

## **A REVIEW ON BUCCAL MUCOSAL ROUTE OF DRUG ADMINISTRATION**

**Monika Bhatt\*, Ganesh Bhatt, Preeti Kothiyal and Swati Chaudhary**

India.

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**\*Corresponding Author**

**Monika Bhatt**

India.

### **ABSTRACT**

Oral route is the most preferred route of drug administration. In oral route buccal mucosal route is one of the advantageous route of drug administration. This route provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism which leads to high bioavailability. The drugs having low bioavailability, shorter half life and those who undergoes extensive first pass metabolism are good candidate for this route. Various formulations have been formulated for this route one of which is buccal

film. Buccal films are prepared by using methods like solvent casting method, hot-melt extrusion method and direct milling method. Buccal films are evaluated for thickness, swelling property, surface pH, drug content, % moisture loss etc.

**KEYWORDS:** first-pass metabolism, bioavailability, solvent casting, systemic circulation.

### **INTRODUCTION**

Among the various routes of drug administration oral route is the most preferred route. But some drugs cannot be delivered effectively through the conventional oral route due to extensive first pass hepatic metabolism which ultimately decreases absorption and ultimately bioavailability of the drug. In addition to this, drugs administered by oral route differs in the rate and extent of absorption due to the various factors which include drug itself, presence of food, drug interactions, and gastrointestinal pH.<sup>[1]</sup> Due to the above demerits of oral route, transmucosal route is the most preferred route of delivering the drug. And also among transmucosal route, buccal mucosa is the most suitable route for administration of drug to local as well as systemic circulation. Buccal route of drug administration provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages includes, excellent accessibility,

low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.<sup>[2]</sup>

#### **Advantage of Buccal drug delivery<sup>[3]</sup>**

- Due to large surface area rapid disintegration and dissolution of drug in oral cavity occurs due to which it promotes the systemic absorption of Active pharmaceutical ingredient.
- No risk of choking.
- The film increases the systemic bioavailability of the drugs, as it bypasses the hepatic first pass metabolism.
- Drug can be protected from degradation by GI enzymes and the acidic environment.
- Rapid onset of action and minimum side effects.
- Self administration is possible.
- Accurate dosing compared to liquid dosage forms.
- Taste masking is possible.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- The formulation can be removed if therapy is required to be discontinued.
- Ease of administration to pediatric, geriatric patients, and also to the patients who are mentally retarded, disabled or non-cooperative.
- Good mouth feel and good stability.

#### **Disadvantage of Buccal drug delivery<sup>[4]</sup>**

- For local action, the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequently increasing the dose.
- Non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
- For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue.

#### **OVERVIEW OF THE ORAL MUCOSA**

The total area of oral cavity is about 100 cm<sup>2</sup>. The outer surface of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria overlying a

submucosa containing blood vessels and nerves. The outermost layer of stratified epithelium which is about 0.5mm thick and is similar to stratified squamous epithelia found in the rest of the body. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 $\mu$ m, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingival measure at about 100-200 $\mu$ m.<sup>[4]</sup>

The mucosa can be divided into three types:

- Masticatory mucosa, found on the gingiva and hard palate.
- Lining mucosa, found on the lips, cheeks, floor of mouth, undersurface of the tongue and the soft palate.
- Specialized mucosa found on the upper surface of the tongue and parts of the lips.



**Structure of Buccal Mucosa**

#### Thickness and surface area of oral cavity membranes<sup>[6]</sup>

Oral cavity membrane	Thickness (mm)	Surface area (cm <sup>2</sup> )
Buccal mucosa	500-600	5.2
Sublingual mucosa	100-200	26.5
Gingival mucosa	200	--
Palatal	250	20.1

