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### BIOADHESIVE BUCCAL DRUG DELIVERY SYSTEMS A SCIENTIFIC MINI REVIEW

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#### Abstract

Administration of drugs via buccal route provides convenient for both systemic and local drug effects. Bio/mucoadhesive biopolymers were utilized in different buccal dosage forms in efforts to achieve systemic circulation of drugs through the buccal mucosa. Development of successful buccal drug delivery systems depends dose/device mucoadhesion on the buccal mucosa is a key factors. Limitations related to the buccal drug delivery systems and its key advantages and challenges is also been discussed in the article.

**Keywords:** Bio/mucoadhesive polymers, Site-site-specific, Buccal delivery.

#### Introduction

Over the past few decades, controlled drug delivery and site-site-specific drug delivery have made rapid advances. Bioadhesive systems now play a major role in this field, due to their interesting potentialities. Besides acting as platforms for sustained release dosage forms, bioadhesive polymers can themselves exert some control over the rate and amount of drug release, and thus contribute to the therapeutic efficacy of bioadhesive drug delivery system.

#### Bioadhesion and bioadhesives are classified in to three type based on phenomenological observation

**Type-I:** It is characterized by adhesion occurring between biological objects without involvement of artificial materials.

**Type-II:** It refers to adhesion of biological materials to artificial substrates.

Ex. Cell adhesion onto culture dishes.

**Type-III:** It refers to adhesion of artificial substrates to biological substrates.

Ex. Adhesion of polymers to skin or other soft tissues.

Bioadhesive polymers are polymers that will attach to relate tissues or the surface coating of the tissues. In case of polymer attached to the mucin layer of mucosal tissue, the term "mucoashesive" is employed. The idea of mucoadhesive came in to existence from the need to localize drug at a certain site in the body. Often, the extent of drug absorption is limited by the residence time of the drug at the absorption site. In oral drug delivery,

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the drug absorption is limited by the gastrointestinal transit time of the dosage form. Since many drugs are absorbed only from the upper small intestine, localizing oral drug delivery systems in the stomach or duodenum, would significantly improve the extent of drug absorption.

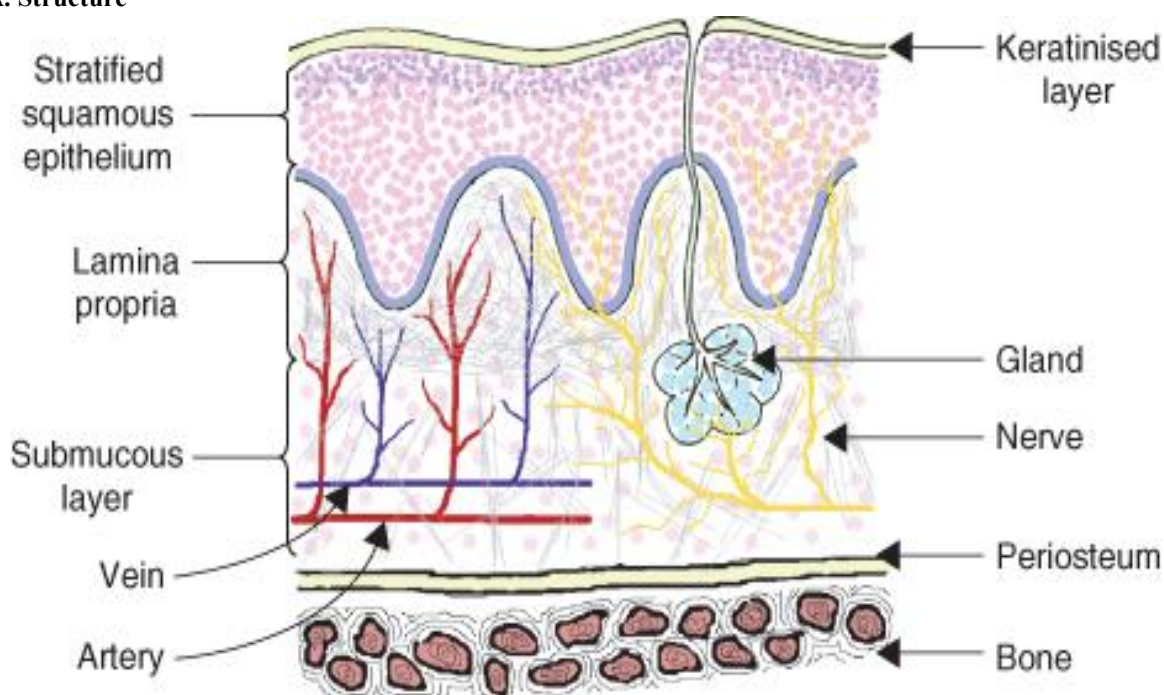
#### **Mucoadhesion phenomenon satisfied the following features of controlled release systems**

