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# Creation and Assessment of Buccal Mucoadhesive Sustained Release Oral Films

			
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## ABSTRACT

Patient compliance always remains the major concern of inquiry for all researchers working in the field of pharmacy. In the recent era research is carried out extensively to formulate and fabricate a drug delivery system with improved effectiveness, safety, and patient compliance. One of those delivery systems is the mucoadhesive buccal film dosage forms. The mucosal membrane of the oral cavity allows high permeation to certain drugs having high blood perfusion. Drugs with poor bioavailability, drugs with high first-pass metabolism as well as drugs with short half-life can be administered easily by this route. Buccal films can release topical drugs with sustained and controlled effects. Buccal films also have the advantages of improved patient compliance because of their reduced size with suitable thickness as compared to certain another delivery system like buccal tablets and lozenges. The buccal film favors the delivery of drugs having the danger of wastage through the first-pass effect, drugs having low permeability, enzymatic degradation and can be affected by the variable environment of the gastrointestinal tract. The purpose of the present work is to provide a review of various aspects of mucoadhesive buccal films as a suitable drug delivery system.

## INTRODUCTION

Mucoadhesive drug delivery systems are among the novel drug delivery systems that release the drug in a long time in a slow and controlled manner; providing a high plasma concentration level of the drug and improving the drug efficiency<sup>(1)</sup>. When buccal mucoadhesive drug formulations come in contact with the mucosa for a long time, they release the drug into blood circulations directly via the oral mucosa and increase the drug bioavailability by reducing the hepatic first-pass effect and enzymatic degradation in the gastrointestinal tract. Bioadhesion is defined as a state at which two materials, one of which is biological, are held together for a long time through interfacial forces. The adhesion can occur between a biological membrane such as mucosa and a synthetic material like a polymer. In such a case, it is referred to as mucoadhesion. The oral mucosa is preferred because of its availability, robust epithelium, and high permeation. Mucoadhesive polymers contain several hydrophilic groups such as hydroxyl, carboxyl, amide, and sulfate, which adhere to the mucosa via hydrogen bonds as well as electrostatic and hydrophobic forces. In contact with water, these polymers become hydrated and inflated, and their adhesive parts become exposed. The most appropriate region to place a slow-release product in the oral cavity is the upper gum<sup>(2)</sup>.

A drug can be administered in the body through many routes, for instance; oral, parenteral, transdermal, submucosal, etc. The oral route is the most widely accepted route for drug administration among all these routes. Reasons for admiration of oral route are low therapy cost, the comfort of administration and self-medication. Above 70% of the marketed drugs are in the form of oral dosage forms due to pain evasion and adaptability. But around 50% of the population, generally pediatric and elderly patients avoid taking solid oral preparations such as tablets and capsules due to choking hazard, leading to patient's in compliance<sup>(3)</sup>. Purpose of recent advances in novel drug delivery systems is to augment the safety and effectiveness of drugs by formulating a dosage form that is convenient for administration and better in achieving patient compliance. Modification in the oral drug delivery lead to the evolution of dosage form, from ordinary solid dosage forms to altered release tablets/capsules to oral dispersible tablet and finally development of Mucoadhesive films.

Mucoadhesive films are usually consisting of two or three layers and due to their flexibility, they are preferred over adhesive tablets<sup>(4)</sup>. The small thickness of the film with strong mucoadhesiveness of the polymer request only minimal changes in the patients' normal

activities such as eating, drinking or speaking. Also, they can circumvent the relatively short residence time of oral gels on the mucosa and provide a measured dose of a drug to the application site. Moreover, they can also help protect the wound surface or cover mucosal defects of the oral cavity, which leads to pain reduction <sup>(5)</sup>. Flexible patches of various sizes allow their adaptation to the morphology of the oral cavity and size of the defect <sup>(6)</sup>. In this review mucosal lining of the oral cavity, films biopharmaceutical aspects, their characteristics, their ideal properties, formulation aspects, manufacturing techniques, and characteristics are discussed.

### **Overview of the mucosal lining of the oral cavity**

The oral mucosa consists of an outermost layer of stratified squamous epithelium followed by a basement membrane, a lamina propria and finally by the submucosa as the innermost layer. Permeability of the buccal mucosa is expected to be 4–4000 times higher than the skin, which differs in different regions. The order is such that; sublingual > buccal > palatal according to thickness and keratinization of these regions. Across the oral mucosa: paracellular and transcellular routes are the two permeation pathways for passive drug delivery <sup>(7)</sup>. Intercellular spaces and cytoplasm are hydrophilic, so help penetrate hydrophilic drugs while the cell membrane is lipophilic and facilitate the permeation of lipophilic drugs. Also, high blood supply, robustness, short recovery time after stress or damage and virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens. One of the major limitations associated with oral mucosal drug delivery is the low flux leading to low drug bioavailability of certain drugs, so there may always be a need to add permeation enhancer <sup>(8)</sup>.

