



## BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEM: A NOVEL DRUG DELIVERY TECHNIQUE

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### ABSTRACT

Oral drug delivery is the most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation etc. However in case of the oral route there are several challenges such as first pass metabolism and drug degradation in gastrointestinal environment and poor pharmacological response. Other routes of administration proposed are nasal, pulmonary, transdermal, buccal or rectal drug delivery. These routes offer advantages but they also require some development time. A candidate drug can enter into the development phase but there are problems in delivery of the drug. Drugs having low oral bioavailability show low plasma profile. The buccal mucosa is one of the administration sites that might provide an alternative for per oral administration. This review will provide an insight into this route of drug delivery and the formulations that are, or can be, used and it will also describe the challenges or possibilities of this route of administration. There is novel drug delivery system like buccal drug delivery system in which drug enters directly in systemic circulation thereby by passing the first pass effect. Contact with digestive food of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs. This is painless and without discomfort, precise dosage form and facilitates ease of removal without significant associated pain. Moreover it shows better stability, patient compliance; uniform and sustained drug release and above all easy and cheap methods of preparation which can be done with various commonly available biocompatible polymers.

**KEYWORDS:** Buccal delivery, Formulation, Polymer, Mechanism of action.

### INTRODUCTION

Buccalmucoadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa. Among the various routes of drug delivery, transmucosal drug delivery offer distinct advantages over per oral administration for systemic effect. In recent years delivery of therapeutic agents via Mucoadhesive drug delivery system has become highly interesting. Certain drugs have lack of efficacy due to decreased bioavailability, GI intolerance, unpredictable and erratic absorption or pre-systemic elimination of other potential route of administration.<sup>[1]</sup>

Adhesion as a process, simply defined as the “fixing” of two surfaces to one another. There are many different terminological subsets of adhesion depending upon the environment in which the process occurs. When adhesion occurs in a biological setting it is often termed “bioadhesion”. Bioadhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extended periods of time by interfacial forces. For drug delivery purposes, bioadhesion term implies the attachment of a drug carrier

systems to a specific biological location. The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If the adhesive attachment is to a mucous coat, then the phenomenon is known as mucoadhesion. Mucoadhesive drug delivery systems offer benefits over conventional delivery methods in terms of extended residence time of the drug at the site of application, a relatively large permeability of the mucus membranes that allow rapid uptake of a drug into the systemic circulation and enhanced bioavailability of therapeutic agents resulting from the avoidance of some of the body's natural defense mechanisms. Mucoadhesive drug delivery has been a topic of interest in the design of drug delivery systems to lengthen the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the formulation with the underlying absorption surface, so as to improve and enhance the bioavailability of drug. Mucoadhesive controlled drug delivery systems are beneficial, since they give a controlled drug release over a period of time and can also be utilized for localizing the drug to a specific site in the body. These drug delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive

on hydration and hence can be used for targeting drug to particular region of the body for extended period of time. The ability to maintain a delivery system at particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability.<sup>[1,2]</sup>

Various mucoadhesive devices, like films, patches, tablets disks, ointments and gels, strips. Buccal patch is of greater comfort and flexibility than the other devices because mucogels are easily washed away by saliva, excellent accessibility, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, easy withdrawal, low enzymatic activity, painless administration, facility to include permeation enhancer or enzyme inhibitor or pH modifier in the formulation.<sup>[2]</sup>

#### (A) ADVANTAGES OF BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEM<sup>[3]</sup>

Mucoadhesive delivery system offers several advantages over conventional drug delivery systems which are as follows:

- Excellent accessibility, rapid onset of action possible.
- Rapid absorption because of enormous blood supply and good perfusion rates.
- An alternative to oral route, whereby the drug is protected from degradation in GIT
- Better patient compliance.
- Moreover, rapid cellular recovery and healing of the local site.
- Reduced dosing frequency.
- Shorter treatment period.
- Avoid hepatic first pass metabolism.
- Rapid onset of action.
- Maintains constant blood levels for longer period of time.
- Decrease side or unwanted effects.
- Decrease gastrointestinal side effects.
- Improved patient compliance.
- Easy to discontinue in case of toxic effects.
- Self medication is possible
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of drug administered.
- Prolongs the residence time of the dosage form at the site of absorption.

