



## A Comprehensive Review on Mucoadhesive Drug Delivery System

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### ABSTRACT :

Mucoadhesion is currently a topic of interest for medication delivery system designers. The adhesion between two materials, at least one of which is a mucosal surface, is known as mucoadhesion is also referred to as bioadhesion. To enable the dosage form to remain at the application or absorption site longer and to provide close contact between the dosage form and the underlying absorbing surface, a mucoadhesive drug delivery system may be developed. Controlling the release of the medication from a dosage form and extending the residence period of the drug at a specific location are particularly helpful in establishing a controlled plasma level of the drug and enhancing bioavailability. When these dosage forms are applied to mucosal surfaces, medication molecules that are not soluble in water may benefit. In this review, mucoadhesion, mucoadhesive polymers, and their application in the development of various mucoadhesive drug delivery systems for the gastrointestinal tract, nose, eyes, vagina, and rectal regions are discussed. To successfully translate the notion into a practical use in controlled medication delivery, however, more advancements in the field of mucoadhesives research are required.

**Keywords:** Mucoadhesion, Bioadhesion, Mucoadhesive systems, Drug delivery.

### Introduction:

Over the past twenty years, mucoadhesion has attracted increased attention as a means of extending the residence time of mucoadhesive dosage forms in drug delivery applications via a variety of mucosal routes. Mucoadhesive drug delivery systems work by interacting with mucin molecules and the mucus layer covering the mucosal epithelial surface to extend the dosage form's residence time at the site of absorption. For both systemic and local effects, numerous mucoadhesive drug delivery systems have been developed recently for the oral, buccal, nasal, rectal, and vaginal routes.

Utilising herbal and artificial polymer, mucoadhesive drug delivery is the way of managed drug released which lets for intimates contact between the polymers and the target tissue. Topical and local systems based on mucoadhesive have demonstrated improved absorption. Mucoadhesive drug delivery's large surface area and high blood flow allow for quick absorption and superior bioavailability.

By delivering drugs through the mucosa, one can circumvent the breakdown of gastrointestinal enzymes and the first-pass hepatic metabolism. Therefore, the distribution of an increasing number of high-molecular-weight sensitive compounds, such as oligonucleotides and peptides, may be facilitated by mucosal drug delivery systems. In this report, the aim is to provide detailed understanding of mucoadhesive drug delivery system.

### Advantages of Mucoadhesive Drug Delivery System:

Drugs demonstrate bypassing metabolism first, then increasing bioavailability.

- 2) Drug therapy can be easily delivered in an emergency situation.
- 3) Some drugs are not stable in acidic environment of stomach can be administered by buccal delivery.
- 4) Drug release for prolonged period of time.
- 5) The medication is absorbed in this system through passive diffusion.

### Limitations of Mucoadhesive Drug Delivery System:

- 1) Drug which not stable at buccal pH cannot be administered.
- 2) Drugs which have bitter taste or not pleasant taste or good or bother mucosa can't be administered.
- 3) Drug needed with little portion must be controlled.
- 4) Those medications which are consumed by active.

### Routes of mucoadhesive drug delivery systems:

1. Mucoadhesive drug delivery system includes:
2. Buccal and sublingual delivery system.
3. Nasal delivery system.

4. Ocular delivery system.
5. Vaginal and rectal delivery system
6. Gastrointestinal delivery system.

#### **Buccal and sublingual delivery system:**

The buccal cavity has a surface area of around 45 cm<sup>2</sup>, yet its accessibility makes it ideal for administering medicinal compounds. Delivery through this site avoids hepatic first-pass metabolism and also aids in local remedy of the oral infections. The buccal cavity offers low enzymatic activity. Moreover; it can be instantly discontinued in cases of toxicity by removing the dosage form. The sublingual mucosa is more permeable than the buccal mucosa, making it suitable for quick release formulations.

#### **2. Nasal drug delivery system:**

The nasal mucosa has a surface area of around 150-200 cm<sup>2</sup>, yet its residence time ranges between 10 and 30 minutes. The nasal cavity avoids first-pass because it has a highly vascularized surface area and blood conduits that lead straight from the nose into the systemic circulation. For immediate relief from nasal congestion, intranasal active substances in solution form including sympathomimetic vasoconstrictors are most effective.

#### **3. Ophthalmic drug delivery systems:**

The active pharmaceutical ingredient is quickly removed from the ocular cavity for a variety of reasons, including constant tear formation, blinking of the eyes, and lacrimal drainage, resulting in reduced bioavailability of the active ingredients, which can be avoided by administering the medicaments via ocular inserts or patches. Additionally, the eye has a limited storage capacity of approximately 30µl. To enhance retention time, use a variety of dosage forms such as liquid drops, gels, ointments, and solid ocular inserts. Another intriguing delivery technique is in situ gelling polymers, which undergo phase transitions as a result of ionic, pH, or temperature changes upon application.

