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# A Review Article on Oral Mucosal Drug Delivery System

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***Abstract—*** *A New Drug Delivery, such as a Mucoadhesive System, can enhance the effectiveness of drugs, by eliminating Enzymatic degradation and first-pass metabolism caused by Gastro intestinal region, oral mucosal drug delivery system are frequently used as a Novel site for administration of drugs for Immediate and Controlled release. A sophisticated method called mucoadhesion that uses a polymer drug delivery system involves polymer chain interaction through Wetting, Adsorption and Other Mechanisms. Many polymer based characteristics including the level of Cross-Linking, Chain Length, and existence of different Functional Groups, have an Impact on the Effectiveness and Degree of Mucoadhesive Binding. By maintaining Intimate Interaction with the tissue that absorbs, the mucosal surface release the medicine at the site of action, improving both Local and Systemic Effects. The mucosa contains number of blood stream and is Comparatively permeable. The mucosa of the buccal cavity is ideal due to its Accessibility, Smoothness, Immobile Surface, and Bioadhesion System Suitability. Moreover, It is conceivable to provide medication to individuals who are unconscious and uncooperative. It covers a variety of dosage forms with different combination of polymers and Absorption Enhancers, such as adhesive Patches, adhesive Gels, adhesive Tablets and many more*.

***Keywords—*** *Mucoadhesive; Bioadhesion; Buccal Dosage; Mucosa; Patches; Permeation Enhancer*.

## I. INTRODUCTION

A drugs may be targeted to a specific body part for a prolonged amount of time using Mucoadhesive drug delivery system, which make use of the bioadhesion of certain polymer that become adhesive when moistened. The word mucoadhesion refers to the attachment of a polymer or biological substrate to the mucin layer of the mucosal tissue[1]. Oral mucosal drug delivery system is further separated into sublingual and buccal, In general, the buccal cavity is favourable for administering medications through mucosa ,while In the case of sublingual route, which is primarily advantageous to take action as soon as possible, like in the case of angina pectoris. Buccal formulations are inserted in the mouth between the cheek and the upper gingivae for the treatment of both Local and Systemic disorders.[2]

Drug distribution through mucosal routes are :

- Buccal Delivery Routes
- Nasal Delivery Routes
- Ocular Delivery Routes
- Vaginal Delivery Routes
- Gastrointestinal Delivery Routes
- Rectal Delivery Routes

Advantages of Oral Mucoadhesive Drug Delivery System

- Prolongs the dose forms, stay at the absorption site. Hence, the bioavaibility is Increased.
- Rapid response and excellent accessibility.
- Medication is protected against degradation in the GIT's acidic environment.
- Patient compliance has improved.[3]
- Injection-related pain is eliminated.
- Administering medications to individuals who are unconscious or uncooperative.[4]
- Sustained drug delivery.
- Compared to taking a medication orally, one can get a reasonably quick Onset of action.
- Rapid and comprehensive medication absorption is facilitated by mouth cavity's due to its large contact surface.[4]

Disadvantage of Oral Mucoadhesive Drug Delivery System

- Local ulceration effects that results from prolonged contact of medications with ulcerogenic properties.
- One of the biggest barriers is the absence of a model for in-vitro testing to identify medications appropriate for such administration which preventing the evolution of Oral Mucosal Drug Delivery.
- Patient acceptance with regard to taste and irritability.
- Eating and drinking issues are problematic.[3]
- Due to saliva's flushing activity, the medication is rapidly eliminated, hence requiring frequent and regular dosage.
- There is a chance some oral cavity regions could not get doses of the medicine if it is not distributed uniformly in saliva.

