International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

# A Review on Mucoadhesive Buccal Tablets

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Date Of Submission: 20-03-2021 Date Of Acceptance: 05-04-2021

**ABSTRACT:** The delivery of drugs through the buccal mucosa has received a great deal of attention over the last two decades, and yet there are not many buccal delivery products available on the market. The buccal route offers an attractive alternative for systemic drug delivery of drugs because of better patient compliance, ease of dosage form removal in emergencies, robustness, and good accessibility. Use of buccal mucosa for drug absorption was first attempted by Sobrero in 1847, and since then much research was done to deliver drugs through this route. The oral mucosa provides a protective covering for the underlying tissue, being as a barrier for microorganisms and toxins. This article extensively reviews the anatomy and physiology of buccal mucosa, buccal drug delivery system andtheir components, theories, factors affecting drug absorption through buccal mucosa and evaluation.

**Key Words:**Buccal drug delivery, Mechanism, Theories, Polymers, Evaluation.

## I. INTRODUCTION

Among the various routes of drug delivery, oral route is perhaps the most preferred by the patient. However, peroral administration of drugs has disadvantages such as hepatic first-pass metabolism and enzymatic degradation within the GI tract that prohibit oral administration of certain classes of drug[1].Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates)andmost importantlypatientcompliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance[2].Absorption of drugs through the oral cavity was noted as early as 1847, and systemic studies of oral cavity absorption were first reported in 1935. Since then, substantial effort has been focused on drug absorption from a drug delivery system in a particular region of the oral cavity[3].

Numerous features of the oral cavity make it a complex and difficult area for systemic drug delivery. The oral cavity comprises several structures and serves many functions. The oral cavity is a moist environment; the membranes that line the oral cavity are covered with mucus which is derived mainly from minor salivary glands and are constantly bathed in saliva, an aqueous substance rich in inorganic salts, proteins and bacteria. Saliva has a variety of functions and is continuously secreted into, distributed around and removed from the oral cavity. This review examines the potential of the oral cavity as a site for drug delivery. The advantages, limitations and future directions of this route are critically evaluated[4].

## BUCCAL DRUG DELIVERY SYSTEM

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology[5].In the last decade considerable interest has been focused on buccal drug delivery systems using the oral mucosal cavity as an attractive administration route. Several advantages such as relative permeability, robustness and short recovery after stress or damage are related to mucous membrane. However, oral mucosa has been considered advantageous to the oral route because they bypass the hepatic first-pass effect and pre-systemic metabolism into the gastrointestinal track. Furthermore, drug absorption can be discontinued in the case of toxic effects by discharging the formulation from the buccal cavity. Bioadhesive formulations have been developed to enhance the bioavailability of drugs that undergo substantial first-pass hepatic effect and to control the drug release to a constant rate[6].

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

**Bioadhesion:**Bioadhesive may be defined as the state in which two materials, atleast one of which is of biological nature, are held together for extended periods of time by interfacial force. For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue, or the mucous coat on the surface of a tissue. If adhesive attachment is to mucous coat, the phenomenon is referred to as mucoadhesion.

**Mucoadhesion:** Mucoadhesive may be defined as drug delivery systems that utilize property of bioadhesion of certain water-soluble polymers that become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time.The mucosal layer lines a number of regions of the gastrointestinal (GI) tract, the airways, the ear, nose, and the eye[7].

**Buccal delivery** is defined as administration of drugs through the mucosal membranes that line the cheeks (buccal mucosa)[8].

Buccal mucosa is highly vascularized, and blood flow drains directly into jugular vein; therefore, drugs absorbed through the buccal mucosa bypass the gastrointestinal route and hepatic first-pass effect[9].Because of the rich blood supply, higher bioavailability, lymphatic drainage and direct access to systemic circulation, the oral mucosal route is suitable for drugs which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver. The thin mucin film, which exists on the surface of the oral mucosa, may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged period, if it is designed to be mucoadhesive. Such system ensures close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the differential pathway[10].

