INTRODUCTION

In recent years, there has been a growing interest in the drug delivery via various absorptive mucosa, such as ocular, nasal, pulmonary, buccal, sublingual, rectal and vaginal as non-parenteral routes for systemic action of therapeutic agents. Amongst the various routes of transmucosal drug delivery, buccal route is perhaps the most preferred to the patients and clinicians alike.\(^1\)

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 extend 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.\(^2\)

Theories of Buccoadhesion

![Figure 1: Theories of Mucoadhesion.](image-url)
a). **Electronic Theory**: The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces 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.

b). **Adsorption Theory**: The adsorption theory of bioadhesion proposes that adhesion of a polymer to a biological tissue results from

1. Primary chemical bonds that are somewhat permanent and therefore undesirable in bioadhesion.
2. Vander Waals, hydrogen, hydrophobic and electrostatic forces, which form secondary chemical bonds.

c). **Wetting Theory**: Primary application to liquid bioadhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant.

d). **Diffusion Theory**: The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi permanent adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers, and the diffusion co-efficient is known to depend on molecular weight and cross-linking density.

e). **Fracture**: Fracture theory of adhesion is related to separation of two surfaces after adhesion.\(^3\)

**Factor affecting buccoadhesion**

- **Polymer based factors**

1. **Molecular weight of polymer**

As the molecular weight of polymer is low, it can penetrate better in the mucus. The molecular weight can increase with increase in molecular weight up to 10,000 above that the buccoadhesive strength decreases. For linear polymer the bio adhesiveness improve with increase in molecular weight which depends on two things that for lower molecular weight, interpenetration is more critical and entanglement is important for higher molecular weight.\(^4\)
2. **Concentration**
For maximum bioadhesion it requires optimum concentration of bioadhesive polymer. In highly concentrated system beyond the optimum level, adhesive strength drops because coiled molecule become separated from medium. When concentration of polymer is too low, the number of penetrating polymer chain per unit volume of mucus is also low. The concentration from 1 2.5% can show increased potential of bioadhesion.\[^5\]

3. **Flexibility of polymer chains**
For good bioadhesion it requires diffusion of polymer chains in interfacial region. So there must be requiring that polymer chain contain substantial degree of flexibility in order to achieve better adhesion. In mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients. The higher flexibility of a polymer causes greater diffusion into the mucus network.\[^6\]

4. **Swelling factor**
It is an important factor that affects Buccoadhesive strength of polymeric component. Hydration is required for a buccoadhesive 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. Polymer swelling results interpenetration by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. However, a critical degree of hydration of the buccoadhesive polymer exists where optimum swelling and bioadhesion occurs.\[^7\]

5. **Degree of cross linking**
There are three important inter related structural parameters of polymer network are average pore size, average molecular weight and density of cross-linking. It is found that increase in density of cross linking water diffuse in polymer network at very lower rate, which shows insufficient swelling of polymer and interpenetration between polymer and mucin decreases.\[^7\]

 Goldberg factors
1. **pH**
The charge density is an important factor which consider for bioadhesion. Depending on method of determination and flow rate of saliva the optimized pH can be inbetween 6.5-7.5.
Polyanions are mostly preferred than polycations when two factors are considered, toxicity and bioadhesion. In case of carboxylic acid, pH value below pKa value is more favorable. It is suggested that within poly acrylic acid system approximately 80% of protonation of carboxylic group.

2. Applied strength
To reside a solid bioadhesive system, it is compulsory to concern a defined strength. Whatever the polymer, carbopol 934, poly (acrylic acid / vinyl benzene poly (HEMA) or, the adhesion strength increases up to an optimum with the applied strength or with the period of its application. The pressure firstly applied to the buccoadhesive tissue contact site can impact the depth of interpenetration. The polymer used becomes bioadhesive even they don’t have interaction capacity when high pressure is applied.\cite{8,9}

**Buccal drug delivery system**
Buccal delivery is defined as drug administration through the mucosal membranes lining the cheeks (buccal mucosa). Buccal drug delivery was introduced by Orabase in 1947, when gum tragacanth was mixed with dental adhesive powder to supply penicillin to the oral mucosa (Sudhakar et al., 2006). In recent years, delivery of therapeutic agents through various transmucosal routes has gained significant attention. Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing.

