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MUCOADHESIVE POLYMERS: A REVIEW

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Review Article

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Abstract

Purpose: Aim of the study is to explore the concept of mucoadhesion, theories and the various polymers used in mucoadhesive drug delivery. **Approach**: An extensive review is carried out on mechanism of mucoadhesion, theories, polymers used in mucoadhesive dosage forms and its applications. **Finding**: Mucoadhesive polymers increases the residence time, prolongs the absorption, enhances solubility and dissolution characteristics of poorly soluble drugs. **Conclusion**: Mucoadhesive polymers was found to be a novel drug carrier used in buccal, nasal, vaginal, ocular, rectal drug delivery which improves bioavailability of poorly soluble drugs.

Keywords: Mucoadhesive polymer, mucoadhesion, bioavailability

1. INTRODUCTION

Oral administration of drugs has been the most common and preferable route for delivery of most therapeutic agents. The major hindrance for the absorption of a drug taken orally is extensive first pass metabolism and stability problems within the gastrointestinal environment such as instability in gastric pH, gastric irritation and complexation with mucosal membrane. These obstacles can be overcome by altering the route of administration.[1]

Transmucosal delivery of therapeutic agents is an important method in pharmaceutical technology that offer many benefits compared to other routes of drug delivery. Unlike oral drug delivery, which presents a hostile environment for drugs, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of tissues provides a much milder environment for drug absorption. This results in reduction of drug dose and consequent minimization of systemic side effects.[2]

Mucoadhesion can be defined as the interaction of molecules with the mucous layer. These drug delivery system, have received a great deal of attention in pharmaceuticals due to their potential to increase residence time and maintain a high concentration gradient of drug across the epithelium.[3] Mucoadhesive formulation contains one or more hydrophilic polymers along with drug.

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When it comes in contact to saliva, it wets, swells up and releases drug from the system.[4]

Mucoadhesive polymers are water-soluble and water insoluble in nature. They form swellable networks, jointed by cross-linking agents by the processes such as wetting, mutual adsorption and interpenetration of polymer and mucus. Mucoadhesive polymers should present some characteristics which facilitate the interactions with mucins. Polymers should present suitable chain flexibility at the pH and ionic strength of the mucus this expected to favor interpenetration and mucoadhesion.[5]

ADVANTAGES

- Prolongs the residence time of the dosage form, thus enhances absorption and the therapeutic efficacy of the drugs
- Excellent accessibility
- Rapid absorption can be achieved from the region with enormous blood supply and good blood flow rates such as buccal, vaginal, sublingual etc
- Increases drug bioavailability due to prevention of first pass metabolism
- Protects the drug against acidic environment such as gastro intestinal tract
- Improved patient compliance
- Ease of drug administration
- Localized drug therapy
- Faster onset of action is achieved due to high vascularization of mucosal surface[6,7]

DISADVANTAGES

- Chances of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property
- They are not suitable for high dose of drug
- Candidate which shows irritant property on mucosa cannot be administered
- Patient acceptability in terms to taste, irritancy and mouth feel is a concern with buccal drug delivery[8]

CHARACTERISTICS OF AN IDEAL MUCOADHESIVE POLYMER

- It should be nontoxic and non-absorbable from the site of absorption such as buccal, vaginal etc
- It should be nonirritant to the mucous membrane
- It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces
- It should have an optimum degree of cross linking density, pH, and hydration
- It should allow easy incorporation of the drug and should offer no hindrance to its release
- It should adhere quickly to moist tissue and should possess some site-specificity
- The polymer must not decompose on storage or during the shelf life of the dosage form
- The cost of the polymer should be ecnomical[9]

MECHANISM OF MUCOADHESION

The mechanism of mucoadhesion is generally divided into two steps

- Contact stage
- Consolidation stage
- Contact stage: This stage explains the contact between the mucoadhesive polymer and the mucus membrane, with spreading and swelling of the formulation
- Consolidation stage: here mucoadhesive materials are activated by the presence of moisture , plasticizes the system, allows the mucoadhesive molecules to break free and further bonded by weak Vander Waals and hydrogen bonds[10]

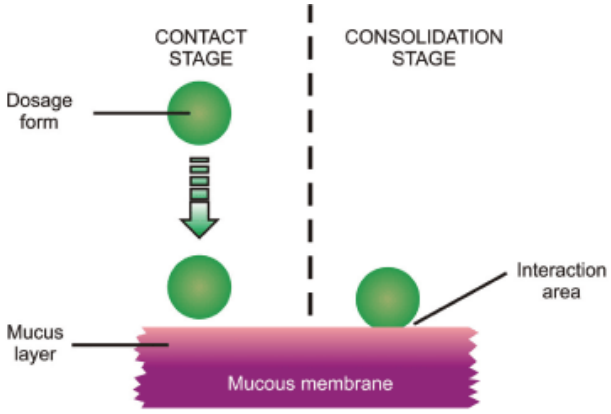

FIGURE 1 – The two steps of the mucoadhesion process.

