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# Buccal drug delivery system: A new hope for high drug bioavailability

**Alka Sharma**

Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Institutional Area, Greater Noida (UP) -201306

**Sushma Verma**

Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Institutional Area, Greater Noida (UP) -201306  
Corresponding author email: [SUSHMAVERMA76@GMAIL.COM](mailto:SUSHMAVERMA76@GMAIL.COM)

**Suhail Khan**

Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Institutional Area, Greater Noida (UP) -201306

**Syed Akhlaque Ahmed**

Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Institutional Area, Greater Noida (UP) -201306,

**Abstract**--It is well known that certain medications suffer hepatic first-pass metabolism or deteriorate in the digestive system, the buccal drug delivery method may be an alternative to oral administration. Because it is painless and may be swiftly and readily removed if the treatment must be terminated or interrupted, the buccal mucosa has long been ideal for administering medications. This paper focuses on the buccal drug delivery system had the goal of gathering recent literature and presenting a concise explanation of buccal patches by discussing the characteristics of an ideal mucoadhesive system, benefits of buccal delivery and disadvantages thereof, factors affecting buccal absorption, and various types of patches as well as the preparation method and composition thereof. The compilation of the data is also enhanced by adding market products as well as the patented, so that reader will get the complete knowledge about the buccal drug delivery.

**Keywords**---Mouth-to-mouth drug delivery systems, mucoadhesive patches for the mouth, mechanisms of the buccal mucosa a description of the patches, composition Analyze of the buccal patch.

## 1. Introduction

As a result of pharmaceutical industry advancements, the quality of life for many people has been considerably improved. Scientists and researchers in the drug development industry have been concentrating on finding new methods of administration to enhance the efficacy of already-approved drugs or circumvent the oral route's disadvantages. The oral route is still the most often used method of administering medications. However, certain issues with oral medication delivery methods still need to be addressed (1). The pharmacokinetics, pharmacodynamics, toxicity, immunogenicity, and effectiveness of pharmaceuticals may now be better controlled via the development or design of various drug delivery techniques. Each method has advantages and disadvantages. Mucoadhesive drug delivery (buccal mucosa) is administering a medicament through the buccal mucosa (2). The "challenge" obstacle to drug absorption prevents the first-pass impact (the liver's rapid absorption of the medication and reduction of inert molecules). However, delivery is now limited to small molecule medications with lipophilic qualities, which can easily traverse the membrane. Intranasal (IN), buccal/sublingual, pulmonary, and transmucosal modes of drug delivery encompass the mucosal linings of the nasal, rectal, vaginal, ophthalmic, and oral cavities properly possibilities and viable advantages over oral delivery for systemic drug delivery (3). Many formulations have been created for buccal distribution, such as pills, gels, tablets, and patches. Mucoadhesive drug delivery methods have recently received a lot of attention and interest as it prevents the medicine from being destroyed by GIT contents or inactivated in the liver during the first pass (4). These drugs are delivered using the subsequent methods:

- a) Sublingual Drug Delivery System
- b) Rectal Drug Delivery System
- c) Buccal Drug Delivery System
- d) Vaginal drug delivery system
- e) Ocular drug delivery system
- f) Nasal Drug Delivery System

### 1.1 Features of an ideal mucoadhesive system

The following are characteristics of an optimal mucoadhesive system: – (5)

- 1) Firstly, it must be fast adhesive to the buccal mucosa, have appropriate mechanical strength and spreadability, swelling and wetting capabilities, biocompatibility, and the ability to penetrate oral mucosal tissues.
- 2) Controlled drug release is essential and convenient for patients to use.
- 3) It needs to speed up and enhance how quickly the medicine is absorbed.
- 4) It should not interfere with everyday activities like talking, eating, or drinking, and should not impede them, and illnesses such as dental caries or tooth roots should be avoided.
- 5) It should be able to deliver medications to the mucosa in a single path.
- 6) Because saliva and water wash it out, it must be able to stand up to these forces.

### **1.2 Advantages or Benefits of buccal drug delivery system-**

With a buccal drug delivery method, there are numerous benefits:

- a) It's easy to get drugs to the membrane locations and administer them without causing any discomfort. It's also easy for them to be withdrawn if treatment must be ended, paused, or discontinued in an emergency.
- b) To avoid the first-pass metabolism, creating medications that are unstable in acidic conditions and do not encounter the digestive fluid is necessary.
- c) The absorption time of the dosage forms is prolonged.
- d) Rapid absorption is facilitated in the systemic circulation.

### **1.3 Drug distribution via buccal route has the following disadvantages or limitations:**

The use of buccal medicine administration has several drawbacks.

- a) Medication that is not buccal pH stable irritates the mucosa, tastes bitter or unpleasant, or has a strong odor cannot be administered with this approach.
- b) Food and water may be restricted during administration.
- c) Administering or administering large doses of medication can be difficult.

### **1.4 Oral Structure of Buccal Cavity**

The oral epithelium protects the tissue from infections and fluid loss. The lamina propria and submucosa descend. It is 1-2 mm thick (6). Oral mucosa sensory taste receptors are situated on the tongue. Oral mucosa has three types. The buccal and sublingual mucosa cover around 60% of the mouth's surface (below the tongue). The tongue's dorsal surface has specialized mucosa (15%) and masticatory mucosa (25%) (gums) (7). Masticatory epithelial cells are keratinized and attach to lamina propria. A thin elastic lamina connects the lining mucosa to the submucosa and lamina Propria (8). The epithelium comprises two types of non-keratinized epithelium in the soft palate, dorsal aspect of the tongue, and oral cavity floor, and keratinized epithelial layer in the hard palate and non-flexible portions (9). The buccal epithelium is 500-800 μm thick in humans, dogs, and rabbits. The basement membrane separates tissues and epithelium. Mechanical assistance and adhesion between epithelial and supporting tissues are provided to the epithelium. The connective tissues beneath the oral mucosa account for many of its mechanical properties.

