

Mucoadhesive Polymers in Pharmaceutical Formulations

Introduction

This technical brief will cover the use of polymers in a variety of dosage forms (buccal/sublingual tablets, liquid, semi-solid formulations, and oral care products) to impart mucoadhesion. The basic mechanism of mucoadhesion and methods to evaluate it in the context of pharmaceutical applications will also be reviewed.

Mucoadhesion basics and mechanism

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 one of the surfaces is mucus or a mucous membrane. In pharmaceutical applications, mucoadhesion can enhance drug delivery and/or provide other therapeutic advantages (local protection, lubrication, etc.).^{1,2}

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

1. **Initial contact with the mucus (wetting)** - The ability of the polymer to hydrate quickly, allowing the dosage form that incorporates it to quickly establish contact with the mucus upon administration.
2. **Consolidation of adhesion** - As adhesion is established, various physicochemical interactions occur between the polymer and the mucus to consolidate and strengthen the adhesion joint. This is important because it helps prevent dislodging (as the surfaces aren't generally stationary) and prolongs adhesion. Consolidation of adhesion is achieved by hydrogen bonding and/or macromolecular interpenetration.
 - **Hydrogen Bonding** - Mucoadhesive polymers establish hydrogen bonding with the glycoproteins in the mucus through functional groups such as carboxylic, hydroxy, amino, etc.
 - **Macromolecular Penetration** - interpenetration between the polymer chains and the glycoprotein chains in the mucus form a network.
3. **Adhesion endpoint** - 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. For stronger adhesives, the adhesion endpoint might occur at the mucus layer (due to mucus turnover) or due to the whole system being overhydrated and washed out.

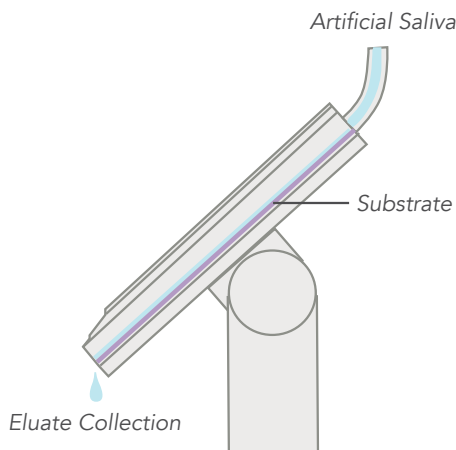
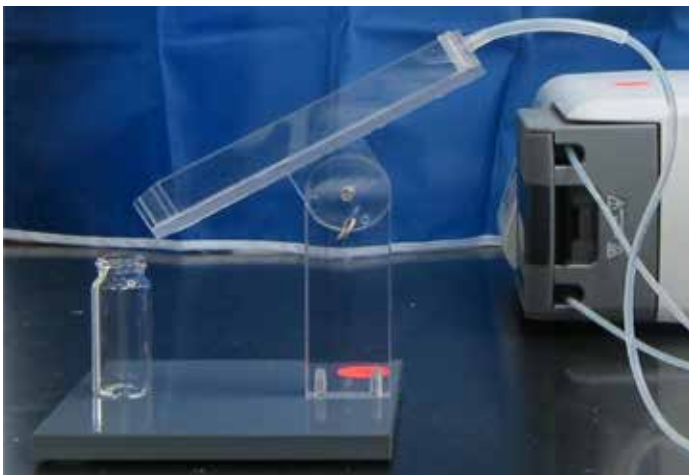


Methods to measure in-vitro mucoadhesion

A critical step in developing a mucoadhesive drug product is the ability to verify adherence to the mucus. Literature abounds in methods used to measure mucoadhesion, however no standard is available.^{3,4} Some measure mucoadhesive ability based on the force required to detach the sample from a mucosal surface, or the time it takes for detachment when subject to applied forces (e.g., tensile assay, continuous flow assay). Others study the interaction between the mucoadhesive polymer and mucin to link properties determined from rheology studies or spectroscopic analysis to mucoadhesion.

Lubrizol Life Science Health (LLS Health) has developed a method based on the in vitro oesophageal retention (IVOR) model that allows for mucoadhesion evaluation in a dynamic environment. The dosage form is subjected to continuous fluid flow during testing. The device is depicted in Figure 1.

Figure 1. In vitro esophageal retention model used to evaluate adhesive properties



Polymers with mucoadhesive properties

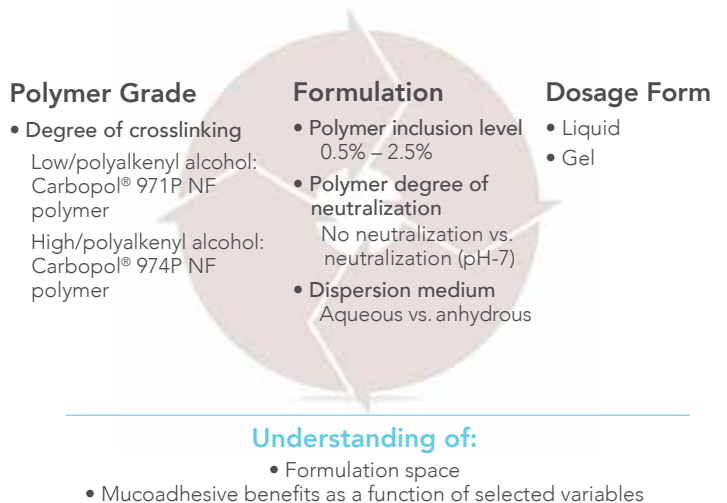
Polymers with mucoadhesive properties are natural or synthetic hydrophilic molecules containing functional groups that could interact with the mucin glycoproteins via non-covalent bonds such as hydrogen bonds, van der Waals forces and ionic interactions. Examples include carbomers (e.g., Carbopol® polymers), xanthan gum, sodium carboxymethylcellulose, and carrageenan.^{5,6}

Benefits of Carbopol® polymers in designing mucoadhesive pharmaceutical formulations

Carbopol® polymers (carbomers) are high molecular weight polymers of acrylic acid crosslinked with polyalkenyl alcohols and are used in a variety of commercial pharmaceutical formulations.⁷⁻⁹ These excipients, 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, such as controlled drug release, rheology modification, and mucoadhesion.

