An Overview: Mucoadhesive Buccal Drug Delivery System

Prashant Patil, Sanika Landge, ShrutiHajare, Gaurav Deshmukh, Sayali Kathmale, Vaishnavi Palve, Vishal Pande*

Department of Pharmaceutics, N N Sattha College of Pharmacy, Ahmednagar, Maharashtra-414001, (India).

Abstract

Mucoadhesion is the process where a material sticks to biological tissues, like the inside of the mouth or nose. It happens in three steps: first, the mucoadhesive material swells or wets; second, the polymer chains of the material interact with each other; and third, chemical bonds form between these chains. Several factors affect how well this adhesion works, including the features of the material (e.g., size, structure, and charge) and environmental conditions (e.g., how long it stays in exposure of the tissue).This system helps improve how well drugs are absorbed by keeping them in contact with the tissue longer. This is especially useful in treatments like buccal drug delivery, where medications are absorbed through the lining of the mouth. This review discusses how mucoadhesion works, the types of materials used, and how these systems are made and tested for use in drug delivery. Delivery through buccal system is the step by step of administering the medication through the oral cavity mucosal membrane lining of buccal system . This article's goal is to cover buccal medication delivery by going over the environment and structure of the buccal mucosa, emphasizing drug penetration processes, and outlining of evaluation process for buccal formulations. A synopsis of the benefits, drawbacks, and theories pertaining to mucoadhesion is also included in this review, along with information on how to prepare the mucoadhesive system, mucoadhesive polymer, and buccal system classification.

Keywords: Mucoadhesion**,** Buccal Drug Delivery**,** Mucoadhesive Polymers**,** Drug Absorption**,** Mucosal Membrane

INTRODUCTION

Mucoadhesion is described as sticking in living settings. Activity of mucoadhesion occurs in 3 steps the very first wetting of polymer. The second stage embraces percolation of the mucoadhesive polymer chains, and for the third stage creation of compound connections between linked chains. Multiple polymer-related parameters, such as mass of the molecule, length of series or sequence, percentage of bonding, swelling, reactive groups, polymer concentration, charge and additional environmental conditions and physiological factors such as adhesion time, mucoid viscoity, mucus replacement rate, influence the properties of mucoadhesion. Researchers have designed and created many polymers with mucoadhesive property for use in biological availability addition, site specific medication administration. The delivery of drug through bioadhesive based method include interaction of mucin molecules with the mucus layer extending the time period for absorbtion of drug reaching to target site . For increased therapeutic efficacy, bioadhesive formulations may be created to offer regulated drug release rates and long-term retention at the application site. The capacity of the dosage form to attach to mucoidal surfaces rely on a number of parameters, such as the biophysical characteristics of the polymeric formulation and the composition of the mucosal tissue. The topics of bioadhesion mechanisms and theories, bioadhesion polymers and polymers, and different dose forms and micro bead manufacturing techniques. Numerous advantages are provided by the oral mucosa for prolonged action, regulated pharmaceuticals administration. Both of them vascular and lymphatic removal are adequate for the mucosa, and pre-absorbtion elimination in the GIT and hepatic first-pass effect are prevented. The patient seems to find the location agreeable and it is ideally suited for a retentive device. It is possible to manage and alter the mucosa's permeability and local environment to allow for medication penetration with the proper dosage form design and compostion of drug.(1)

1. THE MUCUS LAYER

Mucus, it is a thin gel blanket which is translucent and viscid on mucosal membrane epithelial surface. The average density of this membrane in people ranges from 50 to 450 µm. It is released by mucus cells that line the epithelium or by ductal glands with goblet cells called acini. The mucus layer make-up changes according on species, location, and pathophysiological state. The mucous was composed of water (50%), glycolipid (5%), mineral salts (1%) and free proteins (1%).

Objective of Mucin layer

The major operation of this layer

1. Their hydrophobicity provides natural protection.

2. The mucin layer, which acts as a obstacle to medication and substrate absorption, has a significant impact on bioavailability.

3. The mucus layer lubricates and keeps the mucosal membrane wet. The goblet cell secretes mucus continuously to balance out the loss of the mucin layer owing to decomposion or breakdown, microbial degradation, and mucus volatilization.

4. Mucus forms a continuous gel layer on the surface of epithelial cells because to its high adhesive capabilities.(2)

1.1 Permeability barriers through buccal mucosa. (2)

Epithelium: The mucosae, the mouth's lining, regulates how quickly drugs are absorbed. Each place has a different level of ease of passage:

1. Sublingual (behind the tongue): thin, delicate, and easiest to pass

2. Oral (inside the cheek): broad but not hardened, modest passage

3. The hardest channel, the palatal (mouth roof), is somewhat thick and hardene. Surprisingly, 44000 times more medication can flow via the buccal mucosa (inside the cheek) than through the skin.

Granules coating membrane: MCGs are oval organelles (100-300 nm in size) noticed in the intermediary cell layer of stratified epithelia. MCGs release its contents across the intercellular space, contributing to permeability barrier. This barrier can be found on the outside 200µm of the underlying layer.(7)

1.2 Over lasting factor(2)

Size of molecules: Hydrophilic compounds are distinguished by enhanced molecular weight, size, and radius that correlates to a reduction of permeability. Smaller molecules (Molecular weight less than 100 Daltons) are easily conveyed through the mucosa.

