueous dispersions which are less susceptible to agglomeration and easier to pump and handle due to its low dispersion viscosity before neutralization. Aqueous dispersions of Carbopol® ETD 2020 NF polymer are, therefore, easier to prepare at higher polymer solids. Suggested applications include oral care products, clear gels, hydro-alcoholic gels, and high electrolyte systems.

Carbopol® Ultrez 10 NF Polymer
(USP/NF Monograph: Carbomer Interpolymer Type A)

Carbopol® Ultrez 10 NF polymer is specifically designed to produce aqueous dispersions which are less susceptible to agglomeration and easier to pump and handle due to its low dispersion viscosity before neutralization.

Carbopol® Ultrez 10 NF polymer is chemically similar to standard Carbopol® polymers. It is a homo-polymer of acrylic acid, crosslinked with a polyalkenyl polyether. Carbopol® Ultrez 10 NF polymer differs from other Carbopol® polymers in that it is produced with a proprietary polymerization aid in a toxicologically preferred cosolvent system.

Carbopol® Ultrez 10 NF polymer can be used in topical formulations as an alternative to Carbopol® 934, 940 or 980 polymers.

The unique dispersion performance of Carbopol® Ultrez 10 NF polymer allows it to wet quickly, yet hydrate slowly. This property helps minimize agglomeration, which can be troublesome when turbulent mixing is not available during dispersion. The lower viscosity unneutralized dispersion also allows easier handling in mixing tanks and in process lines. Once the polymer is neutralized, it provides the type of highly efficient thickening for which Carbopol® polymers are known.

Pemulen™ TR-1 NF Polymer (USP/NF Monograph: Carbomer Copolymer Type B)
Pemulen™ TR-2 NF Polymer (USP/NF Monograph: Carbomer Copolymer Type A)

Pemulen™ TR-1 NF and Pemulen™ TR-2 NF polymers are primary emulsifiers for oil-in-water emulsions. Pemulen™ TR-1 NF polymer can emulsify up to 30% oil by weight while Pemulen™ TR-2 NF polymer can emulsify up to 65 - 80% oil by weight. These products enable formulation of emulsions, even at elevated temperatures, without the use of surfactants.

When formulated with little or no surfactant, the oil phase in a Pemulen™ emulsion can spread rapidly and cannot re-wet. As a result, emulsions based on polymers deposit an occlusive layer on the skin, delivering the topical medication in the form of low irritancy lotions and creams. Pemulen™ polymers can also be used for high clarity topical gels with hydrophobic or highly ionic components.