IJPSR (2012), Vol. 3, Issue 1 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 August, 2011; received in revised form 03 October, 2011; accepted 12 December, 2011

BUCCAL DRUG DELIVERY USING ADHESIVE POLYMERIC PATCHES

R. Venkatalakshmi*[1], Yajaman Sudhakar [2], Madhuchudana Chetty C.[3], Sasikala C.[1] and Mohan Varma M.[4]

Faculty of Pharmacy, Masterskill University College of Health Sciences [1], Batu 9, 43200 Cheras - Selangor, Malaysia
Government Polytechnic for Women [2], Kadapa, Andhra Pradesh, India
Annamacharya College of Pharmacy [3], Rajampet, Andhra Pradesh, India
Shri Vishnu College of Pharmacy [4], Bhimavaram, West Godavari District, Andhra Pradesh, India

Keywords:
Oral cavity,
Buccal mucosa,
First pass metabolism,
Enzymatic degradation,
Patch (film)

Correspondence to Author:

R. Venkatalakshmi

Faculty of Pharmacy, Masterskill University College of Health Sciences, Batu 9, 43200 Cheras - Selangor, Malaysia

ABSTRACT

The buccal mucosa has been investigated for local drug therapy and the systemic delivery of therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract. The mucosa of the oral cavity presents a formidable barrier to drug penetration, and one method of optimizing drug delivery is by the use of adhesive dosage forms and the mucosa has a rich blood supply and it is relatively permeable. The buccal mucosa is very suitable for a bioadhesion system because of a smooth and relatively immobile surface and accessibility. Therefore, drugs with a short biological half life, requiring a sustained released effect and exhibiting poor permeability, sensitivity to enzymatic degradation, or poor solubility may be good candidates to deliver via the oral cavity. To overcome the drawbacks of tablets flexible patches for use in the mouth have been developed. Erodible and non-erodible adhesive films have been used as bioadhesive films. These adhesive patches for oral mucosal delivery can be used to designed uni or bidirectional systems for buccal tissue absorption. The objective of this article is to review buccal drug delivery of patches (films) by discussing buccal mucosa and pathways of drug absorption and their formulations.

INTRODUCTION: 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. Although the sublingual mucosa is known to be more permeable than the buccal mucosa, the latter is the preferred route for systemic transmucosal drug delivery. This is because the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems. Thus, the buccal mucosa is more appropriate for sustained delivery of less permeable molecules and peptide drugs [1].

Structure and Design of Buccal Dosage Form:

Buccal Dosage form can be of;

1. **Matrix type:** The buccal patch designed in a matrix configuration contains 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.

FIG. 1: BUCCAL PATCH DESIGNED FOR BIDIRECTIONAL DRUG RELEASE

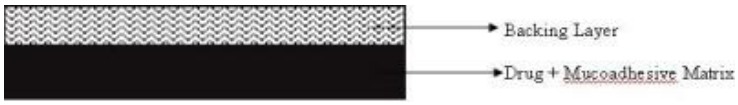

FIG. 2: BUCCAL PATCH DESIGNED FOR UNIDIRECTIONAL DRUG RELEASE

Structure of Oral Mucosa: The oral mucosa is comprised of squamous stratified (layered) epithelium, basement membrane, the lamina propria and submucosa. It also contains many sensory receptors including the taste receptors of the tongue.

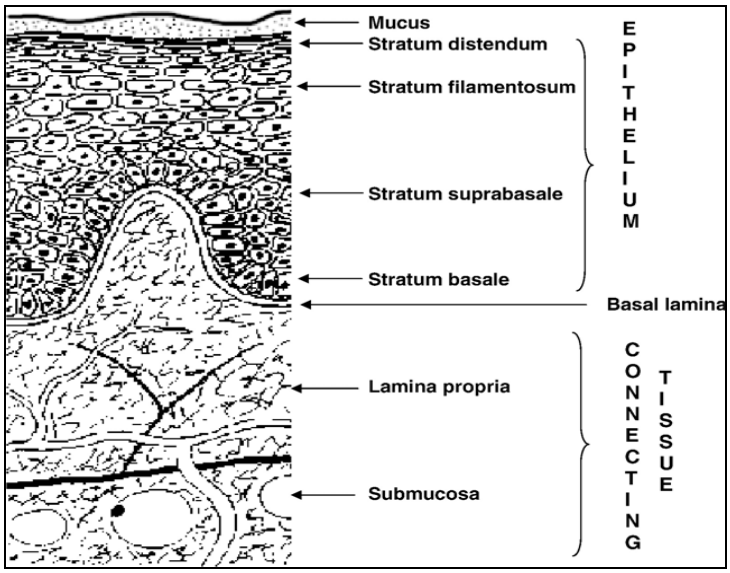

FIG. 3: CROSS-SECTION OF BUCCAL MUCOSA

Buccal Mucosa Environment: The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva [2].

