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# Mucoadhesive Buccal Patches: A Promising Approach for Enhanced Drug Delivery

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***Abstract:*** The buccal region of the oral cavity is a desirable location for the administration of the most common drugs, especially when trying to overcome the drawbacks of the latter way of administration. By administering the drugs via the buccal route, difficulties such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be avoided. Furthermore, compared to the oral route, a quicker onset of action can be obtained, and the formulation may be discontinued if therapy needs to be terminated. Drugs can also be given to less cooperative and unconscious individuals. Adhesive mucosal dosage forms, such as adhesive tablets, adhesive gels, adhesive patches, and many more dosage forms with different combinations of polymers and absorption enhancers, were suggested for oral delivery to prevent accidental drug swallowing. In the pharmaceutical sector, natural polymers have gained more importance recently. Mucoadhesive polymers are employed to extend the dosage form's residence time and duration of contact with the mucous membranes, which enhances drug delivery. The process by which polymers adhere to a biological substrate, a manmade or natural macromolecule, mucus, or an epithelial surface is known as mucoadhesion. The phenomenon known as mucoadhesion occurs when the biological substrate adheres to a mucosal layer. Drug delivery can be facilitated at a particular delivery point for an extended period by the substrate that contains bioadhesive polymers. A useful knowledge of mucoadhesion and several variables that may impact a polymer's mucoadhesive characteristics can be gained from research on mucoadhesive polymers. Mucoadhesive buccal patches are made with both synthetic and natural polymers. Studies on the development of controlled or slow-release delivery systems for both local and systemic treatment of diseases affecting the oral cavity have also been carried out.

***Keywords-*** Buccal Patch, Mucoadhesion, Buccal Formulation, Permeation enhancers.

## INTRODUCTION

The oral route is the most preferred drug delivery method among the various choices for patients and medical professionals. One component of the mucoadhesive medication delivery system is the buccal drug delivery system. A buccal medication is administered to the systemic circulation through the cheek lining). The submucosa serves as the deepest layer of the buccal mucosa, which is made up of stratified squamous epithelium, which is the outermost layer (about 40 to 50 layers thick).[1-4] The oral mucosa is split into two sections:
Epithelium, first as a layer of defense protecting the tissues below, the epithelium is divided into: The nonkeratinized surfaces of the lips, cheeks, alveolar mucosa, vestibule, ventral surface of the tongue, and the mucosal lining of the soft palate.[1] Keratinized epithelium, is present in the non-flexible areas of the oral cavity and the hard palate.[1]

The basement membrane and connective tissue function as a barrier to keep the connective tissue and the epithelium's basal layer apart. It is made up of extracellular components. The majority of connective tissue makes up the organization that controls the mechanical stability, resistance to deformation, and extensibility of tissue. [5] A mucus is a translucent, viscous fluid that adheres to the mucosal epithelial surface in the form of a thin, continuous gel blanket. In humans, this layer's average thickness ranges from roughly 50 to 450 mm. Goblet cells that line the epithelia or specific exocrine glands with mucus-cell acini secrete it. [3] According to species, anatomical location, and pathophysiological state, the precise makeup of the mucus layer varies greatly. However, it is generally composed of the following:

1. Water 95%
2. Lipids and glycoproteins: 0.5 to 5%
3. Salts of minerals: 0.5 to 1%
4. Free Proteins, between 0.5 and 1%.[5

