excipients

Properties of mucoadhesive polymers and their use in tablets and other dosage forms

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This article describes how several specialty polymers are used to formulate swallowable (peroral), buccal, and sublingual tablets, as well as topicals, suspensions, solutions, and mucoadhesive products.

Carbopol polymers (carbomers), Noveon polycarbophil and Pemulen polymers are high molecular-weight polymers of acrylic acid chemically crosslinked with polyalkenyl alcohols or divinyl glycol [1, 2, 3]. These polymers are used in commercial formulations of different dosage forms for various applications, including peroral, chewable, buccal, and sublingual tablets; topicals (lotions, creams, gels); oral suspensions/solutions; oral-care products; and mucoadhesive products.

These polymers, when placed in contact with an aqueous medium, hydrate and swell through hydrogen bonding or electrostatic repulsion (when neutralized). These mechanisms are the basis of the excipients' functionality in various pharmaceutical applications:

- Bioadhesion in buccal, intestinal, ophthalmic, nasal, vaginal, and rectal applications.
- Controlled-release from solid dosage forms. Carbopol polymers form gel matrices that control the release of active pharmaceutical ingredients (APIs) from tablets, lozenges, pastilles, and multiparticulate forms. The polymers are efficient. They have demonstrated slower release rates at lower concentrations than other commercially available excipients, enabling companies to reduce formulation costs and to make smaller tablets, which increases productivity and makes the tablets easier to swallow.

Table 1

Carbomers, polycarbophil, and carbomer copolymers for use in drug products

Product	Properties		Applicable compendial monograph			Route of administration	
	Polymerization solvent	Viscosity [a] (cP)	United States (USP/NF)	Europe (Ph Eur)	Japan (JPE) [b]	Oral	Topical
Carbopol polymers							
971P NF	Ethyl acetate	4,000 - 11,000	Carbomer homopolymer type A	Carbomers	Carboxyvinyl polymer	●	●
71G NF	Ethyl acetate	4,000 - 11,000	Carbomer homopolymer type A	Carbomers	Carboxyvinyl polymer	●	●
974P NF	Ethyl acetate	29,400 - 39,400	Carbomer homopolymer type B	Carbomers	Carboxyvinyl polymer	●	●
5984 EP	Cosolvent [c]	30,500 - 39,400	Carbomer homopolymer type B	Carbomers	Carboxyvinyl polymer		●
980 NF	Cosolvent	40,000 - 60,000	Carbomer homopolymer type C	Carbomers	Carboxyvinyl polymer		●
981 NF	Cosolvent	4,000 - 10,000	Carbomer homopolymer type A	Carbomers	Carboxyvinyl polymer		●
Ultrez 10 NF	Cosolvent	45,000 - 65,000	Carbomer interpolymer type A				●
ETD 2020 NF	Cosolvent	47,000 - 77,000 [d]	Carbomer interpolymer type B				●
Noveon polycarbophil							
AA-1 USP	Ethyl acetate	2,000-12,000 [e]	Polycarbophil			●	●
Pemulen polymers							
TR-1 NF	Cosolvent	10,000-26,500 [d]	Carbomer copolymer type B				●
TR-2 NF	Cosolvent	4,500-13,500 [d]	Carbomer copolymer type A				●

a Specification at 0.5 weight percent at pH 7.5, unless otherwise noted
b Upon request, Lubrizol certifies select lots of product against JPE's Carboxyvinyl Polymer Monograph
c Cosolvent is a mixture of ethyl acetate and cosolvent
d 1.0 weight percent
e 0.2 weight percent

- Rheology modification at very low concentrations—less than 1 percent—to produce a wide range of viscosities and flow properties in lotions, creams, and gels; oral suspensions; and transdermal gel reservoirs.
- Suspension of insoluble ingredients in oral and topical liquids and semisolids.
- Emulsification of topical oil-in-water systems with essentially no need for surfactants.