MUCOADHESION THEORIES

- Electronic theory
- Adsorption theory

- Diffusion theory
- Wetting theory
- Fracture theory
- Mechanical theory
- Cohesive theory

- **Electronic theory**: Theory explains the adhesion take place by means of electron transfer between the mucus and the mucoadhesive system arising through differences in their electronic structures. This results in the formation of electrical double layer of charges at the mucus and mucoadhesive interface. Electrostatic forces are an important cause of bond adhesion rather than merely a result of high joint strength.[11]
- **Adsorption theory**: this theory explains intermolecular forces (hydrogen bonding) and Vander Waal' forces, results in adhesive interaction amongst the substrate surfaces.[12]
- **Diffusion theory**: The theory explains interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. The adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility, nature of the mucoadhesive chains, mobility and contact time. The depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2–0.5 μm. The depth of penetration of polymer and mucin chains can be estimated by the following equation,

$$l = (tDb)^{1/2}$$

Where t is the contact time and Db is the diffusion coefficient of the mucoadhesive material in the mucus.[13]

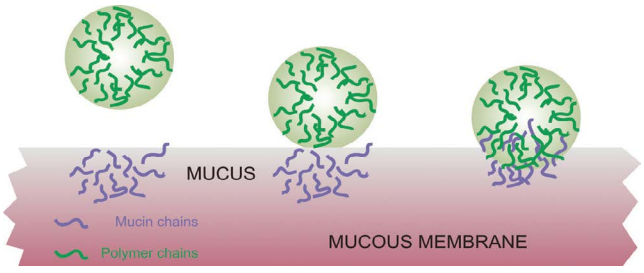

FIGURE 2. Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus [14]

- **Wetting theory:** The wetting theory explains surface spreading property of liquid systems measured by contact angle. As a general rule, the lower the contact angle, the greater is the affinity. The contact angle should be equal or close to zero to provide adequate spreadability. The spreadability coefficient SAB, can be calculated from the difference between the surface energies γB and γA and the interfacial energy γAB, as indicated in the equation given below,[15]

$$SAB = \gamma B - \gamma A - \gamma AB$$

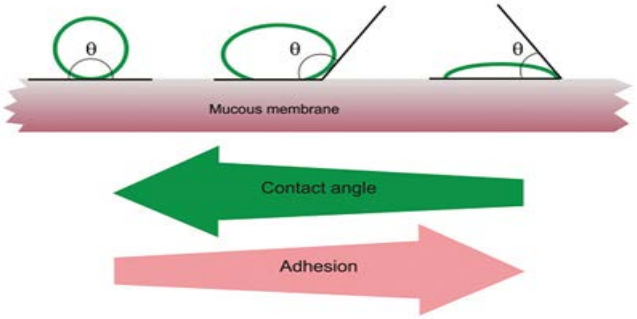

FIGURE 3. Influence of contact angle between device and mucous membrane on bioadhesion [14]

- **Fracture theory:** According to this theory, the adhesive bond between systems is related to the force required to separate both surfaces from one another. "Fracture theory" relates the force for polymer detachment from the mucus to the strength of their adhesive bond.[13]

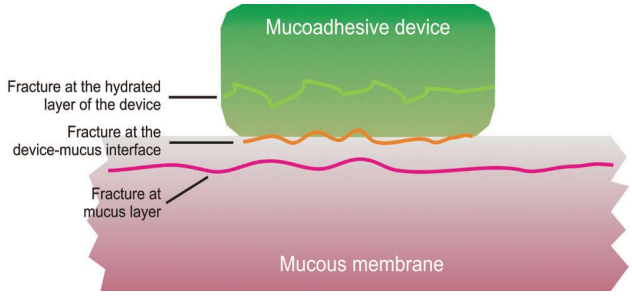

FIGURE 4. Regions where the mucoadhesive bond rupture can occur [14]

- **Mechanical theory**: It explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.[15]

- **Cohesive theory**: The phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like molecules. [16]

Table 1. CLASSIFICATION OF MUCOADHESIVE POLYMERS [17]

