FORMULATION AND EVALUATION OF PANTOPRAZOLE BUCCAL PATCHES: - A REVIEW

Ankit Singh*, Pallavi Tiwari, Preeti Saxena, Sagar Singh Jough, Akash Srivastva, Dharmendar Kumar

M.Pharm Scholar Advance Institute of Biotech and Paramedical Sciences, Kanpur.

ABSTRACT

Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration, since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs. The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration. The buccal cavity is easily accessible for self medication. The buccal cavity is easily accessible for self medication, and hence it is safe and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. The strategies include manipulation of the formulation (e.g. inclusion of penetration enhancers or protease inhibitors etc.), maximizing retention of the delivery system at the site of absorption, and alteration of the peptide so as to optimize affinity for endogenous transport systems, build in chemical and metabolic stability, minimize the size and optimize the balance between lipophilicity and hydrogen bonding potential. The aim of the present investigation was to formulate and evaluate buccal patches comprising drug (atenolol) containing mucoadhesive polymeric layer (using SA, CP 934 P, NaCMC and HPMC) and drug free backing membrane composed of PVA-aluminum foil. Aluminum foil was used with adhesive polymer PVA to prevent back release of the drug from the buccal patches.

KEYWORDS: Buccal delivery, Patches, Gastrointestinal drug.
INTRODUCTION

Extensive research efforts have recently been focused on placing a drug delivery system in a particular region of the body for maximizing biological drug availability and minimizing dose-dependent side effects. Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration, since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs.\textsuperscript{[1-2]}

The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration.\textsuperscript{[3-5]} The buccal cavity is easily accessible for self medication. The buccal cavity is easily accessible for self medication, and hence it is safe and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries. The aim of the present investigation was to formulate and evaluate buccal patches comprising drug (atenolol) containing mucoadhesive polymeric layer (using SA, CP 934 P, NaCMC, and HPMC) and drugfree backing membrane composed of PVA aluminum foil. Aluminum foil was used with adhesive polymer PVA to prevent back release of the drug from the buccal patches.\textsuperscript{[5]}

\textbf{MATERIAL AND METHODS}

\textbf{Materials}

Hydrochlorothiazide and lisinopril were provided by Yarrow Chemicals Pvt. Ltd., Mumbai. Hydroxypropyl cellulose, Hydroxypropylmethyl cellulose K4M, Polyvinyl pyrrolidone K-30 were provided by CDH Laboratory Reagent, New Delhi. Polyvinyl alcohol and propylene glycol were provided by Loba Chemie Pvt. Ltd., Mumbai. All other chemicals/reagents used were of analytical grade.\textsuperscript{[6]}

\textbf{Methods}

\textbf{Preparation of buccal patches using PVP K-30 and HPMC/ HPC}

Buccal patches were prepared by solvent casting method (Table 1). The weighed amount of drugs were dissolved in 2 ml of Dimethyl sulfoxide, followed by addition of PVP K-30. Stirred till the contents were dissolved and 10 ml of ethanol was added into the solution. The second polymer, HPMC/HPC was dissolved in it. Propylene glycol was added as plasticizer and the volume was made up to 20 ml using ethanol. The solution was then poured into glass
moulds of diameter 9 cm containing backing layer and kept aside covered with funnel for controlled evaporation of solvent. The dried patches were cut into circular patches of 1.5 cm diameter, so that each patch contains about 7.5 mg of LP and 20 mg of HCZ.\(^7\)

**THE STRUCTURE OF THE ORAL MUCOSA**

- **Structure**
  - The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.\(^8\) The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.\(^8\)\(^-\)\(^9\)
  - 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 therapeutic agent for local as well as systemic delivery, so that first pass metabolism and GI degradation can be avoided. For the preparation of patches commonly used technique is solvent casting technique. The oral cavity is easily accessible for self-administration, stopping of drug is feasible if required, safe and, hence is well accepted by patients. To avoid the swallowing of dosage form or dose dumping, bioadhesive polymers have received considerable attention for platforms of buccal controlled delivery. Due to bioadhesion, the immobilization of drug carrying particles at the mucosal surface would result in, a prolonged residence time at a site of absorption or action, a localization of the drug delivery system at a given target site and Increase in the drug concentration gradient due to the instant contact of the particles with mucosal surface. 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.\(^10\)
  - 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 for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease.[11]

- These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for desired length of time.