Role of Saliva:

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

Role of Mucus:

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

Buccal Mucosa and Pathways of Drug Absorption: The buccal mucosal tissues consist of a multilayered, stratified squamous epithelium covered with mucous. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual mucosa contains somewhat fewer layers [3]. The epithelial cells increase in size and become flatter as the travel from the basal layers to the superficial layers. The basal lamina connects the epithelium to a connective tissue layer, the lamina propriya [4]. The thickness of the buccal mucosa is about 500-800 µm. the buccal epithelium is not keratinized and has small amounts of ceramide, neutral but polar lipids and cholesterol sulfate in the intercellular lipid region.

Buccal epithelia have been found to be considerably more permeable to water than keratinized epithelia present in other regions of the oral mucosa [5]. Apart from the intercellular lipids, the basement membrane may present some resistance to permeation as well. The basic drugs transport mechanism for the buccal epithelium is the same as that for other epithelia in the body. Two major routes are involved: Transcellular (intracellular) and Paracellular (intercellular) [6].

The transcellular route may involve permeation across the apical cell membrane, intracellular space and basolateral membrane either by passive transport (diffusion, P^H partition) or by active transport (facilitated and carrier-mediated diffusion, endocytosis). The transcellular permeability of a drug is a complex function of various physicochemical properties including size, lipophilicity, hydrogen bond potential, charge and conformation. Transportation through aqueous pores in the cell membranes of the epithelium is also possible for substances with low molar volume (80 cm^3/mol) [7].

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 [8].

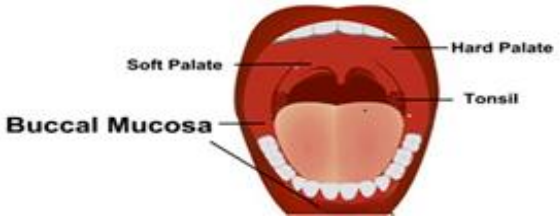

FIG 4: OVERVIEW OF ORAL CAVITY

TABLE 1: THICKNESS AND SURFACE AREA OF ORAL CAVITY MEMBRANES

Oral cavity membrane	Thickness (mm)	Surface area (cm^2)
Buccal mucosa	500-600	5.2
Sublingual mucosa	100-200	26.5
Gingival mucosa	200	--
Palatal	250	20.1

Buccal Drug Delivery Systems: Hydrogels are hypdrophilic polymeric matrices that are capable of swelling when placed in aqueous media. These include natural gums and cellulose derivatives. They swell infinitely and the component molecules dissolve from the surface of the matrix. Drug release then occurs through the spaces or channels within the network as well as through the dissolution and /or disintegration of the matrix. Often, hydrogels are across -linked so that they do not dissolve in the medium and only absorb water [9].

Multilayered tablets are one of the commonly employed dosage forms. They can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed and removed by saliva. Unlike conventional tablets, they lack a disintegrating agent and tend to remain intact during the drug release period. Generally, the buccal tablets have a drug-incorporated polymeric matrix with a backing impermeable membrane. The drug-releasing surface is placed on the mucosal surface and the backing membrane faces the oral cavity. The rate of release from such systems is usually diffusion controlled. Buccal tablets are considered relatively bulky when compared to buccal films [10].

Striant is a monoconvex, tablet-like, mucoadhesive buccal system recently approved by United States food and drug administration (FDA). Striant adheres to the gum tissue above the incisors, with the flat surface facing the check mucosa. The active ingredient in striant is testosterone. Insertion of striant twice a day, in the morning and in the evening, provides continuous systemic delivery of testosterone.

Other pharmacologically inactive ingredient in striant are anhydrous lactose NF, carbomer 934P, hypromellose USP, magnesium sterate NF, lactose monohydrate NF, polycarbophil USP, colloidal silicon dioxide NF, starch NF, and talc USP [11].

Buccal films are preferred to adhesive tablets because of their flexibility and comfort. Moreover, they are also suitable for protecting wound surfaces, thus reducing pain and increasing the effectiveness of treatment. Buccal films or patches are designed either as matrix-controlled or membrane-controlled devices. Some biodegradable or erodible formulations for the timed release of drugs are being investigated.

Atrix laboratories, Colorado, USA have developed Bio-erodible Mucoadhesive (BEMA) technology, which is designed to deliver either local or systemic levels of drugs across mucosal tissues. The BEMA system consists of a small disc with bio-erodible layers that can deliver drugs rapidly at specified time intervals. The BEMA disc adheres to the buccal mucosa and delivers the drug into the mucosa as the disc erodes in the mouth [12].

