



ORAL AND PARENTERAL TO MINIMIZE THE NASAL DELIVERY BY THERMOREVERSIBLE MUCOADHESIVE – A REVIEW

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❖ Abstract

The adhesion between two materials, at least one of which is a mucosal surface, is generally referred to as mucoadhesion. Mucosal medication delivery has drawn a lot of interest during the past few decades. Mucoadhesive dosage forms may be created to provide a regulated rate of drug release for a better therapeutic result by enabling prolonged retention at the site of application. Drug molecules that are not suitable for oral administration, such as those that undergo acid degradation or substantial first-pass metabolism, may benefit from the application of dosage forms to mucosal surfaces. The nature of the mucosal tissue and the physicochemical characteristics of the polymeric formulation are just two examples of the many variables that affect a dosage form's capacity to adhere to mucous membranes. This review article seeks to give a general overview of the numerous mucoadhesion issues, Mucoadhesive materials, factors affecting mucoadhesion, evaluation techniques, and ultimately various Mucoadhesive drug delivery systems (buccal, nasal, ocular, gastro, vaginal, and rectal).

In the past 20 years, mucoadhesion has attracted fresh interest in drug delivery applications that involve extending the residence time of Mucoadhesive dose forms through various mucosal channels. Topical and local systems based on Mucoadhesive have demonstrated improved absorption. Since Mucoadhesive drug administration has a large surface area and a strong blood flow, it provides quick absorption and good bioavailability. Drug distribution over the mucosa avoids first-pass hepatic metabolism and gastrointestinal enzyme degradation. In order to distribute a rising number of high-molecular-weight sensitive compounds, such as peptide and oligonucleotides, mucosal drug delivery systems may be useful. The goal of this review is to provide a thorough explanation of mucoadhesion, most popular routes of administration for mucoadhesives along with oral and parenteral routes for minimisation of the nasal delivery by thermoreversible mucoadhesive.

❖ Keywords

Mucoadhesion, mucoadhesive drug delivery systems, nasal and parenteral routes, Thermoreversible Mucoadhesive

❖ Bioadhesion and Mucoadhesion

The situation in which two materials, at least one of which is biological in nature, are kept together for a long time by interfacial forces is known as bioadhesion [1]. Bioadhesion in biological systems can be divided into three categories:

- Type 1: Adhesion between two biological phases, for example - platelet aggregation and wound healing.
- Type 2: Refers to the attachment of a biological phase to an artificial substrate, such as the adhesion of cells to culture dishes and the development of biofilms on prosthetic devices and inserts.
- Type 3: Adhesion of an artificial substance to a biological substrate, as in the case of sealants' adhesion to dental enamel and the adhesion of artificial hydrogels to soft tissues [2].

The term "bioadhesion" for drug delivery indicates attachment of a drug carrier system to a particular biological site. Epithelial tissue or a tissue's mucus coat could be the biological surface. Mucoadhesion is the term used to describe the phenomena where an adhesive attaches to a mucus coat. Mucoadhesion was defined by Leung and Robinson [3] as the interaction of a mucin surface and a synthetic or natural polymer. Contrary to popular belief, mucoadhesion is not the same as bioadhesion, which refers to the attachment of a polymer to a biological membrane. Instead, the word mucoadhesion is used when the substrate is a mucus membrane.

❖ Mucoadhesive Materials

Numerous hydrophilic groups, including hydroxyl, carboxyl, amide, and sulphate, are present in mucoadhesive polymers. By means of a variety of interactions, including hydrogen bonds, hydrophobic interactions, and electrostatic interactions, these groups adhere to mucus or the cell membrane. These hydrophilic groups also lead polymers to expand in water, exposing the stickiest sites possible [4]. The following qualities should be present in an ideal polymer for a bio adhesive drug delivery system:

- Both the polymer and the byproducts of its decomposition must be nontoxic and non absorbable.
- It should be nonirritant.
- Preferably, it should create a strong non covalent connection with the mucus or epithelial cell surface.
- It should have some site specificity and attach to wet tissue fast.
- It should make the medicine easy to incorporate and present no obstacles to its release.
- Neither during storage nor the dosage form's shelf life may the polymer begin to break down.
- To maintain the competitiveness of the produced dosage form, the cost of the polymer shouldn't be too high.

There are three major groups of polymers that attach to biological surfaces: [5, 6].

