WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 4, 529-546 Review Article ISSN 2278 – 4357

MUCOADHESIVE BUCCAL PATCHES: A REVIEW ON

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Article Received on
25 Jan. 2019,

Revised on 15 Feb. 2019,
Accepted on 08 March 2019

DOI: 10.20959/wjpps20194-13448

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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. Buccalbioadhesive 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. The adhesive properties of such drug delivery platforms can reduce the enzymaticdegradation due to the increased intimacy between the delivery vehicle and the absorbing membrane. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Transmucosal routes of drug delivery offer distinct advantages over per oral administration for systemic drug delivery.

KEYWORDS: Buccal drug delivery, Oral mucosa, Buccal patches, Mechanism Mucoadhesion, Evaluation.

INTRODUCTION: Buccal delivery of drugs is one of the alternatives to the oral route of drug administration, particularly to those drugs that undergo first-pass effect. The stratified squamous epithelium supported by a connective tissue lamina propria, which is present in buccal mucosa, was targeted as a site for drug delivery several years ago. Problems

accompanied with oral route of administration such as extensive metabolism by liver, drug degradation in gastrointestinal tract due to harsh environment, and invasiveness of parenteral administration can be solved by administering the drug through the buccal route. The buccal route appears to offer a number of advantages, like good accessibility, robustness of the epithelium, usage of the dosage form in accordance with need, and comparatively less susceptibility to enzymatic activity.[1,2,3,4,5]

Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for the drug absorption 1. 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.[6,7]

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.[8]

The structure of the oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Figure 1). 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. 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.[9,10,11,12]

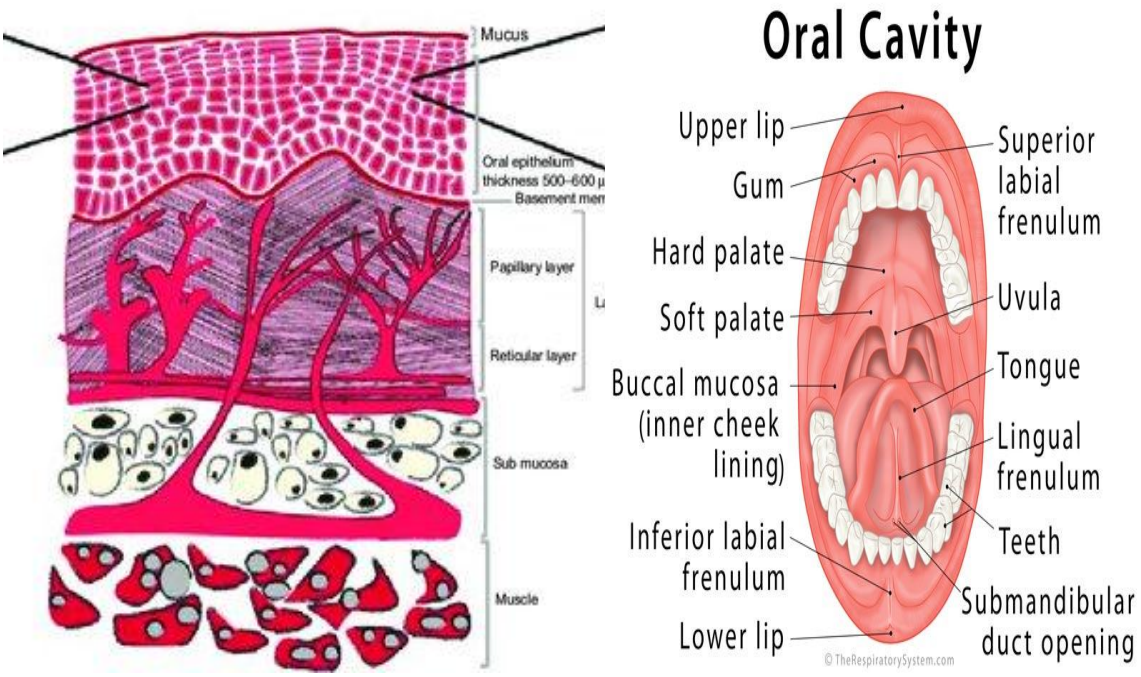


Fig no. 1: Anatomy of Oral mucosa.

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. 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.[9,13,14]

Buccal Mucosa Environment[15]

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.

