Excipients for Oral Solid Dosage Forms
Pharmaceutical Polymers for Oral Solid Dosage

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 polymers and Noveon polycarbophil are high-molecular-weight polymers of acrylic acid, chemically crosslinked with polyalkenyl alcohols or divinyl glycol. These polymers have been successfully formulated into a variety of different commercial tablet forms including swallowable (peroral), chewable, buccal and sublingual tablets.

Carbopol polymers and Noveon polycarbophil can provide highly effective controlled-release properties at low concentrations. Typical usage levels in extended-release tablets are 5–30%, depending on the drug properties, co-excipients and processing parameters.

Additionally, the polymers can provide bioadhesion, taste-masking and good binding characteristics. Carbopol polymers and Noveon polycarbophil offer formulation flexibility because they can be used with a variety of pharmaceutical active ingredients and excipients and can be processed by direct compression, dry granulation (roller compaction, slugging) or wet granulation (high/low shear, extrusion spheronization, pelletization) methods.

Lubrizol LifeScience Polymers are supported by substantial literature references citing their performance in solid dosage forms. Additionally, Lubrizol researchers support customers in the development of new products, concepts, prototype formulations and custom formulations through regional technical service centers in the U.S., Mexico, India and China.
Recommended Polymers for Solid Dosage Forms

The products that Lubrizol recommends for use in controlled-release matrix tablets are Carbopol 71G NF, Carbopol 971P NF and Carbopol 974P NF polymers. These polymers are manufactured in ethyl acetate, which is a Ph. Eur./USP/ICH Class III solvent with Generally Recognized as Safe (GRAS) status.

Table 1. Carbopol polymers and Noveon polycarbophil for oral solid dosage forms.

<table>
<thead>
<tr>
<th>Product Trade Name</th>
<th>Pharmacopeia Monograph Compendial Name</th>
<th>Polymerization Solvent</th>
<th>Crosslinker Type</th>
<th>Physical Form</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Carbopol® Polymers</td>
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<tr>
<td>71G NF</td>
<td>Carbomer Homopolymer Type A</td>
<td>Carbomers</td>
<td>Carboxyvinyl Polymer</td>
<td>Ethyl Acetate</td>
<td>Allyl ethers of pentaerythritol</td>
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<tr>
<td>971P NF</td>
<td>Carbomer Homopolymer Type A</td>
<td>Carbomers</td>
<td>Carboxyvinyl Polymer</td>
<td>Ethyl Acetate</td>
<td>Allyl ethers of pentaerythritol</td>
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<tr>
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<td>Carbomer Homopolymer Type B</td>
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<td>Carboxyvinyl Polymer</td>
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<td>Noveon® Polycarbophil</td>
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<tr>
<td>AA-1 USP</td>
<td>Polycarbophil</td>
<td>—</td>
<td>—</td>
<td>Ethyl Acetate</td>
<td>Divinyl glycol</td>
</tr>
</tbody>
</table>

1 Lubrizol’s benzene polymerized polymers do not meet the European Pharmacopoeial “Carbomers” monograph because the residual benzene levels exceed the 2 ppm limit stipulated in the monograph.

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

Some commercially available formulations contain Carbopol 934P NF polymer which is polymerized in benzene. This material should not be used for new product development due to regulatory restrictions on the presence of benzene in pharmaceutical products.

Regulatory Status of Polymers

Regarding compendial classification, the European Pharmacopoeia has only one monograph which applies to Carbopol polymers titled “Carbomers.” Similarly, the Japanese Pharmaceutical Excipients (JPE) also has a single monograph titled “Carboxyvinyl Polymer.”

The United States Pharmacopoeia/National Formulary has several monographs for different carbomer grades. The monographs titled “Carbomer XXX” (where XXX is a numerical designation) are assigned to products manufactured with the use of benzene.