Lubrizol manufactures all three polymers under GMP standards and offers them in a variety of functional grades suitable for different dosage forms.

Table 1 provides an overview of the products and summarizes their recommended uses in drug development and manufacture. Polymers manufactured in either ethyl acetate or a cosolvent mixture of ethyl acetate and cyclohexane are used in topical products, while the polymers manufactured in ethyl acetate are intended for use in orally administered pharmaceutical products.

Mucodhesion

Bioadhesion is the state in which two materials, at least one of which is biological in nature, are held together for extended periods by interfacial forces. Mucoadhesion is a type of bioadhesion in which two surfaces—one of which is mucus or a mucous membrane—adhere to each other. In pharmaceutical applications, mucoadhesion can enhance drug delivery and/or provide other therapeutic advantages (local protection, lubrication, etc.).

Mucoadhesion is a complex phenomenon and multiple factors influence it, including mucus properties, the dosage form characteristics, displacement forces, and other substances present at the interface, etc. Adhesion requires:

Initial contact with the mucus (wetting). The fast hydration of Carbopol polymers allows dosage forms that include it to quickly establish contact with the mucus upon administration.

Consolidation of adhesion. As adhesion is established, various physicochemical interactions occur between the Carbopol polymers and the mucus to consolidate and strengthen the adhesive joint. This is important because it prevents various dislodging effects (as the surfaces aren't generally stationary) and prolongs adhesion. Consolidation of adhesion is achieved by hydrogen bonding and/or macromolecular penetration.

Mechanisms of adhesion. There are two primary mechanisms: hydrogen bonding and macromolecular interpenetration.

- Because the polymers have a large amount of carboxylic groups, they can establish hydrogen bonding with the mucus. This bonding occurs when the polymer is used "as is," without neutralization, such as in solid dosage forms (granules, tablets), anhydrous systems, etc.
- When the polymer's neutralized form is used (in liquid or semisolid dosage forms containing buffers or bases), the polymer swells to its largest extent and can interpenetrate the glycoprotein chains in the mucus to form a network (macromolecular interpenetration).

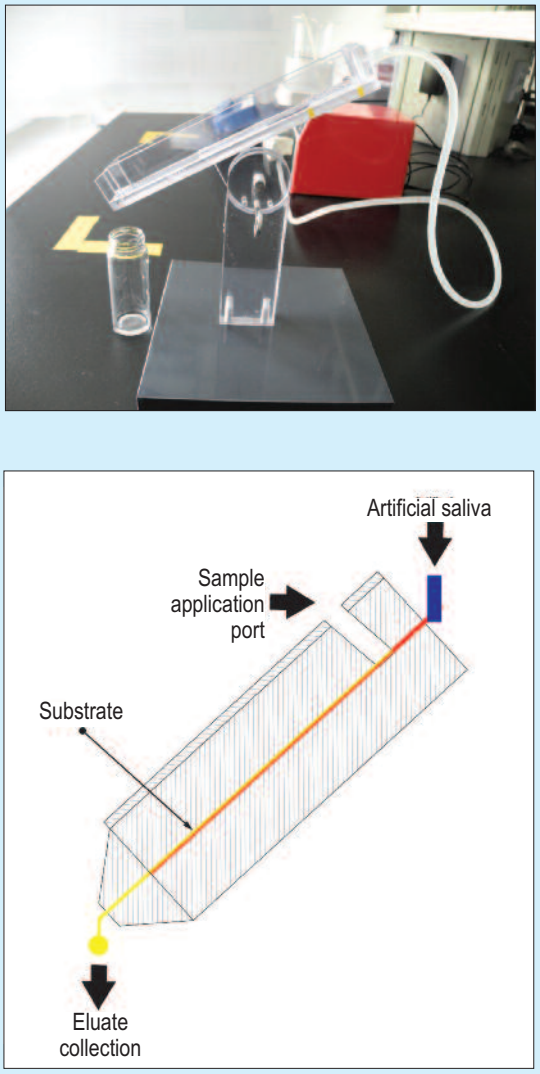
Duration of adhesion. Mucoadhesion is temporary, and its duration is determined by the strength of the adhesive forces and/or the mucus turnover. In the case of weaker adhesives, breakup occurs at the interface between the dosage form and the mucus. We recommend that formulators opt for the stronger adhesives so that the dosage form is removed only by mucus turnover or when the whole system is overhydrated and washed out (elution).