- Adhering polymers that interact in general, non covalent ways that are essentially electrostatic in nature
- Hydrophilic functional groups in polymers that form hydrogen bonds with analogous groups on biological substrates
- Certain receptor sites on the cell or mucus surface are bound by distinct polymers.

Lectins and thiolated polymers fall within the latter type of polymers. Generally speaking, lectins are nonimmune proteins or glycoprotein complexes that have the ability to bind sugars non covalently and selectively [7]. Lectins have been widely investigated, particularly for applications involving medication targeting, since they have the ability to bind to carbohydrates on the mucus or epithelial cell surface [8, 9]. These second-generation bioadhesives enable subsequent endo- and transcytosis in addition to cellular binding. Thiomers, commonly known as thiolated polymers, are hydrophilic macromolecules with free thiol groups on the polymeric backbone. These functional groups significantly enhanced a number of characteristics of polyacrylates and cellulose derivatives [10]. Thiol groups included in the polymer enable stable covalent connections to form with cysteine-rich subdomains of mucus glycoproteins, extending residence duration and enhancing bioavailability [11]. The enhanced tensile strength, quick swelling, and water absorption behaviour of thiolated polymers are some additional beneficial mucoadhesive characteristics.

❖ Factors Affecting Mucoadhesion

Hydrophobicity, molecular weight, cross-linking, swelling, pH, and the concentration of the active polymer are a few of the variables that may have an impact on mucoadhesion [12, 13, 14].

- **Hydrophilicity**

Numerous hydrophilic functional groups, including hydroxyl and carboxyl, are present in bioadhesive polymers. These groups enable the formation of hydrogen bonds with the substrate, which causes swelling in aqueous conditions and maximises the exposure of possible anchor sites. Additionally, swollen polymers have the greatest space between their chains, increasing chain flexibility and facilitating effective substrate penetration.

- **Molecular Weight**

Low-molecular-weight polymers encourage intermolecular interactions, whereas higher-molecular-weight polymers encourage entanglements. The kind of polymer will determine the ideal molecular weight for the greatest mucoadhesion; bioadhesive forces increase with polymer molecular weight up to 100,000. There is no more benefit at this point [15].

- **Cross-linking and Swelling**

The amount of swelling is negatively correlated with cross-link density [16]. More flexibility and hydration occur with greater cross-link densities, and mucoadhesion is improved by polymers with bigger surface areas. It is preferred to use a weakly cross-linked polymer to produce a high degree of swelling. However, a slippery mucilage forms and may be readily dislodged from the substrate if there is too much moisture present and the degree of swelling is too extreme [17]. By using adhesion promoters in the formulation, such as free polymer chains and polymers grafted onto the premade network, cross-linked polymers' mucoadhesion can be improved [14].

- **Spatial Conformation**

In addition to molecular weight and chain length, a polymer's spatial conformation is crucial. Dextrans have an extremely high molecular weight (19,500,000), although their adhesive strength is comparable to that of polyethylene glycol (PEG), which has a molecular weight of 200,000. In contrast to PEG polymers, which have a linear conformation, dextran has a helical shape that may conceal multiple adhesively active groups, which are principally in charge of adherence [12].

- **pH**

The adherence of bioadhesives with ionizable groups might be affected by the pH at the bioadhesive to substrate contact. Many bioadhesives that are employed in medication delivery are polyanions with functionalities for carboxylic acids. It will be mostly ionised if the local pH is above the polymer's pK; if the pH is below the polymer's pK, it will be primarily unionised. The pKa of the polymers in the poly (acrylic acid) family ranges between 4 and 5. Around pH 4-5, these polymers' highest adhesive strength is shown, and it progressively declines above pH 6. The protonated carboxyl groups, not the ionised carboxyl groups, react with mucin molecules, most likely via the concurrent creation of many hydrogen bonds, according to a thorough analysis of the processes of mucoadhesion [18].

- **Concentration of Active Polymer**

According to Ahuja [6], there is an ideal polymer concentration that corresponds to the optimal mucoadhesion. Beyond the optimal concentration, the adhesive strength in highly concentrated solutions substantially decreases. The coiled molecules become solvent-poor and there are fewer chains available for interpenetration in concentrated solutions. Only formulations that are more or less liquid mucoadhesive appear to find attention in this outcome. Duchene [19] shown that the stronger the mucoadhesion is for solid dosage forms like tablets, the greater the polymer content.

