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Mucoadhesive Drug Delivery System: A Review

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ABSTRACT

The main goal of review studies is to provide an overview on bio adhesive pulsatile drug delivery systems. A bio adhesive and pulsatile combination that is appropriate for a certain area and time of drug release. Bio adhesion is described as the adhesion of two materials, at least one of which is of biological origin, that are maintained together to extend time of drug release by interfacial forces. Pulsatile drug delivery is described as the quick and transient release of a certain amount of drug in a specified period of time. Pulsatile release of drugs is dependent on the timing and location which delivers customized and timed distribution, which improves patient compliance. This approach is based on the body's circadian cycle which is the requirement for medication release after a lag period is met by approaching a gastro-retentive drug delivery system.[1,2,7]

Key words: Mucoadhesive, Bio-adhesive, Pulsatile, Methods, Mechanism

INTRODUCTION

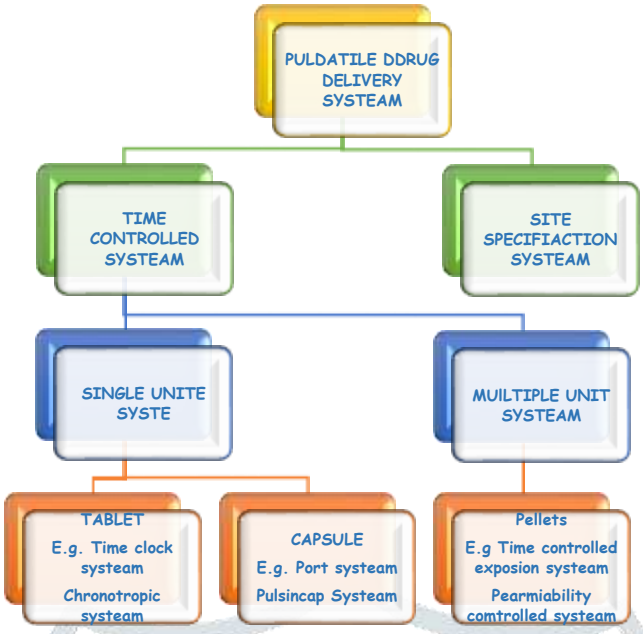
The oral cavity is the best target for administering the medicine of choice. Buccal delivery refers to the administration of drugs through the buccal mucosal membrane lining of the mouth cavity. Unlike oral drug administration, which produces a hostile environment for pharmaceuticals, especially proteins and polypeptides, caused by acid hydrolysis and the hepatic first-pass effect, the buccal mucosal lining provides a much gentler environment for drug absorption remaining drug administration routes, such as nasal, ocular, pulmonary, rectal, and vaginal, have shown promise for delivering a wide range of chemicals. Further the mucosal lining of the oral cavity has distinct advantages. It's well-vascularized, forming drug administration and removal a medication. [2-7]

Bio adhesion as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. It is also defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time.

The mucoadhesive drug delivery system may include the following [7]

Buccal delivery system, Sublingual delivery system, Vaginal delivery system, Rectal delivery system, Nasal delivery system, Ocular delivery system, Gastrointestinal delivery system.

Classification of Mucoadhesive pulsatile drug delivery system [8]



Mechanism of mucoadhesion [9]

The mucoadhesion is joint to the drug along with a suitable carrier to the mucous membrane. In the phenomenon Mucoadhesion which include wetting, Adsorption and interpenetration of polymer chain. Mucoadhesion is occord by the mechanism of intimate between a bioadhesive and a membrane (wetting or swelling phenomenon) and penetration of bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration).

Work of adhesion

A recently developed by Marti to observe the likelihood of mucoadhesive materials to join to the oesophagus is alternate method used to measure the in vitro mucoadhesive capacity of various polymers. The sheep's intestine was removed and stored in a Tyrode solution at 4 degrees Celsius. Segments of 6-7 cm were cut from the intestine, with the lower end attached to a glass tube with a diameter of 15mm. The paracetamol in matrix tablets (2:1) ratio, 6mm paracetamol plane tablets, paracetamol tablets layered on one side with mucoadhesive polymer, and paracetamol tablets layered on one side with mucoadhesive polymer were all manufactured. VH/AB The tablets were drilled with a fine hole in the centre to be tested with a fine needle. It was knotted around the tablet with a thread that had been threaded through it. The glass rod hanging to the stand is linked to the other end of the thread. To the other end of the glass rod, into which a beaker was placed. The assembly is left undisturbed for 30 minutes to an hour after placing the vh/ab tablet into the gi segment and lightly pushing the gi segment with the tablet with a forceps.