In common, the delivery of a drug requires some type of dosage form, present in the oral cavity, to release a drug, which then diffuses through the mucosa into the local blood flow and is then taken added to the systemic blood circulation\cite{10}. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for controlled systemic drug delivery. Buccal delivery is the administration of drugs through the mucosal membrane lining the cheeks.\cite{11} The buccal route has been advocated as a possible route of administration for drugs which undergo extensive hepatic first pass metabolism or which are susceptible to degradation in the gastrointestinal tract.\cite{12} Buccal drug delivery is a highly effective way to improve bioavailability. This is because the buccal mucosa has a rich blood supply which facilitates direct entry of drug molecules into the systemic circulation. Buccal drug delivery is well accepted by patients as the buccal cavity is easily accessible for self-medication. In addition, buccal dosage forms allow drug absorption to be rapidly terminated in case of an adverse reaction.\cite{13}
Advantages of buccoadhesive drug delivery systems

Drugs administration via oral mucosa offers several advantages

1. Ease of administration.
2. Termination of therapy is easy.
3. Permits localization of drug to the oral cavity for a prolonged period of time.
4. Can be administered to unconscious patients.
5. Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
6. A significant reduction in dose can be achieved thereby reducing dose related side effects.
7. Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route.
8. Drugs which show poor bioavailability via the oral route can be administered conveniently.
9. It offers a passive system of drug absorption and does not require any activation.
10. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
11. Systemic absorption is rapid.
12. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
13. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.

Limitations of Buccal drug administration

Drug administration via buccal mucosa has certain limitations.

1. Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste and odor cannot be administered by this route.
2. Drugs, which are unstable at buccal pH cannot be administered by this route.
3. Only drugs with small dose requirements can be administered.
4. Drugs may swallow with saliva and loses the advantages of buccal route.
5. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
6. Eating and drinking may become restricted.
7. Swallowing of the formulation by the patient may be possible.
8. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.\cite{14,15,16,17,18}

**Factors Influencing Drug Absorption from the Oral Cavity**

As the oral mucosa is a highly vascular tissue, the main factors that influence drug absorption from the mouth are:

a) The permeability of the oral mucosa to the drug.

b) Physicochemical characteristics of the drug.

c) Miscellaneous factors.

**a) Permeability of the oral mucosa to drugs**

Permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicated by a wide range in this reported values, there are considerable differences in permeability between different regions of the oral cavity. In general, permeability of the oral mucosa decreases in the order of sublingual greater than buccal and buccal greater than palatal. This is based on the relative thickness and degree of keratinization of these tissues. The keratin layer is an effective barrier to penetration of human skin by water soluble substances. The permeability barriers of the oral mucosa are supposed to reside within the superficial layers of the epithelium. It has been shown that for some compounds the barrier to penetration is not the upper one third of the epithelium. Alfano and his coworkers studied the penetration of endotoxins through nonkeratinized oral mucosa. The results indicated that the basement membrane is a rate limiting barrier to permeation. Some workers have suggested that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called “Membrane Coating Granules” (MCGs). The barriers exist in the intermediate cell layers of many stratified epithelia and are of 100-300 nm in diameter. Other factors which may affect the permeability of molecules include exogenous substances placed in the mouth for their local effects, such as mouthwashes and toothpastes, which contain surfactants and nutritional deficiencies.\cite{19}

**b) Physicochemical characteristics of the drug**

The various physicochemical characters that play an important role in absorption of drug from the oral cavity are considered below:
i) Molecular weight
Molecules penetrate the oral mucosa more rapidly than ions and smaller molecules more rapidly than larger molecules. In case of hydrophilic substances, the rate of absorption appears to be rapid for small molecules (molecular weight less than 75-100 Da), but permeability falls off rapidly as the molecular size increases.