1. It localizes the drug in particular region of gastrointestinal tract, thereby improving and enhancing bioavailability for those drugs with bioavailability problems.

2. The strong interaction between the polymer and the mucus lining of the tissue helps increase contact time and permit localization.
3. To inhibit metabolizing enzymes in a localized area.
4. To deliver agents locally for the purpose of modulating antigenicity.
5. To provide intimate contact between a dosage form and absorbing tissue which may result in high drug concentration in a local area and hence high drug flux through the absorbing tissue.

#### **Overview of the oral mucosa**

##### **A. Structure**



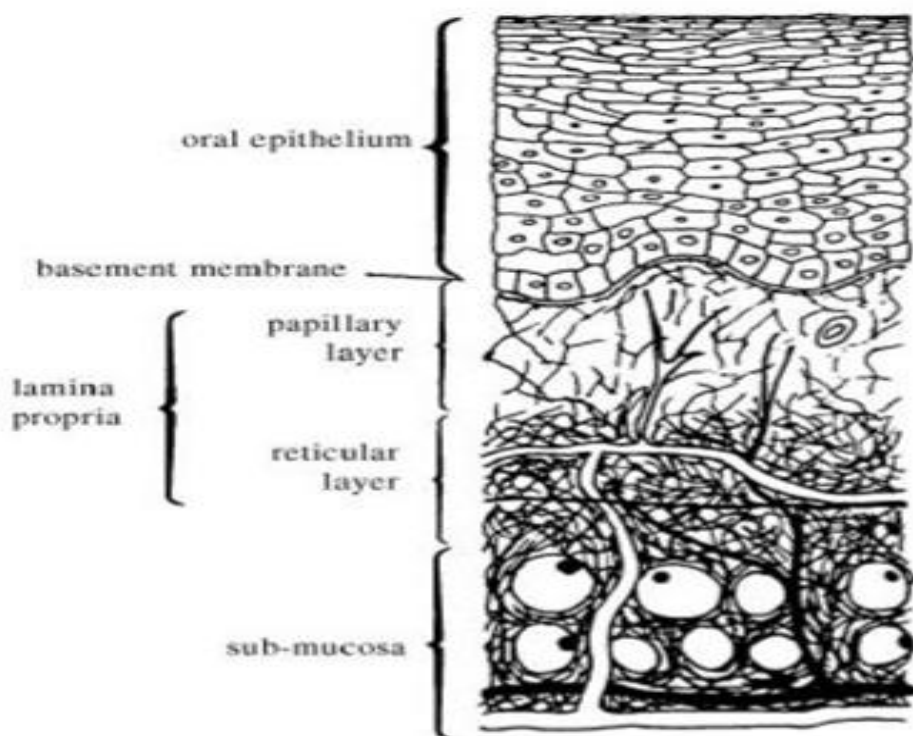
The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium<sup>3</sup>. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

The turnover time for the buccal epithelium has been estimated at 5-6 days, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800  $\mu\text{m}$ , while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingiva measure at about 100-200  $\mu\text{m}$ . The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingiva and hard palate) are keratinized similar to the epidermis. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelia contain

neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and

only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholestersulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithel.

## B. Permeability



The oral mucosae in general are somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane

coating granules' (MCG). When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200 $\mu$ m of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase and lanthanum nitrate. When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the submucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. According to these results, it seems apparent that flattened surface cell layers present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable. In both keratinized and non-keratinized epithelia, the limit of penetration coincided with the level where the MCGs could be seen adjacent to the superficial plasma membranes of the

epithelial cells. Since the same result was obtained in both keratinized and non-keratinized epithelia, keratinization by itself is not expected to play a significant role in the barrier function. The components of the MCGs in keratinized and non-keratinized epithelia are different. The MCGs of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinized epithelium contains MCGs that are non-lamellar. The MCG lipids of keratinized epithelia include sphingomyelin, glucosylceramides, ceramides, and other nonpolar lipids, however for non-keratinized epithelia, the major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids. Aside from the MCGs, the basement membrane may present some resistance to permeation as well, however the outer epithelium is still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules.