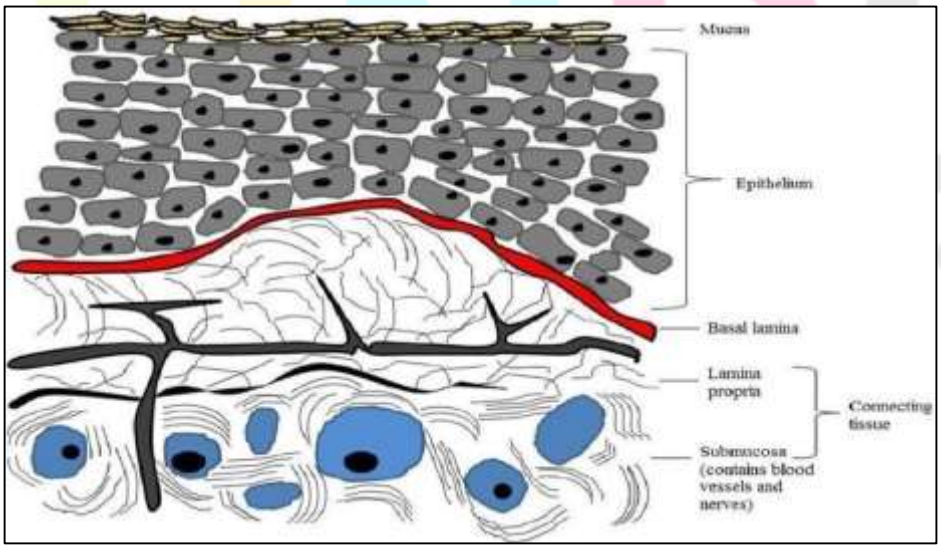


**Figure 1- Structure of buccal mucosa[1]**

The outermost layer of the oral mucosa is made up of stratified squamous epithelium (Figure 1). A basement membrane, a lamina propria, and the sub mucosa the deepest layer are located beneath this. The epithelium has a mitotically active basal cell layer that progresses through a number of developing intermediate layers to the superficial layers, where cells are shed from

the epithelium's surface, similar to stratified squamous epithelia seen in the rest of the body.[2] The sublingual epithelium includes slightly fewer cells than the buccal mucosa's epithelium, which has roughly 40–50 cell layers. As epithelial cells move from the basal layers to the surface layers, they enlarge and flatten. According to estimates, the buccal epithelium turns over every 5 to 6 days. The buccal mucosa measures 500–800 m, while the mucosal thickness of the floor of the mouth, the ventral tongue, the hard and soft palates, and the gingiva measures approximately 100– 200 m. These differences in thickness are due to anatomical factors. Depending on the location in the oral cavity, the epithelium's composition changes as well. The gingival and hard palate is two examples of mucosa that are keratinized similarly to the epidermis in places that are prone to mechanical stress.

However, there is no keratinization of the buccal, sublingual, or soft palate mucosa.[2] Saliva and mucus play important roles in the body's physiological processes. The mucosal tissues are further covered in mucus, which is negatively charged and contains large glycoproteins known as mucins. These keep the pH of saliva between 5.8 and 7.4 and are thought to greatly contribute to its viscoelastic properties. A protein core that is abundant in O-glycosylated serine and threonine and contains many proline residues that break helixes makes up mucin. Saliva is produced by the same salivary glands that produce mucus, protecting soft tissues from chemical and mechanical abrasions. [8, 9] For systemic medication distribution, the buccal route is a desirable mode of administration. In comparison to conventional dose forms, buccal bioadhesive films offer several advantages since they slowly and precisely release topical medications into the oral cavity.(1, PI) Mucoadhesion has gained popularity over the years due to its ability to improve localized drug delivery by keeping a dosage form at the site of action.[10]However, the use of mucoadhesive polymers in buccal drug administration offers a wider range of applications. Tablets, films, patches, discs, strips, ointments, and gels are just a few of the mucoadhesive products that have lately been produced. But compared to other technologies, buccal patches offer more comfort and versatility.[10] Buccal route drug delivery offers direct access to the systemic circulation through the jugular vein, bypassing the first pass hepatic metabolism and resulting in high bioavailability.[11] The buccal cavity is easily accessible for selfmedication, making it safe and well-accepted by patients. Additionally, buccal patches can be applied and even removed from the application site, stopping the input of the drug whenever desired.[12] Mucosal surfaces typically have a lot of blood supply, which allows for fast drug transport to the systemic circulation while preventing degradation by gastrointestinal enzymes and first-pass hepatic metabolism.[3]The buccal mucosa offers a fresh idea for regulated medication administration among the several trans-mucosal routes. Compared to other on-call trans mucosal drug delivery methods, it has great accessibility and high patient satisfaction. [3,9]

## ADVANTAGES [12-14]

1. A healthy blood supply permeates the mouth mucosa. Drugs enter the systemic circulation through the brachiocephalic vein, internal jugular vein, and deep lingual or face vein after being absorbed by the oral cavity's mucosa.[1]
2. The buccal patch is well known for its easy access to the tissues that line the oral canal, which makes application comfortable and painless.
3. Through buccal administration, the medicine bypasses the first pass effect and enters the systemic circulation directly. Avoiding contact with the digestive fluids of the gastrointestinal tract protects several medications against degradation, including insulin and other proteins, peptides, and steroids.

