

## Recent Advancements in Site Specific Mucoadhesive Drug Delivery Systems and Polymers

Sunena<sup>1\*</sup> and Nanda Arun<sup>2</sup>

<sup>1</sup>Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hissar, Haryana (India).

<sup>2</sup>Department of Pharmaceutical Sciences, Maharshi Dayanand university, Rohtak, Haryana(India).

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### Abstract

Mucoadhesive drug delivery systems are used to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drug.

**Keywords:** Mucoadhesive, gastroretentive, bioavailability, drug delivery systems.

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### Introduction

Mucoadhesion can be defined as the ability of synthetic or biological macromolecules to adhere to mucosal tissues such as the mucosa of the stomach, small intestine etc. The concept of mucoadhesion has gained considerable interest to develop novel, highly efficient dosage forms especially for oral drug delivery (Kamath and Park 1994). To increase the residence of drug formulations at or above the absorption window main approaches used are bioadhesive microspheres that have a slow intestinal transit; the gastroretentive dosage system, which is based on multiparticulates or large single unit systems and floating drug delivery systems. Among these, mucoadhesive drug delivery systems have several advantages like localization at a given target site, prolonged residence time at the site of drug absorption, and an intensified contact with the mucosa increasing the drug concentration gradient leads to enhancement in bioavailability and reduction in dosing frequency (Arora et al. 2005, Singh and Kim 2000). Different types of polymers have been investigated for potential use as mucoadhesives. These include synthetic polymers such as poly(acrylic acid) (PAA), hydroxypropyl methylcellulose and poly(methylacrylate) derivatives, as well as naturally occurring polymers such as hyaluronic acid, tragacanth, chitosan etc. The development of novel, advanced and mucosa-compatible polymers, are providing new commercial and clinical opportunities for delivery of drugs with narrow absorption window at the target site. The tailored polymers offer better opportunities for and broader applicability to highly variable and challenging drugs and therapy of various gastrointestinal disorders (Lehr 2004).

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\*Corresponding author: garhwal\_s@rediffmail.com

### *Various novel mucoadhesive drug delivery systems*

*Mucoadhesive oral drug delivery systems*

*Mucoadhesive ocular drug delivery systems*

*Mucoadhesive vaginal drug delivery systems*

*Mucoadhesive nasal drug delivery systems*

*Mucoadhesive rectal drug delivery systems*

*Mucoadhesive oral drug delivery systems*

*Types of oral mucoadhesive drug delivery systems:*

- 1) *Mucoadhesive gastroretentive drug delivery*
- 2) *Mucoadhesive buccal drug delivery*

### *Oral absorption of drugs*

A drug given orally must encounter with low pH and numerous GI secretions, including potentially degrading enzymes in stomach. Peptide drugs (e.g. insulin) are particularly susceptible to degradation and are not used orally. Oral drug absorption involves transport across membranes of the epithelial cells in the GI tract. Oral absorption is affected by luminal pH along the GI tract, surface area per luminal volume, blood perfusion, the presence of bile and mucus, and the nature of epithelial membranes. The oral mucosa has a thin epithelium and rich vascularity, which favor absorption; however, contact is usually too short for substantial absorption. The drugs which are placed between the gums and cheek (buccal administration) or under the tongue (sublingual administration) are retained longer, so enhance absorption and bioavailability (Alur et al. 2001).

Relatively large epithelial surface, thick mucous layer and short transit time of the stomach limits its absorption. Mainly absorption occurs in the small intestine and its gastric emptying is often the rate-limiting step. Food, especially fatty food, lowers gastric emptying rate and enhance drug absorption, that's why some drugs absorbed better in empty stomach. Drugs that affect gastric emptying (e.g. parasympatholytic drugs) affect the absorption rate of other drugs. Food may enhance the extent of absorption for poorly soluble drugs (eg, griseofulvin), reduce it for drugs degraded in the stomach (eg, penicillin G), or have little or no effect.