#### Permeability

The oral mucosa is leaky epithelia between between the epidermis and intestinal mucosa. Aungst, 1989 estimated that the permeability of the buccal mucosa is 4-4000 times greater than of the skin. As the range of permeability of buccal mucosa is so wide so it indicates that there are considerable differences in the permeability between different regions of the oral

cavity as the structure and function of the oral mucosa is diverse. The permeability of buccal is greater than palatal and less than sublingual. The permeability of the oral mucosa is result of the relative thickness and degree of keratinization of these tissues. The sublingual mucosa is relatively thin and non-keratinized, the buccal mucosa is thicker and non-keratinized, and the palatal mucosa is intermediate in thickness but is keratinized. Gandhi in 1994 estimated that the permeability barrier (exists in the outermost 200µm of the superficial layer) in the oral mucosa is a result of intercellular material derived from the 'membrane coating granules' (MCG). When the cells go through the process of differentiation, MCG starts forming and at the apical cell surfaces they fuse with the plasma membrane and discharge their contents into the intercellular spaces at the upper 1/3<sup>rd</sup> of the epithelium. Passive diffusion acts as primary mechanism for the transport of drugs across the buccal mucosa. however carrier mediated transport is reported to have a small role.<sup>[7]</sup>

### Environment

Intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates surrounds the cells of the oral epithelia. These complexes may be free or maybe attached to certain regions on the cell surfaces. This matrix may help in cell-cell adhesion, may also act as a lubricant thus allowing cells to move relative to one another. The mucus is also believed to help in bioadhesion of mucoadhesive drug delivery systems. The minor salivary gland contributes up to 70% of the total mucin found in saliva. The pH range of saliva is from 5.5 to 7, which depends on the flow rate. When the flow rate is high, the sodium and bicarbonate concentrations increases thus leading to an increase in the pH. 0.5 to 2 liters of saliva is produced daily and it is the amount of fluid that is available to hydrate oral mucosal dosage forms. The water rich environment of the oral cavity is the main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral Transmucosal drug delivery systems.<sup>[8]</sup>

### Role of saliva

Saliva is a complex fluid containing organic and inorganic materials. It is produced by the three pairs of major glands (parotid, submandibular and sublingual) each situated outside the oral cavity and in minor salivary glands situated in the tissues lining most of the oral cavity. The total average volume of saliva produced daily in an adult is around 750 ml. Chemically, saliva is 99.5% water and 0.5% solutes. The solutes include ions (sodium, potassium,

magnesium, phosphate, bicarbonate and chloride), dissolved gases, urea, uric acid, serum albumin, globulin, mucin and enzymes [lysozyme and amylase (ptyalin)].

The various physiological functions of saliva are:

- Oral flora modulation.
- Remineralization of the teeth with calcium phosphate salts.
- Neutralization of acid in the oral cavity and esophagus.
- Lubrication and the cleansing of the oral, pharyngeal and esophageal mucosae.
- Assistance in bolus formation
- Hydration of oral mucosal dosage forms.
- Stimulation of epithelial proliferation.
- Initiation of fat and starch digestion.<sup>[9]</sup>

### **Role of mucus**

Mucus is a thick secretion composed mainly of water, electrolytes and a mixture of several glycoproteins, which themselves are composed of large polysaccharides bound with smaller quantities of protein. It is secreted over many biological membranes of body for example, throughout the gastrointestinal tract walls. Mucus is secreted by special type of epithelia called mucosa. The mucus secreted in buccal cavity admixtures with saliva of salivary glands in oral cavity to produce whole saliva.

The function of mucus are:

- Excellent lubricant.
- Protectant for biological membranes.
- Bioadhesion of mucoadhesive drug delivery systems.
- Cell- cell adhesion.<sup>[10]</sup>

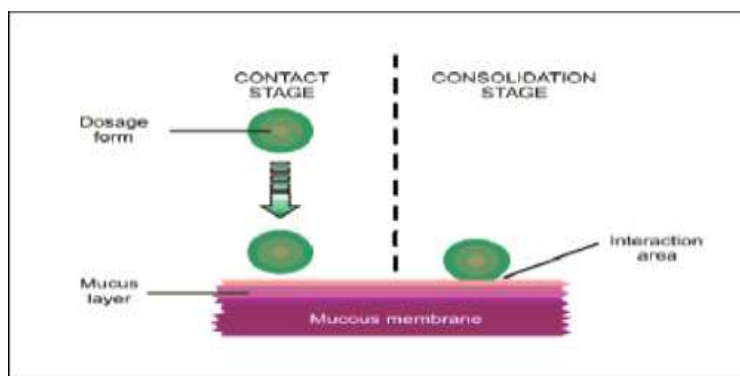
### **Mechanism of Bioadhesion/ mucoadhesion**

Bioadhesion is an interfacial phenomenon in which, two materials, at least one of which is biological, are held together by interfacial forces. The attachment can be between an artificial material and biological substrate, like the adhesion between polymer-copolymer and a biological membrane. Whereas mucoadhesion is a process in which polymer is attached to the mucin layer of mucosal tissue.