## II. ANATOMY OF THE BUCCAL MUCOSA

The sub-mucosa serves as the Innermost shealth and is backed up by the lamina propria, which is the outside shealth of the oral mucosa. Also There are several sense receptors, including taste receptors on the tongue. Keratinous tissue is said to be absent from the blood epithelium. Collagen fibers are found in the lamina propria tissues, which shields the blood vessels, the connective tissue layer, and the smooth muscles[5]. The membrane lining in the buccal cavity is divided into masticatory, lining, and specialized mucosa. The Keratinized tissues make up the masticatory mucosa, while a Non-Keratinized tissue lines the lips, cheeks, and other areas of the mouth. There are variable thicknesses and compositions of both types of tissues throughout the oral cavity, The mouth's surface area is made up of 50% keratinized tissue and



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30% non-keratinized tissue[6]. The buccal mucosa's non-keratinized epithelium is made up of a squamous stratified epithelium. The connective tissue with several cell layers on top is called the lamina properia. The basal membrane serves as a barrier between the epithelia and the connective tissue layer. The majority of the layer of tonofilament contains a significant quantity of protein[7]. There are five primary areas of the oral cavity that make up the oral mucosa divided into :

- The Mouth's Floor or sublingual regions.
- Cheek Tissue, or Buccal Mucosa.
- Ginigiva, or Gum.
- The Mucosa of the Palate.
- Lips Inner Side.

## III. Theory of Bioadhesion

There are various ideas available to clarify the experimental data developed around the Bioadhesion concept. However, No Theoretical Model can adequately capture the complexity of collaboration that includes bioadhesive bonds and five significant hypotheses, which can be differentiated below.[14] [15]

### *A. Wetting Theory*

This Theory, which mostly applies to liquid bioadhesive systems, looks at adhesive and closeness manners in relation to a liquid or a mush that can extend across a biological system.

### *B. Diffusion Theory*

According to Diffusion Theory, a semi-permeable adhesive connection can be formed between a polymeric series and a mucus mixture. The exact distance that the polymer chain series may go through the mucus which is affected by its contact span and diffusing coefficient. Also, when a cross-linking density decreases, the diffusion coefficient, which is proportional to the ratio of molecular mass among cross-links, significantly decreases.

### *C. Electronic Theory*

This hypothesis proposes that when a mucus glycoprotein is in close contact to a adherent polymer, electronic transmission takes place because of variations in their electrical structures. An electronic bilayer forms at the interface as a result of the attraction force occurring across the double membrane.

### *D. Fracture Theory*

The splitting of two surfaces after adhesion is related to this adhesion concept or Equals to the adhesive intensity denoted as fracture strength.

### *E. Adsorption Theory*

These ideas state that two different chemical bond types, including primary chemical and secondary chemical interactions, are a part of the adsorption process because the atoms in the middle of the two surfaces are being affected by surface forces.

## IV. Novel Buccal Dosage Types

### *A. Buccal mucoadhesive Tablets*

They are an essential dry formulation that must be moistened before being in close contact with the buccal mucosa. As an example, Think of a two-layered tablet with a cocoa butter core within that contains sodium Glycocholate and Insulin, also an adhesive matrix layer made of Hydroxypropyl cellulose.[8]

### *B. Patches and Films*

In the buccal patches, there are two laminations a watery polymeric adhesive solution that is fixed in a non-permeable backing sheath structure and splits into the required oval structure and a Gelatin which is a special mucoadhesive film made of an alcohol, Hydroxypropyl cellulose, and organic acid solution. When applied to the buccal mucosa region, can stay in place for up to 12 hours.[8]

### *C. Semi-solid Formulation*

when compared to solid muco bioadhesive dosage forms, gels and ointments that are existing in bioadhesive forms do not have as high patient compliance rate. Most dosage forms are used for local drug delivery. The oral formulation Orabase, is a gel and it can stay in place for 15 to 150 minutes.[8]

### *D. Powders*

As compared to oral solution, the Rat's Basement Membrane shows a significant Improvement in Residence Time when Hydroxypropyl cellulose and Beclomethasone are retained on the Basement Membrane for more than four hours.[8]

## V. Methods for Enhancing Absorption In Buccal Drug Administration

### *A. Permation Enhancers*

The epithelium that lines the Basement Membrane is one of the major obstacles to drug absorption. A substance that permits oral permeation is referred to as an absorption enhancer. The majority of absorption enhancers were created to boost drug effectiveness, decrease toxicity, and improve absorption. Hence, the collection and efficacy of an enhancer depend on the drug's physiochemical properties, the site of administration and the kind of vehicle, etc.[5]

