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BUCCAL PATCHES AS EMERGING TREND

P.Ilavarasan*, K.Ezhumalai, A.N.Rajalakshmi

College of Pharmacy,

Mother Theresa Post Graduate and Research Institute of Health Sciences, Puducherry-605 006.

Email:ilavarasansing@gmail.com

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Abstract

Rapid developments in the field of molecular biology and gene technology resulted in generation of many macromolecular drugs including peptides, proteins, polysaccharides and nucleic acids in great number possessing superior pharmacological efficacy with site specificity and devoid of unwanted and toxic effects. However, the main impediment for the oral delivery of these drugs as potential therapeutic agents is their extensive presystemic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Parenteral route of administration is the only established route that overcomes all these drawbacks associated with these orally less/inefficient drugs but, these formulations are costly, have least patient compliance, require repeated administration, in addition to the other hazardous effects associated with this route. Buccal drug delivery leads direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. 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, provide distinct advantages over traditional dosage forms for treatment of many diseases. This article aims to review the recent developments in the buccal adhesive drug delivery systems to provide basic principles to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design.

Keywords: Buccal mucosa, Buccal patch/film, Permeation, Transmucosal, Buccal drug delivery, Mucoadhesive.

Introduction

Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity)^[1]. Well defined bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion.

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.

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^[2].

Components or structural features of oral cavity (Figure 1)

- Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions.
- Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).

- Oral cavity proper, which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate.
- The tongue projects from the floor of the cavity.

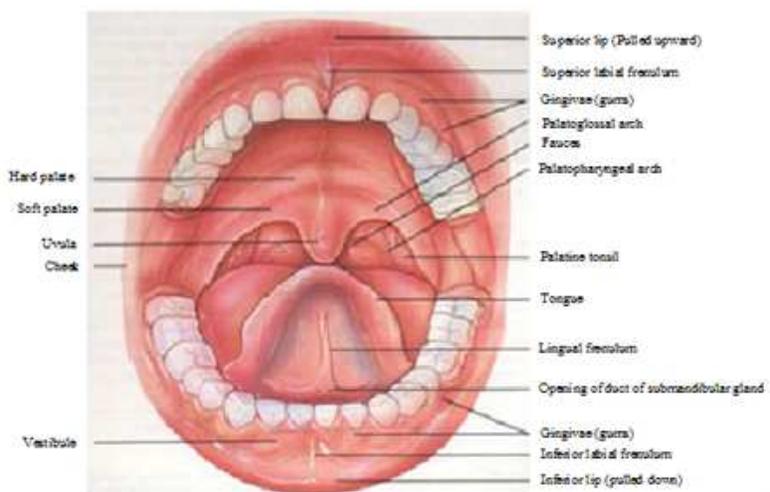


Figure 1: Anatomical structure of Oral Cavity (Anterior View)

PHYSIOLOGICAL ASPECTS AND FUNCTIONS OF ORAL CAVITY

- As a portal for intake of food material and water.
- Helps in chewing, mastication and mixing of food stuff.
- Helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds of tongue.
- To initiate the carbohydrate and fat metabolism.
- To aid in speech and breathing process.

Novel buccal dosage forms

The novel type buccal dosage forms include buccal adhesive tablets, patches, films, semisolids (ointments and gels) and powders.

A. Buccal mucoadhesive tablets

Buccal mucoadhesive tablets are dry dosage forms that have to be moistened prior to placing in contact with buccal mucosa. Example: a double layer tablet, consisting of adhesive matrix layer of hydroxy propyl

cellulose and polyacrylic acid with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

B. Patches and Films

Buccal patches consists of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape. A novel mucosal adhesive film called “Zilactin” – consisting of an alcoholic solution of hydroxy propyl cellulose and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hours even when it is challenged with fluids.