The mucoadhesive buccal drug delivery system offers several advantages as compare to traditional methods of systemic drug administration. In addition to this, drug can be easily applied and localized to the application site, and can be removed from there if necessary[11]. Among these the buccal mucosa has several advantages like

- excellent accessibility,
- an expanse of smooth muscle,
- immobile mucosa,
- moderate permeability,
- less enzymatic activity and
- suitable for the administration of retentive dosage forms.

Thebuccal tablets are small, flat and are intended to be held between the cheek and teeth or in the cheek pouch and an ideal buccal adhesive system must have the following properties:

- should adhere to the site of attachment for few hours,
- should release the drug in controlled manner and
- should provide the drug release in an unidirectional way in to the mucosa[12].

In general, drugs penetrate the mucous membrane by simple diffusion and are carried in the blood, which richly supplies the salivary glands and their ducts into the systemic circulation via the jugular vein. Active transport, pinocytosis and passage through aqueous pores usually play only insignificant roles in moving drugs across the oral mucosa. Two sites within the buccal cavity have been used for drug administration. Using the sublingual route, in this the medication is placed under the tongue, usually in the form of rapidly dissolving tablet. The second anatomic site for drug administration is between the cheek and gingival, although this second application site is itself known as buccal absorption[13].

Bioavailability of hepatically metabolized drugs (such as steroids) can be substantially improved by buccal or sublingual dosing, because when administered by these routes, the drug is not exposed too quickly to the metabolic enzymes of the intestines and the liver during absorption. On contact with the buccal mucosa, the drug permeates across the mucosal tissue to reach the systemiccirculation. An important factor that precedes permeation of drug is the solubilization of drug in aqueous media. Solubilization of a poorly water-soluble drug by complexing with cyclodextrins and then delivering it via the buccal or sublingual mucosa may be advantageous in increasing its absorption. Some of the early reports describing the use of cyclodextrins for increasing the bioavailability of poorly water-soluble drugs such as testosterone and its derivatives[14].

**Mucoadhesive dosage form:**The primary objectives of mucoadhesive dosage forms are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Due to mucoadhesion, certain water-soluble polymers become adhesive on hydration and hence can be used for targeting a

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

drug to a particular region of the body for extended periods of time. The mucosa lines a number of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose, and eye. These represent potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery system may include the following:

1. Gastrointestinal delivery system.
2. Nasal delivery system.
3. Ocular delivery system.
4. Buccal delivery system.
5. Vaginal delivery System.
6. Rectal delivery system[15].

**Mucoadhesive Drug Delivery System in Oral Cavity:**Drug delivery via the membranes of the oral cavity can be subdivided as follows:

1. Sublingual Delivery: drugs are delivered through mucosal membrane lining the floor of mouth into systemic circulation.
2. Buccal Delivery: drugs are delivered through mucosal membrane into systemic circulation by placing drug in between cheeks and gums.
3. Local Delivery: drugs are delivered into the oral cavity.

**CLASSIFICATION OF BUCCAL BIOADHESIVE DOSAGE FORM:**

- Buccal Bioadhesive Tablets.
- Buccal Bioadhesive semisolids.
- Buccal Bioadhesive patch and films.
- Buccal Bioadhesive Powders.

1. **Buccal Bioadhesive Tablets:** Buccal bioadhesive tablets are dry dosage forms that are to be moistened after placing in contact with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. These tablets are solid dosage forms that ate prepared by the direct compression of powder and can be placed into contact with the oral mucosa and allowed to dissolve or adhere depending on the type of excipients incorporated into the dosage form. They can deliver drug multidirectional into the oral cavity or to the mucosal surface.
2. **Buccal Bioadhesive Semisolid Dosage Forms:** Buccal bioadhesive semisolid dosage forms consist of finally powdered natural or synthetic polymers dispersed in a polyethylene or in aqueous solution example: Arabase.
3. **Buccal Bioadhesive Patches and Films:**Buccal bioadhesive patches consists of two ply laminates or multilayered thin film that are round or oval in shape, consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films arc formulated by incorporating the drug in alcohol solution of bioadhesive polymer.
4. **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 the reduction in diastolic B.P after the administration of buccal tablet and buccal film of Nifedipine[16].