Penetration enhancers can improve absorption in a variety of ways, including:

- Mucus Rehology alteration.
- Improve the fluidity of the membrane with Two layers of lipid.
- Functioning on the constituent at the compressed junction through the removal of the Enzyme's Blockage.
- Enhanced Thermodynamic medication effects behavior.[9]

### *B. Enzyme Inhibitors*

Another method to increase drug absorption through the buccal cavity is to combine Inactive drugs with enzyme inhibitors. This is especially true for peptide and protein medications, which are stabilized using a variety of methods,



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including changing the way enzymes work by modifying the structure of peptides or proteins and employing Enzyme inhibitors like aprotinin and bestatin, as well as some bile salts also make the medications less sensitive to enzyme degradation.[10]

### C. Prodrugs

The oral mucous membranes of dogs were made to salivate excessively by swallowing the bitter drugs nalbuphine and naloxone. The medication was therefore properly bioavailable. Uses of nalbuphine and naloxone as prodrugs did not have a negative effect, and their oral bioavailability was significantly increased by 35% to 50%, which is typically 5% or less.[8]

## VI. BIOADHESION

The Term "bioadhesion" (sometimes referred to as "mucoadhesion") was coined by Longer and Robinson to refer to a macromolecule attachment to mucus or its surface. There is still a general idea of polymer adhesion to biological or mucosal surfaces. A substance that can work with and adhere to organic material over a prolonged period of time is referred to as a bioadhesive.[11]

## VII. MECHANISM OF MUCOADHESION

There is currently a lack of knowledge on the mechanism by which some macromolecules adhere to the surface of mucus tissue. The spread of the mucoadhesive over the substrate surface is necessary to start Close contact and thereby maximize superficial contact. This also makes it easier for their chains to spread through the mucus. There are forces of attraction and repulsion, and a mucoadhesive materials must succeed in overpowering the attraction forces. Each phase can be aided by the nature of the dosage and how it is administered. Moreover, the mucoadhesion process often involves two steps.[12]

### A. Contact stage

There is close wetting between the Mucoadhesive and the mucous membrane. These two surfaces can occasionally be physically combined while still being preserved, such as inside the vagina, oculum, or oral cavity.[13]

### B. Consolidation stage

There are many physicochemical interactions that make up the adhesive bond blend and make them harder, resulting in adhesion that lasts for a long time. When mucoadhesive materials are moist, they adhere strongly stable at dry surface areas. This allows effective mucoadhesive molecules to frozen, after they conform to the shape of the surface and are mostly bonded by hydrogen, and the Vander wall bonding process which is weaker.[13]

## VIII. FACTORS AFFECTING MUCOADHESION

The factors listed below determine a drug carrier's mucoadhesion to the membrane.[16]

### A. Variables based on polymers

- Molar Mass
- Used polymer concentration
- Factor of Swelling
- Stereochemistry of polymers

### B. Ecological variables

- Applied Force
- Proximity Duration

### C. Physiological variables

- Sickness conditions
- Rate of Mucin Turnover

TABLE I. Formulations that are Marketed and designed for Buccal Medication administration.[17]

| Manufacturers | Products | Applications |
|---|---|---|
| Cephalon | Fentanyl citrate oral Transmucosal Solid Dose Form | Pain Management for Cancer |
| Ergo pharm | Norandrodiol Buccal Tablets | Nutritional Supplement |
| Columbia laboratories | Desmopressin Buccal Tablets | Controlling Increased thirst and Excessive Urine prevents Dehydration. |
| Generex Biotechnology Corp. | Buccal Insulin Spray | Diabetes Mellitus Type 2 |
| Leo pharmaceutical | Mucoadhesive Nicotine Pill | Relieves Withdraw Symptoms |
| Pharmax limited | Glyceryl trinitrate | Angina Treatment |
| Reckin benckiser | Bupronorphine HCL and Naloxone HCL | Addiction Treatment for Opioids |
| Rhone Poulenc Rorer | Prochlorperazine bioadhesive buccal Tablets | A Treatment for migrane as well as other causes of nausea, vomiting, and dizziness |
| Teijin Ltd | Triamcinolone acetonide | Treatment of different skin conditions |
| Wyeth pharmaceuticals | Lorazepam buccal Tablets | Treatment for insomnia and anxiety problems |

