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# A MUCOADHESIVE DRUG DELIVERY SYSTEM : REVIEW

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## ABSTRACT

The mucoadhesive system is one of the novel drug delivery technologies that can improve the effects of medications. The medicine is released at the action site by keeping this system adjacent to the mucous membrane, the absorption tissue, which enhances the effects both locally and systemically. There are several variations of the mucoadhesive drug delivery system. The main objective of the current study was to create a buccal mucoadhesive drug delivery system for perindopril. Solvent casting was utilized to manufacture perindopril buccal mucoadhesive patches, which were made of sodium carboxymethylcellulose (SCMC), polycarbophil, hydroxy propyl methylcellulose (HPMC), and sodium alginate as polymers for a longer release of perindopril. Glycerine and DMSO were used as plasticizers and penetration enhancers, respectively. Dichloromethane, methanol, and ethanol were used as solvents. The FTIR and DSC analysis results did not reveal any drug-polymer interaction. The level of medicine in the perindopril patches was found to be constant. The films displayed superb physical and mechanical attributes. The pH of the surface of each patch was within the range of salivary pH. Patches with solvent residue content are lower than permitted. During ex vivo permeation studies, it was discovered that the patches' non-Fickian diffusion mechanism permitted a longer release of the medication for up to 12 hours. The results of this study demonstrated the feasibility of developing a buccal medication delivery system for perindopril.

Keywords: polycarbophil, perindopril, mucoadhesion, ex vivo permeation, and non-Fickian diffusion.

# • INTRODUCTION

## MUCOADHESIVE DRUG DELIVERY SYSTEM :

Mucoadhesive drug delivery systems work by taking advantage of a certain polymer's bioadhesion feature, which becomes adhesive upon hydration and allows a drug to be delivered to a specific area of the bodyfor prolonged periods of time. An example of an interfacial phenomenon is bioadhesion, where two materials are held together by interfacial forces, at least one of which is biological. Adhesion between a polymer and a biological membrane is one example of how an artificial material and biological substrate can attach. The term "mucoadhesion" refers to a polymer that is affixed to the mucin layer of a mucosal tissue. [2]

## Bioadhesion and Mucoadhesion:

The term "bioadhesion" broadly refers to adhesive interactions with any material that is biological or derived from biology. Bioadhesion is used in drug delivery to create a bond between artificial or natural polymers and mucosal soft tissues. [3-6] When a bond is formed with a mucosal surface, the term "mucoadhesion" can be used. A state known as mucoadhesion is one in which interfacial forces enable two components, one from the biological source, to remain together for extended periods of time.[7] Three types of bioadhesion can be distinguished:

- **Adhesion between two distinct stages of life.**

Tissue growth, maintenance, and communication among cells all depend on cell adhesion. Cell behavior and function can be influenced by and governed by the mechanical interactions that occur between a cell and its extracellular matrix (ECM). Considering the crucial role that adhesion plays, there has been a great deal of interest in creating techniques for assessing and researching cell adhesion characteristics. The categories of cell adhesion research are cell adhesion attachment and cell adhesion detachment events. For many important purposes, the research of cell adhesion has been thoroughly examined via both events in the fields of cellular biology, biomedicine, and engineering. Cell adhesion attachment and detachment events could be further categorized using the cell population and single cell approach. Numerous methods have been employed to quantify cell adhesion. Developing tissue-on-a-chip and organ-on-a-chip in tissue engineering, studying the effects of biochemical treatments and environmental stimuli on cell adhesion, exploring the potential of drug treatments, studying cancer metastasis, and identifying the adhesion properties of normal and cancerous cells are just a few of the many fields of study to learn about cell signaling pathways. An overview of the many techniques for examining cell adhesion through attachment and detachment events was given in this review. [8,9]

- **A biological phase's adherence to an artificial substrate.**

Tissue engineering is an advanced, multidisciplinary scientific field that was established in response to the growing need for easily accessible, safe, and functional replacements for irreparably damaged tissues and organs. The original biomaterials were meant to be long-lasting (non-biodegradable) and "two-dimensional," which meant that cells could only adhere to their surface. Conversely, the new generation of biomaterials' so-called three-dimensional porous or scaffold-like architecture encourages cell attachment, growth, and differentiation within the material, which is subsequently progressively removed and replaced with fully functionally regenerated tissue. These materials are furnished with a specific range of bioactive molecules, including hormones, enzymes, synthetic cell behavior regulators, and ligands for cell adhesion receptors, which are integrated in particular concentrations and have the ability to regulate the processes involved in the adherence of a synthetic material to a living environment.

- **Adhesion of a synthetic substance to a biological phase.**

Complex coacervation enables important wet adhesion processes in both artificial and natural systems. Regretfully, their translations are severely hindered by the limited wet adhesion properties, lack of thermoresponsiveness, and poor biodegradability of currently available synthetic coacervate adhesives. Here, we report the development of a temperature-sensitive wet bioadhesive using surfactant and recombinant protein, with the help of supramolecular assembly and thoughtful protein design. The mechanical performance of the bioglue system can be actively adjusted thanks to thermal triggers. In cold conditions, the bioadhesive's adhesion strength was only about 50 kPa. Raising the temperature demonstrates the strength up to 600 kPa, which is significantly stronger than other biological counterparts. The production of coacervate, which enhances wet adhesion bonding, and the thermally induced phase transition of the engineered protein are most likely to blame for this.[2,3]

## Mucous Membrane

As illustrated in Fig. 1,[98] the mucosal membrane serves as the primary site of administration for bioadhesive devices. The lamina propria, the epithelium, and the muscularis, a smooth muscle layer, make up a mucosa's two or three layers. Their epithelial layer, which has mucus coating their surface, sets them apart. The glycoprotein known as mucin controls the mucus membrane's structure. Mucus in the mouth cavity can be less than 1 μm thick, while it can range from 50 to 500 μm in the stomach.[12-13]

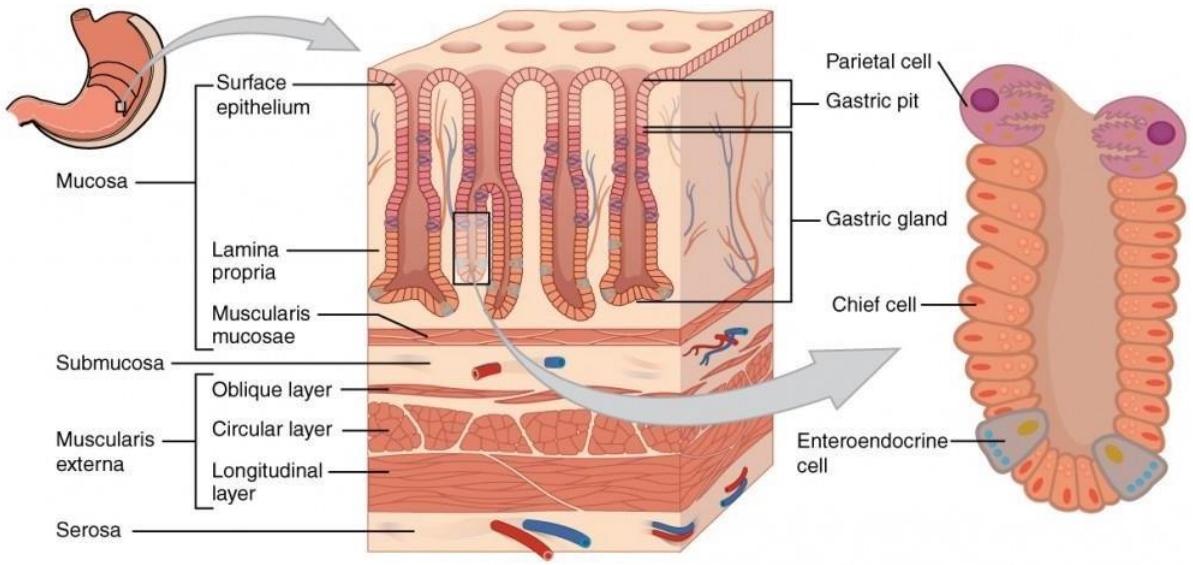


Fig. 1: Mucous membrane composition.

## The makeup of the mucous layer

The main ingredients of mucus are water, lipids, salts, and glycoproteins. The liquid has a high degree of hydrophilicity. The oligosaccharide units N-acetyl-Dglucosamine, L-fructose, D-galactose, sialic acid, and N-acetyl-D-galactosamine are associated with mucus glycoproteins, which are high molecular weight proteins.[14,15]

## The role of the mucous layer

Mucous membranes serve as barriers, secretory organs, and absorbers. The mucous layer's hydrophobicity makes it protective.

- Its strong bonding with the epithelial cell surface forms a continuous gel layer that aids in adhesion and influences the bioavailability of drugs by impeding their tissue absorption.[12]
- It plays a crucial role in keeping the mucosal membrane lubricated and moist.
- Mucus secreted by goblet cells, multicellular mucous glands, or both frequently covers them. In

order to prevent bacteria and foreign objects from entering the tissues and to facilitate theirexpulsion from the

body, mucus traps them.[14]

## MUCOADHESIVE DRUG DELIVERY SYSTEMS' ROUTES

Among the mucoadhesive drug delivery systems are:

1. A system of buccal and sublingual delivery;
2. Nasal administration apparatus;
3. Delivery system for eyes;

i. Rectal and vaginal delivery methods;

ii. Delivery system in the intestines.

