Carbopol® Polymers for Controlled Release Matrix Tablets

Frequently Asked Questions

1. Which products does Lubrizol recommend for controlled release matrix tablets and what are the properties of these products?

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 GRAS status.

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.

Product Trade Name	Residual Solvent	Crosslinker Type	Physical Form	Comments
Carbopol® Polymer				
71G NF	Ethyl acetate	Allyl ethers of pentaerythritol	Granular	Chemically the same as Carbopol® 971P NF polymer with no additives. Ideal for direct compression processes due to its improved flow properties.
971P NF	Ethyl acetate	Allyl ethers of pentaerythritol	Powder	Lightly crosslinked polymer. Typically, the most efficient grade for controlling drug release.
974P NF	Ethyl acetate	Allyl ethers of pentaerythritol	Powder	Highly crosslinked polymer.

2. What are the key differences between the granular and powder grades of Carbopol® polymers?

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.

Carbopol® 971P NF polymer (powder form)

Carbopol® 71G NF polymer (granular form)

3. What are the main benefits of using Carbopol® polymers in controlled release matrix tablets?

The main benefits of using Carbopol® polymers in controlled release matrix tablets are as follows:

- Highly efficient at low polymer levels (typical use levels are 3 – 30%), enabling smaller tablet sizes and overall formulation cost savings.
- Provides flexibility in achieving a target release profile by varying the polymer level in the formulation. Compared to cellulosic materials, the drug release profile from a Carbopol® polymer matrix can be more easily modulated by changing the polymer level.
- Provides good binding characteristics, thus allowing formulation of matrix tablets without the addition of a tablet binder.
- Synthetic, reproducible polymer.
- Provides bioadhesive properties.
- Enables development of patentable technologies for product differentiation and/or life cycle extension.

4. What is the difference between the designation "Carbopol®" polymer and "Carbomer"?

Carbopol® polymer is a product brand name of The Lubrizol Corporation. There are 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) and European Pharmacopeia (Ph. Eur.) include various carbomer monographs.

5. What is the current compendial nomenclature that applies to Carbopol® polymers?

The European Pharmacopeia has only one monograph which applies to Carbopol® polymers called "Carbomers". Similarly, the Japanese Pharmaceutical Excipients also has a single monograph called "Carboxyvinyl Polymer".

The United States Pharmacopeia/National Formulary has several monographs for different carbomer grades. The monographs called "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).

Lubrizol Polymers for Oral Applications

Product Trade Name	Residual Solvent	Pharmacopeia Monograph Compendial Name		
		United States (USP/NF)	Europe (Ph. Eur.)	Japan (JPE)
Carbopol® Polymer				
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
934P NF	Benzene	Carbomer 934P		Carboxyvinyl Polymer
Noveon® Polycarbophil				
AA-1 USP	Ethyl acetate	Polycarbophil		

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

6. What is the United States Pharmacopeia/National Formulary nomenclature that applied to Carbopol® homopolymers prior to January 1, 2006?

Prior to January 1, 2006, the carbomer monographs within the U.S. Pharmacopeia/National Formulary (USP/NF) were based on mucilage viscosity and residual solvent levels. The monographs did not distinguish the type of polymerization solvent.

Initially, Carbopol® polymers were polymerized in benzene. Over time, Lubrizol has expanded its product offering to include products polymerized in 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 (as long as they meet the viscosity and residual solvent level criteria). As a result, one compendial designation could apply to more than one Carbopol® polymer product trade name (e.g. Carbomer 940 applied to Carbopol® 940 NF polymer and to Carbopol® 980 NF polymer).