A study was designed to establish the impact of Carbopol® polymer characteristics on mucoadhesive properties in liquid and semisolid formulations. Typically, the polymer was dispersed at the desired concentration in deionized water or anhydrous medium (glycerin/propylene glycol/PEG 400 mixture), followed by neutralization (when required). Mucoadhesive studies of Carbopol® polymers formulations were performed using an in-house adapted in-vitro esophageal retention (IVOR) model to simulate oral/peroral conditions (Figure 1). Eluted fractions were collected up to 45 minutes and quantified by UV-Vis using a marker. The design space for this study is presented in Figure 2.

Figure 2. Design summary for the study of mucoadhesive liquid and semisolid formulations containing Carbopol® polymers

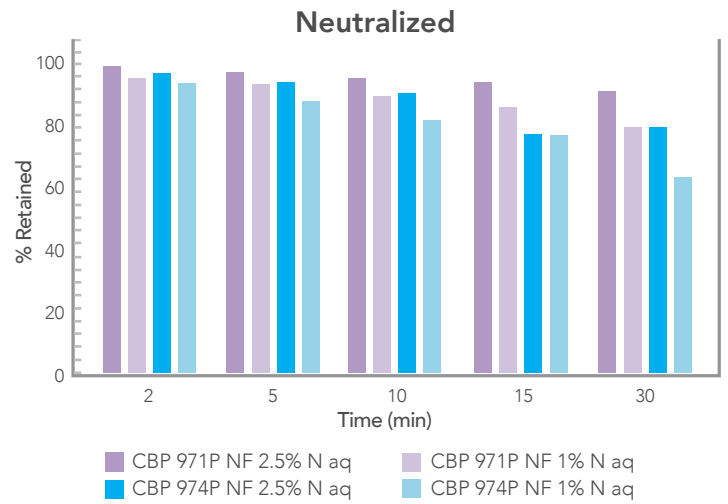
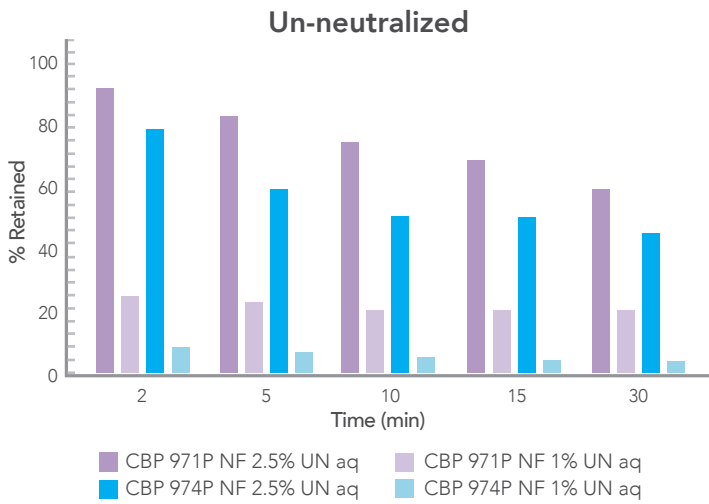


The results of the study showed that Carbopol® polymers had better mucoadhesion in their neutralized vs. un-neutralized form for same dispersion medium and concentration (Figures 3-6). The impact of concentration on the mucoadhesion of the studied formulations was more pronounced in the aqueous un-neutralized form. Carbopol® 971P NF polymer in aqueous systems, despite lower viscosity, showed better retention on membrane

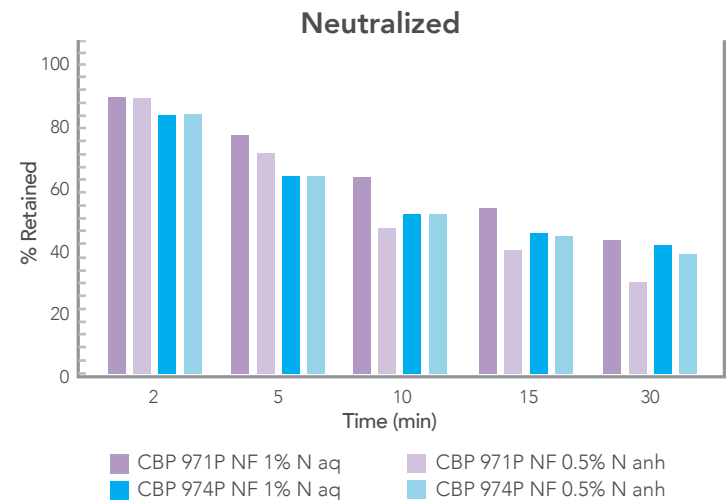
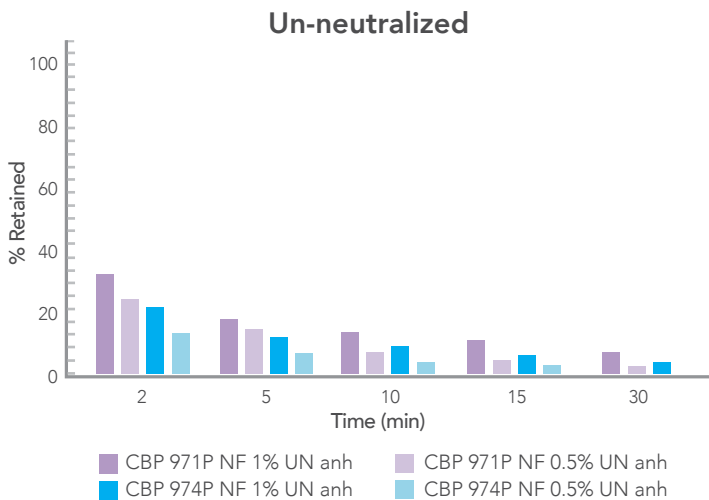
when compared to Carbopol® 974P NF polymer. This demonstrates that **though viscosity of the dispersion may impact retention, it is not the determining parameter for increased mucoadhesion** (Figure 7 and 8)

Anhydrous formulations tend to have similar retention as the aqueous formulations for the initial time points (2 - 5 min), however they eluted much faster as time progressed.

