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Buccal Mucoadhesive Drug Delivery Systems

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ABSTRACT

Buccal drug delivery is the most innovative delivery system which releases the drug to buccal mucosa by avoiding first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. Buccal route is an attractive route of administration for systemic drug delivery. Buccal bioadhesive films, releasing topical drugs in the oral cavity at a slow and predetermined rate, The mucosa of the buccal cavity is the most easily accessible transmuocosal site. Buccal transmucosal delivery helps to bypass first- pass metabolism by allowing direct access to the systemic circulation through the internal jugular vein.

Keywords: First-pass metabolism, Buccal route

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INTRODUCTION

Delivery of drug via buccal route is considered to be a foremost choice to the oral and parenteral routes of systemic drug delivery. Administration of the drug via the mucosal layer is a novel technique that delivers treatment more effective and safe, for both topical and systemic diseases. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action. Buccal administration of drugs provides a convenient route of administration for both systemic and local drug actions involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.[1-5]

Three different categories of drug delivery fall within the oral cavity: sublingual, buccal, and local. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability's of many drugs, and is convenient, accessible, and generally well accepted. The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are most often one of two designs: those composed of rapidly disintegrating tablets and those consisting of soft gelatin capsules filled with liquid drug.[7-9]

The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short. residence time of oral gels on mucosa, since the gels are easily washed away by saliva.[12-14]

Advantages of buccal patch[1-9]:

- It allows local modification of tissue permeability, inhibition, of protease activity or reduction in immunogenic response, thus selective use of therapeutic agents like peptides, proteins and ionized species can be achieved.
- The buccal membrane is sufficiently large to allow delivery system to be placed at different sites on the same membrane for different sites on same membrane for different occasions, if the or other excipients cause reversible damage or irritate mucosa.

- Avoid first pass metabolism.
- Termination of therapy is possible.
- Patients can control the period of administration or terminate delivery in case of emergencies.
- The buccal drug delivery systems easily administered into the buccal cavity.
- A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.

Disadvantages of buccal patch[1-9]

- Only those drug which are absorbed by passive diffusion can be administered by this route.
- Drug which are unstable at buccal pH cannot be administered by this route.
- Over hydration may lead to formation of slippery surface and structural integrity of formulation may get disrupted.
- The drug contained in swallowed saliva follows the per oral route & advantages of buccal route is lost.
- There is possibility that patient may swallow the tablet.
- Drug which irritate mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.

Mucoadhesion

Mucoadhesion is the mechanism by which two biological material are held together by interfacial force. Mucoadhesion describe the attractive force between a biological material and mucus or mucous membrane. Mucus membrane adhere to epithelial surface such as the gastrointestinal track , the vaginal, the lung, the eye etc. mucoadhesion involve several types of bonding mechanisms, and it is the interaction between each process that allows for the adhesive process.[21-26]

Buccal mucosa

The buccal mucosa is the inner lining of the cheeks and lips, which is an anatomic region that include all the mucous membrane lining of the inner surface of the cheeks and lips, from the line of contact of the opposing lips to the line of attachment of mucosa to the alveolar ridges and pterygomandibular raphe, which occupies an area of 50-60 cm^2. Maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer (2.4ml/min/cm2) than that in the sublingual, gingival and palatal regions, thus facilitates passive diffusion of drug molecules across the mucosa. The thickness of the buccal mucosa is measured to be 500–800 μm and is rough textured, hence suitable for retentive delivery systems.[26-28]