Solvency of lipid: Neutral products often have greater drug permeability as their degree of lipophilicity increases. To improve absorption, drugs must be existing in the salivary pellicle within the solubility threshold.

pH: the Kramer and the Flynn pH-solubility profile showed that unionized and ionization of drug species can be saturated at a particular pH, known as pH max, leading in greater transbuccal permeability in relation to other pH ranges.

Ionization: Ionizable medicines possess greatest absorption at certain pH levels that require little ionization. Where the medication is primarily in a unionized form.

Elasticity: Polymer chains first diffuse between surfaces to initiate bioadhesion. These chains must be elastic and flexible for optimal adherence. The deeper the polymer penetrates the mucus, the more flexible it is. In overall case , flexible polymers adhere better and move more quickly.

Concentration: Strong adhesion chain length dependent that passes through the mucus layer. The contact is poor, though, if the strength or density of the macromolecule (polymer) is too low. Adhesion can be enhanced by increasing the concentration of the polymer, but only to a certain extent. The polymer chains get excessively twisted at a particular concentration, which hinders their ability to pass through mucus and actually weakens adhesion.

Swelling: In order to function, a mucoadhesive polymer must:

1. Create a mesh that fits the mucin network by absorbing water (hydrate).
2. Give its chains permission to flow and entwine with the mucin.
3. Make locations for dipole-dipole and electrostatic with the mucosal web visible.

The polymer chain may efficiently swell and stick to the biological surface once it reaches a particular degree of hydration.

1.3 Mucoadhesive polymers as permeability enhancers and enzyme inhibitors

It has been demonstrated that specific mucoadhesive polymers can:

1. Prevent the breakdown of drugs by enzymes
2. Increase the gut's permeability to drugs
3. Offer buffering capabilities

These multipurpose polymers, which include chitosan, polyacrylates, and cellulose derivatives, are good at delivering medications through the mouth. They are able to prevent enzymes from breaking down proteins and peptides; improve absorption through the buccal mucosa.

ADVANTAGES

1. Patient accessibility is high.
2. It is the most appropriate and highly fibro-vascularized method for managing and removing dose.
3. Consistent access to systemic circulation, transfer via jugular vein, and bypass hepatic first pass processing result in high bioavailability.
4. Faster reclamation of localized buccal mucus on smooth surface.

5. Drug sustainability with little and repairable harm.

6. The technique of administration is non-invasive. (3)

DISADVANTAGES

1. Low permeability location in the buccal cavity.

2. Available surface area is only about 170 cm^2.

3. Salivary secretion can cause medication dilution.

4. Inconvenient for the patient to consume.(3)

Organ where mucus layer is present in

1. Ocular drug delivery system

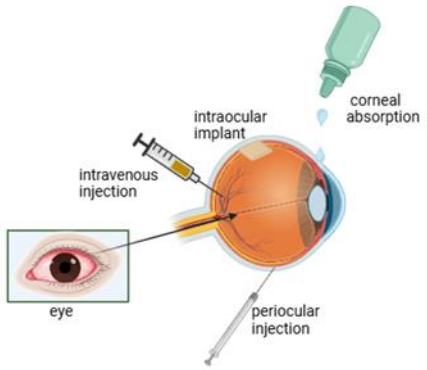
2. Oral drug delivery system

3. Rectal drug delivery system

4. Vaginal drug delivery system

5. Nasal drug delivery system

6. Buccal drug delivery system(2)



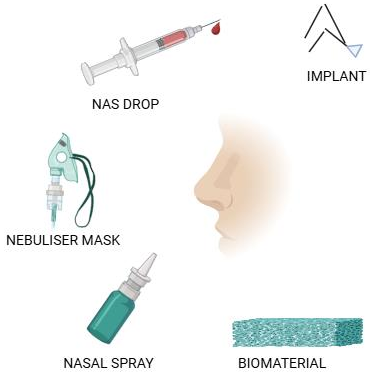


Fig: ocular drug delivery Fig: Nasal drug delivery

2. BUCCAL DRUG DELIVERY SYSTEM

Medications can be easily administered via the mouth's mucus layer, buccal drug administration is a popular technique. Hydrophilic (water-loving) polymers, such polyacrylic acid (PAA), are commonly used bioadhesives for this purpose because they are highly sticky and facilitate efficient oral drug delivery.(4)

Buccal medication distribution is a key non-contact method of delivery. The disadvantage of buccal drug administration can be mitigated by Nano formulations or nanoparticle-based formulations. Nanoparticles are often included in a matrix/gel-based system, and permeation enhancers can be employed to improve buccal medication delivery (4).

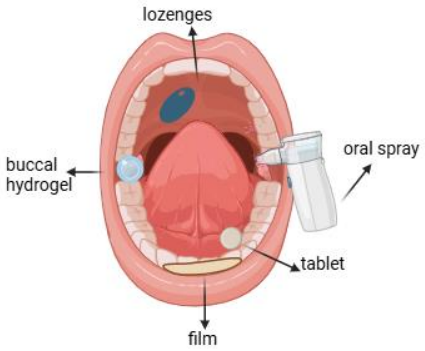


Fig: Buccal drug delivery system

Buccal drug distribution is the method of administering the intended medication via the oral cavity's mucosal membrane lining. This method works well for both transmucosal (systemic effect) and mucosal (local effect) medication delivery.