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

Functions of Oral Cavity[22,23]

- 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 tongue.
- To initiate the carbohydrate and fat metabolism.
- As a portal for intake of food material and water.
- To aid in speech and breathing process.

Advantages of Buccal Drug Delivery System[18,19]

1. It is richly vascularized and more accessible for the administration and removal of a dosage form.
2. Buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration.
3. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery.
4. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery.
5. Avoids acid hydrolysis in the gastrointestinal tract and by passing the first-pass effect.
6. Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa.

Disadvantages of Buccal Drug Delivery System[18,20]

1. Low permeability of the buccal membrane: specifically, when compared to the sublingual membrane.
2. Smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents nonkeratinized tissues, including the buccal membrane.
3. The continuous secretion of saliva leads to subsequent dilution of the drug.

4. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form. These are some of the problems that are associated with buccal.

Ideal Characteristics of Buccal Drug Delivery System[1,21]

- Should adhere to the site of attachment for a few hours.
- Should release the drug in a controlled fashion.
- Should provide drug release in a unidirectional way toward the mucosa.
- Should facilitate the rate and extent of drug absorption.
- Should not cause any irritation or inconvenience to the patient.
- Should not interfere with the normal functions such as talking and drinking.

Design of Buccal Mucoadhesive Patches[15]

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.[15,16]

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.[15,17]

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.

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.

Buccal Absorption

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated in latter sections.[18,24]

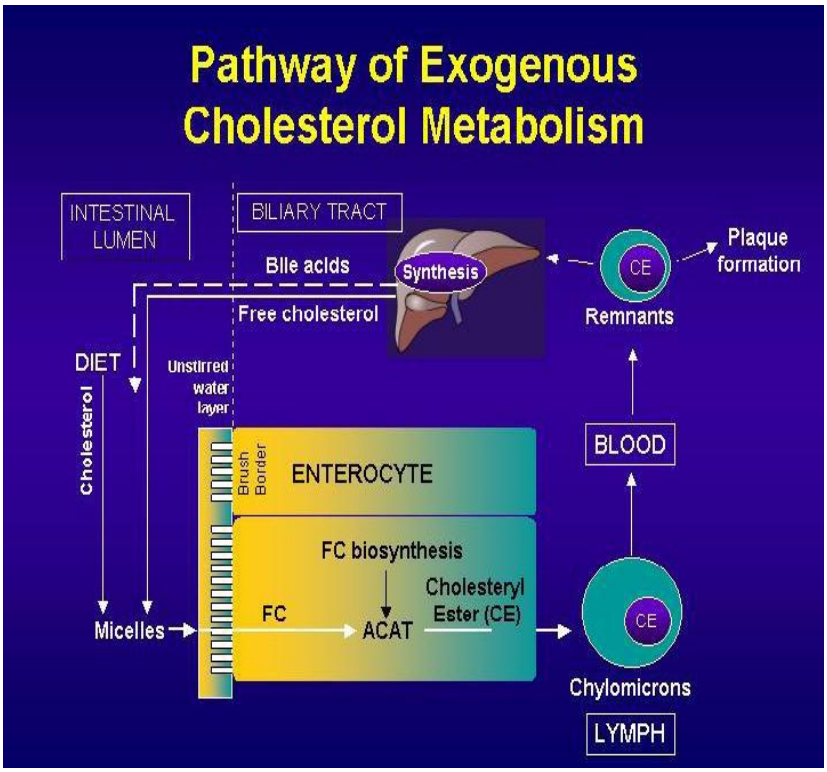


Fig: Buccal Routes of Drug Absorption.[18]

Mechanism: Oral mucosal drug absorption occurs by passive diffusion of the non-ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The buccal mucosa has been said to behave predominately as a lipoidal barrier to the passage of drugs; as is the case with many other mucosa and (within limits) the more lipophilic (or less ionized) the drug molecule, the more readily it is absorbed. It has been concluded that the passive diffuses in accordance with the pH partition theory of drug absorption is the major route of drug absorption for most drugs. However, it has been reported that certain molecules e.g., some sugars and vitamins may be transported by a specialized transport system capable of saturation. It has been proposed that the intercellular route, rather than the transcellular route, is the predominant route for drug absorption. Large hydrophilic molecules are believed to be transported by the intercellular route and the presence of the contents of membrane-coating granules in the intercellular space may inhibit penetration in both keratinized and nonkeratinized mucosa.[18,25]

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;

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.[6,26]

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.[6,27]

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.[6,28]

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.[6,29]

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.[6,29]

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.[6,30]

D. Powders: Hydroxpropyl 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.[6,31]

Types of Buccal Patches

(1) In matrix type-The matrix type buccal patches fabricated by mixing the hydrophilic or lipophilic polymer matrix consistently with the drug. The therapeutic disc with a defined surface area is formed by medicated polymer moulding.