- **Drug / Excipient Concentration**

The concentration of the drug and excipients may affect mucoadhesion. Propranolol hydrochloride's impact on Carbopol hydrogel adhesion, a poly (acrylic acid) polymer with a mild crosslinking, was investigated by Blanco Fuente [20]. Due to an increase in elasticity brought on by the complex formation between the medication and the polymer, the author exhibited greater adhesion when water was limited in the system. Large amounts of water caused the complex to precipitate out, which slightly lessened its sticky properties. Mucoadhesion to porcine cheek tissue was greatly improved by increasing the toluidine blue O (TBO) content in mucoadhesive patches made of Gantrez poly (methylvinylether / maleic acid) [21]. Due to electrostatic interactions between the cationic medication and anionic copolymer, there was an increase in internal cohesion inside the patches, which was the cause of this.

- **Other Factors Affecting Mucoadhesion**

The initial force of application could have an impact on mucoadhesion. Higher pressures result in improved interpenetration and strong bioadhesion [19, 22]. Additionally, the swelling and interpenetration of polymer chains increase with the length of the first contact period between the bioadhesive and substrate [25]. Mucoadhesion can be impacted by physiological factors as well. The presence of a bioadhesive device can also have an impact on the rate of mucus turnover [24]. Additionally, depending on the body location and the existence of a local or systemic illness, the nature of the surface that the bioadhesive formulation is presented with might vary greatly [23].

- ❖ **Routes of Administration for Mucoadhesive-based Drug Delivery Systems**

The wet tissue that borders the mouth, gut, rectum, genital region, nose, and eye lids is known as the mucosa or the mucus membrane. Table 1 lists the different mucus membrane structures according to where on the body they are located. Past formulations of mucoadhesive drug delivery methods included powders, compacts, sprays, semisolids, and films. For instance, powders and nanoparticles have been employed to enhance medication administration to the nasal mucosa, while compacts have been used for drug delivery to the oral cavity [26, 27, 28], oral strips [29] for the tongue or buccal cavities have recently been created. Table 2 provides information on the mucoadhesive dose forms. Alternative delivery system concepts have recently attracted more attention. It has been hypothesised that buccal films might provide more comfort and flexibility than sticky tablets. Additionally, films could solve the issue of oral gels' relatively limited residence period. [30] The manufacturing of bioadhesive films uses cellulose derivatives, poly (acrylic acids) like Carbopol, and Gantrez copolymers such poly (methylvinylether / maleic anhydride) as well as film-forming bioadhesive polymers [30, 31, 32].

Mucus membrane	Relevant anatomical features
Buccal [32]	<ul style="list-style-type: none"> • Buccal mucosa surface area approximately 30 cm² • Comprised of three distinct layers – epithelium, basement membrane, and connective tissues • Buccal mucosa, sublingual are soft palate nonkeratinized tissue, and gingival are hard palate keratinized tissue • Thickness of buccal epithelium is in the range of 500–800 μm, 40–50 cells thick • Mucus secreted by salivary glands, as a component of saliva, forming a 0.1–0.7 mm thick layer • Turnover time for buccal epithelium 5–6 days • Permeability barrier property of oral mucosa due to intercellular materials derived from membrane-coating granules
Nasal [33]	<ul style="list-style-type: none"> • Nasal cavity surface area 160 cm² • Lined with mucous membrane containing columnar cells, goblet cells, and basal cells • Columnar cells are covered with cilia, apart from the anterior part of the nasal cavity • Both keratinized and nonkeratinized epithelial cells present depending upon location within nasal cavity • Cilia responsible for mucociliary clearance • Mucus secreted by the submucosal glands and the goblet cells, forming a mucus layer approximately 5–20 μm thick • Nasal cavity length approximately 60 mm • Nasal cavity volume approximately 20 mL • Turn-over time for mucus is usually 10–15 min
Ocular [34]	<ul style="list-style-type: none"> • Cornea is composed of five layers – epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium • Epithelium consists of 5–6 layers of cells, with the cells of the basal layer being columnar, and the outermost cells flattened polygonal cells • Tight junctions present between the basal cells of the corneal epithelium