Additionally, neither food nor gastric emptying pace affects the rate of medication absorption.[2] 4. Since many medications are coming into longer contact with the mucosa, they should operate better.
5. If therapy needs to be stopped, the formulation can be taken out.[15]

**DISADVANTAGES [7]**

1. There is a small amount of surface area accessible for absorption. It is challenging to deliver drugs in big doses
2. Drugs that irritate the mucosa, have an offensive taste or aroma or have a bitter or unpleasant aftertaste cannot be administered via this route. [7]

Bioadhesion is the term used to describe any attachment that develops between two biological surfaces or a link between a biological surface and a synthetic surface. Bioadhesive drug delivery methods stick to surfaces and soft tissues by forming a connection between the polymers in the polymer chain. The bond that develops when mucus and a polymer interact is referred to as mucoadhesion. Many bioadhesive delivery techniques may target the soft tissue's cell layer (i.e., epithelial cells), but the adhesive bond may actually form with the cell layer, the mucous layer, or a combination of the two. When analysing the bonds that form between mucus and polymers, the terms "bioadhesion" and "mucoadhesion" are interchangeable. While the term "bioadhesion" is used to describe sticky interactions with any biological or biologically produced substance, "mucoadhesion" is specifically used to indicate a relationship involving mucus or a mucosal surface. [16,51]

***Mechanism of Buccal Absorption [17-19]***

Drug absorption in the buccal cavity is caused by the passive diffusion of non-ionized species. Passive diffusion occurs within the epithelium's intercellular gaps and is primarily controlled by a concentration gradient. The main transport mechanism is the passive movement of non-ionic species through the lipid membrane of the buccal cavity. Like many other mucosal membranes, the buccal mucosa has been described as a lipoidal barrier to the passage of medications; the more lipophilic the drug molecule, the more easily it is absorbed. A first-order rate process can accurately capture the kinetics of medication absorption in the mouth. There are several possible obstacles to buccal medication absorption. According to Dearden and Tomlison (1971), salivary secretion alters the buccal absorption kinetics of the drug solution by altering the drug concentration in the mouth.

**Factors affecting Buccal Absorption [17,20,21]**

The oral cavity is a difficult environment for drug delivery since there are numerous independent and interdependent factors that lower the absorbable concentration at the site of absorption;

*1. **Membrane Factors***

The amount of keratinization, the area that can be absorbed, the mucus layer of the salivary pellicle, the intercellular lipids of the epithelium, the basement membrane, and the lamina propria are some of these. Additionally, the absorptive membrane thickness, blood supply/lymph outflow, cell renewal, and enzyme content will all work together to lessen the rate and amount of medication entering the systemic circulation.

## 2. Environmental Factors

### SALIVA

The salivary pellicle or film is the term used to describe the thin layer of saliva that forms over the entire buccal mucosa lining. The salivary film has a thickness of 0.07 to 0.10 mm. The thickness, makeup, and velocity of the film all affect the rate of buccal absorption.[20]

### SALIVARY GLAND

The deep epithelial region of the buccal mucosa, or where the tiny salivary glands are located, is where they are found. They constantly exude mucus onto the buccal mucosa's surface. Mucus an prevents medication from penetrating the body even though it helps mucoadhesive dosage forms remain in place.[12]

### MOVEMENT OF BUCCAL TISSUES

The mouth cavity's buccal portion exhibits less vigorous movements. It is necessary to contain mucoadhesive polymers to maintain the dosage form in the buccal region for extended periods of time in order to withstand tissue movements during talking and, if possible, during eating or swallowing.[12]

### pH

Studies of polyacrylic polymers crosslinked with COOH groups revealed that pH had a substantial impact on mucoadhesion. Mucus and polymers' surface charges are influenced by pH. Due to variations in the dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone, mucus will have a varied charge density depending on pH. The maximum adhesive strength of polycarbophil is at pH 3. As the pH rises to pH 5, the adhesive strength steadily diminishes. Polycarbophil swells significantly more at pH levels over 5 than at pH levels of 3 or lower. However, due to the electrostatic attraction of carboxylate anions at high pH, the chains are fully stretched.[50]