#### (B) DISADVANTAGES<sup>[3]</sup>

- Clinical need must be clearly established.
- The barrier function of the skin changes from one site to another from person to person with age.
- Poor skin permeability limits the number of drugs that can be delivered in this manner.
- As compared to the sublingual membrane the buccal membrane is low permeability.
- Also has smaller surface area.

- The dissolution of drug due to continuous secretion of saliva.
- Ionic drug cannot be delivered by this route

#### (C) LIMITATION<sup>[3,4]</sup>

- There will be a problem in administering those drugs which having a large doses.
- Eating and drinking should be restricted because patient may swallow the tablet while drinking and eating.
- Those drugs which are unstable at buccal pH environment cannot be administered.
- Drugs having unpleasant taste or irritate the mucosa also cannot be administered by this route.
- Most important limitation of this route is its small surface area for absorption.

#### (D) OVERVIEW OF BUCCAL MUCOSA<sup>[4,5]</sup>

The oral mucosa is composed of an outermost layer called stratified squamous epithelium and below a basement membrane; a lamina propria followed by the submucosa as the inner most layer. It also contains many sensory receptors including the taste receptors of the tongue. The blood epithelium is classified as nonkeratinized tissues. It is penetrated by tall and conical shaped connective tissues. These tissues which are referred to as lamina propria, consist of collagen fibers a supporting layer of connective tissues, blood vessel and smooth muscles. The epithelium may consist of a single layer (stomach, small and large intestine, bronchi) or multiple layers (esophagus, vagina). The upper layer contains goblet cells, which secrete mucus components directly onto the epithelial surface. Specialized glands producing components of the mucous layer may also be located beneath the epithelium. The moist surface of the tissue results from the mucus – a viscous, gelatinous secretion whose composition includes glycoproteins, lipids, inorganic salts and up to 95% water. Mucus may be secreted either constantly or intermittently. The volume of secretion changes under the influence of external and internal factors. Mucin (Glycoprotein) are the most important components of mucus and it is also very responsible for gelatinous structure, cohesion and antiadhesive properties. Mucin consist of three dimensional network with large number of loops. The main functions of the mucus are to protect and lubricate the supporting epithelial layer. In the gastrointestinal tract, the mucus facilitates the movement of food boluses along the digestive canal and protects the epithelium from harmful influences due to intrinsic peristaltic movements and proteolytic enzymes. The components of the mucus secreted onto the surface of the eye by goblet cells adhere tightly to the glycocalyx of corneal-conjunctival epithelial cells, protecting the epithelium from damage and facilitating the movement of the eyelids.

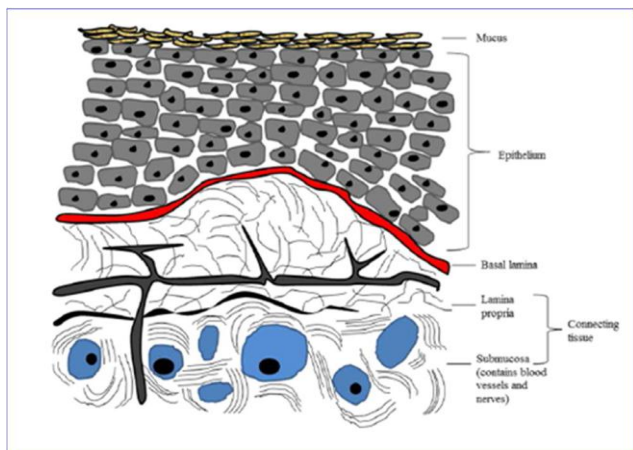


Fig 1. Structure of buccal mucosa.