**Mechanism or pathway-** A medication may be absorbed in two ways:

- a) Transcellular (going through the cell) and,
- b) Paracellular (traversing the cellular membrane) (intercellular, passing around the cell).

**Because of the numerous barriers in the oral cavity, the buccal mucosa can resist invasion,** and medication ion absorption via the buccal mucosa is slower and less complete than it would be without them. The epithelium's outermost quarter to one-third is the primary barrier to penetration (10).

**Granules for Membrane Coating or Granules with a Core-** The accumulation of lipids and cytokeratin's in keratinocytes does not harm epithelial cells that are not covered with hair. Glycoproteins that coat non-keratinizing epithelial cells are spherical, membrane-bound granules that measure 0.2 micrometers in diameter. Non-keratinized human epithelia, including the cervix of the woman's womb and the esophagus, have been shown to contain these granules in other places as well. Even so, new research using ruthenium tetroxide as a post-fixation agent indicates that a minute no of granules in the non-keratinized epithelium containing glass slides can provide intercellular spaces with compartments.

**The basement membrane-** However, it's clear that the basement membrane has a function in keeping things from passing between epithelium and connective tissue, even though the epithelium's outermost layers serve as the principal barrier to the entrance from the outside. The charging on the basal lamina's components may slow the passage of lipophilic substances through the epithelial surface barrier (11).

**Mucus-** To protect the buccal epithelial cells from bacteria, a thin layer of mucus, ranging in thickness from 40 um to 300 um, forms around them. In addition to its action as a lubricant, Mucoadhesive drug delivery may benefit from its use, as it is anticipated to play an important role in their adhesion. Polymers or extended three-dimensional networks may be formed when mucus molecules link together (12). There are a variety of mucus kinds, such as G, L, and S, as well as P and F, which create various gel networks. Oligosaccharide chains are connected to a protein core in the Mucin family of large, glycosylated proteins (13). Mucus has a gel-like consistency because three sections of the protein molecule are glycosylated. Mucins have coddling that prevents them from proteolytic cleavage, which is important for maintaining mucosal barriers.

**Saliva-** The mucosal surface contains a 70-micrometer-thick layer of saliva that acts as an unstirred layer. MG1 may hydrate, lubricate, and concentrate defensive chemicals such as secretory IgM, which prevent bacteria from adhering to the mucosa and thereby reduce the risk of infection (14). Saliva and salivary mucous may help oral tissues maintain their barrier qualities. Several salivary glands produce saliva, including the parotid, submandibular, and sublingual glands, all of which are connected by a network of ducts on the floor of the mouth. Acid-sensitive tooth enamel may be protected by a higher salivary secretion, which neutralizes the acidic environment in the mouth. Salivary secretion stimulates oxygen consumption and the production of vasodilator chemicals; as a result, epithelial blood flow rises. Saliva's pH ranges from 5.6 to 7. Enzymes such as -amylase, lysozyme, and lingual lipase are all found in saliva, among other things (breaking down the fats). 1) Saliva performs various vital activities, including the mouth being moistened, digestion beginning, and teeth being protected from decay by ingesting water. 2) It also regulates oral bacterial flora (15). 3)Saliva has a high concentration of calcium and phosphate, which aids in the mineralization of newly formed teeth and repairing weak enamel. 4) It forms a "protective pellicle" that shields the teeth. Secretory IgA, salivary peroxidase, and the enzyme lysozyme are key components of saliva's antibacterial defense mechanism. Autolysins are activated by lysozyme, which agglutinates bacteria. The adhesion of bacteria to host tissue is disrupted by Ig A. According to Dearden

and Tomlinson (1971), salivation affects the kinetics of the oral absorption of drug solutions. (16). Salivary secretion with time has the following linear relationship:

$$dm/dt = Kc/ViVt$$

Here,

M - Mass of the drug in the mouth at a time,

K - Proportionality constant,

C - Conc. of the drug in the mouth at a time,

Vi - The vol. of the solution put into the mouth cavity, and

Vt - Salivary secretion rate.

Due to a continual flow of saliva inside the mouth cavity, drug retention is very challenging, making it tough for this location to absorb the medication. Saliva plays a crucial part in the development of dental caries, which is a cause for worry. Plaque bacteria, such as streptococci, are accelerated by salivary enzymes that break down natural polysaccharide polymers, causing tooth caries. Due to the structural and functional diversity of the oral cavity, the permeability between different parts of the mouth varies widely (17).

### 1.5 Factors affecting buccal absorption

Various factors that impact drug absorption diminish or delay the rate and amount of medicines entering the bloodstream (Fig1).