Criteria	Categories	Examples
Source	Natural	Agarose, chitosan, gelatin, hyaluronic acid, gums(guar,Xanthan etc)
	Synthetic	Cellulose derivatives(carboxy methyl cellulose (CMC), sodium carboxy methyl cellulose (SCMC), poly acrylic acid based polymers (Carbopol, polyacrylates, polyethylene glycol etc)
Aqeous solubility	Water soluble	Cabopol, sodium carboxy methyl cellulose, sodium alginate
	Water insoluble	Chitosan, ethyl cellulose, polycarbophil
Charge	Cationic	Amino dextran, chitosan
	Anionic	Chitosan, Carbopol, pectin, polycarbophil, sodium alginate, Xanthan gum
	Nonionic	Hydroxy ethyl starch, poly vinyl alcohol, poly vinyl pyrrolidone
Potential mucoadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Carbopol, polycarbophil, polyvinyl alcohol
	Electrostatic ineraction	Chitosan

Cellulose derivatives

The cellulose derivatives widely used in mucoadhesive formulations are hydroxyethylcellulose, hydroxylpropylmethylcellulose, hydroxypropylcellulose and carboxymethylcellulose etc.

- **Hydroxylpropylmethylcellulose (HPMC):** Hydroxylpropylmethylcellulose is semi synthetic, inert, viscoelastic polymers, extensively used not only for mucoadhesion properties but also for its controlled release mechanism. It has been applied to deliver various drugs via different type of dosage forms. HPMC is a non-ionic polymer and lacking of proton donating carboxylic group which causes lesser hydrogen bonding than carboxymethyl cellulose.
- **Carboxymethylcellulose (CMC):** CMC, specifically sodium salt of CMC (Na-CMC) is an extensively used mucoadhesive polymer.CMC possesses better mucoadhesion than HPMC. CMC is an anionic polymer which causes higher hydrogen bonding than nonionic cellulose polymers. Mucoadhesion nature of CMC depends on the pH of the medium used for testing.[18]

Polyacrylates

They are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinylglycol. Poly acrylic acid possesses excellent mucoadhesive characteristics due to the ability of the carboxylic groups to form strong hydrogen bonds with the oligosaccharide chains of mucin. The physical entanglement between the polymer and mucus layers also plays an important role in promoting mucoadhesion. Mucoadhesion results from a series of physico-chemical processes, such as hydrophobic interactions, hydrogen and Vander Waals bonds, which are controlled by pH and ionic composition.[17]

Chitosan

Among all mucoadhesive agents, chitosan is the most abundant polysaccharide after cellulose in use. Chitosan, a cationic mucoadhesive agent is basically a polysaccharide derived from chitin by means of deacetylation. This is a co-polymer of glucosamine and N-acetyl-glucosamine. Chitosan is insoluble in water but soluble in dilute weak acid. The biocompatibility, biodegradation and low toxic nature probably has made chitosan an attractive polymeric component. The mucoadhesion nature of chitosan is attributed to several mechanisms. The abundant mechanism is hydrogen bonding with glycoprotein of mucin due to presence of –OH and $–NH_2$ groups.[18]

Alginates

Alginate is a natural and biodegradable anionic polymer obtained from brown seaweed. It has low toxicity and relatively low cost thus making it extensively being investigated in numerous studies to prepare micro particles, beads with excellent bioadhesive features. Mostly sodium or calcium salt of alginate is used in pharmaceutical research. Alginate has good mucoadhesion property due

to the presence of carboxylic acid moiety which causes hydrogen bonding with the glycoprotein of mucin.[16]

Pectin

Pectin is a natural, biodegradable, biocompatible, non-toxic heterogenous polysaccharide that is extracted from citrus peel or apple pomace. It contains linear chains of (1–4)-linked a-D-galacturonic acid residues that have carboxyl groups. Mucoadhesion mechanism of pectin has been explained in two ways; formation of hydrogen bond with mucin and electrostatic interaction between pectin and mucin molecule. Hydrogen bonding occurs due to the presence of carboxylic acid group in pectin. When pectin is mixed with mucin it results in the formation of aggregates. Mucin and pectin both are negatively charged. Therefore increasing concentration of pectin in aqueous medium causes increase in electrostatic repulsion with mucin. This repulsion causes uncoiling of polymer chain facilitating more entanglement and adhesion.[19]

Novel mucoadhesive polymers

Lectins

Lectins are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and proteins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues. After initial mucosal cell-binding, lectins can either remain on the cell surface or receptor mediated adhesion, internalized by a process of endocytosis. This provides dual functions including targeted specific attachment and controlled drug delivery of macromolecular pharmaceuticals via active cell mediated drug uptake.