Due to the large surface area and high permeability, the drugs are absorbed primarily in the small intestine, and acids, despite their ability as un-ionized drugs to readily cross membranes, are absorbed faster in the intestine than in the stomach. The intraluminal pH is 4 to 5 in the duodenum but becomes progressively more alkaline, approaching 8 in the lower ileum. Gastro-intestinal microflora may also reduce absorption in some cases. Decrease in blood flow may lower the concentration gradient across the intestinal mucosa and reduce absorption by passive diffusion. Intestinal transit time can also affect drug absorption, especially for drugs that are absorbed by active transport (eg, B vitamins), that dissolve slowly (eg, griseofulvin), or that are polar (ie, with low lipid solubility; eg, many antibiotics).

*Oral mucosal membrane* (Figure 1 and 2)

The epithelium of stomach, small intestine, large intestine and bronchi consist of single layer and multiple layers in case of esophagus and vagina. The upper layer contains goblet cells, which secrete mucus directly onto the epithelial surface. Mucus is a viscous and gelatinous

secretion, consist glycoproteins, lipids, inorganic salts, and up to 95% water (Salamat et al. 2005). Mucus is secreted either constantly or intermittently and its volume changes by the influence of external and internal factors (Kharenko et al. 2009).

Glycoproteins (mucins) are the most important components of mucus and are responsible for its gelatinous structure, cohesion, and antiadhesive properties (Pep-pas et al. 1996). The different sites at which mucus is secreted, glycoproteins usually have similar structure and are highly glycosylated protein molecules. The terminal domains of the glycoprotein (C- and N-) are consist more than 10% cysteine. These domains, leads to the formation of large mucin oligomers due to the formation disulfide linkage (Ponchel et al. 1998). Mainly protein part consists of a repeating sequence of serine, threonine, and proline residues. Oligosaccharide chain are attached to 63% of the protein core, at every third residue within the glycosylated areas and results in formation of more than 200 carbohydrate chains per glycoprotein molecule (Ludwig 2005). Each carbohydrate side chain contains from two to twenty sugar residues and account for more than 80% of the molecular weight of the molecule (Ugwoke et al. 2005).

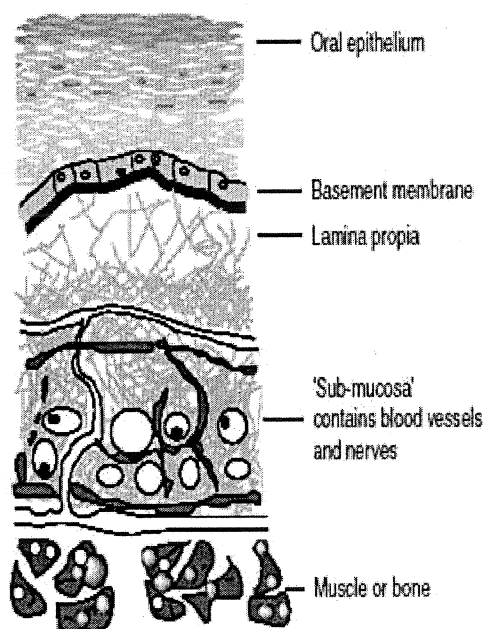
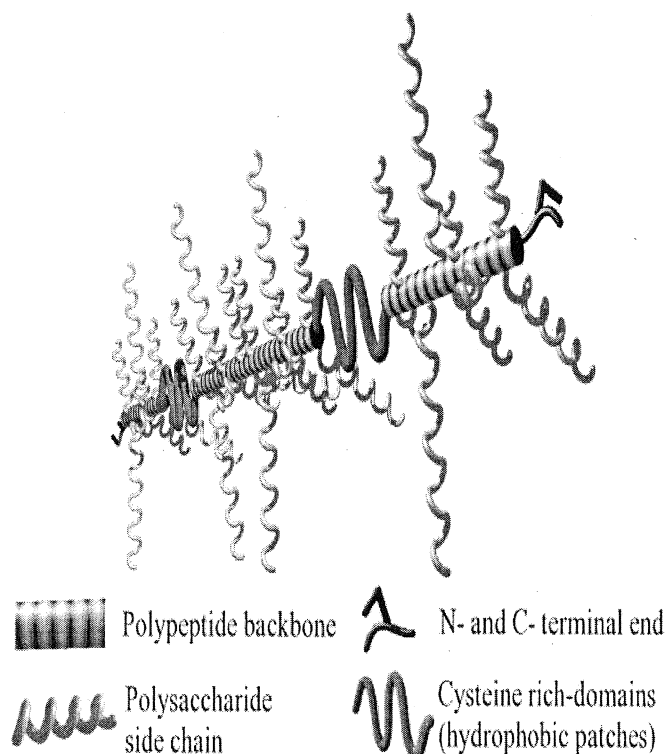