### **Mechanism of action of mucoadhesive preparations**

The main idea of any mucoadhesive preparation is to adhere or attach the drug to the mucous surface. We can say that the mechanism of action of mucoadhesive preparations is divided into two stages:

The first stage: which is also known as "contact stage", where there is a contact between the mucoadhesive drug and the surface of the mucous membrane. After that contact, the drug "or the formulation" spreads and swells to initiate a deep surface connection with the mucosal layer.

The second stage: which is also known as "consolidation stage", where moisture starts to play its main role a plasticizes this drug-mucosal system (i.e. the mucoadhesive formulation is activated due to moisture). After activation, the mucoadhesive drugs link to a mucous membrane by H-Bonds and by van der Waals forces <sup>(9)</sup>.

### **Main Advantages of Buccal Drug Delivery System**

Direct administration of drug into systemic circulation in less time avoids the first-pass metabolism and exposure to GIT fluids, enhanced bioavailability due to prolonged contact time with the mucosa, better patient acceptance compared to other non-oral routes of drug administration, modification by adding permeability enhancers, protease inhibitors to enhance delivery of high molecular weight compounds like peptides, proteins, and ionized species is easy compared to other forms <sup>(10)</sup>.

### **Main Disadvantages of Buccal Drug Delivery System**

Less surface area mucosal barrier, dilution or loss of the drug due to constant secretion of the saliva <sup>(11)</sup>

### **Characteristics of Buccoadhesive System/important features**

The buccoadhesive system should be safe and non-toxic, has good mechanical strength, immediate adherence to the buccal mucosa with controlled drug release and optimum drug absorption <sup>(11)</sup>.

### **Ideal properties of candidate drugs:**

Different drugs are reported in the previous literature. Drugs showed to have the pleasant taste, low doses, having smaller or moderate molecular weight, good stability in the water as well as in saliva, should partially unionized at the pH of the oral cavity, and should permeate oral mucosal tissues <sup>(12)</sup>.

### **Buccal Film Composition**

#### **Mucoadhesive polymers**

One of the main components of the mucoadhesive formulations is "polymer", which is present with the drug in the formulation. This polymer plays a great role in the formulation as

it helps to sustain the action of the drug and also help to retain it attached to the mucous layer<sup>(13)</sup>. Two types of polymers are found in mucoadhesive: Water-soluble and water-insoluble polymers. The water solubility or the polarity of these polymers is important to provide a suitable amount of fluids and the optimal wetting to the formulation to initiate the connection between the drug and the mucosal surface. On the other hand, we find that polymers (water-insoluble ones) also play an important role in the second stage as they adhere to the mucosal surface through electrostatic interactions<sup>(14)</sup>.

### **Characteristics of Ideal Mucoadhesive Polymer**

The perfect polymer found in mucoadhesive formulations must be safe and non-toxic, it should not be of high cost, it should be compatible with the mucosal surface and non-irritating to it, it should not interact with the drug or hinder its flow, it should possess adhering properties to the mucous membrane and it should have long and durable shelf lifetime. Natural polymers are preferred to synthetic polymers as they are non-toxic and compatible with most drugs, have a lower cost than the synthetic ones, accepted by the patient and available in most countries and they have low side effects and drug interactions than synthetic ones.<sup>(15)</sup> Natural polymers include: Tragacanth, Sodium alginate, Guar gum, Xanthan gum, Soluble starch, Gelatin, Chitosan and Lectins while synthetic polymers include Polyacrylic acid (PAA), Polyvinyl alcohol (PVA), Sodium carboxymethylcellulose (NACMC), Hydroxypropylmethylcellulose (HPMC), Hydroxyethylcellulose (HEC), Hydroxypropyl cellulose (HPC), (MC) methylcellulose, (CP) carbopol, (PLGA) poly (D,L-lactide-co-glycolide), Sodium alginate, glyceryl monooleate (GMO), and chitosan<sup>(16-18)</sup>.

#### **1. Plasticizers:**

They are added to improve flexibility, flow, and strength and reduce the brittleness of mucoadhesive films. Glycerol, Propylene glycol, low molecular weight polyethylene glycols are the most commonly used plasticizers<sup>(19)</sup>.

#### **2. Penetration enhancers**

Substances that are used to enhance the penetration of the active moiety are called penetration enhancers. One of the simple examples of penetration enhancer is the use of water. When the skin gets hydrated it gradually increases the permeability as water causes the opening of the compact structure of the needle base. There are various chemicals that can

enhance the penetration that includes surfactants (such as tweens) fatty acids (such as oleic acid), terpenes (like eucalyptus) and solvents (like ethanol)<sup>(20)</sup>.