The mechanism of mucoadhesion is generally divided in two stages, the contact stage and the consolidation stage.

**Stage 1: Contact stage:** An intimate contact (wetting) occurs between the mucoadhesive and mucus membrane either from a good wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.

**Stage 2: Consolidation stage:** Various physicochemical interactions such as hydrophobic interactions, hydrogen bonding and dispersion forces, occurs to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.<sup>[11]</sup>



### Theories of Bioadhesion or Mucoadhesion

Mucoadhesion is a complex process and various theories have been proposed to explain the mechanisms involved in mucoadhesion. These are as follows:

**1. Wetting theory:** Wetting theory is mainly applied to liquid bioadhesive systems and it analyzes the adhesive and contact affinity in terms of a liquid or a paste to spread over a biological system. Affinity can be found by calculating the contact angle. It is a general rule that lower the contact angle greater will be the affinity. For the adequate spreadability the contact angle must be zero or close to zero.

The spreadability coefficient (SAB) can be calculated by the equation:

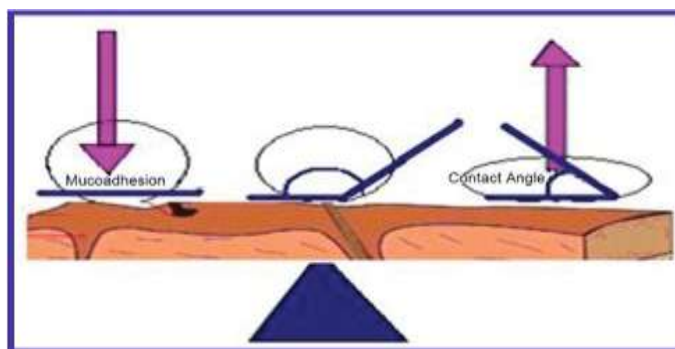
$$SAB = \gamma_B - \gamma_A - \gamma_{AB}$$

Where,  $\gamma_B$  = Surface energy

$\gamma_A$  = Interfacial energy.

If interfacial energy is greater in relating to the individual surface energy, then adhesion work  $W_A$  will be greater, i.e., greater the energy required to separate the two phases.

$$W_A = \gamma_A + \gamma_B - \Gamma_{ab} \quad [12]$$



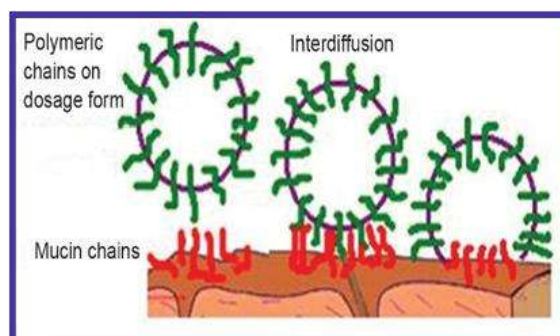
**2. Diffusion Theory:** The interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond is described by diffusion theory. According to this theory, the polymer chains and mucus mixed to a sufficient depth and create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus is dependent on the diffusion coefficient flexibility and nature of the mucoadhesive chains, mobility and contact time. This diffusion coefficient is dependent on the value of molecular weight between cross links. As the cross linking density decreases, the diffusion coefficient also decreases significantly. According to the literature, the depth of interpenetration should lie in the range of 0.2–0.5  $\mu\text{m}$  to produce an efficient bioadhesive bond. This interpenetration depth of polymer and mucin chains can be determined by the following equation:

$$l = (t D_b)^{1/2}$$

Where  $t$  = the contact time

$D_b$  = the diffusion coefficient of the mucoadhesive material in the mucus.