Then water is slowly poured into the beaker from the burette. The force is necessary to get tablet out of intestinal segment is equal to the amount of water required to pull the tablet against adhesion[10-12].

F=0.00981 W/2

W= amount of water.

The latest invention Wilhelm plate method is one of two novel ways for measuring the force of attachment [13], Anionic polymer structural contribution and the modified dual tensiometer approach[14]. A glass plate covered with the polymer layer is suspended from a microbalance into a beaker containing mucus in the modified Wilhelm plate method. The work that was done to separate the polymer from the mucus has been discovered. The lack of biological tissue in this system is a disadvantage. Leung and Robinson invented the recently developed dual correspondent method. Texture analysers, such as the TA-XT2, have also been in work[15].

Theories of mucoadhesion

Mucoadhesive capabilities of theorems in variation to well-established polymers in this issue. The mucoadhesive characteristics of all previously examined polymers were greatly improved due to disabling thiol groups and evaluation by any way. The poly (acrylic acid) cysteine conjugate appears is best example of this observation in anionic mucoadhesive polymers. Display the viscosity of poly (acrylic acid)/mucin

mixtures, which is directly related to the interactions of the polymer with mucus and thus indicates mucoadhesive characteristics, may be enhanced by more than 10-fold [19] In tensile testing and by employing the rotating cylinder method, the same thiolate polymer demonstrated more than 2-fold and 20-fold better mucoadhesive qualities when compared to the corresponding unmodified polymer. [19]. Furthermore, the immobilisation of thiol groups can increase the residence period of poly (acrylic acid) microparticles on the small intestine mucosa by more than 3-fold[20]. The chitosantributylamine compound, on the other hand, appears to be an excellent example of cationic thiomersal, as it has been examined by multiple mucoadhesion test systems. In comparison to unmodified chitosan, the chitosantributylamine combination had a viscosity that was more than 100 times better[17]. More than that mucoadhesive qualities of the thiolate form were 100-fold and 140-fold improved in tensile and rotating cylinder testing, respectively[7,18]. The molecular mass of the polymer chains has effect on the mucoadhesive characteristics of both thiomers. The highest mucoadhesive qualities were achieved for both anionic and cationic thiomers when they had a medium molecular mass. In case of poly (acrylic acid) cysteine, polymer conjugates to show a molecular mass of 450 kDa were more mucoadhesive than once of a molecular mass of 2 kDa, 45 kDA and 1000– 3000 kDa. On the other hand, extensible studies performed with thiolate chitosan exhibiting a molecular mass of 150 kDa, 400 kDa and 600 kDa showed the relatively highest mucoadhesive properties for the medium molecular mass thiomersal [18]. Utilizing a medium molecular mass chitosan–tributylamine conjugate displaying 264 AM thiol groups per gram polymer consequently led to a more than 100-fold improvement in mucoadhesion in comparison to unmodified chitosan[18]. Generally, it could be observed in most performed mucoadhesion studies with thiomersal, that the higher the amount of immobilized thiol groups was, the higher were the mucoadhesive properties. Furthermore, the mucoadhesive properties of thiomersal exhibiting a relative low pH are always higher [22,23].

