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Buccal Drug delivery: A Novel Approach

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ABSTRACT

Among the other route of drug administration, the oral cavity is an attractive site for the drug delivery of the drugs. However, disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract limits its use for certain drugs. Buccal drug delivery involves the administration of drug through buccal mucosal (the lining in the oral cavity). By the buccal route the drug are directly pass through into systemic circulation, less hepatic metabolism and high bioavailability. The buccal mucosa is very suitable for a bioadhesion system because of a smooth and relatively immobile surface and accessibility. The oral cavity is easily accessible for self medication and can be promptly terminated in case of toxicity just by removing the dosage form from buccal cavity. This drug delivery system utilizes the property of larger surface area and rich blood supply. Certain water soluble polymer become adhesive on hydration and hence can be used for targeting a particular site. Buccal drug delivery prolongs the residence time of dosage form at the site and thus improved the therapeutic performance of drug. This drug delivery also called mucoadhesive drug delivery. It shows better stability, patient compliance, and uniform and sustained drug release. Buccal dosage forms are meant to be placed between gingival and cheek. Buccal adhesive dosage forms are those dosage forms which can deliver drugs either locally to treat conditions within the buccal cavity or systemically via the mucosa.

INTRODUCTION

Mucoadhesive drug delivery systems offer benefits over conventional delivery methods in terms of extended residence time of the drug at the site of application, a relatively large permeability of the mucus membranes that allow rapid uptake of a drug into the systemic circulation, and enhanced bioavailability of therapeutic agents resulting from the avoidance of some of the body's natural defense mechanisms [1]. The buccal mucosa lines the inner cheek, and the buccal formulations are placed in the mouth between the upper gums and cheek to treat local and systemic condition. Buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration. The problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be avoided by administering the drug via the buccal route [2].

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Buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. The mucosa is well supplied with both vascular and lymphatic drainage and gives rapid onset of action, high blood levels, avoids first pass metabolism of drugs because of its natural function, the buccal mucosa is less sensitive to irritation and damage, a no of small molecular weight drugs have been found to penetrate the oral mucosa at sufficient rates to achieve effective plasma concentration even peptide drugs were found to pass the oral mucosa.

Advantages of buccal drug delivery [3-5]

1. Avoid hepatic first pass metabolism.
2. Rapid onset of action.
3. Maintains constant blood levels for longer period of time.
4. Decrease side or unwanted effects.
5. Decrease gastrointestinal side effects.
6. Improved patient compliance.
7. Easy to discontinue in case of toxic effects.
8. Self medication is possible.

9. Allow effective the use of drug with short half life.
10. Allow the administration of drug with narrow therapeutic window because drug levels are maintained within the therapeutic window for longer time.

Disadvantages [6, 7]

1. Clinical need must be clearly established.
2. The barrier function of the skin changes from one site to another from person to person with age.
3. Poor skin permeability limits the number of drugs that can be delivered in this manner.
4. As compared to the sublingual membrane the buccal membrane is low permeability.
5. Also has smaller surface area.
6. The dissolution of drug due to continuous secretion of saliva.
7. Ionic drug cannot be delivered by this route.

Limitation

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

Overview of oral mucosa [8]

The oral mucosa presents a surface area of about 100 cm2. The mucosa of the oral cavity refers to the lining of the cheek and the upper and lower lips. The oral mucosal thickness varies depending on the site, the buccal mucosa measures at 500-800 μm. The oral mucosa consist of an outermost layer of stratified squamous epithelium, below which lies a basement membrane, below this lamina propria and sub mucosa. The epithelium may be non-keratinized or keratinized .non keratinized covers the soft palate, inner lips, inner cheeks, and ventral surface of the tongue. Keratinized squamous epithelium is present in the attached gingival and hard palate as well as dorsal surface of tongue.