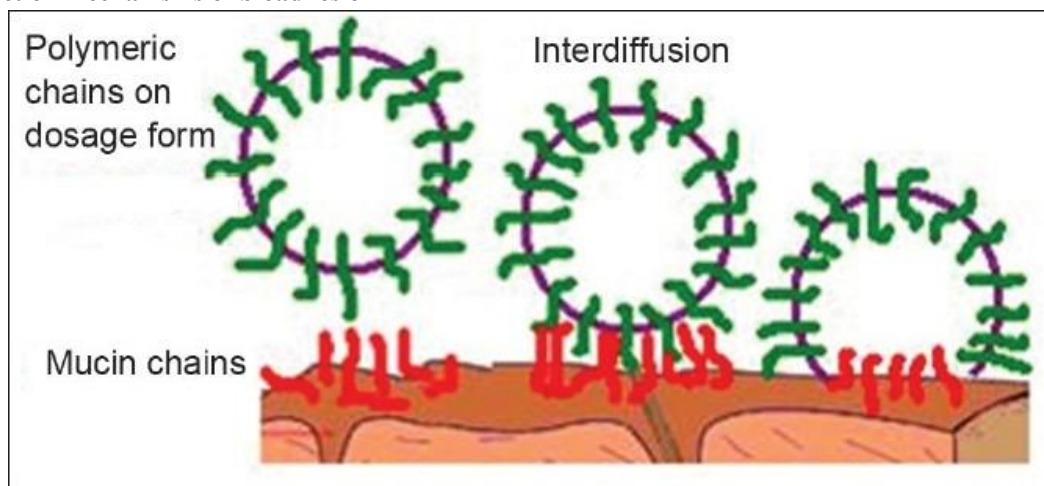
### C. Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized

mucus secreting cells like the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands. At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer.

Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralisation of the tooth enamel after eruption and helps in remineralisation of the enamel in the early stages of dental caries. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation. The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

### Interaction mechanisms of bioadhesion



Adhesion of a polymer to a tissue involves contribution from three main regions; the surface of bioadhesive material, the first layer of the natural tissue, and the interfacial region between the two layers. The development of a successful bioadhesive device is dependent on an understanding of how these components interact so that the proper of the bioadhesive may be modified to optimize the adhesion.

Adhesive between polymer and a tissue to primarily due to three types of interactions; physical or mechanical bonds; secondary chemical bonds or ionic; primary or covalent chemical bonds. Physical and mechanical bond may be formed when the polymer material is deposited on and included in the crevices of the tissue. This inclusion is necessary for the establishment of intimate contact between the polymer and the tissue, which is critical to the occurrence of the good bioadhesive bond.

Secondly chemical bonds, including hydrogen bonding and van der waals forces, can contribute to bioadhesives. The van der waals forces are a combination of two different effects dispersion forces due to movement of the internal electrons, and polar forces due to the orientation of the permanent electric dipoles. The polar forces are more significant than the dispersion forces. Hydrogen bonding between certain groups on the

polymer and the tissue also contribute to a bioadhesive bond when a hydrophilic polymer is used. Some functional groups that form hydrogen bonds contributing to adhesion including hydroxyl, carboxyl, sulphate and amino groups on both the bioadhesive material and on the glycoproteins of the mucus.

Primary bonds are formed by chemically reacting the polymer and the substrate. This type of bonding is only desirable when the connection between the substrate and the adhesive is permanent. For this reason, most bioadhesive bonds are achieved through physical bonds, hydrogen bonds or other secondary bonds.

#### Mucoadhesive polymer characteristics

1. Generally hydrophilic molecules that contain numerous hydrogen bond formation groups like -OH, -COOH.
2. Strong anionic charges containing many carboxyl groups.
3. Surface tension characteristics suitable for wetting mucus/mucosal tissue surfaces.
4. Usually have a high molecular weight i.e., > 100,000.
5. Sufficient flexibility to penetrate the mucus network or tissue crevices.

