BUCCAL FILM: A REVIEW

Author: Jaimin Patel * Harsh chunara*(1), Dr Mittal maheshwari*(2),

* M. pharm student, A-One pharmacy college Ahmedabad
(1) * professor of Pharmaceutics, A-one pharmacy collage Ahmedabad
(2) * professor and HOD of pharmaceutics, A-one pharmacy college Ahmedabad, Address – A
one pharmacy college, enasan, Ahmedabad-382355, Gujarat, India, Institute- A-one
pharmacy collage, enasan, Ahmedabad-382355, Gujarat, India.

• ABSTRACT

Buccal route is an attractive route of administration for systemic drug delivery and it leads direct
access to the systemic circulation through the internal jugular vein by passes drugs from the
hepatic first pass metabolism provides high bioavailability. Buccal bioadhesive 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. This article aims to review the recent
developments in the buccal adhesive drug delivery systems to provide basic principles to the
young scientists, which will be useful to circumvent the difficulties associated with the
formulation design.

• Introduction of Buccal Drug Delivery System

A drug can be administered via a many different routes to produce a systemic
pharmacological effect. The most common method of drug administration is via per oral route in
which the drug is swallowed and enters the systemic circulation primarily through the membrane
of the small intestine. The oral route of drug administration is the most important method of
administering drugs for systemic effect. The parenteral route is not routinely used for self–
administration of medication. It is probable that at least 90% of all drugs used to produce
systemic effects are administered by the oral route. Absorption of drugs after oral administration
may occur at the various body sites between the mouth and rectum.

In general, the higher up a drug is absorbed along the alimentary tract, the more rapid will be
its action, a desirable feature in most instances. A drug taken orally must withstand large
fluctuation in pH as it travels along the gastrointestinal tract, as well as resist the onslaught of the
enzymes that digest food and metabolism by micro flora that live there. It is estimated that 25%
of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor resulting in high incidence of non-compliance and ineffective therapy. Difficulty is experienced in particular by pediatrics and geriatric patients, but it also applies to people who are ill bedridden and to those active working patient who are busy or travelling, especially those who have no access to water. In these cases oral mucosal drug delivery is most preferred.

It has been known for centuries that buccal and sublingual administration drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal juglar vein, and brachiocephalic vein and are then drained into the systemic circulation. Therefore the buccal and sublingual routes of administration can be utilized to bypass the hepatic first-pass elimination of drugs. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. The oral cavity is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply and the virtual lack of langerhans cells makes the oral mucosa tolerant to potential allergens.

- **Oral mucosal sites:**
  Within the oral mucosal cavity, delivery of drugs is classified in to three categories.

1. **Sublingual delivery:** is the administration of the drug via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth to the systemic circulation.

2. **Buccal delivery:** is the administration of drug via the buccal mucosa(the lining of the cheek)to the systemic circulation.

3. **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.
Oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (about 40-50 layers thick), a lamina propria followed by the sub mucosa as the innermost layer. The composition of the epithelium varies depending on the site in the oral cavity. The mucosa of the gingival and hard palate are keratinized similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized contain only small amounts of ceramides.

Figure 0:1 Oral cavity

Structure of Buccal Mucosa
Absorption pathways

The two major routes of drug transport through buccal epithelium include transcellular (intracellular) and paracellular (intercellular) transports. Transcellular route involves permeation across cell membrane, intracellular space and basement membrane either by passive transport (through diffusion and pH partition) or by active transport (viz., facilitated and carrier mediated transport and endocytosis).

Drug transport through transcellular route is a complex function of various physicochemical properties like size, shape, charge, lipophilicity and hydrogen bond potential of substances. Transcellular route is limited to substances with narrow range of molar volume. Paracellular route covers substances with a wide range of molar volumes, within intracellular space, while the hydrophobic molecules pass through the lipid bilayer hydrophilic molecules pass through the narrow aqueous regions adjacent to polar head groups of lipids. Buccal cavity contains a variety of membranes.

![Diagram of absorption pathways](image)

Schematic representation of penetration routes in buccal drug delivery

- **Advantages of Buccal Drug Delivery Systems:**
  - It is possible to stop drug administration as symptoms subsides
  - Localization of drug in oral cavity for prolonged periods of time can be achieved
  - Administration is easy.
  - First pass metabolism can be avoided.
Less amount of drug can be administrated there by dose dependent side effects can be minimized.

Tissue permeability can be locally modified there by immunogenic response can be reduced. This helps in administrating a wide variety of therapeutic agents especially proteins, peptides and ionized species can be administrated through buccal cavity.