Function of oral mucosa

- Protection
- Sensation
- Secretion
- Thermal regulation

Buccal epithelium:

It Provide a protective surface layer between the oral environment and the deeper tissues. Thickness of buccal epithelium which is keratinized varies considerably between the sites. An important feature of oral mucosa is the rapid turnover of the cell, Basement membrane and connective tissue. Basement membrane is a continuous layer of extracellular material, forming the boundary between the basal layer of epithelium and connective tissue of the lamina propriait is composed of blood capillaries and nerve fibers that serve mucosa

Role of Saliva [9]

Play important role in the oral cavity because it act as a protective fluid that protect all the tissue and hydrate the mucosal dosage form which after hydration get swell and release the drug at uniform rate in the oral cavity.

Role of Mucus

Composed of water, glycol proteins, lipids, mineral salt and free proteins.

Play important role in protective, barrier, adhesion and lubrication.

Permeability

The permeability of bucal mucosa is 4-4000 times greater than that of the skin. The permeability of oral mucosa decreases in the order of sublingual greater than buccal, buccal greater than palatal. This is based on the thickness and degree of keratinization of the tissue. The permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called membrane coating granules.

Sublingual: Relatively thin and non- keratinized.
Buccal: Thicker and non-keratinized.
Palatal: Intermediate in thickness but keratinized.

BIOADHESION AND MUCOADHESION [10, 11]

Bio adhesion defined as the state in which two materials, at least one of which being biological nature is held together for an extended period of time by interfacial forces.

Whereas the mucoadhesion drug delivery system utilize the property of bio adhesion of certain water soluble polymer which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time.

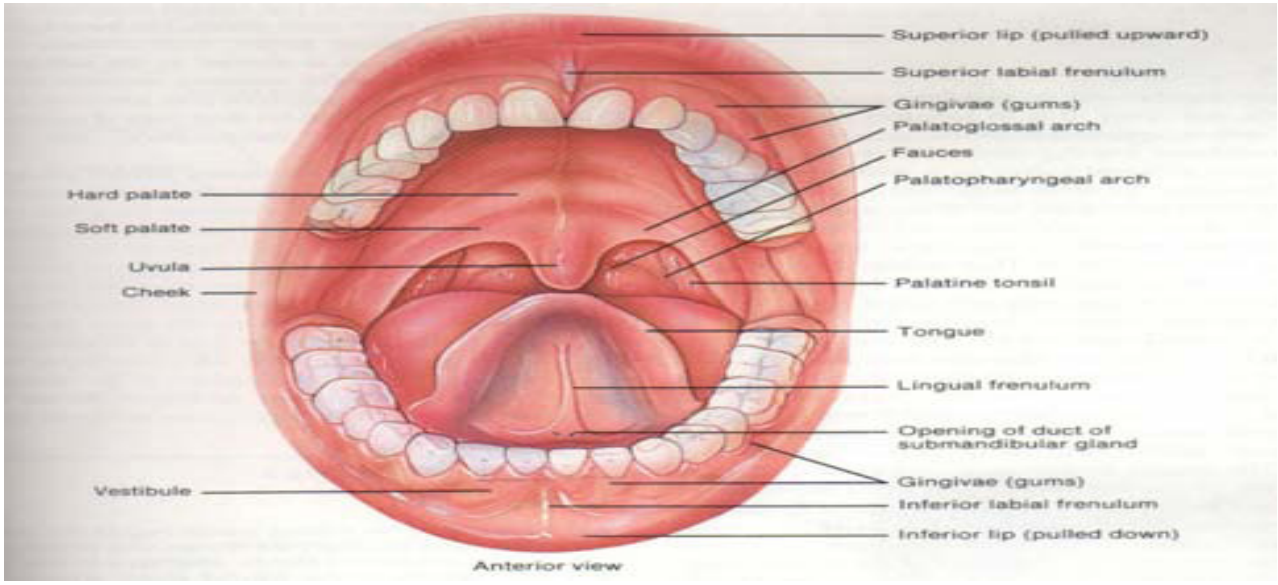

Figure 1: Structure of oral cavity

Contact Stage [12]**:** An intimate wetting occurs between the mucoadhesive and mucous membrane. In some cases these two surfaces can be mechanically brought together.

Consolidation Stage: Different physicochemical interactions happen to combine and toughen the adhesive joint, leading to long-lasting adhesion.