### (E) FACTORS AFFECTING DRUG DELIVERY VIA BUCCAL ROUTE<sup>[6,7,8]</sup>

Oral cavity is a complex environment for drug delivery as there are many interdependent and Independent factors which reduce the absorbable concentration at the site of absorption

#### 1. Membrane factors

These involve degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.

#### 2. Environmental factors

- Saliva: Thin film of saliva coats lining of buccal mucosa throughout and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. Thickness, composition and movement of this film affect the rate of buccal absorption.
- Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.
- Movement of buccal tissues: Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.

#### 3. Formulation related factors

- Molecular size: Smaller molecules (75-100 Da) generally exhibit rapid transport across the mucosa, with permeability decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of buccal epithelium, making this route more suitable for delivery of larger molecules.

- Partition coefficient: partition coefficient is useful tool to determine the absorption potential of a drug. In general, increasing a drug's polarity by ionization or hydroxyl, carboxyl, or amino groups, will increase the water solubility of any particular drug and cause a decrease in lipid/water partition coefficient. Conversely, decreasing the polarity of a drug (e.g. adding methyl or ethylene groups) results in an increased partition coefficient and decreased water solubility.
- pH: partition coefficient is also affected by pH at the site of drug absorption. With increasing pH, the partition coefficient of acidic drugs decreases while that of basic drugs increases. Partition coefficient is also an important indicator of drug storage in fat deposits. Obese individuals can store large amounts of lipid soluble drug in fat stores. These drugs are dissolved in lipid and are a reservoir of slow release from these fat deposits.
- pKa: Ionization of a drug is directly related to both its pKa and pH at the mucosal surface. Only the nonionized form of many weak acids and weak bases exhibit appreciable lipid solubility, and thus the ability to cross lipoidal membranes. As a result, maximal absorption of these compounds has been shown to occur at the pH at which they are unionized, with absorbability diminishing as ionization increases.

### (F) THEORIES INVOLVED BUCCAL DRUG DELIVERY<sup>[8,9]</sup>

#### 1. Adsorption theory

Adhesion is the result of various surface interactions between the adhesive polymer and mucus substrate. Primary bonds due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency. Secondary bonds arise mainly due to Vander Waals forces, hydrophobic interactions and hydrogen bonding. The theory states that there is initial wetting of the mucin and then diffusion of the polymer occurs into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion.

#### 2. Electronic theory

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system, arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of double layer of electrical charges at the mucus and mucoadhesive interface. Thus the formation of attractive forces within this double layer occurs.

#### 3. Fracture theory

This theory is based on mechanical measurement of mucoadhesion. It analyzes the force required to separate two surfaces after adhesion is established. This force,  $S_m$ , is calculated in tests of resistance to rupture by the ratio of the maximal detachment force  $F_m$  and the total

surface area,  $A_0$ , involved in the adhesive interaction.  
 $S_m = F_m/A_0$ .

#### 4. Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity. The contact angle should be equal or close to zero to provide adequate spread ability.

#### 5. Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time.

#### 6. Mechanical theory

The mechanical theory explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion. Adhesion occurs due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding in dissipating energy and can be considered the most important phenomenon of the process.

### (G) MECHANISM OF DRUG ABSORPTION BY BUCCAL ROUTE<sup>[9]</sup>

#### 1. Simple diffusion

Absorption path is based on random motion of molecules from a zone of higher concentration to one of low concentration to substance placed on mucosa.

#### 2. Facilitated diffusion

Absorption involves a carrier system which leads to more rapid absorption such a carrier system exhibit stereo specificity in D- glucose and L-arabinose.

3. Absorption of nicotinic acid and nicotinamide across the buccal mucosa has been shown to depend upon the presence of sodium ions.