Oral mucosal site:

a) **Sublingual mucosa**: Is the route via which the medication is administered to the systemic circulation.

b) **Buccal delivery**: The medication is delivered to the systemic circulation via the cheek lining.

c) **Local delivery**: Applying a bioadhesive device to the palate, gingival tissue, or cheek to treat bacterial infections, ulcers, and periodontal disorders.

Due to differences in their composition, structure, and level of permeability, these delivery locations additionally, they differ in how long they can maintain a delivery system. (5)

2.1 Preparation of BDDS in various forms.

- **Solid medicated forms include**: Tablets, Lozenges, Powders, Patch and Wafers.
- **Semi-solid medicated forms**: Topical application(Gels and ointments)
- **Liquid medicated forms**: Sprays

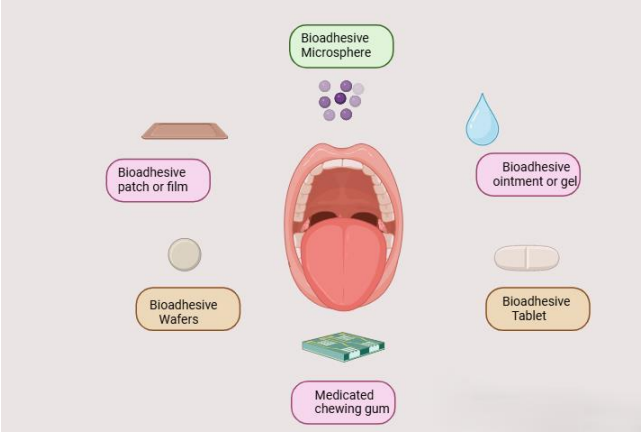


Fig: BDDS

2.1.1 Solid Dosage Form

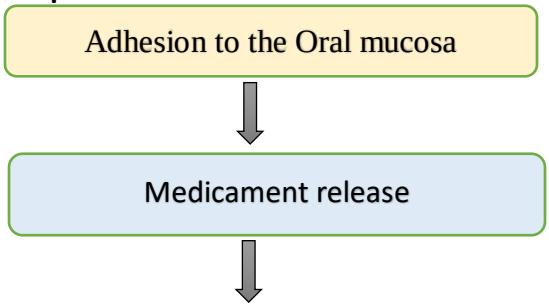
1. Buccal tablet: Buccal tablets are tiny tablets that dissolve or disintegrate gradually and are directly absorbed when placed in the buccal pouch, which is between the gums and the lips or cheek. During this period, it should not be manipulated with the tongue as this could reduce its effectiveness. Because buccal delivery avoids first-pass metabolism by skipping the digestive tract, it can increase the bioavailability of certain medications and work more quickly than oral administration.(14)

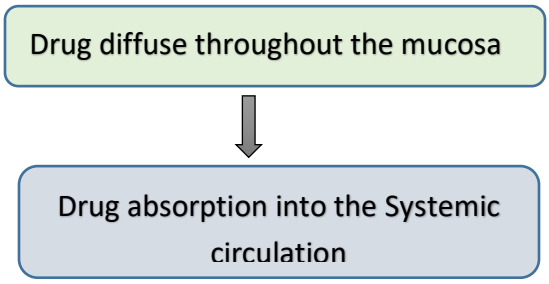
2. Buccal patch: A buccal patch is a thin, non-dissolving film that contains medication and is positioned between the cheek and gums to administer it. Buccal patches consist of several layers, such as: an impermeable layer is as backing layer and layer that contains drug releases the medication in a regulated way. (14)

Mucoadhesive layer: Attaches to teeth, gingiva, or oral mucosa

Drugs can enter the sub mucosal layers, the oral cavity, or both through buccal patches. Either a unidirectional or bidirectional release of the drug occurs. Followed by predetermined span of time, the patch is removed from the mouth.(8)

Mechanism of Buccal patch:





3. Buccal Films: Several mucoadhesive dosage formulation includes tablets, films, discs, ointments, patches and gels, were designed recently in medication delivery in buccal system. But when it comes to patient comfort and flexibility, buccal films are better than mucoadhesive discs and pills(tablet). Further more they also guarantee greater precision in drug dosage and a extended period of residence than semi-solid form.

4. Wafers: Bromberg et al. presented a ideally unique periodontal based drug delivery system designed to treat infections caused by micro-organism linked with periodontitis. The delivery system is a incorporated wafer with adhesive surfaces and a core layer made up of antimicrobial agents, bioresorbable polymers, and base polymers(14)

5. Lozenges: Antibiotics, corticosteroids, antifungals & local anesthetic can all be distributed topically in the mouth via bioadhesive lozenges. Classic cough lozenges cause a large rapid release of drug in the buccal cavity, that quickly decreases to below therapeutic threshold, necessitating frequent dosing. Controlled release bioadhesive lozenges have the capability to extend release of the drug while improving patient acceptance.(14)

6. Powders: Powders are solid dosage forms that contain drugs and other materials that are finely divided and meant to be applied to buccal. A combination of bioadhesive polymers and drugs makes up buccal bioadhesive powders. Which are applied to the buccal mucosa, when diastolic blood pressure decreases administration of nifedipine is followed in form of buccal tablets and buccal films.(14)

7. Microparticles: Microparticles offer more benefits than tablets. Because of their physical properties, microspheres can come into close contact with a large mucosal surface. They also cause no local discomfort at the site and might be used in small accessible areas likely to be the nasal cavity and GI tract. (14)

2.1.2 Semi-solid Dosage forms

1. Buccal Gels and Ointments: Gels and other semisolid dose forms offer various benefits like it spreads easily throughout the oral mucosa, retention at the application location is enhanced by

bioadhesive compositions, controlled or extended medication release results from increased viscosity.

