Carbomer

1 Nonproprietary Names

BP: Carbomers
PhEur: Carbomera
USPNF: Carbomer
Note that the USPNF 20 contains several individual carbomer monographs; *see* Sections 4 and 9.

2 Synonyms

Acritamer; acrylic acid polymer; *Carbopol*; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; *Pemulen*; *Ultrez*.

3 Chemical Name and CAS Registry Number

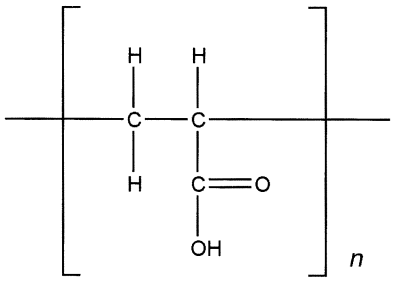
Carbomer [9003-01-4]

Note that carbomer 910, 934, 934P, 940, 941, 971P, and 974P resins share the common CAS registry number 9003-01-4. Carbomer 1342 is a copolymer and has a different CAS registry number.

4 Empirical Formula Molecular Weight

Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allylsucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups calculated on the dry basis. The BP 2001 and PhEur 2002 have a single monograph describing carbomer; the USPNF 20 contains several monographs describing individual carbomer grades that vary in aqueous viscosity and in labeling for oral or non-oral use. The molecular weight of carbomer resins is theoretically estimated at 7×10^5 to 4×10^9. In an effort to measure the molecular weight between crosslinks, M_C, researchers have extended the network theory of elasticity to swollen gels and have utilized the inverse relationship between the elastic modulus and M_C.[1–3] Estimated M_C values of 237 600 g/mol for *Carbopol 941* and of 104 400 g/mol for *Carbopol 940* have been reported.[4] In general, carbomer resins with lower viscosity and lower rigidity will have higher M_C values. Conversely, higher-viscosity, more rigid carbomer resins will have lower M_C values.

5 Structural Formula



Acrylic acid monomer unit in carbomer resins.

Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are crosslinked with allyl sucrose or allylpentaerythritol. *See also* Section 4.

6 Functional Category

Bioadhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels, and ointments for use in ophthalmic,[5–7] rectal,[8,9] and topical preparations.[10–12] Carbomer grades, even with a low residual benzene content, such as carbomer 934P, are no longer included in the PhEur 2002. However, carbomer having low residuals only of other solvents than the ICH-defined 'Class I OVI solvents' may be used in Europe. Carbomer having low residuals only of ethyl acetate, such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets, or sustained release tablet formulations.[13–17] In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipient. In wet granulation processes, water or an alcohol–water blend is used as the granulating fluid. Anhydrous organic solvents have also been used, with the inclusion of a polymeric binder. The tackiness of the wet mass can be reduced with the addition of certain cationic species to the granulating fluid[18] or, in the case of water, with talc in the formulation. Carbomer resins have also been investigated in the preparation of sustained-release matrix beads,[18] as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms,[19,20] as a bioadhesive for a cervical patch[21] and for intranasally administered microspheres,[22] and in magnetic granules for site-specific drug delivery to the esophagus.[23] Carbomers are also employed as emulsifying agents in the preparation of oil-in-water emulsions for external use. For this purpose, the carbomer is neutralized partly with sodium hydroxide and partly with a long-chain amine such as stearylamine. Carbomer 951 has been investigated as a viscosity-increasing aid in the preparation of multiple emulsion microspheres.[24] Carbomers are also used in cosmetics. *See* Table I.

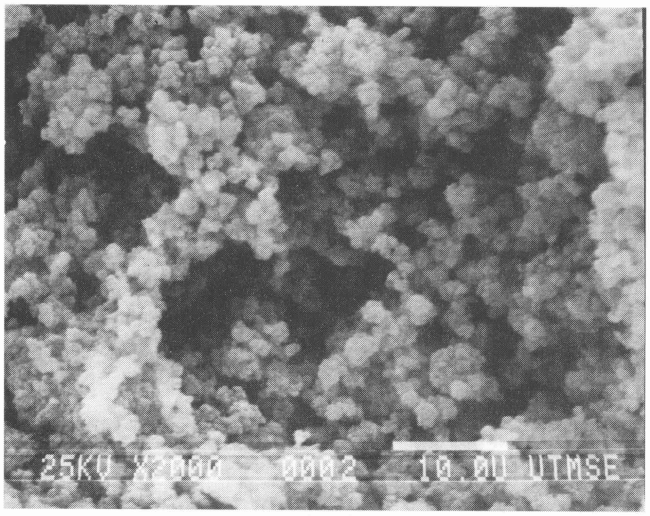
Table I: Uses of carbomers.