ii) Degree of ionization
The average pH of saliva is 6.4. Because the un-ionized form of a drug is the lipid-soluble-diffusible form, the pKa of the drug plays an important role in its absorption. Adequate absorption through the oral mucosa occurs if the pKa is greater than 2 for an acid or less than 10 for a base.

iii) Lipid solubility
A common way of assessing the lipid solubility of a drug is to measure its oil-water partition coefficient. Partition coefficient between 40-2000 is necessary for optimal drug absorption. If the partition co-efficient exceeds 2000, solubility in the saliva is insufficient to provide the concentration gradient necessary for drug absorption. That is in addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids for absorption.

iv) pH of the saliva
The saliva pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentration increases leading to and increase in the pH. Absorption is maximum at the un-ionized form of drug in pH of saliva.

c) Miscellaneous
i) Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.

ii) Storage Compartment: A storage compartment in the buccal mucosa appears to exist which is responsible for the slow absorption of drugs.

iii) Thickness of oral epithelium: Sublingual absorption is faster than buccal since the epithelium of former region is thinner and immersed in a larger volume of saliva.[20]

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.\textsuperscript{[21]} 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\textsuperscript{[22]} 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 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual and the buccal regions, however, are not keratinized.\textsuperscript{[22]} 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.\textsuperscript{[23-25]} They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosylceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.\textsuperscript{[22-24]}

B. Permeability

The oral mucosa in general is a somewhat leaky epithelium 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.\textsuperscript{[26]} 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.\textsuperscript{[22]} 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).\textsuperscript{[27]} 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 200μm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase\textsuperscript{[28]} and lanthanum nitrate.\textsuperscript{[29]} 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.\textsuperscript{[28]} The components of the MCGs in keratinized and non-keratinized epithelia are different, however.\textsuperscript{[23]} 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.\textsuperscript{[23]} 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.\textsuperscript{[30]} Along the same lines, the mucus is also believed to play a role in bioadhesion of buccoadhesive drug delivery systems.\textsuperscript{[31]} 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.\textsuperscript{[30,32]} Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands.\textsuperscript{[30,32]} At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in buccoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer.\textsuperscript{[21]} 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 mineralization of the tooth enamel after eruption and helps in remineralisation of the enamel in the early stages of dental caries.\textsuperscript{[33]} 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.\textsuperscript{[30,32]} 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.

**Methods to increase drug delivery via buccal route**

a). Absorption enhancer

The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances that facilitate the permeation through buccal mucosa are referred as absorption enhancers. As most of the absorption enhancers were originally designed for increase the absorption of drug and improved efficacy and reduced toxicity. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. The most common absorption enhancers are azone, 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-labelleddextrans across a tissue culture model of the buccal epithelium while
Glycerylmonooleates were reported to enhance peptide absorption by a co-transport mechanism.\(^{[34]}\)

**Mechanism**

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows.

- **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 thereby increases 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 altering the partition coefficient. This leads to increased thermodynamic activity resulting better absorption. Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface. Chitosan exhibits several favorable properties such as biodegradability, biocompatibility and antifungal/antimicrobial properties in addition to its potential bioadhesion and absorption enhancer.\(^{[35]}\)

**b). Prodrug**

Hussain et al administrated nalbuphine and naloxone bitter drugs to dogs via buccal mucosa then it is 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.\textsuperscript{[36]}

c). 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 (pH 4.1, 5.8 and 7.0).\textsuperscript{[36]}

**Evaluation of novel buccal drug delivery systems**

1. Permeation studies
Buccal permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. In vitro and/or in vivo both methods are involved to determine the buccal permeation profile and absorption kinetics of the drug.