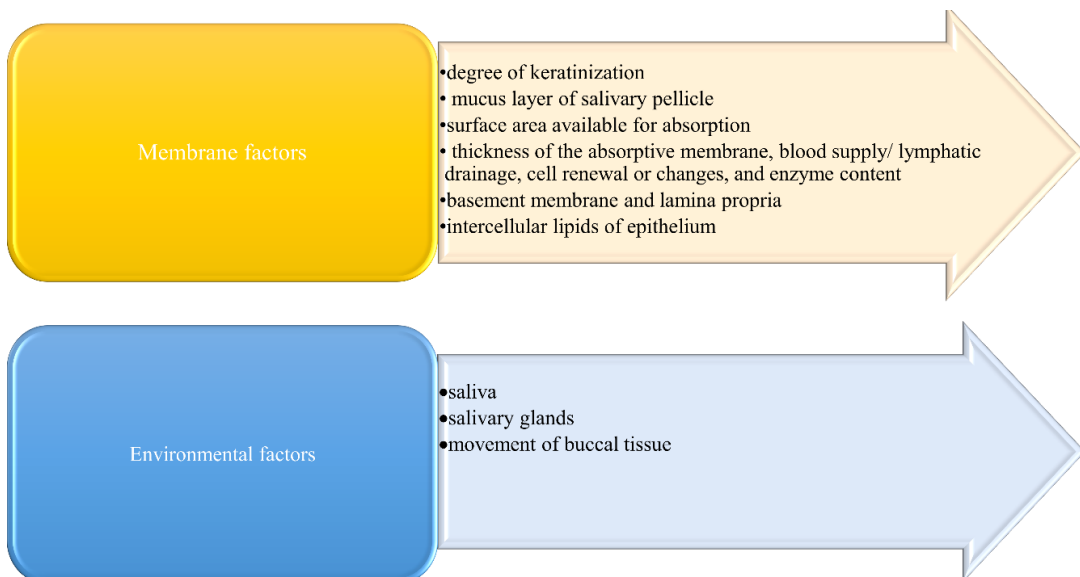


Fig 1: Schematic diagram of Factors affecting buccal absorption

### 1.6 Methods in assessing buccal mucosa permeability

Preclinical testing of buccal mucosa permeability is done using a variety of models, and most properly may be known by in vivo technique. While in vitro and

situ investigations are instrumental dependent studies to know the preclinical compound screening, the revealing mechanism involved in transport and evaluating the potential of penetration enhancer's use in buccal transport enhancement (18).

**In-vitro technique-** In an in vitro permeability experiment, which assesses the barrier nature of a biological tissue, drug diffusion is examined in an environment where parameters such as osmolarity, temperatures, and pH may be easily manipulated. (19) When using in vitro methods to estimate chemical absorption via the human buccal mucosa, selecting an appropriate animal model based on system and permeability similarities to human buccal mucosa is crucial. Using these in vitro diffusion cells has the advantage of allowing researchers to track the time course and kinematics of drug diffusion into tissue.

## **1. Dissemination cells and water movement cells of the Franz type**

### **A. In vitro Studies Using Animal Buccal Mucosal Membranes**

The human buccal mucosa isn't readily accessible; hence permeation experiments employ animal mucosa that has been recently dissected. Regarding permeability, biochemistry, and shape, animals' buccal mucosae should mimic human buccal tissues. Because of their non-keratinized mucosa, rabbits are often utilized in permeation experiments. Because rabbits' oral cavity has such little non-keratinized mucosa, this method is seldom used in permeation investigations (20). Pigs' physiological, anatomical, dietary, and metabolic patterns are very similar to those of humans. Because of this, pigs became the most often employed animal in human illness research. The porcine buccal mucosa is likewise non-keratinized and has many characteristics of the human buccal mucosa.

### **B. Franz-Type Diffusion Cells**

Pharmacological agents may be tested for in vitro skin penetration and in vitro buccal mucosal permeation using Franz-type diffusion cells. The receptor chamber and the donor chamber are separated by the buccal mucosa. Each chamber has a separate supply of medication and buffer solutions. Homogeneity is maintained by keeping the temperature of the receptor phase at 37.1 °C and using a magnetic stirrer to agitate the mixture. For this study, we will analyze using an Ultraviolet spectrophotometer was used to measure the release of medicine over time (21).

### **C. Flow-Through Diffusion Cells**

In contrast to the Franz diffusion cell, which does not have a closed donor chamber and buccal mucosa exposed to air, this flow-through diffusion cell exposes tissue to air, which causes tissue drying and death (Squire et al., 1997; Xiang et al., 2002). There will be no drug buildup in the receptor chamber in this diffusion cell since the receptor solution flows below the implanted buccal mucosa. UV spectrophotometer is used to determine whether the medication has penetrated or diffused through the buccal mucosa after being collected from the receptor solution regularly (22).

## 2. In-vivo technique

### A. Buccal Absorption Test

For determining mucosal permeability, the buccal absorption test is possibly the most widely used method. A known amount of drug was delivered and then swirled about in the subject's mouth for a brief period. The subject is cleaned and discharged into the pharmaceutical solution container. This solution was tested for drug content. Derived from the initial drug solution and the final drug concentration after spinning and washing. Dearden and Tomlinson, 1971 used a correction factor to precisely quantify the quantity of saliva produced throughout each test. Research shows that adding a marker chemical like phenol red or polyethylene glycol to the swirling fluid predicts salivary dilution and inadvertent absorption.

### B. Perfusion Cells

Nonspecific oral absorption limits the ability of perfusion cells to connect to specific mucosa in animals' and humans' mouths. The drug solution is perfused via a perfusion cell in this procedure, and by monitoring how much drug has been withdrawn from the perfusate, we may establish how much medication has been absorbed (23).

## 3. Buccal Mucoadhesive Dosage:

**Type I:** Drugs may be released in any direction from a single-layer device. Swallowing may cause a large loss of medication in this dose form (24).

**Type II:** To avoid drug leakage from the dosage form's upper surface into the oral cavity, a bioadhesive drug loading layer is put on top of an impermeable backing layer. (25).

**Type III:** This is a device that exclusively releases medication from the side that is close to the buccal mucosa, resulting in minimum drug loss. This may be accomplished by applying a coating to everything except the face of the dosage form that will come into touch with the patient's buccal mucosa (26).

- **Buccal Patches:** These patches have a waterproof backing, a drug-containing layer, and a bio-adhesive mucosal surface. Laminates are mouth patches. Solvent molding or direct milling are used to make adhesive patches (27). Solvent casting involves coating a base layer with a drug and polymer solution, then pouring it on top and allowing it to evaporate. This makes the patch plate
- **Formulation of the buccal patch:** If we want to get the intended therapeutic impact via buccal medication administration, API and mucosa contact must be prolonged and augmented. It is best to use buccal adhesive medication delivery devices smaller than 1-3 cm<sup>2</sup> in size and have a daily dosage of 25 mg or less. Buccal delivery might last up to six hours (28). This list of buccal drug delivery formulation's excipients and functional agents is organized by kind for ease of reference. There should also be a GRAS (listing for all the excipients utilized in the formulation (29).