	<ul style="list-style-type: none"> • At the corneal margin, the conjunctiva is structurally continuous with the corneal epithelium • The conjunctival tissue is permeable to molecules up to 20,000 Da, whereas the cornea is impermeable to molecules greater than 5000 Da • The conjunctiva contains around 1.5 million goblet cells, which synthesize secretory mucins and peptides • A volume of about 2–3 μL of mucus so secreted daily • A turnover of the mucus layer occurs in approximately 15–20 h • Exposed part of the eye is covered by a thin fluid layer – percorneal tear film
Mucus Membrane	<ul style="list-style-type: none"> • Relevant Anatomical Features • Tear film thickness is approximately 3–10 μm
Vaginal [35]	<ul style="list-style-type: none"> • Length of vagina varies from 6 to 10 cm • The epithelial layer consists of the lamina propia and stratified squamous epithelium • A cell turnover of about 10–15 layers is estimated to be in the order of 7 days • Although there are no glands in the vagina mucosa, the surface is usually covered with vaginal fluid • Major components of vaginal fluid are cervical mucus and vaginal fluid from the well-vascularized mucosa • The volume, viscosity, and pH of the cervical mucus vary with age and during the menstrual cycle
Rectal [36]	<ul style="list-style-type: none"> • Length approximately 15–20 cm • Surface area of approximately 300 cm^2 • Epithelium consists of a single layer of cylindrical cells and goblet cells secreting mucus • Flat surface, without villi, and with three major fold, the rectal valves • Approximately 3 mL of mucus with a neutral pH spread over the surface

Table 1: Anatomical differences of the mucus membrane

Delivery routes	Tablet	Ointment	Gel	Patch	Film
Buccal	Theophylline, multiple polymers [37]	Benzyl nicotinate, multiple polymers [38]	Benzydamine, chitosan derivatives [39]	Miconazole, PVA/PVP [40]	Fentanyl, PVP [41]
Nasal	N/A	Mupirocin, glycerin ester [42]	Insulin, starch [43]	Insulin, chitosan/PEG [44]	Chlorpromazine, chitosan/pectin [45]
Ocular	Diclofenac, poly (acrylic acid) [46]	Sulphadiazine, multiple polymers [47]	Puerarin, poloxamer/Carbopol [48]	Ciprofloxacin, PVA/CMC [49]	Fluorescein, HPMC [50]
Vaginal	Metronidazole, chitosan [51]	Terameprocol, white petroleum [52]	Amphotericin, pluronic [53]	ALA, PMVE/MA [54]	SDS, multiple polymers [55]
Rectal	Ramosetron, Carbopol [56]	Zinc oxide, petroleum [57]	Quinine, HPMC [58]	N/A	Theophylline, pHEMA [59]

Table 2: Different types of mucoadhesive dosage forms

❖ Oral Mucoadhesive Drug Delivery Systems

Due to its easy accessibility, drug administration through the oral mucosa has attracted a lot of research. The most often utilised routes are thought to be the buccal and sublingual routes. A somewhat permeable barrier to drug transport is provided by the nonkeratinized epithelium in the oral cavity, which includes the soft palate, the mouth floor, the ventral side of the tongue, and the buccal mucosa [60]. Paracellular transport is followed by hydrophilic substances and big or highly polar molecules, while transcellular transport via the lipid bilayer is followed by lipophilic substances [61]. Drug delivery via the oral mucosa has been particularly effective and offers a number of benefits over other drug delivery methods, such as avoiding hepatic first-pass metabolism, increasing drug bioavailability, improving patient compliance, having excellent accessibility, unidirectional drug flux, and having improved barrier permeability when compared, for instance, to intact skin [62, 63]. Local and systemic medication distribution has taken place in the mouth cavity. Disease conditions such as aphthous ulceration, gingivitis, periodontal disease, and xerostoma are treated with local medication treatment. Adhesive gels, pills, films, patches, ointments, mouthwashes, and pastes are a few different dose forms.

Adhesive tablets have traditionally been the widely utilised dosage form for buccal medication distribution. Tablets can be placed on the cheeks, lips, gums, and palate, among other areas of the oral cavity. Buccal pills, in contrast to traditional tablets, allow speaking, eating, and drinking without experiencing any significant discomfort. Perioli [64] investigated how mucoadhesive buccal tablet behaviour and medication release rate were affected by compression force. Hydroxyethyl cellulose (HEC) and carbopol 940 were used in a 1:1 ratio as matrix-forming polymers to create tablets under various compression stresses. Water penetration and polymer chain stretching were not significantly impacted by compression pressures, but mucoadhesion performance and medication release were. While improving in vivo mucoadhesive and hydration time, increased compression force reduced drug release both in vitro and in vivo. Furthermore, it was found that tablets made with the least amount of force had the greatest outcomes as opposed to tablets made with the most amount of force, which produced discomfort during in vivo application and required human volunteers to remove them.