Carbomer Homopolymer	Viscosity Specified (cP)
Type A	4,000 - 11,000
Type B	25,000 - 45,000
Type C	40,000 - 60,000

In January, 2006 the U.S. Pharmacopeia/National Formulary (USP 29-NF 24) introduced a new umbrella monograph called "Carbomer Homopolymer" which applies to homopolymers that are manufactured without the use of benzene as a polymerization solvent. The Carbomer Homopolymer monograph includes three different types based on viscosity (Type A, Type B and Type C) and allows a delayed implementation date up to January 1, 2011. Prior to January 1, 2011 the practice of labeling non benzene carbomer homopolymers as Carbomer 941, Carbomer 934P, Carbomer 934 or Carbomer 940 may be continued*.

Product Trade Name	USP/NF Compendial Name (Prior to January 1, 2006)*	(After January 1, 2006)
Carbopol® 71G NF Polymer	Carbomer 941	Carbomer Homopolymer Type A
Carbopol® 971P NF Polymer	Carbomer 941	Carbomer Homopolymer Type A
Carbopol® 974P NF Polymer	Carbomer 934P	Carbomer Homopolymer Type B

7. What CAS registry numbers and naming conventions are currently noted on the U.S. FDA Inactive Ingredient Guide (IIG) that apply to Carbopol® polymers for oral administration?

Various CAS numbers are currently reported on the IIG list that apply to Carbopol® polymers. Carboxypolymethylene is a generic name that can be used to describe all Carbopol homopolymers including Carbopol® 71G NF, 971P NF and 974P NF polymers.

IIG Name	IIG CAS Number	IIG Route/Dosage Form	IIG Maximum Potency	Chemical Index Name	Alternative CAS Number
Carboxypolymethylene	9007-20-9	ORAL (Suspension) ORAL (Tablet, sustained action)	No calculable potency measurement available 195.00 mg	Carbomer	9003-01-4
Carbomer 934 **Carbomer 934P (lower benzene content 934)**	9007-16-3 None cited	ORAL (Suspension) ORAL (Tablet, sustained action) BUCCAL (Tablet) ORAL (Capsule) ORAL (Suspension) ORAL (Tablet, extended release) ORAL (Tablet, orally disintegrating) ORAL (Tablet, sustained action) ORAL (Tablet, sustained action, coated)	5.00% 90.00 mg 9.37 mg 14.20 mg 1.40% 15.00 mg 0.30 mg 1.50 mg 3.00 mg	Carbomer 934	9003-01-4
Carbomer 941	9003-01-4			2-Propenoic acid, homopolymer	
Carbomer 974*	9003-01-4	ORAL (Granule, for suspension)	No calculable potency measurement available	2-Propenoic acid, homopolymer	
Carbomer 974P*	None cited	ORAL (Tablet, controlled release) ORAL (Tablet, sustained action)	6.25 mg 6.25 mg	Not applicable	9003-01-4

**Carbomer 974 and Carbomer 974P are not compendial monograph names.*

There are several different IIG names that might be associated with a particular Carbopol® polymer grade as outlined in the table. It should be noted that the new USP/NF names (after January, 2006) applicable to carbomer homopolymers might also be used for regulatory submission purposes.

Product Trade Name	IIG Name
Carbopol® 71G NF Polymer	Carboxypolymethylene; Carbomer 941
Carbopol® 971P NF Polymer	Carboxypolymethylene; Carbomer 941
Carbopol® 974P NF Polymer	Carboxypolymethylene; Carbomer 934P; Carbomer 974; Carbomer 974P
Carbopol® 934P NF Polymer	Carboxypolymethylene; Carbomer 934P

8. How does the drug release mechanism from Carbopol® polymer matrix tablets compare with that of 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/swell in aqueous environments.