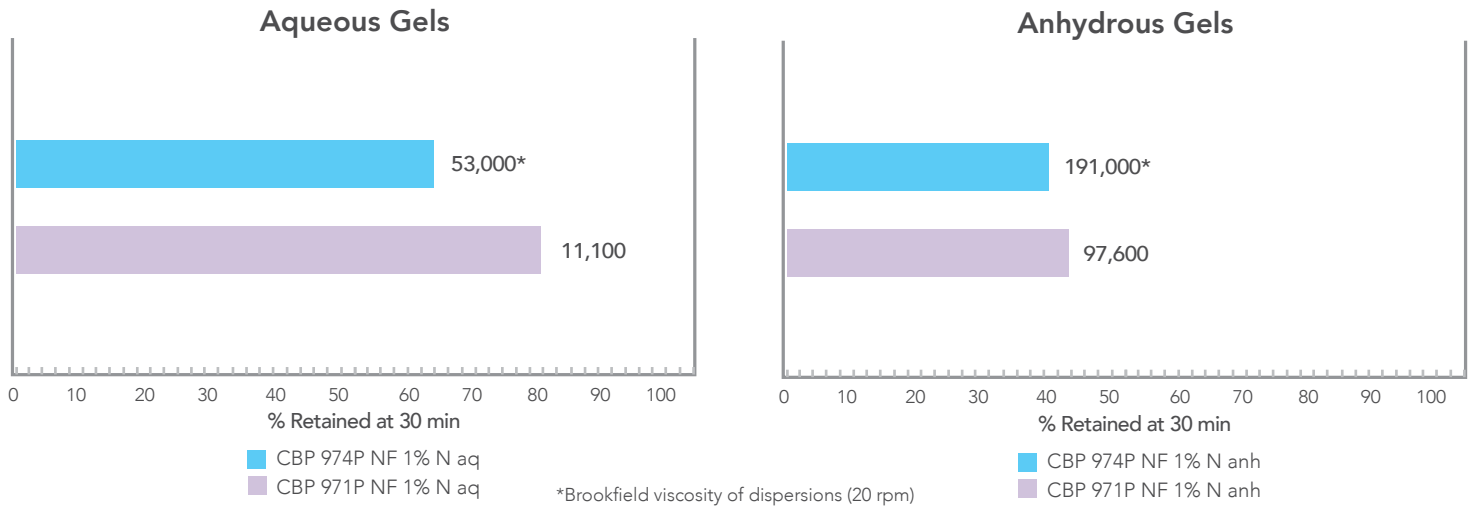
Figures 3 and 4. In vitro evaluation of mucoadhesion of Carbopol® 971P NF (CBP 971P NF) and 974P NF (CBP 974P NF) polymers in aqueous gels, un-neutralized (UN aq) and neutralized (N aq)



Figures 5 and 6. In vitro evaluation of mucoadhesion of Carbopol® 971P NF (CBP 971P NF) and 974P NF (CBP 974P NF) polymers in anhydrous gels, un-neutralized (UN anh) and neutralized (N anh)



Figures 7 and 8. Impact of gel viscosity on in vitro mucoadhesion of Carbopol® 971P NF (CBP 971P NF) and 974P NF (CBP 974P NF) polymers



These results support the mechanism of adhesion for Carbopol® polymers:

- a. **Initial contact with the mucus (wetting):** The hydration potential of Carbopol® polymers allows the dosage form to quickly establish contact with the mucus upon application.
- b. **Consolidation of adhesion:** Hydrogen bonding and/or macromolecular interchain penetration between Carbopol® polymers and components of mucin.

Within the boundaries of the general mucoadhesive mechanism, differences observed for mucoadhesion strength in liquid/semisolid formulations containing Carbopol® polymers were dictated by parameters such as degree of neutralization of the polymer, dispersion medium, and degree of crosslinking.

When the polymer is in its neutralized form, it is swollen to the largest extent; macromolecular interpenetration with the glycoprotein chains in the mucus provide strong mucoadhesion. Conversely, in anhydrous media and in un-neutralized form, the predominant mucoadhesive mechanism is the hydrogen bonding between the carboxylic groups and the mucus components, which leads to less retention of formulation on the membrane.

Furthermore, the mucoadhesive properties of Carbopol® polymers were compared in vitro with other materials, including xanthan gum, carrageenan, sodium carboxymethylcellulose (Na-CMC), copolymer of methyl vinyl ether and maleic anhydride (PVM/MA), and hydroxypropyl cellulose (HPC). In this study, aqueous dispersions of the materials (0.25% and 1% w/w) were evaluated using the LLS Health IVOR model to simulate oral/peroral conditions.



Compared to other materials, Carbopol® polymers provided the longest retention over time at both concentrations studied, even after 30 minutes (Figure 9 and 10).

Figure 9. Retention of aqueous dispersion made from various materials (1.0 weight percent)

