

Lubrizol Pharmaceutical Polymers for Controlled Release Tablets and Capsules

Over time there has been an increasing interest in developing and commercializing controlled release tablets using Carbopol^{®*} polymers and Noveon^{®*} polycarbophil. These polymers have been successfully used as controlled release agents with a variety of pharmaceutical active ingredients and excipients, by using direct compression, roller compaction or wet granulation methods.

This Bulletin reviews the general considerations on Carbopol[®] polymers for controlled-release formulations. Lubrizol Pharmaceutical Bulletin 31 reviews the effect of formulation variables on drug release for controlled release tablets and capsules. Pharmaceutical Bulletin 32 provides information on Carbopol[®] 71G NF polymer, a granulated free-flowing Carbopol[®] polymer, specifically designed for direct compression processes.

Benefits of Lubrizol Pharmaceutical Polymers in Tablet Formulations

Many commercial products available today have been formulated with Lubrizol pharmaceutical polymers. The polymers have numerous features which provide key benefits in tablets:

- Global pharmacopeial status and U.S. and European Drug Master Files (DMFs) to facilitate regulatory approvals.
- Highly efficient controlled release agents - in many cases they have demonstrated slower release at lower use levels than other commercially available excipients, thus enabling cost savings and smaller tablets.
- Provide good tablet characteristics at low compression forces.
- Widely compatible with active pharmaceutical ingredients and commonly used tablet excipients; they can be combined with other matrix forming excipients, if needed, to achieve a desired release profile.
- May enable increased bioavailability.
- Are available in both powder and granular form and can be used in all types of tablet manufacturing process.
- May impart additional functions: taste masking, binding, bioadhesion, etc.
- Are synthetic products and therefore tend to be more consistent than semisynthetic and natural products.

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Physical and Chemical Properties of Carbopol® Polymers and Noveon® Polycarbophil

Carbopol® polymers and Noveon® polycarbophil are high molecular weight polymers of acrylic acid, chemically crosslinked with polyalkenyl alcohols or divinyl glycol – Table 1 (please refer to Product Guide and Regulatory Overview).

Table 1

Lubrizol Pharmaceutical Polymers for Solid Dosage Forms Applications

Product Trade Name	Residual Solvent	Crosslinker	Compendial Name			
			United States (USP/NF)		Europe (Ph. Eur.)	Japan (JPE) ¹
			Previous	Current		
Carbopol® Polymers						
71G NF	Ethyl acetate	Allyl ethers of pentaerythritol	Carbomer 941	Carbomer Homopolymer Type A	Carbomers	Carboxyvinyl Polymer
971P NF	Ethyl acetate	Allyl ethers of pentaerythritol	Carbomer 941	Carbomer Homopolymer Type A	Carbomers	Carboxyvinyl Polymer
974P NF	Ethyl acetate	Allyl ethers of pentaerythritol	Carbomer 934P	Carbomer Homopolymer Type B	Carbomers	Carboxyvinyl Polymer
934P NF	Benzene	Allyl ethers of sucrose	Carbomer 934P	Carbomer 934P		Carboxyvinyl Polymer
Noveon® Polycarbophil						
AA-1 USP	Ethyl acetate	Divinyl glycol	Polycarbophil	Polycarbophil		

Carbopol® polymers and Noveon® AA-1 polycarbophil, USP, as produced, are flocculated powders (average diameter 2 to 7 microns as determined by Coulter Counter) of primary particles of about 0.2 micron in diameter. Those flocculated powders cannot be broken down into the primary particle.

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

Figures 1 and 2 show photomicrographs of particle agglomerates of Carbopol® 974P NF and 971P NF polymers.