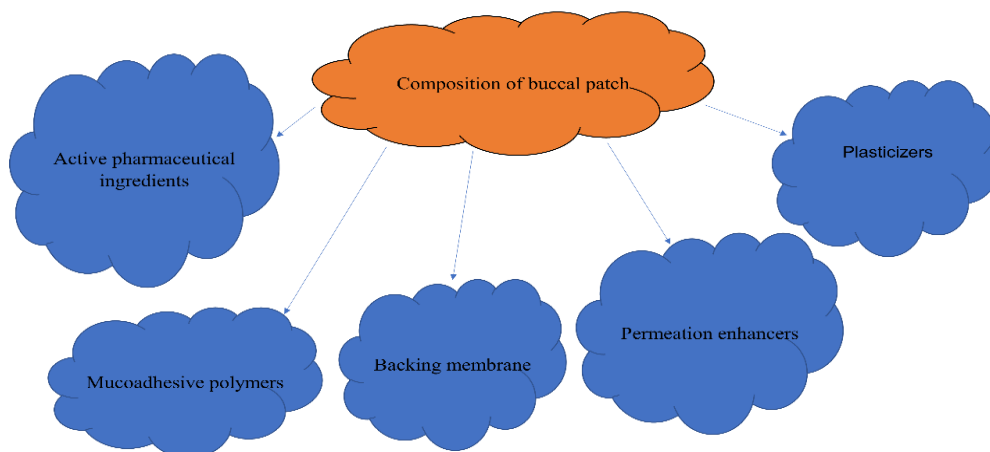


Fig.2: The basic components for the preparation of buccal patches

- 1) **Active Pharmaceutical Ingredient/Drug-** To achieve the intended therapeutic impact, the contact between API and mucosa must be extended and enhanced. The key pharmacological properties that influence patch and buccal mucosa diffusion are molecular weight, chemical functionality, and melting point. The following criteria guide the selection of a buccal patch:
  - It is recommended that a single dosage of the medicine be administered as described below.
  - Pharmaceuticals with a physiological  $\frac{1}{2}$  of 2-8 hours are appropriate for regulated medication administration.
  - When supplied orally, the medicine should be absorbed passively.
  - Drugs should not have a disagreeable taste or odor, and they should be free of irritation, allergy, discoloration, or tooth erosion.
  
- 2) **Mucoadhesive polymers-** Covalent chemical bonds link structural units and repetitive units in polymer molecules, which is what the name "polymer" refers to in general. Meaning many components, the polymer is a compound word formed by combining two Greek words: polys and more (30). Molecules that adhere to the mucus layer can indeed be natural or manufactured that cover the mucosal epithelia, and investigators have been alerted to the possibility of using mucoadhesive to bypass the muscular system in long-term medicine delivery (31). The first purposefully manufactured mucoadhesive, Natural gums were used to make Orabase®. Triamcinolone acetonide's anti-inflammatory and barrier-building properties in Orabase® give local relief from mouth ulcers when used together in Orabase®. Mucoadhesive polymers- classification and examples (Fig 3).

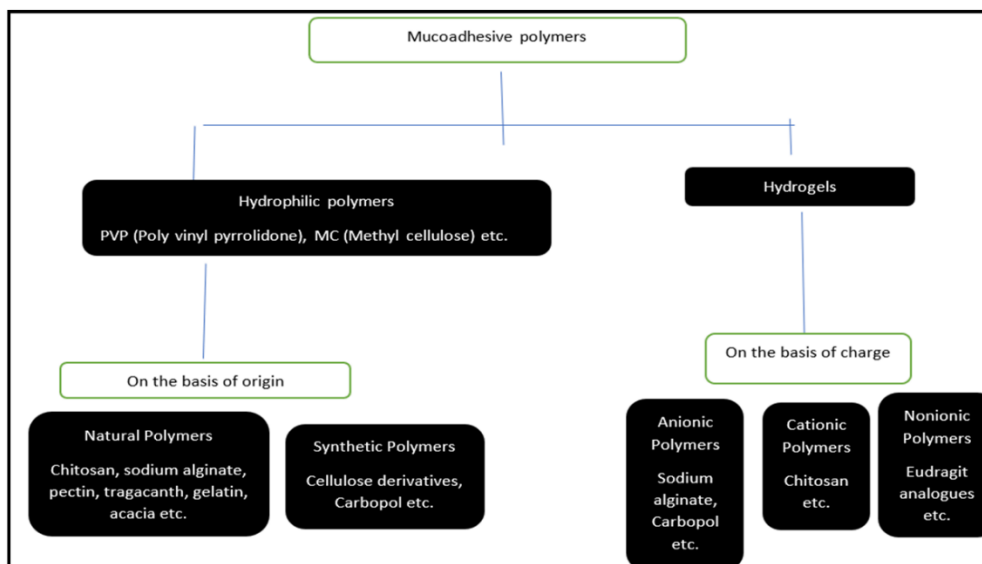


Fig. 3: Classification and examples of Mucoadhesive Polymers

The selection of an appropriate mucoadhesive polymer for designing buccal patches should be supported by the subsequent characteristics-

- a) Poisonous or absorbable in the intestines, the polymer and its metabolic byproducts should be.
- b) The mucus membrane should not be irritated and should not break down during storage.
- c) Non-covalent attachment to the mucous epithelial cell surface is preferred.
- d) When applied to wet tissue, it should attach rapidly and be unique to the treated area.
- e) There should be a wide variety of polymers easily accessible on the market at reasonable prices.

**3) Backing membrane:** Bio-adhesive equipment requires a good supporting membrane to stick to the mucus membrane. Chemically inert & permeable membranes are required for the medicine and penetration enhancer to penetrate. The backing membrane contains magnesium stearate, HPMC, HPC, CMC, and other chemicals.