The one of some instances of bioadhesive polymers found in buccal semisolid dose forms is the semisolid form of sodium carboxymethylcellulose, which is a liquid, finely ground organic or manmade macromolecule distribute in polyethylene or hydrous solution.

2. Medicated Chewing Gum: Medicated gum includes a medicine that, when chewed, releases a large amount of the medicament to demonstrate site specific action in the mouth. Additionally, systemic circulation may demonstrate absorption. For nicotine replacement treatment, medicated chewing gum is available. Similarly, chewing gum with caffeine is also available.

2.1.3 Liquid dose forms

These are pharmaceutical fromulations in proper aqueous carriers. These dosage formulations are often utilized to exert target action in the oral cavity, and a wide range of germicidal mouthwashes and mouth fresheners are business-wise marketed for this intention. The drawback of these liquid prepartion forms is that they are difficult to target to the oral mucosa, resulting in somewhat uncontrolled drug delivery throughout the oral cavity.

1. Bioadhesive Spray:

Buccoadhesive sprays are becoming more popular than other dosage forms due to their versatility, easy, large surface area, and drug presence in solution form.

2.2 The basic components of buccal formulations:(8)

1. Drug substance
2. Bioadhesive polymers
3. Backing membrane
4. Permeation enhancers

1. Drug substance: When designing this drug delivery systems, it's important to consider the desired action (fast/prolonged release or local/systemic effect). To design buccoadhesive drug delivery systems, choose drugs with great absortion properties.

The medicine need to have the below qualities.

- The standard unit dose of the medicine must be small.
- Drugs with a plasma half-life of 2 to 8 hours are suitable to regulated distribution.
- When administered through mouth, the drug's absorption (Tmax) has larger variations and elevated values.

- Drugs administered should not have a first pass effect or presystemic elimination.
- Passive absorption is expected.

2. Bioadhesive polymer:

The very first stage in making buccoadhesive dosage forms that work by choosing and describing appropriate polymers with adhesive property. In buccoadhesive medication administration mechanism, bioadhesive polymers are necessary because they provide a number of advantages.

1. Matrix devices for controlled drug release.
2. Better therapy and patient care.
3. Application versatility.

3. Backing membrane: The another crucial component of bioadhesive devices is backing membrane act by attaching them to the mucin membrane. Key requirements for backing membrane materials include Inertness**,** resistance to medicines and penetration enhancers**,**impermeability to reduce drug loss, flexibility**,** strength**,** water resistance.Common materials used for backing membranes include: Carbopol**,** magnesium stearate**,** Hydroxypropyl Methylcellulose**,** Hydroxypropyl Cellulose**,** Carboxymethyl Cellulose**,** polycarbophil.

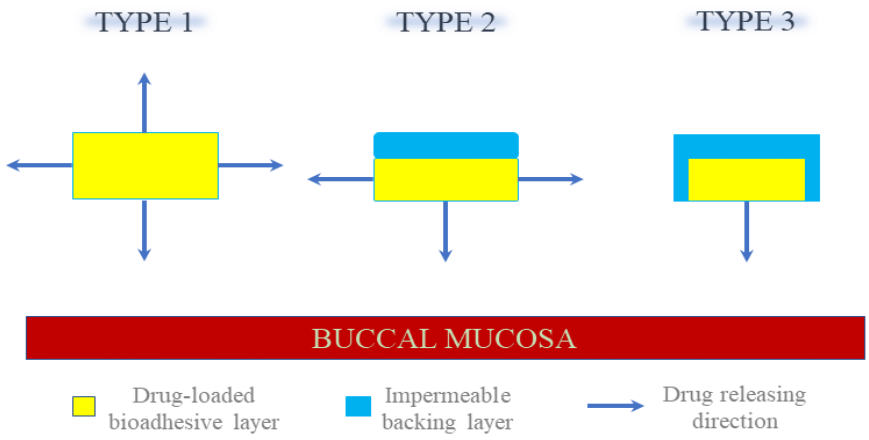
4. Permeation enhancers: Substances that aid in promoting drug diffusion via the buccal epithelium are known as, permeation promoters and absorption enhancers. Agents employed as penetration enhancers must be safe and nontoxic non-irritant, non-allergenic,in both aspect pharmacologically and chemically, .(7)

Aprotinin	Polyoxyethylene
Sodium salicylate	Cetylpyridinium chloride
Sodium taurocholate	Cyclodextrin
Benzalkonium chloride	Methoxysalicylate
Cetyl trim Methyl ammonium bromide	Sulphoxide
Lauric acid	Dextran sulphate
Phosphatidylcholine	Sodium glycodeoxycholate
Menthol	Sodium lauryl sulphate
Sodium taurodeoxycholate	Sodium EDTA

Fig: permeation enhancers.