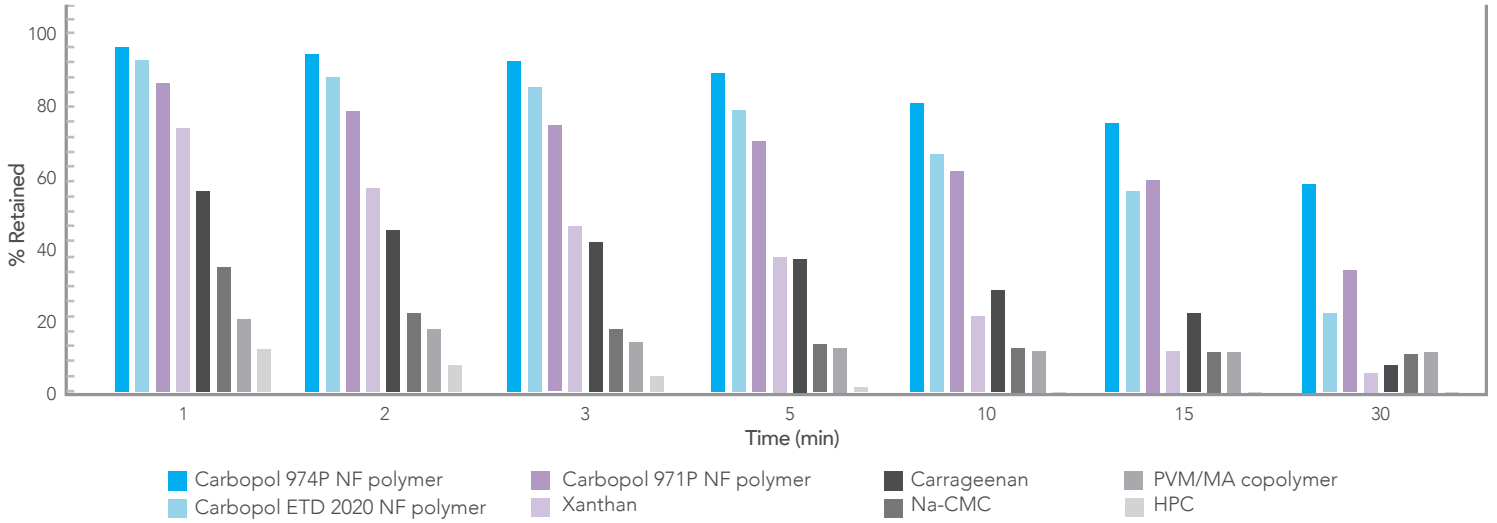
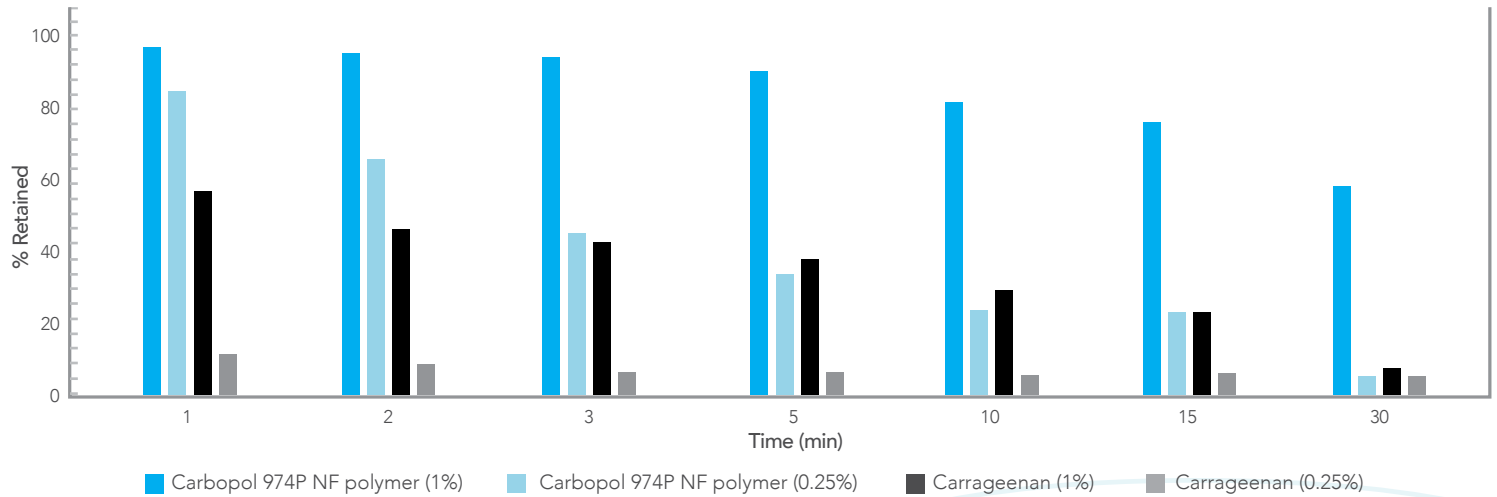


Figure 10. Retention of Carbopol® polymer and carrageenan dispersion at varying concentrations



Case study #1: Mouthwash formulations with and without Carbopol® polymers

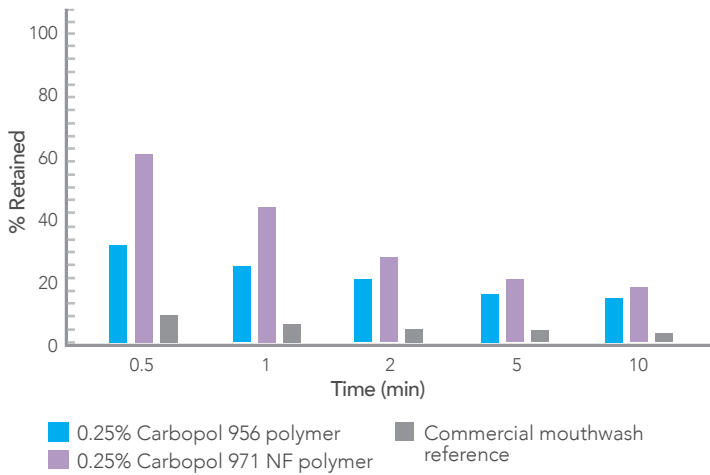
This study evaluated the impact of Carbopol® polymer addition on the mucoadhesive properties of a commercial mouthwash formulation. Samples to be studied were prepared by diluting a Carbopol® polymer neutralized aqueous gel with commercial mouthwash formulation. Utilizing an IVOR model to simulate oral/peroral conditions, polymer type and inclusion level were varied to determine the effects on retention of the formulation over time.

Formulations containing Carbopol® polymers were found to display improved mucoadhesive properties / retention

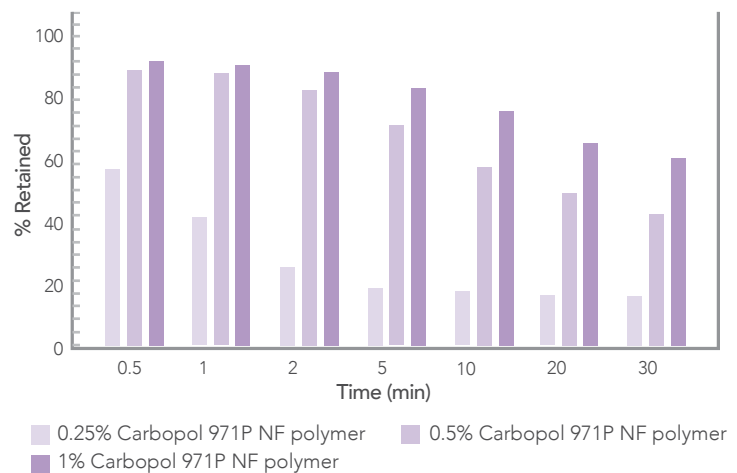
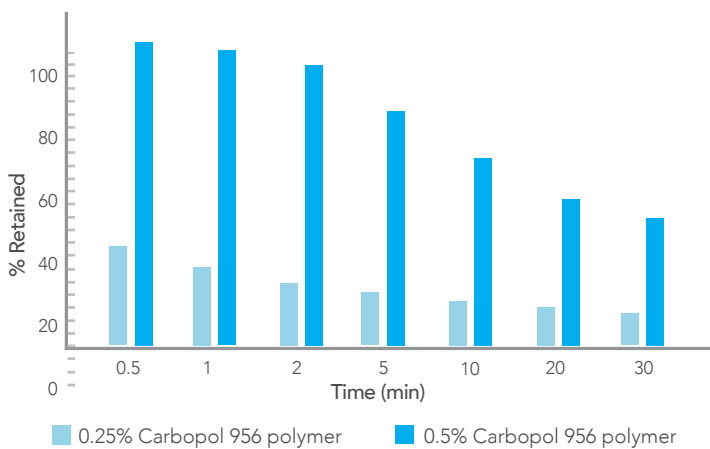
compared to the reference mouthwash formulation that did not contain Carbopol® polymers (Figure 11). Both crosslinked polymers tested (Carbopol® 956 and 971P NF polymers) showed comparable retention over time when used at the same concentration, and longer retention was achieved with higher polymer inclusion levels (Figures 12 and 13).