The electronic theory:

The electronic theory is based on an assumption that the bioadhesive material and the glycoprotein mucin network have different electronic structures. On this assumption, it is believed that upon contact, electron transfer occurs tempt to balance Fermi levels, causing the formation of a double layer of electrical charge at the interface. The bioadhesive force is attributed to attractive forces across this electrical double layer.[15] The electronic theory has produced some controversy regarding whether the electrostatic forces are an important cause or the result of contact between the bioadhesive and the biological tissue.[16]

The fracture theory:

The most useful theory for studying bioadhesion through tensile experiments has been the fracture theory. This theory analyses the forces required to separate two surfaces after adhesion. The maximum tensile stress (σm) produced during detachment can be determined by dividing the maximum force of detachment, Fm, by the total surface area (A•) involved in the adhesive interaction:

$\sigma_m = F_m/A$**.**

In a uniform single-component system, the fracture strength (σf), which is equal to the maximum stress of detachment (σm), is proportional to the fracture energy (Yc), Young's modulus of elasticity (E), and the critical crack length (c) of the fracture site, as described in the following relationship. [26]

The fracture energy (~'c) can be procure from the sum of the reversible work of adhesion, Wr (i.e. the energy required to produce new fracture surfaces), and the irreversible work of adhesion, Wi (i.e. the work of plastic deformation at the tip of the growing crack), where both values are expressed per unit area of the fracture surface (Af):

~'¢ = Wr + Wi

The elastic modulus of the system (E) is re luted to the stress (tr) and the strain (~) through Hooke's Law:

E = -~ ~0 [_A---~OJAt~0]

In this equation, the stress is equal to the changing force (F) divided by the area (Ao), and the strain is equal to the change in thickness (AI) of the system divided by the original thickness (/o) [27.]

One essential hypothesis in the above fracture theory is that the system being investigated is of known physical dimensions and composed of a single uniform bulk material. Considering this, Equation cannot be applied to analyse the fracture site of a multicomponent bio adhesive bond between a polymer microsphere and either

mucus or mucosal tissue. For such analysis, the equations must be expanded to accommodate the dimensions and elastic moduli of each component [28]. Furthermore, to determine the fracture properties of an adhesive union from separation experiments, the failure of the adhesive bond must be assumed to occur at the bio adhesive interface.[26] However, it has been demonstrated that the fracture rarely, if ever, occurs at the interface, but instead occurs close to it [26,30].

The fracture theory only deals with analysing the adhesive force required for separation, it does not assume nor require the entanglement, diffusion or interpenetration of polymer chains. Therefore, it is appropriate to use to calculate fracture strengths of hard, bioadhesive materials, in which the polymer chains may not penetrate the mucous layer (though one must be aware that the measurement may be the fracture strength of the cohesive properties of the mucus instead of the fracture strength of the adhesive bond). Other theories which could be applicable to such a system are the wetting, electronic and adsorption theories, so long as it is assumed that van der Waals' interactions and hydrogen bonds can form between flexible mucin chains and presumably rigid polymer chains of hard surfaces.

Adsorption theory

This theory states that the bioadhesive bond formed between an adhesive substrate and the tissue is due to the weak van der Waals forces and hydrogen bond formation. It is one of the most widely accepted theories of bioadhesion [31,32].

Bioadhesion Measurements by Tensile Strength [33]

Bioadhesive”	Substrate	Instrument
CP 934, HPC	Mouse peritoneal membrane	Spring balance
Gelatine capsule	Porcine oesophagus	Modified prescription balance
Cross-linked PAA, PMA, PHEMA	Rabbit stomach tissue	Modified surface tensiometer
PAA, HPMC	Bovine sublingual mucosa	Tensile apparatus (Instron, U.K.)
CP 934, CP Ex 55, HPMC, HPC	Fresh intestine from male Wistar rats	Modified pan balance
CP, HPC	Mouse peritoneal membrane	Modified spring balance
Modified starch, PAA, PEG, NaCMC	Porcine attached gingiva	Modified tensile apparatus
CP 934, PHEMA, Eu RL 100	Porcine intestinal mucosa	Modified Du Nouy tensiometer
CP, Hyaluronic acid	Porcine gastric mucin gel	Electronic digital microbalance
PAA, HPC	Porcine buccal mucosa	Tensile tester
Chitosan, polycarbophil, CMC, pectin, xanthan gum	Pig intestinal mucosa	Modified tensiometer
Alginate, CMC, chitosan	Intestinal tissue from Sprague Dawley rat	Precise microbalance
CP 934, HPC-M, PVP, NaCMC	Hamster cheek pouch	Modified pan balance
Copolymers of dextran, poly acrylamide, PAA	Cellulose paper disk impregnated with porcine mucine gel	Tensile apparatus
Modified starch PAA	Porcine gingiva	Tensile tester
NaCMC, HPC	Rabbit stomachiintestinal tissue	Modified tensile tester
CP 934, HPMC, chitosan, acacia	PVPkellulose acetate hydrogel	Tensile tester
Na alginate, PEG	Guinea pig ileum mucosa	Tensile apparatus (Instron. U.K.)
Chitosan. Na alginate	Rat peritoneum membrane	Spring tension gauge
CP 934, PVP	Bovine cheek pouch	Modified pan balance
Copolymer of Ecaprolactone and ethylene oxide	Rat duodenum mucosal tissue	Tensile tester
CP 934	Porcine gastric much	Dynamic contact analyzer