Mucoadhesive properties

The adhesive properties of Carbopol polymers have been compared in vitro with other materials, including hydroxypropyl cellulose, sodium carboxymethyl cellulose, xanthan gum, carrageenan, poloxamer, and copolymer of methyl vinyl ether and maleic anhydride (PVM/MA). In one in-house study, aqueous dispersions of the materials at two concentrations (0.25 or 1.00 percent w/w) were evaluated using an adapted in vitro esophageal retention model to simulate oral/peroral conditions (Figure 1).

FIGURE 1

In vitro esophageal retention model used to evaluate adhesive properties



In general, the retention was higher at the 1 percent concentration than at the 0.25 percent level. Compared to other materials, the Carbopol polymers provided the slowest elution (Figure 2) and longest retention (Figure 3). The retention of the 1 percent dispersion of Carbopol polymers exceeded 30 minutes (Figure 4).

Applications of mucoadhesive properties

Mucoadhesion can enhance drug delivery by retaining a dosage form at the site of action (localized delivery) or at the site of absorption (systemic delivery). Localized delivery from mucoadhesive dosage forms containing carbomers has been reported for leuprolide acetate, triamcinolone acetonide, mesalamine, menthol, nystatin, lidocaine, 5-fluorouracil, and other APIs. Target mucosa included oral, colonic, rectal, ophthalmic, vaginal, etc. Carbomers have been evaluated for mucoadhesive dosage forms to provide systemic delivery of testosterone, nifedipine, morphine, fentanyl citrate, doxycycline, buprenorphine, and other APIs.

Figure 2

Elution (percentage washed off) of aqueous dispersions made from various materials (1.0 weight percent)