### 1. Sublingual and buccal delivery method

Despite having a surface area of only 45 cm2, the buccal cavity is a preferred location for the delivery of therapeutic molecules due to its accessibility. Delivery via this site helps treat oral infections locally while avoiding hepatic first-pass metabolism. The buccal cavity has very little enzymatic activity. Moreover, in the event of toxicity, it can be stopped right away by changing the dosage form. The sublingual mucosa receives immediate release formulations because it is comparatively more permeable than the buccal mucosa.[12,16-20]

### 2. Nasal delivery system for drugs

The nasal mucosa is only present for a short period of time—roughly 10 to 30 minutes—despite having a surface area of 150 to 200 cm^2. Foreign particles induce increased activity of the mucociliary layer, which results in this brief period of time.[4] Due to its highly vascularized surface area and direct blood conduits from the nose into the systemic circulation, the nasal cavity avoids first-pass. The most effective use in this case is of the solution-based intranasal active ingredients, which contain sympathomimetic vasoconstrictors to provide rapid relief from nasal congestion.[12,18]

### 3. Drug delivery system for eyes

Due to a variety of factors, including continuous tear production, eye blinking, and lacrimal drainage, the active pharmaceutical ingredient is quickly removed from the ocular cavity. This reduces the active ingredient's bioavailability, which can be mitigated by administering the medication via ocular inserts or patches.[12,21] Furthermore, the eye's holding capacity is only roughly 30µl. To improve retention time, this issue can be resolved by utilizing a variety of dosage forms, such as liquid drops, gels, ointments, and solid ocular inserts. An additional intriguing delivery method involves in situ gelling polymers, which undergo a phase transition as a result of ionic, pH, or temperature changes following application. In vivo, mucoadhesive polymers would only stick to the mucous membrane of the conjunctiva.[12,18]

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**6. Rectal and vaginal drug administration**

It has been investigated to deliver the active agents both locally and systemically via the vaginal and rectal routes.[4] Because of their large surface area, strong blood supply, relatively high permeability to a wide range of drugs, and self-insertion, these routes have certain advantages. Additionally, it prevents pain, tissue damage, infection, and hepatic first-pass, which reduces hepatic side effects. Additionally, compared to other absorption sites like the mucosa of the rectum or intestine, the residence time in the vagina is significantly longer.[18]

**7. gastrointestinal drug administration**

The gastrointestinal mucosa is a crucial location for the creation of mucoadhesive dosage forms that improve both the bioavailability and the GI transit time. It is important to consider the possibility of local ulcers developing as a side effect as a result of the dosage form coming into close contact with the GIT mucosa over an extended period of time. Mucoadhesion as a gastro retentive force is further limited by mucus turnover, which is the continuous production of mucus by the gastric mucosa to replenish the lost mucous through peristaltic contractions and the dilution of the stomach content.[5,18]

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## • MUCOADHEDSIVE DRUG DELIVERY SYSTEM ADVANTAGES[3,35,39]

- The drug is easily administered, and it may be easier to stop therapy in an emergency.
- Extended periods of medication release.
- Drugs can be given to trauma and unconscious patients.
- Because the drug skips metabolism altogether, it has a high bioavailability.
- Some medications that are unstable in the stomach's acidic environment can be delivered buccal.

- Drug absorption takes place through passive diffusion.
- The high rate of absorption is caused by close contact with the surface of the absorbing membrane.
- Quick start of action
- Hepatic first-pass metabolism is circumvented.
- Dosage form administration is simple.
- Patients who are unconscious may receive it.
- Patient adherence is higher.
- This method can be used to administer medications that are unstable in an acidic environment and are broken down in an alkaline or enzymatic environment in the intestine.
- It works with a passive drug absorption system that doesn't need to be activated.
- Increases the dosage form's duration of residence at the absorption site, which boosts its bioavailability.
- Quick absorption due to high blood flow rates and a large blood supply.
- The git's acidic environment prevents the drug from degrading.
- Higher levels of patient adherence.

## • LIMITATIONS OF MUCOADHESIVE DRUG DELIVERY SYSTEM[3,35,39]

- Medication that is unstable at buccal pH cannot be given.
- This route cannot be used to administer a medication that causes irritation, has an unpleasant and bitter taste, or has an offensive odor.
- Only via this route can a drug with a small quantity or dose be administered.
- This method can be used to administer medications that must only be absorbed by passivediffusion.
- Eating and drinking should be avoided.
- When compared to the sublingual route, the buccal mucosa has a lower permeability.
- Saliva swallowing may also result in the loss of dissolved or suspended medication.

## • THE MODE OF MUCOADHESION

To induce a close contact and increase the surface contact, the mucoadhesive dosage form needs to spreadover the substrate and aid in the diffusion of mucus chains.[31, 32] In order for mucoadhesion to be successful, attraction forces must outweigh repulsion forces. Fig. 2 depicts the first two stages, or the contact and consolidation stages.[24]

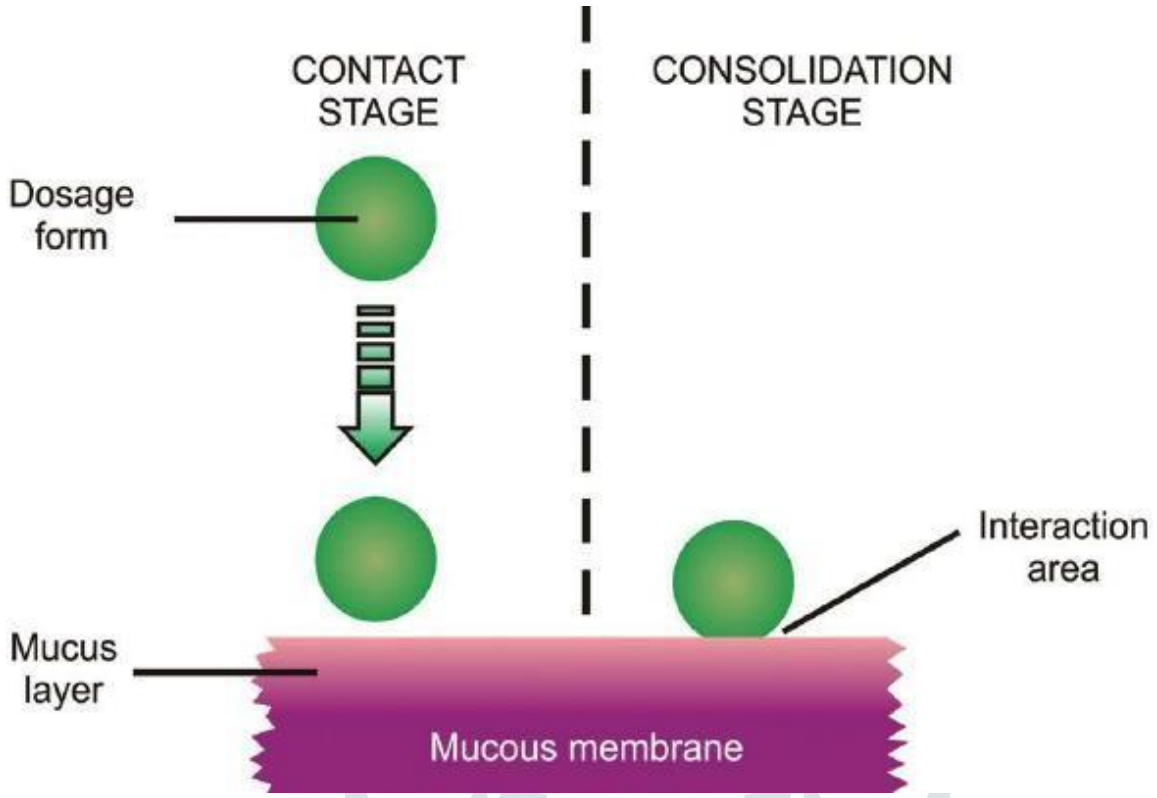


Fig. 2 : The two steps of the mucoadhesion process .