Figure 1. Oral mucosal membrane



**Figure 2.** Mucin glycoprotein chain

#### *Mucoadhesive gastroretentive drug delivery*

Amongst the various approaches for achieving a prolonged and predictable drug delivery in the Gastro intestinal tract (GIT) is to control the gastric residence time. Dosage forms with a prolonged gastric residence time, (e.g., gastro retentive dosage forms) like mucoadhesive, floating and particulate drug delivery systems will provide advanced and better therapeutic opportunities. Among the various approaches, mucoadhesive drug delivery systems have emerged as an efficient means for enhancing the bioavailability of drugs having narrow absorption window by increasing the gastric residence time (Arora et al. 2005, Singh and Kim 2000). The medications that are included in the category of narrow absorption window drugs are mostly associated with improved absorption at the jejunum and ileum due to their enhanced absorption properties, e.g. large surface area, in comparison to the colon or because of the enhanced solubility of the drug in the stomach as opposed to more distal parts of the gastrointestinal tract (Hwang et al. 1998). It was suggested that compounding narrow absorption window drugs with gastro retentive properties would enable an extended absorption phase of these drugs. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention.

In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy, and possible reduction of dose size. (Hoffman et al. 1998) It has been suggested that prolonged local availability of antibacterial agents may augment their effectiveness intreating *H. Pylori* related peptic ulcers (Despande et al. 1996, Singh and Kim 2000, Moes 1993).

Certain types of drugs can benefit from using gastric retentive devices. These include:

- 1) Drugs with a narrow absorption window e.g- Acyclovir, gabapentin, furosemide, biphosphonates, metformin, captopril, baclofin.
- 2) Drugs that are primarily and rapidly absorbed in the stomach or drugs that are poorly soluble at an alkaline pH e.g- Salicylic acid, aspirin, thiopental, secobarbital and antipyrine.
- 3) Drugs that degrade in the colon.
- 4) Drugs acting locally in the stomach e.g- Cimetidine, lansoprazole, misoprostol, omeprazole, Pentagastrin, propanthelin, sucralfate, clarithromycin, amoxicillin, metronidazole.

#### *Mucohesive buccal drug delivery*

Buccal drug delivery is an important route of drug administration. Local drug delivery to oral cavity play a important role in treatment of toothache, periodontal diseases, dental caries, bacterial and fungal infections and aphthous stomatitis. The buccal route has high acceptance due to avoidance of first pass metabolism and possibility of being accessible for controlled drug release. These regions consist of a non-keratinized epithelium, resulting in a somewhat more permeable tissue than the skin. Therefore, drugs with a short biological half life requiring a sustained release effect and exhibiting poor permeability, sensitivity to enzymatic degradation, or poor solubility may be good candidates to be delivered via the oral cavity. Buccal administration is viable alternative for peptide delivery based on excellent site specificity, avoidance hepatic first-pass metabolism, and protection from degradation in the stomach and the intestine. Furthermore, the oral mucosa is less prone to irritation or damage than, e.g., nasal mucosa (Deasy et al. 1989, Ganong 1999, Duchne et al. 1988).

#### *Buccal drug absorption*

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty in permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage (Rathbone and Hadgraft 1990, Merkle and Anders 1990).