(2) In reservoir type-The reservoir system comprises a cavity for the drug and additives distinct from the adhesive. The drug loss is prohibited by attaching a water-resistant backing.

The Buccal patches Composition[32]

(1) Active Pharmaceutical Ingredient (API): The buccal patches delivery system distributes diverse variety of active pharmaceutical ingredient. Large size drugs are problematic to be included but it has size limitation for active ingredient to be added in buccal patches.

(2) Polymers (adhesive layer): Polymer hydration and swelling possessions possibly play the main role. These are the polymers used hydroxyethylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, carbopol.

(3) Diluents: The diluents used in buccal patches are lactose, microcrystalline starch and starch.

(4) Sweetening agents: For sweeting purpose sucralose, aspartame and mannitol are used.

(5) Flavouring agents: The flavoring agents used in formulations are menthol, vanillin, clove oil, Peppermint oil, cinnamon oil, spearmint oil, vanilla, cocoa, coffee, chocolate.

(6) Backing layer: For backing layer in patches ethyl cellulose, Polyvinyl alcohol is used.

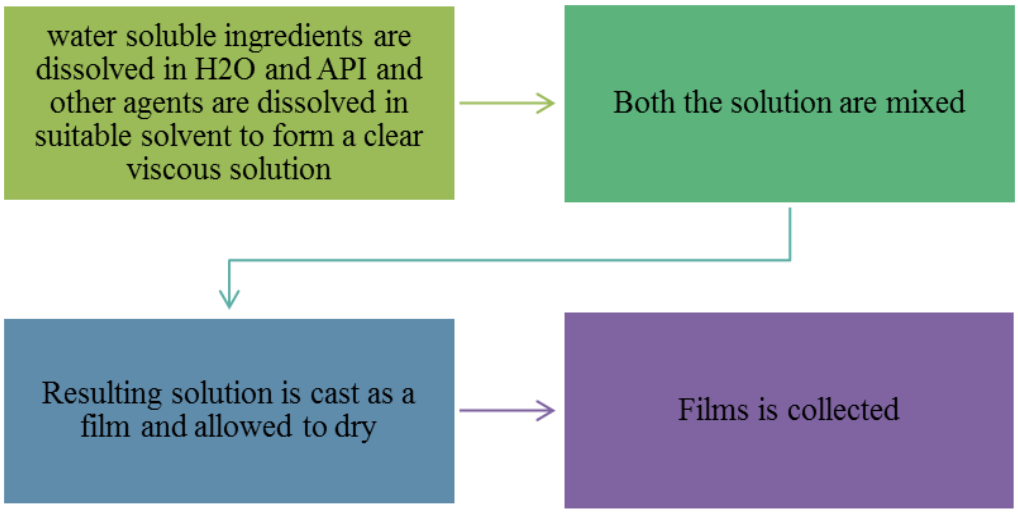
(7) Penetration enhancer: The penetration enhancers such as cyanoacrylate, EDTA, Citric acid, PEG-100, 400, propylene glycol are used.