#### **4. Vaginal and rectal drug delivery:**

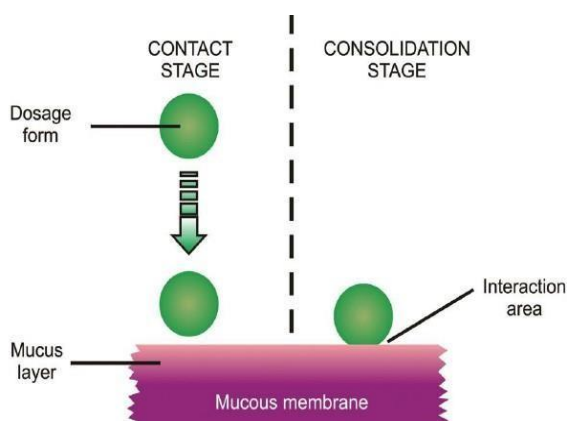
Vaginal and rectal routes have been investigated for the delivery of active drugs both locally and systemically. These routes have certain advantages due to their large surface area, abundant blood supply, relatively high permeability to numerous medicines, and self-insertion. It also eliminates hepatic first pass, which reduces hepatic adverse effects and prevents discomfort, tissue damage, and infection. Furthermore, residence duration in the vagina is significantly longer than in other absorption locations such as the rectum mucosa or the intestine.

#### **5. Gastrointestinal drug delivery:**

Gastrointestinal mucosa is also an important site for the development of mucoadhesive dosage forms for increasing GI transit time as well as bioavailability. The probable occurrence of local ulcers as a side effect due to the intimate contact of the dosage form with GIT mucosa for extended periods of time should not be neglected. The mucus turnover, that is, the unceasing production of mucous by the gastric mucosa to replace the lost mucous through peristaltic contractions and the dilution of the stomach content also limits the possibilities of mucoadhesion as a gastro retentive force.

### **MECHANISM OF MUCOADHESION**

The mucoadhesive dosage form must proliferate over the substrate to induct a close contact and hike the surface contact, assisting the diffusion of mucus chains. Attraction and repulsion forces arise and the attraction forces must dominate for a mucoadhesion to be successful. The two steps of the mucoadhesion process:



**Figure 1: The Two steps of the mucoadhesion process.**

**Step 1: Contact Stage:** When the polymer extends over the mucosal membrane to make intimate contact with the substrate, it begins to moisten and then swell. Polymer swells due to its attraction for water. In ocular, buccal, and vaginal formulations, the delivery system is mechanically attached to the membrane. In other circumstances, deposition is caused by the aerodynamics of the organ to which the formulation is delivered, such as via the nasal route. Peristaltic motions within the gastrointestinal tract can contribute to this interaction. If the particle moves to the mucosal surface, it will come into touch with repulsive and attractive forces. As a result, the particles must overcome the repulsive barrier before they can come into contact.

**Step 2: Interpenetration Stage:** The mucous membrane surface contains glycoproteins, which are high molecular weight polymers. In phase 2 of bio-adhesive bond formation, the mucosal and bio-adhesive polymer chains intertwine and entangle to produce adhesive bonds. The bond strength is determined by the degree of interpenetration between the two polymer groups. If both polymers have similar chemical structures, i.e. they are hydrophilic, a strong chemical connection is created.

**Step 3: Consolidation Stage:** During the consolidation phase, moisture activates mucoadhesive materials, causing molecules to separate and reassemble via weak hydrogen and Van der Waals connections. The consolidation stage is explained primarily by two theories: diffusion and dehydration. According to diffusion theory, mucoadhesive compounds and mucus glycoproteins interact by entangling their chains and establishing secondary connections. According to the notion of dehydration, as illustrated in figure 1. When two materials that easily gelify in an aqueous environment come into contact with mucus, the osmotic pressure differential causes it to dehydrate. Water is sucked into the formulation due to concentration gradient until the osmotic balance is reached, resulting in rise contact time.

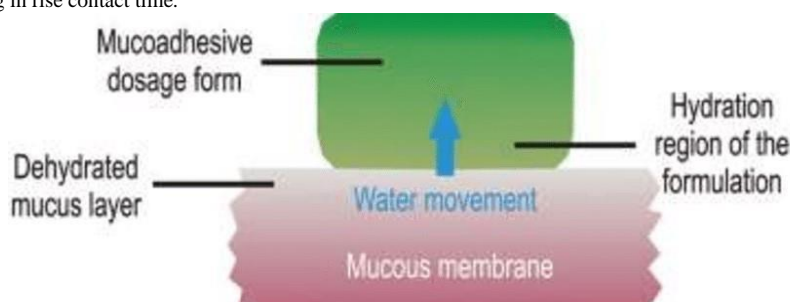


Figure 2: Dehydration Theory of Mucoadhesion.

**Theories of Mucoadhesion / Bonding Mechanism:** Six traditional theories have emerged from research on the performance of various materials and polymer-polymer adherence. Fig. 3 displays how various hypotheses are categorized. Mucoadhesion is greatly influenced by the contact angle and time of contact.

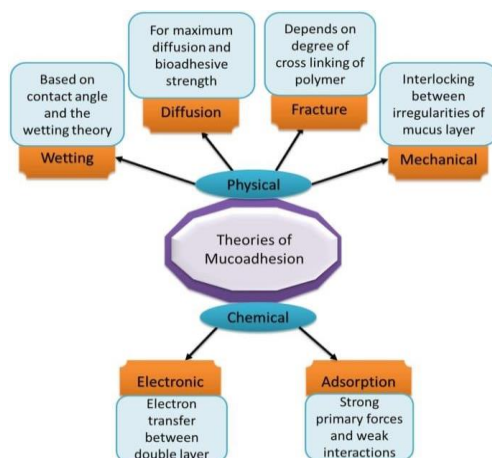


Figure 3: The Classification of Theory of Mucoadhesion.

