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REVIEW ARTICLE BUCCAL PATCHES DRUG DELIVERY SYSTEM - A REVIEW

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ABSTRACT

The aim of this article is to focus on buccal patches. Buccal route found to be more suitable for the delivery of pharmaceutical agents using mucoadhesive polymers due to presence of relative lystatic and smooth surface on which various mucoadhesive dosage forms can be placed. The mucosa of buccal cavity is the most easily accessible transmucosal site delivery help to bypass first-pass metabolism by allowing direct access to systemic circulation. Buccal patch have been become an interesting area of novel drug delivery system as the dosage forms designed for buccal administration should not cause irritation and should be small and flexible enough to be accepted by the patient. Buccal delivery medication gives a convenient route of administration for both local and systemic effects. This presents a brief description the study of buccal patches and include its introduction, types of buccal patches, advantages, limitation, anatomical structure of oral mucosa, potential uses of buccal patches, polymer used, methods of preparation, evaluation.

KEYWORDS

Buccal patches, Mucoadhesion, Buccal mucosa and Polymer NDDS.

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INTRODUCTION

Oral administration of drugs has been the most common and preferable route for delivery of most therapeutic agents. The major obstacle for per oral administration of drug is the extensive hepatic first pass metabolism and stability problems within the gastrointestinal environment such as instability in gastric pH and complexation with mucosal membrane[1]. Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa; this was eventually leads to Orabase[2]. Nasal, ocular, vaginal, rectal and

buccal mucosal membranes have been evaluated as potential alternative routes for peptide absorption. Buccal administration of drugs provides a convenient route of administration for both systemic and local drug actions[3]. Buccal patch consists of mucoadhesive polymer and other excipient. Due to the adhesive property of polymer it will bind to the buccal mucosa and the drug will be released to the systemic circulation[4].

Advantages[5,6]

- Accessibility is excellent.
- Fast absorption because of enormous blood supply and good blood flow rates.
- Improved patient compliance -ease of drug administration.
- Prolonged release.
- A highly fast onset of action can be achieved.

Disadvantages[7]

- Limited surface area is available for absorption.
- There is a possibility that patient may swallow it like tablet.
- Drugs with large dose are difficult to be administered.

Limitations[8,9]

- The drugs having bitter taste cannot be formulated.
- The drugs which irritate oral mucosa, cause allergic reactions and discoloration of teeth cannot be formulated.
- Small dose of drug is required.
- Eating and drinking may mostly restrict.

THE STRUCTURE OF THE ORAL MUCOSA

Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Figure No.1). The lamina propria is also called as basement membrane it is a continuous layer of extracellular materials and forms a boundary between the basal layer of epithelium and the connective tissues, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa it is about 500 to 800µm in thickness with varying degrees of maturity. The uppermost superficial layer of cells is made up of flattened compact differentiated cells having 150µm thickness. rs[10].

There is need to develop a dosage form that bypasses first pass metabolism and GI degradation. Oral cavity provides route for the administration of a the rapeutic agent for local as well as systemic delivery, so that first pass metabolism and GI degradation can be avoided. The oral cavity is easily accessible for self-administration, stopping of drug is feasible if required, safe and, hence is well accepted by patients. The mucosal areas subject to mechanical stress (the gingivae and hard plate) are keratinized similar to the epidermis. The mucosa of the soft palate, the sublingual and the buccal regions, however, are not keratinized contain only small amounts of ceramides[10].

Functions of oral cavity

It helps in chewing, mastication and mixing of food stuff.

It is Helps to lubricate the food material and bolus.

To identify the ingested material by taste buds of the tongue.

To initiate the carbohydrate and fat metabolism[11].

Mucoadhesion and its mechanism[12,13]

The use of mucoadhesive polymers for the formulation of viscous gels and mouthwashes has always provided with better lubrication and retention. They are widely used for the symptomatic relief of ulcerated oral mucosa. An example of this is Oraqix® gel which is a noninjectable periodontal gel.

Bioadhesion

Is defined as a mechanism by which a substance is capable of interacting with biological membrane like buccal mucosa.

Events of bioadhesion

A strong attachment of the bioadhesive with the membrane as it swells up or due to subsequent wetting of the bioadhesive and a membrane.

Bioadhesive penetrates into the tissue

The chains of bioadhesive then cross links and interpenetrates into the mucosa.