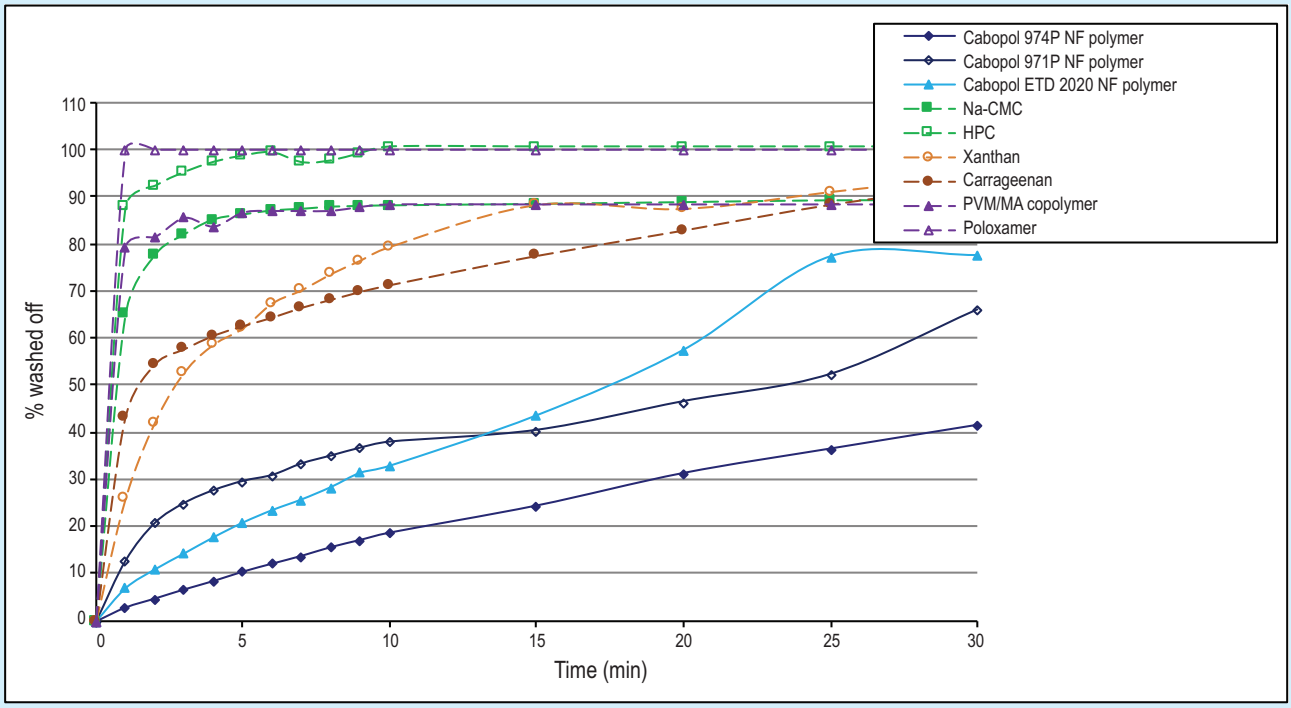


Figure 3

Retention (adhesion) of 1 percent aqueous dispersions of various materials after 15 minutes

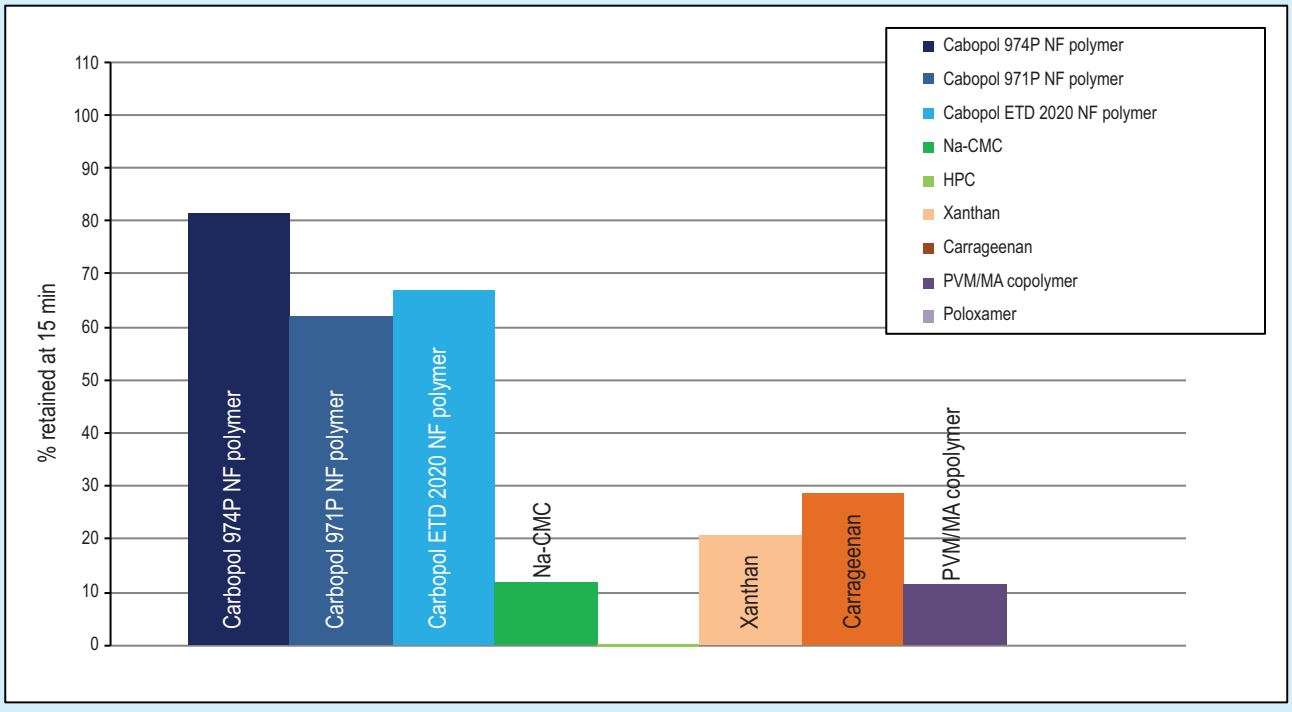
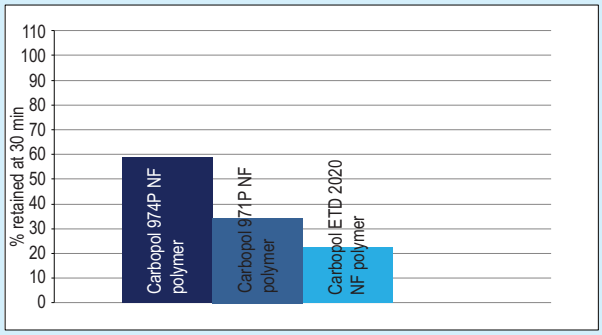