2.3 Buccal Dosage Forms

Based on their appearance, buccal mucoadhesive dosage forms can be divided into 3 types, as shown in the following figure.(7)



2.3.1Design and Structure of Buccal Drug delivery

- **1. Matrix type**: This kind of buccal patchs combines adhesion, additives, and medication in a matrix design. Drug is released in both the mouth and mucosa through bidirectional patches. The matrix type design combines the medication with mucoadhesive matrix.
- **Type Reservoir**: The drug and other ingredients are kept apart from the adhesive by a container system that creates a cavity in the buccal patch. An impermeable backing prevents d loss of drug, minimizes patch distortion and breakdown in the mouth, and controls the way of drug delivery.(8)

2.4 EVALUATION PARAMETER

- **Surface pH:** A combination of glass electrodes is utilized to measure the pH of the surface. The patches are exposed to five milliliters of distilled water for one hour. To measure the pH, place the electrode near to the formulation's area and give it a minute to equilibrate.(8)
- **Measurements of thickness:** To measure film's thickness an electronic digital micrometer is used to find five distinct points (the center and four corners).(10)
- **Content uniformity:** Dispersing every patch in 10 milliliters of solvent and screening it through Whattman filter paper of 0.45 µm allows for the determination of drug content homogeneity. After evaporating the filtrate, the residue is dissolved in 100 milliliters of phosphate buffer of pH 6.8. After diluting the 5 ml solution with phosphate buffer (pH 6.8) in

20 ml, it is filtered through 0.45-µm Whattman filter paper, and the absorbance is evaluated using a UV Spectrophotometer in comparison to a blank of pH 6.8 phosphate buffer. Three duplicates of the tests are conducted, and the regular results are published.

- **Folding Strength:** A patch's folding endurance is assessed by folding it repeatedly in the same spot until it breaks or up to 300 times without breaking. Average values are presented after the experiments are run in triplicate.(8)
- **Water absorption load test:** Circular patches with a surface area of 2.3 cm2 are allowed to grow on agar plates created in simulated saliva (2.38 g Na2HPO4, 0.19 g KH2PO4, and 8 g NaCl per liter of distilled water that has been balanced with phosphate buffer to pH 6.7) in the incubator and temp set at 37°C ± 0.5°C. In a desiccator over anhydrous calcium chloride, samples are measured at different intervals (0.25, 0.5, 1, 2, 3, and 4 hours) and then kept to dry at room temperature for seven days until an even weight is recorded.(8)
- **Ex-Vivo Mucoadhesive strength:** To determine ex-vivo mucoadhesive strength, an adjusted balance procedure is used. Fresh buccal mucosa from a rabbit or sheep was acquired and used within two hours of killing. The mucosal membrane was detached by dividing the underlying fat and loose tissues. The mucosal membrane was rinsed with distilled water and subsequently with phosphate buffer (pH 6.8) at 370 degrees Celsius. The buccal mucosa was cut into minute pieces and sprayed with phosphate buffer (pH 6.8). A piece of buccal mucosa was connected to the glass vial, which contained phosphate buffer. Prior to the investigation, the two sides of the modified balance were equalized by placing a 5 g weight on the right side of the pan. A weight of 5 g was removed from the right side of the pan, lowering the pan and tablet over the mucosa. The equilibrium was maintained for a 5-minute contact time in this position. Water was slowly added to the right side of the pan, equivalent to weight, using an infusion set of 100 drops per minute, until the tablet disengaged from the mucosal surface.(8)

3. MUCOADHESIVE

Medicine can be delivered by mucoadhesion, which makes it adhere to our body's mucus membranes. This prolongs the duration of the medication's action, potentially improving absorption and treatment efficacy. It's particularly helpful for administering medications that are difficult to absorb, such as oligonucleotides and peptides (9). Additionally, mucoadhesion can help evade the body's natural defenses, such as the gut's enzymes, that could break down the

medication. Overall, mucoadhesion is a promising technique to improve how drugs work and make them more effective.

Measure	Classification	Exemplar
Source	Natural /Semi natural	Gelatin, Various gums(gellan, carrageenan, guar, hakea, xanthan pectin, and sodium alginate) Agarose, chitosan
	Synthetic	**Poly(acrylic acid)-based polymers** poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate), CP, PC,poly(isobutyl cyanoacrylate) **Cellulose derivatives** Sodium CMC, HPC, HPMC, Thiolated CMC **Other** Poly (N-2-hydroxypropyl methacrylamide) polyoxyethylene, PVA, PVP.
Aqueous solubility	Water-soluble	HPMC (cold water), sodium CMC, HPC (water38 °C) PAA, sodium alginate.
	Water-insoluble	Chitosan, EC, PC
Charge	Cationic	Amino dextran, dimethylaminoethyl (DEAE)-dextran, trimethylated chitosan.
	Anionic	Chitosan-EDTA, PC, sodium alginate, pectin xanthan gum
	Non-ionic	Hydroxyethyl starch, scleroglucan,
Potential bioadhesive forces	Covalent	Cyanoacrylate
	Electrostatic interaction	Chitosan
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)]

Table : polymer that are used as mucoadhesive in buccal drug delivery(10)