**Ideal Properties/ Characteristics Of Buccal Adhesive Drug Delivery System[17]**

- Should adhere to the site of attachment for a few hours.
- Should release the drug in a controlled fashion.
- Should provide drug release in an unidirectional way towards the mucosa.
- Should facilitate the rate and extent of drug absorption.
- Should not cause any irritation or inconvenience to the patient.
- Should not interfere with the normal functions such as talking, drinking.

**ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM[18]**

1. Buccal mucosahasarichblood supplydueits high vascularization and so the drugs are easily absorbed through it.
2. The absorbeddrugsareeasilytransported through the deep lingual or facial vein, internal jugularveinand brachiocephalic vein intothe systemic circulation.
3. Thedrug gains direct entry into the systemic circulation thereby bypassing the first pass effect.
4. Instability of drugs with the digestive fluids of gastrointestinal tract of orally administered drugs can be avoided by this route e.g., insulin or other proteins, peptides and steroids.
5. The rate of drug absorption is not influenced by food or gastric emptying rate.
6. There is goodaccessibility to the membranes that line the oral cavity which makes application painless and without discomfort.
7. Dosage form localization is easy and facilitates ease of removal without significant associated pain and discomfort.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

8. It has better patient compliance than vaginal or rectal route of drug administration.
9. Permeation enhancers in the formulation to increase systemic availability of the drug without observing permanent damaging effects.
10. Oral mucosa is low in enzyme activity and enzymatic degradation is relatively slow than other routes.

**DISADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM[19]**

- Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 $cm^2$ of which ~50 $cm^2$ represents non-keratinized tissues, including buccal membrane.
- Barrier properties of the mucosa.
- The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
- The hazard of choking by involuntarily swallowing the delivery system is a concern.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

**THE BASIC COMPONENTS OF BUCCAL BIOADHESIVE DRUG DELIVERY SYSTEM[16,20,21]**

- Drug substance
- Bioadhesive polymers
- Backing membrane
- Penetration enhancers

1. **Drug substance:** The drug substances are decided on the basis of, does drug used for rapid release/prolonged release and for local/systemic effect? Before formulating buccoadhesive drug delivery systems, one has to decide whether the intended. The drug should have following characteristics;
   - The drugs having biological half-life between 2- 8 hours are good candidates for controlled drug delivery.
   - The conventional single dose of the drug should be small.
   - The drug absorption should be passive when given orally.
   - Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.
   - Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.
2. **Bioadhesive polymers:** The second step in the development of buccoadhcsive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation." Bioadhesive polymers play a major role in buccoadhcsive 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 an ideal polymer for buccoadhcsive drug delivery systems should have following Characteristics.
   - It should be inert and compatible with the environment.
   - The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
   - It should adhere quickly to moist tissue surface and should possess some site specificity.
   - The polymer must not decompose on storage or during the shelf life of the dosage form.
   - The polymer should be easily available in the market and economical.
3. **Backing membrane:**The polymer whose solution can be casted into thin poreless uniform water impermeable film can be used to prepare backing membrane of patches. It should have good flexibility and high tensile strength and low water permeation. They should be stable on long storage maintaining their initial physical properties

The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva.

The material used for the backing membrane must be inert and impermeable to drugs and penetration enhancers. The thickness of the backing membrane must be thin and should be around 75-100 microns.

Themost commonly used backing materials are Polyester laminated paper with polyethylene. Other examples include cellophane-325, multiphor sheet and polyglassine paper.

