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Review Article

# A Comprehensive Review on Buccal Drug Delivery System

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## ABSTRACT

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to biological surface for an extended period of time. Within the oral mucosal cavity, the buccal region offers an adorable route of administration for systemic drug delivery. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily approachable site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage form because buccal drug delivery system prolong the residence time of dosage form at the site and thus contribute to improved and/or better therapeutic performance of the drug. In this paper main focus is done on oral mucosa, pathway, barriers to penetration of drug, different dosage forms, evaluation methods; this will be useful to circumvent the difficulties associated with the formulation design.

**Keywords**: Bioadhesion, Barriers, Pathway, Transmucosal, Dosage Form.

## INTRODUCTION

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to biological surface for an extended period of time. Among the various routes of drug delivery the oral route is perhaps the most preferred by patients and clinicians alike. However, peroral administration of drugs has disadvantages, such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal (GI) tract, that prohibit oral administration of certain classes of drugs, especially peptides and proteins. Consequently, other absorptive mucosas are considered as potential sites for drug administration[1.]

The mucosa is relatively permeable, has a rich blood supply, is robust, and shows short recovery times after stress or damage[2]. The oral cavity has been used as a site for local and systemic drug delivery. Local therapy is used to treat conditions such as gingivitis, oral candidiasis, oral lesions, dental caries and xerostoma while systemic delivery is used for the treatment of asthma and angina. Systemic activity is researched for the treatment of diseases like angina and asthma[1,3]

## Bioadhesive Delivery of Drug System in Oral Cavity

### 1. Sublingual delivery

Which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth?

### 2. Buccal delivery

Which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa)?

### 3. Local delivery

Which is drug delivery into the oral cavity?.

## Overview of the Oral Mucosa[4, 5]

### A. Structure

The oral mucosa is composed of outermost layer of stratified epithelium. Below lies a basement membrane, a lamina propia 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. The turnover time for the buccal epithelium has been estimated at 5-6 days , and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingival measure at about 100-200µm.

### B. Role of Saliva

1. Protective fluid for all tissues of the oral Cavity.
2. Continious mineralization of the tooth enamel.
3. To hydrate oral mucosal dosage forms.

### C. Role of mucus

1. Made up of proteins and catbohydrates.
2. Cell –cell adhesion.
3. Lubrication.
4. Bioadhesion of mucoadhesive drug delivery system.

### D. Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. In general, the permiabilities of the oral mucosa decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and nonkeratinized and the palatal intermediate in thickness but keratinized.

### E. Structure and Design of Buccal Dosage Form[5]

1. Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.
2. Reservoir type: 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.

### F. Permeability of Drugs through Buccal Mucosa

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

i. Transcellular (intracellular, passing through the cell).
ii. Paracellular (intercellular, passing around the cell).

Permeation across the buccal mucosa has been reported to be mainly by the Para cellular route through the intercellular lipids produced by membrane-coating granules.

## Theories of Bioadhesion[6,7]

The theoretical framework for polymer- polymer adhesion can be easily extended to describe the bioadhesion of polymeric materials with biological surfaces. Pertinent theories include the electronic, adsorption, wetting, diffusion and fracture theory.

### A. Electronic Theory

The electronic theory indicates that there is likely to be electron transfer on contact of the bioachesive polymer and the glycoproteinic net work which have different electronic structures, which will in turn lead to the formation of a double layer of electrical charge at the bioadhesive interface.

### B. Adsorption Theory

According to the adsorption theory, bioadhesive systems adhere to tissue because of Vander walls, hydrogen bonding, and related forces.

### C. Wetting Theory[8]

Intimate molecular contact is a pre - requisite for development of strong adhesive bond, requiring examination of the wetting equilibrium and dynamic behavior of the bioadhesive candidate material with the mucus. Some important characteristic for liquid bioadhessive materials include

I. A zero or near zero contact angle.
II. A relatively low viscosity and
III. An intimate contact that exclude air entrapment.

The specific work of adhesion between bioadhesive controlled release system and the tissue is equal to the sum of the two surface tensions and less than the interfacial tension.