3.1 Factors Affecting Mucoadhesion

Hydrophilicity

Bioadhesive polymers contain a variety of hydrophilic functional groups, like carboxyl and hydroxyl. These groups allow the substrate's structure to form hydrogen bonds, which increases the exposure of possible anchor sites and encourages swelling under aqueous conditions. Additionally, there is ample amount of space between their chains in case of bloated polymer, which promotes chain versatility and permits optimal substrate permeation.(6)

Spatial orientation

In addition to the chain length and molecular mass, a polymer's structural conformation is significant. Their bonding strength compares to that of PEG. PEG have the molecular weight of about 200 thousand, although dextran have high molecular mass of 19.500,000. In contrast to Poly Ethlyene Glycol polymers, typically have a regular conformation, dextran's helical shape is capable of hiding multiple active attachment groups that are mainly responsible for adherence.(6)

pH: The adherence of bioadhesives having ionized groups may be influence by pH at the bioadhesive-substrate junction. Polyanions with carboxylic acid characteristics consist of an extensive range of bioadhesives that are utilized for medicine delivery. If the pH of local is higher than the polymer's pKa, more ionization takes place, whereas lower pH leads more unionization. The poly (acrylic acid) group of polymers has a pKa that is between4-5. These polymers have their maximum adhesive strength between pH 4-5, which gradually declines beyond pH 6. A comprehensive examination of the procedure behind mucoadhesion confirmed conclusively that carboxyl protonated groups interact with mucin molecules compared to ionized carboxyl groups, most likely through the concurrent development.(6)

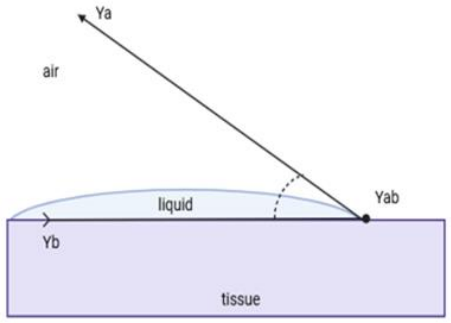
Cross-linking and Swelling

The amount of edema interacts negatively with cross-link density. Volatility and hydration rates rise as cross-link density declines, however mucoadhesion improves as polymer surface area expands. A polymer with a low degree of cross-linking has been chosen to accomplish a high level of swelling. When there is an excessive amount of moisture and swelling, the mucilage becomes slippery and can immediately eliminated from the compound. The use of adherence boosters, such as free chain polymer and polymers attached onto a predefined system, into a mixture of polymers with cross-linked chains can improve mucoadhesion.(6)

3.2 Theories related to Mucoadhesion

1.The Wetting Theory

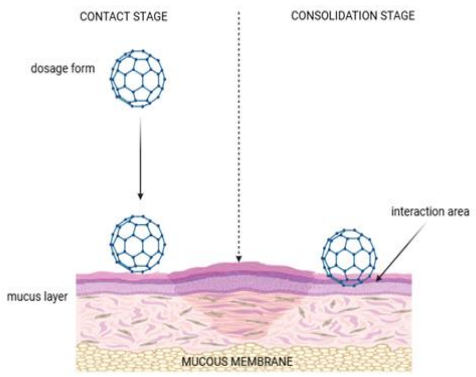
The most well-established theory of adhesion is wetting or swelling theory. This theory performs better in case of low-viscosity bioadhesives. Adhesion is defined as an integrating process whereby adhesive chemicals penetrate flaws in the substrate surface and ultimately solidify to create a large number of sticky anchors. The surface tensions in between two adhering phases less the apparent interfacial tensions in between them make up the adhesive work completed. This theory is used to determine the contact angle and the thermodynamic work of adhesion. Duper's equation states that the work done is related to the surface tension of the adhesive and the substrate; where γb, γτ, and γbt stand for the surface tensions of the adhesive. The substrate, and the bio adhesive polymer, respectively, and ωA is the specific thermodynamic work of adhesion. The total surface tensions of the two adhering phases less the apparent interfacial tensions between them make up the adhesive work completed. Depicts a drop of liquid bioadhesive spreading across a surface made of soft tissue. (10)



2. Electrostatic Theory of Mucoadhesion

Electrons are transferred between the adhering surface and the adhesive interface, according to this theory. As a result, the interface develops an electrical double layer, and contact between the two layers is maintained by a number of forces of attraction.(10)

3.Adsorption Theory of Mucoadhesion



(7)According to adsorption theory, materials stick together subsequent to establishing first contact in surface forces between the chemical structures on the two surfaces area. Polar groups or molecules reorient themselves when they come into touch. When adhesion especially strong, chemisorption may occur. The idea states that one or more secondary forces, such as hydrogen bonds, van der Waal's forces, and hydrophobic bonds are ultimately responsible for tissue.

