International Standard Serial Number (ISSN): 2319-8141
International Journal of Universal Pharmacy and Bio Sciences 7(3): May-June- 2018

INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES

*IMPACT FACTOR 4.018****
*ICV 6.16****

Pharmaceutical Sciences **REVIEW ARTICLE ……!!!**

A REVIEW ON BUCCAL ADHESIVE DRUG DELIVERY SYSTEM: BUCCAL PATCHES

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KEYWORDS:

Buccal mucosa, Permeation, Transmucosal, Drug delivery.

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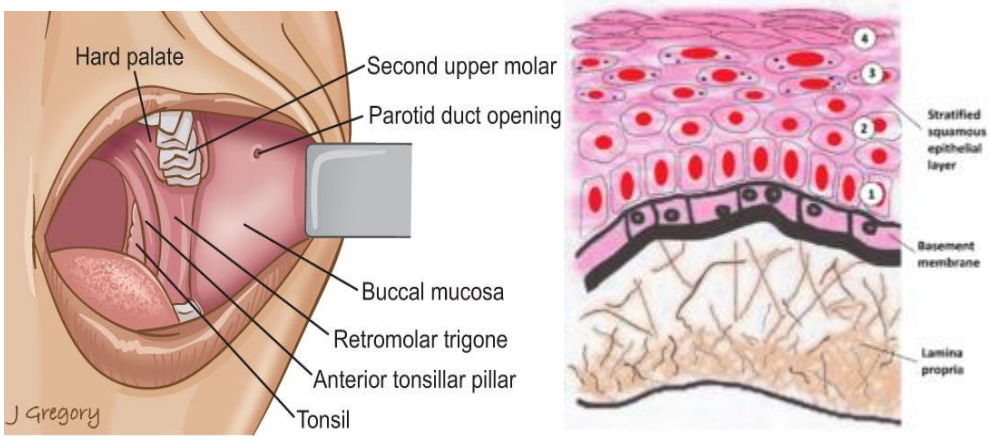
ABSTRACT

Oral route is most preferable, but the main disadvantage of the oral delivery of the drugs is their extensive pre-systemic metabolism, instability in acidic environment thus 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. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. This paper aims to review the developments in the buccal adhesive drug delivery systems to provide basic principles, which will be useful to circumvent the difficulties associated with the formulation design.

A. INTRODUCTION:

In the various routes of drug administration, oral route is the most preferred to the patient. However, factors such as hepatic first pass metabolism and enzymatic degradation within the GI tract limits its use for certain drugs [1] .hence other absorptive mucosas are considered as potential sites for drug administration .Transmucosal routes of drug delivery such as the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities provides distinct benefits over oral administration for systemic effect [2].Buccal mucosa is relatively permeable, has a rich blood supply, is robust, and showsshort recovery times after stress or damage[3]. Buccal administration refers to a topical route of administration by which drug held or applid in the buccal area(in the cheek) diffuse through the oral mucosa and enter directly into the blood stream. Buccal administration may provide better bioavailability of some drugs and a more rapid onset of actioncompared to oral administration because the medication does not pass through the digestive system and thereby avoids first pass metabolism.



(a) **(b)**

Fig.1. Anatomy of oral cavity

Bioadhesion refers to the phenomenon where natural and synthetic materials adhere to biological surfaces. An understanding of the fundamental mechanisms that govern bioadhesion is of great interest for various researchers who aim to develop new biomaterials, therapies and technological applications such as biosensors[4]. Buccal drug delivery system has been investigated for variety of applications including the treatment of periodontal disease(bacterial

infection of the gums and bone),aphthous and dental stomatitis. Nowadays mucoadhesion has gain interest for its systemic delivery by retaining a formulation intimate contact with buccal cavity.

B. a) Advantages of Buccal Patches

1. Avoids first pass metabolism.
2. Permits localization of drug to the oral cavity for extended period of time**.**
3. Termination of therapy is possible
4. Reduction in dose can be achieved, thereby reducing dose dependent side effects
5. 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..
6. The buccal membrane is sufficiently large to allow delivery system to be placed at different sites on the same membrane for different occasions, if the drug or other excipients cause reversible damage or irritate mucosa.
7. Buccal patch offer greater flexibility and comfort than the other devices.

b) Disvantages of Buccal Patches

1. There is possibility that Patient may swallow the tablet
2. The drug contained in swallowed saliva follows the per oral route & advantages of buccal route is lost.
3. Only drug with small dose requirement can be administered.
4. Drug which irritate mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route
5. Drugs which are unstable at buccal pH cannot be administered by this route.