## Step 1: Contact Stage

When the polymer spreads across the mucosal membrane to make intimate contact with the substrate, the wetting and swelling step follow. Because the constituents of polymer have a preference for water, polymer swells. [24,30]The delivery system in vaginal, buccal, or ocular formulations is mechanically bonded to the membrane. In other situations, such as when the formulation is administered via the nasal route, the deposition is caused by the aerodynamics of the organ. Peristalstic movements within the gastrointestinal tract may facilitate this contact.[27,28] The particle encounters both repulsive and attractive forces if it moves toward the mucous surface. In order for contact to occur, the particles must overcome the repulsive barrier.[3]

## Step 2: Interpenetration Stage

Glycoproteins are high molecular weight polymers that are present on the surface of mucous membranes. The mucosal and bioadhesive polymer chains intertwine and form adhesive bonds in the second step of the bioadhesive bond formation process. The degree of interpenetration between the two polymer groups determines the bond strength. A strong chemical bond forms if the two polymers have similar chemical structures, that is, if they are both hydrophilic.[5,34]

## Step 3: Consolidation Stage

The mucoadhesive molecules break free and re-bond via weak Van der Waals and hydrogen bonds during the consolidation step, which is the activation of mucoadhesive materials in the presence of moisture. Diffusion theory and dehydration theory are essentially the two theories that explain consolidation step. By entwining

their chains and creating secondary bonds, the mucoadhesive materials and the mucus's glycoproteins interact with one another, according to the diffusion theory. Placing materials that readily gelify in an aqueous environment in contact with mucus can lead to its dehydration because of the osmotic pressure difference, as demonstrated by the theory of dehydration in Fig. 3. Because of the concentration gradient, water is pulled into the formulation until the osmotic balance is reached.[25,29]

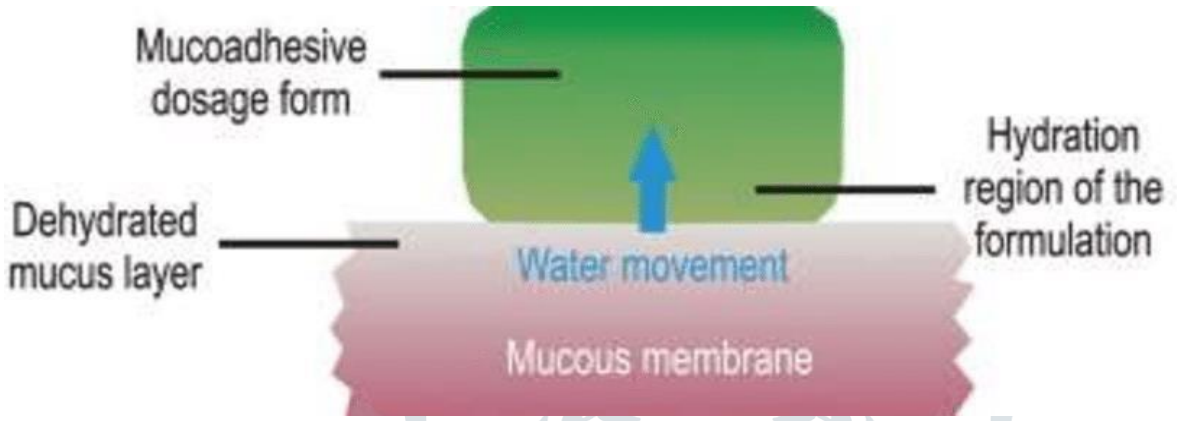


Fig. 3 : Dehydration theory of mucoadhesion.[24]

- **Theories of Mucoadhesion / Bonding Mechanism**

Six conventional theories have been developed as a result of research on the properties of various materials and the adherence of polymers to one another. Fig. 4 depicts how these theories are categorized. As seen in Fig. 5, the contact angle and duration of contact are important factors in mucoadhesion.

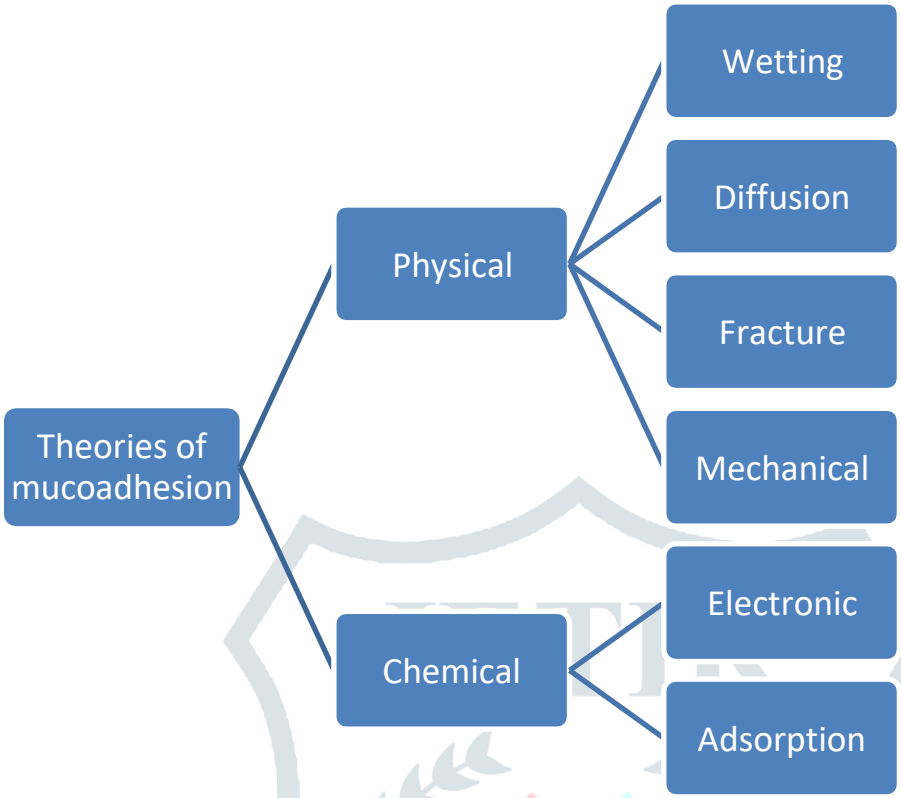


Fig. 4 : Classification of theories of Mucoadhesion

## Wetting theory

Finding the contact angle yields the affinity between the liquid systems and the mucous membrane.15 In general, the affinity increases as the contact angle decreases. For there to be enough spreadability, the contact angle needs to be very close to zero. An illustrative diagram illustrating the impact of the dosage form's and mucous membrane's contact angle is presented in Figure 6.

Equation: The spreadability coefficient (SAB) can be calculated by calculating the difference between the interfacial energy (γAB) and the surface energies (γB and γA).

SAB is equal to γB-γA-γAB.

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

WAB is equal to γA + γB - γAB.

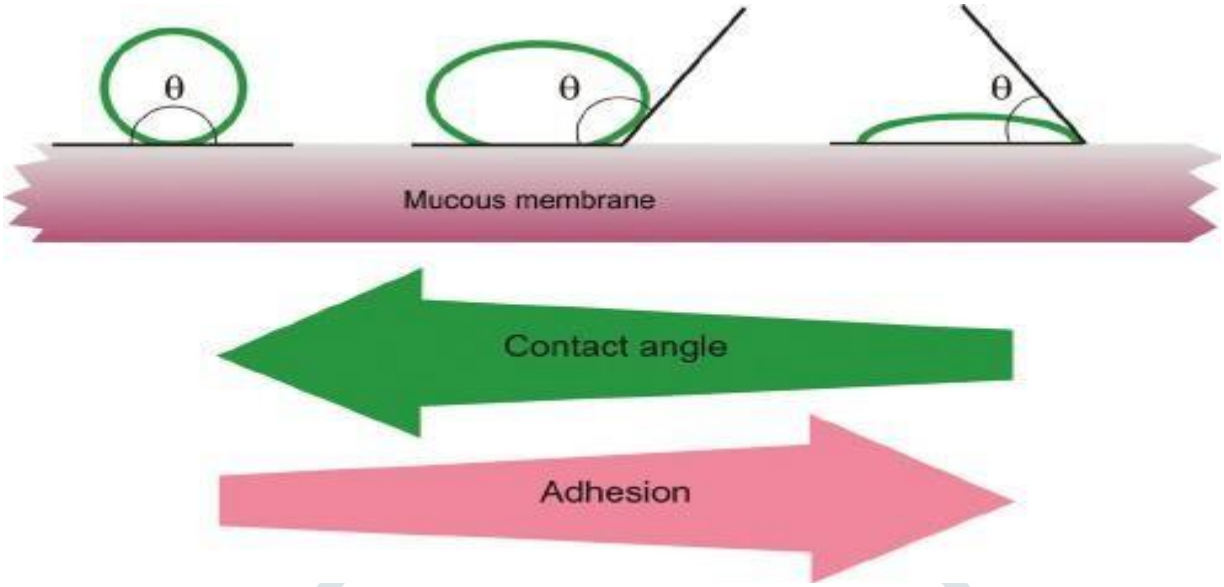


Fig. 5 : Influence of contact angle between device and mucous membrane on bioadhesion .[24]

## Diffusion theory

The phenomenon of the interpenetration and entanglement of the mucous and bioadhesive polymer chains is explained by the diffusion theory. The degree of penetration rises as the bond strength does. Fig. 6 illustrates the secondary interactions brought on by inter-diffusion. [24,25] The degree of penetration is dependent on the following variables: mobility, contact time, mucoadhesive chain nature, flexibility of the polymer chains, and diffusion coefficient. A strong bioadhesive bond can only be formed at a depth of

interpenetration between 0.2 and 0.5 μm. The following formula can be used to determine the depth of polymer and mucin chain interpenetration: I= (tDb)1/2, the interpenetration depth

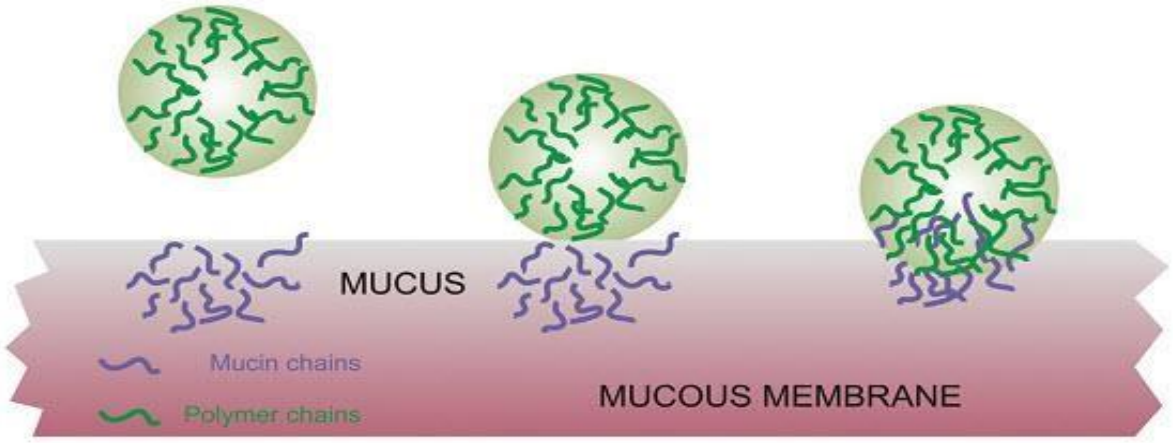


Fig. 6 : The secondary interactions resulting from inter-diffusion of polymer chains of bioadhesive deviceand of mucus.