Additionally, there are three umbrella monographs that separate carbomer products based on polymer structure. These three monographs are “Carbomer Copolymer,” “Carbomer Homopolymer” and “Carbomer Interpolymer,” and they apply to products not polymerized in benzene. The differentiation within each umbrella monograph is based on viscosity characteristics (Type A, Type B and Type C).
Key Benefits of Lubrizol Pharmaceutical Polymers

• Highly efficient controlled-release agents in both monolithic and multiparticulate systems
  - Data demonstrates slower release at lower use levels than other commercially available excipients
  - Carbopol is highly efficient at low polymer levels (typical use levels are 5–30%), enabling smaller tablet sizes and overall formulation cost savings
• Provide flexibility in achieving a target release profile
  - Varying the polymer level in the formulation is an effective formulation tool. Compared to cellulosic materials, the drug release profile from a Carbopol polymer matrix can be more easily modulated by changing the polymer level
  - Active pharmaceutical ingredients (APIs) with different properties can be formulated to achieve various extended-release profiles
• Can be used alone or in synergy with other:
  • Carbopol polymer grades
  • Controlled-release excipients (hypromellose – HPMC; hydroxypropyl cellulose – HPC; carboxymethyl cellulose sodium – CMC; sodium alginates, etc.)
  • Available in both powder and granular forms (Carbopol 71G NF polymer) and can be used in all types of tablet manufacturing processes
• Efficient binders in wet and dry granulation processes, allowing formulation of matrix tablets without the addition of a tablet binder. Also provide excellent tablet hardness and low friability over a wide range of compression forces
• Varying compression force/tablet hardness does not affect drug release from carbomer matrices
• Improve bioavailability of certain drugs
• May impart functional attributes such as taste-masking, bioadhesion and binding
• Widely compatible with commonly used tablet and capsule excipients
• Synthetic, reproducible polymers
• Not affected by Transmissible Spongiform Encephalopathy (TSE)/Bovine Spongiform Encephalopathy (BSE) or Genetically Modified Organism (GMO) concerns
• Products have global pharmacopeial status and are supported by Drug Master Files (DMFs) in the United States and Europe
• Enable development of patentable technologies for product differentiation and/or life-cycle extension
Drug-Release Mechanism from Tablets with Lubrizol Polymers

Carbopol polymers and Noveon polycarbophil are efficient matrix-forming excipients. These polymers are not soluble, but only swellable in water. In contrast, other hydrophilic controlled-release excipients such as hydroxypropyl methyl cellulose and hydroxypropyl cellulose are linear polymers, not chemically crosslinked and, therefore, water-soluble.

The drug is dispersed homogenously throughout the polymer matrix. Drug release from tablets and capsules with Carbopol polymers or Noveon polycarbophil is controlled by:

- Drug diffusion through the gel layer that the polymer forms in contact with the aqueous medium.
- Matrix (polymer) relaxation.

When carbomer tablets are placed in contact with the dissolution medium, the following occurs:

- Drug in the outside layer exposed to the bathing solution is dissolved and then diffuses out of the matrix.
- The polymer swells to form a hydrated matrix layer (hydrogel) (Figure 1). Due to the crosslinked nature of the polymers, the hydrogel is not comprised of single entangled chains of polymers (as is the case with linear polymers), but is comprised of discrete microgels made up of many polymer particles in which the drug is dispersed.
- The hydrated matrix layer controls water penetration (into the nonhydrated core) and diffusion of the drug through the hydrated matrix (Figure 2). Unlike linear polymers, Carbopol polymers and Noveon polycarbophil do not dissolve during the release process.

**Figure 1.** Carbopol® Polymers Hydration Mechanism

![Dry Polymer](Image)

![Hydrated Polymer](Image)

**Figure 2.** Drug Release Schematic

Matrix tablet

- Swelling front
- Diffusion front
- Erosion front
Factors Affecting Drug Release

Polymer Type
- Lightly crosslinked Carbopol polymers (971P NF) tend to be more efficient in controlling drug release than highly crosslinked Carbopol polymers (974P NF). Intermediate drug release can be achieved by combining Carbopol 971P NF and 974P NF polymers.

Polymer Level
- Increasing the level of Carbopol polymer in a formulation leads to slower and more linear drug release.
- At low usage levels, Carbopol polymers can be more effective than cellulosic materials in sustaining the drug release.

Drug Solubility
- Release from Carbopol polymer tablets is generally slower for drugs with low water solubility.

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Dissolution Medium
- Drug release from Carbopol polymer matrices may be medium-dependent due to the anionic nature of the polymer.
  - The swelling and gel formation of the polymers are pH-dependent. However, it is important to note that the pH effect on the polymer does not significantly impact drug release in various media (Figures 5-6). The most significant factor impacting drug release is API solubility and how it is affected by pH.

Figure 3. Ketoprofen release in pH=6.8 phosphate buffer from tablets (200 mg) with Carbopol® polymers.