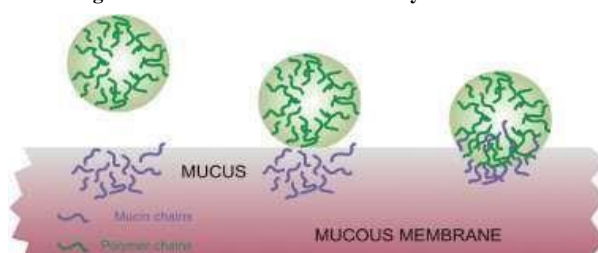


Figure 4: The Secondary interaction resulting from inter diffusion of polymer chains of bio adhesive device and of mucus.

**Wetting theory** : The contact angle is used to determine the affinity between the liquid systems and the mucous membrane. A Fundamentally, the affinity rises as the contact angle falls. A contact angle close to zero is required to ensure adequate spreadability. The spreadability coefficient, SAB, is determined by calculating the difference between the interfacial energy  $\gamma_{AB}$  and the surface energies  $\gamma_B$  and  $\gamma_A$ , as indicated in equation:

$$SAB = \gamma_B - \gamma_A - \gamma_{AB}$$

The work of adhesion, or WA, increases with the individual surface energy of the mucus and device in respect to the interfacial energy.

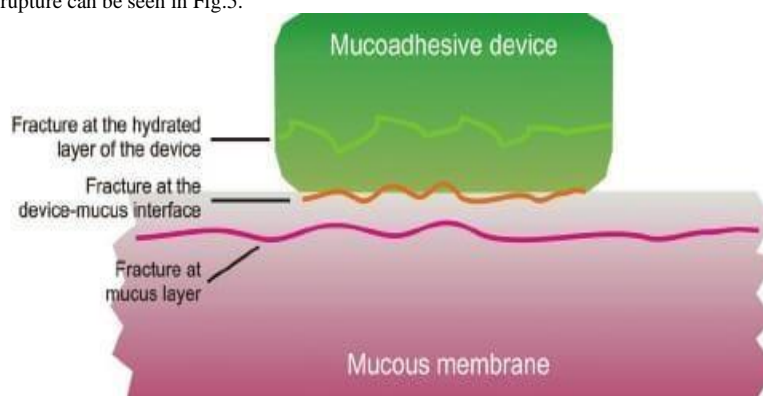
$$WA = \gamma_A + \gamma_B - \gamma_{AB}$$

**Diffusion theory**: The interpenetration and tangling of mucous and bioadhesive polymer chains is a phenomenon that can be explained by the diffusion theory. The degree of penetration rises with increased binding strength. The secondary interactions due to inter-diffusion can be seen in Fig. 4. The depth of interpenetration required to produce a firm bio adhesive bond lies in the range 0.2–0.5 $\mu$ m By using the following equation, one may determine the depth of polymer and mucin chain interpenetration:

$$\text{The interpenetration depth, } I = (tDb)^{1/2}$$

Where t = contact time and Db = diffusion coefficient of the mucoadhesive material in the mucus.

**Fracture theory**: This theory investigates the force required to separate the two surfaces once adhesion has been proven. It has been discovered that longer polyme network fibers or reduction in the degree of cross-linking within such system increase the work of feacture. This concepts connection to the Young's modulus of elasticity (E) facilitates the calculation of fracture strength ( $\sigma$ ) following the separation of two surfaces, the fracture energy ( $\epsilon$ ) and the critical crack length (L) through the following equation:  $\sigma = (E*\epsilon/L)^{1/2}$  The force, Sm, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, Fm, and the total surface area, A<sub>0</sub>, involved in the adhesive interaction: Sm= Fm/A<sub>0</sub>. The regions of mucoadhesive bond rupture can be seen in Fig.5.



**Figure 5: The regions of mucoadhesive bond rupture can occur**

**Mechanical theory**: According to mechanical theory, adhesion occurs when a mucoadhesive liquid fills the holes created by a rough surface. Imperfections enhance the interfacial surface available for interactions, improving energy dissipation. The intrinsic qualities of the formulation, as well as the context in which it is used, influence the mechanisms that govern mucoadhesion. Polymer intrinsic variables include molecular weight, concentration, and chain flexibility.

**Electronic theory** : The electronic theory is based on the notion that the target mucous membrane and the bioadhesive substance have different electronic surface properties. Based on this, when the surfaces come into contact, an electron transfer occurs to balance the Fermi levels, resulting in the creation of an electrical double layer at the bioadhesive-mucous membrane interface. The bioadhesive force is considered to exist due to the attractive forces acting on this double layer.

**Adsorption theory**: According to this idea, the bioadhesive relationship formed between an adhesive substrate and tissue is caused by weak Van der Waals forces and the formation of hydrogen bonds. For example, hydrogen bonds are the predominant interfacial forces in polymers containing carboxyl groups. These pressures are important in adhesive contact processes because, while they may not be particularly strong individually, several interactions can result in significant global adhesion.