4. **Penetration enhancers:**Penetration enhancers (also called accelerants or sorption promoters) are defined as substances that are capable of promoting penetration of drugs into skin, or their permeation through skin, by reversibly reducing the skin barrier resistance. An ideal penetration enhancer should have the following properties:
   - It should be pharmacologically and chemically inert, and chemically stable.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

- It should be non-toxic, non-irritant, non-comedogenic and non-allergenic.
- It should have a rapid onset of action, predictable duration of activity, as well as a reproducible and reversible effect.
- It should be chemically and physically compatible with the formulation ingredients.
- After it is removed from the skin, the stratum corneum should rapidly and fully recover its normal barrier property.
- It should be odorless, tasteless, colorless, and inexpensive.
- It should be pharmaceutically and cosmetically acceptable.
- It should have a solubility parameter similar to that of skin (e.g., 20.5 MPa)

To increases the permeation rate of the membrane of co-administrated drug they are added in the pharmaceutical formulation. Without causing toxicity and damaging the membrane they improve the bioavailability of drugs that have poor membrane penetration. The capability to enhance the penetration is depend upon they are used in combination or alone, nature of vehicle, physiochemical propertied of drug and site of administration.

**Mechanism of penetration enhancers:**[22]

1. 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.
2. Increase in the fluidity of lipid bilayer membrane: The most accepted mechanism for drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid or protein components.
3. Action on the components at tight junctions: Some permeation enhancers act on desmosomes by disturbing and or interacting with the components of the desmosomes, a major component at the tight junctions.
4. Overcoming the enzymatic barrier: The buccal permeation enhancers 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.
5. Increase in the thermodynamic activity of drugs: Some permeation enhancers alter the partition coefficient of the drug there by increase the solubility. This leads to increased thermodynamic activity resulting better drug absorption.

**Table 1: Mucosal penetration enhancers and an overview of some of the proposed mechanisms of action of penetration enhancers[18].**

| CLASSIFICATION | EXAMPLES | MECHANISM OF ACTION |
|---|---|---|
| **Surfactants** | 1.Anionic: sodium lauryl sulfate, Sodium laurate 2. Cationic: cetylpyridinium chloride 3.Nonionic: poloxamer, Brij, Span,tween 4.Bile salts: sodium glycodeoxy cholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate, Azone | Perturbation of intercellular lipids, protein domain integrity |
| **Fatty acids** | Oleic acid, caprylic acid | Increase fluidity of phospholipids domains |
| **Cyclodextrins** | α-, β, γ-cyclodextrin, methylated β-cyclodextrins | Inclusion of membrane compounds |
| **Chelators** | EDTA, sodium citrate Polyacrylates | Interfere with Ca2+ |
| **Positively charged polymers, Cationic compounds** | Chitosan, trimethyl chitosan, Poly-L-arginine, Llysine | Ionic interaction with negative charge on the mucosal surface |

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

## OVERVIEW OF ORAL MUCOSA[23,24,25]

The oral cavity is lined by a relatively thick, dense, and multilayered mucous membrane of a highly vascularized nature. The epithelium of the oral cavity is in principle similar to that of the skin, with interesting difference regarding keratinization and the protective and the lubricant mucus spread across its surface. The oral cavity can be divided into three functional zones:

1. The mucus-secreting regions consisting of the soft palate, the floor of the mouth, the underside of the tongue, and the labial and buccal mucosa, which have a normally non-keratinized epithelium.
2. The hard palate and the gingival are the regions of the masticatory mucosa and have a normally keratinized epidermis.
3. Specialized zone consisting of the borders of the lips and the dorsal surface of the tongue with its highly selective keratinization

A. **Structure:**The oral mucosa is composed of outermost layer of stratified epithelium. Below 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. 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 500-800µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingival measure at about 100-200µm.

B. **Role of saliva:**Protective fluid for all tissues of the oral Cavity, Continuous mineralization of the tooth enamel, to hydrate oral mucosal dosage forms.

C. **Role of mucosa:**Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 m in humans. It is secreted by the globet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and the pathological state. However, it has the following general composition

- Water-95%
- Glycoproteins and lipids-0.5% to 5%
- Mineral salts-1%
- Free proteins-0.5% to 1%

D. **Permeability:**The oral mucosa in general is 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. In general, the permeabilities of the oral mucosa 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 nonkeratinized and the palatal intermediate in thickness but keratinized.