Advantages of mucoadhesive drug delivery systems [34]

- Increases bioavailability by prolonging the residence duration of the dose form at the absorption site.
- Accessibility is excellent, and action takes place quickly.
- Because of the abundant blood supply and high blood flow rates, rapid absorption is possible.
- In the git, the drug is shielded from deterioration due to the acidic environment.
- Improved patient compliance

Disadvantages of mucoadhesive drug delivery systems [34]

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.

Mucoadhesive Materials:

Mucoadhesive polymers have numerous hydrophilic groups, such as hydroxyl, carboxyl, amide, and sulphate. These groups attach to mucus or the cell membrane by various interactions such as hydrogen bonding and hydrophobic or electrostatic interactions. These hydrophilic groups also cause polymers to swell in water and, thus, expose the maximum number of adhesive sites [35].

An ideal polymer for a bioadhesive drug delivery system should have the following characteristics [36,37]:

- The polymer and its degradation products should be nontoxic and nonabsorbable.
- It should be non-irritant.
- It should preferably form a strong noncovalent bond with the mucus or epithelial cell surface.
- It should adhere quickly to moist tissue and possess some site specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not be high so that the prepared dosage form remains competitive. Polymers that adhere to biological surfaces can be divided into three broad categories like Polymers that adhere through nonspecific noncovalent interactions which are primarily electrostatic in nature, polymers possessing hydrophilic functional groups that hydrogen bond with similar groups on biological substrates and polymers that bind to specific receptor sites on the cell or mucus surface[38,39]

Lectins and thiolate polymers fall within the latter type of polymers. Lectins are nonimmune proteins or glycoprotein complexes that have the ability to selectively bind sugars in a noncovalent manner.[40.] Lectins are proteins that can connect to carbohydrates on the surface of mucus or epithelial cells and have been intensively investigated, particularly for medication targeting[41,42.] These second-generation bioadhesives allow for not only cellular attachment but also endo- and transcytosis. Thiolate polymers, commonly known as thiomersal, are polymers that have been thiolate, which have free thiol groups on the polymeric backbone, are hydrophilic macromolecules. Various properties of polyacrylates and cellulose derivatives were significantly improved as a result of these functional groups[43]. Due to the presence of thiol groups in the polymer, stable covalent connections can be formed with cysteine-rich subdomains of mucus glycoproteins, resulting in increased residence duration and better bioavailability[44.] Improved tensile strength, fast swelling, and water uptake behaviour are some of the other beneficial mucoadhesive features of thiolate polymers.

Prepration of core tablet:

Telmisartan core tablets were made by the direct compression process with the following ingredients: polyvinylpyrrolidone, magnesium stearate, sodium starch glycolate (variable quantity), and microcrystalline cellulose, with the tablet weight adjusted. All components were precisely weighed and thoroughly combined for 15 minutes. A Rotary Compression Press (Cadmach) with an 8 mm standard concave punch was used to compress the powder combination into tablets. The weight variance of the tablets was determined using an electronic balance and the weight of 20 tablets. Hardness, thickness, friability and disintegration time (in water) of tablets were studied by Monsanto hardness tester, vernier calliper, Roche friabilator and disintegration test apparatus, respectively [45].