Up to 50% of healthy persons get repeated small mouth ulcers, which is a common disorder known as oral mucosal ulceration (aphthous stomatitis). When treating aphthous stomatitis, Shermer [65] compared the effectiveness and acceptability of a mucoadhesive patch to an oral painkiller. After 12 and 24 hours, it was discovered that the mucoadhesive patch performed better than the oral remedy in terms of healing time and pain severity. Patients who received the mucoadhesive patch had local side effects considerably less frequently than patients who received the oral solution one hour after the therapy.

A mucoadhesive patch containing TBO was described by Donnelly [21] as a viable delivery method for oropharyngeal candidiasis photodynamic antimicrobial chemotherapy (PACT). Patches are made from aqueous mixtures of tripropyleneglycol methyl ether and poly (methyl vinyl ether/maleic anhydride). The scientists came

to the conclusion that oropharyngeal candidiasis, which is only caused by planktonic cells, may be treated with brief application periods of mucoadhesive patches containing TBO. For persistent diseases where biofilms are involved, longer patch application periods may be necessary.

An oral inflammatory condition called periodontitis causes the teeth's supporting tissues to be destroyed [66]. Combining mechanical therapy with chemotherapeutic drugs in the intraperiodontal pocket is one way to treat the disease of inflammatory periodontitis [67]. Syringeable semisolid, bioadhesive networks were created by Jones and Andrews [68, 69], who also reported their formulation and physicochemical characterization (containing tetracycline, metronidazole, or model protein drugs). Such systems may be designed to have the necessary flow characteristics (so they may be readily injected with a syringe into the periodontal pocket), mucoadhesive characteristics (to ensure longer retention inside the pocket), and sustained therapeutic agent release within this environment.

Despite many clinical researches, mucosal medication administration via the buccal route is still highly difficult. Here, we highlight a number of formulations that are either commercial goods or are undergoing clinical testing. The 3M firm has created a buccal patch system that comprises of a backing material and a matrix patch comprising a medication, mucoadhesive polymers, and polymeric elastomers. Their buprenorphine patch has been claimed to provide good patient comfort and can administer the medication for up to 12 hours [70].

Oral in, a brand-new liquid aerosol formulation created by Genex Biotechnology, is now undergoing phase II clinical trials [71]. Through the use of a metered dosage inhaler, oral in delivers accurate insulin doses as tiny, aerosolized droplets that are directed into the mouth. Compared to standard formulations, there is a noticeable rise in medication levels in the mouth. This oral aerosol formulation offers the plasma insulin levels required to prevent postprandial glucose increase in diabetic patients and is quickly absorbed through the buccal mucosal epithelium. This brand-new, painless oral insulin formulation offers a variety of benefits, including as quick absorption, simple administration, accurate dose management (equivalent to injection within one unit), and bolus medication delivery. Additionally, Aphtach (triamcinolone acetonide buccal tablets from Teijin Ltd.), a formulation of BioAlliance Pharma's miconazole tablet (Lauriad), is now commercially available [71].

❖ Conclusion

For the effective creation of new mucoadhesive drug delivery systems, this review of mucoadhesive dosage forms may be helpful. The discovery of new mucoadhesives, device design, mucoadhesion processes, and permeation improvement are some of the uses for mucoadhesive drug delivery systems. Mucoadhesive drug delivery will become even more crucial as a result of the massive flood of novel drug molecules brought on by drug development. The mucoadhesive dosage forms promote patient compliance, minimal enzymatic activity, and extended contact at the site of administration. The choice of an appropriate polymer with superior mucosal adhesive characteristics and biocompatibility is crucial in the creation of mucoadhesive medication delivery systems. The next generation of mucoadhesive polymers (lectins, thiols, etc.) provides higher adhesion and

retention of dosage forms, therefore researchers are now exploring beyond conventional polymers. However, these innovative mucoadhesive formulations need a lot more study before they can be used therapeutically to treat both systemic and localised illnesses.

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