E. **Pathways of drug absorption from buccal mucosa:**Two major routes are involved: Transcellular (intracellular) and Paracellular (intercellular).

- The transcellular route may involve permeation across the apical cell membrane, intracellular space and basolateral membrane either by passive transport (diffusion, PH partition) or by active transport (facilitated and carrier-mediated diffusion, endocytosis). The transcellular permeability of drug is a complex function of various physicochemical properties including size, lipophilicity, hydrogen bond potential, charge and conformation. Transportation through aqueous pores in cell membranes of epithelium is also possible for substances with low molar volume (80 cm3/mol).
- The second route, available to substances with a wide range of molar volumes, is the intercellular route (paracellular route), within the intercellular space, hydrophobic molecules pass through the lipidic bilayer, while the hydrophilic molecules pass through the narrow aqueous regions adjacent to the polar head groups of the lipids.

F. **Structure and design of buccal dosage form:**Buccal Dosage form can be of;

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

1. Matrix type: The buccal patch designed in a matrix configuration containing drug, adhesive, and additives mixed together.
2. Reservoir type: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

## WHY BUCCAL MUCOSA?[26]

The oral mucosa is highly perfused with blood vessels with a high blood flow rate of 20-30mL/min for each 100gm of the tissue. The blood vessels are close to the surface and the lymphatic drainage is also well developed. Hence therapeutic concentrations of the drug can be achieved rapidly. The oral mucosa in general is 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. The permeability coefficients for most compounds are consistently higher for the buccal and oral mucosa than for normal and hydrated skin. There are two permeation pathways for passive drug transport across the oral mucosa, Para cellular and Trans cellular routes. The Para cellular route of drug transport occurs through the intercellular spaces between the cells, whereas transcellular route of drug transport occurs across the cell membranes into the cells. The intercellular spaces are less lipophilic in character than the cell membrane hence hydrophilic compounds have higher solubilities in this environment. The cell membrane, however, is highly lipophilic in nature, and hydrophilic solutes have great difficulty permeating the cell membrane because of a low partition coefficient. Depending on the physio-chemical properties of the diffusant, the solutes traverse from one route more than the other. Therefore, the intercellular spaces pose the major barrier to passive permeation of lipophilic compounds, and the cell membrane acts as the major transport barrier for hydrophilic compounds.

## MECHANISM OF BUCCOADHESIVE[27]

According to Longer and Robinson, bio-adhesion may be defined as "any bond formed between two biological surfaces or a bond between biological and synthetic surface". For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred as mucoadhesion.

Mechanism of polymer attachment to mucosal surface in the buccal cavity are not yet fully understood, but certain theories of bioadhesion suggested that it may be occur via physical entanglement (diffusion theory) and/or chemical interactions, such as electrostatic, hydrophobic, hydrogen bonding, and Vander Waal's interactions (adsorption and electronic theories). However, most research has described bio-adhesive bond formation as a three-step process.

Step 1: Wetting and swelling of polymer
Step 2: Interpenetration between the polymer chains and the mucosal membrane
Step 3: Formation of chemical bonds between the entangled chains

- Step 1: The wetting and swelling step occurs when the polymer spreads over the surface of the biological substrate or mucosal membrane in order to develop an intimate contact with the substrate. This can be readily achieved for example by placing a bioadhesive formulation such as a tablet within the oral cavity. Bioadhesives are able to adhere to or bond with biological tissues by the help of the surface tension and forces that exist at the site of adsorption or contact. Swelling of polymers occurs because the components within the polymers have an affinity for water.
- Step 2: The surface of mucosal membranes is composed of high molecular weight polymers known as glycoproteins. In step 2 of the bioadhesive bond formation, the bioadhesive polymer chains and the mucosal polymer chains intermingle and entangle to form semi permeable adhesive bonds. The strength of these bonds depends on the degree of penetration between the two polymer groups. In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure.
- Step 3: This step involves the formation of weak chemical bonds between the entangled polymer chains. The types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as vanderwaals Interactions and hydrogen bonds. Both primary and secondary bonds are exploited in the

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

manufacture of bioadhesive formulations in which strong adhesions between polymers are formed.