## IX. EVALUATION OF BUCCAL DELIVERY

### A. Drug-excipients interaction studies

Drug-excipient interactions investigations are important when developing solid dosage forms and formulating drugs. Evaluation of studies on potential medication and excipient interactions by Thin layer chromatography, X-ray diffraction, infrared Fourier transform spectrum, and a differential-scanning calorimeter. Due to its ability to display variations in appearance, as well as altering melting endotherms or exotherms, and fluctuation in the accompanying reaction energy levels. the differential scanning calorimeter is used to quickly assess potential incompatibilities also.[18]

### B. Physical evaluation

The homogeneity of the content, weight, and thickness are all included. The ten patches from each batch's average weight that were randomly chosen was compared to each individual patch to evaluate weight variation. In order to determine the mean thickness, the film's thickness needs to be calculated at five different points (the centre and the four corners). Samples containing air bubbles, tears, or nicks with a mean thickness variation of more than 5% should be removed from analysis. Each formulation was divided into three patches with 20 mm diameters, placed in 100 ml volumetric flasks, and stirred



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continuously for 24 hours. 100 ml of phosphate buffer solution with a pH of 6.8 was then added. Filtered, appropriately diluted, and subjected to UV spectrophotometer analysis, the Readings were finalized using the average of three patches.[19]

### C. Surface pH

In order to check for potential side effects in-vivo, the pH of the buccal patch's surface was measured Because an hyper acidic or basic pH levels can discomfort buccal surface, the surface pH should be kept as near to neutral as possible.[20] An electrode made of composite glass was used for this. The buccal patches inflated after coming into touch with 1 ml distill water of pH 6.5 ± 0.05, at room temperature, which they did for two hours. After adjusting for a minute, an electrode was placed on the buccal patches surface to monitor their pH.[21]

### D. Swelling studies

- The weight of the patch increases with swelling:

A 1x1 $cm^2$ drug-loaded patch was retained and balanced on a previously balanced cover slip prior to 50 ml buffered phosphate of pH 6.6 was increased. For a total of 30 min, The cover slip was taken away and balanced every 5 min. The weight variation shows the weight gain brought on by patch swelling and water absorption.[22]

- Swelling increases patch area:

A Petridish was used to store a 1x1$cm^2$ drug-filled patch. To gauge the patch's expanding size, a graph paper was positioned beneath the petridish. the buffered phosphate of pH 6.6, was applied to the petridish in an amount of 50 ml. Up to 60 minutes, the patch's length, width, and area were all measured at five-minute intervals. To calculate the percentage of swelling (% S), the formula below was employed.[23]

$$\%S = Mt - Mo / Mo \times 100$$

Here,
Mt denotes size or weight of expanded patch at time t.
Mo denotes patch initial area or weight at time zero.

### E. Palatability test

A palatability test is carried out on the basis of the flavour that follows the bitterness and the substance's appearance. All batches have the designations A, B, and C in accordance with the requirements. A formulation is regarded as average if it earns at least one A grade. A formulation is considered good when it obtains two A grades, and very good when it receives all the three A grades.[24]

A = Very Good
B = Good
C = Poor

### F. In vitro drug release

The rotating paddle method of the United States Pharmacopoeia (USP) was used to investigate the frequency of medication release from multilayered and bilayered tablets. The dissolving media is pH 6.8 phosphate buffer. At a spin speed of 50 rpm, The experiment was run at 37°C ± 0.5°C. A fast adhesive (cyanoacrylate glue) was used to affix the buccal tablet's backing layer membrane to the glass disc. The disc was put in charge of the disintegration vessel's base. 5 ml samples were taken out and replaced with new medium at regular intervals. After being properly diluted, the raw materials were filtered using Whatman filter paper and subjected to UV spectrophotometry analysis.[25]