The Removal Mechanism: Adhesive failure will normally occur at the weakest component of the joint. For weaker adhesives this would be the mucoadhesive-mucus interface, for stronger adhesives this would initially be the mucus layer, but later may be the hydrating mucoadhesive material.

Mucoadhesive drug delivery system in oral cavity [13]

1. Sublingual delivery: is a systemic delivery of drugs through mucosal membrane lining the floor of mouth.
2. Buccal delivery: alternative to oral route of administration, in which delivery through the mucosal membrane lining the cheeks (buccal mucosa).
3. Local delivery: Involves drug delivery into the oral cavity.

Transport routes and mechanism [14, 15]**:**

Drug penetrates across the epithelium barrier is via two main routes:

The Para cellular route: between adjacent epithelial cells; the Trans cellular route: across the epithelial cells, which can occur by any of the following mechanism: passive diffusion, carrier mediated transport and via endocytic process.

Mechanism of drug absorption by buccal route

1. Simple diffusion: absorption path is based on random motion of molecules from a zone of higher concentration to one of low concentration to substance placed on mucosa.
2. Facilitated diffusion: absorption involves a carrier system which leads to more rapid absorption such a carrier system exhibit stereo specificity in D- glucose and L-arabinose.
3. Intercellular movements: oral epithelium has loose junctions and is leaky therefore is likely to allow passage for substance through intercellular space. The basal lamina limits the passage of molecules with a molecular weight more than 70,000.
4. Endocytosis: although cells of oral mucosa are able to absorb substances by endocytosis it is likely that this mechanism has only a minor role in drug transport from oral cavity.

Structure and Design of Buccal Dosage Form [16, 17]**:**

Matrix type: The buccal dosage form designed in a matrix configuration contains drug, adhesive and additive mixed together. Trans mucosal drug delivery systems can be bidirectional or unidirectional. Bi-directional dosage form release drug in both the mucosa and the mouth.

Reservoir type: The buccal dosage form 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 dosage form deformation and disintegration while in the mouth; and to prevent drug loss.

Types of buccal dosage form [18, 19]

Buccal tablet: is the tablet which dissolves when held between the cheek and gum, permitting direct absorption of the active ingredient through the oral mucosa .Buccal adhesive tablets that are placed directly onto the mucosal surface for local or systemic drug delivery , but tablets have some limitations such as size for tablet due to requirement for the dosage form.

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

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

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

Buccal patches: These are flexible which deliver the drugs directly in to systemic circulation through mucous membrane thereby by passing the first pass effect. Buccal patch formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic condition.

Gels: Gel forming bio adhesive polymers include cross linked poly acrylic acid that has been used to adhere to mucosal surfaces for extended periods of time and provide controlled release of drugs.

An ideal buccal adhesive system must have the following properties:

1. The drug release should be in a controlled fashion
2. Drug release should be in unidirectional way towards the mucosa
3. The rate and extent of drug absorption should be facilitated,
4. Should not cause any irritation or inconvenience to the patient,
5. Should not interfere with the normal functions such as talking, drinking etc
6. Should adhere to the site of attachment for a few hours.

Polymer used in buccal drug delivery [20]:

Muccoadhesive polymers are used to increase the drug delivery by enhancing the dosage forms contact time and residence time with the mucous membrane. These formulations are often water soluble and when in a dry form attract water from the biological surface which in turn leads to a strong interaction between the dosage form and mucosal layer. They have ability to absorb water and swell; there by enhancing the thickness of the film, thus they are an ideal candidate for mucoadhesive buccal delivery. Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin

Characteristics of Ideal buccoadhesive Polymer

1. The polymer should be non-irritant, non-toxic and non-absorbable from the GIT.
2. Form strong non –covalent bond with mucin epithelial cell surface.
3. Adhere quickly to moist tissue and should poses site specificity.
4. Easy incorporation of a drug and offer no barrier during its release.
5. Polymer does not decompose on storage and shelf life.
6. Polymer should be available at lower price so that the prepared dosage form remains competitive.
7. Should not cause any infection during the formulation development for dental caries.