For diffusion to occur, it is important that both the bioadhesive and the mucus components involved must have good mutual solubility, i.e., have similar chemical structures. The greater the structural similarity, the better is the mucoadhesive bond.<sup>[13, 14]</sup>



**3. Electronic Theory:** The electronic theory of adhesion was suggested by Derjaguin and Smigla. According to this theory, because of difference in their electronic structure, electron transfer occurs on contact of adhesive polymer and the mucus glycoprotein network. As a



result of this, the formation of electrical double layer at the interface occurs. Adhesion occurs due to attractive forces across the double layer. This theory describes adhesion occurring by means of electron transfer between mucus and mucoadhesive system arising through differences in their electron structure.<sup>[14]</sup>

**4. Fracture Theory:** According to this theory, the force required to separate both surfaces from one another is related to adhesive bond between systems. This “fracture theory” relates to the force required to detach the polymer from the mucus to the strength of their adhesive bond. Longer the polymer network strands greater will be the work fracture. Or if the degree of cross-linking within such as system is reduced the work fracture will increase. This can be determined by the following equation:

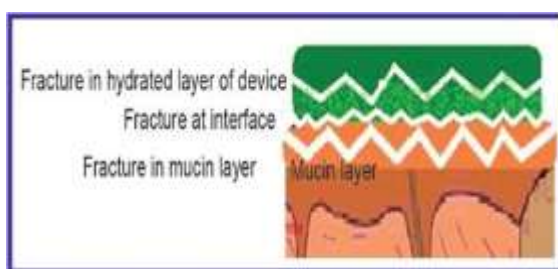
$$r = (E \times e / L)^{1/2}$$

where,  $r$  = fracture strength

$e$  = fracture energy

$E$  = Young's modulus of elasticity

$L$  = the critical crack length<sup>[13]</sup>



**5. Adsorption Theory:** Adsorption theory has been described by Kembell and Hantsherger. According to this theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces. Weak interaction of Vander Wall type plays an important role. However, if adsorption is due to chemical bonding i.e., chemisorption, then ionic, covalent and metallic bonds play an important role at the interface.<sup>[14]</sup>

#### Factors affecting buccal absorption

Oral cavity have many interdependent and independent factors which reduce the absorbable concentration at the site of absorption. Various factors which affects absorption through buccal route are as follows:



**1. Membrane Factors:** Buccal absorption can be affected by, keratinisation degree, surface area of absorption, salivary pellicle's mucus layer, epithelium intercellular lipids, basement membrane and lamina propria. Also, the thickness of absorptive membrane, blood supply/lymph drainage, cell renewal and enzyme content contributes to reducing the rate and amount of drug reaching the systemic circulation.

## 2. Environmental Factors

- a. Saliva:** Buccal mucosa is coated throughout the lining with thin film of saliva and is called salivary pellicle or film. Salivary film is 0.07 to 0.10 mm thick. The thickness, composition and movement of this film affect the rate of buccal absorption.
- b. Salivary glands:** The salivary glands are located in epithelial or deep epithelial region of buccal mucosa. On the surface of buccal mucosa salivary glands constantly secrete mucus. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier for drug penetration.
- c. Movement of buccal tissues:** Less active movements is shown by the buccal region of oral cavity. The mucoadhesive polymers are incorporated in the dosage form to keep it at the buccal region for long periods to withstand tissue movements during talking and even during eating food or swallowing, if possible.<sup>[15]</sup>

## 3. Formulation related factors

- a. Molecular size:** Molecules having smaller size (75 100 Da) generally exhibit rapid transportation across the mucosa. As the molecular size increases the permeability decreases. Absorption enhancers have been used for hydrophilic macromolecules such as peptides, to successfully alter the buccal epithelium permeability, making this route more suitable for delivery of larger molecules.
- b. Partition coefficient:** For determining the absorption potential of a drug partition coefficient is very useful tool. In general, the water solubility of any particular drug can be increased by increasing a drug's polarity by ionization or hydroxyl, carboxyl, or amino groups, and inturn will decrease lipidwater partition coefficient. Viceversa, by decreasing the polarity of a drug by adding methyl or methylene groups, will result in an increased partition coefficient and decreased water solubility.
- c. pH:** pH at the site of drug absorption also affects the partition coefficient. The partition coefficient of acidic drugs decreases with increasing pH, while that of basic drugs increases with increasing pH. In obese individuals large amounts of lipidsoluble drug is

stored in fat stores. These drugs are dissolved in lipid and are a reservoir of slow release from these fat deposits.