Choice of route of administration for drugs that are sensitive to acidic pH in stomach and to those drugs which are unstable at alkaline pH in intestine.

Better bioavailability can be expected for the drugs which show poor bioavailability when administrated through oral cavity.

Presence of large quantity of water in the form of saliva enhances drug dissolution which is advantageous over other routes of drug administration especially transdermal and rectal routes.

Drugs whose half life is short (2-8 hrs) can be administrated by this route. E.g. nitroglycerin (2 hrs).

Since buccal membrane is sufficiently large, dosage form can be placed at different sites on the same membrane for different situations.

• **Disadvantages of Buccal Drug Delivery Systems**
  - Excess hydration causes over swelling of dosage form. This may damage structural integrity of dosage form due to disruption.
  - Placing of dosage form for prolonged periods in buccal cavity may lead to discomfort.
  - Chances of swallowing dosage form may occur.
  - Portion of drug that gets dissolved in saliva follows absorption mechanism of peroral route. Thus benefits of buccal delivery may not be fulfilled.
  - Only those drugs which are required in small doses can be administrated by this route.
  - Drugs with unpleasant taste/ odour or those which irritate mucosa cannot be administrated by this route.
  - Drugs which are sensitive to buccal pH cannot be administrated.

Different types of buccal patches are
1) **Matrix type (bidirectional) buccal patch:**

This type of buccal patch has a matrix layer containing drug, adhesive polymer and additives mixed together. This patch is capable of releasing drug in both directions i.e. into the mucosal layer and into mouth.

2) **Reservoir type (unidirectional) buccal patch:**

This type of buccal patch contains a drug reservoir layer. One side of the layer is covered with backing layer and other side is covered with adhesive layer. Adhesive layer helps in promoting adhesion of buccal patch to mucus layer. Backing layer controls direction of drug delivery and minimizes deformation and disintegration while in mouth.

- **Basic Components of Buccal Patch**

  Different components of buccal patch are:

  a. Drug
  b. Polymer
  c. Plasticizer
  d. Penetration enhancer

**a) Drug**

The properties of drug that make it suitable for buccal delivery are molecular weight, chemical functionality and melting point. Selection of drug for buccal delivery depends on pharmacokinetic properties of drug.

Ideal characteristics of drug substance for buccal drug delivery are:

- Single dose of drug should be low
- Drug that exhibit first pass effect or pre-systemic elimination when administrate through oral route
- The drug should not be adversely affecting natural microbial flora of oral cavity
- Drug should not have unpleasant taste, cause allergy, discoloration or erosion of teeth.

**b. Polymer:**

A buccal patch may contain polymer for any of the following purpose.

a. For mucoadhesive layer
b. For matrix layer
c. For backing layer Polymer for mucoadhesive layer

Mucoadhesion is one of the key factors in buccal drug delivery. Mucoadhesive property of polymer may be considered as result of combination of following steps

→ Polymer hydration
→ Wetting of buccal mucosa
→ Diffusion into buccal mucosa
→ Chemical bonding with glycoprotein

Hydration of polymer enhances wetting of mucosa encouraging intermolecular forces that arise at polymer – mucin interface. Initial contact between hydrated polymer and mucin layer promotes in establishing primary and secondary bonds between polymer and mucin layers. These bonds results in interpenetration of polymer chains and mucin layers. Thus, bioadhesive polymer should ideally have sufficient surface energy and chain flexibility encouraging spreading and diffusion into mucin layers. Examples of such polymers are cellulose derivatives like sodium carboxy methyl cellulose, methyl ethyl cellulose and hydroxy ethyl cellulose, natural gums like karaya and pectin and miscellaneous polymers like starch and sodium alginate.

**Polymers for matrix layer**

Drug is usually incorporated in the matrix layer. Polymers which are insoluble in saliva are used to prepare matrix system. Drug release from matrix layer can be controlled as required. Examples of such polymers are ethyl cellulose and butyl rubber.