Use	Concentration (%)
Emulsifying agent	0.1–0.5
Gelling agent	0.5–2.0
Suspending agent	0.5–1.0
Tablet binder	5.0–10.0

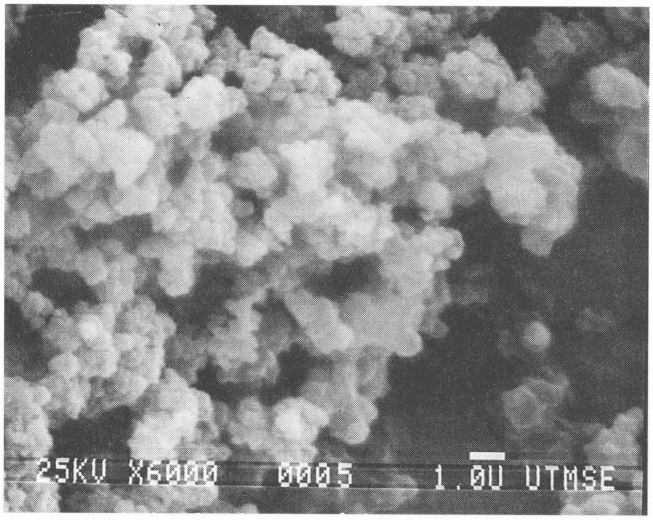
8 Description

Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a slight characteristic odor.

SEM: 1
Excipient: Carbomer 971P (*Carbopol 971P*)
Manufacturer: BF Goodrich
Magnification: 2000×
Voltage: 25 kV



SEM: 2
Excipient: Carbomer 971P (*Carbopol 971P*)
Manufacturer: BF Goodrich
Magnification: 6000×
Voltage: 25 kV



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for carbomers.

Test	PhEur 2002 (Suppl 4.2)	USPNF 20
Identification	+	+
Characters	+	–
Aqueous viscosity (mPa s)	300–115 000	–
Carbomer 910 (1.0% w/v)	–	3 000–7 000
Carbomer 934 (0.5% w/v)	–	30 500–39 400
Carbomer 934P (0.5% w/v)	–	29 400–39 400
Carbomer 940 (0.5 w/v)	–	40 000–60 000
Carbomer 941 (0.5 w/v)	–	4 000–11 000
Carbomer 1342 (1.0% w/v)	–	9 500–26 500
Loss on drying	⩽3.0%	⩽2.0%
Sulfated ash	⩽4.0%	–
Heavy metals	⩽20 ppm	⩽0.002%
Benzene	⩽2 ppm	–
Carbomer 910	–	⩽0.5%
Carbomer 934	–	⩽0.5%
Carbomer 934P	–	⩽0.01%
Carbomer 940	–	⩽0.5%
Carbomer 941	–	⩽0.5%
Carbomer 1342	–	⩽0.2%
Free acrylic acid	⩽0.25%	–
Assay (COOH content)	56.0–68.0%	56.0–68.0%

Note that the USPNF 20 has several monographs for different carbomer grades, while the BP 2001 and the PhEur 2002 have only a single monograph. Other grades of carbomer meet the existing USPNF 20 standards as indicated above. Carbomer 974P is covered by the monograph for carbomer 934P in the USPNF 20. Likewise, carbomer 980 meets the specifications for carbomer 940; carbomers 971P and 981 meet the monograph limits for carbomer 941. Carbomer resins are also covered either individually or together in other pharmacopeias. Unless otherwise indicated, the test limits shown above apply to all grades of carbomer.