## Fracture theory

The force required to separate two surfaces once adhesion has been established is examined by this theory.[24,26]It has been discovered that longer polymer network fibers or a reduction in the degree of cross-linking within such a system increase the work of fracture.[15,25] This idea helps with the measurement of fracture strength (σ) following the separation of two surfaces by relating it to the critical crack length (L),the

fracture energy (ε), and the Young's modulus of elasticity (E) using the following equation: σ=(E*ε/L)Half a

In tests of resistance to rupture, the force, Sm, is commonly determined by dividing the maximal detachment force, Fm, by the total surface area, A0, that is engaged in the adhesive interaction:

Sm = Fm / Ao

Fig. 7 shows the regions where the mucoadhesive bond ruptured.[40,41]

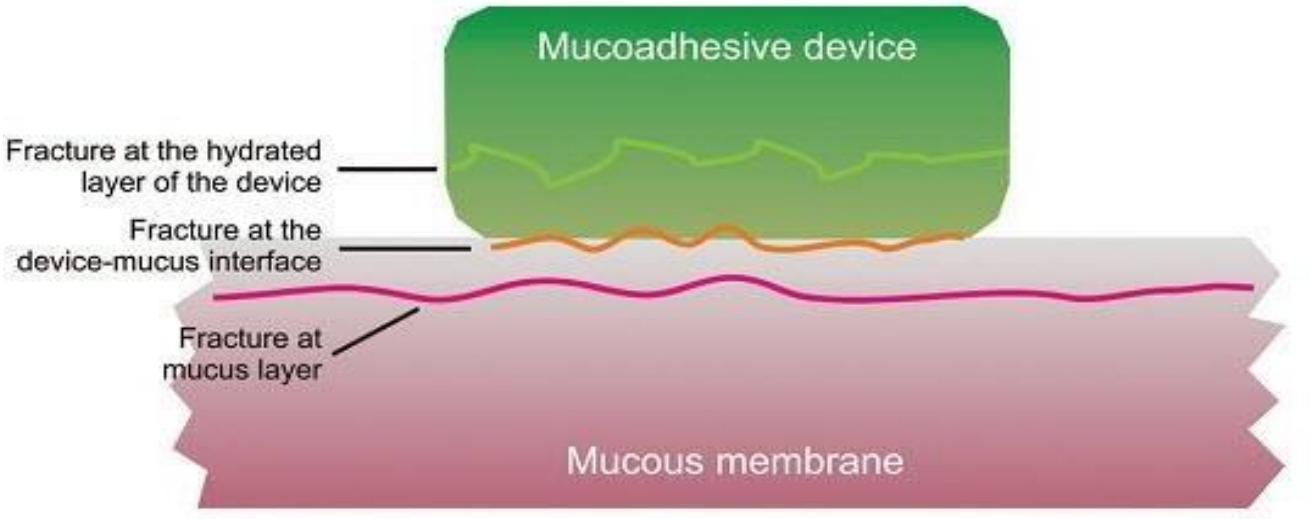


Fig. 7 : Regions of mucoadhesive bond rupture can occur .[24]

## Mechanical theory

According to mechanical theory, adhesion results from a mucoadhesive liquid filling in the voids left by a rough surface. Energy dissipation is improved by the irregularities because they increase the interfacial area that is available for interactions. The inherent characteristics of the formulation and the setting in which it is used also influence the mechanisms governing mucoadhesion. The polymer's molecular weight, concentration, and chain flexibility are considered intrinsic factors. Mucoadhesion for linear polymers is directly correlated with molecular weight; however, this is not the case for non-linear polymers.

## Electronic theory

The electronic theory is predicated on the idea that the target mucous membrane and the bioadhesive material possess a variety of electronic surface characteristics.][3,40]Accordingly, there is an electron transferto balance the Fermi levels when the surfaces come into contact with one another. This is caused by the creation of an electrical double layer at the interface between the mucous membrane and the bioadhesive. Because of the attractive forces across this double layer, it is assumed that the bioadhesive force exists.[44]

## Adsorption theory

According to this theory, weak Van der Waals forces and hydrogen bond formation are what cause the bioadhesive bond to form between an adhesive substrate and the tissue. Ionic bonding, covalent bonding, hydrogen bonding, Van der Waals bonding, and hydrophobic bonding are some examples of mucoadhesive interactions.[5,24] Hydrogen bonds, for instance, predominate as interfacial forces in polymers containing

carboxyl groups. Although these forces may be weak on their own, a large number of interactions can produce a strong global adhesion, which makes them crucial to the adhesive interaction phenomena.[25]

## • FACTORS AFFECTING MUCOADHESIVE DRUG DELIVERY SYSTEM

### A) Polymer related factors

### 1) Molecular weight-

The bio adhesive property of a linear polymer is directly correlated with its molecular weight. However, in the case of nonlinear polymers, molecular weight may or may not influence the bioadhesiveness. For bio adhesion to be successful, the molecular weight must be at least 100,000.[4]

### 2) Concentration of active polymer-

A minimum amount of active polymer is needed. Beyond a certain optimal point in a remarkably concentrated system, the adhesive strength sharply decreases as the coiled molecules separate from the medium, limiting the amount of chain length that can permeate. The number of penetrating polymer chains per unit volume of mucous is low and the interaction between polymers and mucous becomes erratic at very low polymer concentrations.[26]

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### 5) Flexibility of polymer chain-

The individual polymer chain mobility decreases with cross-linking of water soluble polymers, thereby reducing the effective chain length that can permeate the mucus layer and lowering the mucoadhesive strength. Diffusion coefficient and viscosity both affect flexibility. More polymer flexibility results in increased mucus network diffusion. [25]

### 6) Spatial conformation–

Despite having high molecular weight of about 2,00,00,000, the adhesive strength of dextrans is similar to that of PEG whose molecular weight is 100 times lesser. The helical, in contrast to linear conformation of polymers, may hide many active groups, which are responsible for adhesion, thus decreasing the mucoadhesive strength of the polymer.[25,46]

### 1) Swelling-

In order to increase the entanglement process between the polymer and mucin, mucoadhesive polymer needs to be hydrated in order to expand and form a suitable macromolecular mesh of the desired size. Hydration also causes the polymer chain to become more mobile. The concentration of polymers, ionic strength, and water content all affect swelling. Bioadhesion is a dynamic process that reaches its peak in vitro when the water content is ideal.[45]

### 2) Cross linking density–

A polymer network's three primary and interconnected structural parameters are the density of cross linking, the average pore size, and the average number molecular weight of the cross-linked polymers. Smaller pore sizes result from higher cross linking densities, which slow down the rate at which water diffuses into the polymer network. This causes insufficient polymer swelling, which lowers the amount of polymer that penetrates the mucin. [40,26]

### 3) Hydrogen bonding capacity-

Functional groups that can form hydrogen bonds, such as carboxylic and hydroxyl groups, should be present in the polymers. Good hydrogen bonding capacity is exhibited by polymers such as polyvinyl alcohol, hydroxylated methacrylate, poly methacrylic acid, and all of their co-polymers.[45]

### 4) Charge-

Ionic polymers always have a greater level of bioadhesiveness than non-ionic ones. A cationic polymer such as chitosan exhibits superior mucoadhesive properties in neutral or slightly alkaline media.[25,36]

## C) Environmental related

### 1) pH of polymer substrate interface-

The surface charge of polymers and mucus are both impacted by pH. Because of variations in the dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone, which may affect adhesion, mucus will have a different charge density depending on pH.