### D. Diffusion Theory

Interpenetration of the chains of polymer and mucus may lead to formation of a sufficiently deep layer of chains. The diffusion mechanism is the intimate contact of two polymers or two pieces of the same polymer. During chain interpenetration the molecules of the polymer and the dangling chains of the glycoproteinic network are brought in intimate contact. Due to the concentration gradient, the bioadhesive polymer chains penetrate at rates that are dependent on the diffusion coefficient of a macromolecule through a cross-linked network and the chemical potential gradient. In addition, good solubility of the bioadhesive medium in the mucus is required in order to achieve bioadhesion. Thus the difference of the solubility parameters of the bioadhesive medium and the glycoprotein should be as close to zero as possible. Thus the

bioadhesive medium must be of similar chemical structure to the glycoproteins.

### E. Fracture Theory[10]

The facture theory of bioadhesion relates the difficulty of separation of two surfaces after adhesion to the adhesive bond strength.

### Advantages of buccal drug delivery system[11,12]

Mucoadhesive via buccal route offers following advantages:

1. Relatively large surface area
2. Accessibility
3. Rich blood Supply
4. Low metabolic activity
5. Robust
6. Prolonged retention
7. Intestinal alternative
8. Zero-order controlled release
9. Ease of use and Low variability.

### Limitations of buccal drug delivery system[13,14]

1. Drugs with large dose are difficult to be administered.
2. Eating and drinking may be restricted.
3. Possibility of the patient to swallow the tablet.
4. This route cannot administer drugs, which are unstable at buccal pH.
5. This route cannot administer drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor.
6. Small surface area is available for absorption.

### Disadvantages of buccal drug delivery system[15,16]

1. Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170cm$^2$ of which ~50cm$^2$ represents non-keratinized tissues, including buccal membrane.
2. The barriers such as saliva, mucus, membrane coating granules, basement membrane etc. retard the rate and extent of drug absorption through the mucosa.
3. Continuous secretion of the saliva (0.5-2 L/day)leads to subsequent dilution of the drug.
4. The hazard of choking by involuntarily swallowing the delivery system is a concern.
5. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

### Mechanism of Buccal Absorption[17]

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 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. 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

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.

### Physiological factors affecting buccal bioavailability[18]

1. 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 that the sublingual mucosa.
2. Thickness of epithelium: The thickness of the oral epithelium varies considerably between sites in the oral cavity. The buccal mucosa measures approximately 500-800µm in thickness.
3. 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.
4. Metabolic activity: Drug moieties adsorbed 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.
5. 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.
6. Ability to retain delivery system: The buccal mucosa comprises an expense of smooth and relatively immobile surface and thus is ideally suited to the use of retentive delivery systems.
7. Species differences: Rodents contain a highly keratinized epithelium and thus are not very suitable as animal models when studying buccal drug delivery.
8. Transport routes and mechanism: Drug permeation across the epithelium barrier is via two main routes:

- The paracellular route: Between adjacent epithelial cells;
- 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.

### Buccal Formulations[19]

The size of the delivery system varies with the type of formulation, i.e., a buccal tablet may be approximately 5-8mm in diameter, whereas a flexible buccal patch may be as large as 10 -15$cm^2$ in area.

Mucoadhesive buccal patches with a surface area of 1–3 cm2 are most acceptable. It has been estimated that the total amount of drug that can be delivered across the buccal mucosa from a 2$cm^2$ system in 1 day is approximately 10-20mg. The shape of the delivery system may also vary, although for buccal drug administration, an ellipsoid shape appears to be most acceptable. The thickness of the delivery device is usually restricted to only a few millimeters. The location of the delivery device also needs to be considered. The maximal duration of buccal drug retention and absorption is approximately 4-6 h because food and/or liquid intake may require removal of the delivery device. Physiology of mucus membrane under disease condition need to be accounted for (e.g.: Cancer patients suffer from oral candidiasis).

## Novel Buccal Dosage Forms[20,21]

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 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.

### 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.

### D. Powders

Hydroxypropyl 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.

## Characterization

### 1. Drug-excipients interaction studies

Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transform Infra-Red Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography and X Ray Diffraction (XRD) can be used to assess possible drug excipient interaction. DSC allows the fast evaluation of possible incompatibilities, because it shows changes in appearance, shift of melting endotherms and exotherms, and variation in the corresponding enthalpies of the reaction[22].