C. Semisolid Preparations (Ointments and Gels)

Bioadhesive gels or ointments have less patient acceptability than solid bioadhesive dosage forms, and most of the dosage forms are used only for localized drug therapy within the oral cavity. One of the original oral mucoadhesive delivery systems –“orabase”– consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes.

D. Powders

Hydroxypropyl cellulose and beclomethasone in powder form when sprayed onto the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours.

BUCCAL DRUG DELIVERY SYSTEM

A delivery system designed to deliver drugs systemically or locally via buccal mucosa. Buccal delivery refers to the drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva^[3].

BUCCAL ABSORPTION

Buccal absorption leads systemic or local action via buccal mucosa.

MECHANISM OF BUCCAL ABSORPTION

Buccal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophilic the drug molecule, the more readily it is absorbed^[4]. The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows

$$\frac{-dm}{dt} = \frac{KC}{V_i V_t}$$

Where,

M - Mass of drug in mouth at time t

K - Proportionality constant

C - Concentration of drug in mouth at time

V_i - The volume of solution put into mouth cavity and V_t - Salivary secretion rate

FACTORS AFFECTING BUCCAL ABSORPTION

The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption^[5].

1. Membrane Factors

This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.

2. Environmental Factors

A. Saliva: The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film affect the rate of buccal absorption.

B. Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

C. Movement of buccal tissues: Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.

COMPOSITION OF BUCCAL PATCHES

- A. Active ingredient.
- B. Polymers (adhesive layer): Hydroxy ethylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers.
- C. Diluents: Lactose DC is selected as diluent for its high aqueous solubility, its flavouring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. other example : microcrystalline starch and starch.
- D. Sweetening agents: Sucralose, aspartame, mannitol, etc.
- E. Flavouring agents: Menthol, vanillin, clove oil, etc.
- F. Backing layer: Ethyl cellulose, etc.
- G. Penetration enhancer: Cyano acrylate, etc.
- H. Plasticizers: PEG-100, 400, propylene glycol, etc.

METHOD OF PREPARATION

Two methods are used to prepare adhesive patches.

1. Solvent casting

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry^[6].

2. Direct milling

In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described^[7].

While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues^[8].

EVALUATIONS OF BUCCAL PATCH

1. Surface pH

Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch^[9].

2. Thickness measurements

The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer^[10].

3. Swelling study

Buccal patches are weighed individually (designated as W1), and placed separately in 2% agar gel plates, incubated at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$, and examined for any physical changes. At regular 1-hour time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper^[11]. The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated using the following formula.

$$SI = \frac{(W_2 - W_1) \times 100}{W_1}$$

4. Folding endurance

The folding endurance of patches is determined by repeatedly folding 1 patch at the same place until it breaks or is folded up to 200 times without breaking^[12].

5. Thermal analysis study

Thermal analysis study is performed using differential scanning calorimeter (DSC).

6. Morphological characterization

Morphological characters are studied by using scanning electron microscope (SEM).

7. Water absorption capacity test

Circular Patches, with a surface area of 2.3 cm² are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na₂HPO₄, 0.19 gKH₂PO₄, and 8 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccator over anhydrous calcium chloride at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation

$$\text{Water uptake (\%)} = \frac{(W_w - W_f) \times 100}{W_f}$$

Where,

W_w is the wet weight and W_f is the final weight. The swelling of each film is measured^[13].

8. Ex-vivo bioadhesion test

The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan

attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface^[14]. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength (Figure 2).