FIGURE 4

Retention (adhesion) of 1 percent aqueous dispersions of Carbopol polymers after 30 minutes



Carbomers can also provide other therapeutic advantages by coating and protecting damaged tissues (gastric ulcers or lesions of the oral mucosa) and by acting as lubricating agents (in the oral cavity, eye, and vagina). Examples include mouthwash that forms a protective layer over lesions in the mouth caused by radiation therapy or from canker sores, dental braces, etc.

Carbomers have been included in liquid, gel, and solid formulations to treat xerostomia (dry mouth). In the case of lozenges containing a carbomer or polycarbophil, the dosage form interacts with saliva to produce a hydrogel that adheres to the mucosa and forms a protective film over irritated areas.

When used in artificial tears or other ophthalmic preparations, a carbomer or polycarbophil can form a transparent lubricating and moistening film on the eye's surface. It has also been shown to increase how long an API remains on the eye's surface.

Carbomers and polycarbophil have been formulated in vaginal products to provide mucoadhesion, moisturization, lubrication, and to maintain/buffer vaginal pH.

The mucoadhesive properties of carbomers and polycarbophil have been demonstrated in many studies and discussed in several papers [4-20]. The polymers are also used in numerous commercial products. See Table 2.

In summary, Carbopol polymers, Noveon polycarbophil, and Pemulen polymers enhance drug delivery and/or offer other therapeutic advantages due their mucoadhesion properties, as have been shown in various applications, including oral, colonic, rectal, gastric, nasal, ophthalmic, and vaginal products. *T&C*

TABLE 2

Commercial products that contain carbomers and/or polycarbophil for mucoadhesion [21]

Product	Active ingredient	Other ingredients
	Buccal products	
Onsolis soluble film	Fentanyl citrate	Carboxymethyl cellulose, citric acid, hydroxyethyl cellulose, hydroxypropyl cellulose, methylparaben, monobasic sodium phosphate, peppermint oil, polycarbophil, propylene glycol, propylparaben, red iron oxide, sodium benzoate, sodium hydroxide, sodium saccharin, titanium dioxide, tribasic sodium phosphate, vitamin E acetate, water
Striant mucoadhesive	Testosterone	Anhydrous lactose, Carbomer 934P, hypromellose, magnesium stearate, lactose monohydrate, polycarbophil, colloidal silicon dioxide, starch, talc
Aftab tablets	Triamcinolone acetonide	Hydroxypropyl cellulose, carbomer, magnesium stearate, talc, aluminum magnesium silicate, lactose monohydrate, carmellose calcium, yellow-orange S (E 110).
Canker Cover canker sore patch	Menthol	Carbomer homopolymer Type A, polyvinyl pyrrolidone, xylitol, hydroxypropyl cellulose, silicon dioxide, carnallite, citrus oil, annatto
OraMoist dry mouth relief patch	—	Xylitol, polyvinyl pyrrolidone, carbomer homopolymer, triglyceride, lemon flavor, citric acid, calcium carbonate, hydroxypropyl cellulose, sodium chloride, silicone dioxide, magnesium stearate, glucose oxidase, lysozyme, lactoferrin, carmine CI 75470