**4) Permeation enhancers:** Permeation enhancers are chemicals that help drugs pass through the buccal mucosa more easily. Non-allergenic and non-toxic are great properties for the chemical ingredient we employed in the formulation process. To augment or boost medication flow across the mucosal barrier, many substances have been explored as buccal penetration and absorption enhancers.

Table 1- classification, examples, and mechanism of permeation enhancers

Sr. No.	Classification	Examples	Mechanism
1	Fatty acids	Oleic acid, caprylic acid, lauric acid,	Phospholipid domain fluidity should be increased.
2	Surfactants	Anionic- sodium lauryl sulfate Nonionic – tween 80 Cationic-L-lysine, trimethyl chitosan	Intercellular lipid perturbation, protein domain integrity On the mucosal membranes, an ionic contact with a negative charge occurs.
3	Bile salts	Sodium deoxycholate, sodium taurocholate	Intercellular lipid perturbation, protein domain integrity
4	Sulfoxides	Dimethyl sulfoxide, decyl methyl sulfoxide	Intercellular lipid perturbation, protein domain integrity
5	Chelators	EDTA, citric acid salicylates	Ca polyacrylates cause problems.

**The following are some of the factors that influence permeation enhancement selection and efficacy:**

- a) physiochemical features of the drug and nature of the vehicle used
- b) administration site
- c) additional excipients

**The following mechanisms are hypothesized to boost mucosal absorption:**

- a) Changing mucus rheology: Drug absorption is hampered by a viscoelastic barrier of varying thickness formed by mucus. The mucus layer is additionally impeded by the presence of saliva, which obstructs and inhibits the absorption.
- b) The intracellular pathway of the buccal mucosa is the most popular method of medication absorption. Some enhancers affect intracellular fat packing by interacting with lipid or protein components.
- c) Tight junction components are targeted by certain enhancers, which increase medication absorption by acting on desmosomes, a critical tight junction component.
- d) It does this by suppressing the many peptidases and proteases prevalent in the buccal mucosa, thereby breaking down the enzyme barrier. The enzymatic activity may be influenced indirectly by changes in membrane fluidity.
- e) Increased thermodynamic activity: Some enhancers improve the solubility of medicines, modifying their partition coefficient. Better absorption is achieved as a direct consequence of increased thermodynamic activity.

**5) Plasticizers-**Plastics and blends of plastics are often used to make thin films that are both malleable and soft. The plasticizers help liberate the medicinal component from the polymer base and improve penetration. When the plasticizer ingredient solvates the polymer and alters interactions between polymers.

Examples- Polyols (glycerol, propylene glycerol, PEG), Organic esters (phthalate esters, dibutyl sebacate), and Oils (castor oil, acetylated monoglycerides)

**Muoadhesion mechanisms and theories:** (32)

Muoadhesion mechanism has three stages:

- 1) contact stage
- 2) interpenetration stage
- 3) stage of consolidation

Table 2: Various theories and their mechanism for Muoadhesion

S No.	Theory	Explanation
1	Electronic theory	With differing electrical charges, a much adherent polymer and a mucous membrane generate an electrostatic attraction.
2	Adsorption theory	Intermolecular adhesion between mucus and polymer molecules.
3	Wetting theory	The muoadhesive polymer's capacity to spread is determined by the substance's mucosal surface tension. The equation is used to compute the spreadability coefficient- $SAB=YB-YA-YAB$ Where: YB is surface energy and YA is interfacial energy.
4	Diffusion theory	It's possible to create an interpenetration layer via diffusion of polymers into mucus and back again. For polymer and mucin chains, the interpenetration depth may be estimated as follows: $l = (tD_b)^{1/2}$ where t denotes the contact time and $D_b$ denotes the muoadhesive material's mucus diffusion coefficient.
5	Fracture theory	After adhesion, it is necessary to separate the two surfaces. Fracture strength and adhesive strength are compared using the equation below: $G=(E\epsilon/L)l/2$ Where: E is young's modulus of elasticity, $\epsilon$ is fracture energy and L is critical crack length when two surfaces are separated.
6	Mechanical theory	A bigger contact area helps with adhesion because of rougher surfaces.

**Muoadhesion-affecting factors-**

- Factors associated with polymers: molecular weight, the concentration of active polymer, polymer chain flexibility, spatial confirmation, and many others.
- Environment-related factor- i) pH ii) applied strength iii) selection of model substrate
- Physiological variables- i) mucin turnover ii) disease state

**Methods for preparing buccal patches:** Preparation of mucoadhesive buccal patches and mucoadhesive films -(33)

1) **Solvent casting method-** The method for preparing buccal patch by solvent casting method is as follows: (34)



Fig.4: Solvent casting method

2) **Direct milling method-** In this method, patches are created without using solvents. The following is the approach to preparing a buccal patch using the direct milling method. (35)

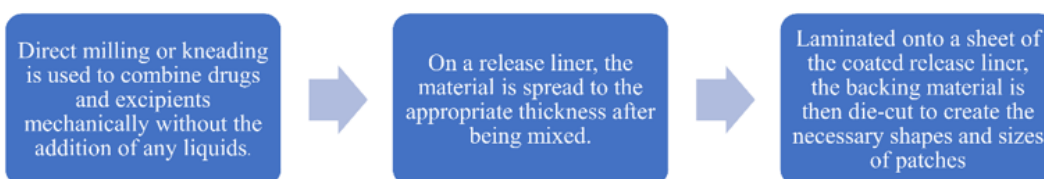


Fig. 5: Direct milling method

3) **Hot melt extrusion method-** Unlike other pharmaceutical processing processes, this technology is a feasible option and offers various benefits. Molten polymers can be used as thermal binders, drug repositories, or release retardants during the extrusion process after cooling and solidification. Whereas the molten polymer is aggressively mixed and agitated with the rotating screw, the suspended particles of the polymer disaggregate. Extrusion procedures for pharmaceuticals can be classed as either ram extruded or screw extrusion.