## THEORIES OF BIOADHESIVE[28,29,30]

Many theories have been hypothesized for explaining mucoadhesion, although the chemical and physical basis of mucoadhesion is not yet clearly understood. There are six classical theories which have resulted from studies on the performance of several materials and polymer-polymer adhesion. The contact angle and time of contact plays a significant role in mucoadhesion.

1. **Wetting theory:**The wetting theory applies to liquid systems or low viscosity bioadhesives. It describes the affinity to the surface in order to spread over it. The surface energy of both polymer and tissue is an important consideration to predict mucoadhesive performance. This affinity can be found by using measuring techniques such as the contact angle. This theory states that if lower the contact angle, the greater is the affinity. The contact angle should be equal or close to zero for proper speeding.

The spreadability coefficient, SAB, can be calculated: by taking difference between the surface energies γB and γA and the interfacial energy γAB, as specified in the equation given below.

This theory explains the importance of contact angle and reduction of surface and interfacial energies to achieve good amount of mucoadhesion.

$S = \gamma SG - (\gamma SL - \gamma LG)$

2. **Diffusion theory:**The phenomenon of the interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains is explained by the diffusion theory. The bond strength increases with the enhancement in the degree of the penetration. Diffusion coefficient, flexibility and nature of mucoadhesive chains, mobility and contact time of polymer chains are the factors on which the degree of penetration depends. The depth of interpenetration required to produce a firm bioadhesive bond lies in the range 0.2–0.5μm.

This interpenetration depth of polymer and mucin chains can be found out by the following equation The interpenetration depth,

$l = (tDb)^{1/2}$

Where, t is the contact time and Db is the diffusion coefficient of the mucoadhesive material in the mucus.

The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better is the mucoadhesive bond.

3. **Electronic theory:**The adhesive polymer and mucus typically have different electronic characteristics. When these two-surface come in contact, a double layer of electrical charge forms at the interface, and then adhesion develops due to the attractive force from electron transfer across the electrical double layer.
4. **Fracture theory:**Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$G = (E\varepsilon/L)^{1/2}$

Where, E- Young's modules of elasticity, ε- Fracture energy, L- Critical crack length when two surfaces are separated.

5. **Adsorption theory:**According to the adsorption theory, later an initial contact between two surfaces the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be notable. (i) Primary chemical bonds of covalent nature, which are undesirable in mucoadhesion because their high strength may result in permanent bonds.

(ii) Secondary chemical bonds contain many different forces of attraction including Vander Waals forces, electrostatic forces, hydrogen and hydrophobic bonds.

6. **Mechanical theory:**Mechanical theory proposes that the adhesion is due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. The roughness enhances the interfacial area available to interactions thereby aiding dissipation of energy.

## FACTORS AFFECTING BIOADHESION[31,32]

Structural and physicochemical properties of a potential bioadhesion material influence bioadhesion.

**I. Polymer related factors:**

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

**a)** Molecular weight:
- The bioadhesive force increases with molecular weight of polymer up to 10,000 and beyond this level there is no much effect.
- To allow chain interpenetration, the polymer molecule must have an adequate length.

**b)** Concentration of active polymers:
- There is an optimum concentration of polymer corresponding to the best bioadhesion.
- In highly concentrated systems, the adhesive strength drops significantly.
- In concentrated solutions, the coiled molecules become solvent poor and the chains available for interpenetration are not numerous.

**c)** Flexibility of polymer chain:
- Flexibility is an important factor for interpenetration and enlargement.
- As water soluble polymers become cross linked, the mobility of individual polymer chain decreases.
- As the cross-linking density increases, the effective length of the chain which can penetrate into the mucus layer decreases further and mucoadhesive strength is reduced.