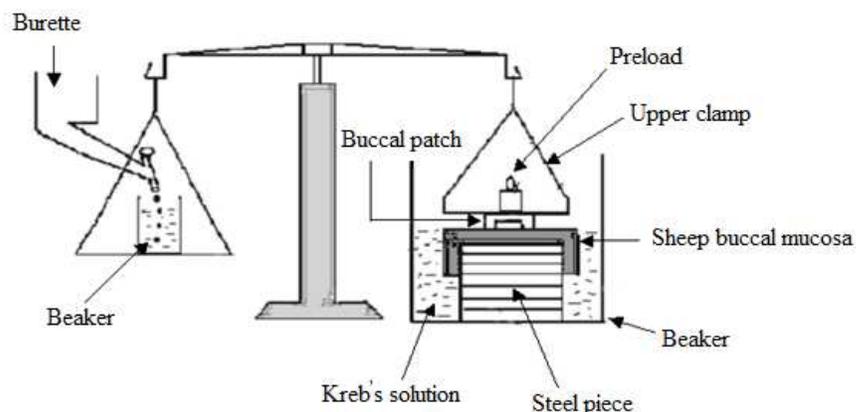


Figure 2: Measurement of Mucoadhesive Strength

9. In vitro drug release

The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution. The in-vitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with buffer (Figure 3).

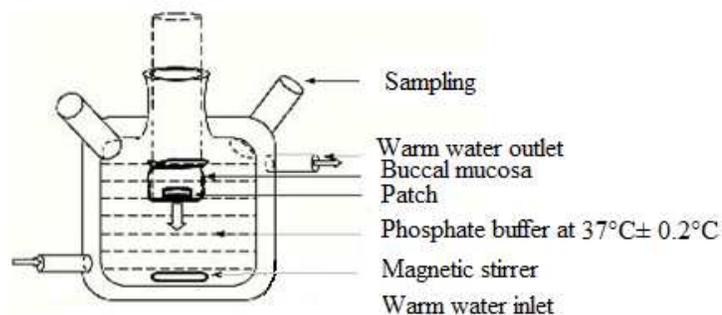


Figure 3: Schematic Diagram of Franz Diffusion Cell for Buccal Patch

10. Permeation study of buccal patch

The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content^[15].

11. Ex-vivo mucoadhesion time

The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit)^[16]. The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours. The time for changes in colour, shape, collapsing of the patch, and drug content is noted^[17, 18].

12. Measurement of mechanical properties

Mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp

moving at a rate of 2 mm/sec until the strip break. The force and elongation of the film at the point when the strip break is recorded. The tensile strength and elongation at break values are calculated using the formula^[19].

$$T = \frac{m \times g}{b \times t} \text{ Kg/mm}^2$$

Where,

M - is the mass in gm, g - is the acceleration due to gravity 980 cm/sec²

B - is the breadth of the specimen in cm

T - is the thickness of specimen in cm.

Tensile strength (kg/mm²) is the force at break (kg) per initial cross-sectional area of the specimen (mm²).

13. Stability study in human saliva

The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50years). Buccal patches are placed in separate petridishes containing 5ml of human saliva and placed in a temperature-controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), the dose formulations with better bioavailability are needed. Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentively, low enzymatic activity, economy and high patient compliance. Adhesion of buccal adhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers) to reduce the overall dose required and minimize side effects that may be due to systemic administration of drugs. Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. 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 formulations and delivery of small proteins/peptides.

ADVANTAGES OF BUCCAL PATCHES

- The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation.
- Buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect. Contact with the digestive fluids of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate.
- The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, additionally; there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.
- Buccal patch has been well known for its good accessibility to the membranes that line the oral cavity, which makes application painless and with comfort.
- 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.
- The novel buccal dosage forms exhibits better patient compliance.

LIMITATIONS IN BUCCAL PATCHES

- The area of absorptive membrane is relatively smaller. If the effective area for absorption is dictated by the dimensions of a delivery system, this area then becomes even smaller.
- Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. Involuntary swallowing of saliva results in a major part of dissolved or suspended released drug being removed from the site of absorption. Furthermore, there is risk that the delivery system itself would be swallowed.

- Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allergy and adverse properties such as discoloration or erosion of the teeth may limit the drug candidate list for this route.
- Conventional type of buccal drug delivery systems did not allow the patient to concurrently eat, drink or in some cases, talk.

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Corresponding Author:

P.Ilavarasan*,

Email:ilavarasansing@gmail.com