### Applied Strength

Applying a specific strength is required to position a solid bioadhesive system. Whatever the polymer, be it Carbopol 934, poly (acrylic acid/divinyl benzene poly (HEMA), or poly(acrylic acid/divinylbenzene), the adhesion strength increases with the applied strength or with the time of its application, up to an optimal level. Polymers can become mucoadhesive even when they do not appealingly interact with mucin if strong pressure is applied for a long enough time.[50]

### Initial contact time

The degree of swelling and the interpenetration of polymer chains are determined by the initial contact . The first contact time and starting pressure both period between mucoadhesives and the mucus layer which has a significant impact on a system’s performance. As the initial contact time rises, the mucoadhesive strength grows. Even so, the viability of the tissue should be considered before a longer first contact time.[17]

### SELECTION OF MODEL SUBSTRATE SURFACE

Since physical and biological changes in the mucus gels or tissues under experimental circumstances are possible, handling and treating biological substrates is a crucial factor when testing mucoadhesive. By looking at characteristics like permeability, electrophysiology, or histology, one should be able to determine whether the biological substrate is viable.[21]

### Swelling

This trait relates to both the polymer's surroundings and the polymer itself. Because polymer chains are disentangled and free of interactions, interpenetration of chains is simpler. Both the concentration of the polymer and the presence of water affect swelling. There is a decrease in bioadhesion when edema is excessive.[21]

**Mechanism of mucoadhesion**

Several ideas explain how polymers and mucus interact to cause mucoadhesion. Wetting, adsorption, and interpenetration of polymer chains are all important aspects of the complicated phenomenon known as mucoadhesion.[16] The contact phase and the consolidation step are the first and second steps in the mechanism of mucoadhesion, respectively.[16]

The following mechanism is present first Close physical contact (wetting or swelling phenomena) between a bioadhesive and a membrane and Penetration of the bioadhesive into the tissue or into the mucous membrane surface.[22] The dosage form and mucus surface will get moist during the contact stage. The moisture during the consolidation step activates the polymers' plasticizing and adhesive activities, which support the development of hydrogen bonds and van der Waals forces. The consolidation phase, in which the polymer molecules and the mucus layer's glycoprotein interface and create secondary bonds, is also explained by the theory of diffusion. This will make the adhesion stronger and last longer.[23] Highly hydrated forms or solid formulations are not covered by the dehydration hypothesis. [16] Several broad theories, including the electrical theory, the adsorption theory, the wetting theory, the diffusion theory, the fraction theory, and the mechanical theory, may be used to describe mucoadhesion.[24-27]

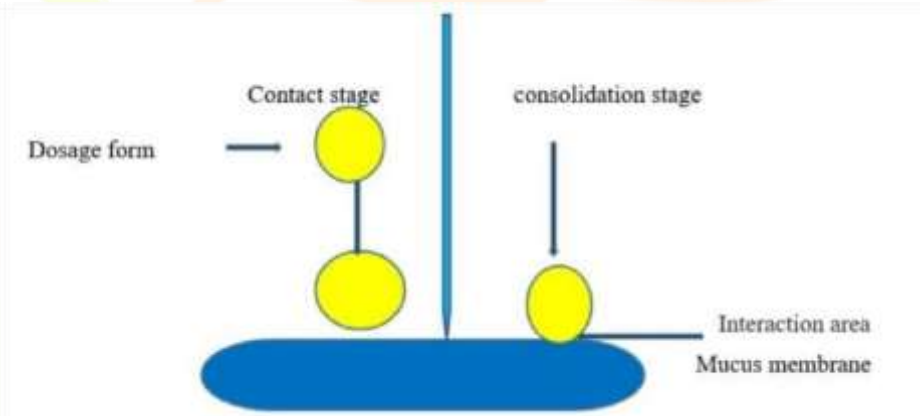


**Figure 2- Steps of mucoadhesion**

**Theories of mucoadhesion *[4,13,28–30,51]***

***1)* Electronic theory**

According to electronic theory, electron transfer occurs when an adhesive polymer comes into contact with a mucus glycoprotein network due to variations in their electrical topologies. An electrical double layer consequently developed at the contact.

***2)* Absorption theory**

As per this theory, the surface force acting between the atoms on the two surfaces the material to first attach to the surfaces. Two types of chemical bonds form Primary chemicals bond covalent in nature because of their undesirable bioadhesion and high strength, which may result in a permanent bond Secondary chemical bonds are included in this list, and different forces of attraction are included, such as the electrostatic force, Vander Waal forces, and hydrogen and hydrophobic bonds.