**d)** Spatial conformation:
- Beside molecular weight or chain length, spatial conformation of a molecule is also important.
- Despite a high molecular weight of 19,500,000 for dextrans, they have same adhesive strength to that of polyethylene glycol with a molecular weight of 200,000.
- The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, different PEG polymers which have a linear conformation.

**II. Environment related factors:**

**a)** pH: The pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on pH Because of change in dissociation of functional groups on the Carbohydrate moiety and amino acids of the polypeptide back bone.

**b)** Strength: To place a solid bioadhesive system, it is necessary to apply a defined strength.

**c)** Initial contact time: As soon as the mucoadhesive strength increases, the initial contact time also increases.

**d)** Selection of the model substrate surface: The viability of biological substrate should be confirmed by examining properties such as permeability, Electrophysiology of histology.

**e)** Swelling: Swelling depends on both polymers concentration and on presence of water. When swelling is too great a decrease in bioadhesion occurs.

**III. Physiological variables**

**a)** Mucin turnover: The natural turnover from the mucus layer is important for at least two reasons.
- The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layers.
- Mucin turnover results in substantial amounts of soluble mucin molecules.

**b)** Diseased states: Physicochemical properties of mucus are known to Change during diseased states, such as common cold, gastric ulcers, Ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the Female reproductive tract and inflammatory conditions of the eye.

## FORMULATION DEVELOPMENTAND PREPARATION OF BUCCAL TABLETS[26]

The mucoadhesive bilayered buccal tablets consist of drug-releasing polymer layer and a backing layer of ethyl cellulose, which allow unidirectional release of the drug. They are prepared by the direct compression method involving two steps. In the first step, the drugpolymer mixture is to be prepared by homogeneously mixing the drug with mucoadhesive polymers. The other excipients present in the formulation like the diluents, permeation enhancers, organoleptic agents etc., are to be added to the above mixture in a glass mortar and triturated to achieve a homogeneous blend. The lubricant is now mixed to the blend and compressed within the die cavity of single-stroke multi station tablet machine or single punch tablet compression machine.The upper punch should then be removed and backing layer material, ethyl cellulose to be added over it and finally compressed at a constant compression force. Along with this method Dry Granulation and Wet Granulation method can also be used to develop mucoadhesive buccal tablets.

## Evaluation Of Buccal Tablets[1,11,33,34,35,36,37,38]

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

- **Pre-compression parameters:**

**Angle of Repose:** Angle of repose is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

flow characteristics of different microcapsules were studied by measuring the angle of repose employing fixed funnel method. The angle of repose was calculated by using the following formula.

$$\text{Tan}\Theta = \frac{\text{height of the pile}}{\text{radius of the base of the pile}}$$

Where, $\Theta = \tan^{-1}[h/r]$

$\Theta$=angle of repose

**Bulk Density & Tapped Density:** Bulk density and tapped density were measured by using 10 ml of graduated cylinder. The pre weighed sample was placed in a cylinder; its initial volume was recorded (bulk volume) and subjected to tapings for 100 times. Then the final volume (tapped volume) was noted down. Bulk density and tapped density were calculated from the following formula.

$$\text{Bulk density} = \frac{\text{mass of microparticles}}{\text{bulk volume}}$$

$$\text{Tapped density} = \frac{\text{mass of microparticles}}{\text{tapped volume}}$$

**Carr's Index's:** Compressibility index (CI) or Carr's index value of microparticles was computed according to the following equation:

$$\text{Carrs's index (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped denisty}} \times 100$$

**Hausner's Ratio:**Hausner ratio of microspheres was determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner's Ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

- **Post compression studies:**

**Hardness test:** Hardness test was conducted using Pfizer hardness tester for three tablets from each batch and average values were calculated.

**Weight variation test:**Weight variation test was performed for ten tablets from each batch using an electronic balance and average values were calculated.

**Tablet thickness:** Thickness of each formulation was measured using vernier calipers. Ten buccal tablets from each batch were used and average values were calculated.