#### 4. Intercellular movements

Oral epithelium has loose junctions and is leaky therefore is likely to allow passage of substance through intercellular space. The basal lamina limits the passage of molecules with a molecular weight more than 70,000.

#### 5. Endocytosis

Although cells of oral mucosa are able to absorb substances by endocytosis it is likely that this mechanism has only a minor role in drug transport from oral cavity.

### (H) POLYMER USED IN BUCCAL DRUG DELIVERY<sup>[10]</sup>

Mucoadhesive polymers are used to increase the drug delivery by enhancing the dosage forms contact time and residence time with the mucous membrane. These formulations are often water soluble and when in a dry form attract water from the biological surface which in

turn leads to a strong interaction between the dosage form and mucosal layer. They have ability to absorb water and swell; thereby enhancing the thickness of the film, thus they are an ideal candidate for mucoadhesive buccal delivery. Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin.

#### a) Classification of mucoadhesive polymers

##### 1. Synthetic Polymers

- Cellulose derivatives (Methylcellulose (MC), Ethyl cellulose (EC), Hydroxy ethyl cellulose (HEC), Hydroxyl propyl cellulose (HPC) Hydroxy propyl methylcellulose (HPMC), Sodium carboxy methylcellulose (NaCMC).
- Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
- Poly hydroxyl ethyl methacrylate.
- Poly ethylene oxide.
- Poly vinyl pyrrolidone.
- Poly vinyl alcohol.

##### 2. Natural Polymers

- Tragacanth
- Sodium alginate
- Guar gum
- Xanthan gum
- Soluble starch
- Gelatin
- Chitosan.

#### b) An ideal polymer should have following characteristics<sup>[10,11]</sup>

1. Should be inert and compatible with environment
2. Polymer and its degradation products should be non-toxic, non-irritant, free from leachable impurities and absorbable from mucous layer.
3. Should adhere quickly to moist tissue surface and possess some site specificity.
4. Must not decompose on storage or during the shelf life of dosage form.
5. Should be easily available in the market and economical.
6. Should allow easy incorporation of drug in to the formulation
7. Should have good spreadability, wetting, swelling, solubility and biodegradability properties.
8. Should adhere quickly to buccal mucosa and possess sufficient mechanical strength.
9. Should possess peel, tensile and shear strengths at the bioadhesive range.
10. Should show bioadhesive properties in both dry and liquid state.
11. Should demonstrate local enzyme inhibition and penetration enhancement properties.
12. Should demonstrate acceptable shelf life.
13. Should have optimum molecular weight.



14. Should possess adhesively active groups.
15. Should have required spatial conformation.
16. Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
17. Should not aid in development of secondary infections such as dental caries.

### c) Polymer properties desirable for mucoadhesion<sup>[11,12]</sup>

#### 1. Functional group

The mucoadhesive polymer possessing hydrophilic functional group such as COOH, OH, NH<sub>2</sub> and SO<sub>4</sub>H may be more favourable in formulating targeted drug delivery system. The functionalized polymer interacts with mucus not only through physical entanglement but also through chemical bonds, resulting in formation of cross linked network. Example: Urea is well accepted hydrogen bonding disruptor which decreases mucoadhesiveness of mucin/pectin samples.

#### 2. Degree of hydration

Hydration is essential for the relaxation and interpenetration of polymer chains. Excess of hydration could lead to decreased mucoadhesion and/or retention due to the formation of slippery mucilage. In this situation cross-linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect.

#### 3. Chain length

Chain length and its flexibility is critical for interpenetration and entanglement with the mucus gel. Increased chain mobility leads to increase inter diffusion and interpenetration of the polymer within the mucus network. Long polymer chains lose their ability to diffuse and interpenetrate through mucosal surfaces. Hence as the chain length decreases interpenetration increases.

### (I) FACTORS IMPORTANT FOR MUCOADHESION<sup>[12]</sup>

#### a) Polymer-related factors

##### 1. Molecular weight

The optimum molecular weight for most bioadhesion depends on the type of bioadhesive polymer at issue. It is usually implicit that the threshold required for successful bioadhesion is at least 100,000 molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has enhanced and a PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for linear polymers imply two things.