![Fig-1 Structure of oral mucosa](6)

**Advantages of buccal drug delivery system**

- **Mucoadhesive via buccal route offers following advantages:**[13]
  - Relatively large surface area  Accessibility
  - Rich blood Supply  Low metabolic activity
  - Robust  Prolonged retention
  - Intestinal alternative  Zero-order controlled release
  - Ease of use and Low variability
  - Rapid on set of action.
  - Quick termination of drug therapy
  - Ease of administration
  - Termination of therapy is easy
  - Permit localization of drug to the oral cavity for prolong period of time.
• Can be administered to unconscious patients.
• The mucosal lining of buccal tissues provides a much milder environment for drug absorption.
• Avoidance of drug degradation in stomach
• It offers a passive system for drug absorption and does not require any activation.
• The oral mucosa has a rich blood supply
• Direct entry into systemic circulation by first pass effect.
• The rate of drug absorption is not influenced by food or gastric emptying rate.

❖ Disadvantages
• Limited absorption area- the total surface area.
• Membranes of oral cavity available drug absorption is including buccal membrane.
• The barriers such as saliva, mucus, membrane coating granules, basement membrane etc.
• Retard the rate and extent of drug absorption through the buccal mucosa.
• Continuous secretion of the saliva(0.5-2 l/day)leads to subsequent dilution of the drug.
• The hazard of choking by involuntarily swallowing the delivery system is a concern.
• Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug.
• Ultimately the involuntary removal of the dosage form.

• Limitation of buccal drug administration
• Drugs, unstable at buccal Ph can not be administered by this route.
• A bitter or unpleasant taste can not be administered.
• Drug which irritate the mucosa and have a abnoxious odour can not be given by this route.
• Unstable drugs at buccal pH can not be administered.
• Requirement of small dose drug can be administerted.
• Saliva containing drugs follows the peroral route and lost the advantage of buccal route.
• Drugs absorbed by passive diffusion can be administered.
• Drugs with large dose are difficult to be administered
• Eating and drinking may be restricted
• Possibility of the patient to swallow the tablet
• This route cannot administer drugs, which are unstable at buccal pH.
• This route cannot administer drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour.
• Small surface area is available for absorption.

**Mucosadhesive Buccal Patch Drug delivery system**[14]

The case of oral mucosal cavity, the classification of drugs can be divided into three category.

1. **Sublingual Delivery**: This is a systemic delivery of drug through the mucosal membranes which lining the mouth.
2. **Buccal Delivery**: This drug administered through the mucosa Membrane lining the cheeks.
3. **Local delivery**: This is a drug delivery into the oral cavity.
   - Mucosadhesive drug delivery system has been studied from different proportions, including the development of a novel buccal patches, the design of device, mode of action of mucoadhesion and the permeation enhancement.
   - The large amount and number of a new drugs molecules from drug discovery, and the buccal drug delivery play the important role in delivery of molecules.
   - The oral mucosal delivery accessible, so dosage form can be suitably administered, even removed from its particular site.
   - In the sense of natural function of oral mucosa is exposed to a multitude of external component.

- **Components or structural features of oral cavity** (Figure 2)[15]
  - 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.
  - Helps to lubricate the food material and bolus.
  - To identify the ingested material by tast buds of tongue
Composition of buccal patches\(^{[17]}\)

- **Active ingredient**
  - A. **Polymers (adhesive layer):** Hydroxy ethylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers.
  
  - B. **Diluents:** Lactose DC is selected as diluents 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.
  
  - C. **Sweetening agents:** Sucralose, aspartame, mannitol, etc.
  
  - D. **Flavouring agents:** Menthol, vanillin, clove oil, etc.
  
  - E. **Backing layer:** Ethyl cellulose, etc.
  
  - F. **Penetration enhancer:** Cyano acrylate, etc.
  
  - G. **Plasticizers:** PEG-100, 400, propylene glycol, etc.
METHODS OF PREPARATION OF BUCCAL PATCHES\cite{18}

1. Solvent casting
   In this method of buccal patch preparation, the appropriate mucoadhesive polymers are collected and required quantity of polymer or polymers is allowed to mix with suitable solvent on a magnetic stirrer to allow proper mixing and thus swelling of polymer solution. Then weight quantity of plasticizer is added to the mixture and again kept on stirrer. Finally, drug is added to the solution and the mixture is poured into the pre lubricated petri dishes. These are allowed to dry in oven or at room temperature and finally cut into desired patch.

2. Direct milling
   In this method, there is no use of solvents at any stage of formulation. The active pharmaceutical ingredient and the other excipients are mixed well together and spread on the liner of roller. The roller compresses and directly formulates the appropriate patches or films. Films are then collected separately.

3. Solid dispersion extrusion
   In this method no solvent is required, therefore, no residual solvent is left behind after the formulation and so no stability issues occur in the shelf life of a product. The immiscible solid ingredients are mixed with the active pharmaceutical ingredient and solid dispersions are prepared for better formulation. Solid dispersion refers to the formulation of two or more non soluble compounds. The prepared mixture is then poured into dye and collected after drying and cut into appropriate portions.