C) Approaches of Buccal Drug Delivery System

1. Matrix Type

Drug, adhesive, and additives are mixed together. Bi-directional patches release drug in both the mucosa and the mouth[5]. The structure of the matrix type design is basically a mixture of the drug with the mucoadhesive matrix. Matrix type of dosage forms are following ;

-Conventional buccal tablets

-Novel buccal adhesive tablet

2.Reserviour Type

The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive[6]. 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. Matrix type of dosage forms are following

-Buccal patches

3.Buccal films

Buccal films 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.

4.Buccal mucoadhesive hydrogel

Buccal mucoadhesive hydrogel systems are formulation that are using for topical administration of many drugs. They offer various advantageous properties such as easy application, spreadability and bio compatibility also showing number of different physiological properties that make them remarkably systems for different applications**.**

5.Buccal Microsphere

Bio adhesive microspheres offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue

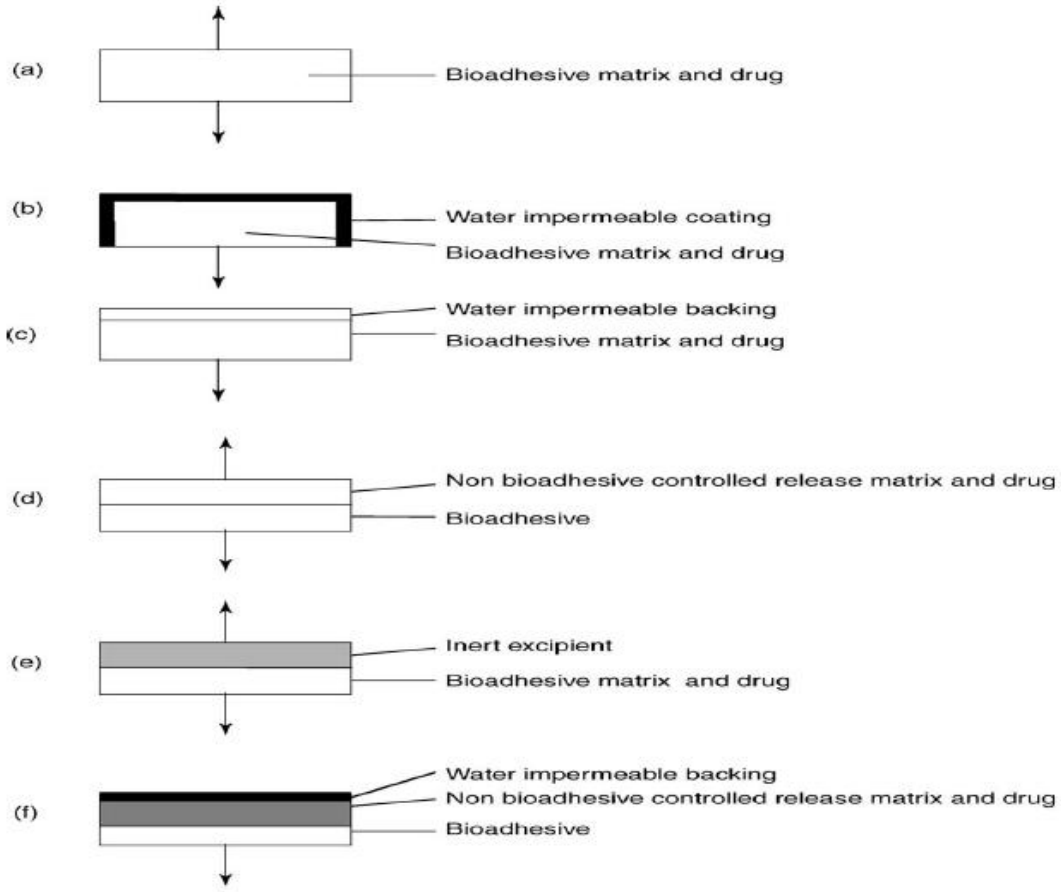


Fig.2 Schematic representation of different matrix tablets for buccal delivery. Arrows indicate the direction of drug release[7].