ENVIRONMENT OF BUCCAL MUCOSA

Role of Saliva

Saliva has moisturize nature for buccal dosage forms

It has protecting fluid for all the muscles of oral cavity

Continuous mineralization is another feature of the saliva

Role of Mucus

The human mucus composed of carbohydrates and protein. They provide lubricating effect.

Mucus are the also responsible for adhesion dosage forms with buccal mucosa.

Permeability of Drugs through Buccal Mucosa

There are two permeation pathways or routes for passive drug transport across the oral mucosa: paracellular and transcellular routes.

Trans-cellular

Para-cellular

Mechanism of bioadhesion[14-16]

For bioadhesion to occur, three stages are involved,

There are many chemical bonds responsible for the mucoadhesion. Ionic (where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond), covalent (where electrons are shared, in pairs, between the bonded atoms in order to fill the orbital in both) are the stronger bonds which help the formulation to adhere to the mucosa. The weaker bonds involved in mucoadhesion are hydrogen bonds, Van-der-Waals bonds and other hydrophobic bonds.

Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bonds can then settle.

The bonding between the mucus and the biological substance occurs chiefly through both physical and chemical interactions results from enlargement of the adhesive material and chemical bonds due to electrostatic interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.

Theories of Bioadhesion or Mucoadhesion[17-20]

Wetting Theory

This theory is developed predominantly in regard to liquid adhesives, uses interfacial tensions to predict spreading and in turn adhesion. The study of surface energy of both polymers and tissues to predict mucoadhesive performance.

Diffusion Theory

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond.

Electronic Theory

According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucous glycoprotein network because of differences in their electronic structures. This results in the formation of an electronic double layer at the interface. Then the adhesion occurs due to attractive forces across the double layer.

Fracture Theory

According to Fracture theory of adhesion is related to separation of two surfaces after adhesion.

Adsorption Theory

According to the in-adsorption theory after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. There are two types of chemical bonds resulting from these forces can be distinguished. Primary chemical bonds of covalent nature. And the secondary chemical bonds having many different forces of attraction including electrostatic forces and hydrogen hydrophobic bonds.

PATCHES ABD FILMS

The buccal patches there is a consist of two laminates, and with an aqueous solution of the adhesive polymer being cast onto an impermeable of the backing sheet, then which is the cut into the required oval shape. A novel mucosal adhesive film called “Zilactin” -consisting of an alcoholic solution of hydroxyl propylcellulose 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[21].

Mechanism of Buccal Absorption

In this mechanism of oral mucosal drug absorption occurs by the passive diffusion of the non-ionized 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 activity 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 membranes and the more lipophilic the drug molecule, the more readily it is absorbed 13. 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[22]. The linear relationship between salivary secretion and time is given as follows: Where

$dm/dt = Kc/ViVt$

Where,

M-Mass of drug in mouth at time t, K-Proportionality constant,

C-Concentration of drug in mouth at time,

Vi-The volume of solution put into mouth cavity and

Vt -Salivary secretion rate.

Composition of buccal patches

Active ingredient

Polymers (adhesive layer)

Hydroxy ethylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, Carbopol and other mucoadhesive polymers.

Diluents

As the patches are of buccal use taste and odor are also taken into considerations for that purpose flovours and sweeteners are used. Diluents are used as fillers for the low dose of the drug. Diluents- eg. Lactose, Microcrystaline starch, starch.

Sweetening agents

Sucralose, aspartame, mannitol, etc.

Flavouring agents

Menthol, vanillin, clove oil, etc.

Backing layer

Ethyl cellulose, etc.

Penetration enhancer

Cyano acrylate, etc. H. Plasticizers: - PEG-100, 400, propylene glycol, etc[23].

METHOD OF PREPARATION

Two method are used as follow

Solvent casting

1. In this method at First disperse drug in an organic solvent and then add all patch excipients.
2. These solution coat onto the sheet of release liner.
3. Allow this for solvent evaporation material is laminates on the sheet of coat release liner.
4. These laminates die-cut to form patches of the proper size and geometry[23].

Direct milling

1. These is solvent free method
2. Drug and excipients mixture form by mechanical milling or by the kneading and avoid any liquid presence
3. The resultant material is role on a release liner to achieve the proper thickness[24].

API and excipients are blended by direct milling

↓

Blended mixture is rolled using rollers

↓

Backing material is laminated

↓

Film is collected

List of drugs delivered via buccal route

In an effort to determine the feasibility of buccal route as a novel route of drug delivery, as follows[25],

- Active Ingredients
- Acitretin
- Chitosan
- Morphine sulphate
- Nifedipine

- Omeprazole
- Oxytocin

EVALUATION OF BUCCAL PATCHES

Thickness[26]

Three patch/films of every formulation were weighed individually in a digital balance and the mean weight was calculated. The mean value of film thickness was calculated by measuring thickness of three patch of each formulation at three different places using Micro meter Screw Gauge.