4. Semisolid casting
   In semisolid casting method, firstly, a solution of water soluble polymers is prepared. Then this solution is added slowly to the acid insoluble polymer mixture. Now suitable plasticizer is added to the above mixture to form a mixture with gel like consistency. Finally this gel is poured onto the drum rollers and allowed to dry. Patches are collected after drying.
5. **Hot melt extrusion**

The Hot-melt extrusion (HME) technique is an attractive alternative to traditional processing methods and offers many advantages over the other pharmaceutical processing techniques. Patches prepared through this method have better content uniformity. The numbers of processing and time-consuming drying steps are reduced. The intense mixing and agitation imposed by the rotating screw cause de-aggregation of suspended particles resulting in a more uniform dispersion and the process is continuous and efficient. In hot melt extrusion method, firstly the drug is mixed with carriers without any use of solvent, in solid form. Then the extruder consisting of heaters are used to melt the mixture. Finally, the melted mixture is given the shape of films or patches with the help of dies. Hot-Melt Extrusion processes can be classified as:

(a). Ram extrusion

(b). Screw Extruders are of two types

i). Single Screw Extruder,

ii). Twin-Screw Extruders

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![Hot melt extrusion apparatus](image-url)

- **Evaluations of buccal patch**

  - **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.
- **Thickness measurements:** The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.

- **Swelling study:** Buccal patches are weighed individually (designated as W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°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.

- The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated using the following formula.

  \[
  SI = \frac{(W2 - W1)}{W1} \times 100
  \]

- **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.

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

- **Morphological characterization:** Morphological characters are studied by using scanning electron microscope (SEM).

- **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 g KH2PO4 and 8 g 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 desiccators 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 – Wi)/Wf x 100**
Where, Ww is the wet weight and Wf is the final weight. The swelling of each film is measured.

- **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.

- **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°C ± 0.5°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 inv vitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at 37°C± 0.2°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.

- **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 with drawn at predetermined time intervals.

- **Ex-vivo mucoadhesion time**
  The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). 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.\cite{21}

- **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.\cite{21}

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

- Where,
  - M - is the mass in gm, g - is the acceleration due to gravity
  - 980 cm/sec 2
  - 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)

- **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 18-50 years). 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.[21]

EVALUATION OF BUCCOADHESIVE DOSAGE FORM[22]

✓ In vitro / Ex vivo methods
  ➢ The most commonly employed in vitro techniques are:
    • Methods based on measurement of tensile strength
    • Methods based on measurement of shear strengths
    • Other in vitro methods are

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<td>Flow channel method</td>
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<td>Mechanical spectroscopic method</td>
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<td>Falling liquid film method</td>
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✓ In vivo methods
  ➢ The most common in vivo techniques to monitor bioadhesion include:

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<td>Use of radioisotopes</td>
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<td>Use of gamma scintigraphy</td>
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CONCLUSION

• The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The area is well suited for a retentive device and appears to be acceptable
to the patient. 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. In conclusion, the mucosal adhesive dosage forms are now on the starting line. The advantages are tremendous which make further study in this field extremely important. The formulation of these drug delivery systems depends on the developments of suitable polymers with excellent mucosal adhesive properties, stability and biocompatibility.[22]

- The main advantages of the buccal route of administration over the traditional per oral route are that drug degradation in the stomach is avoided, first-pass metabolism is avoided, and therapeutic drug levels of drug can be achieved rapidly. Clearly these advantages are presently clinically relevant for only a limited number of drugs. However, with the recent developments of new formulation types, such as mucoadhesive preparations and the use of peptides as drugs, this number may increase in the future.[22-23]

- **Future aspects**[23]
  - In mucoadhesive placebo buccal patches we can use any potent drugs which fulfil the criteria for buccal patch as drug delivery system.
  - We can perform the dissolution of medicated mucoadhesive buccal patch for drug release profile studies.
  - We can further perform the in-vivo studies for the prepared mucoadhesive buccal patches.
  - We can perform the stability test for the prepared mucoadhesive buccal patches.
  - Various strategies are being employed to achieve oral absorption of peptides.
  - These strategies include manipulation of the formulation (e.g. inclusion of penetration enhancers or protease inhibitors etc.), maximizing retention of the delivery system at the site of absorption and alteration of the peptide so as to optimize affinity for endogenous transport systems, build in chemical and metabolic stability, minimize the size and optimize the balance between lipophilicity and hydrogen bonding potential.[24]

**REFERENCE**