#### Factors affecting bioadhesion



1. Concentration of active polymer
2. pH
3. Polymeric chain length
4. Polymer molecular weight
5. Molecular flexibility

#### 1. Concentration of active polymer

There is an optimum concentration of polymer corresponding to the best bioadhesion. In highly

concentrated system, the adhesive strength drops significantly.

## 2. pH

pH was found to have a significant effect of mucoadhesion are observed in studies of polyacrylic polymer cross linked with COOH group. pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different chart density depending on pH because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids of polypeptide backbone.

Polycarbophil show the maximum adhesive strength at pH 3, the adhesive strength decreases gradually as the pH increases upto 5 polycarbophil does not show any mucoadhesive property above pH 5. This study, the first systematic investigation of the mechanism of mucoadhesion, clearly shows that the protonated carboxyl group rather than ionised carboxyl group react with mucin molecules presumably by numerous simultaneous hydrogen bonds.

## 3. Polymer chain length

The polymer molecule must have an adequate length.

## 4. Polymer molecular weight

The optimum molecular weight for the maximum bioadhesion depends on the type of polymers. The bioadhesive forces increases with the molecular weight of bioadhesive polymer.

## 5. Molecular flexibility

It is important for interpenetration and enlargement. As water soluble polymers become cross linked, the mobility of the individual polymer chain decreases. As the cross linking density increases, the effective length of chain which can penetrate into the mucus layer decreases even further and mucoadhesive strength is reduced.

## Buccal bioadhesive drug dosage form

Buccal bioadhesive dosage forms are specialised dosage form which adhere to buccal mucosa for specific period of time and deliver the drug therein for local or systemic effect.

Because of the presence of smooth relative immobile surface of placement of bioadhesive dosage form, the buccal region appears to more suitable for controlled delivery of the therapeutic agent using a bioadhesive system.

There is a limit to the size of the bioadhesive dosage form. Only a limited amount of drug can be used in this system. In general any drug with a daily requirement of 25mg or less is suitable for buccal delivery.

## Advantages of buccal bioadhesive drug delivery systems

- a) Ease of administration and can be removed from the site of application.
- b) Permits localized and systemic action of the drug to the oral cavity for longer period of time.
- c) A significant reduction, in dose can be achieved, thereby reducing dose dependent side effects.
- d) Increased bioavailability can be obtained by this route.
- e) It can be administered to unconscious patients
- f) Offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering greater bioavailability.
- g) Buccal mucosa is highly perfused with blood vessels and offers greater permeability than skin.
- h) Therapeutic serum concentration of the drug can be achieved more rapidly.
- i) Drugs which are degraded in the acidic environment of stomach or destroyed by enzymatic or alkaline environment of the intestine can be administered by this route.

## Disadvantages of buccobioadhesive drug delivery system

The disadvantages of buccal bioadhesive drug delivery systems are

1. Once placed at the absorption site, the tablet should not be disturbed
2. Drugs having unpleasant taste or odour, instability at buccal pH, irritability to buccal mucosa cannot be administered by this route.
3. The drug swallowed with saliva is lost.
4. Patient compliance is difficult to achieve

## Limitations of buccobioadhesive drug delivery system

The drug administration via buccal route has certain limitations

1. Only those drugs with small dose requirements can be administered.

2. Only those drugs which are absorbed by passive diffusion can be administered by this route.
3. Eating and drinking may become restricted.
4. Drugs which irritates the mucosa or having bitter and unpleasant taste or odour cannot be administered by this route.
5. There is always a possibility that the patient may swallow the tablet.
6. Drugs which are unstable at pH cannot be administered by this route
7. Drugs contained in the swallowed saliva leads to the loss of drug.
8. Once placed at the absorption site, the tablet should not be disturbed.
9. Drugs should have short biological half-life (2-8 hours).

### **Basic components of buccal bioadhesive drug delivery system**

The basic components of buccal bioadhesive drug delivery system are

1. Drug substance
2. Bioadhesive polymers
3. Backing membrane
4. Penetration enhancers and Adhesives

#### **1. Drug substance**

Before formulating buccoadhesive drug delivery systems, one has to decide whether the intended action is for rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery systems should be based on pharmacokinetic properties.

The drug should have following characteristics:

1. The conventional single dose of the drug should be small. The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
2. T<sub>max</sub> of the drug shows wider-fluctuations or higher values when given orally.
3. Through oral route drug may exhibit first pass effect or presystemic drug elimination.
4. The drug absorption should be passive when given orally.