- d. pKa:** pKa and pH of drug at the mucosal surface is directly relates to its ionization. The nonionized form of many weak acids and weak bases shows appreciable lipid solubility, and this in turn shows the ability to cross lipoidal membranes. As a result, at the pH where the drug is unionized, maximum absorption is shown to occur. As the ionization of the drug increases, absorption decreases.<sup>[16]</sup>

### Oral mucosal sites

- 1. Sublingual delivery:** In this type of drug delivery, the dug is administered via the sublingual mucosa i.e., the membrane of the ventral surface of the tounge and the floor of the mouth to the systemic circulation.
- 2. Buccal delivery:** In this type of drug delivery, the drug is administered via the buccal mucosa i.e., the lining of the cheek to the systemic circulation.
- 3. Local delivery:** This type of drug delivery is used for the treatment of conditions of the oral cavity like ulcers, fungal conditions and periodontal disease.<sup>[17]</sup>

### Oral Mucosal Dosage Forms

Various oral mucosal dosage forms have been developed at the laboratory scale by many researchers either for local or systemic actions. These are broadly classified into

1. Solid buccal adhesive dosage forms
2. Semi-solid buccal adhesive dosage forms
3. Liquid buccal adhesive dosage forms

**1. Solid buccal adhesive dosage forms:** They are dry formulations which achieve bioadhesion via dehydration of the local mucosal surface.

- a) Fast Dissolving Tablet (FDT):** Fast dissolving drug delivery systems have recently gained popularity and acceptance as new drug delivery system, because it is easy to administer them, thus leading to better patient compliance. Various techniques like direct compression, sublimation, melt granulation, moulding, volatilization and freeze drying can be used to prepare FDTs. Some of the patented technologies for drugs which are poorly water soluble and have a variable bioavailability and bio-inequivalence related to its poor water solubility are zydis, orasolve, durasolv, flash dose, wowtab, flash tab etc. The solubility of low soluble drug was increased by using various methods like solid dispersion technique, by cogranulation with beta – cyclodextrin etc to make a fast

dissolving tablet. Taste masking of the drugs become essential for patient compliance because fast dissolving systems dissolves or disintegrate in patient's mouth, thus making the active constitute to come in contact with the taste buds. Taste masking of such drugs can be done by various methods like addition of sweeteners, or by mass extrusion technique using eudragit E100.<sup>[15]</sup>

- b) **Bilayer mucoadhesive tablets:** These are dry dosage forms and before placing in contact with buccal mucosa they have to be moistened. These are specialized tablet formulations containing two layers. They are designed so that unidirectional drug absorption can be promoted, drug leakage into buccal cavity can be minimized, and biphasic drug release can be achieved. Iga and Ogawa formulated a sustained released slowly disintegrating gingival tablet of isosorbide dinitrate and nitroglycerin. Lactose and hydroxypropyl cellulose were used to prepare flat-faced tablets 8 mm in diameter. The tablets were covered with a bioadhesive containing polyethylene film with a 5 mm hole in the center of the top surface in order to control the deformation of the tablet which can be caused by softening and mouth movements. When these tablets were evaluated in dogs, they remained in position for about 10 hours, as compared to plain tablets which disintegrated within 3–6 hours. For about 10 hours constant blood drug levels were maintained from the covered tablets. The rate of tablet disintegration, which in turn affects the buccal residence and the drug blood levels, can be controlled by changing the hole size.<sup>[18]</sup>
- c) **Bioadhesive hydrogel tablets:** Bioadhesive tablets consisting of hydrogels can adhere to the buccal mucosa. These are similar to conventional tablets and are prepared by the process of wet granulation, dry granulation, or direct compression. Upon the hydration and adhesion of the device the drug is released from the tablet. To ensure a prolonged period of bioadhesion and sustained or controlled release the buccal tablets should be fabricated and optimized for swelling behavior and drug release. Generally, flat punches with dimensions less than 10 mm in diameter and 2 mm thick are used to formulate the tablets, to establish intimate contact with buccal mucosa and reduce their interference with normal activities. Most of the tablets contain water-soluble excipients such as high-molecular-weight polyethylene glycols and mannitol, in addition to mucoadhesive components. A single-layer buccal tablet of triamcinolone acetonide, Aftach®, is used in the treatment of aphthous ulcers.<sup>[18]</sup>
- d) **Bioadhesive Wafers:** In this delivery system, the surface layers possess adhesive properties, and the bulk layer contains antimicrobial agents, biodegradable polymers and

matrix polymers. Bioadhesive wafers are used as periodontal drug delivery system used for the treatment of microbial infections associated with periodontitis.<sup>[19]</sup>