METHOD OF PREPARATION

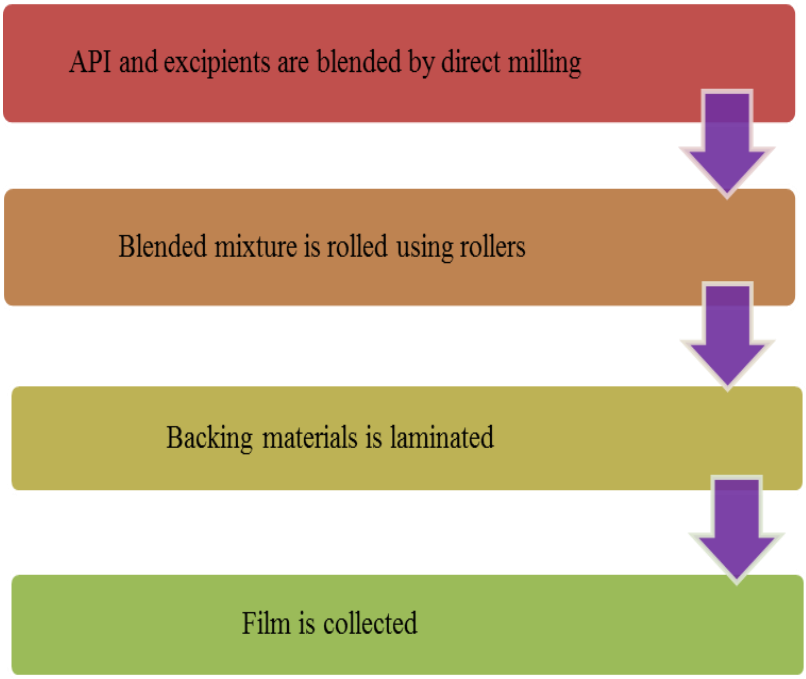
Methods used to prepare adhesive patches include,

1. Solvent casting

In this, all patch excipients including the drug codispersed 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. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost, and environmental concerns due to the solvents used. Thes drawbacks can be overcome by the hot-melt extrusion method.[33,34]



2. Direct milling: In this, patches are manufactured without the use of solvents (solvent-free). 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. An impermeable backing membrane may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during application period.[30,32] While there are only minor or even no differences in patch performance between patches fabricated with the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.[33,35]



2. Hot melt extrusion: In hot melt extrusion method blend of pharmaceutical ingredients is molten and different shapes yielded by forcing mixture through an orifice. Hot melt extrusion has been used for the fabrication of controlled release matrix tablets, pellets, granules, oral disintegrating films dosage forms. Solid dispersion extrusion immiscible components are extruding with drug and then solid dispersions are formulated. Finally, the solid dispersions are shaped into films by means of dies.

3. Semisolid casting: In the semisolid casting process initially a solution of water soluble film forming polymer is organized. The resulting solution is added to a solution of acid insoluble polymer which was prepared in ammonium or sodium hydroxide. Then appropriate aggregate of plasticizer is added so that a gel mass is acquired. Finally, the gel mass is casted into films or ribbons using heat controlled drums.

4. Rolling method: In this method solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on rollers and cut into desired shapes and sizes.[32,37]

Evaluation of Buccal Drug Delivery Systems[22]

1. Surface pH[38]**:** Buccal patches are left to swell for 2hr 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.

2. Thickness measurements[39]: The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.

3. Swelling study[40]: Weighed the buccal patches individually (M0), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 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 (Mt) and the swelling index (SI) were calculated using the following formula.

$$SI = \frac{(M_t - M_0)}{M_0} \times 100 \qquad (1)$$

4. Folding endurance[41]: Folding endurance can be done by folding the patches upto200 times with our breaking.

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

6. Morphological characterization[42]: Morphological characters are studied by using scanning electron microscope (SEM).

7. Water absorption capacity test[43]: 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 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 desiccators over anhydrous calcium chloride[44] at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation.[45]

$$\left[water\ uptake\ (\%) = \frac{(Ww - Wf)}{Wf} \times 100 \right]$$

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

8. Ex-vivo bioadhesion test[46]: 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.[47] Two pans of the balance are balanced with a 5g weight. The 5g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa.[48] 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.

9. In vitro drug release:- The dissolution medium consisted of phosphate buffer pH 6.8 maintaining a temperature 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.[49] 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 in a UV spectrophotometer.[50] The in-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. The donor compartment is filled with suitable buffer.

10. Permeation study of buccal patch[51]:- 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.

11. Ex-vivo mucoadhesion time[52]:- The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit).[53] 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.[54] The time for changes in color, shape, collapsing of the patch and drug content is noted.

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. 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.

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.

CONCLUSION

Mucoadhesive buccal patches have gained importance in drug delivery. The use of Natural polymers is increasing in the formulation of buccal patches. 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 is avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. This review focuses on the preparation of novel drug delivery systems which will provide least adverse effects and maximal therapeutic response.

ACKNOWLEDGEMENT

The Author and Co-author are thankful to P.S.G.V.P.M's College of pharmacy, Shahada, Dist. Nandurbar for continuous support and encouragement throughout this review work.

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