### 3. Taste masking and Sweetening agents

To enhance patient compliance it is important to mask the bitter taste of drugs. A compound that gives sweet taste is called as a sweetener. Low molecular weight carbohydrate and in particular sucrose are traditionally the most widely used sweetening agent<sup>(21)</sup>.

### 4. Flavoring agents

The choice of flavors depends on age, taste, and liking of the people. Younger people like fruit punch, raspberry, etc. while the geriatric patient prefer orange, lemon and mint flavor. The selection of flavor is done on the type of drug candidate. Almost 10% w/w flavors are added in oral film preparations. Cooling agents can also be added to enhance the flavor strength<sup>(22)</sup>.

### 5. Coloring agents

When formulation ingredients or drug candidates are present in insoluble or suspension form pigments like titanium dioxide or FD&C approved coloring agents which are incorporated up to 1% w/w<sup>(22)</sup>.

### Examples of Mucoadhesive Sustained Release oral Films

**Table No. 1: List of investigated buccal mucoadhesive films for local action<sup>(23)</sup>**

Drug	Bioadhesive polymers
benzylamine. lidocaine	CP. xanthan gum. tamarind sum
cetylphidinium chloride	PVA. HEC. chitosan
chlorhexidine diacetate	EC
Ciprofloxacin	HPMC. PVA
Clotrimazole	HPC. PC
Flufenamic acid	Chitosan
Ibuprofen	PVP. NaCMC. Eudragit.HPMC. CP
Lidocaine	HPC. HPMC.
Miconazole nitrate	NaCMC. Chitosan. HEC. PVA. HPMC
paracetamol	NaCMC
Ofloxacin. Miconazole.	HPC
Tetracycline HCl	PLGA

**Table No. 2: List of investigated buccal mucoadhesive films for systemic action** <sup>(23)</sup>

Drug	Bioadhesive polymers
Acyclovir	Chitosan.
Carvedilol	HPMC.
Chlorpheniramine maleate	Polyoxyethylene
Diltiazem HCl	NaCMC, PVP. PVA
Famotidine	HPMC. NaCMC. PVA
Glibenclamide	Chitosan
Glipizide	HPMC. Sodium CMC. Eudragit
Losartan potassium	HPMC. EC or Eudragit
Nifedipine	Sodium alginate. MC.
Propranolol HCl	Chitosan v. sodium alginate.
Salbutamol sulphate	HPMC. EC. Eudragit
Terbutaline sulphate	HPMC. chitosan
Testosterone	Eudragit

### Manufacturing techniques

Various methods for producing oral films are classified as follows: (a) solvent casting (b) semi-solid casting. (c) hot melt extrusion (d) solid dispersion extrusion (e) Rolling method.

a) Solvent- Casting Method The oral film is mostly prepared by using the solvent-extraction method, in which water-soluble ingredients are dissolved to form a clear viscous solution. The active pharmaceutical ingredient and other agents are dissolved in a small amount of solution and combine with bulk. This mixture is then added into aqueous solution. Remove entrapped air and the resulting solution is casted as film and then dried which is then cut into pieces of the desired sizes <sup>(24)</sup>.

b) Semi-solid Casting: First of all, a solution of water-soluble film-forming the polymer is prepared in the semi-solid casting method. Then the resulting solution is added to insoluble polymer like cellulose acetate butyrate, cellulose acetate phthalate, etc., prepared in sodium or ammonium hydroxide. Then add an accurate amount of plasticizer to get gel mass. Finally, cast gel mass into films by using heat controlled drums.

c) Hot-Melt Extrusion Hot melt extrusion is a widely employed method to formulate granules, sustained-release tablets; transdermal and transmucosal drug delivery system. Processing film involves shaping a polymer into a film by using the heating process. Filled the hopper with drug carrier mix and is conveyed, mixed and melted by the extruder. Then die shaped melt in the desired film form.

d) Solid-Dispersion Extrusion In this method, drug is firstly dissolved in a suitable liquid solvent and then this solution is incorporated in the melt of PEG below 70°C. The selected solvent or drug could not be miscible with the melt of PEG and polymorphic form of drug precipitated in solid dispersion may be affected by solvent.

e) Rolling method In rolling method, film is formulated by preparation of premix, by adding active and subsequent formation of the film. The pre-mix batch includes film-forming the polymer, polar solvent and other ingredients except API added to the masterbatch feed tank. Then a predetermined amount of the masterbatch is fed by the first metering pump and control valve. The desired amount of drug is added into the mixer and then blended for a sufficient time to form a homogenized matrix. A specific amount of matrix is fed into the pan through the second metering pump. The metering roller determined the thickness of the film. The film is finally formed on a substrate and carried away by the support roller. The wet is dried by using controlled bottom drying <sup>(25)</sup>.