### Factors Affecting Mucoadhesive Drug Delivery Systems

#### A) Polymer related factors

1. **Molecular weight**: The bio adhesive property of a linear polymer is proportional to its molecular weight. However, in the case of nonlinear polymers, bioadhesiveness may or may not be dependent on molecular weight. The minimal molecular weight necessary for effective bio adhesion is 100,000.
2. **Concentration of active polymer**: An appropriate concentration of active polymer is required. Beyond a certain optimal level, the adhesive power of a highly concentrated solution drops rapidly when the coiled molecules detach from the medium, limiting the length of chain available for permeation. When the polymer concentration is low, there are fewer penetrating polymer chains per unit volume of mucous, resulting in uneven polymer-mucous interactions

3. Flexibility of polymer chain: As a water-soluble polymer becomes cross-linked, the mobility of individual polymer chains decreases, reducing the effective chain length that can penetrate the mucus layer and therefore decreasing mucoadhesive strength. Flexibility is determined by the viscosity and diffusion coefficient. Higher polymer flexibility results in higher diffusion into the mucus network.
4. Spatial conformation: Despite its large molecular weight of approximately 2,000,000,000, dextrans' adhesive strength is comparable to that of PEG, which has a molecular weight 100 times lower. In contrast to linear polymer conformation, helical polymers can conceal many active groups responsible for adhesion, reducing the polymer's mucoadhesive strength.
5. Swelling: Mucoadhesive polymers require hydration to expand and produce a suitable macromolecular mesh of the necessary size, as well as to generate mobility in the polymer chain, hence increasing the entanglement process between polymer and mucin. Swelling is determined by polymer content, ionic strength, and the presence of water.
6. Cross linking density: The higher the cross linking density, the smaller the pore size, such that water diffuses into the polymer network at a slower pace, resulting in insufficient polymer swelling and less polymer penetration into the mucin.
7. Hydrogen bonding capacity: Polymers should have functional groups capable of forming hydrogen bonds, such as carboxylic and hydroxyl groups. Polyvinyl alcohol, hydroxylated methacrylate, polymethacrylic acid, and related co-polymers are polymers with high hydrogen bonding capacity.
8. Charge: Ionic polymers exhibit higher bioadhesive properties than nonionic polymers. Neutral cts have better mucoadhesive properties

#### **B) Environmental related:**

1. pH of polymer substrate interface: pH affects the surface charge of both polymers and mucus. The charge density of mucus varies with pH due to variations in dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone, which may influence adherence.
2. Applied strength: The pressure originally applied to the mucoadhesive tissue contact site can influence the depth of interpenetration. If strong pressure is applied for an extended amount of time, polymers become mucoadhesive despite having no favorable interactions with mucin.
3. Initial contact time : 1. Bioadhesive strength is proportional to the first contact time. It also controls the degree of swelling and interpenetration of polymers. It is a neutral or slightly alkaline medium with cationic polymers similar to chitosan that can be controlled for gastric systems.
4. Moistening : Moistening helps the mucoadhesive polymer to spread across the surface, forming a macromolecular network large enough for polymer and mucin molecules to penetrate and improve the mobility of polymer chains.
5. Presence of metal ions: Combining with charged polymer and/or mucous groups can lower the number of interaction sites and weaken mucoadhesive bonding strength.

#### **C) Physiological factors**

1. Mucin turnover : Mucin turnover: Frequent high mucin turnover is not advantageous, because:

**a.** Bioadhesive polymers have good bioadhesive properties, but their residence length is limited due to fast mucus turnover and detachment from the mucin layer.

**b.** High mucin turnover rates can lead to soluble mucin molecules that interact with the polymer and then the mucin layer. As a result, mucosal adhesion will be insufficient.

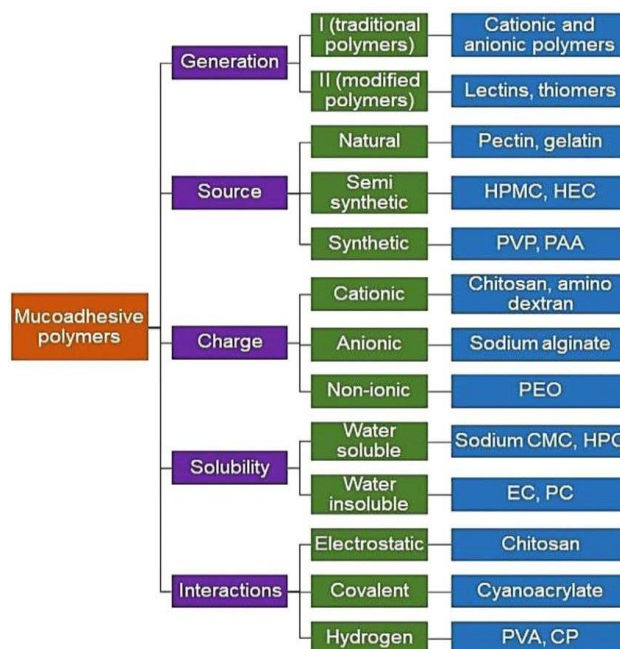
Disease state: Mucus' physicochemical properties can change during certain illness states, such as the common cold, stomach ulcers, ulcerative colitis, bacterial and fungal infections, and so on.

2. Renewal rate of mucosal cells: Renewal rate of mucosal cellifers considerably on the basis of types of mucosa. It limits the endurance of bio-adhesive systems on mucosal surfaces.

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## **Mucoadhesive Polymers**

Mucoadhesive polymers are either water soluble or insoluble, and they form swellable networks that are linked together by crosslinking agents. Fig.6: An overview of muco-adhesive polymers classifications based on different ways that is their source, charge, solubility and mechanism of bonding.