Buccal mucoadhesive dosage forms

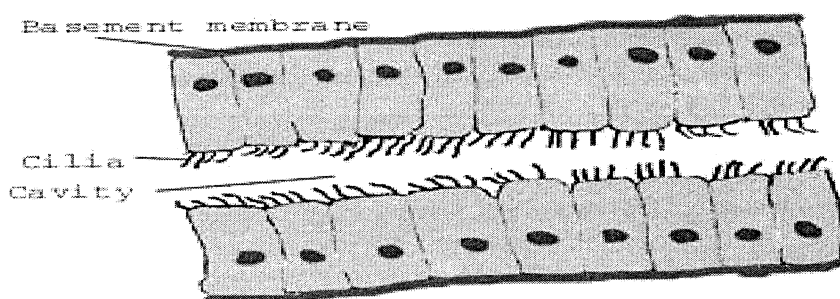
- 1) Buccal tablets
- 2) Buccal films
- 3) Buccal patches
- 4) Buccal gels and ointments

### *Mucoadhesive vaginal drug delivery*

The conventional preparations, have very short residence time due to the self-cleaning action of the vaginal tract, so require frequent dosing to ensure the desired therapeutic effect. The vaginal mucoadhesive drug delivery systems are highly suitable for treatment of local conditions like contraception and sexually-transmitted diseases (Mauck et al. 2008). To prolong the drug residence time in the vaginal cavity, mucoadhesive systems have been explored in the form of semi-solid and solid dosage forms.

### *Vaginal drug absorption (Figure 3)*

Vaginal route is an important site of drug administration for both local and systemic diseases. For drugs that are susceptible to gut or hepatic metabolism or which cause GI side effects, vaginal drug delivery may provide many advantages over the other routes of administration due to its large surface area, rich blood supply, avoidance of the first-pass effect, relatively high permeability to many drugs. The vagina is a fibromuscular tube connecting the uterus to the exterior of the body. The surface area of the vagina is increased by numerous folds in the epithelium and by microridges covering the epithelial cell surface (Robinson et al. 1987).



**Figure 3.** Vaginal mucosal membrane

Mucoadhesive vaginal drug delivery systems are given below

- 1) Mucoadhesive gels
- 2) Mucoadhesive tablets
- 3) Mucoadhesive films
- 4) Emulsion type mucoadhesive systems
- 5) Pessaries or suppositories

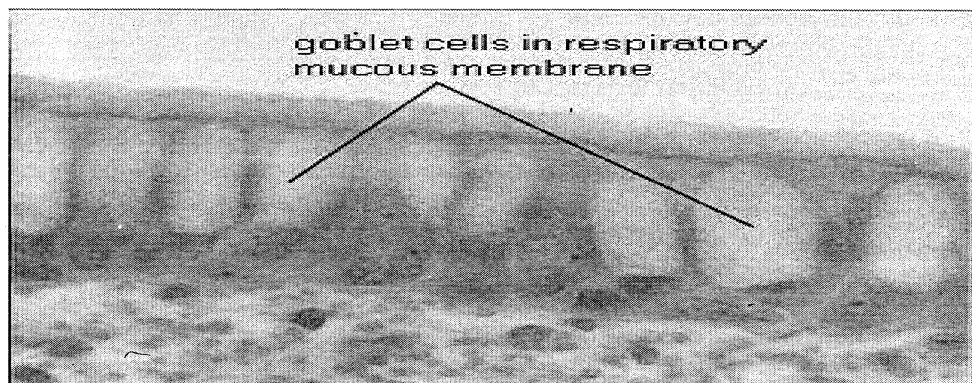
### *Mucadhesive nasal drug delivery*

The nasal mucosa provides a promising route for systemic delivery of drugs including biopharmaceuticals. Nasal mucoadhesive drug delivery systems are used for the delivery of organic molecules, antibiotics, proteins, vaccines and DNA. Nasal drug delivery avoids first-

pass hepatic metabolism which provide fast onset of action in management of chronic situations like cardiac arrest, epileptic seizures, severe nausea and vomiting (Ugwoke et al. 2005, Datta and Bandyopadhyay 2006, Martin et al. 1998). Despite the potential advantages, there are certain factors like mucociliary clearance, mucous and epithelial barriers and enzymic activity, leads to poor bioavailability of drugs administered intranasally. Thus mucoadhesive agents make intimate contact with the mucin of mucosa, thereby, prolonging residence time of the drug in nasal cavity, which leads to improved drug absorption (Illum 2002, Türker et al. 2004, Ugwoke et al. 2001).