This suggests Carbopol® polymers can provide enhanced mucoadhesive effects while allowing formulators flexibility to tailor their mouthwash formulation; viscosity and formulation retention can be varied based on Carbopol® polymer type, concentration, and addition method.

Figure 11. Effect of Carbopol® polymers on elution



Figures 12 and 13. Effect of Carbopol® polymer concentration on elution



Case Study #2: Oral care formulations containing Sanqui extract (traditional Chinese medicine)

Sanqui powder (*Panax notoginseng*) is a traditional Chinese medicine (TCM) with hemostatic and anti-inflammatory properties used in oral care products to reduce bleeding and swelling of gum tissue.

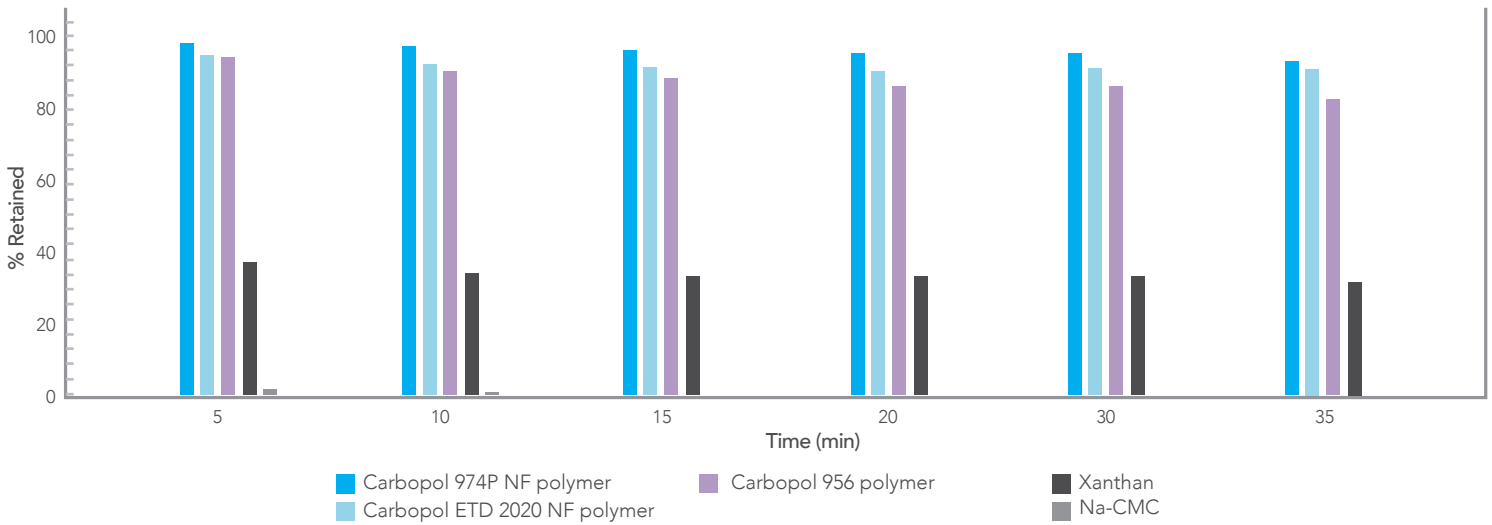
The objective of this study was to compare the retention of Sanqui extract from oral care gels formulated with Carbopol® polymers vs. other polymers commonly used as toothpaste binders (xanthan gum and Na CMC). The Carbopol® polymers used were Carbopol 974P NF and Carbopol 956 (oral care grade) and Carbopol ETD 2020 NF (designed for easy dispersion). The formulations contained polymer and Sanqui extract at 1% inclusion level,

respectively. The mucoadhesive properties were evaluated using the IVOR model simulating oral/peroral conditions.

Carbopol® polymers provided the longest and largest retention of Sanqui extract when compared to other polymers (Figure 14). NaCMC and xanthan gum formulations displayed very quick elution (>90% and >50% after 5 minutes, respectively). In comparison, all Carbopol® polymers gels showed prolonged retention with <20% of Sanqui eluted after 35 minutes.

This study demonstrates the potential for enhanced therapeutic effects of actives, such as Sanqui, via prolonged active retention when formulating with Carbopol® polymers. Mucoadhesion with Carbopol® polymers also offers a new opportunity for claim differentiation in oral care formulations.