**(a) Ram extrusion** - To force materials through the die, a high-pressure positive displacing ram is used. Materials are fed into a hot cylinder during the ram extrusion process to get them ready for use. Ram extrusion is based on the notion of high pressure. To put it another way, ram extrusion has a limited melting capacity compared to extrudates treated by screw extrusion, which causes poor temperature consistency and lower homogeneity in the extrudates (36).

**(b) There are two types of screw extruders: There are two types of extruders: the single screw and the twin screw.**

- **Single Screw Extruder** - Extrusion systems that use a single screw are the most prevalent worldwide. One screw is used for feeding, melting, devolatilization, and pumping inside the barrel. Solid conveyance, melting, and pumping are the three basic operations of a single screw extruder (37).

- **Twin-Screw Extruders**- The advantages of twin-screw extruders over single-screw extruders are simpler material loading, improved kneading and dispersion capacity, reduced propensity to overheat, and quicker transit time (38).

**4) Rolling method:** The rolling technique involves rolling an emulsion or solution of medicine on a carrier. Most of the solvent consists of water and a mixture of water and alcohol. A monitored bottom drying process on rollers dehydrates or dries the patch, which is cut into the necessary sizes and shapes (39).

**5) Semi-Solid casting method-** Semi-solid casting begins with a water-soluble polymer solution that forms a film. The resulting solution is thickened with ammonium or sodium hydroxide from a polymer that is insoluble in acid (e.g.- Cellulose acetate phthalate and cellulose acetate butyrate). Finally, the gel mass is shaped into films or ribbons by heat-controlled drums. The proportion of alkaline polymer to film-forming polymer should be 1:4. (40).

#### **Evaluation of buccal patches:**

According to the following parameters, the assessment of the buccal patch can be described:

##### **i) Physiochemical evaluation:**

1. **Surface pH:** A pH meter and color may determine the surface pH. A warm pH 6.8 phosphate buffer solution is used to dissolve 2 percent (w/v) agar in a Petri dish until it gels at room temperature. This solution is poured into the container to enable the buccal patches to swell for two hours. To determine the patch's pH, place pH paper on its surface. The average of three readings is determined (41).
2. **Thickness measurement:** Digital vernier calipers with deviation or an electronic micrometer are used to measure the density of each film at five separate points (the center plus four corners). An average value is then computed (42).
3. **Weight uniformity/ weight variation:** Five randomly chosen patches are sliced into 2x2 cm<sup>2</sup> squares and then weighed using a Shimadzu sensitivity balance, and the difference in weight between each square is determined (43).
4. **Folding endurance:** Repetitive folding was done manually until the patch broke or folded up to 300 times, which is deemed acceptable for revealing excellent patch qualities (44).
5. **Thermal analysis study:** Differential scanning calorimeters (DSCs) are used to conduct thermal analysis investigations on buccal patches (45).
6. **Morphological Characterization** - A scanning electron microscope (SEM) is used to examine the morphological characteristics of buccal patches (46).
7. **Drug content uniformity:** To achieve uniform dispersion of medication content, a 3 cm patch (excluding backing membranes) is placed in 100ml of a 20:80 Ethanol/Saliva Solution mixture (20:80) for 12 hours with periodic shaking. Using a spectrophotometer, the concentration of the medication in the filtrate is determined. The drug amount in question was determined using a standard calibration curve (47).

- 8. Measurements of mechanical properties:** For assessing the mechanical qualities of the patches, elongation at break is evaluated using the Wilhelmy plate method on a specialized microprocessor-based tensile strength tester. A 60 x 10-millimeter film clip was cut & positioned above two clamps that have been 3 cm away. Clamping the strip at a pace of 2 mm/sec till they break, the upper clamp holds them in place during the test and avoids crushing them. The bottom clamp is firmly in place, preventing any movement. At the moment where the strip breaks, the film's force and length are recorded (48).

Tensile strength= Force at break(kg)/ initial cross-sectional area of the sample (cm<sup>2</sup>)

Percentage elongation: When the patch is exposed to tensile stress, the sample is stretched or elongated, resulting in deformation. A texture analyzer is used to determine the ductility of polymers.

It is calculated by the formula:

$$\% \text{ Elongation} = \text{Increase in length} \times 100 / \text{Original length}(\text{cm}^2)$$

- 9. Water absorption capacity test:** patches of 2.3 cm<sup>2</sup> on agar media prepared with simulated spit (2.38 g Na<sub>2</sub>HPO<sub>4</sub>, 0.19 g KH<sub>2</sub>PO<sub>4</sub>, & 8 g NaCl per liter of filtered water ph was adjusted 6.7) and kept at 37°C - 0.5°C for 24hrs in an incubator are allowed to expand. The final constant weights are obtained by drying the samples in a centrifuge tube over calcium chloride at room temp for 7 days (0.25,0.5,1,2,3, and 4 hours). How much water a plant takes up is determined using this formula (49).

$$\text{water uptake (\%)} = (\text{Ww}-\text{Wi})/\text{Wf} \times 100$$

where Ww is the wet weight and Wf is the final weight.

