

Review article

A REVIEW ON BUCCAL PATCHES

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ABSTRACT

The aim of this article is to study the buccal patches. Buccal patch is a nondissolving thin matrix modified release dosage form composed of one or more polymer films or layers containing the drug and/or other excipients. Buccal patches 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. The study of buccal patches include its introduction, types of buccal patches, advantages, limitation, potential uses of buccal patches, polymer used, methods of preparation, evaluation.

Keywords: Buccal patches, modified release, matrix, novel drug delivery system

INTRODUCTION

Buccal patch is a non-dissolving thin matrix modified release dosage form composed of one or more polymer films or layers containing the drug and/or other excipients.[1,2,3] Buccal drug delivery is a highly effective way to increase bioavailability. This is because the buccal mucosa has a rich in blood supply which facilitates the direct entry of the drug into the systemic circulation. [4]In addition, buccal dosage forms allow drug absorption to be rapidly terminated in case of an adverse reaction. Formulations of buccal dosage forms include- tablets, gels and patches of which patches are preferable in terms of flexibility and comfort [4]

THE STRUCTURE OF THE ORAL MUCOSA

Structure

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.[5,6,7]

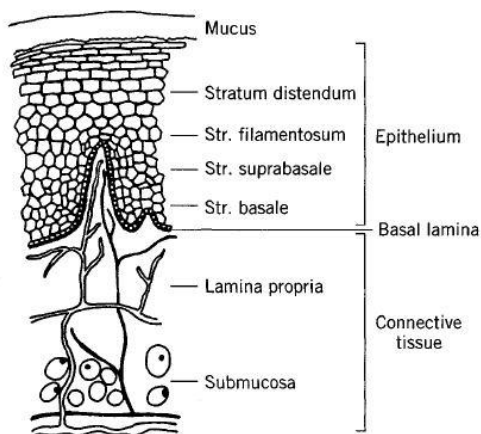


Fig. 1: Schematic cross section through the oral mucosa showing the epithelium, basal lamina, and connective tissue [5,6, 7]

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.[8]The oral cavity is easily accessible for self-administration, stopping of drug is feasible if required, safe and, hence is well accepted by patients[9]. 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]

Advantages of buccal patches

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

Limitations in buccal patches

1. The area of absorptive membrane is relatively smaller. If the effective area for absorption is dictated by the dimensions of a delivery system, this area then becomes even smaller.

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3. Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. Involuntary swallowing of saliva results in a major part of dissolved or suspended released drug being removed from the site of absorption. Furthermore, there is risk that the delivery system itself would be swallowed.
4. Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allergy and adverse properties such as discoloration or erosion of the teeth may limit the drug candidate list for this route. A conventional type of buccal drug delivery systems did not allow the patient concurrently eat, drink or in some cases, talk.[10,11,12]

TYPES

1. **Matrix type (Bi-directional):** The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.

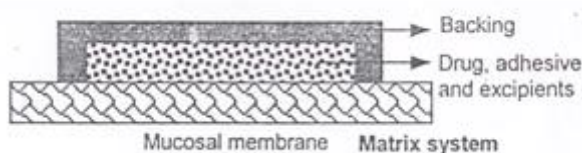


Fig. 2: Buccal Patch designed for Bidirectional drug release

2. **Reservoir type (Unidirectional):** The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An 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.

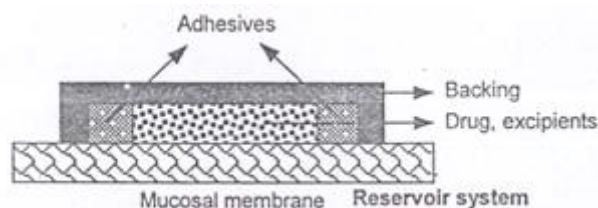


Fig. 3: Buccal Patch designed for Unidirectional drug Release[1,12]

Bioadhesive Delivery of Drug System in Oral Cavity

- **Sublingual delivery:** which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
- **Buccal delivery:** This is drug administration through the mucosal membranes lining the cheeks (buccal mucosa).
- **Local delivery:** for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease. 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 a desired length of time.[10,11,12,13]

Physiological factors affecting buccal bioavailability

Inherent permeability of the epithelium

The permeability of the oral mucosal epithelium is intermediate between that of the skin epithelium, which is highly specialized for barrier function and the gut, which is highly specialized for an adsorptive function. Within the oral cavity, the buccal mucosa is less permeable than the sublingual mucosa.