Weight uniformity[27]

The uniformity evaluation the ten patches of the 1cm 2 were weighed individually and the average of those patches is the measured

Surface ph study[28]

The prepared buccal patches are left to swell for 2 hrs on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature.

Content uniformity[29]

The 5 films or patch were the weighed and dissolved in 100ml isotonic phosphate buffer pH 6.8 and the then using magnetic stirrer. The solution was filtered and after the suitable dilution analyzed for drug spectrometrically.

Folding endurance[30]

Folding endurance of the patches determined by repeatedly folding one patch at the same place till it broke or folded up to 200 or 300 times manually, which was considered satisfactory to reveal good patch properties. Then the number of times of the film can be fold at the same place without breaking gave the value of the folding endurance.

Swelling % study[31,32]

Buccal patches are weighed individually (W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C. Plates 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. And the swollen patches are then reweighed (W2) and the swelling index (SI) is calculated using the following formula.

SI= (W2-W1)/W1× 100.

Water absorption capacity test[33]

Circular Patches, with a surface area of 2.3cm 2 are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38g Na2HPO4, 0.19g KH2PO4, and 8g NaCl per litter 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

Water uptake (%) = (Ww-Wf)/W x100

Where,

Ww is the wet weight and Wf is the final weight. The swelling of each film is measured

***In vitro* drug release**[34]

For *in vitro* release study the drug release from the buccal patches 200mL of phosphate buffer (pH 6.8) used as the dissolution medium, at 37.0 ± 0.5°C and a rotation speed of paddle was 50rpm. The patches are evaluated for drug release using Franz diffusion. The disk was put in the bottom of the dissolution vessel 24 Samples (5mL) were withdrawn at half-hour intervals and replaced with fresh medium to maintain the sink condition. The sample analyzed in U.V. spectrophotometer at 26nm.

Permeation study of buccal patch[35]

The permeation study of buccal patch receptor compartment is filled with the 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.

***Ex-vivo* mucoadhesion time**[36]

The *ex-vivo* mucoadhesion (residence) time is determined by locally modified USP disintegration apparatus using 800mL of simulated saliva (pH 6.2) and the temperature is maintained at (37±1)°C. A porcine buccal mucosa obtained from local

slaughter house within 2 h of slaughter is used to mimic the human buccal mucosa in the *in-vivo* conditions. The mucosal membrane is carefully separated by removing the underlying connective tissues using surgical scissors. The separated mucosal membrane is washed with deionized water and then with simulated saliva (pH 6.2). 58 Porcine buccal mucosa (3cm diameter) is glued on the surface of a glass slab. The buccal patch of one side is hydrated with one drop of simulated saliva (pH 6.2) and brought into contact with porcine buccal mucosa by gentle pressing with a fingertip for few seconds. The glass slab is vertically fixed to the shaft of the disintegration apparatus and allowed to move up and down (25 cycles per min). The patch is completely immersed in simulated saliva at the lowest point and is out of the solution at the highest point. The time of complete erosion or detachment of the patch from the mucosal surface is recorded as *ex-vivo* mucoadhesion time[37].

Tensile strength[38,39]

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 10mm and without any visual defects cut and positioned between two clamps separated by a distance of 3cm. Then the clamps design 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 the 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.

$T = m \times g / b \times t$ Kg/mm^2

Where,

M - is the mass in gm,

g - is the acceleration due to gravity 980cm/sec2

B - is the breadth of the specimen in cm,

T - is the thickness of specimen in cm.

Table No.1: Categories of mucoadhesive polymers used in buccal patches[13]

S.No	Natural Polymers	Synthetic Polymers
1	Tragacanth	Cellulose derivatives(MC,EC,HEC etc)
2	Sodium alginate	Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
3	Guar gum	Poly hydroxyl ethyl methyl acrylate
4	Xanthan gum	Polyethylene oxide
5	Soluble starch	Polyvinylpyrrolidone
6	Gelatin	Polyvinyl alcohol
7	Chitosan	---