### G. In vitro drug permeation

Medications have been studied in vitro for their ability to permeate throughout the Mucosal tissue of rabbits or sheep. Which is carried out at 37°C ± 0.2°C using a glass diffusion cell of the Keshary-Chien or Franz type. It has a fresh buccal mucosa as well as donor and receptor compartments. The compartments were clamped together, with the buccal tablet's within side that is facing the mucosa. One milliliter of Buffered phosphate of pH 6.8 and one millilitre of Buffered phosphate of pH 7.4 are put into the donor and receptor compartments, respectively. A magnetic bead was used to stir at 50 revolutions per minute in order to maintain the hydrodynamic state in the receptor compartment. A UV spectrophotometer set to the appropriate wavelength can be used to extract one milliliter of the sample and evaluate it for drug content at predetermined intervals.[26]

### H. Human saliva stability study

According to ICH guidelines, each batch of quick dissolving films undergoes a stability examination. The films were checked for their physical characteristics, drug content, and disintegration time after a predefined length of time. The improved mucoadhesive patch formulation's stability was examined over a three-month period at 40°C, 37°C ± 5 C°, and 75 ±5% RH. With the exception of minor but significant changes in the metrics volume entrapment effectiveness, expansion, and release of drugs after eight hours, all parameters values were same after three months.[27]

## X. Buccal Patch Applications

Nowadays, it's standard procedure to provide drugs to patients through means of their buccal mucosa. When compared to other methods, giving medication by means of the buccal mucosa has a number of benefits. These are some potential applications for buccal patches:

- Vaccines.
- A Steady Controlled Released.
- Nicotine Replacement Treatment.
- Medications for asthma, emetic medications for nausea, and herpes.
- Heart Condition Management.
- Targeted treatment for oral cancer,
- Hypoglycemic medications.

## XI. Future Prospects and Challenges

There is a serious problem with oral absorption for hydrophilic macromolecular medicines, which is poor and inconsistent. Large-scale synthetic production of pharmacologically active peptides and proteins is now achievable because to developments in synthetic chemistry and biotechnology. These substances do, however, have the potential to be medicinally useful if reliable delivery systems



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can be developed and put into place. Non-parenteral administration of entire proteins and peptides into the circulatory system, as well as the cloning and synthesis of polypeptides, will be the main areas of pharmacological research in the future. To increase buccal permeation, a number of penetration-enhancing substances may be applied to the mucosal and dermal surfaces of the oral cavity and skin. In addition to conventional polymer networks, researchers are also looking at other drug transport mechanisms. The development of buccal films or patches that contain nanoparticles as well as other fictionalization techniques are being studied in order to improve systemic targeting and buccal mucosal penetration. Examples of innovative materials for prolonged release buccal adhesive drug delivery include block copolymers, complex forming networks sensitive to hydrocarbon bonds, and biodegradable polymers that break down from food sources. Scientists are now focusing on developing buccal adhesive systems that could boost the bioavailability of orally less ineffective medications by changing formulation techniques that involve pH adjustments, enzyme blocking agents, and permeability boosters. It is still being studied. It is being investigated if the buccal mucosa can affect how medications are absorbed. Before oral delivery by the buccal mucosa to be regarded effective and safe, a number of problems must be resolved. Before developing new formulations, it is important to thoroughly understand the chemical composition and physical properties of these novel materials.

## XII. CONCLUSION

For a number of therapeutic candidates, regulated drug delivery methods can be modelled after mucoadhesion. There is no denying that taking medication by mouth is the most preferred and, probably, the most difficult method of medicine administration. Numerous benefits for long-term controlled medication delivery are offered by the buccal mucosa. In that circumstance, pre-systemic clearance in the digestive tract and first-pass metabolism in the liver are avoided. An effective way to administer medication is through the well-supplied lymphatic and vascular drainage into the mucosa.

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