### 1) Applied strength-

The depth of interpenetration may vary depending on the initial pressure exerted on the mucoadhesive tissue contact site. If high pressure is applied for a sufficient amount of time, polymers that do not have attractive interactions with mucin become mucoadhesive.[27,40]

### 2) Initial contact time –

The initial contact time directly relates to the bioadhesive strength. It also establishes the degree of polymer swelling and penetration. Gastric systems are unable to regulate it.[40]

### 3) Moistening –

When the mucoadhesive polymer is moistened, it spreads across the surface and forms a large enough macromolecular network to permit the penetration of mucin molecules and polymer, increasing the mobility of polymer chains.[37,38]

## D)Physiological factors

### 1) Mucin turnover

Frequently occurring high mucin turnover is not advantageous for the following reasons: a. Despite the polymer's good bioadhesive properties, the high mucin turnover shortens the time the polymer remains in the mucin layer after detaching.

b. A high mucin turnover rate can result in soluble mucin molecules, which first interact with the polymer and then the mucin layer. There won't be enough mucoadhesion as a result.[27]

### 2) Disease state-

In certain disease states, such as the common cold, gastric ulcers, ulcerative colitis, bacterial and fungal infections, etc., the physicochemical properties of mucus may change.[31]

### 1) Renewal rate of mucosal cells–

The rate at which mucosal cells renew varies greatly depending on the type of mucosa. It restricts how long bioadhesive systems on mucosal surfaces can last.[22]

- **Mucoadhesive Polymers**

Mucoadhesive polymers are networks of swellable, cross-linking agents-connected polymers that are either water soluble or insoluble.[32]Fig. 8 displays several classes of mucoadhesive polymers.

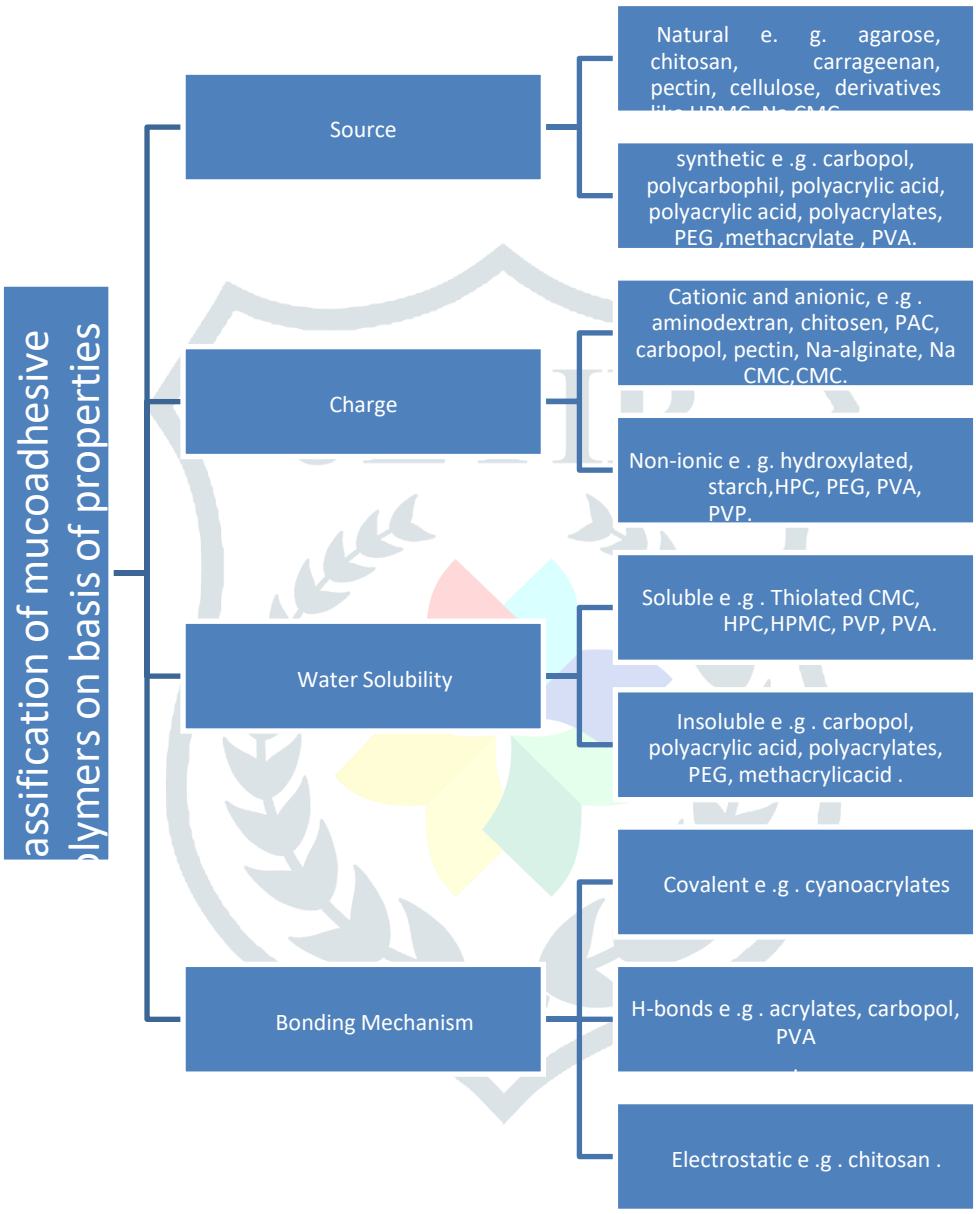


Fig . 8 : An outline of the various classifications of mucoadhesive polymers, such as those based onsource, charge, solubility, and bonding mechanism.

## Properties of an ideal mucoadhesive polymer[11,25,25,34]

- The polymer must have a high viscosity, the right amount of cross linking, and the right spatial conformation. It must also be nontoxic, non-irritating, and non-absorbable from the GIT.
- It ought to stick to most tissues quickly and be site-specific.
- It cannot deteriorate while the dosage form is on the shelf.
- The polymer must contain strong H-bonding groups (-OH, -COOH) in order to bond with the mucousmembrane.
- The polymer should have a large molecular weight and strong anionic charges.
- It must have enough flexibility to pass through tissue fissures or the mucous membrane.
- It should possess the proper surface tension properties that are appropriate for moisturizing the mucous surface.

## PAA derivatives

Derivatives of polyacrylic acid are acrylic acid polymers that have been cross-linked using divinyl glycol or polyalkenyl ethers.[25,57] They come from primary polymer particles with a diameter of one to five microns. Every main particle is a network structure made up of polymer chains connected by cross links.[40] A derivative of PAA, carbopol swells in water up to 1000 times its original volume and gels at pH values between 4.0 and 6.0. Repulsion between the negative charges is caused by the carboxylate group, which causes the polymer to swell and increase its mucoadhesive strength.[30,35]

## Chitosan

By deacetylating chitin, chitosan, a cationic semi-synthetic polymer, is produced.[28] Research findings indicate that chitosan can improve the uptake of hydrophilic molecules by reorganizing protein structures linked to intercellular junctions. Ionic bonds between the amino group and sialic acid residues allow chitosan to adhere to the mucosa. Because chitosan is linear, the polymer chain is more flexible.[40]

## Collagen

One of nature's proteins is collagen.[38,40] It is a molecule with three helices.[38] Collagen molecules are classified into nineteen different types. Collagen exhibits enhanced biocompatibility, minimal antigenicity, and reduced degradation upon implantation.

## Gelatin

Collagen is typically denaturated to produce gelatin, a naturally occurring protein that is soluble in water.[70] It is lowly antigenic, biodegradable, and biocompatible. It serves as a scaffold for cell culture, gene delivery, and more recently, tissue engineering. Zero order release of biologically active agents, including drugs, peptides, and proteins, is possible with gelatin-based systems. Bioactive substances can be ensnared in pegylated liposome-gelatin gel.[31]

## Albumin

To create mono PEGylated albumin hydrogels, serum albumin was coupled to polyethylene glycol and then cross-linked. It is possible to evaluate these hydrogels as scaffold materials for drug delivery in tissue engineering.[40]

## Alginate

One type of linear polysaccharide that occurs naturally is alginate. Because of its improved biocompatibility, biodegradability, low toxicity, non-immunogenicity, water solubility, relatively low cost, better gelling properties, stabilizing properties, and high viscosity in aqueous solutions, alginate and its derivatives are used for drug delivery and tissue engineering applications.[33-39]

## Dextran

Dextran is a naturally occurring linear glucose polymer that is partially branching of 1,3 cross-linked side chains and cross-linked by a 1,6-glucopyranoside. Because of its excellent water solubility, biocompatibility, and biodegradability, it is finding more and more uses in the pharmaceutical industry.[20,23]

## Newer second generation polymers

There are now newer polymers available with improved mucoadhesive qualities. Figure 9 illustrates the mechanisms of mucoadhesion by these novel polymers, such as lectins, thiomers, and alginate poly ethylene glycol acrylate.