Thickness of epithelium

The thickness of the oral epithelium varies considerably between sites in the oral cavity. The buccal mucosa measures approximately 500-800 μm in thickness.

Blood supply

A rich blood supply and lymphatic network in the lamina propria serve the oral cavity, thus drug moieties which traverse the oral epithelium are

readily absorbed into the systemic circulation. The blood flow in the buccal mucosa is 2.4 mL min^{-1}

Metabolic activity

Drug moieties absorbed via the oral epithelium are delivered directly into the blood, avoiding first-pass metabolism effect of the liver and gut wall. Thus oral mucosal delivery may be particularly attractive for the delivery of enzymatically labile drugs such as therapeutic peptides and proteins.

Saliva and mucous

The activity of the salivary gland means that the oral mucosal surfaces are constantly washed by a stream of saliva, approximately 0.5-2L per day. The sublingual area in particular, is exposed to a lot of saliva which can enhance drug dissolution and therefore increase bioavailability.

Ability to retain delivery system: The buccal mucosa comprises an expanse of smooth and relatively immobile surface and thus is ideally suited to the use of retentive delivery systems.

Species differences: Rodents contain a highly keratinized epithelium and thus are not very suitable as animal models when studying buccal drug delivery.

Transport routes and mechanism: Drug permeation across the epithelium barrier is via two main routes:

1. The paracellular route: between adjacent epithelial cells;
2. The transcellular route: across the epithelial cells, which can occur by any of the following mechanism: passive diffusion, carrier-mediated transport and via endocytic processes.[13,14,15,16]

B. Patches and Films

Buccal patches consist 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 hydroxyl 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 [10, 17]

Mechanism of buccal absorption

Buccal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membranes and the more lipophilic the drug molecule, the more readily it is absorbed. [7] The dynamics of buccal absorption of drugs could be adequately described by first-order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows

$$dm/dt = Kc/ViVt$$

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 [10, 18]

Various mucoadhesive polymers can broadly be categorized as follows:

(I) Synthetic polymers:

1. Cellulose derivatives

(Methylcellulose (MC),
Ethyl cellulose (EC),

Hydroxy ethyl cellulose (HEC),
Hydroxyl propyl cellulose (HPC),

Hydroxy propyl methylcellulose (HPMC),
Sodium carboxy methylcellulose (NaCMC).

2. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
3. Poly hydroxyl ethyl methyl acrylate.
4. Poly ethylene oxide.
5. Poly vinyl pyrrolidone.
6. Poly vinyl alcohol.

(II) Natural polymers

1. Tragacanth
2. Sodium alginate
3. Guar gum
4. Xanthan gum
5. Soluble starch
6. Gelatin
7. Chitosan [19,20]

Composition of buccal patches:

A. Active ingredient.

B. Polymers (adhesive layer): HEC, HPC, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), carbopol and other mucoadhesive polymers.

C. Diluents: Lactose DC is selected as diluents for its high aqueous solubility, its flavoring characteristics, and its physicochemical properties, which make it suitable for direct compression. Another example: microcrystalline starch and starch.