- e) **Bioadhesive Lozenges:** A slow release bioadhesive lozenge offers prolonged drug release with improved patient compliance. Bioadhesive lozenges can be used for the delivery of drugs like antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals, that acts within the mouth. A bioadhesive lozenge has been reported as a means to deliver antifungal agents to the oral cavity. The bioadhesive lozenges has some limitations like, the short residence time at the site of absorption and depends to the size and type of formulation. Since the lozenges dissolves within 30min, the total amount of the drug that can be delivered to the circulation is limited. The dissolution or disintegration of lozenges is usually controlled by the patient and depends on how hard they suck the unit. Uncontrolled swallowing and loss of drug down the GI tract can be caused by increasing sucking and saliva production. Thus, such dosage form generally have a much higher inter-individual and intra-individual variations in absorption and thus bioavailability. Unidirectional release of drugs cannot be achieved by these types of system. Another major hurdle to the performance of such dosage forms is continuous secretion of saliva.<sup>[19]</sup>

## 2. Semi-solid dosage forms

- a) **Medicated chewing gums:** Chewing gum is one of the most advanced approach for oral transmucosal drug delivery and is a useful for systemic delivery of the drug. Chewing gum has an advantage of controlled release of drug over an extended period of time over other oral mucosal drug delivery systems and also have the potential to improve the variation in drug release and retention times. Another advantage of chewing gum is convenience. Also, the drug intake can be controlled by individuals by simply changing the rate and vigor of chewing, or expelling the gum altogether. Since chewing gum is also an open system, it also possess same limitations as that of solid formulations. Although there is difficulty in regulation of the administered dose in case of medicated chewing gums, they still have advantages as drug delivery devices can be used particularly in the treatment of diseases associated with oral cavity and in nicotine replacement therapy.<sup>[20]</sup> Currently medicated chewing gums are available for relieving pain, smoking cessation, travel illness and freshening of breath. For the formulation of chewing gum a hydrophobic gum was used. A new chewing gum device in the form of a three layer tablet has also been developed.<sup>[15]</sup>

Some commercial medicated chewing gums are available in the market. Caffeine chewing gum, Stay Alert®, was developed recently for alleviation of sleepiness. It is absorbed at a significantly faster rate and its bioavailability was high as compared to the capsule formulation. Nicotine chewing gums (e.g., Nicorette® and Nicotinell®) have been marketed for smoking cessation.<sup>[19]</sup>

**b) Mucoadhesive Gels:** Mucoadhesive gel are the semisolid form of drug dosage form used for providing easy dispersion of drug through the mucosa. Bioadhesive polymers used for formulating gels include cross-linked polyacrylic acid, used to adhere to the mucosal surfaces for extended periods of time and helps to provide controlled release of drug at the site of absorption. These mucoadhesive gels facilitate the rapid release of drug molecules at the site of absorption by forming an intimate contact with the oral mucosal membrane. Majorly mucoadhesive gels are used in the treatment of oral conditions like, periodontitis, recurrent aphthous stomatitis, traumatic ulcers, oral mucositis, chronic immunologically mediated oral lesions and salivary hypofunction. The gel formulations have limitation that it is unable to deliver a measured dose of drug to the site of action and thus cannot be used for drugs having narrow therapeutic window.<sup>[19, 21]</sup>

**c) Mucoadhesive patches:** Flexible adhesive patches have been developed so that some of the drawbacks of other dosage forms can be overcome. Transmucosal delivery patches have unique characteristics. It shows rapid onset of drug delivery relatively, sustained release of drug and rapid decline in the serum drug concentration when the patch is removed. Also, a buccal patch is used in the buccal area, where it is attached and therefore there is less inter- and intra-individual variability in the drug absorption.<sup>[20]</sup>