Figure 14. Polymer effect on Sanqui elution

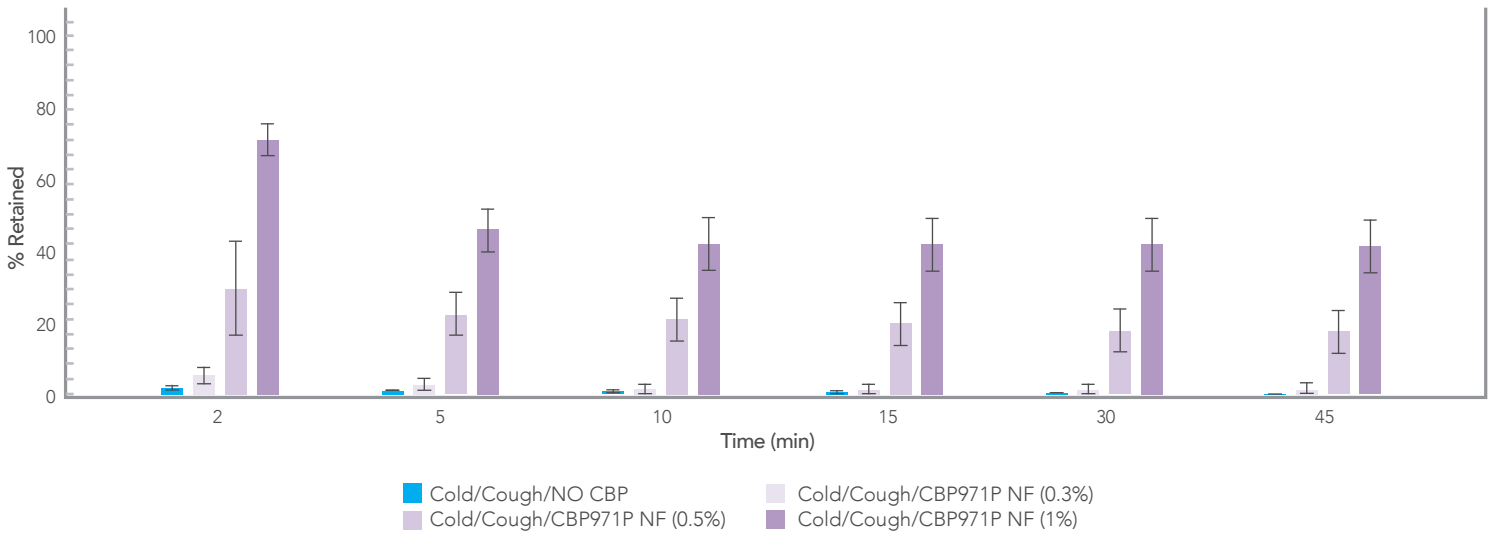


Case Study #3: Liquid cold and cough formulation

Mucoadhesion with Carbopol® polymers offer a new opportunity for differentiation in oral liquid formulations; these polymers provide prolonged retention of actives at the site of action with potential for enhanced therapeutic effects. This was demonstrated in a study that compared the mucoadhesive properties of a commercial liquid cough &

cold formulation with or without Carbopol® polymers. Carbopol® polymer inclusion level was varied to determine the effects on retention of the formulation over time. Formulations containing Carbopol® polymers had significantly higher active retention than formulations that did not contain Carbopol® polymers (Figure 15). Additionally, higher retention was achieved with higher polymer concentration.

Figure 15. Impact of Carbopol® 971P NF polymer (CBP971P NF) on mucoadhesion in oral liquids

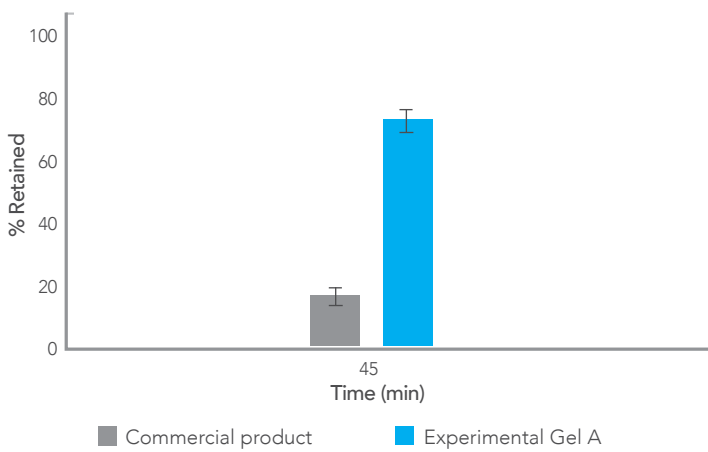


Case Study #4: Vaginal gel formulation improvement

This case study explored formulation improvement for longer duration of efficacy of an existing commercial vaginal gel. The commercial product contained carbomer homopolymer type B, which is similar to Carbopol® 974P NF polymer, and polycarbophil. The commercial gel was compared to formulations containing Carbopol® 974P NF polymer and Noveon® AA-1 polycarbophil.

The experimental vaginal gel formulation containing Lubrizol polymers showed three-fold increased retention at 45 min when compared to the commercial product (Figure 16). This suggests that Carbopol® polymers and Noveon® AA-1 polycarbophil polymers exhibit superior mucoadhesive performance when compared to other carbomers and polycarbophils. Additionally, Noveon® AA-1 polycarbophil and Carbopol® polymers may provide buffering capacity (pH regulation), rheology and viscosity control (not affected by body temperature), and benefits in the treatment of bacterial vaginosis.

Figure 16. Effect of Carbopol® polymers on elution in vaginal gels



Case Study #5: Mucoadhesion enhancement of films containing Carbopol® polymers

Polyvinyl alcohol is known in pharmaceutical formulation as a film former, while Carbopol® polymers have demonstrated mucoadhesive properties. A study was designed to establish the mucoadhesive properties of PVA (polyvinyl alcohol) films containing Carbopol® polymers. Film formulations containing Carbopol® polymer and PVA were prepared by solvent casting from aqueous/ethanolic gels. Typically, the Carbopol® polymer was dispersed at the desired concentration in water/ethanol mixture, followed by neutralization when required. An aqueous PVA solution and plasticizer were added to the Carbopol® polymer dispersion. Films of various thickness were cast from the resulted gels.

Mucoadhesive studies of Carbopol® polymers/PVA films were performed using a modification of the in-vitro esophageal retention (IVOR) model to simulate oral/

peroral conditions. The design space for this study is presented in Figure 17.

The mucoadhesion strength of the films was influenced by Carbopol® polymer degree of crosslinking, longer retention being ensured by films containing Carbopol® 971P NF polymer. Film thickness impacted mucoadhesion as expected, thicker films showing better retention.

At similar thickness, PVA films containing Carbopol® 971P NF polymer showed longer retention when compared to benchmark PVA films (Figure 18). After 90 minutes, the PVA film was almost entirely washed off, whereas the Carbopol® polymer-containing PVA film was retained to some extent even at 240 minutes.

This case study demonstrated successful placebo film formulation containing Carbopol® polymers and PVA. The presence of Carbopol® polymers in CBP/PVA films enhanced mucoadhesive properties of the films, offering flexibility of formulation.