### Quality Control Tests For buccal Films

Various parameters for the characterization of buccal films are done.

- 1. Organoleptic evaluation:** Visual inspection of developed film formulation can provide results of desired organoleptic properties like color, flavor, and taste. Uniformity in color and odor along with good taste brings patient acceptability. <sup>(26)</sup>
- 2. Surface pH:** pH of the film should be near to 7 or neutral to get absorbed through oral mucosa without irritation and toxic effects. Film dissolved in a suitable solvent is used to determine surface pH by using the pH meter. <sup>(26)</sup>
- 3. Swelling studies:** Swelling studies for buccal films can be determined gravimetrically in phosphate buffer, of pH 6.8. Put films to pre-weighed glass supports using a cyanoacrylate adhesive sealant. Immerse supports with films into the phosphate buffer at 37 °C. Remove



the devices at predetermined time intervals, from the media, blot with tissue paper to remove excess water, and weigh. <sup>(27)</sup> After the determination of the wet weight, the films should be dried at 40°C until constant mass. Determine Swelling index (S.I) and erosion gravimetrically according to the following equations.

$$\text{Erosion (\% mass loss)} = \frac{\text{Original weight} - \text{remaining dry weight}}{\text{Original weight}} \times 100$$

$$\text{Swelling index (\%)} = \frac{W_s - W_d}{W_d}$$

Where  $W_d$  and  $W_s$  are the weights of dry and swollen films, respectively.

**4. Folding endurance:** Folding endurance is used to observe the flexibility of the film which is an important physical property of a buccal film.

**5. The thickness of the film:** Measurement of thickness of film either is done by micrometer screw gauge or calibrated digital Vernier Calipers or any other specially designed measurement apparatus. Five different locations i.e four corners and center should be used to determine thickness. <sup>(28)</sup>

**6. Tensile strength of the film:** Maximum stress applied when film specimen breaks are called tensile strength. It is a measure of applied weight at rupture divided by the cross-sectional area of the film.

$$\text{Tensile strength} = \frac{\text{weight at failure} \times 100}{\text{film thickness} \times \text{film width}} \quad (29)$$

**7. Percent elongation:** Stretching capacity of the film after application of stress up to deformation of the film before it gets broken can be expressed in percent elongation capacity. It is calculated by the formula:

$$\% \text{ Elongation} = \frac{\text{Increase in length of film} \times 100}{\text{Initial length of the film}} \quad (29)$$

**8. Tear resistance:** Tear resistance is the measure of maximum resistance offered at a low rate up to 50 mm/min by a film before tearing specimen offers when some load or force is applied on the film specimen. Hard and brittle films show a high tensile strength. <sup>(30)</sup>

**9. Percentage moisture loss:** To determine physical stability and integrity of the film, the percentage moisture loss of films to be determined. Loss in weight of  $2 \times 2 \text{ cm}^2$  film after

keeping the film in simple desiccators containing fused anhydrous calcium chloride for 72 hr. by using:

$$\text{Percent moisture loss} = (\text{Initial weight} - \text{Final weight}) / \text{Initial weight} \times 100 \quad (31)$$

**10. Percentage moisture absorption:** The Buccal films were weighed accurately and placed in the desiccators containing 100 ml of a saturated solution of aluminum chloride up to 86% relative humidity. After 3 days, the films were taken out and weighed <sup>(32)</sup>.

$$\text{Percent moisture absorption} = (\text{Final weight} - \text{Initial weight}) / \text{Initial weight} \times 100$$

**11. Drug content uniformity:** Content uniformity is determined by as per standard assay described for the specific active drug in any of the standard pharmacopeias. It varies in the range of 85-115 %. <sup>(32)</sup>.

**12. In vitro dissolution studies:** Dissolution studies are important to determine the release of the active drug into the dissolution medium per unit time at controlled conditions of liquid/solid interface, concentration and  $37 \pm 0.5^\circ\text{C}$  of temperature and 50 rpm.55.

**13. Permeation studies:** Even though permeability of oral mucosa is 4-1000 times greater than that of skin, permeation studies should be carried out. To study the permeability, modified Franz diffusion cell can be used along with porcine buccal mucosa.

**14. Stability study as per ICH guidelines:** To determine the stability of formulation International Conference on Harmonization (ICH) guidelines are used. Well-packed films should be stored for 3 months at different storage conditions of humidity, temperature and then all possible parameters like drug content, disintegration time, and physical properties should be determined. <sup>(32)</sup>

## CONCLUSION:

It can be concluded that buccal drug delivery is the most promising drug delivery in mucoadhesive system. Buccal adhesive systems offering numerable advantages in terms of accessibility, administration, and withdrawal, retentivity, low enzymatic activity, economy, and high patient compliance. This overview of the mucoadhesive buccal patches might be a 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.

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