Figure 1 – SEM Photomicrograph of Carbopol® 974P NF Polymer (3,000x)

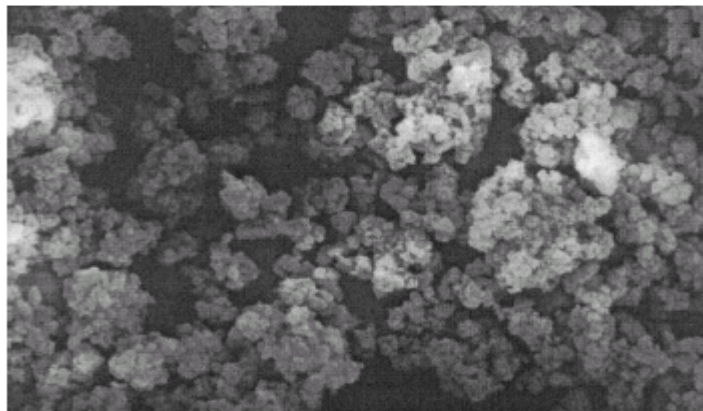
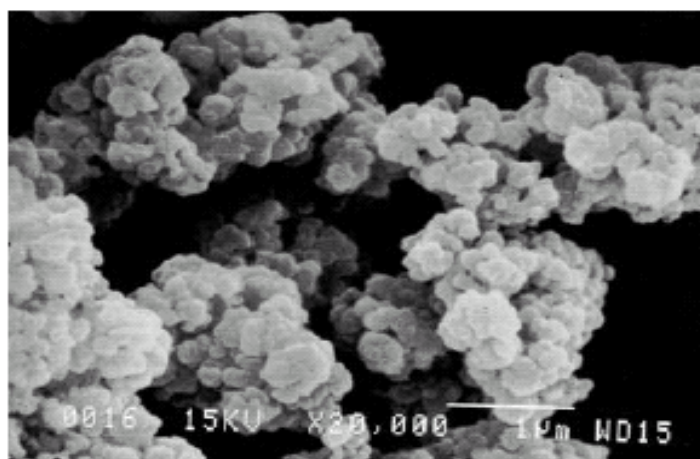


Figure 2 – SEM Photomicrograph of Carbopol® 971P NF Polymer (30,000x)