##### 2. Concentration of active polymers

There is an optimum concentration of a bioadhesive polymer to produce maximum bioadhesion. In extremely concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

### 3. Flexibility of polymer chains

It is critical for interpenetration and entanglement. As water-soluble polymers become crosslinked, mobility of character polymer chains decrease and thus the valuable length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

### 4. Spatial conformation

Besides molecular weight or chain length, spatial conformation of a molecule is also main. In spite of a high molecular weight of 19,500,000 for dextrans, they have related adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily dependable for adhesion, unlike PEG polymers which have linear conformations.

#### b) Environment related factors

##### 1. Applied strength

To place a solid bioadhesive system, it is required to concern a defined strength. Whatever the polymer, poly(acrylic acid/vinyl benzene poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the period of its application, upto an optimum. the pressure initially applied to the mucoadhesive tissue contact site can influence the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

##### 2. Ph

It can manipulate the formal charge on the surface of mucus as well as certain ions capable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of efficient groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration of crosslinked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then a reduce as alkalinity and ionic strength increase.

##### 3. Initial contact time

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Bioadhesive strength increases as the initial contact time increases.

##### 4. Swelling

It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration results in the formation of a slippery mucilage without adhesion.

#### c) Physiological variables

##### 1. Mucin turnover

The natural turnover of mucin molecules is important for as a minimum two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter, how high the adhesive strength, mucoadhesive are detached from the surface due to mucin turn over. Second, mucin turnover results in substantial amounts of soluble mucin molecules.

These molecules interact with the mucoadhesive before they have a chance to act together with the mucus layer. Mucin turnover may depend on other factors such as presence of food.

## 2. Disease states

The physicochemical properties of mucus are known to adjust during disease conditions such as common cold, gastric ulcers and ulcerative colitis, bacterial and fungal infections of the female reproductive tract.

### (J) DIFFERENT BUCCAL MUCOADHESIVE DOSAGE FORMS<sup>[13,14]</sup>

Even though the mucoadhesive buccal drug delivery offers some distinct advantages, the ideal candidate for designing such formulations is always limited due to several factors. One of the important factors is size limitation. For an effective and comfortable buccal drug delivery system, the quantity of drug moiety enclosed should be reasonably small, ideally 25 mg or less is more appropriate for buccal drug delivery. The drug having a short biological half life can be formulated as buccal drug delivery and thus offering a sustained, prolonged and controlled delivery of drug from the designed dosage form. The different type of buccal drug delivery system includes, adhesive tablets, adhesive gels, adhesive patches, adhesive ointments, adhesive powders and buccal chewing gums etc.

#### A. Mucoadhesive buccal films

These are mainly referred to transparent drug loaded films which are intended to be placed in the buccal mucosa because of its adhesive character. Buccal films can be more preferred over other dosage forms because of its flexibility and comfortness. They are highly transparent and have immediate adhesion capacity with the buccal mucosa. Hydrophilic polymers, Hydrogels, Thiolated Lecithin based polymers can also be used as mucoadhesive polymers. A unique feature of buccal films are that they must not produce any irritation or allergies to the patients.

The mucoadhesive buccal patches can be of two types

##### a) Matrix type

Drug, adhesive and additives mixed together and this mixture is then designed in the form of patches.

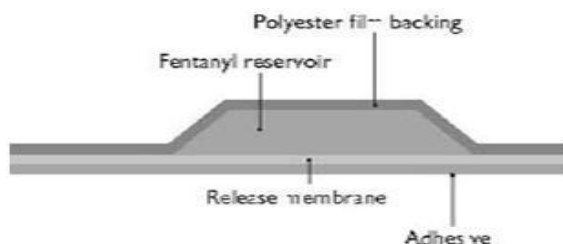


Fig 2. Matrix type.