#### *Nasal mucosal drug absorption* (Figure 4)

With a surface area of 150 cm<sup>2</sup>, a highly dense vascular network, and a relatively permeable membrane structure, the nasal route has good absorption potential. This large mucosal surface covered with a rich vascular bed of highly permeable capillaries creates an opportunity for intranasal drug delivery. Thus nasal mucosal absorption provide drug directly into the blood stream.



**Figure 4.** Nasal mucosal membrane

Mucoadhesive nasal drug delivery systems are given below:

- 1) Nasal gels
- 2) Micoemusions
- 3) Mucoadhesive nanoparticles

#### *Mucoadhesive ocular drug delivery*

The poor bioavailability of ocular drug delivery systems is due to the continuous formation of tears and blinking of eye lids which leads to rapid removal of the drug from the ocular cavity. Ophthalmic dosage forms can be improved by increasing the time the active ingredients remain in contact with eye tissues. The mucoadhesive polymers used for the ocular delivery include thiolated poly(acrylic acid), poloxamer, celluloseacetophthalate, methyl cellulose, hydroxy ethyl cellulose, poly(amidoamine) dendrimers, poly(dimethyl siloxane) and poly (vinyl pyrrolidone) mucoadhesive dosage forms that have been developed are liquid systems, in situ gelling systems, dispersed, systems and solid systems (Chen et al. 1997, Zignani et al. 1995, Gutter et al. 1995)

### *Corneal drug absorption*

Mucin is secreted by conjunctival goblet cells, but there are no goblet cells on the cornea. On this basis, a mucoadhesive polymer will firmly attach to conjunctival mucus (Liaw et al. 1992, Greaves and Wilson 1993). Drugs administered by instillation must penetrate the eye primarily through cornea.

Cornea is a lipid-water-lipid sandwich like structure and consist of three basic layers: Epithelium-lipophilic, Stroma-hydrophilic, Endothelium-lipophilic .Most effective penetration is obtained with drugs having both lipophilic and hydrophilic properties

### *Rectal drug delivery system*

Rectal drug administration is used in situations when patients are vomiting or suffering from nausea. The first-pass elimination of drugs is also partially avoided by rectal administration and furthermore the rectum environment is quite constant with respect to pH; composition, volume and viscosity of fluid; and less influenced by food. Despite substantial inter-individual variability and differences between high clearance drugs, drugs should be administered and absorbed as close as possible to the anus in order to obtain maximum. This offers the opportunity for rate controlled rectal drug delivery.

Various drug delivery systems and mucoadhesive polymers have been explored for drug delivery through rectum. Hydrogels administered rectally have proven to be useful for drug delivery (Nagai 1985). The hydrogels using hydroxy ethyl methacrylate cross-linked with ethylene glycol dimethacrylate are studied by many scientists for rectal drug delivery.

### *Mucoadhesive polymers*

Mucoadhesive delivery systems are being explored for the localization of the therapeutic agents to a particular location/ site. Polymers have played an important role in designing the systems which increase in residence time of the drug at the target site.

Mucodhesive polymers that adhere to the mucin-epithelial surface divided into three broad classes:

- (a) Polymers that swells when placed in water and owe their mucoadhesion to stickiness.  
Examples -Polyacrylic acid, poly(methylacrylates), polycarbophil, carbopol, polyox etc.
- (b) Polymers that adhere through nonspecific, noncovalent interactions that are primarily electrostatic in nature (mainly hydrogen and hydrophobic bonding).  
Examples- Poly(methyl vinyl ether-co-malic anhydride etc.
- (c) Polymers that bind to specific receptor site at the mucosal membrane  
Examples- Lectins, thiolated polymers etc.