**Figure 6: An overview of muco-adhesive polymers classifications based on different ways i.e. source, charge, solubility and their mechanism of bonding.**

### Properties of an ideal mucoadhesive polymers:

1. The polymer and its degradation products should be non-toxic and not absorbed by the gastrointestinal tract.
2. The product should not cause irritation or abrasion to the mucous membrane.
3. It is preferable to build a strong non-covalent bond with the mucin-epithelial cell surface.
4. It should attach readily to most tissues and have some site specificity.
5. Surface tensions.
6. The medicine should be easily incorporated and released.
7. The polymer must not breakdown throughout storage or the dosage form's shelf life.
8. Ensure polymer costs are affordable to maintain competitiveness of produced dosage forms.
9. The muco-adhesive should have a good drug loading capability.
10. It should be flexible enough to penetrate the mucous membrane or tissue fissures.
11. Polymers should contain strong H-bonding groups (-OH, -COOH) for bonding with mucous membrane.
12. The dosage form should not degrade during its shelf life.

**PAA derivatives :** Derivatives of polyacrylic acid are acrylic acid polymers that have been cross-linked with divinyl glycol or polyalkenyl ether. Every primary particle is a network structure composed of polymer chains linked by cross connections.

Carbopol, a PAA derivative, swells up to 1000 times its original volume in water and gels at a pH of 4.0 to 6. The carboxylate group causes repulsion between the negative ions, causing the polymer to swell and therefore increasing the polymer's mucoadhesive strength.

**1. Chitosan:** Chitosan, a cationic semi-synthetic polymer, is obtained from chitin by deacetylation. Studies have shown that chitosan can enhance absorption of hydrophilic molecules by rearrangement of protein structures associated to the intercellular junctions. Chitosan binds to the mucosa via ionic bonds between the amino group and sialic acid residues.

**2. Collagen:** Collagen is a natural protein. This is a tri-helical molecule. Nineteen different types of collagen molecules have been identified. Collagen has increased biocompatibility, minimal antigenicity, and degrades less when implanted.

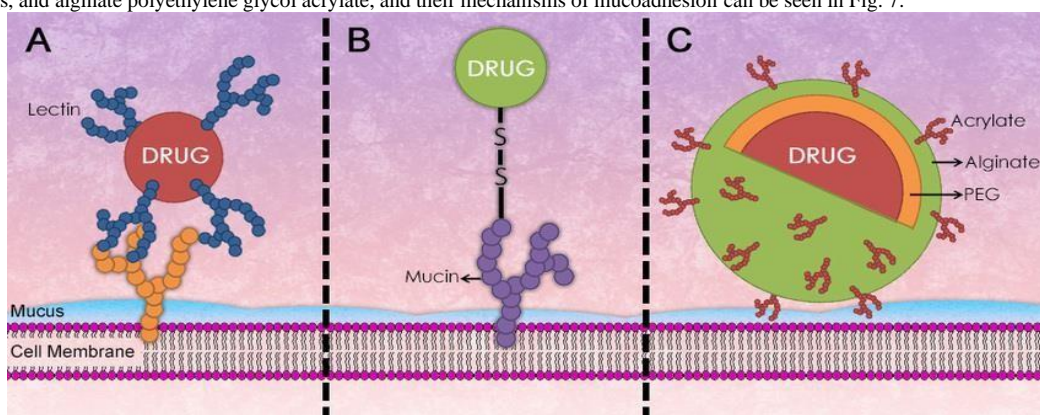
**3. Gelatin:** Gelatin is a naturally occurring protein that dissolves in water that typically obtained through the denaturation of collagen. It possesses minimal antigenicity, high biodegradability, and biocompatibility. It is employed as a supporting material for tissue engineering, gene transfer and cell culture, among other innovative uses. It is used as a support material for tissue engineering, gene transfer, and cell culture, among other novel applications.

**4. Albumin Serum:** MonoPEGylated albumin hydrogels were formed by conjugating albumin with polyethylene glycol and cross-linking it. These hydrogels can be considered drug-carrying tissue engineering scaffold materials.

**5. Alginate:** Alginate is a linear polysaccharide that occurs naturally. Alginate and its derivatives are used in medication delivery and tissue engineering because of their exceptional gelling and stabilizing properties, low toxicity, non-immunogenicity, water solubility, high viscosity in aqueous solutions, and low cost.

**6. Dextran:** Dextran is a linear natural polymer of glucose that is linked by a 1,6-glucopyranoside and has some branching of 1,3-linked side chains. Its high water solubility, biocompatibility, and biodegradability account for its expanding use in the pharmaceutical industry.

**7. Newer second generation polymers:** There are now newer polymers available with better mucoadhesive properties. These novel polymers, such as lectins, thiomers, and alginate polyethylene glycol acrylate, and their mechanisms of mucoadhesion can be seen in Fig. 7.



**Figure 7: Mechanisms of mucoadhesion by these novel polymers like lectins, thiomers and alginate poly ethylene glycol acrylate.**

**8. Lectins:** Lectins are natural proteins that aid in the identification of cells and proteins. They are structurally varied proteins and glycoproteins that bind to certain carbohydrate residues in a reversible manner. After adhering to a cell, they may remain on the cell's surface or undergo endocytosis. Thus, give site-specific and regulated medication release. The drawback is that they are immunogenic.