**Polymers for backing membrane:**

Backing membrane is very important in buccal patch as it provides support for the matrix layer. The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa thereby preventing release of drug into saliva. It should be inert and impermeable to water, drug and other ingredients of buccal patch. Polymer that can be made into thin and poreless films can be used for preparing backing membrane. Cellulose acetate in acetone with 10% plasticizer is the best combination for backing layer. Similarly ethyl cellulose in 1:4 mixtures of alcohol and toluene with suitable plasticizer is also popular.

c. Plasticizer:

Smoothness and flexibility of buccal patch counts to stability of buccal patch. These properties can be incorporated into patch by using plasticizer [48]. Commonly used plasticizers
are glycerin, propylene glycol, poly ethylene glycol 200, poly ethylene glycol 400 etc. Usually the quantity of plasticizer should be in the range of 10 – 50 % of total weight of the polymer used. Plasticizers, to some extent, aids in drug release from polymer layer and also acts as penetration enhancers. Principle of selecting plasticizer into formulation counts on ability of plasticizer to solvate polymer and its capacity to alter interactions between polymers. It is believed that plasticizer bring up flexibility to patch by reducing molecular rigidity.

d. Penetration enhancer:

Penetration enhancers are those ingredients which promote drug permeation through buccal mucosa. The material used as penetration enhancer should be non toxic, pharmacologically inert and non–irritant. The process of promotion is usually followed by alteration in structural integrity in associated tissue. So, when the permeation enhancer is removed the tissue should revert back to its normal integrity.

Propylene glycol, n–methyl pyrrolidone, poly vinyl pyrrolidone and dimethyl sulfoxide have been used as penetration enhancers in buccal dosage forms.

• Preparation of Buccal Patches:

Buccal patches can be prepared by any of the following methods;

a) Solvent casting method: In this method, a solution of drug is prepared in suitable organic solvent followed by adding this solution to polymer solution. Polymer solution is also prepared with same organic solvent. This is followed by dispersing all other excipients. The solution is mixed by means of mechanical stirrer for further distribution. The solution is then poured into petri dish or spread on liners. Sufficient time is given for the solvent to evaporate until a thin layer is formed. This thin layer is then laminated on a backing membrane. The laminate formed is cut into desired size.

b) Direct milling: In this method patches are prepared without using any solvent. So, this method is referred as solvent free method. Drug/s and other ingredients are mixed mechanically by direct milling or by kneading. The resultant mixer is rolled on a release liner, until desired thickness is achieved. This is followed by placing on backing membrane with sufficient pressure. The laminates formed are cut into required sizes.
c) **Hot melt extrusion of films:** In this method all the ingredients are mixed and melted. The melted mass is then passed forcibly through an orifice to yield homogeneous mixture as films. This method is preferred for manufacturing of matrix tablets, pellets and granules as well as oral disintegrating films. Buccal patches are rarely prepared by hot melt extrusion method.

**Evaluation of Buccal Patches**

**Weight Variation/Film Weight:**
For evaluation of film weight three films of every formulation were taken and weighed individually on a digital balance. The average weights were calculated.

**Thickness:**
Three films of each formulation were taken and the film thickness was measured using Vernier calliper at three different places and the mean value was calculated.

**Surface pH of films:**
The surface pH of all formulations was determined to check whether each film causes irritation to the buccal mucosa. To measure the surface pH of prepared buccal patches, they were kept in 5 ml distilled water for 10 min to swell. After complete swelling, the surface pH was measured by pH meter. pH probe was in contact with the surface of each film and was allowed to equilibrate for 1 min. The average values are reported.

**Folding endurance:**
Three films of each formulation of size (1 × 1 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of three readings and standard deviation were recorded.

**Swelling ratio (%)**
After calculating the primary weight of 1 × 1 cm² film (W1), the swelling properties of films was determined by placing films in PBS (pH 6.8) at 37 °C. At specified time interval (2 hour) of films
were removed from PBS solution and excess PBS was removed with filter paper until the films
degraded. The swollen films were weighed (W 2) and swelling ratio was calculated using
following equation;

\[ \text{Swelling (\%)} = \frac{(w_1 - w_2)}{w_1} \times 100 \]

**Drug content**

Three Films were cut into 1 × 1 cm² pieces and placed in a solution of 100 ml pH 6.8 phosphate
buffer. Dissolve the films completely and filtered through whatman filter paper. The solution was
checked using UV spectrometry method at 212 nm wavelength. The average of drug contents of
three films was taken as final reading.

**In vitro drug release study**

USP Type-2 rotating paddle dissolution test apparatus was used to study the dissolution profile
of buccal patches). The dissolution medium used was 250 ml 6.8 phosphate buffer at 37 ± 0.5 °C
which was stirred at 50 rpm. The patch of 1 X 1 cm² diameter was fixed on the glass disk with
the help of a cyanoacrylate adhesive. The disk was put at the bottom of the dissolution vessel so
that the patch remained on the upper side of the disk. Samples (5 ml) were withdrawn at pre-
determined time intervals (30, 60, 90, 120, 150 and 180 min) and replaced with equal volume of
dissolution medium. The samples were filtered through 0.45 μm filter and appropriately diluted
with 6.8 phosphate buffer and assayed spectrophotometrically at 212 nm.