4. Mucoadhesive Diffusion Theory

According to this theory bio adhesive's polymeric chains interpenetrate into the glycoprotein mucin's chains and enter the opposing matrix sufficiently deeply to form a semi-permanant attachment. From the initial point of touch, the process can be seen.(10)

5. Adhesive Fracture Theory

This hypothesis explains the strength required to detach two surfaces following adhesion. The tensile strength is equivalent adhesive strength through the following equation. Theory is used to study of bioadhesion by tensile apparatus. Fracture strength is similar to adhesive strength, calculated as

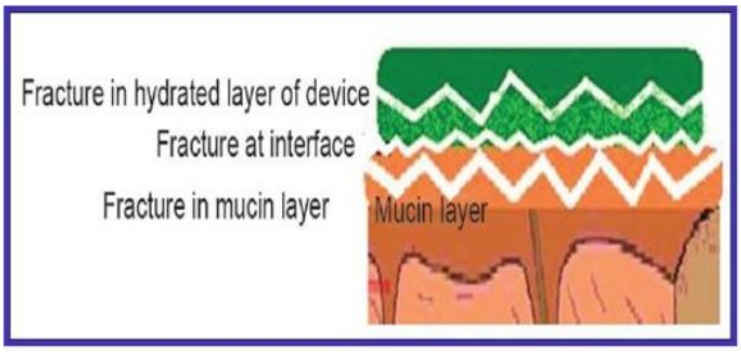
$G = (E\varepsilon. /L)$ ½.

where:

L represents the critical length of the fracture when the two layers are separated.

E= Young's module of elasticity

ε = Fracture energy



(10)

6. Mucoadhesive Materials

Polymers such as hydroxyl, amide, and carboxyl.These agent stick to the cell membrane by a number of connection, including hydrophobic and electrostatic interactions, as well as hydrogen bonding. Furthermore, because of these hydrophilic groups, polymers expand in water, revealing the greatest number of sticky places.(10)

3.3 Advantages and Disadvantages

Advantages

The buccal route of mucoadhesive provides the following advantages:

i. Easy to administer and discontinue pharmacological action.

ii. Permits for prolonged medication retention in a distinct location of the buccal cavity.

iii. Avoid first pass metabolism.

iv. Medicament with low permeability due to strong first pass metabolism can be administered easily the passive method for absorption consumes no energy.

v. Convenient drug delivery for unconscious patients.(11)

Disadvantage

i. The administration of large doses of drugs can be difficult.

ii. Patients might forget to swallow their tablets.

iii. Eating and drinking may be restricted unless the medication is completely released.

iv. This route is not acceptable for medications that are unstable in the pH of the oral environment.(11)

4. Bioadhesive

Bioadhesive is elucidated as ability of drug carrier system to attach to a biological substrate for a longer duration of time. The biological substrate may be mucus containing organs. Bioadhesion

plays a vital role in drug delivery systems, optimizing local or systemic delivery for different routes of administration. . (10)

1. Extend period of contact

2. Localization of any drug delivery

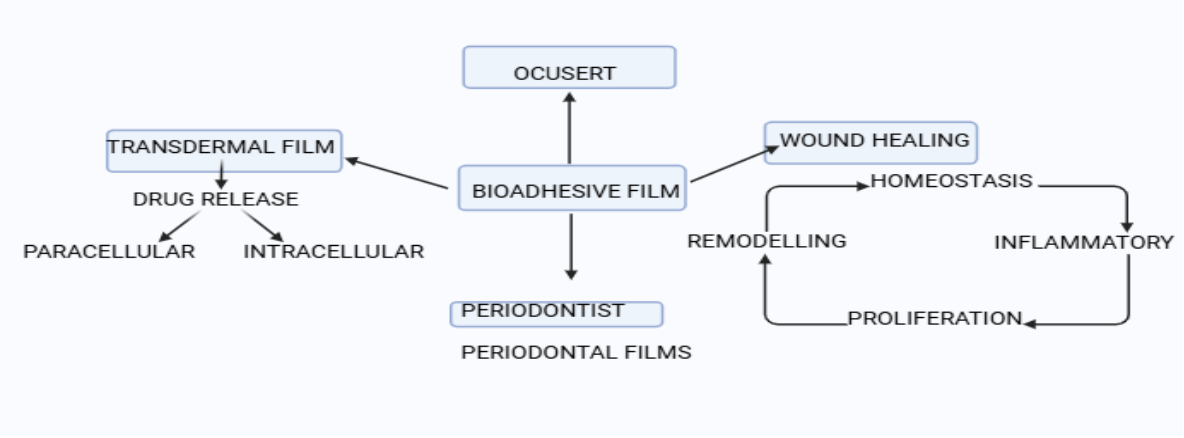
Type1 (Adhesion between two biological phases): protein-protein interactions involving disulfide bonds, avidin-biotin interactions, and thrombin-fibrinogen interactions.(12)

Type2 (Biological Phase Adhesion to an Artificial Substratum) Biofilm development on prosthetic implants and devices.(12)

Type3 (Synthetic hydrogels for connective tissues and adhesive for dental enamel).(12): The term "bioadhesion" in the context of drug delivery describes how a drug transporter system adheres to a specific biological location. The mucus lining of a tissue or epithelial tissue are examples of biological surfaces. The phenomenon of sticky attachment to a mucus lining is known as mucoadhesion. Differentiating between mucoadhesion and bio adhesion is essential.

Ideal Characters

1. Must be non-irritating.
2. Ideally, it robust form a strong, non-covalent bond with the epithelial cell surface.
3. It should be site specific and stick to wet tissue immediately.
4. It should make the drug's inclusion straightforward and remove any barriers to its unleash.
5. The polymer must not degrade during storage or throughout the storage duration of the dosage form. (11)



4.2 Types of Bioadhesive Mechanisms

1. Physical bioadhesion is based on physical forces like Van der Waals forces or electrostatic interactions.

2. Chemical bioadhesion: A covalent interaction between the bioadhesive and the tissue.

3. Mechanical bioadhesion: Predicated on the bioadhesive and tissue mechanically locking together.(13)

4.3 Bioadhesives' Mechanism of Action (MOA):

Bioadhesives function by creating a close, powerful connection with biological tissues, including wounds, mucous membranes, and skin. The MOA includes a number of crucial steps:

1.**Wetting:** The bio adhesive's surface energy enables it to wet the biological tissue's surface when it comes into touch with it.