**Friability:** The friability of 10 tablets will determine using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets will place in the friabilator and will subject to 100 revolutions. Tablets will dedust using a soft muslin cloth and reweigh.

**Drug content uniformity:** Ten tablets from each formulation were taken, crushed and mixed. From the mixture, 10 mg of drug equivalent was extracted thoroughly with 100 ml of methanol. The amount of drug present in extract was determined using Shimadzu UV spectrophotometer.

**Swelling index:** 10 The swelling index of the buccal tablet was evaluated by using pH 6.8 phosphate buffer. The initial weight of the tablet was determined (w1). The tablets was placed in pH 6.8 phosphate buffer (25 ml) in a Petri-dish placed in an incubator at 37 ± 1˚C and tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h), excess water was removed using filter paper without pressing and reweighed (w2). The swelling index was calculated using the formula:

$$\text{Swelling index} = 100 \times \frac{w2 - w1}{w1}$$

**Measurement of Surface pH:** The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping them in contact with 1ml of distilled water (pH 6.8) for 2 hours and pH was noted by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for 1 min. This test was done in triplicates and mean was calculated.

**In-Vitro Bioadhesive Strength:** The term bioadhesion implies attachment of a drug carrier system to a specific biological location. In–vitro bioadhesive strength of tablets was measured using modified physical balance. Porcine buccal mucosa was used as a model membrane and phosphate buffer pH 6.8 was used as moistening fluid. Bioadhesive studies were performed in triplicate and average bioadhesive strength was determined. From the mucoadhesive strength, force of adhesion was calculated,

$$\text{Force of adhesion (N)} = \frac{\text{bioad hesive strengt h}}{100} \times 9.81$$

**Assessment of duration of mucoadhesion:** To evaluate duration of mucoadhesion, an in-house apparatus was applied. The apparatus had three test cells; two lower and upper platforms were placed in each of them. Each test cell was filled with phosphate buffer (pH 6.8). Sheep buccal mucosa was placed on the lower platform and the tablet was clung to the upper platform. The mucosa and tablet were then placed in contact with each other and a constant force by fingertip was applied for 1 min to them. Next, through two pulley systems, a 15.0 g weight was applied to each upper platform

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 110-122 www.ijprajournal.com ISSN: 2249-7781

(this weight was chosen through initial studies). As soon as the tablet was separated from the mucosal surface, a small flap dropped onto a photocell detector, stopping the timer device (recording the elapsed time to 0.1 min) and measured the duration of mucoadhesion of the tablet. Each experiment was run in triplicate, and the results were expressed as mean ± SD.

**Drug release from backing layer:**For determination of drug release from the backing layer, Franz diffusion cell was used. A bilayered buccal tablet was placed between donor and receptor compartment. The complete unit was maintained at 37°C; donor compartment (3 mL) was filled with simulated saliva, pH 6.8 (sodium chloride 4.50 g, potassium chloride 0.30 g, sodium sulfate 0.30 g, ammonium acetate 0.40 g, urea 0.20 g, lactic acid 3 g, and distilled water up to 1,000 mL, adjusting pH of the solution to 6.8 by 1 M NaOH solution), and receptor compartment (21 mL) contained phosphate buffer, pH 7.4, with synchronous stirring. At predetermined interval, 2 mL sample was removed from donor compartment and analyzed by UV spectrophotometric analysis.

**sInvitro drug release studies:**

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the tablets. The dissolution medium consists of 500 ml of phosphate buffer pH 6.8. The release was performed at 37 ± 0.50 C, with a rotation speed of 50 rpm. The buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Five ml sample were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometer.

## II. CONCLUSION

Mucoadhesive buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drug as well as a feasible and attractive alternative for noninvasive delivery of potent peptide and protein drug molecules. However, the need of safe and effective buccal permeation and absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site-specific targeting can be predicted, monitored and controlled. The buccal mucosa is a promising delivery route for drugs that need to avoid the gastrointestinal tract due to degradation by the gastric pH, intestinal enzymes or due to a substantial hepatic first pass effect. With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals.

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