Design of Buccal Mucoadhesive Patches:

The different components of Buccal Mucoadhesive Patches are as following:

1. Drug
2. Polymers (Mucoadhesive polymers, polymers controlling rate of release and Polymers to prepare backing membrane).
3. Backing membrane.
4. Plasticizer
5. Penetration enhancer.

1. **Drug**: The important drug properties that affect its diffusion through the patch as well as the buccal include molecular weight, chemical functionality and melting point. The selection of a suitable drug for design of buccal mucoadhesive drug delivery system should be based on pharmacokinetic properties.

Following are the critical properties for candidature to Buccal Mucoadhesive Drug Delivery:

- The conventional single dose of drug should be low.

- Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.
- The drug should not adversely affect the natural microbial flora or oral cavity.
- Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

2. **Mucoadhesive polymers:** As the contact between the formulation and the buccal mucosa is one of the key factors in successful buccal delivery, more emphasis is now given to the use of mucoadhesive polymers in the formulation of buccal drug delivery systems [13].

The adhesion of materials with mucosa can be considered as the result of the following steps: Polymer hydration, wetting of mucosa, diffusion into the mucus and chemical bonding with glycoprotein. Hydrated polymer wets the mucus when interatomic and intermolecular forces occur at the interface. The formulation of an assembly is determined by a liquid - solid contact step and thus, the criteria of good wetting and free energy of interaction between the two materials should be considered.

After the initial contact between the hydrated polymer and the mucus, the mucoadhesion strength is determined by the formation of secondary chemical bonds due to polymer chain/mucin interpenetration, which is affected by polymer flexibility and mobility. Hence, the ideal bioadhesive polymer should have satisfactory surface energy and chain flexibility favouring its spread and diffusion into the mucus and functional groups forming secondary chemical bonds (for examples, ionic and hydrogen bonds) [14].

Appropriate materials for bioadhesion are mostly hydrogel-forming polymers that are cellulose derivatives such as sodium carboxymethylcellulose, methylcellulose, methyethylcellulose and hydroxyethyl cellulose. Natural gums such as karaya and pectin and other polymers such as starch, sodium alginate and poly vinyl pyrrolidone can also be used. The high molecular weights of polyethylene oxide (PEO) and polyethylene glycol (PEG) show good mucoadhesive characteristics because of their linear flexible molecular structure and ability to form physical bonds entangling the mucus [15].

Polymers controlling rate of release of drug from buccal mucoadhesive patches: The polymers which are insoluble in saliva or water can be used as efficient matrix systems through which rate of release of drug can be controlled as desired. Examples for this category include ethyl cellulose and butyl rubber. Water-soluble polymers can be used for controlling rate of release in which, rate of polymer dissolution will be release rate determining [16].

3. **Polymers used to prepare 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 per se. The cellulose acetate in concentration of 2.4% w/v in acetone with 10% of plasticizer (PEG 4000 or glycerol) of total polymer weight when air dried produces a thin film suitable for backing membrane purpose. Similarly, 2-4% w/v solution of ethyl cellulose in 1:4 mixture of alcohol: toluene and suitable plasticizer can be casted into film [17].

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

4. **Plasticizer:** These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. Examples of common plasticizers used are glycerol, propylene glycol, PEG 200, PEG 400, castor oil etc. Usually the percentage of polymer falls in the range of 10-50% of total polymer weight. The plasticizers help in release of the drug substance from the polymer base as well as act as penetration enhancers.

The choice of the plasticizer depends upon the ability of plasticizer material to solvate the polymer and alters the polymer- polymer interactions. When used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity [18].

5. Penetration Enhancers in Buccal Drug delivery: Substances that help to promote drug permeation through the buccal epithelium are referred to as penetration enhancer, permeation promoters or absorption enhancer. The chemical used as penetration enhancers should ideally be safe and nontoxic, pharmacologically and chemically inert, non irritant and non-allergenic. In addition, the tissue should revert to its normal integrity and barrier properties on removal of the chemical, surfactants, anions such as sodium laurate and sodium lauryl sulfate, cations such as cetylpyridium chloride and nonions such as poloxamers, brij, span, myrj and tween are known to disrupt the intercellular lipid domain and protein domain integrity, thus enhancing the penetration of hydrophilic molecules. Bile salts are believed to act by the extraction of membrane fluidization and reverse micellisation in the membrane, creating aqueous channels. Fatty acids such as oleic acid and carpylic acid increase the fluidity of phospholipids in the intercellular lipid domain, cyclodextrins act as drug penetration enhancers by including membrane components. Cationic polymers such as chitosan and poly-L-arginine are known to act by neutralizing the charge of the mucosal surface and by opening the tight junctions. Because of the similarities between buccal mucosa and the skin, chemical enhancers and vehicles that increase transdermal delivery have also been used on the buccal mucosa.