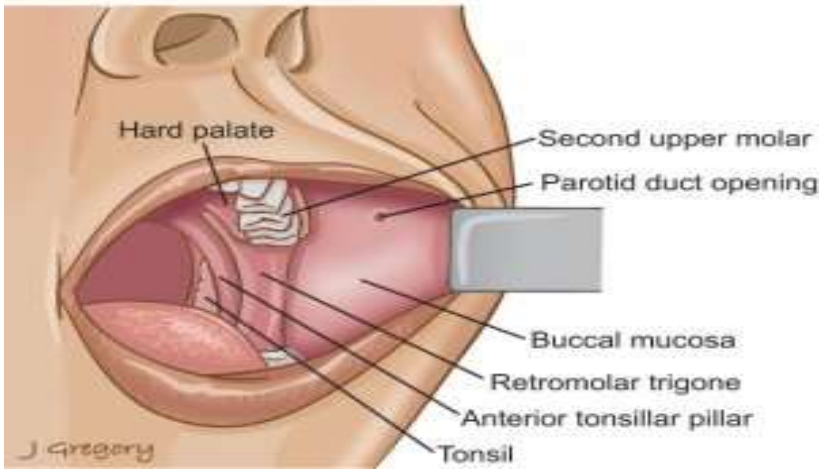

Figure 1- Structure of Buccal Mucosa

Function of Buccal Mucosa[25-26]

- Its main purpose is to act as a barrier.
- It protect the deeper tissue such as fat, muscle, nerve and blood supplies from mechanical insults.
- It also prevent the entry of bacteria and some toxic substance into the body.
- It is important for recognization of taste.

Buccal Cavity

The buccal cavity is more commonly known as the mouth, and it is the beginning of the digestive system for humans and animals. A buccal cavity is a cavity on the front surface of your tooth. It start with lips and end with the throat, and covered by oral cavity. the primary function of the buccal cavity is digestion, but it has an important role in communication. Amongst mucosal route buccal region of the oral cavity is an attractive target to deliver molecules for which oral route is hostile especially for molecule like protein and peptide due to acid hydrolysis and hepatic first pass effect. Amongst various mucosal routes like buccal, nasal, ocular, pulmonary, rectal, and vaginal, the mucosal living of the oral cavity offers some distinct advantages like high vascularization and accessibility for the administration and removal of a dosage form, in addition to high patient acceptability compared to other non-oral routes of drug administration.[33-34]

Anatomy of Buccal Cavity

the buccal cavity(mouth) include the lips, cheeks, palate, floor of the mouth and the part of the tongue in the mouth. a mucous membrane lines and protects the inside of mouth. The structure of buccal cavity play an important role in speech, taste and the first step of digestion.[32-33]

Structure of Buccal Cavity

The buccal cavity at the border between the skin and lips. The roof of mouth is formed by the hard palate. The inner surface of the cheeks formed the sides of the oral cavity. The lowest part of the oral cavity is the floor of the mouth, which is covered by the tongue.[29,33]

Specific areas of buccal cavity is[6,10,15]

- Lips
- Labial mucosa(inner lining of the lips)
- Oral tongue(the front two-third of the tongue)
- Floor of the mouth.
- Buccal mucosa (the inner lining of cheeks).
- Hard palate.
- Teeth
- Lower jaw (mandible).
- Upper jaw (maxilla).