Different patch systems are designed, that adhere to the oral mucosa to deliver drugs. The patches have longer acting action as compared to solid forms such as tablets and lozenges and shows sustained drug release for treating oral candidiasis and mucositis. The patches dissolves slowly and completely during. But significant amounts of drug is lost in the oral cavity. Therefore, these are better used for delivering the drugs into oral cavity as compared to the oral mucosa to which they are applied.<sup>[11]</sup>

**d) Fast dissolving films:** This is one of the recent development in novel drug delivery system which is developed to enhance the safety and efficacy of drug molecule. This film is a very thin oral strip which when taken in the oral cavity releases the active ingredient immediately. This preparation has both advantage of tablet as well as liquid dosage form. Advantage of tablet like precise dosage, easy application and of liquid dosage like easy swallowing and rapid bioavailability. The delivery system is placed on the patient's oral mucosal tissue.

When instantly wet by saliva the hydration of the film occurs rapidly and the medication is released from the film for oromucosal absorption.<sup>[15]</sup>

**e) Mucoadhesive films:** Mucoadhesive films mainly consists of a polymeric drug-loaded layer which is acts as an impermeable backing layer. This backing layer promotes unidirectional release of the drug. Thin strips of these adhesive films can load up to 20 mg of drug that can be rapidly delivered to treat certain oral conditions. There are some advantage of this film like long term treatment, rapid drug delivery, patient comfort.<sup>[21]</sup>

### 3. Liquid Dosage Form

**a) Mucoadhesive sprays and oral rinses:** Mucoadhesive sprays and oral rinses are adhesive liquid forms. When these dosage form are applied, they forms a thin coat over the entire oral mucosa. They increase the total surface area through which the drug molecules can be absorbed rapidly. These are prepared for the treatment of some oral diseases, such as oral lichen planus, recurrent aphthous stomatitis, oral mucositis, hyposalivation, leukoplakia and erythroplakia. These have advantage like good mucoadhesion and viscoelasticity and increased patient compliance. Disadvantage of these includes drug dosage may not be accurate and unintended administration through the gastrointestinal tract can occur by swallowing.<sup>[19]</sup>

**b) Mouthwashes:** Mouthwashes are solutions or suspensions of drugs dissolved in a suitable aqueous vehicles. These types of dosage forms are employed to show local action in the oral cavity and to show antibacterial activity. Some limitation of these liquid dosage forms are that they are not completely retained or targeted in the buccal mucosa and the drug delivery from these dosage form cannot be controlled throughout the oral cavity.<sup>[19]</sup>

### Formulation Aspects of Buccal Films

The basic components of buccal bioadhesive drug delivery system are:

1. Active Pharmaceutical Ingredient
2. Mucoadhesive polymers
3. Plasticizers
4. Penetration enhancers
5. Sweetening agents
6. Saliva stimulating agent
7. Flavoring agents
8. Coloring agents

## 1. Active Pharmaceutical Ingredient

The buccal film can be formulated from any active ingredient which is absorbed orally or through buccal mucosa. API incorporated in the buccal film preparation must be from 5%-25% w/w of total weight of the polymer according to literature. For effective formulation, dose of the drug must be less than 30 mg/day. In case of water soluble APIs, they are added in dissolved state or in the solid solution form in the buccal film. While, the water insoluble drugs are uniformly dispersed in the film. APIs can also be added in the formulation as milled, micronized or in the form of nanocrystals or particles depending upon the release profile.

Mostly the APIs, that are good candidates for buccal film technology are bitter in taste. Thus, the formulation becomes unpalatable especially in case of pediatric preparations. Thus before incorporating the API in the buccal film, we need to mask the unpalatable taste. Various techniques can be used to improve the palatability of the formulation like, mixing and co-processing of bitter tasting API with excipients with good taste. Barrier technologies can also be used to mask the bitter taste such as complexation, polymeric coating, conversion into microparticles/microcapsules, coated particles or coated granules.