A. In vitro methods
For examine drug transport the in vitro studies are carried out with animal buccal tissues. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the *in vitro* permeation experiments. Buccal cell cultures have also been suggested as useful in vitro models for buccal drug permeation and metabolism.\textsuperscript{[37]} However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled.\textsuperscript{[38]}

B. In vivo Methods
In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test. Using this method, the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of the sample solution and the inability to localize the drug solution.
within a specific site (buccal, sublingual, or gingival) of the oral cavity. However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled. (Other in vivo methods include those carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs.\textsuperscript{[39]} The perfusion chamber is attached to the tissue by cyanoacrylate cement. The drug solution is circulated through the device for a predetermined period of time and sample fractions are then collected from the perfusion chamber (to determine the amount of drug remaining in the chamber) and blood samples are drawn after 0 and 30 minutes (to determine amount of drug absorbed across the mucosa). For study the permeation characteristics of buccal drug delivery systems special attention is require to choice of experimental animal species for such experiments. Many researchers have used small animals including rats and hamsters for permeability studies. However, such choices seriously limit the value of the data obtained since, unlike humans, most laboratory animals have an oral lining that is totally keratinized. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue but it is hard to isolate the desired non-keratinized region due to sudden transition to keratinized tissue at the mucosal margins. The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys, dogs and pigs which are having non-keratinized tissue.

2. Dissolution and drug release test

Drug release studies for buccal tablets are normally performed using USP apparatus. However some authors are develop special apparatus or methods for drug release study of buccal tablets. Ikinci et al. used an alternative method to study the release of nicotine from buccal tablets. They used modified Franz diffusion cells for this purpose. The dissolution medium was 22 ml phosphate buffer saline (PBS) (pH 7.4) at 37°C. Uniform mixing of the medium was provided by magnetic stirring at 300 rpm. To provide unidirectional release, each bioadhesive tablet was embedded into paraffin wax which was placed on top of a bovine buccal mucosa as membrane.\textsuperscript{[40]} Mumtaz and Ch’ing introduced another method for studying the dissolution of buccal tablets. The device that they introduced is based on the circulation of pre-warmed dissolution medium through a cell as shown in Fig- II. Here the buccal tablet was attached on chicken pouches. Samples were removed at different time intervals for drug content analysis. They stated “the results obtained by using this apparatus for the release of drug from bioadhesive tablets concurred with the predicted patterns”.\textsuperscript{[41-44]}
Formulation of Buccal Drug Delivery System

Formulation design

a. General criteria for selection of drug candidate

- Buccal adhesive drug delivery systems with the size 1–3 cm² and a daily dose of 25 mg or less are preferable. (James and Boylan 2001)
- The maximal duration of buccal delivery is approximately 4–8 hr (Alur et. al, 1999).
- Drug must undergo first pass effect or it should have local effect in oral cavity.
- Local drug irritation caused at the site of application is to be considered while selecting the drug.[45-47]

b. Pharmaceutical considerations

Great care needs to be exercised while developing a safe and effective buccal adhesive drug delivery device. Factors influencing drug release and penetration through buccal mucosa, organoleptic factors and effects of additives used to improve drug release pattern and absorption, the effects of local drug irritation caused at the site of application are to be considered while designing a formulation.[45-47]

c. Buccal adhesive polymers

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many, and meros meaning parts (Rathbone et al., 1996).

The key feature that distinguishes polymers from other molecules is the repetition of many identical, similar, or complementary molecular subunits in these chains. These subunits, the monomers, are small molecules of low to moderate molecular weight and are linked to each other during a chemical reaction called polymerization.

Instead of being identical, similar monomers can have varying chemical substituent. The differences between monomers can affect properties such as solubility, flexibility and strength. The term buccal adhesive polymer covers a large, diverse group of molecules, including substances from natural origin to biodegradable grafted copolymers and thiolated polymers. Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces.
and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue and visco-elastic properties.\cite{48,49}

d. Ideal characteristics

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.
- Polymer must be easily available and its cost should not be high.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.