Figure 4. Guaifenesin release in 0.1 N HCl from tablets (100 mg).
Is drug release from Carbopol polymer matrices pH-dependent?

Due to the anionic nature of the polymers, drug release from Carbopol polymers matrices may be pH-dependent.

At lower pH values, the polymer is not fully swollen and there are larger regions of microviscosity. The dissolution medium can penetrate fast and deep into the glassy core, and the drug is released faster, before complete gel formation occurs.

As the pH increases, the ionization of the carboxylic acid groups causes maximum swelling, resulting in fewer and smaller regions of microviscosity. The rapid gel formation acts as a barrier for the release of the drug, thus prolonging the release.

However, Lubrizol has demonstrated that Carbopol polymers have the ability to form robust tablets which can extend drug release in both acid and buffer media. No significant difference has been observed in the release profiles due to dissolution medium in the case of drugs with pH-independent solubility.

**Figure 5.** Acetaminophen release in different media from tablets (100 mg) with 10% Carbopol® 971 NF polymer (wet granulation).

**Figure 6.** Guaiifenesin release in different media from tablets (600 mg) with Carbopol® 971P NF polymer (5%) and 71G NF (7.5%).
Synergistic Effects of Carbopol Polymers and Hypromellose for Matrix Tablets

Carbopol polymers can be used alone as a controlled-release agent in matrix tablets or in combination with hypromellose. Potential benefits to be derived from the polymer combination matrix (Carbopol polymer/hypromellose) versus use of a single polymer matrix (Carbopol polymer or hypromellose) are as follows:

- Lower total polymer level needed
  - Formulation cost savings
  - Better patient compliance with smaller tablets
- Performance consistency with regard to drug release
- Flexibility in modulating drug release

The synergistic effects of a polymer combination matrix have been demonstrated in a variety of APIs with different solubilities. Benefits were observed in matrix tablets manufactured by direct compression and wet granulation with both low- and mid-dose tablets. Results for tablets manufactured by wet granulation are shown in Figures 7 and 8. In buffer, the synergistic interpolymer interaction is by chain entanglements between hypromellose and swollen carbomer particles. The polymer combination forms a more cohesive network, more resistant to diffusion and erosion.

The synergistic use of Carbopol polymers with other extended-release excipients (hydroxypropyl cellulose, sodium carboxymethyl cellulose, sodium alginate, polyethylene oxide and methacrylic polymers) has also been reported in the literature.

Guaifenesin (High Solubility)

Figure 7. Guaifenesin release (pH=6.8 buffer) from tablets (100 mg) with 10% polymer.

Ketoprofen (Low Solubility)

Figure 8. Ketoprofen release (pH=6.8 buffer) from tablets (100 mg) with 30% polymer.

Formulation Tips for Use of Carbopol Polymers in Extended-Release Tablets

Active Pharmaceutical Ingredient (API)

API Dose

- Higher API dosages generally require higher polymer levels.

API Solubility

- Higher API solubility requires higher polymer levels.
- For water-soluble drugs, 10% powder grade polymer (wet granulation) or 25% granular grade polymer (direct compression) may be a good starting concentration. Lower polymer levels may be sufficient for low-solubility drugs.

- For higher-soluble/high-dose drugs, some other approaches may be required in conjunction with increasing the polymer level. For example, use of a polymer combination matrix or combined technologies (addition of the polymer intra- and extragranularly, coating of the matrix tablets, etc.).

- Low-solubility APIs can be formulated with carbomers in extended-release matrix tablets. Examples of commercial tablets include nifedipine, lithium carbonate and mesalamine. For this type of API, the predominant in vitro drug-release mechanism from Carbopol polymer matrix tablets is polymer relaxation (erosion).
API Ionic Character

- Cationic APIs can interact with Carbopol polymers, and this interaction requires the ionized form of the polymer (occurs in the buffer).
  - The molar ratio of API to Carbopol polymer (carboxyl) is important for the interaction. A high stoichiometric ratio of carboxyl to API is favorable for interaction.
  - API properties are important for the ionic interaction (solubility, amine group strength, steric orientation, molecular weight and size).
  - Ionic interaction can slow the drug release and provide taste-masking properties.
  - Ionic interaction will not occur with all cationic drugs and is API- and formulation-dependent.
  - Examples of commercial products containing cationic APIs and carbomers are tablets of dextromethorphan, diethylpropion, glucosamine, metformin, metoprolol and pseudoephedrine.