D. Sweetening agents: Sucralose, aspartame, Mannitol, etc.

E. Flavouring agents: Menthol, vanillin, clove oil, etc.

F. Backing layer: EC etc.

G. Penetration enhancer: Cyano acrylate, etc

H. Plasticizers: PEG-100, 400, propylene glycol, etc [19]

Chitosan

Chitosan a derivative form of chitin is a naturally occurring biopolymer. Chitosan is a linear polysaccharide composed of randomly distributed β -(1-4)-linked D-glucosamine (deacetylated unit) and N acetyl-D-glucosamine (acetylated unit). Commercial chitosan is derived from the shells of shrimp and other sea crustaceans, including *Pandalus borealis*. [10]

Properties of chitosan

1. Used in trans-dermal drug delivery.
2. Mucoadhesive nature
3. Chitosan ability to produce much different form
4. In drug delivery, it shows positive charge under acidic conditions. [22]

Guar gum

Guar gum is naturally occurring form of galactomannan and also called guaran [20]. It is primarily ground endosperm of guar beans. Guar gum contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. The molecular weight of guar gum is approximately 1 million that give high viscosity in solution. The high viscosity of guar gum is due to its long chain structure and high molecular weight. Guar gum is a polysaccharide composed of the sugars galactose and mannose. [23, 24]

Tragacanth

Tragacanth is a natural gum obtained from the dried juice of several species of the genus *Astragalus*, including *A. adscondens*, *A. gummifer*, *A. brachycalyx* and *A. tragacanthus*. Tragacanth gum is a viscous, odorless, tasteless and water-soluble mixture of polysaccharides. [25,26]

Sodium alginate

Alginic acid or alginate is an anionic polysaccharide, also called as algin and obtained in the cell walls of brown algae. It has ability of binding with water and forming a viscous gum. Alginic acid is capable of

absorbing 200-300 times its own weight in water when water extracted from alginate. 29 Alginate is mainly extracted from seaweed. Alginic acid is mainly produced by two bacterial genera such as *Pseudomonas* and *Azotobacter*. These play an important role in the preparation of its biosynthesis pathway. [27]

METHOD OF PREPARATION

Two methods used to prepare adhesive patches include

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. Weighed quantity of HPMC E15 was taken in a boiling tube. To this, 20 ml of solvent mixture of dichloromethane: methanol (1:1) was added and vortexed. Sufficient care was taken to prevent the formation of lumps. The boiling tube was set aside for 6 hours to allow the polymer to swell. After swelling, measured quantity of propylene glycol was added to this mixture and vortexed. Finally weighed quantity of CPH was dissolved in 5 ml of solvent mixture, added to the polymer solution and mixed well. It was set aside for some time to exclude any entrapped air and was then transferred into a previously cleaned amber petriplate. Drying of these patches for 8 hrs was carried out in oven placed over a flat surface. The procedure is repeated for HPC EF without addition of plasticizer [1,28]

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 [18]. 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 [1]

Potential Benefits of Buccal Films

1. Buccal films provide large surface area that leads to rapid disintegration and dissolution in the oral cavity due to which it promotes the systemic absorption of Active pharmaceutical ingredient.
2. No need of chewing and swallowing.
3. No risk of choking.
4. The film increases the systemic bioavailability of the drugs, as it bypasses the hepatic first pass metabolism.
5. Drug can be protected from degradation by GI enzymes and the acidic environment.
6. Rapid onset of action and minimum side effects.
7. Self-administration is possible.
8. Accurate dosing compared to liquid dosage forms.
9. Taste masking is possible.
10. Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
11. Ease of administration to pediatric, geriatric patients, and also to the patients who are mentally retarded, disabled or non-cooperative.
12. Good mouth feel and good stability. [29,30]

Evaluation of Buccal Films

The buccal films are evaluated by the following parameters:

Weight and thickness of the film

For evaluation of film weight, three films of every formulation are taken and weighed individually on a digital balance. The average weights are calculated. Similarly, three films of each formulation were taken and the film thicknesses are to be measured using micrometer screw gauge at three different places, and the mean value is to be calculated.

Surface pH of films

For determination of surface pH, three films of each formulation are allowed to swell for 2 h on the surface of an agar plate. The surface pH is to be measured by using a pH paper placed on the surface of the swollen patch. A mean of three readings is to be recorded.

Swelling index

After determination of the original film weight and diameter, the samples are allowed to swell on the surface of agar plate kept in an incubator maintained at $37 \pm 0.2^\circ\text{C}$. The weight of the films ($n=3$) is determined at different time intervals (1-5 h). The percent swelling is calculated using the following equation:

$$\text{Percent swelling } [\% S] = [X_t - X_o / X_o] \times 100,$$

Where, X_t = The weight of the swollen film after time t ,

X_o = The initial film weight at zero time.