##### b) Reservoir type

Drug and additives should be separated from the additives. Depending on the presence or absence of a backing membrane, the release from the patch

is unidirectional or bi-directional. The presence of backing membrane offers a unidirectional drug release, which reduces patch deformation and disintegration and ultimately prevent drug loss and offers a sustained and controlled release. The unidirectional patches release the drugs only to the backing membrane offers a bi-directional release of drug. Thus drug releases in to both mucosa and mouth, hence offering a rapid dissolution of drug. These patches are mainly used for designing of drug for rapid onset of action. The adhesive part of the buccal patches may be used as a drug carrier or help in the retention of the drug in the non-adhesive layer. It also helps to increase the residence time of the patches in the desired site.

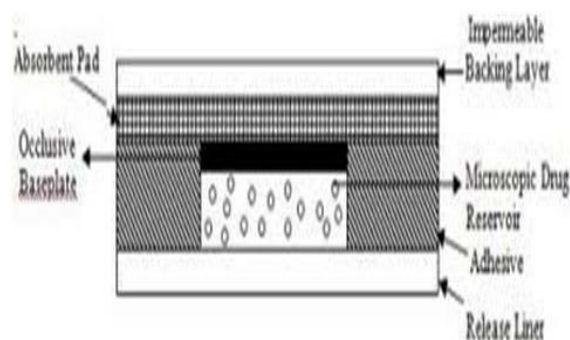


Fig 3. Reservoir type.



Fig 4. Mucoadhesive buccal film.

#### B. Mucoadhesive buccal tablets

These are similar to conventional tablets, but they have the property of mucoadhesion, and instead of swallowing, they held in between cheeks and gums. These tablets are sufficiently dissolved by the medium, provided from locations where they are replaced. But the dissolution of tablet should be slowing order to ensure a sustained and controlled release. A care should be given to ensure the controlled dissolution of such dosage forms. Hence the adhesive tablets does not contain any disintegrants. The usage of flavoring agent and sweeteners will be minimum, in order to control the flow rate of saliva. These are referred to those tablets which are intended to adhere with the buccal cavity and gets softened due to the production of saliva continuously in the mouth and which ensures the complete drug release in the systemic circulation through the blood capillaries in the

buccalcavity and thereby by-passes the hepatic metabolism.

Buccal adhesive tablets are prepared either by procedure used for granulation or by direct compression. During the formulation, care should be given to ensure that all ingredients should be finely grinded form. This is because the buccal adhesive tablet should stay in the mouth for a longer period and if it is not grounded well, then there will be a chance of irritation. The buccal bioadhesive tablet may be monolithic or laminated form. The main disadvantage with monolithic form is the multidirectional release, so that the chances of swallowing of drug will be more. In order to avoid such disadvantages, bi-layered mucoadhesive tablets were formulated. This tablet has two layers – drug containing core layer and backing layer. Usually water insoluble polymer like ethyl cellulose is used for the construction of backing layer. The other advantages of bi-layered system includes, avoiding sticking of the tablet to the finger during the application in the oral cavity.



Fig 5. Buccal tablets.

#### C. Semi solid buccal mucoadhesive dosage form

Gels and ointments as semisolid dosage form for mucoadhesive drug delivery marches out significant approaches throughout the oral mucosa. An disadvantage of using such gels is their poor retention at the site of application which can be overcome by adding certain polymers which possess bioadhesive properties which changes its phase from liquid to semisolid and thereby their viscosity is enhanced and promotes sustained and controlled drug delivery. These types of drug delivery systems are mainly used for local effect and have less patient acceptability than solid bio adhesive dosage form. But compared to solutions, they can prolong their residence time and shows higher bio availability. Usually hydrophilic gel forming polymers are used for the formulation of adhesive semisolid preparations (eg: methyl cellulose, carbopol, hydroxyl ethyl cellulose etc). These are usually used to treat buccal ulcers and burned buccal tissues. The major advantage with these systems is that they show a plastic rheological behavior, and thus offer a prolonged residence time with the surface application.