### *3)* Wetting theory

In this theory, liquid bioadhesive systems are applicable for analyzing Adhesives. The ability of liquid or paste to spread over a biological system. The spreadability coefficient ($S_{AB}$) is calculated by, $AB$

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

Where: Surface energy $\gamma_B$ & $\gamma_A$ and Interfacial energy $\gamma_{AB}$

If greater the interfacial energy in relating to the individual surface energy, greater the adhesion work $W_A$, i.e., greater the energy needed to separate the two phases.

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

### *4)* Diffusion theory

This idea states that the mucus and polymer chains combine thoroughly to form a semi-permanent sticky bond. The time of contact and the diffusion coefficient, which rely on the molecular weight between crosslinks and drop dramatically as the cross-link density increases, determine the precise depth to which the polymer chains enter the mucus.

### *5)* Fracture Theory

This is the most studied theory for measuring the mucoadhesion mechanism. The theory relates to the resulting separation of two surfaces. According to this, the fracture strength is equal to the adhesive strength as given by

$G = (E\frac{\in}{L})^{1}/_{2}$

Where: E is Young's modules of elasticity ∈Is Fracture energy

L is Critical crack length when two surfaces are separated.[4, 13, 28–30,51]

**Types of buccal patch** [12,31]

#### 1) MATRIX TYPE (BI-DIRECTIONAL)

The buccal patches are designed in a matrix configuration and contain drug adhesive and additives mixed together. The main advantage of this matrix type is the drug release in both the mucosa and mouth through the bi-directional patches.

#### 2) RESERVOIR TYPE (UNIDIRECTIONAL)

The reservoir-type buccal patch has a cavity for the medication and any additives separate from the adhesive. In order to regulate the direction of medication distribution, prevent patch deformation, and prevent patch disintegration while in the mouth, an impermeable backing is used, as well as to stop drug loss. Unidirectional types play an important role. Different kinds of buccal patches are utilized in the buccal cavity to have both local and systemic effects.

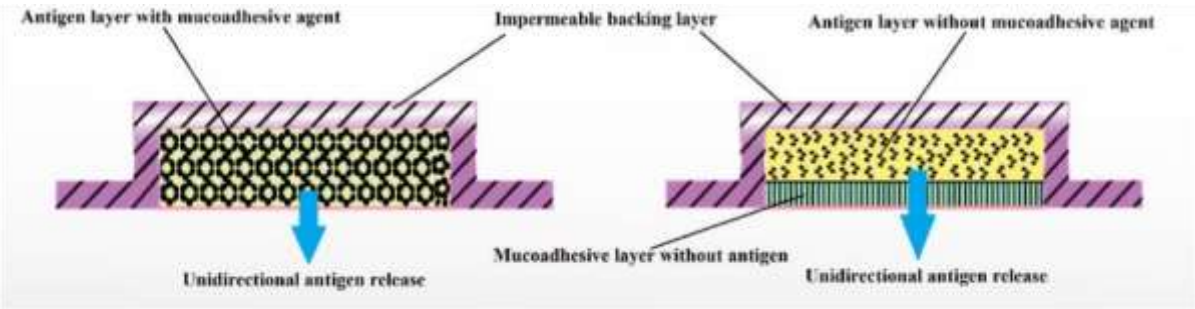


**Figure 3-Possible designs of multilayered vaccine comprised buccal film with different functions for unidirectional release of antigen.[13]**

**Methods to increase drug delivery via buccal route *[32, 33]***

*1)* **Absorption enhancers**

High-molecular-weight substances like peptides, which typically have low buccal absorption rates, have been effectively delivered via absorption enhancers. These may exert their effects by a variety of
methods, including enhancing the fluidity of the cell membrane, removing intracellular or extracellular lipids, changing cellular proteins, or changing surface mucin. Azone, fatty acids, bile salts, and surfactants like sodium dodecyl sulphate are the most popular absorption enhancers. Gels or solutions of chitosan were found to increase the transport of mannitol and fluorescently labelled dextrans across a tissue culture model of the buccal epithelium, while glyceryl monooleates were found to increase peptide absorption by a co-transport mechanism.