10 Typical Properties

Acidity/alkalinity:
pH = 2.7–3.5 for a 0.5% w/v aqueous dispersion
pH = 2.5–3.0 for a 1% w/v aqueous dispersion

Density (bulk): 1.76–2.08 g/cm^3

Density (tapped): 1.4 g/cm^3

Glass transition temperature: 100–105°C

Melting point: decomposition occurs within 30 minutes at 260°C. *See* Section 11.

Moisture content: normal water content is up to 2% w/w. However, carbomers are hygroscopic and a typical equilibrium moisture content at 25°C and 50% relative humidity is 8–10% w/w. The moisture content of a carbomer does not affect its thickening efficiency, but an increase in the moisture content makes the carbomer more difficult to handle because it is less readily dispersed.

Particle size distribution: primary particles average about 0.2 μm in diameter. The flocculated powder particles average 2–7 μm in diameter and cannot be broken down into the primary particles. Recently, a granular carbomer having a particle size in the range 180–425 μm has been introduced. Its bulk and tap densities are also higher than those of other carbomers.

Solubility: soluble in water and, after neutralization, in ethanol (95%) and glycerin.

Although they are described as 'soluble', carbomers do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally crosslinked microgels. Furthermore, the pharmacopeial specifications are unclear, in that neutralization with long-chain aliphatic amines or ethoxylated long-chain amines is required for swellability in ethanol, and with water-soluble amines for swellability in glycerin.

Specific gravity: 1.41

Viscosity (dynamic): carbomers disperse in water to form acidic colloidal dispersions of low viscosity that, when

neutralized, produce highly viscous gels. Carbomer powders should first be dispersed into vigorously stirred water, taking care to avoid the formation of indispersible lumps, then neutralized by the addition of a base. BF Goodrich has introduced the *Carbopol ETD* and *Ultrez 10* series of carbomers to help overcome some of the problems of dispersing the powder into aqueous solvents. These carbomer resins wet quickly yet hydrate slowly, while possessing a lower unneutralized dispersion viscosity. Agents that may be used to neutralize carbomer polymers include amino acids, borax, potassium hydroxide, sodium bicarbonate, sodium hydroxide, and polar organic amines such as triethanolamine. Lauryl and stearyl amines may be used as gelling agents in nonpolar systems. One gram of carbomer is neutralized by approximately 0.4 g of sodium hydroxide. During preparation of the gel, the solution should be agitated slowly with a broad, paddlelike stirrer to avoid introducing air bubbles. Neutralized aqueous gels are more viscous at pH 6–11. The viscosity is considerably reduced at pH values less than 3 or greater than 12 or in the presence of strong electrolytes.[18,25] Gels rapidly lose viscosity on exposure to ultraviolet light, but this can be minimized by the addition of a suitable antioxidant. *See also* Section 11.

11 Stability and Storage Conditions

Carbomers are stable, hygroscopic materials that may be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency. However, exposure to excessive temperatures can result in discoloration and reduced stability. Complete decomposition occurs with heating for 30 minutes at 260°C. Dry powder forms of carbomer do not support the growth of molds and fungi. In contrast, microorganisms grow well in unpreserved aqueous dispersions and therefore an antimicrobial preservative such as 0.1% w/v chlorocresol, 0.18% w/v methylparaben–0.02% w/v propylparaben, or 0.1% w/v thimerosal should be added. The addition of certain antimicrobials, such as benzalkonium chloride or sodium benzoate, in high concentrations (0.1% w/v) can cause cloudiness and a reduction in viscosity of carbomer dispersions. Aqueous gels may be sterilized by autoclaving[7] with minimal changes in viscosity or pH, provided care is taken to exclude oxygen from the system, or by gamma irradiation, although this technique may increase the viscosity of the formulation.[26,27] At room temperature, carbomer dispersions maintain their viscosity during storage for prolonged periods. Similarly, dispersion viscosity is maintained, or only slightly reduced, at elevated storage temperatures if an antioxidant is included in the formulation or if the dispersion is stored protected from light. Exposure to light causes oxidation that is reflected in a decrease in dispersion viscosity. Stability to light may be improved by the addition of 0.05–0.1% w/v of a water-soluble UV absorber such as benzophenone-2 or benzophenone-4 in combination with 0.05–0.1% w/v edetic acid. The UV stability of carbomer gels may also be improved by using triethanolamine as the neutralizing base; *see* Section 10.