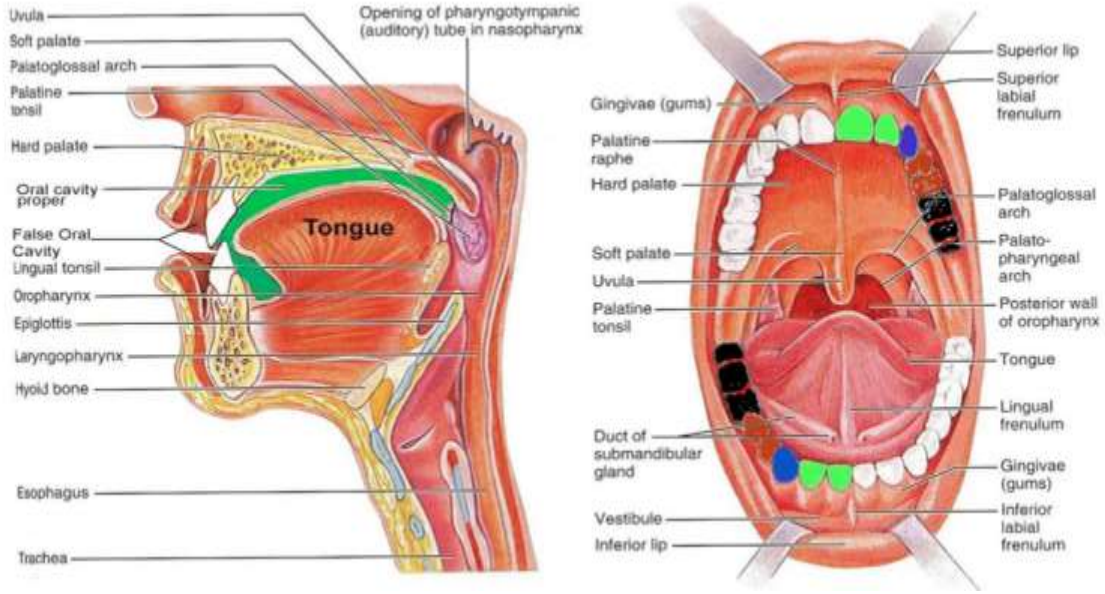

Figure 2- Structure of buccal cavity

PATHOLOGY OF THE BUCCAL CAVITY[21-28]

MANIFESTATIONS OF DISEASES OF THE ORAL CAVITY

Pain-

the oral cavity- richly supplied with sensory nerve endings- pain is a feature of all diseases, including disorders of the teeth

Changes of the oral mucosa

such as ulcerations, vesicular lesions (blisters), changes in colour.

Ulcer

Occur in many diseases, including infections, allergy, trauma, and neoplasns

Malenin pigmentation

Peutz-Jeghers syndrome-is rare congenital syndrome with autosomal dominance, characterized by melanotic pigmentation of mucosal and skin surfaces, and increased risk of carcinoma of pancreas, breast, lung and ovary, in addition patients have multiple polyps in small intestine and colon

Non-neoplastic disorders of the oral mucosa[8-10]

1. Developmental anomalies
2. White lesions and patches
3. Infections
4. Pseudotumors

DEVELOPMENTAL ANOMALIES:[14-19]

Oral mucosa is subject to the same range of developmental anomalies such as skin, and may be involved in head and neck syndromes, but also there are anomalies confined to the oral mucosa itself

1. Fordyce spots- heterotopic development of sebaceous glands in oral mucosa- produce yellow spots and nodules

2. Peutz-Jeghers syndrome- (periorifaciallentiginosis)- autosomal dominant condition with nearly complete penetrance, it is composed of melanocytic macular pigmentation of the lips, oral mucosa, skin together with intestinal polyposis, most numerous hamartomatous polyps in small intestine, the polyps have a low malignant potential, those in colon with higher risk.

3. Congenital epulis- present at birth as mass attached to the gingiva, histologically composed of large granular cells with eosinophilic cytoplasm, covered by stratified hyperplastic squamous epithelium- completely benign.

WHITE PATCHES.

- **White sponge nevus**- is rare autosomal dominant inherited condition, may be congenital or develop later in life. mainly affects buccal mucosa, may involve lips and other oral mucosa.
  - **smoking related keratosis-** smoking can result in intraoral plaque formation- histologically-atrophic or hyperkeratotic epithelium with patchy inflammation and melanin pigment in the underlying corium- pigmentary incontinence-release of melanin from damaged cells.

- **hairyleukoplakia-** patients infected with HIV frequently develop painless, white plaques on the lateral border of the tongue and occasionally elsewhere in the mouth.

INFECTIONS- VIRAL, BACTERIAL AND FUNGAL

infections of the oral mucosa are comparatively infrequent given the number of microorganisms present in the mouth.