**Drug Release Kinetic Study**

Data obtained form in vitro drug release studies were fitted to disso calculation software. The
kinetic models used are zero order, first order, Korshmers and Pepps, Hexon crowell and Higuchi
equation.

The rate and mechanism of release of drug from the prepared formulation were analyzed by fitting
the dissolution data into the zero-order equation: \( Q = k_0 t \)

Where, \( Q \) is the amount of drug released at time \( t \), \( k_0 \) is the release rate constant.

The dissolution data fitted to the first order equation: \( \ln (100 - Q) = \ln 100 - K_1 t \) Where, \( k_1 \) is the release rate constant.

The dissolution data was fitted to the Higuchi’s equation: \( Q = K_2 t^{1/2} \) Where, \( k_2 \) is the diffusion rate constant.
The dissolution data was also fitted to Korsmeyer equation, which is often used to describe the drug release behavior from polymeric systems:

$$\log \left( \frac{M_t}{M_\infty} \right) = \log k + n \log t$$

Where $M_t$ is the amount of drug released at time $t$, $M_\infty$ is the amount of drug release after infinite time, $K$ is a release rate constant incorporating structural and geometric characteristics of the tablet, $n$ is the diffusional exponent indicative of the mechanism of drug release.

**In vitro drug permeation**

The *in vitro* buccal permeation of films was studied through the sheep buccal mucosa using Franz-diffusion cell. Freshly obtained buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa and the compartments clamped together. The donor compartment was slightly wetted with 1 mL of phosphate buffer. The receptor compartment was filled with phosphate buffer pH 6.8. The diffusion cell was thermostated at 37 ± 0.2 °C and the receptor compartment was stirred at a rate of 100 rpm. One milliliter sample was withdrawn at predetermined time intervals using a butterfly canula and syringe. The buffer was immediately replaced using blank pre-warmed buffer. After filtration through 0.45 μm filter and appropriate dilution the samples were analysed for the drug content spectrophotometrically at 212 nm.

![Schematic representation of the modified Franz diffusion cell](image)

**Ex vivo mucoadhesion time**

A locally modified USP disintegration apparatus was used to determine the *ex vivo* mucoadhesion (residence) time. The mucosal membrane (fresh sheep buccal mucosa) was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water.
and then with 6.8 phosphate buffer at 37 °C. Pig cheek mucosa, 4 cm long, was glued to the surface of a glass slide. One side of the patch was wetted with one drop of 6.8 phosphate buffer and pasted to the sheep buccal mucosa by applying a light force with fingertip for 20 s. The glass slide was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The beaker was filled with 800 mL of 6.8 phosphate buffer and was kept at 37 ± 1 °C. The time required for the patch to detach from the buccal mucosa was recorded as the mucoadhesion time.

In vitro mucoadhesion strength
The mucoadhesive strength of patches was measured in triplicate on a modified physical balance. A piece of sheep buccal mucosa was tied to the mouth of a glass vial filled completely with 6.8 phosphate buffer. The glass vial was tightly fitted in the centre of a beaker filled with 6.8 phosphate buffer at 37±1 °C. Patches were stuck to the lower side of rubber stoppers with glue and the mass (g) required to detach the patches from the mucosal surface was taken as the mucoadhesive strength (shear stress).

![Modified physical balance](image)

**Figure 0:2 Modified physical balance used to measure mucoadhesive strength**

Tensile strength and percentage elongation
Tensile Strength is the maximum stress applied to specified part of films without tearing. % Elongation is the maximum deformation of films length without tearing. Film ($L_0$ initial length, $t$ thickness, $w$ width) was placed between the clamps lever of instrument, and an extension force at the speed of 2 mm/min was applied to each film. At tearing time, load at failure ($F$) and final length ($L$) was measured. Tensile Strength and % Elongation were calculated using following equations;

Tensile strength (N/cm$^2$) = $\text{Force} \times \frac{100}{\text{Area}}$

% Elongation = $\left(\frac{L-L_0}{L}\right) \times 100$
Accelerated stability study

Selected patches were subjected to accelerated stability testing by wrapping them in aluminium foil and packing them in glass vials. These patches were kept at 40°C/ 75% RH for 1 month. The data presented were the mean of three determinations. The patches were examined for changes in appearance, thickness, folding endurance, drug content, surface pH, % swelling and drug release.

REFERENCES