2. Penetration: The bioadhesive creates a solid attachment with the tissue by penetrating the tissue surface.

3. Adhesion: Through a variety of processes, including hydrogen bonding, electrostatic interactions, and hydrophobic interactions, the bioadhesive creates a strong adhesive contact with the tissue covalent connection.

4. Retension: The bioadhesive maintains its adhesive qualities over time, enabling tissue repair, wound healing, or extended drug administration.

Factors Influencing the Bio adhesive Mechanism:

1. Surface energy influences the wetting and spreading of the bioadhesive.
2. **Tissue properties**: These influence the bioadhesive's adherence and retention.
3. Bioadhesive formulation influences adhesion mechanism and strength.
4. **Environmental factors**: Affecting the stability and effectiveness of the bio adhesive.

Understanding the MOA of bio adhesives is critical for developing and optimizing bio adhesive systems for a variety of medicinal applications.(12)

Table2: Polymer used as bio-adhesive in drug delivery

polymer	Sensitivity towards bio adhesive
Poly(acrylic acid/divinyl benzene)	+ + +
Carboxymethyl cellulose	+++
Tragacanth	+++
Caropol934	+++
Hydroxyl ethyl cellulose	+++
Guar gum	++
Gelatin	++
Thermally modified starch	+
Gum karaya	++

Polycarbophil	+++
Sodium alginate	+++
Polyvinyl pyrrolidone	+
Acacia	+
Poly ethylene glycol	+
Psyllium	+
Pectin	+
Amberlite200 resin	+
Hydroxyethyl methacrylate	+
Chitosan	+

*imp +++(excellent), ++(fair), +(poor)

CONCLUSION

Compared to other drug delivery methods, buccal medicine distribution has a higher permeability. Despite the benefits of the rectal, vaginal, and ocular mucosa, their usage is restricted to local applications rather than systemic drug administration due to the low patient acceptance associated with these sites. In contrast, patients find the buccal cavity to be quite pleasing; the mucosa is moderately permeable and has a large blood supply; it is robust and bounces back fast from stress or injury; and the buccal mucosa is tolerant of possible allergens due to the lack of Langerhans cells. Additionally, medication administered buccal trans mucosally avoids the first pass effect and stops the GI tract's pre-systemic clearance. For long-term, controlled drug administration, the buccal mucosa offers several advantages.First-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided by the mucosa's sufficient vascular and lymphatic drainage. The placement is appropriate for a retentive device, and the patient seems to find it appealing. The permeability of the mucosa and surrounding environment can be controlled and adjusted to allow for the penetration of medication with the proper dosage form arrangement and layout.

Refrences

1. Agarwal S, Aggarwal S. Mucoadhesive polymeric platform for drug delivery; a comprehensive review. Current drug delivery. 2015 Apr 1;12(2):139-56.

2. Akhter MH, Gupta J, Faisal MS, Mohiuddin MA. Comprehensive review on buccal drug delivery systems. International Journal of Pharmaceutical Research and Development. 2012;3(11):59-77.

3. Verma NA, Chattopadhyay P. Polymeric platform for mucoadhesive buccal drug delivery system: a review. International journal of current pharmaceutical research. 2011;3(3):3-8.

4. Dalei G, Das S. Polyacrylic acid-based drug delivery systems: A comprehensive review on the state-of-art. Journal of Drug Delivery Science and Technology. 2022 Dec 1;78:103988.

5. Freag MS, Saleh WM, Abdallah OY. Exploiting polymer blending approach for fabrication of buccal chitosan-based composite sponges with augmented mucoadhesive characteristics. European Journal of Pharmaceutical Sciences. 2018 Jul 30;120:10-9.

6. Boddupalli BM, Mohammed ZN, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. Journal of advanced pharmaceutical technology & research. 2010 Oct 1;1(4):381-7

7. Verma S, Kaul M, Rawat A, Saini S. An overview on buccal drug delivery system. International journal of pharmaceutical sciences and research. 2011 Jun 1;2(6):1303.

8. Gandhi Pankil A, Patel KR, Patel MR, Patel NM. A review article on muccoadhesive buccal drug delivery system, Inter. J. of Pharm. Res. Development. 2011;3(5):159-73.

9. Chore SA, Dighade SJ. A review on mucoadhesive vaginal drug delivery system

10. Rao NR, Shravani B, Reddy MS. Overview on buccal drug delivery systems. Journal of pharmaceutical sciences and research. 2013 Apr 1;5(4):80.

11. Shaikh R, Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. Journal of pharmacy and Bioallied Sciences. 2011 Jan 1;3(1):89-100.

12. Wise DL. Handbook of pharmaceutical controlled release technology. CRC press; 2000 Aug

13. Palacio ML, Bhushan B. Bioadhesion: a review of concepts and applications. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2012 May 28;370(1967):2321-47.

14. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs. Journal of controlled release. 2006 Aug 10;114(1):15-40.