9. What is the relationship between Carbopol® polymer viscosity and drug release rate?

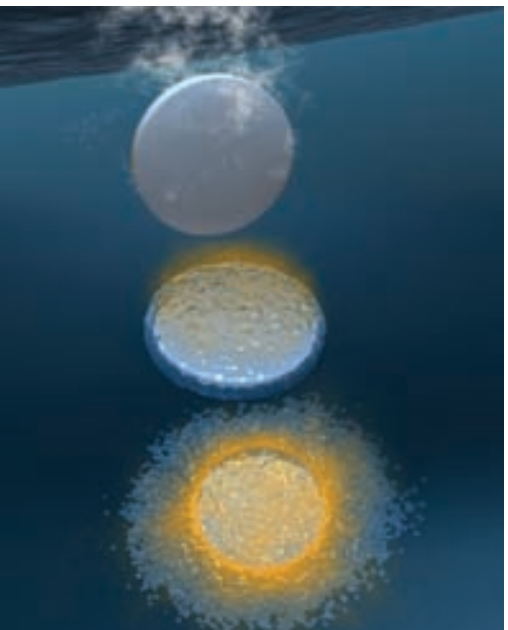
Drug release from Carbopol® polymer matrix tablets is controlled more by the polymer structure (crosslink density) than by viscosity. Lightly crosslinked polymers have fewer crosslink sites to constrain the polymer, and a homogeneous gel structure forms at lower concentrations compared to highly crosslinked polymers. As a result, the active is less subject to diffusion through the gel layer.

In contrast to linear polymers, higher viscosity does not result in slower drug release with carbomers. 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).

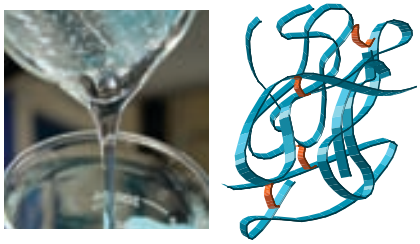
10. In comparison with hypromellose, what are the typical levels of Carbopol® polymer that are used to obtain extended release properties?

For powder grade Carbopol® polymers (Carbopol® 971P NF and 974P NF polymers), typical usage levels are 3 – 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.

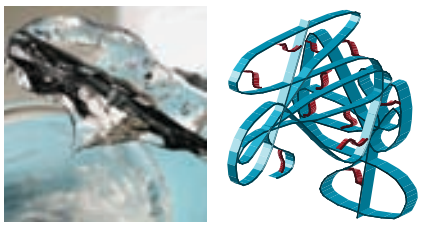


Carbopol® 971P NF Polymer



Lightly crosslinked gel

Carbopol® 974P NF Polymer



Hightly crosslinked gel

11. 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.

12. Does the acidic nature of Carbopol® polymer provide any benefit in formulation?

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.

13. Is there a potential for ionic interaction with certain APIs when Carbopol® polymers are incorporated in a matrix tablet?

Due to their anionic character, Carbopol® polymers may form ionic complexes with cationic drugs. Carbopol® polymers are weak acids (pKa=6 ±0.5). It is important to note that the complex formation is generally reversible as the endogenous cations displace the drug from the polymer upon administration. The potential for ionic interaction is determined by the API properties (pKa/alkalinity, steric hindrance and molecular size/shape) and polymer to API molar ratio. Typically, if an ionic interaction occurs, it will result in slower drug release.

Ionic interaction will not occur with all cationic drugs and is API and formulation dependent.

Examples of commercial products containing cationic APIs and Carbopol® polymers are tablets of dextromethorphan, diethylpropion, glucosamine, metformin, metoprolol, and pseudoephedrine.

14. Can Carbopol® polymers be used as a controlled release excipient in combination with low solubility APIs?

There is a variety of low solubility APIs formulated with Carbopol® polymers as 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).

15. What are the potential benefits of a combination matrix (Carbopol® polymer and hypromellose) vs. use of a single polymer matrix? Are there other polymer combinations that can be used?

Data demonstrates a synergistic interaction may occur when Carbopol® polymers are used in combination with hypromellose. Specifically, a lower total polymer level could be used in a formulation, thus enabling smaller tablet sizes and overall formulation cost savings. Additionally, more consistent drug release can be achieved. By varying the total polymer level and ratio of the two polymers it is possible to modulate the drug release profile.