**9. Thiolated Polymers:**

Thiolated polymers are composed of water-soluble polymers such as de-acetylated gellan gum, chitosan, and polyacrylate. Thiomers mimic the normal production of mucus glycoproteins, which are covalently connected to the mucus layer via disulfide bonds. Thiol groups extend residence time, which increases covalent binding with mucus-containing cysteine. Because of their increased stiffness and crosslinking, disulphide bonds may alter how medications are released from the delivery mechanism.

## Evaluation Studies of Mucoadhesive Drug Delivery System

In vitro/ex vivo tests:

1. Methods of mucoadhesive strength measurement

A) Methods determining tensile strength

B) Falling liquid film method

C) Fluorescent probe method

D) Colloidal gold mucin conjugate method

2. Swelling index

3. Thumb method

4. Electrical conductance

5. Stability studies

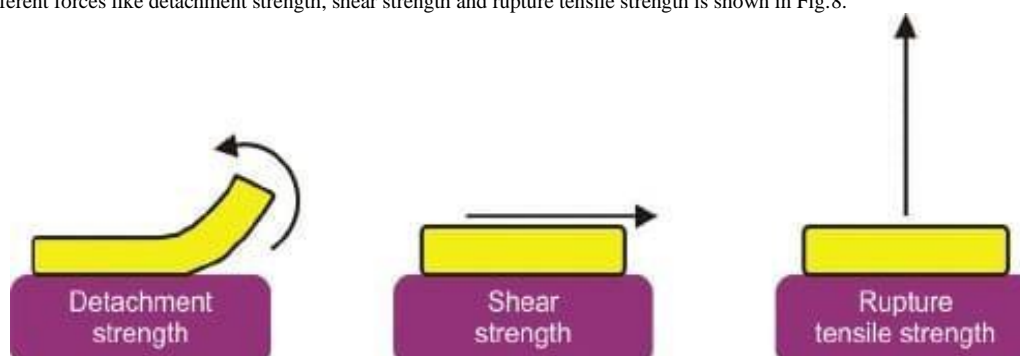
6. Measurement of the Residence Time/ In Vivo Techniques

A) GI Transit using Radio-Opaque Tablets

B) Gamma Scintigraphy Technique

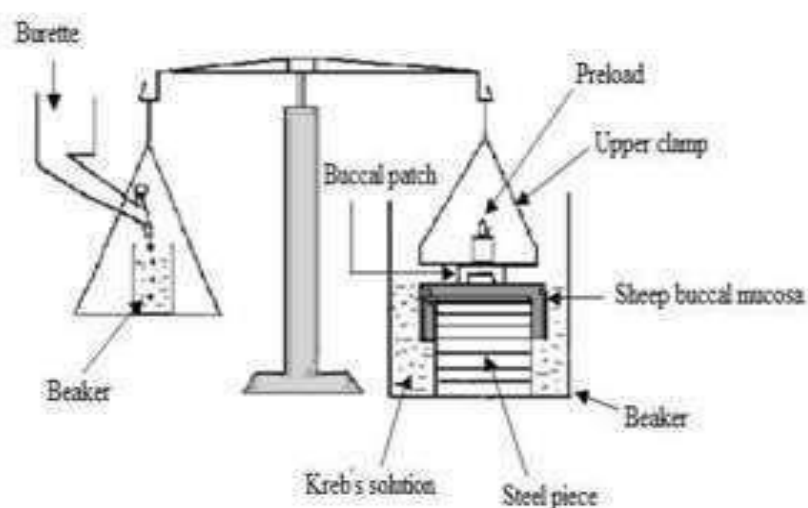
## 1 Methods of muco-adhesive strength measurement

**A) Methods determining tensile strength:** In tensile and shear tests, stress is evenly distributed across the adhesive joint, whereas in peel strength tests, stress is concentrated at the joint's edge. Thus, mechanical properties are measured using tensile and shear tests, whereas peel strength is used to measure peeling force. A texture profile analyzer, among other methods, can be used to quantify the removal of bioadhesive films from sectioned tissue in vitro. The different forces like detachment strength, shear strength and rupture tensile strength is shown in Fig.8.

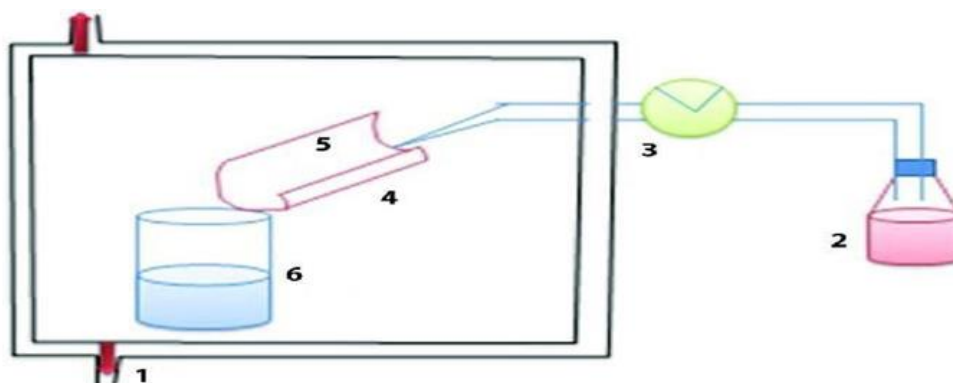


**Figure 8: The different forces like detachment strength, shear strength and rupture tensile strength**

Another method uses modified physical balance to measure mucoadhesive strength of the dosage form as shown in Fig.9. The apparatus is constructed from a modified double beam physical balance, with the right pan replaced with a glass slide with copper wire and additional weight to balance the weight on both sides of the pan.