### 2. Physical evaluation

It includes Weight uniformity, Content uniformity, and Thickness uniformity. Weigh variation was tested by comparing the averages weighed of 10 different randomly selected patches from each batch with individual patch. The thickness of the film sample should be measured at five locations (centre and four corners), and the mean thickness is calculated. Samples with air bubbles, nicks or tears and having mean thickness variation of greater than 5% are excluded from analysis. Three patches (each of 20mm diameter) of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analyse by using UV spectrophotometer. The average of three patches was taken as final reading[23].

### 3. 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[24]. 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 noted down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute[25].

### 4. Swelling studies

Weight increase due to swelling: A drug-loaded patch of 1x1 $cm^2$ 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[26].

Area increase due to swelling: A drug loaded patch size of 1x1$cm^2$ was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. Fifty ml of phosphate buffer, pH 6.6, was poured into the petridish. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling (%S) was calculated using the following equation[27]

$$\% = \frac{Xt - Xo}{Xo} \times 100$$

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.

### 5. 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 scores two A grade then it would be considered as good and the one with all three A grade would be the very good formulation[28].

Grades: A = very good,
B = good,
C = poor.

### 6. *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 $37^0$ C. 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 5g weight on the right-hand pan. A weight of 5g 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 righthand 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[29] .

### 7. *Ex- vivo* mucoadhesive 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 was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a finger tip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8, and kept at 37°C ± 1°C. After 2 minutes, a 50 rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time for the tablet to detach from the buccal mucosa was recorded as the mucoadhesion time [30].

### 8. *In vitro* drug release

The United States Pharmacopoeia (USP) XXIII rotating paddle method used to study the drug release from the bilayered and multilayered tablets. The dissolution medium consist of phosphate buffer pH 6.8.The release was performed at $37^0$ C± $0.5^0$ C, with a rotation speed of 50 rpm. The backing layer of buccal tablet attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5 ml) 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[31].

### 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[32].

### 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[33].

The stability study of optimized mucoadhesive patch formulation was performed at $40^0$C, 37 ± $5^0$C & 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[34].

### 11. Measurement of mechanical properties

Mechanical properties of the patches were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25kg load cell. Film strip with the dimensions 60 x 10 mm and without any visual defects were cut and positioned between two clamps separated by a distance of 3cm. Clamps were designed secure the patch without crushing it during the test, the lower clamp was held stationary and the strips were pulled apart by the upper

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clamp moving at a rate of 2mm/sec until the strip broke. The force and elongation of the film at the point when the strip broke was recorded.The tensile strength and elongation at break values was calculated using the formula [35].

$$\text{Tensile strength (kg. mm}^{-2}) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm}^2)}$$

$$\text{Elongation at break (\%.mm}^{-2}) = \frac{\text{Increase in length (mm)}}{\text{Original length Cross sec tionalarea (mm}^2)} \times 100$$

### 12. Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times the patch could be folded at the same place without breaking gives the value of the folding endurance. This test is done on five patches[36].

### 13. Viscosity

Aqueous solutions containing both polymer and plasticizer prepared in the same concentration as that of the patches. A model LVDV-II Brookfield viscometer attached to a helipath spindle number 4 used. The viscosity measured at 20 rpm at room temperature. The recorded values the mean of three determinations[37].

### 14. Ageing

Patches subjected to accelerated stability testing. Patches packed in glass Petri dishes lined with aluminum foil and kept in an incubator maintained at 37±0.5°C and 75±5%RH for 6 months. Changes in the appearance, residence time, release behavior and drug content of the stored Bioadhesive patches investigated after 1, 2, 3, 4, 5 and 6 months. The data presented the mean of three determinations. Fresh and aged medicated patches, after 6 months storage, investigated using scanning electron microscope[38].

## CONCLUSION

Buccal adhesive systems offering numerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. This overview about the mucoadhesive buccal patches might be useful tool for the efficient design and characterization of mucoadhesive buccal patches. Mucoadhesive buccal patches have applications from different angles includes avoiding first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. 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 in 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. With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals.