Folding endurance

Three films of each formulation of required size are cut by using sharp blade. Folding endurance is to be determined by repeatedly folding the film at the same place, till it is broken. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance.

Moisture content

The prepared films are to be weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The films are to be weighed again after a specified interval, until they show a constant weight. The percent moisture content is to be calculated by using following formula

$$\% \text{ Moisture content} = [\text{Initial weight} - \text{Final weight} / \text{Final weight}] \times 100$$

Moisture uptake

Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

$$\% \text{ Moisture uptake} = [\text{Final weight} - \text{Initial weight} / \text{Initial weight}] \times 100$$

In-vitro residence time

The *in vitro* residence time is determined using IP disintegration apparatus using 900 mL of the disintegration medium maintaining at $37 \pm 2^\circ\text{C}$. The segments of rat intestinal mucosa, each of 3 cm length, are to be glued to the surface of a glass slab, which is then vertically attached to the apparatus. Three mucoadhesive films of each formulation are hydrated on one surface and the hydrated surface is brought into contact with the mucosal membrane. The glass slab is vertically fixed to the apparatus and allowed to move up and down. The film is completely immersed in the buffer solution at the lowest point, and is out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface is to be recorded.

Drug content uniformity

Three film units (each of 20 mm diameters) of each formulation have to be taken in separate 100 mL volumetric flasks, 100 mL of solvent has to be added and continuously stirred for 24 h. The solutions have to be filtered, diluted suitably and analyzed at specified nm in UV spectrophotometer. The average of drug contents of three films has to be taken as final reading.

Surface characterization studies

The scanning electron photomicrograph of the film is taken at 6000 X magnification. The prepared film containing drug is examined for clear and colorless surface. The photomicrographs of the film with the drug and the blank film are compared, and are examined whether the drug is distributed uniformly throughout the film in an amorphous form.

In-vitro dissolution studies

Dissolution studies are carried out for all the formulations, employing USP dissolution apparatus at $37 \pm 0.5^\circ\text{C}$, rotated at constant speed of 50 rpm using 900 mL of dissolution medium. A sample of drug film is used in each test. An aliquot of the sample is periodically withdrawn at suitable time interval and the volume is replaced with fresh dissolution medium. The sample is analyzed spectrophotometrically at specified nm.

Organoleptic evaluation

The prepared buccal film should possess the desired features of sweetness and flavor, which is acceptable to a large mass of population. Controlled human taste panels are used for psychophysical evaluation of the product. *In-vitro* methods of utilizing taste sensors, specially designed electronic tongue measurement devices can be used for this purpose.

Packaging

Many options are available for buccal films packing, such as single pouch, blister card with multiple units, multiple-unit dispenser and continuous roller dispenser. Single packaging is mandatory for films. An aluminium pouch is the most commonly used packaging system. There are some patented packaging systems for oral films. Lab tec company has patented packaging technology called Rapid card and Amcor Flexibilities Company has patented Core-peel technology.[30]

Mass uniformity and patch thickness

Assessment of mass and thickness is done on ten patches. The mean and standard deviation are calculated.

Content uniformity

The drug loaded patch was allowed to dissolve in 100 mL phosphate buffer, pH 6.8. The amount of drug in the patch was measured spectrophotometrically at λ_{max} of 226 nm ($n = 3$).

Radial swelling

Radial swelling was determined by diameter method. After determination of the original patch diameter, the patch was allowed to swell on the surface of an agar plate kept in an incubator maintained at 37°C . Measurement of the diameter of the swollen patch was done at one hour intervals for 6 h. Radial swelling was calculated from the following equation:

$$\text{SD } (\%) = [(D_t - D_o) / D_o] \times 100$$

Where SD (%) is the percent swelling,

D_t is the diameter of the swollen patch after time t , and

D_o is the original diameter of the patch at time zero.