Criteria followed in polymer selection

1. It should form a strong non covalent bond with the mucin/epithelial surface
2. It must have high molecular weight and narrow distribution
3. It should be compatible with the biological membrane

Classification of some mucoadhesive polymers [21, 22]

A. **Synthetic polymers**:

1. Cellulose derivatives- methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxyl propyl cellulose, hydroxyl propylmethyl cellulose, sodium carboxyl methyl cellulose, Poly (acrylic acid) polymers (carbomers, polycarbophil). Polyhydroxyl ethyl, Polyethylene oxide. Poly vinyl pyrrolidone Poly vinyl alcohol

Natural Polymers: Chitosan, Gelatin, Tragacanth, Soluble starch, Sodium alginate, Xanthan gum

Methods to Increase Drug Delivery via Buccal Route [23]

Absorption enhancers

Term absorption enhancer usually refers to an agent whose function is to increase absorption by enhancing membrane permeation ,rather than increasing solubility, this mainly involve permeation of protein and peptides and other pharmacological active compounds that have poor membrane permeability.

Mechanisms of action of Permeation Enhancers [24]

1) Changing mucus rheology
2) Increasing the fluidity of lipid bilayer membrane.
3) Acting on the components at tight junctions
4) By overcoming the enzymatic barrier
5) Increasing the thermodynamic activity of drugs

Table 1: List of penetration enhancer [24, 25]

Sr. no.	Permeation enhancer
1	Azone
2	Aprotinin
3	Benzalkonium chloride
4	Cetylpyridinium chloride
5	Cyclodextrin
6	Dextran sulfate
7	Lauric acid
8	Menthol
9	Oleic acid
10	Poiysorbate 80
11	Sodium EDTA
12	Sodium lauryl sulfate
13	Sodium salicylate
14	Sodium glycocholate
15	Sulfoxides

Table 2: List of Active Ingredients delivered via a buccal route [15, 26-27]

Sr.No.	Active ingredients
1	Clotrimazole
2	Lidocaine
3	Atenolol
4	Insulin
5	Nifedipine
6	Ofloxacin
7	Buprenorphine
8	Testosterone
9	Cetylpyridinium chloride
10	Acyclovir
11	Lignocaine
12	Miconazole nitrate
13	Melatonin
14	Terbutaline sulfate
15	Zinc sulphate
16	Diclofenac sodium

Application of buccal drug delivery [5]

Drugs which on oral administration result in poor bioavailability and are rapidly degraded provides advantages of high accessibility and low enzymatic activity. These systems involve the delivery of peptides, proteins and polysaccharides, hydrophilic polymers like SCMC, HPC and polycarbophil were used for the treatment of periodontal diseases. Mucoadhesive paste has been used as barrier system for mouth ulcers and gaining advantages of high patient compliance because of the high permeability and the rich blood supply it is capable of producing rapid onset of action and making drug with short delivery period requirements with infrequent dosing regimen.

RECENT ADVANCES: [13]

1. Alginate Raft System
2. Bacterial Cellulose
3. Bioadhesive Films
4. Biogels
5. Blood Plasma Gels
6. Cellulose Films
7. Lyophilisates
8. Poly saccharides gels
9. Skin wounds
10. Tablets
11. Oral Mucosal patches
12. Carbopol Organogels

Future scope of buccal delivery

There are only a few mucoadeshive formulation available currently, it can be concluded that drug delivery using mucoadhesive formulation offers a great potential both for systemic and local use in the near future .various strategies are being employed to achieve oral absorption of peptides. These strategies include manipulation of the formulation, maximizing retention of the delivery system at the site of absorption, alteration of peptide so as to optimize affinity for endogenous transport system.

Buccal permeation can be improved by using various transmucosal and transdermal penetration enhancer such as bile salts and surfactants, fatty acid derivatives chelators and cyclodextrins. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulation and delivery of small protein peptides [28].

CONCLUSION

It was concluded that development of bioadhesivebuccal delivery was one of the alternative routes of administration to avoid hepatic first pass effect and to improve bioavability through buccal mucosa and enhance the release of drug for extended period of time these form reduce the need of frequent administration and enhance patient compliance. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. More efforts should be made in order to utilize this delivery system using more buccal permeation enhancers for better future aspects of this delivery system.

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