Based on molecular structure lectins can be classified into,

- Merolectins: lectins having only one carbohydrate recognizing domain
- Hololectins: lectins with two or more carbohydrate recognizing domains
- Chimerolectins: lectins with additional unrelated domains [20]

Thiolated polymers

Special class of multifunctional polymers called thiomers which are modified by the addition of thiol group. These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Thiomers are capable of forming intra and inter chain disulphide bonds within the polymeric network leading to strongly improved cohesive properties and stability of drug delivery systems such as matrix systems. Due to the formation of strong covalent bonds with mucus glycoproteins, thiomers show the strongest mucoadhesive properties.

Thiolated polymers includes,

- Chitosan–iminothiolane, Chitosan–thioglycolic acid
- Poly(acrylic acid)–cysteine, poly(acrylic acid)–homocysteine etc [21]

Bioadhesive nanopolymers as drug carriers

Mucoadhesive nanopolymers appear to be an effective solution in the challenge of achieving bioavailability with topical drugs especially in ocular drug delivery system. [20]

Poloxomer

Poloxomer are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). Poloxomer gels show phase transitions from liquids to mucoadhesive gels at body temperature and allow in-situ gelation at the site of interest. [21]

Factors affecting mucoadhesion

Polymer related factors

- Molecular weight: The mucoadhesive property depends on the molecular weight of selected polymer. Mucoadhesion is successful if molecular weight is 100,000 and more.
- Concentration of active polymer: If there is an optimum concentration of mucoadhesive polymer, maximum mucoadhesion. In highly concentrated systems, beyond the optimum level the adhesive strength drops significantly. This is because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.
- Flexibility of polymer chains: Chain flexibility is critical for interpenetration and entanglement. As water soluble polymers become cross linked, mobility of individual polymer chain can pene-

trate in to the mucous layer decreases which can reduce mucoadhesive strength. [23]

Environmental factors

- Applied strength: The adhesion strength increases with the applied strength or with the duration of its application. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.
- PH: mucoadhesion can be influenced by the charges present on the surface of mucus as well as certain ionisable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration.
- Initial contact time: Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Bioadhesive strength increases with increase in contact time.
- Swelling: It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration results in the formation of a slippery mucilage without adhesion.[23,24]

Physiological factors

- Mucin turn over: Mucin turnover is expected to limit the residence time of the mucoadhesive device on the mucus layer. If the adhesive strength is high, mucoadhesive are detached from the surface due to mucin turn over.
- Disease state: The physiochemical properties of mucus are known to change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract. [25]

Evaluation of mucoadhesive dosage form [26, 27,28,29,30]

In vitro/ex vivo tests

- Tensile strength
- Shear stress
- Fluorescent probe method
- Falling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Swelling properties
- Stability studies

In vivo methods

- Use of radio opaque markers
- Use of gamma scintigraphy
- X ray studies
- Isolated loop technique
- Use of electron paramagnetic resonance

Methods determining tensile strength

Texture profile analyzer is an instrument used to measure the force required to remove mucoadhesive films from excised tissue *in vitro*. For this test, a piece of animal mucous membrane is taken and tested for the force required to take away the formulation from a model membrane which consists of disc composed of mucin.[26]

Methods determining shear stress

Stainless steel rotating cylinder which is coated with freshly excised porcine intestinal mucosa to which polymer discs were attached.The cylinder is placed in a dissolution apparatus and rotated at 125 RPM. It is analyzed every 30 minutes for the attachment of the polymers discs.[27]

Fluorescent probe method

Membrane lipid bilayer and membrane proteins are labeled with pyrene, fluorescein isothiocyanate, respectively. The cells are mixed with the mucoadhesive agents and changes in fluorescence spectra were monitored.[28]

Swelling index

The extent of swelling can be measured in terms of % weight gain by the dosage form. The swelling index is calculated using following formula.

$$\text{Swelling Index (S.I)} = \frac{W_t - W_o}{W_o}$$

Where, S.I = Swelling index
Wt = Weight of tablet at time t
W_o = Weight of tablet before placing in the beaker[29]

Colloidal gold staining technique

The technique employs red colloidal gold particles, which are adsorbed on mucin molecules to form mucin–gold conjugates, which upon interaction with bioadhesive hydrogels develops a red color on the surface.[27]

Viscometeric method

Viscosities of 15% w/v porcine gastric mucin dispersion in 0.1M HCl (pH 1) or 0.1M acetate buffer (pH 5.5) is measured with a Brookfield viscometer in the absence or presence of selected neutral, anionic, and cationic polymers.[26]