*2)* **Prodrugs**

Opioid agonists and antagonists were delivered by Hussain et al. in bitterless prodrug forms, and it was discovered that the drug had a low prodrug bioavailability. When delivered to dogs through the buccal mucosa, the bitter medicines nalbuphine and naloxone resulted in excessive salivation and swallowing. The medication had limited bioavailability as a result. Naloxone and nalbuphine were administered as prodrugs without causing any negative side effects, and their bioavailability ranged from 35 to 50%, a significant improvement over their oral bioavailability, which is typically 5% or less.

*3)* **pH**

Shojaei et al. investigated the permeability of the drug acyclovir in the presence of the absorption promoter sodium glycocholate and pH levels ranging from 3.3 to 8.8. Acyclovir was found to have pHdependent in vitro permeability, with flow and permeability coefficients increasing at both pH extremes (3.3 and 8.8) in comparison to the mid-range values (4.1, 5.8, and 7.0).

*4)* **Patch design**

Several *invitro* investigations on the kind and quantity of supporting materials and the drug release profile have been done, and they have revealed a relationship between the two. The pattern of drug release varied between single-layered and multi-layered patches as well.

**Composition of buccal patch 1) Active pharmaceutical ingredients *[11,12, 34, 35]***

To obtain the desired therapeutic effect with buccal delivery of medication, the interaction between API and mucosa must be prolonged and enhanced. The molecular weight, chemical activity, and melting point of a drug all have an impact on how well it diffuses through the patch and buccal mucosa. Selecting a suitable medication for the development of buccal buccal patches can commonly contain active pharmaceutical ingredients in doses ranging from 5%w/w to 30%w/w. For example:

Antiulcers– omeprazole

Antiasthmatics- Salbutamol, sulphate can be packaged as mouth-dissolving films.

The following should form the basis of a mucoadhesive medicine delivery system:

The normal single dose of the medication must belittle.

The biological half-lives of the medicines, which range from 2 to 8 hours, make them excellent candidates for controlled drug delivery.

When taken orally, the drug absorption ought to be passive.

*2)* **Mucoadhesive polymer** ***[34]***

Mucoadhesive polymers interact with mucus and are important components of mucoadhesive dosage formulations. They are selected and distinguished by their capacity to attach to mucosal surfaces. Mucoadhesive polymers are essential in mucoadhesive dosage forms because they interact with mucus. They are also utilized in matrix devices to control the time of drug release.

In matrix devices, polymers are also employed to embed the drug, which regulates the timing of the drug release. Polymer hydration and swelling characteristics are critical for mucoadhesion. Polymer hydration improves mucin cohesiveness, which aids in adhesion. Swelling increases the flexibility of polymer chains and their interaction with mucin chains. Depending on the formulation, different polymers such as Carbopol, hydroxyethyl cellulose, polyvinyl alcohol etc. are utilized.

**Characteristics of ideal mucoadhesive polymers:**

- The polymer and the byproducts of its breakdown must not be poisonous or absorbed by the GIT.
- It shouldn't aggravate the mucous membrane.
- It should have rapid adhesion to a wet tissue surface and some site specificity.
- It should make the drug's integration simple and not obstruct its release.
- The polymer must not break down while being stored or during the dosage form shelf life.
- The polymer needs to be reasonably priced and widely accessible in the market.

3) **Backing membrane [36, 37]**

The mucus membrane is the primary surface on which bioadhesive devices are attached. The substances utilized as the backing membrane should be neutral, impermeable to the drug, and capable of enhancing penetration. Backing membranes frequently employ Carbopol, magnesium stearate, HPMC, HPC, CMC, and polycarbophil, among other compounds.

*4)* **Plasticizer** ***[38, 39]***

These are the components used to make thin films of polymer or a polymer blend flexible and soft. Castor oil, glycerol, propylene glycol, PEG 200, and PEG 400 are a few examples of commonly used plasticizers. The plasticizers operate penetration promoters and aid in drug material release from the polymer base. The selection of the plasticizer is based on how well it can solvate the polymer and change the interactions between the polymers. These materials provide flexibility by reducing the molecular stiffness when utilized in the proper ratio with the polymer.

5**) PERMEATION ENHANCERS [40]–[42]**

Permeation enhancers are substances that help substances pass through the buccal mucosa more easily. The physicochemical qualities of a drug and its administration site, vehicle type, and other excipients all affect the selection of an enhancer and its efficacy.