**Figure 9: Measure of mucoadhesive strength.**



**Figure 10: Falling liquid film method.**



A teflon block of specific dimensions is kept in a beaker filled with buffer of 0.1N HCl and pH 1.2, which is then placed at the bottom of the right side of the balance. The stomach mucosa of goats or rats can be utilized as a model membrane, and buffer is used as a moistening aid. One side of the formulation is fixed to the glass slide of the right arm of the balance and then the beaker is slowly lifted until contact between goat mucosa and mucoadhesive dosage form is established.

A preload of 10 g is placed on the slide for 5 min (preload time) to establish adhesive bonding between mucoadhesive dosage form and the stomach mucosa. The preload and preload time are kept constant. At the end of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water is stopped when mucoadhesive dosage form is detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive dosage form from stomach mucosa is noted as mucoadhesive strength in grams.

$$\text{Force of Adhesion (N)} = (\text{Mucoadhesive strength} * 9.81)/1000$$

$$\text{Bond strength (N/m}^2\text{)} = \text{Force of adhesion (N)/ surface area of tablet (m}^2\text{)}.$$

- **Falling liquid film method:** It is a quantitative in situ approach that determines the percentage of particles retained on mucosal tissue. To summarize, a suspension of microspheres is allowed to run down a plastic slide at a 45° angle relative to the horizontal plane as shown in Figure 10.
- The difference between the applied and flowed microsphere amounts was used to estimate the adhered microsphere amount. The percentage of adhered microparticles was calculated as mucoadhesion (Shahi et al. Citation2011).
- **Fluorescent probe method:** Pyrene and fluorescein isothiocyanate are employed to mark the membrane lipid bilayer and membrane proteins, respectively. When mucoadhesive drugs are combined with cells, changes in fluorescence spectra are seen. This gives an indicator of polymer binding and its involvement in polymer adhesion.
- **Colloidal gold staining method:** The technique used red colloidal gold particles that were stabilized by adsorbed mucin molecules (mucin-gold conjugates). When bioadhesive hydrogels interacted with mucin-gold conjugates, the surface turned red. Thus, the interaction between them may be easily evaluated, either by measuring the intensity of red color on the hydrogel surface or by measuring the decrease in contraction of the conjugates from the absorbance changes at 525nm.

**2. Swelling index:** The amount of swelling is quantified in terms of % weight gained by the formulation. It is calculated using following formula:

$$\text{Swelling index (S.I)} = (W_t - W_o)/W_o$$

Where, S.I = Swelling index;  $W_t$  = Weight of tablet at time t;  $W_o$  = Weight of tablet before placing in the beaker.

**3. Thumb method:** This is used to qualitatively determine the polymer's peel adhesive strength, which is useful in the development of buccal adhesive delivery systems. The strain required to remove the thumb from the adhesive is assessed as a function of pressure and contact time.

**4. Electrical conductance:** The electrical conductivity of several semisolid mucoadhesive ointments was measured using a modified rotational viscometer, and it was discovered to be low in the presence of adhesive substance.

**5. Stability Studies:** Stability studies are the sole way to measure the success of an effective formulation. The goal of stability testing is to produce a stable product that ensures its safety and efficacy until the end of its shelf life under specified storage conditions and peak profiles. The ICH guidelines might be followed in this regard.

**6. Measurement of the Residence Time/ In Vivo Techniques:** Measuring the residence period of a mucoadhesive at the application site provides quantitative information about its mucoadhesion capabilities. The GI transit durations of numerous mucoadhesive preparations were investigated using radioisotopes and fluorescent labeling techniques.

**A) GI Transit using Radio-Opaque Tablets:** Encapsulated in mucoadhesive tablets to investigate the impact of mucoadhesive polymers on gastrointestinal transit time. The process is simple and involves using radio-opaque markers, such as barium sulfate.

**B) Gamma Scintigraphy Technique:** A study was conducted to document the amount and distribution of radioactivity in the vaginal canal after administering technetium-labeled hyaluronan-based biomaterial (HYAFF) tablets. After 12 hours of distribution to the stomach epithelium, it was revealed that the dry powder formulation of mucoadhesive-radio-tagged tablets based on HYAFF polymer retained more of the tablets than the necessary formulation.

## DOSAGE FORMS

### Tablets and Lozenges:



**Figure 11: Muco-adhesive tablets based on effervescence**

Tablets are oval, flat, and measure approximately 5-8 mm in diameter. Unlike regular tablets, muco-adhesive tablets do not cause substantial discomfort while drinking or speaking. These are used to deliver medications directly to the mucosal surface, either locally or throughout the body. These become softer, adhere to the mucosa, and remain there until the breakdown or release process is complete.

Even though mucoadhesive tablets are frequently used for controlled release drug administration, they have additional benefits when paired with a tablet. Its high surface-to-volume ratio, for example, allows for much closer contact with the mucosal layer, increased drug bioavailability, and effective absorption. The capacity to modify mucoadhesive tablets to adhere to any mucosal tissue, including stomach mucosa, allows for both systemic and localized controlled drug release.