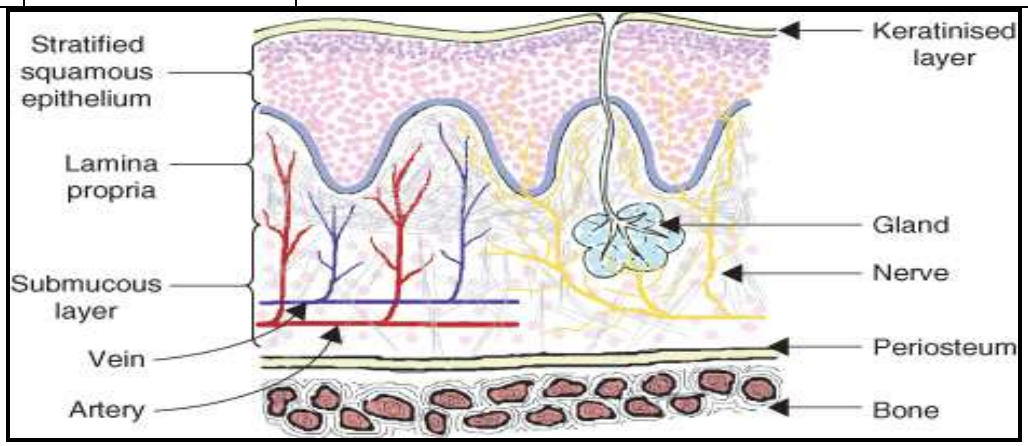

Figure No.1: Schematic cross section through the oral mucosa showing the epithelium, basal lamina, and connective tissue

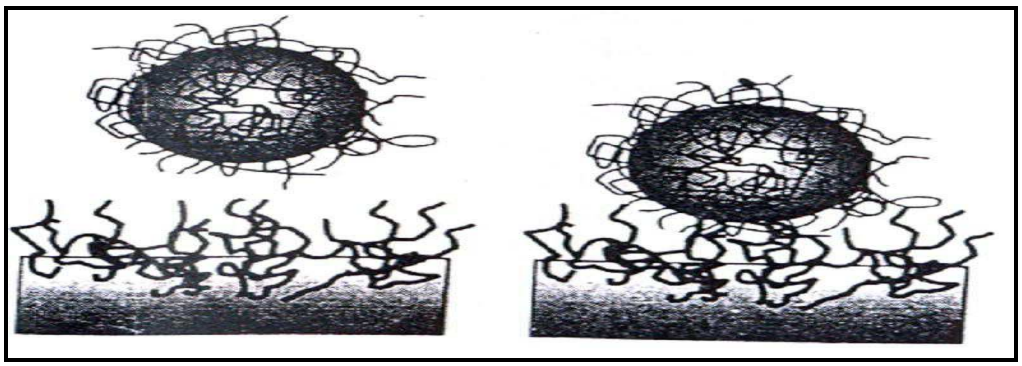

Figure No.2: Inter penetration of bioadhesive and mucus polymer chain

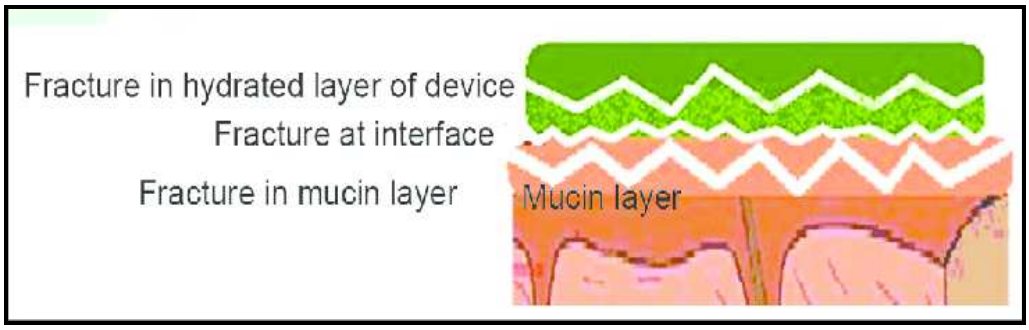

Figure No.3: Fracture occurring for Mucoadhesion

CONCLUSION

Buccal drug delivery is useful for the drugs that undergo first pass metabolism and GI degradation. In this drug delivery system the formulation keeps in contact with the mucosal surface resulting in better absorption and prolonged resident time. Buccal patches are shows better patient compliance because of decrease in frequency of administration, hence increases bioavailability of the drug. Hence, buccal drug delivery is more advantageous over the other oral dosage forms. Then 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 the order to accommodate drug permeation, buccal drug delivery is a promising area for continued research with the 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.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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