VIRAL:

herpes simplex stomatitis-caused by HSV type 1- common viral infection- usually is subclinical- in only few per cent of infected individuals, there are more severe symptoms presenting as widespread gingivostomatitis, characterized by multiple vesicles and ulcers- in children and young adults- systemic symptoms- like fever are present-HS virus passes up the nerve trunks and infects the ganglia in acute phase, it remains in latent form for long time there.

Herpeslabialis-in some patients- attacks of reactivation of the infection as painful localized vesicular and ulceral lesion -reactivation is always precipitated by exposure to sunlight, fever, common cold, etc.

herpangina-is uncommon infection of the oral mucosa by coxsackie virus A, occurs as vesicular lesion on the palate.

aphtous stomatitis-common lesion characterized by recurrent attacks of painful shallow ulcers on the oral mucosa- nonspecific acute in filtrate cause is unknown- no infectious agent has been identified- self-limited lesion.

viral warts- viral warts of the oral mucosa present as a lesion similar to condyloma accuminatum.

- **Bacterial-:**
  - **Actinomycosis-** infection of oral mucosa by actinomyces presents as swelling of the mucosa, the organisms are normally present in the mouth- infection is opportunistic
  - **Tuberculosis**- infection of oral mucosa by tbcbacili is now uncommon, presents with tuberculosis ulcers that are secondary to pulmonary tuberculosis
- **Fungal-:**
  - **candidosis**-is caused by Candida albicans, which is present as normal commensal of the mouths of about one-half of the population.

BUCCAL DRUG DELIVERY -:

Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy

withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.[34,36]

IDEAL CHARACTERISTICS OF BUCCAL ADHESIVE POLYMERS[7-12]

1) Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.

2) Should have good spreadability, wetting, swelling and solubility and biodegradability properties.

3) Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.

4) Should possess peel, tensile and shear strengths at the bioadhesive range.

5) Polymer must be easily available and its cost should not be high.

6) Should show bioadhesive properties in both dry and liquid state.

7) Should demonstrate local enzyme inhibition and penetration enhancement properties.

8) Should demonstrate acceptable shelf life.

9) Should have optimum molecular weight.

10) Should possess adhesively active groups.

11) Should have required spatial conformation.

12) Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.

13) Should not aid in development of secondary infections such as dental caries.

MUCUS:

The adherent mucus gel lining the alimentary tract has a minimum thickness of ≈40–50 μm and a maximum thickness of ≈300 μm**[3]** depending on the individual and the region of the alimentary tract. Although most of mucus is water (≈95–99% by weight) the key macromolecular components are a class of glycoprotein known as mucins (1–5%).Mucins are large molecules with molecular masses ranging from 0.5 to over 20 MDa. They contain large amounts of carbohydrate (for gastrointestinal mucins 70–80% carbohydrate, 12–25% protein and up to ≈5% ester sulphate.[9-11]

ANATOMY OF MUCOUS MEMBRANE:

Mucous membranes (mucosae) are the moist surfaces lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. Mucus is present as either a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are

mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of its weight, making it a highly hydrated system. The mucin glycoproteins are the most important structure-forming component of the mucus gel, resulting in its characteristic gel-like, cohesive and adhesive properties.[2-8, 35]

Role of Mucus[6-8]

- Made up of proteins and carbohydrates.
- Made up of proteins and carbohydrates.
- Cell-cell adhesion
- Lubrication
- Bioadhesion of mucoadhesive drug delivery systems

BUCCAL DRUG DELIVERY DEVICE: [11-13]

Buccal patch:

The buccal patch is mainly composed of active pharmaceutical ingredient, film forming polymers and plasticizers. The plasticizers provide strength and rigidity to the film. After application of the patch it adheres to the mucosa of the buccal cavity due to hydration of the patch by saliva. Saliva is responsible for the hydration and finally disintegration of the dosage form in the mouth. This dosage forms has certain advantages that make it well accepted over other. In this dosage form no water is required for swallowing the medicaments also low doses can be administered by formulating into buccal patches.