Buccoadhesive dosage forms may be classified into three types

- A single layer device with multidirectional drug release.
- An dosage form with impermeable backing layer which is superimposed on top of an drug loaded bioadhesive layer, creating a double layered device and preventing loss from the top surface of the dosage form into the oral cavity.
- Unidirectional release device, the drug is released only from the side adjacent to the buccal mucosa.\cite{48,49}

METHODS OF EVALUATION

Evaluation of buccoadhesive Dosage Form

1. Precompression parameters

- Bulk density
- Tapped density
- Carr’s index (%)
- Hausner ratio
Angle of repose.

a). Bulk density:- A simple test has been developed to evaluate the flowability of a powder by comparing the poured density ($\rho_{B_{\text{min}}}$) and tapped density ($\rho_{B_{\text{max}}}$) of a powder and the rate at which it packs down. Tapped density was determined by taking 20 g of the granules in 50 ml measuring cylinder and tapping it to a constant volume in a bulk density apparatus.

b). Tapped density: The measuring cylinder containing a known mass of blend was tapped for a fix time. The minimum volume ($V_t$) occupied in the cylinder and the weight ($M$) of the blend was measured. The tapped density ($\rho_t$) was calculated.

c). Carr's index:- Based on the poured density and tapped density, the % compressibility of the granules was computed using the Carr’s compressibility index:

\[
\text{Carr’s index} (\%) = \frac{\text{Tapped density} - \text{poured density}}{\text{Tapped density}} \times 100
\]

d). Hausner ratio:- Hausner ratio was calculated using the formula

\[
\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured density}}
\]

e). Angle of repose:- Angle of repose of the granules was determined by height and cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface. The angle of repose was calculated using the formula:

\[
\tan \Theta = \frac{h}{r}
\]

Where $h$ and $D$ are height and diameter of the pile respectively.

2. Postcompression parameters

- The prepared tablets were evaluated for,
- Thickness
- Hardness
- Friability
- Weight variation
- Swelling study
- Drug content
- Bioadhesion Studies
In-vitro dissolution studies.[50]

a). Thickness:- Six tablets were randomly selected and the thickness of each was measured by digital Vernier caliper. Mean and standard deviation were computed and reported.

b). Hardness:- The hardness of ten tablets was measured using Monsanto Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kg/cm².

c). Friability:- The friability of the tablets was determined using Roche friabilator. Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25rpm for four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula:

\[
\text{% Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100
\]

d). Weight variation:- Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit.

e). Swelling study:- Six Buccal tablets were individually weighed (W1) and placed separately in Petri dishes with 5 ml of phosphate buffer of pH 6.8. At the time interval of 1 hr, 2hr, 4 hr and 8hr, tablet was removed from the Petri dish and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the following formula

\[
\text{Swelling Index} = \frac{(W2 - W1)}{W1} \times 100
\]

f). Drug content uniformity:- Uniformity of drug content test as described in the IP was followed. One tablet was powdered and transferred to a 25 ml volumetric flask. 15 ml of pH 6.8 phosphate buffer was added and the mixture shaken for 10 minutes. The volume was made up and filtered. The first 5 ml of the filtrate was rejected, and after suitable dilution (here 10 times) the sample was analyzed spectrophotometrically at 296.0 nm, and the drug was determined. This test was carried out individually for five tablets from each batch of formulations and the drug content range of five from minimum to maximum was recorded.
g). Bioadhesion Studies:- Modified physical balance method was used for determining the \textit{ex-vivo} bioadhesive strength. Fresh sheep buccal mucosa obtained from a local slaughterhouse was stored in pH 6.8 phosphate buffer at 40°C upon collection. The experiment was performed within 3 hours of procurement of the mucosa. The sheep buccal mucosa was fixed and placed in a beaker; then pH 6.8 phosphate buffer was added into the beaker up to the upper surface of the sheep buccal mucosa to maintain buccal mucosal viability during the experiment. Then the tablet was attached to the upper clamp of the apparatus and the beaker was raised slowly to establish contact between sheep buccal mucosa and the tablet. A preload of 50 gm was placed on the clamp for 5 mins to establish adhesive bond between the tablet and sheep buccal mucosa. After completion of preload time, preload was removed from the clamp and water was added into the beaker from burette at a constant rate. The weight of water required to detach the tablet from sheep buccal mucosa was noted as buccoadhesive strength and experiment was repeated with fresh mucosa in an identical manner.