#### D. Buccal chewing gum

Medicated chewing gum is particularly used in the treatment of oral cavity and in nicotine replacement therapy. The major drawback of such

formulations is that, it is very difficult to regulate the administered dose. One of the best example for such formulation is Nicotine chewing gum (Nicorette<sup>®</sup> and Nicotinell<sup>®</sup>), It is found to increase the acceptability of such formulation for cessation of smoking. Such formulations slowly generate a steady state plasma concentration, rather than the rapid sharp peak which occurs during the smoking. The major drawback with nicotine chewing gum is the considerable loss of nicotine due to swallowing which leads to first pass metabolism and gastric discomfort, thus reducing the effectiveness of such preparation. Buccal patches are preferred as best mucoadhesive buccal drug delivery system because of its flexibility and patient comfort.

#### E. Microparticles

Have more advantages than tablet. The physical properties of microspheres enable to make them closely contact with a large mucosal surface. They can also be delivered to less accessible sites like GI track and nasal cavity and they cause less local irritation at the site of adhesion but the success of these microspheres is limited due to their short residence time at site of absorption.

#### F. Wafers

A novel periodontal drug delivery system. This is used for the treatment of microbial infection. Surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers, matrix polymer.

#### G. Lozenges

Are used as topically within mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. In lozenges multiple daily dosing is required because the release of drug in oral cavity is initially high and then rapidly decline.

### (K) METHODS TO PROMOTE BUCCAL ABSORPTION<sup>[15]</sup>

#### Prodrugs

Hussain *et al* delivered opioid agonists and antagonists in bitter less prodrug forms and found that the drug exhibited low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less.

#### pH

Shojaei *et al* evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8 and in the presence of the absorption enhancer, sodium glycocholate. The *in vitro* permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH

extremes (pH 3.3 and 8.8), as compared to the mid-range values.

### Absorption enhancers

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inter/intracellular lipids, altering cellular proteins or altering surfacemucin. The most common absorption enhancers are fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labeled dextrans across a tissue culture model of the buccal epithelium while Glycerylmonooleates were reported to enhance peptide absorption by a co-transport mechanism.

### 1. Examples of membrane permeation enhancers<sup>[15,16]</sup>

- Bile salts: Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium glycodeoxycholate.
- Surfactants: Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxyethylene-20-cetylether, Benzalkonium chloride.
- Fatty acids: Oleic acid, Capric acid, Lauric acid, Lauric acid/propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholi.
- Chelators: EDTA, Citric acid, Sodium salicylate, Methoxy salicylates.
- Non-surfactants: Unsaturated cyclic ureas.
- Inclusion complexes: Cyclodextrins.
- Others: Aprotinin, Azone, Cyclodextrin, Dextran sulfate, Menthol, Polysorbate 80, Sulfoxides and various alkyl glycosides.
- Thiolated polymers: Chitosan-4-thiobutylamide, Chitosan- 4-thiobutylamide/gsh, Chitosan-cysteine, Chitosan- 4-thiobutylamide/gsh.

### 2. Mechanisms of action of permeation enhancers<sup>[16]</sup>

- Changing mucus rheology: Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers act by reducing the viscosity of the mucus and saliva overcomes this barrier.
- Increasing the fluidity of lipid bilayer membrane: The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.
- Acting on the components at tight junctions: Some enhancers act on desmosomes, a major component at the tight junctions there by increase drug absorption.

- By overcoming the enzymatic barrier: These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly
- Increasing the thermodynamic activity of drugs: Some enhancers increase the solubility of drug thereby alters the partition coefficient. This leads to increased thermodynamic activity results in better absorption.