Mechanism-Permeation enhancers change the rheology of the mucus by reducing its viscosity, and saliva moves through this barrier. By interacting with either lipid or protein constituents, it increases the fluidity of the lipid bilayer membrane and disrupts the intracellular lipid packing. By inhibiting different peptidases and proteases found in the buccal mucosa, it operates on the components at tight junctions and break down the enzymatic barrier. Additionally, it modifies the fluidity of the membranes, which impacts enzymatic activity. It

change the partition coefficient of pharmaceuticals by making them more soluble, enhancing their thermodynamic activity.

**Mechanism of Permeation enhancers *[40][42]***

Changing bilayer → Increasing the fluidity of lipid → Acting on the tight junctions → Increasing the activity of drug → Increasing the thermodynamic → mucus rheology membrane

*Table 1: Mucoadhesive Polymers for Buccal Patches*

| Category | Example | Mechanism |
|---|---|---|
| Surfactants & Bile Salts | Surfactants and Bile Salts<br>Sodium dodecyl sulphate<br>Sodium lauryl sulphate<br>Polysorbate 80 | Affect the components at tight junctions increasing the lipid bilayer membrane's fluidity. |
| Fatty Acids | Oleic acid,<br>Cod liver oil,<br>Capric acid,<br>Lauric acid | Increasing the lipid bilayer membrane's fluidity |
| Polymers & their Derivatives | Chitosan<br>Trimethyl chitosan<br>Chitosan-4- thiobutylamide | Increasing the lipid bilayer membrane's fluidity; Increasing the drug's retention at the mucosal surface |
| Others | Ethanol<br>Azone<br>Octisalate, | Acting on the elements at tight junctions; making the lipid bilayer membrane more fluid |
| | Padimate Menthol | |

**Methods of preparation of buccal patch Two methods to use to prepare adhesive patches include,**

**1) Solvent casting**

Solvent casting involves dispersing the medicine and all excipients for the patch together in an organic solvent before coating the sheet of release liner. A thin layer of the protective backing material is laminated onto the substrate following solvent evaporation. A laminate made from a coated release liner sheet that is die-cut into patches of the specified size and

geometry despite being straightforward, the solvent casting method has certain drawbacks, such as a lengthy production time, a high cost, and environmental concerns related to the solvents utilized. Hot melt extrusion can be used to get around these problems.[43]–[45]

### 2) DIRECT MILLING

In this process, patches are made solvent-free (without the use of solvents). Direct milling or kneading is typically used to mechanically combine the drug and excipients without the use of any liquids. Once the material has been mixed, it is rolled on a release liner until the desired thickness is obtained. Additionally, an impermeable backing membrane can be used to regulate drug release direction, stop drug loss, and reduce the device's deterioration during the application period. Although there are very few, if any, changes in patch performance between patches made with different Given a choice between two methods, the solvent-free process is chosen because there are no linked health problems brought on by solvents.[12]

## Evaluation of buccal patches

### 1) Surface pH

On an agar plate, buccal patches are allowed to swell for two hours. By placing a pH paper on the surface of the swollen patch, the surface pH is measured.[12, 46]

### *2)* Thickness Measurement

Using an electronic digital micrometer, the thickness of each film is measured at specific positions (the center and four Separate corners). [47]

### *3)* Swelling Studies

Swelling-related weight gain and area growth were measured. Swelling-related weight gain: On a preweighed cover slip, a 1x1 $cm^2$ drug-loaded patch was weighed.50 cc of phosphate buffer and a petridish were used to store it. Addition of pH 6.6. The cover slip was taken off and weighed up to 30 minutes after every five minutes. Due to the patch swelling and water absorption, weight differential causes weight to grow. Area swelling increase: A 1x1 cm2 drug-loaded patch was cut and inserted in a Petri dish. The paper graph was used to gauge the area's expansion beneath the Petri dish. 6.6 pH phosphate buffer, 50 milliliters, was the Petri dish with liquid. Over 60 minutes, the patch's length and width grew, and its area was measured at 5-minute intervals. Using the following equation, the percent swelling, *%S*, was determined:

$$Xt - Xo\%S = x\ 100Xo$$

Where *Xt* represents the weight or area of the enlarged patch at time t, and *Xo* represents the weight or area of the original patch at time zero.[48]

### *4)* Folding Endurance

Folding endurance tests are conducted by repeatedly folding the film at the same location until the film fails. The value is provided as the Number of folds the film can withstand before rupturing and the test's upper limit of 300 times is occasionally stated.[43, 49]

*5*) **Viscosity**

Water-based mixtures are made with the same amount of plasticizer and polymer as the patches.