- 10. Swelling index study:** Incubation at 37°C±1°C is used to assess any physical changes in the buccal patches (identified as W1). The buccal coverings are then individually weighed and placed in two percent agar gel plates. Excessive water is removed completely from the gel plates using filter paper at frequent intervals for 3 hours. Re-weighing and calculating the Swelling Index using the following procedure is then performed on the swollen areas (50)

$$\text{SI} = (\text{W2}-\text{W1})/\text{W1} \times 100$$

Where W2- reweighed patch and W1 weighed individually

## ii) Ex - vivo evaluation-

1. **Ex- vivo mucoadhesive strength:** The amount of force required to remove the patch from the mucosal membranes was used to determine mucoadhesive strength. For this experiment, we employed a texture analyzer, which is a type of physical balance. After a few droplets of artificial saliva were applied to the swine buccal mucosa, the dish's mucosal surface was pushed outward (pH 6.2). The right-side pane of the balancer was modified with a 3 cm buccal area of fused glass. Equal oscillation was achieved by balancing the weight of the left pan with the weight of the right pan. The weight differential was used to calculate the mucoadhesive strength (w2-w1) (51). The equation used to compute the mucoadhesive force was:

$$\begin{aligned} \text{mucoadesive force ((kg/m)/s)} = \\ (\text{Mucaoadhesive strength (g)} \times \text{acceleration due to gravity})/1000 \end{aligned}$$

Here, acceleration due to gravity is 9.8 m/s<sup>-1</sup>

**2. Ex- vivo mucoadhesion time:** The ex-vivo mucoadhesion (residence) duration of 800mL of simulated saliva is measured using a breakdown of a locally customized USP disintegration apparatus (pH 6.2). Surgical scissors are used to carefully detach the mucosal membrane from the underlying connective tissues. Before applying stimulating saliva, the mucosal membrane must be detached and rinsed with deionized water (pH 6.2). A 3 cm diameter sample of porcine buccal mucosa is bonded to the glass surface. Wet one side of the buccal patch with artificial saliva (pH 6.2) and a fingertip, then gently squeeze for several seconds. While the glass slab may move up and down, the vertical shaft of the disintegration apparatus cannot (25 cycles per minute). At the bottom, the patch is covered in mimicked saliva, and at the top, it is free of the liquid. The duration during which the patch entirely detaches from the mucosal surface and is no longer attached to the mucosa is known as ex-vivo mucoadhesion time. (52).

**3. Ex-vivo permeation studies:** At 37°C and 5°C, a Franz diffusion cell was used to evaluate buccal patches for ex vivo penetration. A phosphate solution (pH 6.8) comprising a magnetic bead was used to fill the receptor compartment. When the mucosa was covered with a buccal patch, it was then clamped together. The magnetic stirrer was used to keep the hydraulic performance in the chamber at 50 rpm (53). Formula-based calculations were used to determine the membrane's flow (J):

$$J = dQ/(A dt)$$

$dQ/dt$  is the slope calculated from the stable portion of the curve, and  $A$  is a region of diffusion ( $\text{mg h}^{-1}\text{cm}^2$ ) ( $\text{cm}^2$ ).

**4. Ex vivo bio adhesion test:** Dissolution cells are used for adhesion tests including colloidal gold staining or fluorescence probes. Gingival mucosa adhering to the lip of an open vial keeps the pH level at 6.8. The glass vial is placed as near to the mucosa's surface as possible in a glass beaker loaded with phosphate buffer (pH 6.8, 37°C 1°C). An adhesive called cyanoacrylate is used to adhere the patch to the rubber stopper. Using two pans of the balance, a 5gm weight is evenly distributed. After removing the 5 g of weight from the left-side pane, the pan linked to the patch was placed on the mucosa. 5 minutes of face-to-face time are required for this exercise. The adhesive strength was calculated by weighing a patch of the mucosal surface and dividing the weight by the weight of the patch. (54).

### iii) *In vitro* evaluation

1. **In- vitro residence time:** Modified USP dissolution test equipment is used to get an accurate reading of this parameter. pH 6.8 phosphate buffer was used as the experimental medium in this example (800mL). The mucoadhesive patch was put to the glass slab after being hydrated on one side using a phosphate buffer. The patch was dropped into the buffer solution and lifted to a point where it was completely vulnerable to ambient air using a vertically mounted glass slab. The time it took for the patch to completely detach from the glass slab was used to compute the in-vitro residence duration (55).

2. **In-vitro drug release:** Franz diffusion cells or kesharyChien cells were used to examine the buccal patch profile over the dialysis membrane (Cellophane membrane with 0.45 pores). A phosphate buffer (pH 6.8) containing a magnetic bead was placed in the receptor compartment (16 ml capacity). Between the donor and recipient chambers, a dialysis membrane was installed. A magnetic stirrer was used to keep the container's hydrodynamics at 50 rpm. In 1 ml samples obtained at predefined intervals, a UV spectrophotometer with a 6.8 pH phosphate buffer was utilized to identify drug content (56) The following equation was used to obtain the flux value:

$$\text{Flux} = \frac{\text{amount of drug release(mg)}}{\text{Time (hr.)} \times \text{Area( cm}^2\text{)}}$$

3. **Stability study in human saliva:** It is subjected to a stability investigation in human saliva. The collecting of human saliva yields human saliva (age 18-50 years). Five milliliters of human saliva are deposited in separate Petri dishes with buccal patches, and the plates are then heated from 37°C for six hours. At regular intervals, the patches are inspected for colour, shape, and pharmaceutical content (57).