Formulation of Bio-adhesive Pulsatile Tablet:

The optimized formulation of core tablet was used for the preparation of bio-adhesive pulsatile tablet. The bio-adhesive pulsatile tablet formulated by core tablet, Magnesium stearate, Polyvinylpyrrolidone, Ethyl cellulose, Carbopol, Microcrystalline cellulose. A 40 percent bio-adhesive pulsatile release layer (Polyvinylpyrrolidone, Ethyl Cellulose, Carbopol) was placed in a 12 mm die and a core tablet was placed on it to make a bio-adhesive pulsatile tablet. The remaining quantity was then added to the die to cover the core tablet and ultimately compressed using a Rotary compression machine with a 12 mm die and punch set utilising the direct compression method.[45].

Methods of evaluation:

In vitro and in vivo studies can be used to assess the adhesion strength of mucoadhesive polymers and drug delivery systems. [46].

In vitro tests / vivo methods is decide by tensile strength, methods determining shear stress, adhesion weight method, fluorescent probe method, flow channel method , mechanical spectroscopic method , falling liquid film method , colloidal gold staining method , viscometer method , thumb method , adhesion number , electrical conductance , swelling properties , in vitro drug release studies & Mucor tentability studies. [47,48-52] For in vivo methods radioisotopes, use of gamma scintigraphy, use of pharmacoscintigraphy, use of electron paramagnetic resonance (EPR) oximetry, X ray studies & Isolated loop technique are used. [46,53,54]

Factor affecting mucoadhesion

Molecular weight

With molecular weights above 100,000, a polymer's mucoadhesive strength increases. The mucoadhesive strength of polyoxymethylene polymers is relative to their molecular weights, with a range of 200,000–7,000,000[55]

Flexibility

Polymer chain diffusion in the interfacial region is the first step in mucoadhesion. In order to accomplish the required entanglement with the mucus, the polymer chains must have a high degree of flexibility.[56] Following the addition of polyethylene glycol, the polymer's structural flexibility increased, resulting in improved chain interpenetration. Polymer mobility and flexibility are inversely proportional to their viscosities and diffusion coefficients, with greater flexibility resulting in greater diffusion into the mucus network.[57]

Cross-linking density

Three significant and interrelated structural factors of a polymer network are the average pore size, the quantity and average molecular weight of cross-linked polymers, and the density of cross-linking. As a result, it is possible to assume that as cross-linking density increases, water diffusion into the polymer network slows, resulting in insufficient polymer swelling and a slower rate of interpenetration between polymer and mucin.[57]

Hydrogen bonding capacity

Hydration is essential for a mucoadhesive polymer to expand and form a suitable macromolecular mesh of sufficient size, as well as to induce mobility in the polymer chains to improve the interpenetration process between the polymer and the mucin. By exposing the bioadhesive sites for hydrogen bonding and/or electrostatic contact between the polymer and the mucus network, polymer swelling allows for mechanical entanglement.[57] However, there is a critical level of hydration of the mucoadhesive polymer at which swelling and mucoadhesion occur[57].

Charge

Non-ionic polymers appear to have a lower degree of adhesion than anionic polymers, according to previous generalisations regarding the charge of bioadhesive polymers. One of the needed properties for mucoadhesion is a strong anionic charge on the polymer.[57] In a neutral or slightly alkaline media, some cationic polymers are expected to have greater mucoadhesive characteristics.[58] Furthermore, some cationic high molecular weight polymers, such as chitosan, have demonstrated excellent adhesive qualities.[59] Although there is no major research on the effect of membrane charge on mucoadhesion, the pH of the membrane has an effect on mucoadhesion because it influences the ionised or un-ionized forms of the polymers.[60]

Concentration

The importance of this element can be explained by the length of polymer chain available for penetration into the mucus layer, which is critical for forming a strong adhesive connection with the mucus. The number of penetrating polymer chains per unit volume of mucus is small when the polymer concentration is too low, and the polymer-mucus interaction is unstable. The concentrated polymer would have a longer penetrating chain length and, in general, better adhesion. However, due to its coiled structure, each polymer has a certain concentration at which it forms an "unperturbed" state. As a result, the solvent's access to the polymer is reduced, and the polymer's chain penetration is significantly reduced. As a result, greater polymer concentrations do not always improve mucoadhesive properties, and in some cases, they actually exacerbate them. According to one study, high concentrations of flexible polymeric films based on polyvinylpyrrolidone or poly (vinyl alcohol) as film-forming polymers did not increase the polymer's mucoadhesive properties. [61]