h). \textit{In-vitro} Dissolution Studies:- \textit{In-vitro} dissolution study was performed by using USP Type II Apparatus (Paddle type) [Electrolab (TDT-06T) Tablet Dissolution Tester] at 100 rpm. Distilled water 900 ml was used as dissolution medium and the temperature of which maintained at 37 ± 0.5°C. Aliquots of dissolution medium (10 ml) was withdrawn at specific time intervals (1 hr) and was filtered and the first 5 ml of the filtrate was rejected. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 296.0 nm. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.\textsuperscript{[50]}

\textbf{Rationalist Approach of Buccoadhesive drug delivery system towards different diseases}

- Cardiovascular disease

Hypertension, one of the major cardiovascular diseases, needs a lifelong therapy to remain under control. Most of the antihypertensive drugs like carvedilol, metoprolol, propranolol, isosorbidemononitrate etc. have low oral bioavailability and smaller half-life. Two main reasons for low bioavailability are poor aqueous solubility and high first pass metabolism. The buccal mucoadhesive route of drug delivery provides direct access to the systemic circulation through the internal jugular vein by bypassing the first pass metabolism, leading to high bioavailability.\textsuperscript{[51]}
• **Fungal/microbial infections**

Oral candidiasis is an opportunistic fungal infection caused by *Candida albicans*. These yeast infections are usually treated locally by application of gels or suspensions. Release of drugs from these preparations involves an initial burst of activity whose level rapidly declines to subtherapeutic concentrations. Thus, systemic antifungals such as fluconazole are usually preferred for treating oral candidiasis. The oral dose of fluconazole for the treatment of oral candidiasis (100 mg/day for 1 or 2 weeks) results in notable side effects varying from headache, nausea to liver dysfunction and hepatic failure. Furthermore, oral fluconazole is reported to interact with a number of medications, including oral hypoglycemics, coumarin-type anticoagulants, cyclosporins, terfenadine, theophylline, phenytoin, rifampin, and astemizole. The pathogenic yeasts in oral candidiasis are usually detected in the superficial layers of the oral mucosa. Thus, the effectiveness of the systemic fluconazole may be partially topical through its concentration in oral fluids. The reported topical efficacy of fluconazole together with the adverse effects and drug interaction of systemic fluconazole justifies the design of BDDS containing a small dose of fluconazole to increase the contact between the drug and the pathogenic yeast for a long time.[52]

• **Migraine**

Migraines are thought to occur when certain blood vessels in the brain become swollen (dilated). Drugs used for the treatment include the “triptan” group, comprising of sumatriptan, zolmitriptan and rizatriptan. These drugs work by helping blood vessels in the brain to return to normal size. It may also block pain signals in the brain. The model drug, sumatriptan is administered orally, in doses of 25, 50 or 100 mg as a single dose, nasally in doses of 10 mg or 20 mg and also subcutaneously as two 6-mg doses over 24 hours. However, a substantial proportion of patients suffer from severe nausea or vomiting during their migraine attack, and also low oral bioavailability (15%) due to high first-pass metabolism may make oral treatment unsatisfactory. Nasal route and subcutaneous route have their own limitations, like lower retention time for nasal solution and inability of self-administration for injectables, respectively.

This justifies a need to develop an effective formulation, which allows the drug to directly enter the systemic circulation, bypassing the first-pass metabolism, thereby increasing bioavailability of sumatriptan succinate. Buccal mucosal route is one such alternative.[53]
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- **Nausea and vomiting**
  Ondansetron HCl, chosen as a model drug for treating postoperative nausea and vomiting associated with emetogenic cancer chemotherapy, possesses certain characteristics that a drug should have to get absorbed through buccal mucosa viz., biphasic solubility and low molecular weight. Moreover, the primary route of ondansetron clearance is by hepatic phase I metabolism, so its bioavailability may be improved when delivered through the buccal mucosal route. Patients may have frequent vomiting following chemotherapy and they may be unable to swallow a tablet to prevent vomiting. It justifies the need to develop a buccal patch/film of ondansetron hydrochloride, which increases patient compliance. Its bioavailability when administered by oral route is only 50% to 60% and its dose is low i.e., 4-8 mg; hence, it can be conveniently loaded onto a patch.[54]