A helipath spindle number 4 was used in conjunction with a Brookfield viscometer type LVDV-II at 20 rpm and room temperature, the viscosity was measured. The values that were recorded were the average of three analyses.[31]

**6) Thermal Analysis Study**

A differential scanning calorimeter (DSC) is used to conduct a thermal analysis investigation.[1]

**7) Morphological characterization**

SEM (scanning electron microscope) is used to study morphological traits.[31]

*8)* **Water absorption capacity test**

Agar plates containing simulated saliva (2.38 g $Na_2HPO_4$, 0.19g $KH_2PO_4$, and 8 g NaCl per litter of distilled water adjusted with phosphoric acid to pH 6.7) are created with circular patches with a surface area of 2.3 cm2 and are then allowed to expand. The circular patches are then placed in an incubator that is kept at 37°C plus or minus 0.5°C. Samples are weighed at different time intervals (0.25, 0.5, 1, 2, 3 and 4 hours), and then they are dried for 7 days in a desiccator over anhydrous calcium chloride at room temperature. The final constant weights are then recorded. Using the following equation, water uptake (%) is calculated:

$$Water\ uptak(\%) = (Ww - Wf) \times 100 \div Wf$$

In this case, *Ww* stands for the wet weight and *Wf* for the final weight.

Each film has its swelling quantified.[12]

*9*) **InVitro Drug Release**

The rotating paddle method described in United States Pharmacopoeia (USP) XXIII was employed to examine the medication. Release from the patches with two and more layers.The phosphate buffer with a pH of 6.8 served as the dissolving media. At a speed of 50 rpm and a temperature of 37 $^0$C ± 0.50 $^0$C, the release was carried out. With the help of instant adhesive (cyanoacrylate adhesive), the backing layer of the buccal patches was secured to the glass disc. The disintegration vessel's bottom was given over to the disc. At predetermined intervals, samples (5ml) were removed and replaced with new media. After being properly diluted, the samples were filtered using Whatman filter paper and subjected to UV spectrophotometry analysis at the appropriate nm.[12]

10) **INVITRO DRUG PERMEATION**

Using a glass diffusion cell of the Keshary/Chien/Franz type and operating at a temperature of 37°C ±0.2°C, the in vitro buccal drug permeation research of Drugs via the buccal mucosa (sheep and rabbit) was conducted. Between the donor and receptor compartments, new buccal mucosa had grown. The core of the buccal pill was positioned facing the mucosa, and the compartments were fastened together.1 cc of pH 6.8 phosphate buffer was placed in the donor compartment. A magnetic bead was used to agitate the phosphate buffer at 50 revolutions per minute while the receptor compartment was filled with the solution, which had a pH of 7.4.At regular intervals, one ml of the sample can be taken out and put into a UV spectrophotometer to be examined for drug content at the appropriate nm.[50]

### *11*) Stability Study in human

The optimal bilayered and multilayered patches' stability is investigated using saliva samples taken from people between the ages of 18 and 50. Five milliliters of human saliva are placed in each of the individual petri plates containing buccal patches. After that, the dishes are kept at 37±0.2°C for six hours in a temperature-controlled oven. On schedule at 0, 1, 2, 3, and 6-hour intervals, the dosage formulations with superior bioavailability must be present enhanced techniques for transmucosal and transdermal medication delivery techniques are crucial since they eliminate the pain factor. About the parenteral medication administration routes. Buccal glue Systems are advantageous in terms of administration withdrawal, and accessibility, economy, high patient compliance, low enzymatic activity, and retainability.[33]

## Conclusion

The buccal mucosa offers several advantages for controlled, long-term drug delivery. The mucosa frequently experiences both vascular and lymphatic drainage, which prevents first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. The patient seems to find the area satisfactory, and it is suitable for a retentive device. It is possible to regulate and modify the mucosa's permeability and local environment to allow for medication absorption through appropriate dosage form design and formulation. Buccal drug delivery is a promising field that requires more investigation to administer inefficient oral medications systemically and provide an effective and attractive substitute for the non-invasive delivery of potent peptide and protein therapeutic molecules. For the area of buccal delivery of medicines to have a bright future, safe and efficient enhancers for buccal permeation and absorption are essential.

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