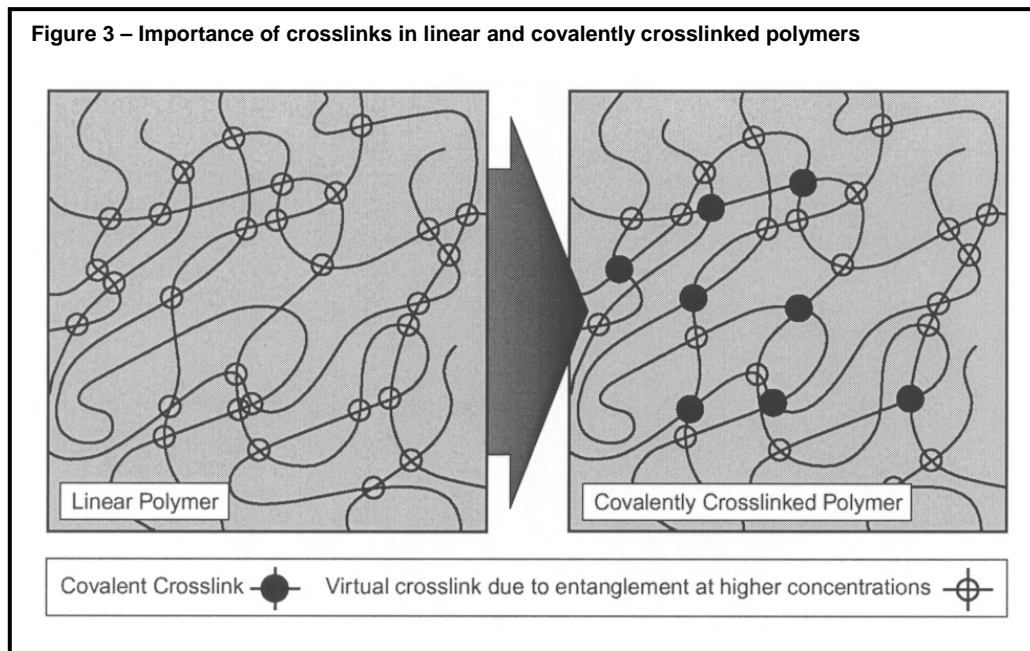


Each primary particle can be viewed as a network structure of polymer chains interconnected by crosslinks, which results in polymers with molecular weights in the billions. Without the crosslinks, the primary particle would be a collection of linear polymer chains, physically intertwined but not chemically bonded. Unlike the linear hydrophilic polymers that are soluble in polar solvent (water or alcohol), the crosslinked Carbopol® polymers and Noveon® polycarbophil are not soluble, but only swellable in water.

It is not possible to directly measure the molecular weight of Lubrizol pharmaceutical polymers as they are crosslinked and water insoluble; based on stoichiometric and theoretical calculations, the molecular weights of Carbopol® polymers and Noveon® polycarbophil could be as high as 3 - 4 billion, due to the chemical linkage of hundreds of polymer chains.

Due to their inherently crosslinked structure, Carbopol® polymers can form strong matrices at low concentrations. It is important to emphasize that because Carbopol® polymers and Noveon® polycarbophil are already crosslinked, molecular weight is not a key parameter in controlling drug release, unlike the case of linear, soluble matrix agents.

Other hydrophilic controlled release excipients, such as hypromellose, hydroxypropyl cellulose, etc., are linear polymers, not chemically crosslinked and therefore water soluble (Figure 3). During the drug release process, those polymers dissolve and erode.



The glass transition temperature of Carbopol® polymers is 105°C in powder form. However, the glass transition temperature drops dramatically as the polymer comes into contact with water. Plasticization of the Carbopol® polymers or Noveon® polycarbophil by water causes the polymer chains to start gyrating. As the radius of gyration becomes bigger and bigger, and the end-to-end distances increase, the polymer swells on a macroscopic level. These polymers swell up to 1000 times their original volume (and ten times their original diameter) in water to form a gel when exposed to a pH environment above their pKa of 6±0.5 (Figure 4)

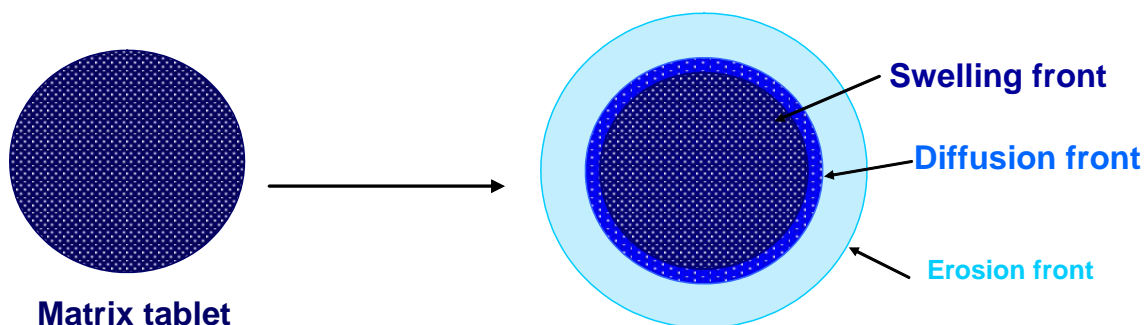
Figure 4 - Particle size of Carbopol® polymers

Dry Polymer	Hydrated Polymer	Neutralized Polymer
Ø = 2 - 7µm	pH = 3.0	Ø = 20- 70µm pH = 7.0

Drug Release from Tablets with Carbopol[®] Polymers

Carbopol[®] polymers are efficient matrix forming excipients. The drug is uniformly dispersed in the polymeric matrix. When carbomer tablets (granules, capsules, etc.) are placed in contact with dissolution media, the external surface of the tablet becomes hydrated, swells and forms a gel layer (hydrogel) that further controls the release of the drug from the tablets – Figure 5.