### CONCLUSION

This review concludes that the mucoadhesive drug delivery system was found to be a better alternative to the conventional oral route. It is a unique alternative to conventional drugs by virtue of its ability in overcoming hepatic metabolism, reduction in dose, frequencies and enhancing bioavailability. This delivery system will show a controlled release of drug; ease of application and the formulation and evaluation of such systems does not have any complication. So we can expect that the mucoadhesive system may be one of the important dosage form in the future pharmaceutical and health care sector.

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### REFERENCE

1. D.K. Sanghi, Rakesh Tiwle. An Over View on Buccal Drug Delivery System. *Inter. J. of Pharmacotherapy*, 2015; 5(1): 8-16.
2. Anay R Patel, Dhagash A. Patel, Sharad V. Chaudhry. Mucoadhesive buccal drug delivery system. *Int. J. of Pharm. & Life Sci*, 2011; 2(6): 848-856.
3. Bhattacharjee S, S. Nagalakshmi, S. Shanmuganathan. Mucoadhesive Buccal Drug Delivery System -A Unique Novel Drug Delivery System of the Modern Era. *Int. J. Pharm. Sci. Rev. Res*, 2014; 27(1): 102-104.
4. A.H. Shojaei, Buccal mucosa as a route for systemic drug delivery. *J. Pharm. Pharmaceut. Sci*, 1998; 1(1): 15-30.
5. D. Harris, J.R. Robinson, Drug delivery via mucous membrane of the oral cavity. *J. Pharm. Sci*, 1992; 81(1): 1-10.
6. K V Shijith, Chandran S, Vipin K V, Ann Rose Augusty, K. Premaletha. Review On Basics Behind Development Of Muco Adhesive Buccal Drug Delivery Systems *Int. J. Advans Phar Bio & Chem*, 2013; 2(2): 310-317.



7. Mathias NR, Hussain MA. Non-invasive systemic drug delivery: developability considerations for alternate routes of administration. *J Pharm Sci*, 2010; 99(1): 318-325
8. Nishan N. Bobade, Sandeep C. Atram, Vikrant P. Wankhade. A Review on Buccal Drug Delivery System. *Int. J. Pharm. Pharma sci*, 2013; 3(1): 35-40.
9. Vaishali A. Chaudhari, S. M. Sarode, B. S. Sathe, G. P. Vadnere. Mucoadhesive Buccal Drug Delivery System: A Review. *Int. j. pharma sci*, 2014; 5(2): 142-162.
10. Andrews GP, Thomas P, Lavery TP, David S, Jones SD. Mucoadhesive polymeric platforms for controlled drug delivery. *Eur. J. Pharm. Biopharm*, 2009; 71(4): 505-518.
11. Prajapati V., Bansal M., Sharma P.K. Mucoadhesive Buccal Patches and Use of Natural Polymer in Its Preparation – A Review. *Inter. J. of Pharm Tech Res*, 2012; 4(2): 582-589
12. Punitha S, Girish Y, polymers in Mucoadhesivebuccal drug delivery system- A review. *Int. J. Res. Pharm, Sci.*, 2010; 1(2): 170-186.
13. Ajeet, Singh B., Juneja R. Recent Findings in Concern to Buccal patches: A Review. *Inter. J. of Current Pharm. Res*, 2012; 4(1): 12-17.
14. Santanu R, Rajesh Gupta, Sourav Saha. A Review on Buccal Mucoadhesive Drug Delivery System. *Indo Glo. J. Pharma Sci*, 2011; 1(3): 223-233.
15. Madhavi R B, Varanasi SN Murthy1, Prameela Rani A, Kumar G D. Buccal Film Drug Delivery System- An Innovative and Emerging Technology. *J Mol Pharm Org Process Res*, 2013; 1(3): 114-134.
16. T.M. Pramodkumar, K.G. Desai, H.G. Shivakumar, Mechanism of buccal permeation enhancers. *Ind. J. Pharm. Edu*, 2002; 36(3): 147-152.