#### **2. Bioadhesive polymers**

The first step in the development of buccoadhesive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the

formulation." Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs. Bioadhesive polymers are by far the most diverse class and they have considerable benefits upon patient health care and treatment. The drug is released into the mucous membrane by means of rate controlling layer or core layer. Bioadhesive polymers which adhere to the mucin/ epithelial surface are effective and lead to significant improvement in the oral drug delivery. An ideal polymer for buccoadhesive drug delivery systems should have following Characteristics.

1. It should be inert and compatible with the environment
2. The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
3. It should adhere quickly to moist tissue surface and should possess some site specificity.
4. The polymer must not decompose on storage or during the shelf life of the dosage form.
5. The polymer should be easily available in the market and economical.
6. It should allow easy incorporation of drug into the formulation.

#### **Criteria followed in polymer selection**

1. It should form a strong non covalent bond with the mucin/epithelial surface.
2. It must have high molecular weight and narrow distribution.
3. It should be compatible with the biological membrane.
4. The polymers that are commonly used as bioadhesives in pharmaceutical applications are:

Natural polymers: Gelatin, sodium alginate.

Synthetic and semi synthetic polymers: PVA, PEG, HPMC, PVP, carbomers etc.

#### **3. Backing membrane**

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucous membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents

the drug loss and offers better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc.

#### 4. Penetration enhancers

Penetration enhancers are used in buccoadhesive formulations to improve the release of the drug. They aid in the systemic delivery of the drug by allowing the drug to penetrate more readily into the viable tissues. The commonly used penetration enhancers are sodium lauryl sulphate, CPC, polysorbate -80, laureth -9, sodium fusidate, polmitoyl carnitine, azone, sodium glycocholate, dimethyl formamide etc.

#### 5. Bioadhesives

Bioadhesives are the substances that are capable of interacting with the biological material and being retained on them or holding them together for extended period of time.

Bioadhesive can be used to apply to any mucous or nonmucous membranes and it also increases intimacy and duration of contact of the drug with the absorbing membrane. The commonly used bioadhesives are sodium alginate, carbomers, polycarbophil, HPMC, HPC, gelatin etc.

#### The bioadhesive should have the following characters:

1. It should not produce any residue on mucosa layer.
2. It should be inert and compatible with biological environment.
3. It Should adhere to the mucus membrane aggressively
4. It should preferably form a strong non-covalent bond with mucin/ epithelial cell surface.

#### Classification of buccal bioadhesive dosage forms

- A. Buccal Bioadhesive Tablets
- B. Buccal Bioadhesive Patches and Films
- C. Buccal Bioadhesive Semisolids(ointments and gels)
- D. Buccal Bioadhesive Powders

#### A. Buccal bioadhesive tablets

Buccal bioadhesive tablets are dry dosage forms, that are to be moistened prior to placing in contact

with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. The two buccal bioadhesive tablets Commercially available buccoadhesive tablets in UK are "Bucastem" (Nitroglycerine) and "Suscard bucca" (Prochlorperazine).

Examples:

1. Nitroglycerin bioadhesive tablets for the treatment of angina pectoris.
2. Sumatriptan succinate buccal adhesive tablet which is effective in the acute treatment of migraine and cluster headache.
3. Verapamil buccal tablet with compressed verapamil (15ml) mucoadhesive polymer like sodium alginate and HPC - EXF with standard tablet excipients.

#### B. Buccal bioadhesive patches and films

Buccal bioadhesive patches consists of two ply laminates or multilayered thin film round or oval as consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films are formulated by incorporating the drug in alcohol solution of bioadhesive polymer.

Example:

1. Isosorbide dinitrate in the form of unidirectional erodible buccal film are developed and characterised for improving bioavailability.
2. Buccal film of salbutamol sulphate and terbutalin sulphate for the treatment of asthma.
3. Buccoadhesive film of clindamycin used for pyorrhoea treatment.

#### C. Buccal bioadhesive semisolid dosage forms

Buccal bioadhesive semisolid dosage forms consists of finely powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution, Example: Arabase.

#### D. Buccal bioadhesive powder dosage forms

Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa.



### Conclusion

The buccal mucosa offers several advantages over controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

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