Ethanol at different concentrations (5% and 30%), propylene glycol, n-methylpyrrolidone and dimethylsulfoxide have been used as penetration enhancers in buccal dosage forms. Protease inhibitors such as aprotinin, bestatin, puromycin and bile salts, which have been tested and shown to stabilize peptides again buccal mucosal enzymes, have also been used.

TABLE 2: LIST OF INVESTIGATED SOME BUCCAL MUCOADHESIVE PATCHES

Active ingredient	Polymers used	Investigators [Ref.]
Clotrimazole	Carbopol 974P; Clotrimazole; SCMC	S. Singh *et al*.
Lidocaine	HPC	Okamoto *et al*.
Nifedipine	Chitosan with or without an anionic crosslinking polymer (PC, Sodium alginate, Gellan gum)	Remun˜a´n-Lo´pez *et al*.
Insulin	Gelatin and CP 934P	Ritschel *et al*.
Chlorpheniramine Maleate	Hydroxyethylcellulose	K. V. S. Naidu
Atenolol	Ethylcellulose, Hydroxypropyl methylcellulose	M. Jug
Fluconazole	Hydroxypropyl methyl cellulose (HPMC), Hydroxyethyl cellulose, Chitosan, Eudragit, Sodium alginate and Polycarbophil	S. Ali Yehia
Nifedipine	Sodium alginate, MC, PVP, and PEG	Save et al.
Glibenclamide	Chitosan and PVP	Ilango *et al.*
Tetracaine, ofloxacin,	HPC	Oguchi *et al.*
Acyclovir	Copolymers of acrylic acid and PEG, Monomethylether, Monomethacrylate (PEGMM) acid and PEG monomethylether	Shojaei *et al*.
Testosterone	PC and EudragitR S-100 (Polymethacrylic acid-co-methyl methacrylate)	Jay *et al.*
Buprenorphine	CP 934P, Polyisobutylene, and Polyisoprene	Guo and Cooklock
Cetylpyridinium chloride	PVA, HEC, or Chitosan	Nafee *et al*.
Lignocaine	Proprietary mucoadhesive support system	Brook *et al*.
Melatonin	CP 934P and Polyisobutylene	Be´ne`s *et al*.
Metoprolol tartrate	EudragitR NE40D with HPMC, Sodium CMC or CP	Wong *et al.*
Miconazole nitrate	Sodium CMC, Chitosan, PVA, HEC, HPMC	Nafee *et al*.
Protirelin (TRH)	HEC, HPC, PVP, or PVA	Anders and Merkle
Oxytocin	CP 974P	Li *et al.*
Terbutaline sulfate	CP 934, CP 971, HPMC, HEC, or Sodium CMC	Mohamed and Mortada

Thyrotropin-releasing hormone (TRH)	Organic polymers	Li *et al*.
Thyrotropin-releasing hormone (TRH)	Not mentioned in the article	Schurr *et al.*
Triamcinolone acetonide	CP, Poloxamer, and HPMC	Chun *et al*.
Thiocolchicoside	Gelatin and CMC	Artusi *et al*.
Salmon calcitonin	PC and Eudragit R S-100	Cui and Mumper

Advantages and disadvantages of Buccal Drug Delivery: The advantages of buccal drug delivery are that the direct entry of the drug into systemic circulation obviates first pass hepatic metabolism and that the formulation can be easily administered and, if necessary, removed from the site of application. Fast onset of action, no, or little, irritation expected, not painful and patient compliance are the other advantages. The buccal mucosa also used for controlled drug delivery for extended periods of time [19].

The drawbacks of buccal delivery include the need for the device to maintain its position for many hours against buccal motion and salivary flow, the latter also being responsible for dissolving important parts of the drug, thus reducing mucosal absorption. Another disadvantage is the smaller area of tissue available for dug administration, when compared to the skin, intestinal or lung epithelium [20].

Evaluation of Buccal Patch:

The following tests are used to evaluate the Buccal Patches: Drug Content Uniformity, *Ex-Vivo* Residence Time, Thickness Testing, *In-vitro* drug permeation studies, *In-vitro* release studies, Moisture absorption studies, Surface pH study, *In-vitro* bioadhesion measurement, *In-vitro* permeation through porcine buccal membrane, Stability in human saliva, FTIR studies etc [5-6, 21].

CONCLUSION: The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal film may be preferred over adhesive tablet in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which is easily washed away and removed by saliva.

Moreover, the buccal film is able to protect the wound surface, thus reduce pain and also could treat oral diseases more effectively. Buccal drug delivery has been proposed as an alternative to parenteral administration of drugs. The buccal cavity offers many advantages for drug delivery application, the most pertinent being high accessibility and low enzymatic activity.

Additionally, buccal drug delivery can be promptly terminated in cases of toxicity through the removal of dosage form thereby offering a safe and easy method of drug utilization.

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