Table 3-Marketed Formulation of Buccal Patches

Brand name	Active drugs	Uses	Manufacturer
Nicoderm CQ	Nicotine	Cessation of Smoking	Pfizer
Anadrol-50	Androgen	Hormonal agent	Thomson Healthcare
Fentora-800mcg	Fentanyl	Reduces pain in cancer patients	SmarCk1936
Breaky-400mcg	Fentanyl	Reduces pain in cancer patients	MEDA
Fentanyl MTX Patch	Fentanyl	Reduces pain in cancer patients	Sandoz

Table 4: Various Patents of Buccal Patches

Sr.No.	Patent Buccal Patches	Description	Applicant	Patent No.
1.	Desmopressin buccal patch composition	Desmopressin and a matrix are combined in a buccal patch that is shaped and sized to attach to the mouth mucosa and release desmopressin into the circulation through transmucosal absorption.	East Riding Laboratories	US5298256A (58)
2.	Transmucosal formulations of levosimendan	Levosimendan or a pharmaceutically acceptable salt thereof may be administered transmucosal, especially to the oral or nasal mucosa, to a patient. Maintaining a source of levosimendan in touch with an	Orion Corporation	WO1999032081A1 (59)

		unbroken mucous membrane for a significant amount of time is necessary to administer levosimendan to a patient, according to this approach. Additionally, levosimendan's transmucosal preparations are detailed.		
3.	Canker sore patch	In a canker sore treatment patch, a mucoadhesive layer and a protective layer, wherein the protective layer has a pressure-sensitive adhesive layer, have been described.	Coloplast AS	US20110160634A1 (60)
4.	Soft, adherent, soluble oral patch	A hydrophilic polymer that is liquid in the mouth at human body temperatures is incorporated into a soft, adherent, soluble oral patch for the administration of topical medicament. This polymer gels at temperatures that are slightly below the temperature of the human mouth. Oral patches have a mesh-like construction that dissolves slowly in saliva but stays solid at human mouth temperatures. The hydrophilic polymer and a desirable medicament are found in the network's pores. By combining and hydrating the materials, heating them to just below boiling point, and then chilling them to form a gel, the oral patch is created.	Halley Jaffrey.T	US20030124178A1 (61)
5.	A water-soluble pharmaceutical film with enhanced stability	An Oral Thin Film capable of transporting an active component for oral administration that is moisture stabilized and does not stick or curl when exposed to 70% RH at 25°C for at least 2 minutes up to 2 hours, and a method for producing the same. A technique for producing Oral Thin Films is also disclosed. The active ingredient may include a pharmacological, nutraceutical, or cosmetic component.	Zim Laboratories Ltd.	WO2015083181A3 (62)

Table 5: List of Molecules in clinical trials (63-69)

Sr.No.	Condition/Disease	Intervention	Phase	Locations
1.	Oral Lichen Planus	Drug: Clobetasol Propionate	II	United States
2.	Oral Lichen Planus	Drug: Licorice Drug: Triamcinolone Acetonide	II	--
3.	Estrogen Receptor-positive Breast Cancer HER2-negative Breast Cancer Oral Complications	Drug: mucoadhesive oral wound rinse	II	Los Angeles, California, United States
4.	Mucositis	Drug: Triamcinolone Acetonide Drug: licorice mucoadhesive films	I II	Omid (or Sayyed-O-Shohada) Hospital Isfahan, Iran
	Wound Healing Pain	Drug: Phenytoin paste Drug: Placebo	I	Shahid Beheshti Medical University Tehran, Iran, the Islamic Republic of
	Oral Mucositis	Drug: Clonidine Lauriad® 50µg Drug: Clonidine Lauriad® 100µg Drug: Placebo Lauriad®	II	1st Century Oncology of Arizona Sun City, Arizona, United States Compassionate Cancer Care Medical Group Corona, California, United States City of Hope Duarte, California, United States

### Applications of Buccal Patches

In today's world, it's common practise to provide medications via the buccal mucosa of the patient. There are several advantages to administering medication through the buccal mucosa rather than another method. The following are some possible uses for buccal patches (57).

- i) vaccines
- ii) controlled and sustained release
- iii) nicotine replacement therapy
- iv) antifungal infections, asthma & antiemetics
- v) management of herpes and cardiovascular diseases
- vi) targeted therapy for oral cancer
- vii) hypoglycemic agents

**Future challenges and opportunities:** Hydrophilic macromolecular drugs are hindered by poor and variable oral absorption, which is a significant issue. Because of advancements in biotechnology and synthetic chemistry, it is now possible to synthesise large quantities of pharmacologically active peptides and proteins. However, these compounds offer medicinal potential if dependable delivery mechanisms can be designed and implemented. The future of pharmaceutical research will be focused on the non-parenteral administration of complete proteins and peptides to the circulatory system and polypeptide cloning and synthesis. Several penetration enhancers may be placed on the mucosal and dermal interfaces of the mouth and skin to improve buccal permeation. Researchers are increasingly studying drug transport pathways other than typical polymer networks. Research is focused on nanoparticle-enabled buccal films or patches and different functionalization strategies to facilitate buccal mucosal penetration and systemic targeting. Block copolymers, complex formation network responsive to hydrocarbons bonds, and biodegradable polymers from food sources are examples of novel materials for sustained release buccal sticky drug delivery. By modifying formulation methods such as pH modifiers, enzyme inhibitors, and permeability enhancers, scientists are now working on creating buccal adhesive systems that might increase the bioavailability of orally less/ineffective drugs. This study is ongoing. The buccal mucosa is studied as a potential route to influence medication absorption. Several issues must be solved before oral administration through the buccal mucosa may be deemed successful and safe. These novel materials' chemical and physical properties must be well understood before new formulations can be developed. Transmucosal medicine delivery devices are predicted to expand at an annual rate of 11% from 2003 to 2007. The bulk of the \$3 billion global market income comes from the United States (55 per cent), Europe (30 per cent), and Japan (10 per cent).

### **Conclusion**

Buccal patches were shown to offer various benefits over more traditional methods of medication administration. In recent years, mucoadhesive buccal patches have acquired prominence in medication delivery and attention in the pharmaceutical industry. Mucoadhesive buccal patches made from natural or synthetic polymers are still the subject of many studies all over the globe. For the systemic distribution of orally ineffective medicines, more study into buccal drug delivery is encouraged. Oral films and buccal patches may be made using a variety of novel processes, including electrospinning, electrospraying, and 3D printing, every of comes with its own set of benefits and drawbacks. These conclusions are based on a study of previous research on mucoadhesive buccal patches and a forecast of what's to come.

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