Types of patch

1. Matrix type (Bi-directional): The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Bi-directional patches release drug in both the mucosa and the mouth[18-22]

2. Reservoir type (Unidirectional): 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.[30-32]

Buccal tablet:

Buccal tablet is usually a small, flat tablet intended to be inserted in the buccal patch, where the active ingredient is absorbed directly through the oral mucosa; such a tablet dissolve or erodes slowly. Tablet have been the most preferred dosage form for buccal drug delivery. These tablet can be applied to different sites in the oral cavity like palate, mucosa lining of cheek or between the lip and the gum.[17,19]

Buccal films:

Films may be preferred over adhesive tablets because of their flexibility and comfort. Also they provide intimate contact between formulation and mucosal surface. On other hand they can not control the release of drug over long periods of time because amount of polymer used, and thickness is constraint. Films are more preferred in the case of local delivery for oral diseases, protection of the wound surface and help to reduce pain and treat the disease more effectively.[18,21]

Buccal gels and ointment:

Owing to advantage of easy dispersion, semisolid dosage forms have got their place in investigation. However, drug dosing from semisolid dosage forms may not be as accurate as from unit dosage form e.g. tablet, patches and films hence these are more popular for local action where dose accuracy is of less concern.[29,33]

EVALUATION OF BUCCAL PATCHES[1-9]

Mass uniformity and Thickness:

The assessment of weight and patch thickness is done on 10 different randomly selected patches from each batch. For determination of mass, patches were directly weighed on a digital balance and the patch thickness was measured at 5 different randomly selected spots on patches using a screw gauge.

Folding endurance:

Three patches of each formulation of size (2x2 cm) are cut by using sharp blade. Folding endurance determined by repeatedly folding a small strip of patch at the same place till it broke. The number of times, the patch could be folded at the same place without breaking gave the value of folding endurance. The mean value is calculated.

Drug content uniformity:

buccal patches are allowed dissolve in 10 mL of simulated saliva pH (6.2), under occasional shaking for 3 hr, withdraw 2 mL sample solution filter with filter paper after that suitable dilutions was made and amount of drug present in per patch determine by using UV spectrometer (Shimadzu 1800, Japan) at 272nm .

Surface pH Determination:

The surface pH are determined by the method similar to that used by Bottenberg *et al*., 6. A combined glass electrode is used for this purpose. The patches are allowed to swell by keeping them in contact with 1 ml of distilled water (pH pH 6.8±0.1) for 2 h at room temperature, and pH note down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The surface pH of the patches are determined on order to investigate the

possibility of any side effects, in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt made to keep the surface pH of the patch close to the neutral pH.

Swelling index:

The degree of swelling of bioadhesive polymer is important factor affecting adhesion. Upon application of the bio adhesive material to a tissue a process of swelling may occur. The patches are allowed to swell on the surface of agar plate kept in an incubator maintained at 37±0.20. Increase in the weight of the patch was determined at present time intervals (1-3 hrs). The percent swelling of the patches calculated using the formula

$$\% S = (Xt – X0/X0) \times 100,$$

Where,

Xt is the weight of swollen patch after time t,

X0 is the initial patch weight at zero time.

In Vitro Release Studies

In vitro drug release studies is determined by using dissolution test apparatus type II (USP) paddle method using 200 ml of phosphate buffer (pH 6.8) as the dissolution medium at 50 rpm at 37 ± 0.5 C for 8 To provide unidirectional release, one side of each patch attach to a glass disk with the help of adhesive

FTIR Study

The possible interaction between drug and polymers are assessed using Fourier transform infrared spectroscopy (FTIR), model Shimadzu FTIR 8400. FTIR spectra are obtained at room temperature, about 2mg of pure drug, polymers and formulations are dispersed in KBr powder and the pellets made by applying 6000kg/cm2 pressure. FT-IR spectra obtained by powder diffuse reflectance on FT-IR spectrometer.

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