Mucoadhesive Dosage Forms

Tablets

Tablets have a diameter of 5–8 mm and are tiny, flat, and oval in shape. Mucoadhesive tablets, unlike regular pills, allow you to drink and talk without feeling queasy. They soften, adhere to the mucosa, and stay there until they disintegrate and/or release completely. In general, mucoadhesive tablets have the potential to be used for controlled release medicine delivery, but combining mucoadhesive features with tablet traits provides additional advantages. Mucoadhesive tablets can be customised to adhere to any mucosal tissue, including those in the stomach, allowing for both localised and systemic controlled medicine release. The delivery of medications with localised action is accomplished by applying mucoadhesive tablets to the mucosal tissues of the gastric epithelium. Mucoadhesive tablets are commonly used because they release the medicine for a longer period of time, minimise drug administration frequency, and enhance patient compliance. The lack of physical flexibility of mucoadhesive tablets is a key disadvantage, resulting in poor patient compliance for long-term and repetitive administration.[63-65]

Films

Mucoadhesive films may be preferred to adhesive tablets in terms of flexibility and comfort. They can also avoid the oral gels' brief stay on the mucosa, which is readily washed away and cleared by saliva. Furthermore, while treating oral problems locally, the films help to maintain the wound surface, minimising pain and allowing for more effective therapy. It must also have strong mucoadhesive strength to be held in the mouth for the optimum length of action. To reduce discomfort, any swelling of the film should be kept to a minimum[66].

Patches

Patches are made up of three layers: an impermeable backing layer, a drug-containing reservoir layer that releases the medication in a controlled manner, and a mucoadhesive surface for mucosal attachment. Transdermal medication delivery devices are comparable to patch systems. Solvent casting and direct milling are two methods for making adhesive patches. The intermediate sheet from which patches are punched is generated using the solvent casting process, which involves casting the drug and polymer(s) solution onto a backing layer sheet and then letting the solvent(s) to evaporate. The formulation ingredients are homogeneously combined and compacted to the correct thickness in the direct milling procedure, after which patches of predetermined size and shape are cut or punched out. During the application phase, an impermeable backing layer may be used to control the direction of medication release, prevent drug loss, and limit device deformation and disintegration. [67,68].

Gels and ointments

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Certain mucoadhesive polymers, for example, sodium carboxymethylcellulose,[68] carbopol,[69] hyaluronic acid,[70] and xanthan gum,[71] undergo a phase change from liquid to semisolid. Hydrogels are also a promising dosage form for buccal drug delivery. They are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion .[72] The application of mucoadhesive gels provides an extended retention time in the oral cavity, adequate drug penetration, as well as high efficacy and patient acceptability. A major application of adhesive gels is the local delivery of medicinal agents for the treatment of periodontitis, which is an inflammatory and infectious disease that causes formation of pockets between the gum and the tooth, and can eventually cause loss of teeth. It has

been suggested that mucoadhesive polymers might be useful for periodontitis therapy when incorporated in antimicrobial-containing formulations that are easily introduced into the periodontal pocket with a syringe.[73-75] HPMC has been used as an adhesive ointment ingredient. Additionally, a highly viscous gel was developed from Carbopol and hydroxypropyl cellulose for ointment dosage forms that could be maintained on the tissue for up to 8 hours.[76]

CONCLUSION

The chemical modification of well-established mucoadhesive polymers via derivatisation with various reagents bearing sulfhydryl functions causes a dramatic improvement in the polymer's properties. Mucoadhesive ness and cohesiveness are strongly improved. Furthermore, thiolate polymers display in situ-gelling features. The efficacy of this new generation of mucoadhesive polymers could already be demonstrated by various in vivo studies in different species on the gastrointestinal, nasal and ocular mucosa.

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