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.

16. Are Carbopol® polymers effective tablet binders? What is the best way of incorporating them as binders in a matrix system?

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.

17. What manufacturing processes can be used to produce solid dosage forms containing Carbopol® polymers?

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

18. Can Carbopol® polymers be used in wet granulation processes? How?

Carbopol® polymers can be used in wet granulation processes. Key recommendations to facilitate processing are as follows:

- In order to avoid fast and extensive swelling of the polymer, use a low amount of granulation liquid added at a slow rate in fine droplets (uniform distribution of the water in the wet mass). In general, a lower quantity of granulation liquid is used with Carbopol® polymers compared to hypromellose.
- Incorporation of microcrystalline cellulose improves the processability of the formulation. Generally less than 10% of microcrystalline cellulose should be used to prevent disintegration of the tablets.
- Granulation should be controlled in order to prevent overwetting (sticky, rubbery mass).
- It is very important to control the drying process and residual moisture in the granules (typical values 1 - 3%), however these parameters are formulation specific. If overdried, Carbopol® polymers form hard granules. High residual moisture might lead to tablets sticking to the punches and stability problems.

19. What is the recommended procedure for cleaning equipment after processing with Carbopol® polymers?

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. The electrolyte solution facilitates equipment cleaning by collapsing the gel.

20. How do you quantify the API level in a Carbopol® polymer matrix tablet?

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).

21. How stable are 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 dessi-cap vials. No change in dissolution profile was observed in tablets stored under accelerated conditions for 6 months or long term for 1 year.

22. Have any in vivo studies been conducted on Carbopol® polymer matrices?

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

Emami J, Tavakoli N, Movahedian A. Formulation of sustained-release lithium carbonate matrix tablets: influence of hydrophilic materials on the release rate and in vitro-in vivo evaluation. J Pharm Pharm Sci. 2004, 7(3), 338-44.

Xiaoqiang X, Minjie S, Feng Z, Yiqiao H Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers. Int J Pharm 2006, 310, 139-145.

Parojcić J, Ibrić S, Djurić Z, Jovanović M, Corrigan OI. An investigation into the usefulness of generalized regression neural network analysis in the development of level A in vitro–in vivo correlation. Eur J Pharm Sci. 2007, 30(3-4), 264-72.

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

WO0224203: Controlled release formulations for oral administration

US20030224050: Drug delivery system for sustained delivery of glipizide

WO2005039555: Extended release tablet formulations of venlafaxine

US 20070031491: Bioadhesive progressive hydration tablets

WO0132165: Method for administering a phosphodiesterase 4 inhibitor

WO2005030178: Extended release formulation of beta-lactam antibiotics

WO2006082523: Pharmaceutical compositions of metformin

23. Do Carbopol® polymers add any taste masking properties to a tablet?

Carbopol® polymers have the ability to mask the taste of some APIs (mostly cationic drugs) by forming insoluble adsorbates through weak ionic bonding. Those adsorbates dissolve rapidly after ingestion (the endogenous cations displace the drug from the polymer). Literature references highlighting this property include macrolide antibiotics, enofloxacin and dextromethorphan.

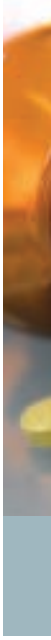
Carbopol® polymers have been used in combination with film forming materials for taste masking coating compositions. Additionally, Carbopol® polymers have been reported to ameliorate the throat catch (unpleasant taste and sensation in the throat) caused by ibuprofen. Possible mechanisms involve binding 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.

24. Do Carbopol® polymers provide bioadhesive properties?

Carbopol® polymers and Noveon® polycarbophils 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.



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Detailed product information and samples of Lubrizol's high performance specialty chemicals for the pharmaceutical industry can be obtained through our web site at www.pharma.lubrizol.com or contact your sales representative or nearest Lubrizol office.

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