- The acidic nature of Carbopol polymer can modulate the microenvironmental pH in the tablet. This is important for API stability and solubility inside the matrix.

API Assay

In order to ensure total recovery of the API from the Carbopol polymer tablets, it is recommended to run the analysis after grinding the tablets. Key considerations are as follows:

- The API is extracted from the crushed tablets by sonication or other mixing techniques.
- The criteria for solvent selection are API solubility and reduced polymer swelling. Examples of solvents in which the polymer does not swell extensively are anhydrous ethanol or an acidic aqueous solution at pH~1.2.
- The extraction method has to be optimized; generally larger solvent volume and longer sonication time improve the API recovery, but have to be tested to determine if they affect the API stability.
- Addition of an electrolyte (sodium chloride) to the extraction solvent may improve the recovery (ion effect on the polymer).

Carbopol Polymers

Trade Name Versus Generic Name

- Carbopol polymer is a product brand name of The Lubrizol Corporation. There is a variety of Carbopol polymer grades, which differ in their performance characteristics. These grades are distinguished by a number designation following the product brand name (e.g., Carbopol 971P NF polymer and Carbopol 71G NF polymer).
  - In contrast, “carbomer” is one of the generic names that can be used to describe Carbopol polymers. Carbomer can be defined as a high-molecular-weight polymer of acrylic acid crosslinked with allyl ethers of polyalcohols. The United States Pharmacopeia (USP) includes various carbomer monographs while the European Pharmacopeia (Ph. Eur.) includes only one.

Effect of Viscosity on Drug Release

- Drug release from Carbopol polymer matrix tablets is controlled more by the polymer structure (crosslink density) than by viscosity. Lightly crosslinked polymers have fewer crosslink sites to constrain the polymer, and a homogeneous gel structure forms at lower concentrations compared to highly crosslinked polymers. As a result, the API is less subject to diffusion through the gel layer or erosion.
  - Lightly crosslinked carbomers such as Carbopol 971P NF polymer (lower viscosity) are generally more efficient in controlling drug release than highly crosslinked carbomers such as Carbopol 974P NF polymer (higher viscosity).
  - In contrast to linear polymers, higher viscosity does not result in slower drug release with carbomers.

Granular Versus Powder Grades

- Lubrizol manufactures several powder grades of Carbopol polymers for oral solid dosage forms such as Carbopol 971P NF polymer and Carbopol 974P NF polymer. A granular grade (Carbopol 71G NF polymer) is manufactured by roller compaction of Carbopol 971P NF polymer with no additives. Carbopol 71G NF polymer has been designed for direct-compression processes, and it can be incorporated extragranularly in formulations.
  - The differences between Carbopol 971P NF polymer and Carbopol 71G NF polymer are particle size and density.
Acidic Nature of Carbopol Polymer

- The acidic nature of Carbopol polymer can modulate the microenvironmental pH in the tablet. This is important for API stability and solubility inside the matrix. Control of microenvironmental pH can provide consistent release of cationic drugs throughout the gastrointestinal tract.

Carbopol Polymer Versus Linear, Hydrophilic Polymers (Hypromellose)

- The drug-release mechanism from Carbopol polymers and linear, (soluble) hydrophilic polymers is similar in that both are forming hydrophilic matrices. In the case of soluble drugs, the predominant drug-release mechanism is diffusion through the gel layer. While in the case of low-solubility drugs, the predominant mechanism is polymer relaxation or erosion.

- Unlike linear, hydrophilic polymers, Carbopol polymers are chemically crosslinked. As a result, they are able to form gels at lower concentrations than linear polymers. Linear polymers form gels through virtual crosslinking (chain entanglement), and higher polymer levels are usually required to obtain extended-release properties. Additionally, Carbopol polymers do not dissolve, but only disperse and swell in aqueous environments.

- For powder-grade Carbopol polymers (Carbopol 971P NF and 974P NF polymers), typical usage levels are 5–10% wt. In comparison, typical usage levels of hypromellose are 20–40% wt.

- The granular grade Carbopol 71G NF polymer is typically used at 10–30% wt. in direct-compression formulations or when added extragranularly. Powder grades of Carbopol polymer are more efficient in extending drug release than the granular grade due to the larger surface area (faster hydration), thus lower levels of polymer are generally needed.

