

Oral Suspensions

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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 used worldwide in oral suspensions for many years to suspend insoluble ingredients, modify flow characteristics, and provide bioadhesion. They provide excellent suspending ability and virtually eliminate the problem of settling, even when used at very low levels.

Carbopol® polymers swell when hydrated and neutralized, forming a colloidal dispersion. The insoluble ingredients in the suspensions are then permanently trapped in the interstitial spaces between the hydrogel particles.

Carbopol® Polymers for Oral Suspensions

Lubrizol promotes Carbopol® 974P NF, Carbopol® 971P NF and Carbopol® 71G NF polymers and Noveon® AA-1 polycarbophil for oral suspensions (Table 1). These are toxicologically preferred alternatives to Carbopol® 934P NF polymer which has been used in oral suspensions worldwide since the mid 1960s (for more information, please refer to [Lubrizol Pharmaceutical Bulletin 1: "Polymers for Pharmaceutical Applications"](#)).

Carbopol® 974P NF polymer is highly crosslinked (similar to Carbopol® 934P NF polymer) and produces highly viscous gels with short flow rheology similar to mayonnaise.

Conversely, Carbopol® 971P NF polymer is lightly crosslinked, with longer rheology, similar to honey; it provides low viscosities and excellent yield values at low usage levels. Carbopol® 71G NF polymer is a granular form of Carbopol® 971P NF polymer, with the same rheology. Noveon® AA-1 polycarbophil, USP has been studied primarily for its bioadhesive properties.

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Table 1
Lubrizol Pharmaceutical Polymers for Oral Suspensions

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

Benefits of Carbopol® Polymers for Oral Suspensions

Carbopol® polymers are generally used in aqueous formulations of oral suspensions, although elixirs with as much as 40% alcohol have been successfully formulated. The polymers are also compatible with glycerin, propylene glycol, sorbitol, polyethylene glycol and various sugars commonly used in formulations.

Carbopol® polymers have numerous features which provide key benefits in oral suspension formulations:

- Are safe and effective in oral applications.
- Have very high yield values, even at low concentrations.
- Broad viscosity range can be achieved by varying the polymer grade and concentration, without compromising the stability of the suspension.
- Form stable suspensions over a wide pH range.
- Formulations are stable to repeated freezing and thawing.
- Can mask the taste of certain bitter-tasting drugs.
- Have bioadhesive properties, thus enabling increased bioavailability.
- Are synthetic polymers and do not support microbial growth (but do not prevent it).
- Global pharmacopeial status and U.S. and European Drug Master Files (DMFs) to facilitate regulatory approvals.

Some of the active pharmaceutical ingredients successfully formulated as suspensions (commercial products) using Lubrizol pharmaceutical polymers are Clarithromycin, Domperidone, Ibuprofen, Nevirapine, Nifuroxazide, Nystatin, etc.

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

Due to the rheological characteristics, carbomers have been used in combination with cellulose derivatives to formulate stable semisolid dosage forms that provide spill-resistance while still maintaining measurability and dispensability (Mehta and Moros, 2003).

Carbopol[®] polymers have been successfully used to mask certain bitter tasting active ingredients in oral suspensions. D-methorphan taste can be masked by reacting it with Carbopol[®] 934P NF polymer. The resulting water insoluble product is readily dispersible in aqueous vehicles to form suspensions or can be compressed into sustained release tablets (Magid, 1967).

Carbopol[®] polymers reduced the bitterness of macrolide antibiotics (erythromycin, clarithromycin) by forming insoluble adsorbates through weak ionic bonding. Those adsorbates dissolved rapidly after ingestion (the endogenous cations displace the drug from the polymer). The taste protection was further improved by polymer coating. When reconstituted, the dry suspensions provided palatability (maintained for two weeks) and adequate bioavailability (Fu Lu et al., 1991, Fu Lu and Borodkin, 1989). Carbopol[®] polymers were selected over the conventional exchange resins as they readily swell, allowing rapid cation exchange and they also possess bioadhesive properties.

Physical and Chemical Properties of Carbopol[®] Polymers

Carbopol[®] polymers are high molecular weight crosslinked polymers of acrylic acid. Each primary particle can be viewed as a network structure of polymer chains interconnected by crosslinks, which results in polymers with molecular weights of up to 3 - 4 billion daltons. Without the crosslinks, the primary particle would be a collection of linear polymer chains, physically intertwined but not chemically bonded.

These polymers swell up to 1,000 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 ; the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative particles, which adds to the swelling of the polymer. The gel contains a large amount of swollen microgel particles, with interstitial spaces in which insoluble particles can be entrapped (suspended). Carbopol[®] polymer microgels are easily moved by shear, but once the shear stops, the macro-gel structure immediately forms again. This enables highly viscous suspensions to be stirred or pumped easily, with instantaneous recovery once the stirring or pumping ceases.

Rheology Aspects

Yield value, viscosity and thixotropy are key measurements of how well a liquid will suspend insoluble ingredients. Yield value is the minimum amount of shear stress needed before flow begins. This property defines how well a liquid system can suspend insoluble drug actives and other solid particles. Unless the force of gravity operating on a suspended particle of a given mass exceeds the liquid's yield value, the insoluble particles will not settle.