A list of mucoadhesive polymers are given below in Table 1:



**Table 1.** A list of mucoadhesive polymers

Natural polymers	Synthetic polymers
(a) Cellulose derivatives	
	(a) Tragacanth
methylcellulose, ethylcellulose, hydroxy-ethylcellulose,	(b) Sodium alginate
hydroxyl propyl cellulose, hydroxy propyl methylcellulose,	(c) Karaya gum
sodium carboxy methylcellulose	(d) Guar gum
(b) Poly (acrylic acid) polymers	(e) Xanthan gum
carbomers, polycarbophil	(f) Lectin
	(g) Soluble starch
(c) Poly (hydroxyethyl methylacrylate)	(h) Gelatin
(d) Poly (ethylene oxide)	(i) Pectin
(e) Poly (vinyl pyrrolidone)	(j) Chitosan
(f) Poly (vinyl alcohol)	

#### *Novel and new generation mucosa compatible polymers*

Mucoadhesive site-specific drug delivery is important in targeting different regions of GIT using more selective compounds capable of distinguishing between the types of cells found in different areas of the GIT. The term "cytoadhesion," is specifically based on certain materials that can reversibly bind to cell surfaces in the GIT. New generation of mucoadhesives function with greater specificity because they are based on receptor-ligand-like interactions in which the molecules bind strongly and rapidly directly onto the mucosal cell surface rather than the mucus itself. One such class of compounds that has these unique requirements are called lectins (Lehr 2004).

#### *Lectin-Based Delivery*

Lectins are proteins or glycoproteins have the ability to bind specifically and reversibly to carbohydrates. They exist in either soluble or cell-associated forms and possess carbohydrate-selective and recognizing parts. Lectins have the capacity to recognize cell-surface carbohydrates; this includes their applicability in various biological processes, such as phagocytosis, cell activation, and cell adhesion. Lectin-based drug delivery systems have applicability in targeting epithelial cells, intestinal M cells, and enterocytes. The intestinal epithelial cells possess a cell surface composed of membrane-anchored glycoconjugates. It is these surfaces that could be targeted by lectins, thus enabling an intestinal delivery concept (Lehr 2004, Haltner et al. 1997).

#### *The novel polymers 'Thiomers'*

Thiolated polymers, or thiomers, interact with cysteine-rich subdomains of mucus glycoproteins forming disulfide bonds between the mucoadhesive polymer and the mucus layer. The formation of disulfide bonds between thiomers and mucus glycoproteins has been studied by applying various analytical approaches. Owing to the immobilization of thiol groups on already well-established mucoadhesive polymers, their mucoadhesive properties are strongly enhanced (Leitner et al. 2003). Covalent bonds are believed to be formed not only between thiomers and mucus, but also within the thiomers themselves. This theory was confirmed by the decrease in free thiol groups within thiomers resulting in an increase in viscosity (Bernkop-Schnurch et al. 2003). Inter- and intramolecular disulfide bonds improve the cohesive properties of the thiolated polymer compared to the unmodified polymer.

### Thiolated Chitosans

Various properties of chitosan are improved by the immobilization of thiol groups. Due to the formation of disulfide bonds with mucus glycoproteins, mucoadhesive property get enhanced.

Thiolated chitosan polymers offer advantage of high mucoadhesive, controlled release and permeation enhancing properties leading to strongly improved therapeutic potential of drugs.

Thiolated polymers, which are interesting candidates for mucoadhesive drug delivery are given below in Table 2.

**Table 2.** Thiolated polymers, which are interesting candidates for mucoadhesive drug delivery

Polymer	Mucoadhesive Potential
Chitosan-iminothiollane	250-fold improved mucoadhesive properties
Poly(acrylic acid)-cysteine	100-fold improved mucoadhesive properties
Poly(acrylic acid)-homocysteine	Approximately 20-fold improved mucoadhesive properties
Chitosan-thioglycolic acid	Tenfold improved mucoadhesive properties
Poly(methacrylic acid)-cysteine	Improved cohesive and mucoadhesive properties
Sodium carboxymethylcellulose-cysteine	Improved mucoadhesive properties
Alginate-cysteine	Fourfold improved mucoadhesive properties

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