Coexcipients

- Fillers can have an impact on the release due to their solubility and disintegrating properties.

- Synergistic effects of Carbopol polymers with other polymeric excipients (hypromellose, hydroxypropyl cellulose, polyethylene oxides, etc.) may enhance drug release properties.

Method of Tablet Manufacture

- Carbopol polymers can be processed by direct compression or by various granulation technologies (wet, dry, fluid bed, spray drying, extrusion spherization and hot melt extrusion).

- Direct compression with granular carbomer generally requires higher polymer levels (15–30%) than granulation with powder grades (5–15%) mainly due to differences in polymer surface area. Specifically, there is a smaller surface area for the granular grade used in direct compression than for the powder grades used. Use of combinations of powder and granulation grades added intra-/extragranularly allows for processing versatility, efficiency, and flexibility in controlling drug release.

Polymer Functionality

Carbopol Polymers as Tablet Binders

- Carbopol polymers are efficient tablet binders. Formulations comprising Carbopol polymers generally do not require an additional binder to be used.

- In the case of wet-granulation formulations, it is recommended to incorporate the polymer in the powder blend (0.5–3.0% w/w) versus adding it as an aqueous dispersion due to the high viscosity of the polymer. Carbopol polymer dispersions (maximum 1%) can be used for fluid-bed granulation.

Bioadhesive Properties

- Carbopol polymers and Noveon polycarbophil can provide bioadhesive and/or controlled-release properties. A significant amount of information is available regarding the use of those polymers as a bioadhesive.

- Carbopol 971P NF polymer was included in a doxycycline sublingual tablet formulation to provide both bioadhesion and sustained drug release.

- Formulations of buprenorphine sublingual tablets containing Carbopol 974P NF polymer provided adequate mucoadhesive strength and drug release.

Application in Floating Tablets

- Carbomers do not dissolve and are not metabolized in the gastrointestinal tract. In gastric mediums, the polymers hydrate and swell, enabling floating. Carbomers can be used alone or in combinations with other polymers or effervescent systems to formulate gastric floating dosage forms.

Taste Masking

- Carbopol polymers have the ability to mask the taste of some APIs (mostly cationic drugs) by forming insoluble adsorbates through weak ionic bonding. These adsorbates dissolve rapidly after ingestion (the endogenous cations displace the drug from the polymer). Literature references highlighting this property include macrolide antibiotics, enrofloxacin and dextromethorphan.
• Carbopol polymers have been used in combination with film-forming materials for taste-masking coating compositions. Additionally, Carbopol polymers have been reported to ameliorate the throat catch (unpleasant taste and sensation in the throat) caused by ibuprofen. Possible mechanisms involve binding to specific sites in the throat or coating the mucosa to prevent contact of the bitter and/or throat catch producing agent with the mouth and throat mucosa.

In Vivo Studies

There are several references in the literature regarding Carbopol polymer matrices which confirm the ability of the polymer to extend drug release in vivo.


• US 5,484,608: Sustained-release drug delivery system

• US 5,681,581: Controlled-release pharmaceutical formulations of AZT

• US 5,741,805: Controlled-release pilocarpine delivery system

• WO2224203: Controlled-release formulations for oral administration

• US20030224050: Drug delivery system for sustained delivery of glipizide

• WO2005039555: Extended-release tablet formulations of venlafaxine

• US 20070031491: Biodegradable progressive hydration tablets

• WO0132165: Method for administering a phosphodiesterase 4 inhibitor

• WO2005030178: Extended-release formulation of beta-lactam antibiotics

• WO2006082523: Pharmaceutical compositions of metformin

Stability of Carbopol Polymer Matrix Tablets

• Carbopol polymers are hygroscopic materials, and packaging of tablets containing the polymers should provide moisture protection. It is recommended that the stability of the final product should be evaluated as part of the formulation-development activities. Lubrizol has conducted a study under ICH conditions on tablets containing Carbopol polymers packed in desiccant vials. No change in dissolution profile was observed in tablets stored under accelerated conditions for 6 months or long-term for 1 year.

Recommended Cleaning Procedure

• Water, solution of electrolytes (sodium chloride) or diluted caustic solutions can be used to clean equipment after processing with Carbopol polymers. Spraying those solutions under pressure generally increases cleaning efficiency. Manufacturing equipment should be promptly cleaned after processing carbomer dispersions.

• Gelled residue may be removed by power washing 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)
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