Figure 5 - Schematic representation of the drug release from Carbopol[®] polymer tablets



Due to the crosslinked nature of the polymer, the hydrogel is not simple entangled chains of polymer (as in the case of the water soluble polymeric matrix), but discrete microgels made up of many polymer particles, in which the drug is dispersed.

Since the carbomer is not water soluble, it does not dissolve, and erosion in the manner of linear polymers does not occur. Rather, when the hydrogel is fully hydrated, osmotic pressure from within may break up the structure, essentially by sloughing off discrete pieces of the hydrogel.

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Drug release rates are affected by differences in the rates of hydration and swelling of the polymer hydrogel, which are dependent on the molecular structure of the polymers, including crosslink density, chain entanglement, and crystallinity of the polymer matrix.

Finally, drug solubility is another key factor for the drug release from a tablet matrix based on Carbopol[®] polymers (please refer to Bulletin 31). Drugs exhibiting poor solubility tend to partition into the more hydrophobic domains of the system (such as the acrylic backbone of the Carbopol[®] polymers) from where they would be released in a linear or almost linear manner. Highly water soluble drugs are released mainly by diffusion.

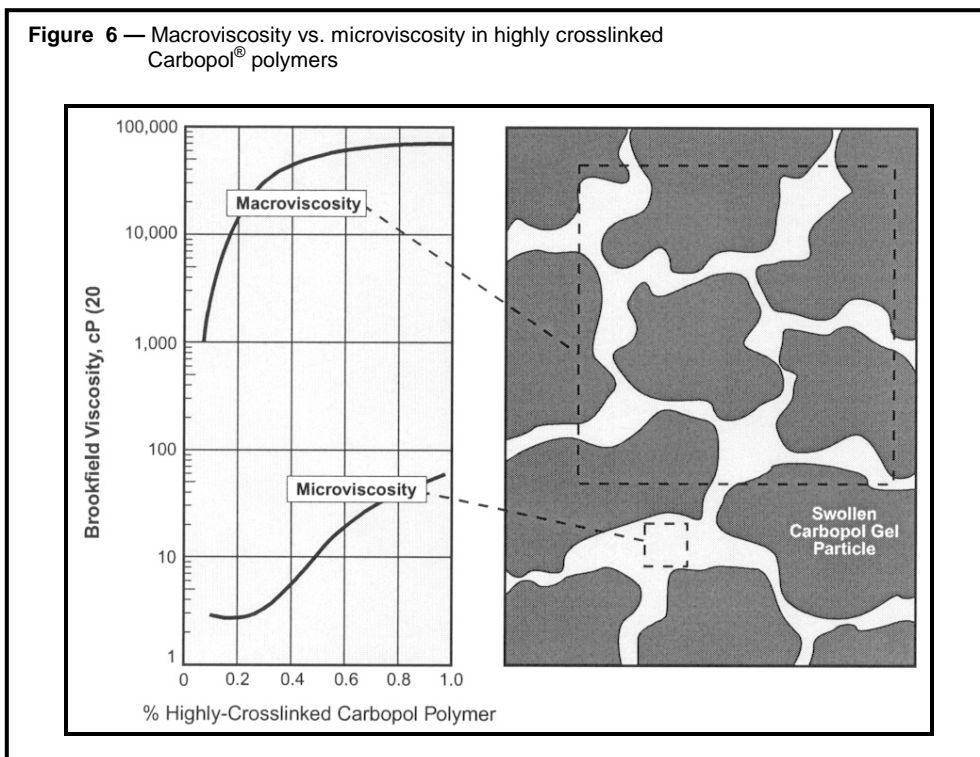
In the case of highly crosslinked Carbopol[®] polymers (such as Carbopol[®] 974P NF polymer) the release is faster as the drug diffuses out through the water-filled interstitial spaces between the microgels. In comparison, Carbopol[®] 971P NF polymer is lightly crosslinked, thus the microgels form a more uniform and continuous structure resulting in a slower drug release.