Figure 17. Design space for evaluation of mucoadhesion properties of Carbopol® polymer/PVA films

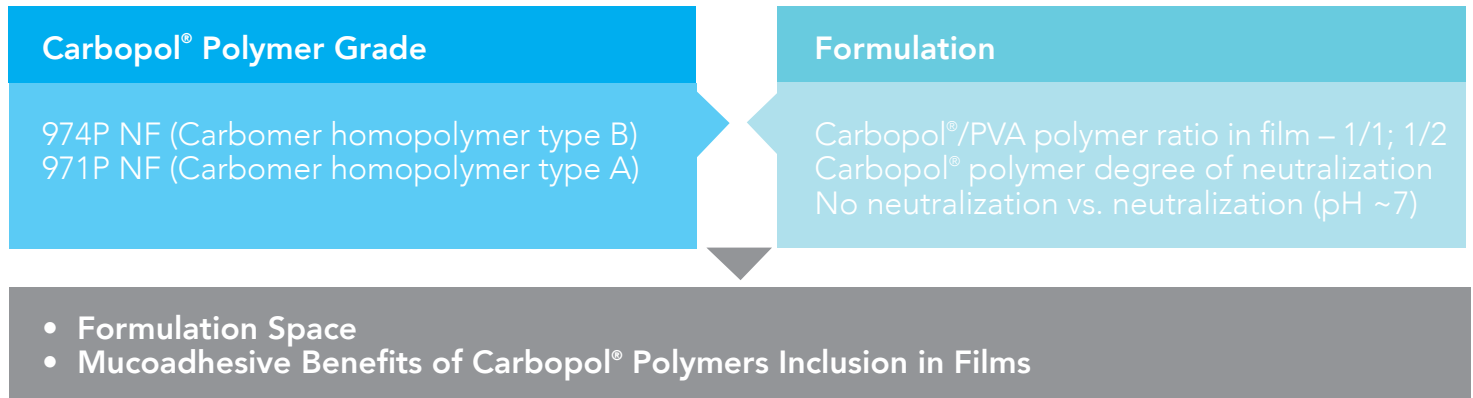
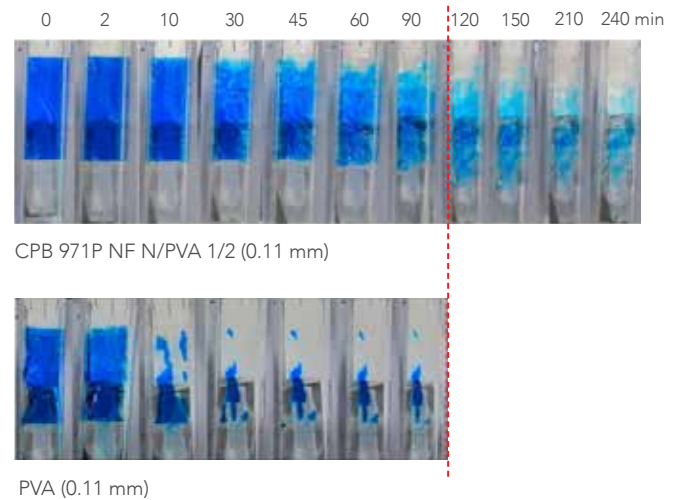
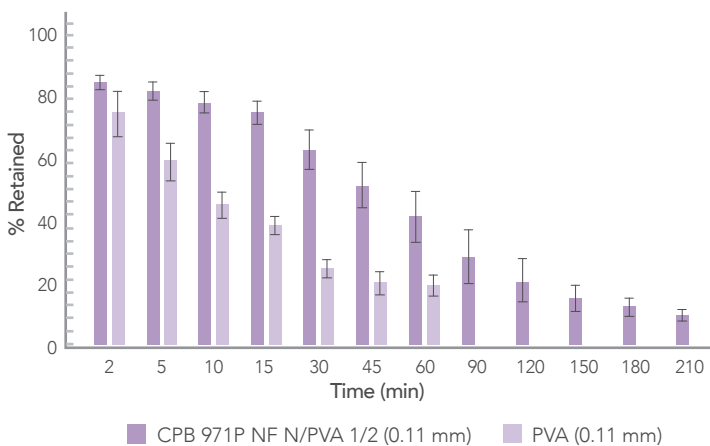


Figure 18. Comparison of PVA films with and without Carbopol® 971P NF polymer (CBP 971P NF) over time



Practical application & the importance of mucoadhesion

Formulating with mucoadhesive excipients has been shown to enable more efficient active delivery (localized and systemic), facilitate enhanced contact time with the target tissue, which in turn can enhance bioavailability, and provide lubrication as well as surface hydration.

The mucoadhesive properties of carbomers and polycarbophil have been demonstrated in many studies.¹⁰⁻²³ The polymers are also used in numerous commercial products (Table 1). Localized delivery from mucoadhesive dosage forms containing carbomers has been reported for active pharmaceutical ingredients (APIs) such as leuprolide acetate, triamcinolone acetonide, mesalamine, menthol, nystatin, lidocaine, and 5-fluorouracil. For systemic delivery, carbomers have been evaluated for mucoadhesive formulations of testosterone, nifedipine, morphine, fentanyl citrate, doxycycline, buprenorphine, and other APIs. The target mucosa in these products included oral, ophthalmic, and vaginal, as well as colonic, rectal, and others.

• Oral:

- Carbomers have been utilized in **mouthwashes** to form a mucoadhesive, protective layer over oral lesions caused by a variety of factors, such as radiation therapy, canker sores, or dental braces. Carbomer mucoadhesive properties also aid in active ingredient retention and breath freshening in mouthwashes.

- Carbomers have additionally been included in **liquid, gel, and solid formulations, such as lozenges**, to treat xerostomia (dry mouth) and soothe irritation.

• Ophthalmic:

- Carbomers have been employed in **eye drops** to form a transparent lubricating/moistening film and prolong the retention time of the drug on the eye's surface, resulting in increased efficacy when compared to other formulation types.

• Vaginal:

- Carbomers have been successfully formulated into vaginal products to provide mucoadhesion, moisturization, lubrication, and to maintain/buffer vaginal pH.