**Sprays:** Oral sprays provide drug-containing water droplets directly to the mouth. The droplet velocity and size are monitored to ensure that they reach the oral cavity rather than the lungs. They may transport big substances, such as insulin, across the mouth mucosa. Glyceryltrinitrate is a tiny chemical that can be rapidly given over the sublingual oral mucosa via a spray to relieve angina. Generex Biotechnology Corporation has created a Rapid Mist spray that can transport big molecules such as insulin over the oral mucosa.

**Pastes:** Pastes have been utilized to provide controlled release in oral care formulations, as well as antibacterial compounds to promote healing of the extraction socket following tooth extractions in HIV patients. Mucoadhesive pastes containing methylprednisolone hydrogen succinate were described with carbomer polymer.

**Patches:** Several different patch systems that attach to the oral mucosa and administer medications have been developed. There are different types of oro - adhesive patches:

- a) Patches with a dissolvable matrix for drug delivery to the oral cavity: These patches act longer than solid forms like pills and lozenges, allowing for continuous medication release in the treatment of oral candidiasis and mucositis. They dissolve gently and completely while in use, leaving nothing to remove.
- b) Non-dissolvable backing patches systems: These provide systemic medication distribution and protection against saliva. The patches administer a regulated, concentrated amount of the medicine to the oral mucosa for 10-15 hours.

**Wafers/ Films:** Buccal disintegrating mucoadhesive films, because to their tiny size, thin structure, and flexibility, tend to have higher patient compliance than buccal tablets. BioDelivery Sciences International has used its BEMA (BioErodible Mucoadhesive) technology to create a line of buccal transmucosal films, including Onsolis, a buccal soluble film containing fentanyl citrate for the treatment of breakthrough pain in cancer patients who are already tolerant to opioids.

**Gels and ointments:** Semisolid dose formulations, such as gels and ointments, offer the benefit of being easily dispersed throughout the oral mucosa. The use of mucoadhesive formulations has overcome the gels' poor retention at the application site. Certain mucoadhesive polymers, such as sodium carboxymethylcellulose, carbopol, hyaluronic acid, and xanthan gum, change phase from liquid to semisolid. This modification increases the viscosity, resulting in a more continuous and regulated release of medicines.

### Recent innovations:

#### Gel Forming Liquids:

This type of formulation begins as a liquid and transitions to a viscoelastic gel in response to stimuli such as temperature, ionic strength, or pH. Carbomers become more viscous as pH increases. Gellan gum and alginate both gel when exposed to increasing ionic strength (especially  $\text{Ca}^{2+}$  ions). Poloxamers and smart hydrogel (Advanced medical solution) gel around body temperature.

**Slowly disintegrating buccal mucoadhesive plain tablet (SDBMPT):**

SDBMPTs are prepared by incorporating large amounts of HPC. For example, a tablet containing 20mg medication, 20mg HPC, 20mg CMC, and 60mg lactose is mixed and compressed with an 8mm diameter flat-faced die. The restriction is that it softens over time and loses shape, making long-term management of disintegration difficult.

**BCTS (Buccal Covered Tablet System):**

The S-DBMP-T system is enclosed by two polyethylene sheets. The lower sheet is made of adhesives, while the upper sheet has a hole to absorb water. It's a mechanism for getting drugs beyond the mucosal barrier. is less than pKa for a weak base, as proved by effervescent technology; as a result, ionization and solubilisation occur. Although various unique drug delivery systems are already used, including bio- and muco-adhesion strategies, there is potential to improve these approaches using other tactics such as nanoparticles, bacterial adhesion, changed amino acid sequence, and antibody mechanism. These potential novel strategies for mucoadhesion can be seen in Fig.12

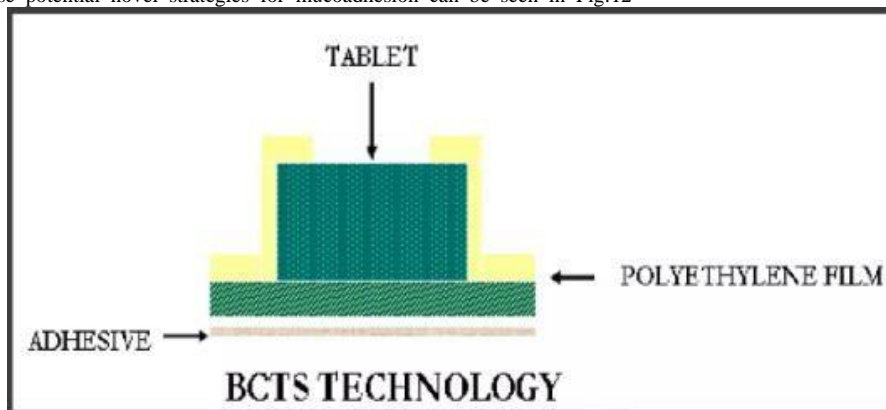


Figure12: Buccal Covered Tablet System.

**CONCLUSION**

This study aimed at focusing on development in mucoadhesive drug delivery system. The study discuss the mucoadhesive concepts, polymers used, theories and mechanisms of mucoadhesion, and factors affecting the mucoadhesive dosage forms. Based on the study available, it is identified that the majority of studies suggest mucoadhesive drugs delivery systems as the best substitute approaches for the traditional dosage forms to improve bioavailability of poorly soluble drugs and to prevent GIT degradation and first pass metabolism of some drugs.

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