Viscosity is an expression of the resistance of a fluid to flow; the higher the viscosity, the greater the resistance. It is defined in terms of the force required to move one planar surface continuously past another under specified steady-state conditions, when the space between is filled by the liquid in question (USP 31). Generally, the thicker the liquid, the higher the viscosity (for more information, please refer to [Lubrizol Pharmaceutical Bulletin 7: "Flow and Suspension Properties"](#)).

Yield value is more important than viscosity when determining suspending ability of a vehicle. While viscosity can only slow down the rate of settling, a high yield value is necessary to create permanent suspensions. For example, a sand suspension with 0.1% Carbopol[®] polymer (neutralized) and Brookfield viscosity of approximately 2,000 cP was more stable than a suspension with 2.5% locust bean and Brookfield viscosity of 22,800 cP (please see [Lubrizol Pharmaceutical Bulletin 7: "Flow and Suspension Properties"](#)).

Carbopol[®] polymers are unique in that they provide a wide range of viscosity profiles and have very high yield values, even at low concentrations. These combined features enable the formulation of oral suspensions that are stable with low levels of polymer.

Carbopol[®] polymers are more efficient in delivering yield value or suspending ability than cellulose or natural gums. Carbopol[®] polymers can be used to formulate suspensions with a broad viscosity range. The yield value of the formulation will prevent fast sedimentation and thus maintain content uniformity. The polymer shear thinning behavior will allow filling (pumping) and dosing. When the stress ceases, the recovery to the original viscosity is instantaneous, thus the particles are maintained in the suspended state.

Preparing Oral Suspensions with Carbopol[®] Polymers

Generally the insoluble pharmaceutical active ingredients are suspended in the neutralized dispersions of Carbopol[®] polymers (structured vehicle). Other excipients (buffers, electrolytes etc.) should be added in a careful manner (preferably at the end) to prevent variation of particle size or polymer structure break down (viscosity loss and instability).

Preparing dispersions of Carbopol[®] polymers

Carbopol[®] polymers are hygroscopic powders with a strong affinity for water. Similar to other hygroscopic powders, these polymers tend to agglomerate or incompletely wet-out when improperly introduced in water or other polar solvents. The surface of a powder agglomerate solvates and forms a tough outer layer which prevents complete wetting of the interior polymer particles. This results in dispersion defects such as grainy texture, reduced viscosity or the presence of insoluble particles resembling fish eyes. Thus agglomerates of Carbopol[®] polymers should be avoided by carefully wetting the individual polymer particles in ambient temperature water.

Carbopol[®] polymers can be dispersed by sifting the polymer into rapidly agitating water (800-1,500 rpm). Production dispersing equipment, such as eductors or mechanical powder dispersers, are also effective, especially for large scale. Once the polymer is wetted, the rate of agitation should be reduced (and the mixer repositioned) to minimize air entrapment; the mixing is continued until complete hydration is achieved.

Preferably the polymer should be dispersed in cold water. The water vapor above preheated water can cause pre-swelling of the powder before it reaches the water. Lack of proper dispersion can lead to incomplete hydration of the polymer, resulting in broad pH or viscosity fluctuations.

Carbopol[®] polymers can also be dispersed in anhydrous polar solvents (alcohols, glycols) followed by water addition. Those solvents wet the polymer without rapid swelling.

The polymer dispersions are neutralized by adding an aqueous solution of the neutralizing agent with moderate agitation (300-800 rpm). Due to the high viscosity of the gel, high speed agitation would produce air entrapment and it is not recommended.

(For more information on dispersion and neutralization, please refer to [Pharmaceutical Bulletin 4: "Dispersion Techniques for Lubrizol Pharmaceutical Polymers"](#) and [Pharmaceutical Bulletin 5: "Neutralization Procedures"](#)).

Suspending insoluble active ingredients in Carbopol® polymer dispersions

Drugs are dispersed in the structured vehicle and if homogenization is necessary the suspension is passed through an in-line homogenizer. High shear mixing or pumping, multiple homogenization cycles should be avoided as they may cause breaking down of the polymer structure.

Factors to be considered in Carbopol® suspensions

pH — The optimum pH range for Carbopol® polymers is 4-10. A pH outside of this range may result in an inconsistent or unstable formulation.

High shear (mixing or pumping) — Carbopol® polymers stabilize a suspension by forming a gel matrix in which the soluble ingredients are trapped. High shear mixing or high shear pumping can break down the carbomer structure resulting in viscosity loss and potentially causing settling of the suspension.

Electrolytes — Carbopol® polymers are sensitive to salts. The presence of electrolytes should be minimized whenever is practical.

Monovalent ions reduce the thickening efficiency of systems containing Carbopol® polymers. Multivalent ions (Ca^{2+} , Mg^{2+} , Fe^{3+} , Al^{3+} , etc.) may form an insoluble precipitate if present at high enough levels.

The active ingredient should be used in a non-ionized form whenever possible.

Contamination with transition metals (Fe, Cu, etc.) causes a gradual viscosity loss. Processing in stainless steel or nonmetallic equipment will minimize this effect as can the use of complexing agents such as EDTA.

If salts are included in the formulation, these should be added after neutralization and their effects on the viscosity evaluated.

Incompatibilities — Proteins, povidone, polyethylene glycol and polyethoxylated surfactants complex with unneutralized Carbopol® polymers. These ingredients should be added after neutralization.

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