- **Hypoglycemic agents**
  Certain hypoglycemic agents like glipizide and glibenclamide have been recently exploited for buccal delivery. The short biological half-life (3.4 h) of glipizide necessitates its administration in 2 or 3 doses of 2.5 to 10 mg per day. Semalty et al. Prepared mucoadhesive buccal films of glipizide by a solvent casting technique using HPMC, SCMC, CP-934P and Eudragit RL-100. The effect of glipizide on the swelling behavior and the residence time of various mucoadhesive polymers were observed. The medicated films showed high swelling index in comparison to plain films. The addition of the water-insoluble drug increased the water uptake of the film. The results suggested that therapeutic levels of glipizide could be delivered through the buccal route efficiently.[55] Mucoadhesive buccal films of glibenclamide were prepared by Muzib et al. using different grades of HPMC with different ratios. The amount and properties of the incorporated drug determine matrix integrity. The films containing HPMCK15 showed a higher percent swelling due to the presence of more hydroxyl groups in the HPMC molecules. The incorporation of the drug induced significant reduction in the residence time of various formulations. During dissolution, the loosely bound polymer molecules with HPMC in these films were readily eroded, allowing the easy release of glibenclamide. It was found that the drug release from the films varied with respect to the proportion of polymers. It was concluded that HPMC3000 at low concentrations could be useful for buccal delivery of glibenclamide in a controlled manner.[56]
• **Smoking deterrent**

The habitual nature of smoking is partly due to nicotine (NCT) in tobacco, which is categorized as a psychoactive substance. The NCT delivery routes are the skin and mucosal membranes, such as buccal and nasal mucosa, because both the neutral and protonated NCT could readily permeate across the mucosal membranes.\(^\text{[57]}\)

**Future Prospects and Challenges**

Research in buccal drug delivery has revealed remarkable growth and advances in the past few decades. The buccal mucosa holds a great promise for 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. Mucoadhesive drug delivery systems offer unique carrier system for many pharmaceuticals and can be modified to adhere to any mucosal tissue, including those found in oral cavity, gastrointestinal tract, vagina, eye etc. One of the areas of interest is the novel buccal adhesive delivery system, where the drug delivery is directed towards buccal mucosa by protecting the local environment.

In spite of significant advances in the field of mucoadhesion, there is no consensus between scientists in relation to the mechanisms of the interaction between materials and components of mucosal tissue. Many scientists have addressed the development of MBDDS and studied the efficacy of their use, though here too there remain significant gaps, as there is no generally accepted method for assessing mucoadhesive properties. The lack of standardized techniques often leads to discordant and unclear results. Efforts have to be made to develop standardized in vitro and ex vivo biological models that allow one to characterize and compare different materials and formulations in terms of their capability to promote drug absorption via the buccal route.

Looking into the future, researchers find the fate of buccal adhesive drug delivery turning towards vaccine formulations and delivery of small proteins/peptides. Microparticulate bioadhesive systems are particularly interesting because they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Mucoadhesion can clearly play a fundamental role as non-parenteral drug delivery systems for protein formulations, as well as vaccines able to attach to mucous membranes to stimulate local immunity.
CONCLUSION
At the current global scenario, scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of orally less/inefficient drugs by manipulating the formulation strategies. Polymeric science needs to be explored to find newer mucoadhesive polymers with the added attributes of being biodegradable, biocompatible, non-toxic, mucoadhesive for specific cells or mucosa and which could also function as enzyme inhibitors for the successful delivery of proteins and peptides. However, the invention of new biomaterials, tailor-made copolymers, has excellent potential for mucoadhesive drug delivery, but the formulations based on them still have to go a long way to find their path in actual clinical practice.

REFERENCES