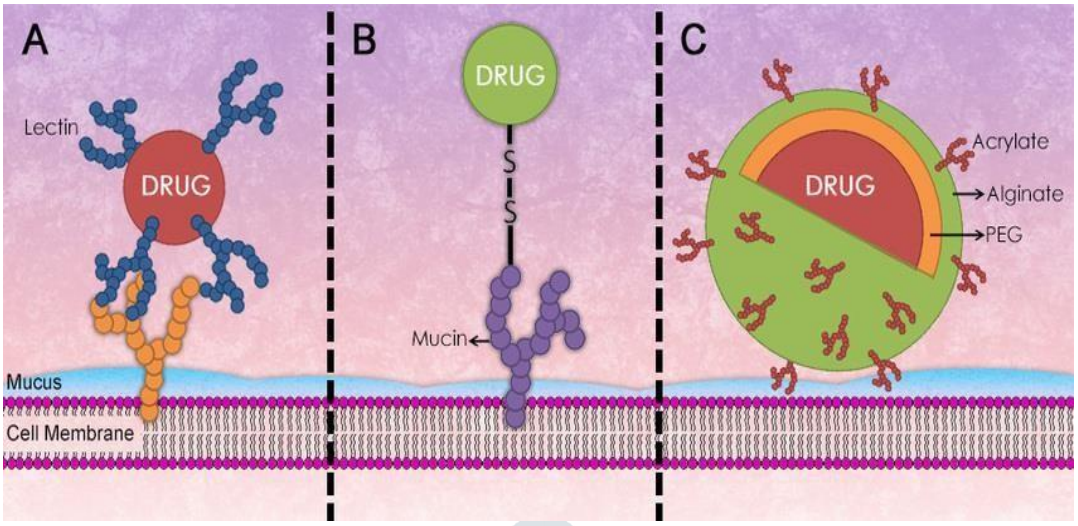


Fig. 9: The mechanisms underlying mucoadhesion by lectins, thiomers, and alinate poly ethylene glycolacrylate are as follows in fig.[18]

Their advantages are: [5,6]

- The so-called cytoadhesiveness, which is site specific.
- Unaffected by high turnover of mucus.
- Drug targeting.

**Lectins**

Natural proteins called lectins are helpful for protein and cell biorecognition.These are glycoproteins and proteins with different structural patterns that bind to particular carbohydrate residues in a reversible manner. These may remain on the cell's surface after binding to it or they may undergo endocytosis. thereby enabling controlled and site-specific drug release. They have the drawback of being immunogenic.[25]

**Thiolated Polymers**

Water soluble polymers such as polyacrylates, chitosan, or deacetylated gallan gum are the source of thiolated polymers. The mucus gel layer is created when disulphide bonds are formed between polymers and the cysteine-rich domains of mucus glycoproteins, either through thiol or disulphide exchange reactions or simple oxidation. Thiomers mimic the way that secreted mucus glycoproteins form disulphide bonds to form covalent bonds within the mucus layer.[35] Thiol groups increase the residence time, which encourages covalent bonding with the cysteine found in mucus. The disulphide bonds' increased rigidity and cross-linking may potentially modify the way drugs are released from the delivery system.

Water Soluble Resins (WSR)

One of the water soluble polymers that hydrates the fastest in pharmaceutical systems is POLYOXTM. These high molecular weight polyethylene oxide homo polymers can be made into tablets, films, gels, microcapsules, syrups, and other forms. They are also water soluble, biocompatible, and non-toxic.[36]

- **Evaluation Studies of Mucoadhesive Drug Delivery System**

In vitro/ex vivo tests:

1. Methods of mucoadhesive strength measurement.

A. Tensile strength determination techniques

B. The method of falling liquid film

C. The fluorescent probe approach

D. Gold mucin conjugate colloidal technique

2. Swelling index
3. Thumb method
4. Electrical conductance
5. Stability studies
6. Measurement of the Residence Time/ In Vivo Technique

A. GI Transit using Radio-Opaque Tablets

B. Gamma Scintigraphy Technique

C.

## Methods of mucoadhesive strength measurement

### A)Methods determining tensile strength

In tensile and shear experiments, the adhesive joint experiences a uniform distribution of stress, whereas in peel strength experiments, the stress is concentrated at the joint's edge. As a result, tensile and shear measurements are used to determine mechanical properties, and peel strength is used to determine peeling force. One tool for determining the force needed to remove bioadhesive films from tissue slices in vitro is the texture profile analyzer.[3,4] This was accomplished by testing the force needed to extract the formulation from a model membrane composed of a disc of mucin using a segment of animal mucous membrane.

The low sliding platform, which is also utilized to measure peel strength, is paired with the texture analyzer, which runs in tensile test mode. The animal skin was placed on a movable platform, and then the bioadhesive film was placed on top of it. To measure the peel strength, the film was subsequently pulled vertically. Figure 10 displays the various forces, including rupture tensile strength, shear strength, and detachment strength.

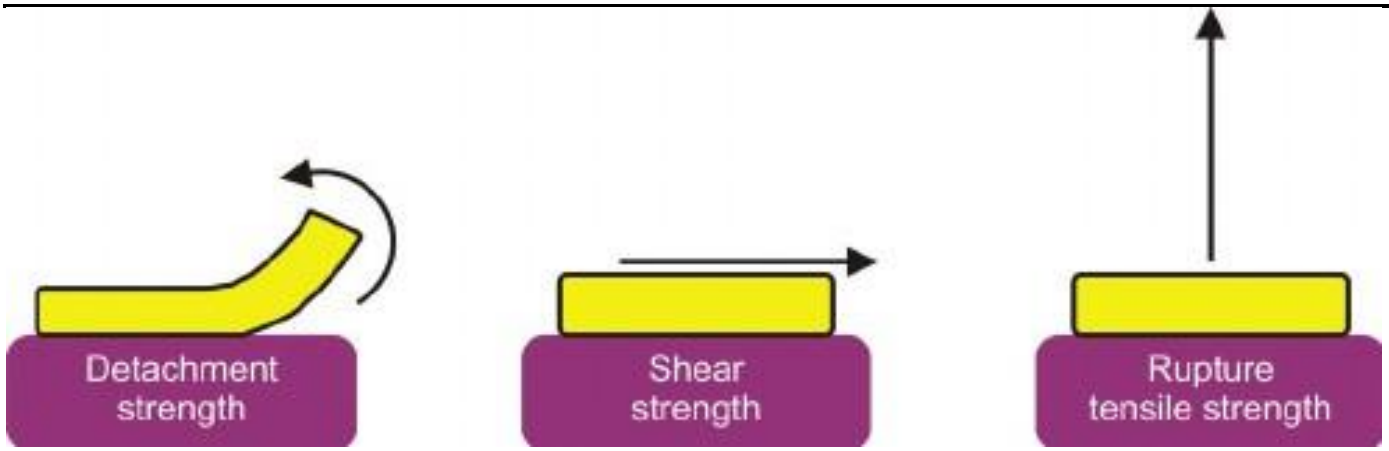


Fig. 10: Different forces evaluated in mucoadhesion test.[24]

As seen in Fig. 11, an alternative technique measures the dosage form's mucoadhesive strength using modified physical balance. To equalize the weight on both sides of the pan, a glass slide with copper wire and extra weight is used in place of the right pan in this modified double beam physical balance apparatus.

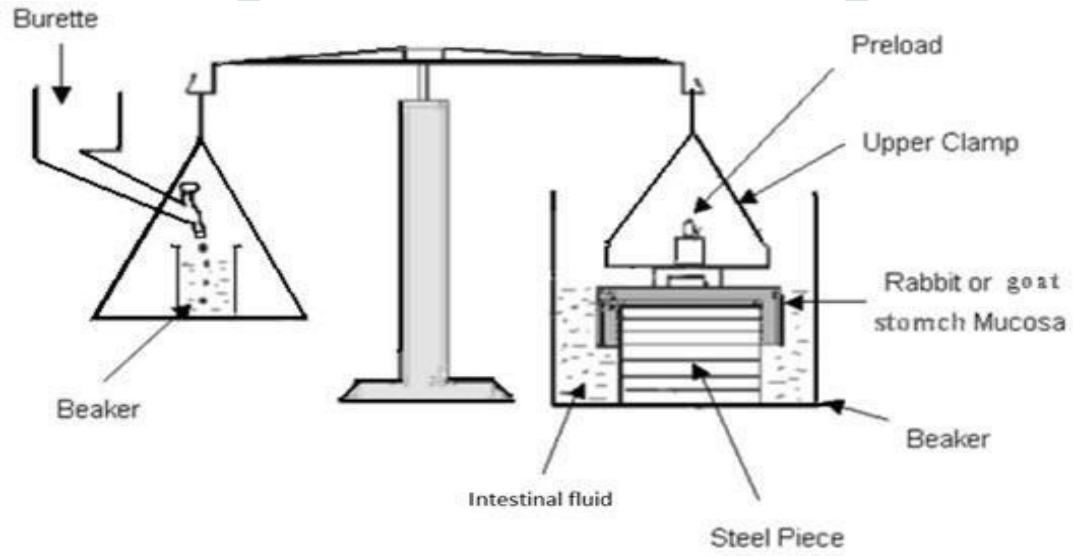


Fig. 11: Measure of mucoadhesive strength.[39]

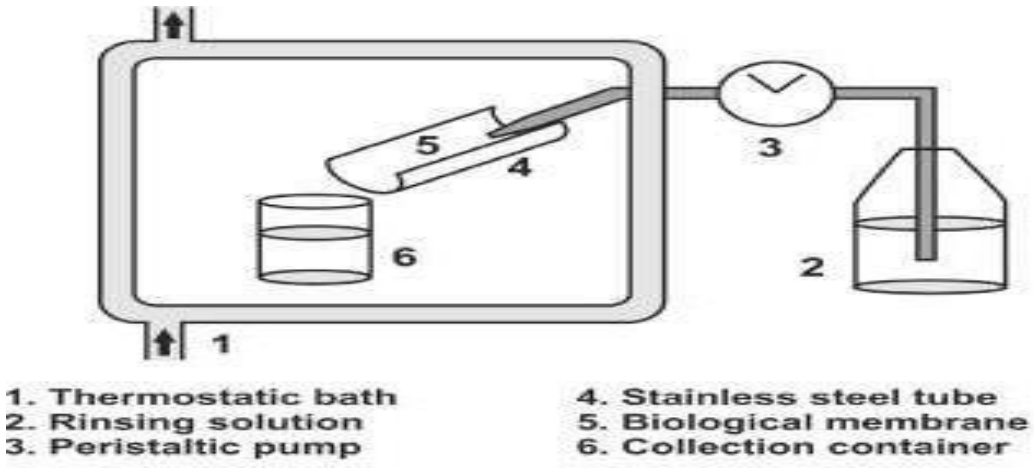


Fig. 12: Falling liquid film method.[24]