Carbomer powder should be stored in an airtight, corrosion-resistant container in a cool, dry place. The use of glass, plastic, or resin-lined containers is recommended for the storage of formulations containing carbomer. Packaging in aluminum tubes usually requires the formulation to have a pH less than 6.5, and packaging in other metallic tubes or containers necessitates a pH greater than 7.7 to prolong carbomer stability.

12 Incompatibilities

Carbomers are discolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids, and high levels of electrolytes. Certain antimicrobial adjuvants should also be avoided or used at low levels, *see* Section 11. Trace levels of iron and other transition metals can catalytically degrade carbomer dispersions. Intense heat may be generated if a carbomer is in contact with a strong basic material such as ammonia, potassium or sodium hydroxide, or strongly basic amines.

Certain amino-functional actives form water-insoluble complexes with carbomer; often this can be prevented by adjusting the solubility parameter of the fluid phase using appropriate alcohols and polyols.

Carbomers also form pH-dependent complexes with certain polymeric excipients. Adjustment of solubility parameter can also work in this situation.

13 Method of Manufacture

Carbomers are synthetic, high-molecular-weight, crosslinked polymers of acrylic acid. These poly(acrylic acid) polymers are crosslinked with allylsucrose or allylpentaerythritol. The polymerization solvent used most commonly was benzene; however, some of the newer commercially available grades of carbomer are manufactured using either ethyl acetate or a cyclohexane–ethyl acetate cosolvent mixture. The *Carbopol ETD* resins are produced in the cosolvent mixture with a proprietary polymerization aid, and these resins are crosslinked with a polyalkenyl polyether.

14 Safety

Carbomers are used extensively in nonparenteral products, particularly topical liquid and semisolid preparations. They may also be used in oral formulations, although only certain grades can be used; *see* Section 18. Acute oral toxicity studies in animals indicate that carbomer 934P has a low oral toxicity, with doses up to 8 g/kg being administered to dogs without fatalities occurring. Carbomers are generally regarded as essentially nontoxic and nonirritant materials; there is no evidence in humans of hypersensitivity reactions to carbomers used topically. In humans, oral doses of 1–3 g of carbomer have been used as a bulk laxative.

LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 934[28]
LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 934P
LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 940
LD_{50} (mouse, IP): 0.04 g/kg for carbomer 934P
LD_{50} (mouse, IP): 0.04 g/kg for carbomer 940
LD_{50} (mouse, IV): 0.07 g/kg for carbomer 934P
LD_{50} (mouse, IV): 0.07 g/kg for carbomer 940
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 934P
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 934
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 940
LD_{50} (rat, oral): 10.25 g/kg for carbomer 910
LD_{50} (rat, oral): 2.5 g/kg for carbomer 934P
LD_{50} (rat, oral): 4.1 g/kg for carbomer 934
LD_{50} (rat, oral): 2.5 g/kg for carbomer 940
LD_{50} (rat, oral): > 1g/kg for carbomer 941

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation

should be minimized to avoid the risk of explosion (lowest explosive concentration is 100 g/m^3). Carbomer dust is irritating to the eyes, mucous membranes, and respiratory tract. In contact with the eye, carbomer dust is difficult to remove with water owing to the gelatinous film that forms; saline should therefore be used for irrigation purposes. Gloves, eye protection, and a dust respirator are recommended during handling.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral suspensions and tablets; ophthalmic, rectal, and topical preparations). Included in nonparenteral medicines licensed in Europe.

17 Related Substances

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18 Comments

A number of different carbomer grades are commercially available that vary in their molecular weight, degree of crosslinking, polymer structure, and residual components. These differences account for the specific rheological, handling, and use characteristics of each grade. Carbomer grades that have the polymer backbone modified with long-chain alkyl acrylates are used as polymeric emulsifiers or in formulations requiring increased resistance to ions.

Polycarbophil, poly(acrylic acid) polymers crosslinked with divinyl glycol, is available for bioadhesive or medicinal applications. Carbomers designated with the letter 'P', e.g. carbomer 971P, are the only pharmaceutical grades of polymer accepted for oral or mucosal contact products. These resins are particularly useful in the production of clear gels.

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