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**Table 1.** List of Reported Active Ingredients Delivered Via Buccal Route[40]

| | | | |
|---|---|---|---|
| 1 | Acitretin | 16 | Piroxicam |
| 2 | Acyclovir | 17 | Diltiazem Hydrochloride |
| 3 | Buprenoprine | 18 | Flubriprofen |
| 4 | Carbamazepine | 19 | Insulin |
| 5 | Chitosan | 20 | Lignocaine |
| 6 | Chiorpheniramine maleate | 21 | Propanolol |
| 7 | Diclofenac sodium | 22 | Salbutomol sulphate |
| 8 | Metronidazole | 23 | Perindoprill |
| 9 | Metoprolol tartrate | 24 | Sodium chloride |
| 10 | Morphine sulphate | 25 | Testosterone |
| 11 | Nicotine | 26 | Tizanidine Hcl |
| 12 | Nifedipine | 27 | Theophylline |
| 13 | Omeprazole | 28 | Ergometrine |
| 14 | Oxytocin | 29 | Sumatriptan |
| 15 | Pantoprazole | 30 | Zolmitriptan |

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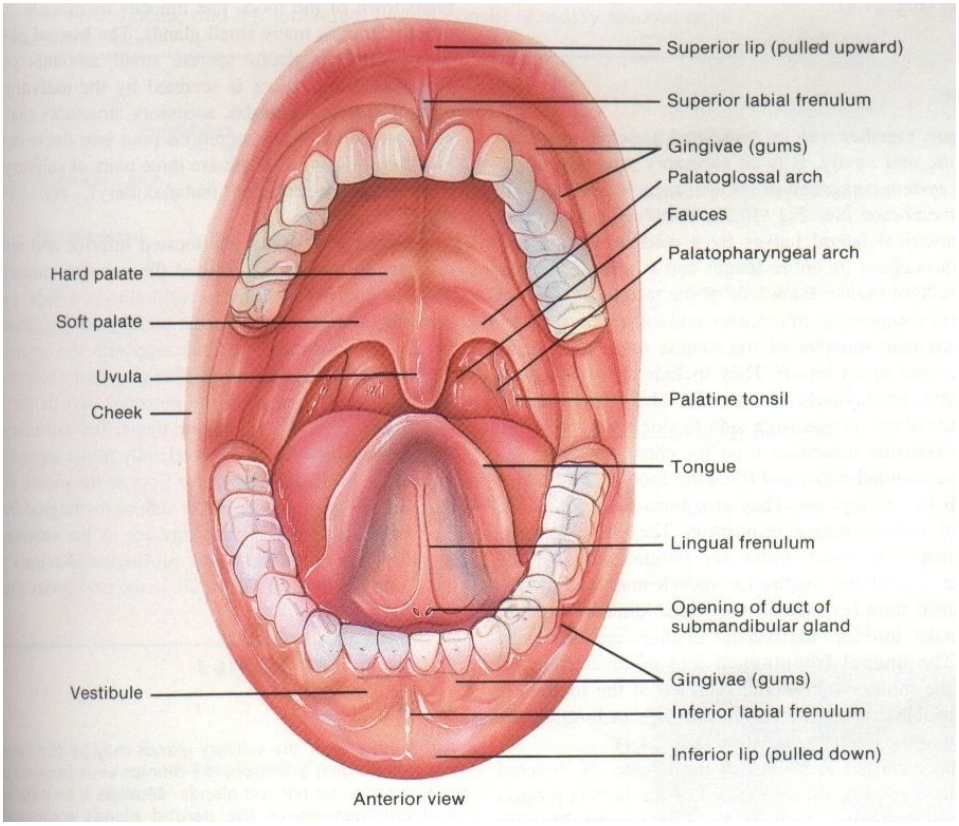


**Figure.1**. Structure of oral cavity

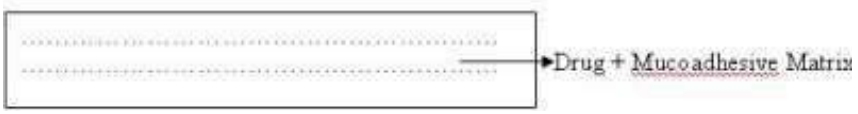


**Figure.2**. Buccal patch designed for bidirectional drug release

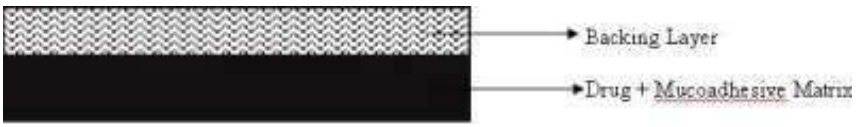


**Figure.3**. Buccal patch designed for unidirectional drug release