A beaker with 0.1N HCl and pH 1.2 buffer is used to hold a teflon block of a certain size. The beaker is then placed at the bottom of the right side of the balance. The stomach mucosa of rats or goats can be utilized as a model membrane, and buffer is used as a moistening agent. After attaching one side of the formulation to the right arm of the balance's glass slide, the beaker is gradually raised until the mucosa of the goat and the mucoadhesive dosage form make contact. In order to create an adhesive bond between the stomach mucosa and the mucoadhesive dosage form, a preload of 10 g is applied to the slide for a duration of 5 minutes. There is no change in the preload or preload time. After the preload period has elapsed, the preload is taken out of the glass slide and water is progressively added using a peristaltic pump to the plastic bottle on the left side of the arm at a rate of 100 drops per minute. When the mucoadhesive dosage form separates from the stomach mucosa of a goat or rat, the water addition is halted. Mucoadhesive strength is measured in grams and is the weight of water needed to separate the mucoadhesive dosage form from the stomach mucosa.

Force of Adhesion (N) = (Mucoadhesive strength * 9.81)/1000

Bond strength (N/m2) = Force of adhesion (N)/ surface area of tablet (m2)

## B) Falling liquid film method

This method involves inserting the mucous membrane into a longitudinally cut stainless steel cylindrical tube, as illustrated in Fig. 12. This support is positioned inclined inside a cylindrical bath that has a thermostat set to maintain a temperature of 37°C. A peristaltic pump is used to push an isotonic solutionthrough the mucous membrane and collect it in a collection container. The amount that is still on the

mucous membrane in the case of particulate systems can then be counted using a coulter counter. In semi-solid systems, high performance liquid chromatography can be used to quantify the non-adhered mucoadhesive. Using polarized light microscopy for analysis, this methodology makes it possible to see how liquid-crystalline mesophase forms on the mucous membrane following fluid flow.[3]

## C) Fluorescent probe method

This technique labels the membrane proteins and lipid bilayer, respectively, using fluorescein isothiocyanate and pyrene. After mixing the mucoadhesive agents with the cells, variations in the fluorescence spectrum are noticed. This illustrates the function of polymer binding in polymer adhesion.[3]

## D) Colloidal gold mucin conjugate method

International Journal of Medicinal Science A method called colloidal gold staining is suggested for researching bioadhesion. The technique forms mucin–gold conjugates by adsorbing red colloidal gold particles on mucin molecules. When these conjugates come into contact with bioadhesive hydrogels, they turn red. The intensity of the red color on the hydrogel surface or the decrease in conjugate concentration as measured by the change in absorbance at 525 nm can be used to evaluate this.[9]

## 2. Swelling index

The percentage of weight gained by the formulation is used to quantify the amount of swelling. The following formula is used to calculate it.:

Swelling index (S.I.) = (Wt-Wo/Wo)

Where, S.I = Swelling index; Wt = Weight of tablet at time t; Wo = Weight of tablet before placing in the beaker.[3]

## 3. Thumb method

This is helpful in the development of buccal adhesive delivery systems and is used to qualitatively determine the polymer's peel adhesive strength. The strain needed to remove the thumb from the adhesive as a function of pressure and contact time is used to determine the adhesiveness.[11]

## 4. Electrical conductance

In order to measure the electrical conductance of different semisolid mucoadhesive ointments, the rotational viscometer was modified. It was discovered that the electrical conductance was low when adhesive material was present.[3]

## 5. Stability Studies

Studies on stability are the only way to assess if a formulation is successful. Stability testing aims to produce a stable product that guarantees its effectiveness and safety through the end of its shelf life at specified storage conditions and peak profile. In this case, ICH guidelines can be adhered to.[3]

## 6. Measurement of the Residence Time/ In Vivo Techniques

Quantitative data on mucoadhesive properties can be obtained by measuring the residence time of the mucoadhesive at the application site.[11,101] Several mucoadhesive preparations' GI transit times have been investigated using fluorescence labeling methods and radioisotopes.[3]

### A) GI Transit using Radio-Opaque Tablets

To find out how mucoadhesive polymers affect GI transit time, a straightforward method uses radio-opaque markers, like barium sulfate, encapsulated in mucoadhesive tablets.[11]

### B) Gamma Scintigraphy Technique

The amount and distribution of radioactivity in the genital tract following the administration of technetium-labeled hyaluronan based biomaterial (HYAFF) tablets have been documented in a study. After 12 hours of administration to the stomach epithelium, it was discovered that the dry powder formulation of mucoadhesive-radio labeled tablets based on HYAFF polymer retained more than the pessary formulation.[3,12,92]

- **Mucoadhesive Dosage Forms**

## Tablets

Tablets have an oval shape, are flat, and have a diameter of about 5 to 8 mm. Speaking and drinking are made possible by the mucoadhesive tablets without causing undue discomfort. They become softer, stick to the mucosa, and stay there until the dissolution and/or release process is finished. Because mucoadhesive tablets have a high surface to volume ratio and enable much more intimate contact with themucus layer, they provide effective absorption, controlled release, and enhanced bioavailability of the drugs.

The tablet formulation that is marketed is called a buccal tablet, such as Aphtac, Nitrostat, Stirant SR, and Buccastem.

tablets under the tongue, such as isosorbide dinitrite.[9]

## Sprays

Glyceryl trinitrate is a small molecule that can be quickly delivered across the sublingual oral mucosa usinga spray for angina relief. The Generex Biotechnology Corporation has developed a RapidMist® spray which is capable of delivering large molecules, such as insulin across the oral mucosa. -Fentora is one of the commercially available formulations of oral sprays. The sprays contain drugs and deliver aqueous droplets to the mouth. The velocity and size of the droplets are monitored to ensure delivery to the oral cavity rather than the lungs.[24]

## Pastes

Pastes have been used to deliver controlled release in oral care formulations and antimicrobial agents for better healing of the extraction socket following tooth extractions in patients with HIV disease. Using carbomer polymer, mucoadhesive pastes containing methylprednisolone hydrogen succinate have been characterized. [15]

Paste formulations that are marketed include Fastum, Bonjela, and Corsodyl gel.

## Patches

Numerous patch systems have been developed that adhere to the oral mucosa and are intended to deliver medication. Oro-adhesive patches come in various varieties.

A) Dissolvable matrix patches: These patches have a longer half-life than solid forms like lozenges and tablets and can deliver a continuous dose of medication to treat mucositis and oral candidiasis. During use, they gradually and totally dissolve, leaving nothing to be removed.

b) Systems for non-dissolvable backing patches: These provide protection from saliva and are used for systemic drug delivery. Using patches, the medication is administered for 10–15 hours to the oral mucosaat a controlled, concentrated dose.

Patch formulations that are marketed include Loramyc and Dentipatch.[35-37]

## Wafers/ Films

Because of their tiny size, thin structure, and flexibility, buccal disintegrating mucoadhesive films typically show better patient compliance than buccal tablets. Using its BEMA® (BioErodible Mucoadhesive) technology, BioDelivery Sciences International has created a variety of buccal transmucosal films, including Onsolis®, a buccal soluble film that contains fentanyl citrate and is intended to treat breakthrough pain in cancer patients who are already tolerant to opioids. Similar wafer technology is already being used to treat migraines, and it is hoped that in the future, many more conditions will be treated quickly and effectively due to the oral mucosa's high blood supply, quick dissolution of the wafers, and self-administrability of the technology. [94]

The following film formulations are marketed: Listerin, Benadryl, Theraflu, and Klonapin Wafers.

## Gels

Gels are applied specifically for a given site to achieve localized action. Gels applied to the oral mucosa have been used to topically deliver antifungal, anti-inflammatory, and mucoprotective agents to the oral mucosa, as well as systemic analgesics, anti-hypertensives, and medications for the treatment of cardiovascular disease.

The gel formulation that is sold is called Bonjela.[33-36]

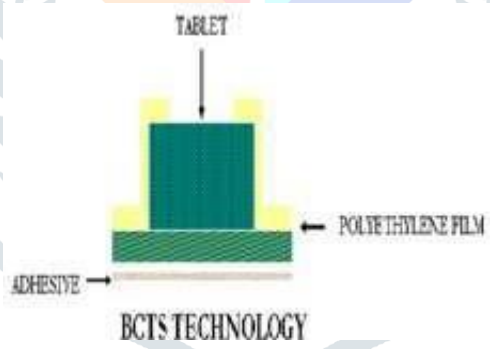


Fig. 13 : BCTS technology

Fig. 14: Mucoadhesive tablet based on effervescence.