In vitro Swelling Studies of Bucco adhesive patch

The degree of swelling of bioadhesive polymer is important factor affecting adhesion. Upon application of the bioadhesive material to a tissue a process of swelling may occur. The swelling rate of the buccoadhesive patch was evaluated by placing the film in phosphate buffer solution pH 6.8 at $37 \pm 0.5^\circ\text{C}$. Buccal patch was weighed (W_1), placed in a 2% (w/v) agar gel plate and incubated at $37 \pm 10^\circ\text{C}$. At regular one-hour time intervals (up to 3 h), the patch was removed from the petridish and excess surface water was removed carefully using the filter paper. Patch was then reweighed (W_2) again and the swelling index was calculated.[11]

$$\text{Swelling index} = W_2 - W_1 / W_1.$$

Bioadhesion force

The tensile strength required to detach the bioadhesion patch from the mucosal surface is applied as a measure of the bioadhesion performance. The apparatus is locally assembled and mainly composed of two-arm balance. The left arm of the balance is replaced by a small platinum lamina vertically suspended through a wire. At the same side, a movable platform is maintained in the bottom in order to fix the mucosal membrane. For determination of bioadhesion force, the mucoadhesive patch is fixed to the platinum lamina using cyanoacrylate adhesive. A piece of rabbit intestinal mucosa was also glued to the platform. The patch surface is moistened with 10 μL of phosphate buffer and left for 20 s for initial hydration. On the right pan, a constant weight of 5 g is added at 2 min interval, until the hydrated patch is brought into contact with the mucosal surface. The total weight required for complete detachment of the patch is recorded and the bioadhesion force is calculated per unit area of the patch as follows:

$$F = (W_w \times g) / A$$

Where

F is the bioadhesion force ($\text{kg m}^{-1} \text{S}^{-2}$),

W_w is the mass applied (g),

g is the acceleration due to gravity (cm s^{-2}),
 A is the surface of the patch (cm^2).

The bioadhesion force data reported represent the mean of three determinations.

In vitro drug release study

For in vitro release study, goat buccal mucosa membrane is used as a barrier membrane with Phosphate buffer (pH 7.4) as a medium. The patches are evaluated for drug release using franz diffusion cells. Buccal mucosa membrane is mounted between the donor and receptors compartments. The patches are placed on the mucosal membrane. The diffusion cell is placed in simulated **saliva** maintained at $37 \pm 2^\circ\text{C}$. The receptor compartment is filled with 50 mL phosphate buffer (pH 7.4) and hydrodynamics is maintained by stirring with a magnetic bead at 300 rpm. Five mL sample are withdrawn and replaced with 5 mL fresh medium to maintain the sink condition. The samples are analyzed in U.V. spectrophotometer at 226 nm. [32]

CONCLUSION

There should be improvement in current treatment in case of safety and efficacy. Buccal drug delivery system bypass the GI tract and hepatic portal system, Increases bioavailability of drug, Patient compliance, Though less permeable than the sublingual area, the buccal mucosa is well vascularised, and drug can rapidly absorbed into the venous system underneath the oral mucosa, Lower inter subject variability than TDDS, The large contact surface of the oral cavity contributes to rapid and extensive drug absorption. Patches are gained importance in pharmaceutical areas due to novel, patient friendly and convenient product. Due to their small size and thickness, they have improved patient compliance, compared to tablets. Moreover, since mucoadhesion implies attachment to the buccal mucosa, patch can be formulated to exhibit a systemic or local action. Due to the versatility of the manufacturing processes, the release can be oriented either towards the buccal mucosa or towards the oral cavity. [31] Patch releasing drug towards the buccal mucosa exhibit the advantage of avoiding the first pass effect by directing absorption through the venous system that drains from the cheek. Buccal patch is a nondissolving thin matrix modified release dosage form composed of one or more polymer patch or layers, containing the drug and/or other excipients. The patch may contain a mucoadhesive polymer layer which bonds to the oral mucosa, for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release). The patch is removed from the mouth and disposed of after a specified time. [8]

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