Effect of Crosslinker Level and Gel Characteristics on Drug Release

As discussed previously, the gel properties of Carbopol[®] polymers and Noveon[®] polycarbophil, which are largely defined by their crosslinker levels, are very important to drug release kinetics. The differences in the hydrated macromolecular structure of Carbopol[®] polymers influence the macro- and microviscosities of the gel layer and, therefore, the drug release characteristics.

Gels of Carbopol[®] polymers may be characterized by macro- and microviscosity regions. Testing of Carbopol[®] polymer gels made using gold sols with particle size of 0.1 microns using quasi-elastic light scattering, showed that the higher viscosity gels (such as Carbopol[®] 974P NF polymer) are not homogeneous in viscosity; rather there are regions of very high macroviscosity, and regions of water-thin microviscosities (also called channels) – Figure 6. In another study, bacterial flagellates were placed in a gel of a highly crosslinked polymer, and observed under an electron microscope. The electron micrographs showed that the size of the flagellates was equal to the channel size and that they were mobile. However, when the flagellates were placed in a lightly crosslinked polymer gel (such as Carbopol[®] 971P NF polymer), they were “frozen in place” and unable to move.

(Lochhead, R. Y.; J. A. Davidson; G. M. Thomas; “Poly(acrylic acid) Thickeners: The Importance of Gel Microrheology and Evaluation of Hydrophobically Modified Derivatives as Emulsifiers,” *Polymers in Aqueous Media: Performance Through Association*, Advances in Chemistry Series #223, p. 113, J. E. Glass, Editor, American Chemical Society: Washington, DC, 1989).

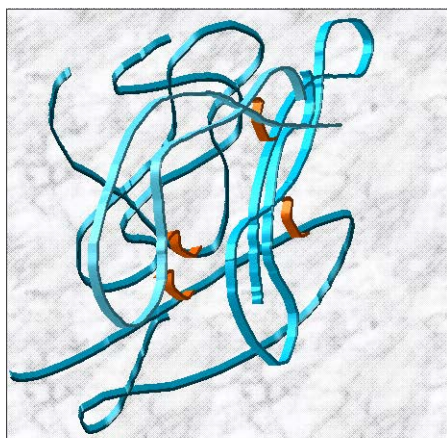


It is postulated that lightly crosslinked polymers, such as Carbopol® 971P NF polymer, have a “fishnet” gel structure upon hydration, as illustrated in Figure 7. Because there are few crosslink sites to constrain the polymer, it opens up easily at low concentrations. Microparticles of Carbopol® 971P NF polymer are flexible when hydrated. Consequently, the interstitial spaces between the swollen gel particles are eliminated, and there is no significant difference between the micro- and macroviscosity. This homogeneous gel structure provides significant resistance to diffusion of drug molecules.

Carbopol® polymers which are highly crosslinked, such as Carbopol® 974P NF polymer, have more of a “fuzzball” type of gel structure – Figure 7. Because there are many crosslinks to constrain the polymer, it does not open up easily, and higher concentrations are required to fill in the spaces between the swollen gel particles. Carbopol® 974P NF polymer has the most rigid gel microparticles when fully hydrated.

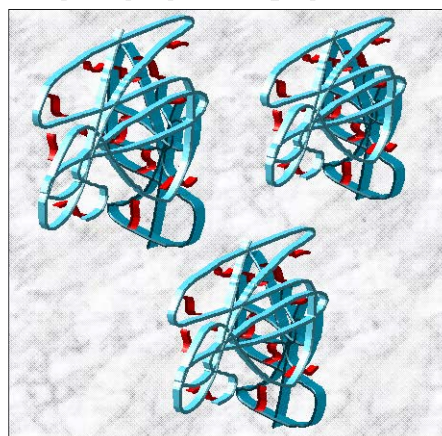
Figure 7 - Effect of crosslink density on the gel structure of Carbopol® polymers

Carbopol® polymer lightly crosslinked



“Fishnet” structure

Carbopol® polymer highly crosslinked



“Fuzzball” structure

As a result, Carbopol® 971P NF polymer tends to be more efficient in controlling the drug release than Carbopol® 974P NF polymer.