• Nasal:

- Carbomers have shown potential for anti-viral, mucoadhesive nasal applications as cited in literature.
 - pH-neutral compositions of carbomers have demonstrated antiviral or anti-allergenic activity in mammalian epithelial cells in vitro - therapeutic utility for the topical and intranasal treatment of viral infection.²⁴
 - A face mask containing a filter composed of Carbopol® polymers deposited on non-woven fibers has shown anti-viral activity against inhaled or exhaled air that may contain viruses that cause colds, Influenza, SARS, RSV, Bird flu.²⁵

Table 1. Example commercial products containing carbomer

Product	Trademark Owner	Route of Administration	Dosage Form	Active	Inactive Ingredients as Identified on Product Packaging
Aftab®	Rottapharm Madaus GmbH	Oral	Buccal Tablet	Triamcinolonacetomid 0.025 mg	Hyprolose, carbomer, magnesiumstearat, talkum, aluminiummagnesiumsilicat (2:1:2), lactose 1H ₂ O, carmellose-calcium, gelborange S (E 110)
Canker Cover®	DenTek	Oral	Buccal Tablet	Menthol 2.5 mg	Carbomer 941, xylitol, hydroxypropyl cellulose, silicon dioxide, carnallite, citrus oil, annatto
Cevitt® Hals & Rachen	Hermes Arzneimittel	Oral	Lozenge	Sodium hyaluronate, carbomer, xanthan	Mannitol, sodium hydrogencarbonate, sorbitol, citric acid, aspartam, vitamin C, flavor, zinc citrate dihydrate
GeloRevoice®	Pohl-Boskamp GmbH & Co. KG	Oral	Lozenge	Sodium hyaluronate, carbomer, xanthan	Mannitol, natriumhydrogencarbonat, xylitol, citronensäure, macrogol, aspartam, aromen, kaliumhydrogenphosphat, zinkstearat, siliciumdioxid

Product	Trademark Owner	Route of Administration	Dosage Form	Active	Inactive Ingredients as Identified on Product Packaging
Isla® Med Hydro+ Pastillen	Engelhard Arzneimittel	Oral	Lozenge	Extract of cetraria islandica, carbomer, xanthan, sodium hyaluronate	Arabic gum, sorbitol, maltitol, anhydrous citric acid, potassium acesulfame K, levomenthol, peppermint oil, anise, bitter fennel oil, medium chain triglycerides, purified water
MuGard® Oral Mucoadhesive	Abeona Therapeutics	Oral	Mouth Rinse		Purified water, glycerin, benzyl alcohol, sodium saccharin, carbomer homopolymer A, potassium hydroxide, citric acid, polysorbate 60 and phosphoric acid
neo-angin® Stimmig Plus Lutschtabletten	Klosterfrau Healthcare Group	Oral	Lozenge		Carbopol, carrageenan, sodium hyaluronate, mannitol, sodium hydrogencarbonat, citric acid, macrogol, sucralose, cherry flavor, levomenthol, potassium monohydrogenphosphate, zinc stearate, silica, sorbitol, xanthan, flavor
Oramoist®	DenTek	Oral	Buccal Tablet		Xylitol, polyvinyl pyrrolidone, carbomer homopolymer type A, lemon flavor, citric acid, calcium carbonate, hydroxy propyl cellulose, triglycerides, sodium chloride, silicon dioxide, magnesium stearate, glucose oxidase, lysozyme, lactoferrin, annatto
Onsolis® Fentanyl Buccal Soluble Film	BioDelivery Sciences International	Oral	Buccal System	Fentanyl citrate	Blue ink, carboxymethylcellulose, citric acid, hydroxyethyl cellulose, hydroxypropyl cellulose, methylparaben, monobasic sodium phosphate, peppermint oil, polycarbophil, propylene glycol, propylparaben, sodium benzoate, sodium hydroxide, sodium saccharin, titanium dioxide, tribasic sodium phosphate, vitamin E acetate, and water
Striant™ Mucoadhesive	Columbia Labs, Inc.	Oral	Buccal System (mucoadhesive tablet)	Testosterone 30 mg	Anhydrous lactose NF, carbomer 934P, hypromellose USP, magnesium stearate NF, lactose monohydrate NF, polycarbophil USP, colloidal silicon dioxide NF, starch NF, talc USP
LIQIVISC™ 2.5 mg/g, Eye Gel	Thea Pharmaceuticals	Ophthalmic	Ophthalmic Gel	Carbomer 974P	Benzalkonium chloride, sorbitol, lysine monohydrate, sodium acetate trihydrate, polyvinyl alcohol. Water for injections
Viscotears® Liquid Gel	Novartis	Ophthalmic	Ophthalmic Gel	Carbomer (polyacrylic acid)	Cetrimide, sodium hydroxide, sorbitol and water for injections

Product	Trademark Owner	Route of Administration	Dosage Form	Active	Inactive Ingredients as Identified on Product Packaging
Viscotears® Single Dose Unit 2.0mg/g Eye Gel	Novartis	Ophthalmic	Ophthalmic Gel	Carbomer (polyacrylic acid)	Sorbitol, sodium hydroxide and water for injections
Crinone® 8% Progesterone Vaginal Gel	Serono/ Allergan	Vaginal	Vaginal Gel	Progesterone	Sorbinsäure 0,9 mg, glycerol, dünnflüssiges paraffin, hydriertes palmölglycerid, carbomer 974P, polycarbophil, natriumhydroxid, gereinigtes wasser
HYALO GYN® Vaginal Hydrating Gel	Fidia Pharma USA	Vaginal	Vaginal Gel	Hydeal-D® (hyaluronic acid derivative)	Propylene glycol, carbomer, methyl p-hydroxy-benzoate, propyl p-hydroxybenzoate, sodium hydroxide, and purified water
Replens™ Vaginal Moisturizer	Church & Dwight	Vaginal	Vaginal Moisturizer		Purified water, glycerin, mineral oil, polycarbophil, carbomer homopolymer type B, hydrogenated palm oil, glyceride, methylparaben, sorbic acid, sodium hydroxide
RepHresh™ Vaginal Gel	Church & Dwight	Vaginal	Vaginal Gel		Purified water, glycerin, polycarbophil, carbomer homopolymer type B, ethylparaben sodium, methylparaben sodium, propylparaben sodium, sodium hydroxide



In summary

Mucoadhesion is a critical product property enabling efficacious active delivery in multiple dosage forms and commercial products. Excipient selection will greatly impact the level and effectiveness of mucoadhesion in a formulation. Carbopol® polymers (carbomers) have a demonstrated history of use in mucoadhesive applications and exhibit higher retention compared to other polymers.

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