Thumb method

The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time.[27]

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.[27]

In vivo techniques

Gamma scintigraphy

Gamma scintigraphy is widely used in monitoring formulations of the gastrointestinal and respiratory tracts. The radiolabelling is generally achieved by the incorporation of an appropriate technetium-99m or indium-Ill labeled radiopharmaceutical into the formulation. Complex dosage forms, such as enteric coated tablets, labelling is best undertaken by the addition of a non-radioactive tracer such as samarium-152 oxide or erbium-170 oxide followed by neutron activation of the final product. Systems investigated include tablets and multiparticulates for oral administration, enemas and suppositories, metered dose inhalers and nebulizers, and nasal sprays and drops. This technique provides information on the deposition, dispersion and movement of the formulation.

A study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium-labeled hyaluronan based biodegradable polymer (HYAFF) tablets. Dimensions of the stomach part of the sheep can be outlined and imaged using labeled gellan gum, and the data collected are subsequently used to compare the distribution of radio labeled HYAFF formulations. The retention of mucoadhesive-radio labeled tablets based on HYAFF polymer was found to be more for the dry powder formulation than for the pessary formulation after 12 h of administration to stomach epithelium. The combination of the sheep model and the gamma scintigraphy method has been proved to be an extremely useful tool for evaluating the distribution, spreading, and clearance of administered stomach mucoadhesive tablets.[30, 31]

Table 2. Marketed dosage forms [32]

Ophthalmic drug delivery		
Brand name	**Contents**	**Uses**
Hyotears®, Snotears®	Poly vinyl alcohol	Lubrication
Pilogel®	Pilocarpine, polyacrylic acid	Glaucoma
Nasal drug delivery		
Brand name	Contents	Uses
Rhincort®	Beclomethasone dipropionate, hydroxy propyl cellulose	Nasal allergy
Nasacort®	Triacinolone acetonide, micro crystalline cellulose	Nasal inflammation and nasal allergy
Buccal drug delivery		
Brand name	Contents	Uses
Corian® pellets	Hydrocortisone, acacia	Mouth ulcer
Corysodl® oral gel	Chlor hexedine gluconate, hydroxy propyl cellulose	Inhibit the formation of plaque
Vaginal drug delivery		
Brand name	Bioadhesive agents	Uses
Aci gel®	Acacia, tragacanth	Maintain vaginal acidity
crinone®	Carbomer	Bacterial vaginosis

Gastro intestinal Transit using Radio-Opaque markers

Use of radio-opaque markers such as barium sulfate encapsulated in mucoadhesive tablets to determine the effects of mucoadhesive polymers on GI transit time. Feces collection (using an automated feces collection machine) and X-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal gastro intestinal motility. Mucoadhesives labeled with Cr-51, Tc- 99m, In-113m, or I-123 have been used to study the transit of the tablets in the gastro intestinal tract.[27]

Table 3. Pharmaceutical applications of mucoadhesive polymers [33]

Polymer	Pharmaceutical applications
Sodium alginate	Suspending agent, gelation for dental films, stabilizer, sustended release agent, tablet coating, mucoadhesive microspheres
Pectin	Thickening agent, suspending agent, protective agents, colon drug delivery, transdermal drug delivery
Carbomer	Suspending agent , emulsifier, bioadhesive for cervical patches, used in cosmetic preparations
Chitosan	Controlled drug delivery, peptide drug delivery, colonic drug delivery
Hydroxy propyl methyl cellulose	Viscosity modifier, film forming, gelling and binding agent
Sodium carboxy methyl cellulose	Produce thixotropic gels as suspending vehicles in pharmaceutical and cosmetic preparations
Hydroxy propyl cellulose	Binder in tableting, film coating, used in extended release matrix former
Hydroxy ethyl cellulose	Thickening agent in ophthalmic preparations, film coating agent for tableting

Conclusion

Mucoadhesive polymers provide an important tool to improve the bioavailability of the active agent by improving the residence time prolongs the absorption, enhances solubility and dissolution characteristics of poorly soluble drugs. Mucoadhesive polymers was found to be a novel drug carrier found application in buccal, nasal, vaginal, ocular, rectal, gastrointestinal tract. Development of novel mucoadhesive delivery systems are being undertaken so as to understand the various mechanism of mucoadhesion and improved permeation of active agents. The mucoadhesive dosage forms offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. The formulation of mucoadhesive drug delivery system depends on the selection of suitable polymer with excellent mucoadhesive properties and biocompatibility.

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