Lozenges		
GeloRevoice throat lozenges	Sodium hyaluronate, carbomer, xanthan	Mannitol, sodium hydrogen carbonate, xylitol, citric acid, macrogol, aspartame, flavor (cherry, menthol), potassium monohydrogen phosphate, zinc stearate, silica
Cevitt Hals & Rachen lozenges	Sodium hyaluronate, carbomer, xanthan	Mannitol, sodium hydrogen carbonate, sorbitol, citric acid, aspartame, vitamin C, flavor, zinc citrate dihydrate
Neo-Angin Stimmig Plus lozenges	—	Carbopol, carrageenan, sodium hyaluronate, mannitol, sodium hydrogen carbonate, citric acid, macrogol, sucralose, cherry flavor, levomenthol, potassium monohydrogen phosphate, zinc stearate, silica, sorbitol, xanthan, flavor
Isla Med Hydro+ lozenges	Extract of Cetraria islandica, carbomer, xanthan, sodium hyaluronate	Arabic gum, sorbitol, maltitol, anhydrous citric acid, potassium acesulfame, levomenthol, peppermint oil, anise, bitter fennel oil , medium-chain triglycerides, water
Mouth rinse		
MuGard oral mucoadhesive	—	Purified water, glycerin, benzyl alcohol, sodium saccharin, carbomer homopolymer Type A, potassium hydroxide, citric acid, polysorbate 60, phosphoric acid
Ophthalmic		
Liquivisc eye gel	Carbomer 974P	Benzalkonium chloride, sorbitol, lysine monohydrate, sodium acetate trihydrate, polyvinyl alcohol, water
Viscotears liquid gel	Carbomer (polyacrylic acid)	Cetrimide, sodium hydroxide, sorbitol, water
Viscotears single-dose eye gel	Carbomer (polyacrylic acid)	Sorbitol, sodium hydroxide, water
Vaginal		
Crinone vaginal gel	Progesterone	Glycerin, light paraffin, hydrogenated palm oil glyceride, carbomer homopolymer Type B, sorbic acid, polycarbophil, sodium hydroxide, water
Hyalo Gyn vaginal hydrating gel	Hydeal-D (hyaluronic acid derivative)	Propylene glycol, carbomer homopolymer Type B, methyl p-hydroxy-benzoate, propyl p-hydroxybenzoate, sodium hydroxide, water
Replens vaginal moisturizer	—	Carbomer 934P, glycerin, hydrogenated palm oil glyceride, mineral oil, polycarbophil, water, sorbic acid
RepHresh vaginal gel	—	Water, glycerin, polycarbophil, carbomer homopolymer Type B, ethylparaben sodium, methylparaben sodium, propylparaben sodium, sodium hydroxide

Note: Trademarked products listed in this table include Onsolis (BioDelivery Sciences International), Striant (Columbia Laboratories), Aftab (Meda Pharma), Canker Cover and OraMoist (Quantum), GeloRevoice (Pohl-Boskamp), Cevitt Hals & Rachen (Hermes Arzneimittel), Neo-Angin (Klosterfrau Healthcare Group), Isla (Engelhard Arzneimittel), MuGard (Abeona Therapeutics), Liquivisc (Thea Pharmaceuticals) Viscotears (Novartis), Crinone (Allergan), Hyalo Gyn (Fidia Pharma USA), and Replens and RepHresh (Church & Dwight).

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