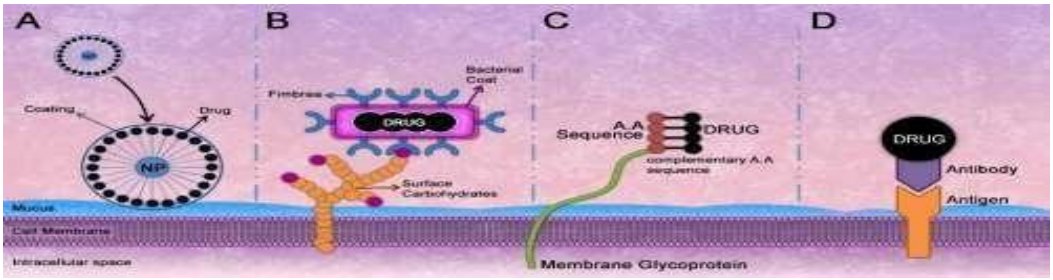

Fig. 15: Potential future novel strategies for muco-adhesive drug delivery using A) Mucoadhesive nanoparticles; B) Bacterial Adhesion; C) Altered amino Acid sequence; D) Antibody mechanism.[40]

## Recent innovations

**Gel Forming Liquids**:

This kind of formulation is liquid at the time of instillation and changes phases to become a viscoelastic gelin response to pH, ionic strength, and temperature.As pH rises, carbomers become more viscous. In reaction to an increase in ionic strength, gellan gum and alginate both gel (particularly with Ca+2 ions). At body temperature, poloxamers and Smart Hydrogel® (Advanced Medical Solution) gel are combined.[23]

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

SDBMPTs are created by utilizing a significant amount of HPC. For instance, a tablet containing 20 mg of medication, 20 mg of HPC, 20 mg of CMC, and 60 mg of lactose would be combined and compressed using an 8 mm diameter flat-faced die. The drawback is that it loses its shape and softens over time, making it difficult to control disintegration over extended periods of time.[23]

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

The S-DBMP-T system is encased in two polyethylene sheets. The lower sheet is composed of adhesives, while the upper sheet has a hole to absorb water. It's a mechanism that moves medication through the mucosal barrier. is less than pKa for a weak base, as demonstrated by effervescent technology; as a result, ionization and solubilization take place. While bio- and mucoadhesion strategies are currently employed ina number of novel ways for drug delivery, other strategies, such as those involving nanoparticles, bacterial adhesion, modified amino acid sequence, and antibody mechanism, have the potential to enhance these approaches. Fig. 15 illustrates these potential novel strategies for mucoadhesion.[40]

# • CONCLUSION

For an effective dosage form, such as a novel mucoadhesive drug delivery system, this overview of mucoadhesion dosage form may be helpful. By lengthening the residence time at the delivery site, mucoadhesive polymers may offer a valuable tool to increase the bioavailability of the active ingredient. According to the literature currently available, the majority of studies recommend mucoadhesive drug delivery systems as the best alternatives to conventional dosage forms in order to improve the bioavailability of poorly soluble drugs, prevent GI degradation, and avoid the drug's first-pass metabolism.

## • REFERENCES

1. Mucoadhesive drug delivery systems: An overview, Bhatti D.A., Pethe A.M. In 2010, the Journal of Pharmacy Research, 3(8), 1743–1747.
2. Mucoadhesive Systems for Oral Medication Administration, Schnürch A. B. 2005's Drug Discov Today 2(1): 83–87.
3. Khan Ab et al. Mucoadhesive drug delivery system review: innovative methods in the contemporary era. 2014; 4: 128–40; Journal of Pharmaceutical Science.
Drug delivery systems that are mucoadhesive, Rahamatullah Shaikh TR et al. (2011) J Pharm Bioall Sci., 3: 89–100.
5. Mucoadhesive drug delivery: mechanism and assessment techniques, Khurana SH et al.(2011) Int J Pharm Biosci, 2: 458–67.
6. Wake WC. Adhesion and adhesive formulation. London: Applied Science Publishers, 1976, pp. 81–82.
7. Polyanionic polymers in bioadhesive and mucoadhesive drugs: Leung SHS, Robinson J A delivery. 1992; 480: 269–84 in ACS Symposium Series.
8. Robinson JR., Longer MA. Essential features of bioadhesion. Pharmaceutical Int, 7 (1986): 9. BV Deraguin,VP Smilga. Adhesion: Foundations and Application. London: McLaren and Sons, 1969; 152–54.
10. Kinloch, A. J. The adhesion science. Section I-. Aspects of the surface and interface. J Mater Sci., 15:2141 (1980).
11. Mucosal Drug Delivery System, Madan J et al. (2010) Int J Pharm Biosci 1: 63–70.
12. Vinod KR et al. Mucoadhesive drug delivery systems: a critical review. JD Med Hygeia, 2012; 4: 1–5.
13. Davis SS, Harding SE. Mucoadhesive drug delivery systems: the gastrointestinal tract's bioadhesion mechanism. Biopolymer Mixtures, 373–419 (1995).
14. A review of the mucoadhesive drug delivery system by Mahajan P et al. 2013; 5: 11–20; International Journal of Drug Development and Research.
Int. J. Res. Pharm. Sci., 2014; 5(3): 205–215, Vivek Kumar P et al., Novel Review on Mucoadhesive DrugDelivery System (2015).
16. Sangeetha S et al. Mucosa as a route for systemic drug delivery. Res J Pharm Biol Chem Sci., 2010; 1: 178-87.
17. Sarmento B, das Neves J. Chitosan-based systems for biopharmaceuticals: delivery, targeting and polymer therapeutics. John Wiley & Sons, 2012: 76-7.
18. Thakur VK, Thakur MK. Handbook of Polymers for Pharmaceutical Technologies, Biodegradable Polymers: John Wiley & Sons, 2015.
19. Gandhi SD et al. Mucoadhesive Drug Delivery Systems-An Unusual Maneuver for site specific drugdelivery system. Pharm Sci Monit an Int J Pharm Sci, 2011; 2(3): 132–152.
20. P.Ilavarasan et al. Buccal Patches as Emerging Trend. International Journal of Pharmacy and Technology, 2011; 973-86.
21. Sanzgiri Y.D et al. Gellan based systems for ophthalmic sustained delivery of methylprednisolone. J Control Release, 1985; 26(3): 195-201.
22. Vermani K, Garg S. The scope and potential of vaginal drug delivery. Pharm. Sci. Technol, 2000; 3: 359–364.
23. S.S.Davis. The design, evaluation of controlled release systems for the gastrointestinal tract. J.Control.Release, 1985; 2: 27-38.
24. Carvalho FC et al. Mucoadhesive drug delivery systems. Brazilian Journal of Pharmaceutical Sciences,2010; 46: 1-7.
25. Phanindra B et al. Recent advances in mucoadhesive/bioadhesive drug delivery system: A review. Int J Pharm Med and Bio Sci., 2013; 2(1): 68-84
26. Khan et al. Mucoadhesive Drug Delivery System: A Review. World Journal of Pharmacy and Pharmaceutical Sciences, 2016; 5(5): 392-405.
27. Dharmendra S et al. Mucoadhesive drug delivery system a review. International Journal of Pharmaceutical & Biological Archive, 2012; 3: 1287-91.
28. Mythri .G et al. Novel Mucoadhesive Polymers –A Review. Journal of Applied Pharmaceutical Science,2011: 37-42.
29. Woodley J. Bioadhesion new possibilities for drug administration. Clin Pharmacokinet,2001; 40: 77-84.
30. Duchene D et al. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Developement and Industrial Pharmacy, 1988; 14: 283-318.

31. Singh R et al. Review on Mucoadhesive Drug Delivery System with Special Emphasis on Buccal Route: An Important Tool in Designing of Novel Controlled Drug Delivery System for the Effective Delivery of Pharmaceuticals. J Dev Drugs, 2017; 6(1): 1-12.
32. Imam ME et al. Evidence for the interpenetration of mucoadhesive polymers into the mucous gel layer. STP Pharma. Sci., 2003; 13: 171–176.
33. Sudhakar Y, Bandyopadhyay AK. Buccal bioadhesive drug delivery- A promising option for orally less efficient drugs. J.Control. Rel., 2006; 114: 15–40.
34. Jimenez-Castellanos MR et al. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm, 1993; 19: 143-94.
35. Nagpal N et al. Mucoadhesion: A New Polymeric Approach. Bulletin of Pharmaceutical Research, 2016; 6: 74-82.
36. Anitha Lekshmi MR et al. Buccal Mucoadhesive Drug Delivery System: A Novel Drug Delivery Technique. European Journal of Pharmaceutical And Medical Research, 2016; 3: 129-37.
37. Khatik AS et al. Evaluation of Mucoadhesive Buccal Tablets: A Review. International Journal of Universal Pharmacy and Bio Sciences, 2015; 4: 359-80.
38. Alexander A et al. Mechanism responsible for mucoadhesion of mucoadhesive drug delivery system: A review. International journal of applied biology and pharmaceutical technology, 2011; 2(1): 434-45.
39. Edsman K, Hagerstrom H. Pharmaceutical applications of mucoadhesion for the non-oral routes. J Pharm Pharmacol, 2005; 57: 3–22.
40. Alexander A et al. Theories and Factors Affecting Mucoadhesive Drug Delivery Systems: A Review. International Journal of Research in Ayurveda & Pharmacy, 2011; 2(4): 1155