D.Mechanism of buccal absorption-The mechanism of Buccal drug absorption is depend on 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. The dynamics of buccal absorption of drugs could be adequately described by first order rate process[8]. 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:

$$\frac{-dm}{Dt} = \frac{KC}{ViVt}$$

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

E.Factors affecting Buccal Absorption: There are various interdependent and independent factors which affects the buccal absorption;

1. **Membrane Factors:** This involves degree of keratinization, surface area available for absorption, mucus layer of salivarypellicle, 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[9,10].
2. **Environmental Factors:**
   i. **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.
   ii. **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
   iii. **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[11]

F.Composition of Buccal Patches:

1. **Active ingredient.**
2. **Polymers (adhesive layer):** Hydroxyethyl cellulose, Hydroxyl propyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers[12,13].
3. **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.
4. **Sweetening agents:** Sucralose, aspartame, mannitol, etc.
5. **Flavouring agents:** Menthol, vanillin, clove oil, etc.
6. **Backing layer:** Ethyl cellulose, Poly vinyl alcohol[14]etc.
7. **Penetration enhancer:** Cyano acrylate, etc.
8. **Plasticizers:** PEG-100, 400, propylene glycol, etc.

G.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[15.]
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. 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[16].

H.Evaluation

1. **Surface pH:** The surface pH of the buccal patch was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose.The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature, and pH was note down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute[17,18].
2. **Swelling studies:** Weight and area increase due to swelling were measured. Weight increase due to swelling: A drug-loaded patch of 1x1 cm2 was weighed on a preweighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.6 was added. After every five minutes, the cover slip was removed and weighed upto 30 minutes. The difference in the weights gives the weight increase due to absorption of water and swelling of patch. Area increase due to swelling: Where Xt is the weight or area of the swollen patch after time t Xo is the original patch weight or area at zero time[19].
3. **Thickness measurements:** The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.
4. **Thermal analysis study:** Thermal analysis study is performed using differential scanning calorimeter (DSC).
5. **Morphological characters:** Morphological characters are studied by using scanning electron microscope (SEM).
6. **Palatability test:** Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A,B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation score two a grade then it would be considered as good and the one with all three A grade it would be the very good formulation. Grades: A = very good, B = good, C = poor

7. **Folding endurance:** The test is performed by repeated folding of the film at the same place until film failure. A maximum of 300 times is sometimes reported as a limit to the test, and the value is reported as the number of times the film can be folded prior to rupture[20].
8. **In vitro drug release:** The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug Release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. the release was performed at 37 0C ± 0.50 0C,with a rotation speed of 50 rpm. The backing layer of buccal patches attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at suitable nm.
9. **In vitro drug permeation:** The in vitro buccal drug permeation study of Drugs through the buccal mucosa (sheep and rabbit) performed using Keshary-Chien/Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment maintained by stirring with a magnetic bead at 50 rpm. A one ml sample can be withdrawn at predetermined time intervals and analyzed for drug content at suitable nm using a UVspectrophotometer[21].
10. **Stability study in Human saliva:** Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content,disintegration time and physical appearance. The stability study of optimized mucoadhesive patch formulation was performed at 400C, 37 ±50C & 75±5% RH for three months. The value of all parameter after three months remain same as their values and minor changes occur in value of volume entrapment efficiency, % elongation & % drug release after 8 hour which was considerable.

11. **Ex vivo mucoadhesive strength:** A modified balance method used for determining the ex vivo mucoadhesive strength. Fresh buccal mucosa (sheep and rabbit) obtained, used within 2 hours of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane washed with distilled water and then with phosphate buffer pH 6.8 at 370C. The buccal mucosa cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The two sides of the balance made equal before the study, by keeping a 5 g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C ±1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive.

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 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. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

ACKNOWLEDGEMENTS:

The authors express their gratitude to the Principal, and Faculty members of Rajgad Dnyanpeeth's College of Pharmacy for their encouragement, support and guidance for this work.

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