Mostly researchers shows interest in developing buccal films for drugs like: Pediatrics (antitussive, expectorants, antiasthmatics), Geriatrics (antiepileptic, expectorants), Gastrointestinal diseases, Nausea (e.g. due to cytostatic therapy), Pain (e.g. migraine), CNS (e.g. antiparkinsonism therapy).<sup>[22, 23]</sup>

The ideal characteristics of a good candidate for buccal film are as follows-

- It should have pleasant taste.
- Dose of the drug should be low generally less than 30 mg.
- Molecular weight should be smaller and moderate.
- It should be stable and soluble in water as well as in saliva
- At the pH of oral cavity, it should be partially unionized.
- It should have the ability to permeate oral mucosal tissue.
- It should have biological half-life between 2-8 hours.
- T<sub>max</sub> of the drug shows wider.<sup>[24]</sup>

**2. Mucoadhesive polymers:** Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular location/ site. Polymers have played an



important role in designing such systems so as to increase the residence time of the active agent at the desired location. Mucoadhesive polymers are water-soluble and water insoluble polymers. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non-covalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface.

All three polymer types can be used for drug delivery.

### Characteristics of an ideal mucoadhesive Polymer

An ideal mucoadhesive polymer has the following characteristic:

- They should be nontoxic and should be non-absorbable from the gastrointestinal tract.
- It should be nonirritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site-specificity.
- It should allow daily incorporation to the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of polymer should not be high so that the prepared dosage form remains competitive.<sup>[25]</sup>

**3. Plasticizers:** Plasticizers are used in the concentration of 0–20%w/w of dry polymer weight. Plasticizer is an important ingredient of the film formulation as it is helpful in improving the flexibility of the film and reducing the brittleness of the film. Plasticizer reduces the glass transition temperature of the polymer thus significantly improving the film properties. Plasticizers decreases the glass transition temperature of polymer in the range of 40–600 °C for non aqueous solvent system and below 75 °C for aqueous systems. With the use of plasticizer the flow of polymer will be improved and also the strength of the polymer will be enhanced. Plasticizer if not used appropriately may lead to cracking of film, splitting and peeling of the film. Use of certain plasticizers also affects the absorption rate of the drug. The selection of plasticizer depends upon its compatibility with the polymer and the type of solvent used in the casting of film. Plasticizer used in the buccal film formulations should be

compatible with drug as well as other excipients used. Some of the mostly used plastisizers are: Glycerol, Propylene glycol, Low molecular weight polyethylene glycols, Phthalate derivatives like dimethyl, diethyl, dibutyl derivatives, Citrate derivatives like triacetin acetyl citrate, etc.<sup>[26]</sup>

**4. Penetration enhancers:** Permeation enhancers are the substance that facilitates the permeation of drug through the buccal mucosa. These are also one of the important ingredient used in buccal film formulation. One of the major disadvantages of buccal drug delivery is that across the mucosal epithelium drugs shows low flux, that results in low drug bioavailability. Therefore, various compounds have been used as buccal penetration and absorption enhancers so that the flux of drugs through the mucosa can be increased. Penetration enhancers are required for a drug to reach the systemic circulation to exert its action. These must have a reversible effect i.e., after the drug has been absorbed the epithelium should be able to recover its barrier properties and should be non-irritant. The most commonly used classes of buccal penetration enhancers are fatty acids that act by disrupting intercellular lipid packing, surfactants, bile salts, and alcohols.<sup>[12, 23]</sup>

**5. Sweetening agents:** Sweetening agents are mostly used excipient in buccal film preparation. These are used in the concentration range of 3-6% w/w of polymer. Sweeteners are important excipient used in the food products as well as pharmaceutical products and are intended to be disintegrated or dissolved in the oral cavity. Especially in case of pediatric population, the sweet taste in formulation is required. In case of buccal formulation natural as well as artificial sweeteners are used to improve the unpalatable taste of the drug. The classical source of sweetener is sucrose, dextrose, fructose, glucose, liquid glucose and maltose. In case of diabetic patients, the use of natural sugars in such preparations must be restricted. Artificial sweeteners includes: Saccharin, cyclamate and Aspartame, acesulfame-K, sucralose, alitame and neotame.<sup>[23, 27]</sup>

**6. Saliva stimulating agent:** Saliva stimulating agents are used to increase production rate of saliva which in turn helps in fast disintegration of the film. So saliva stimulating agents are used in the formulations. These agents are used in the concentration range of 2 to 6% w/w of weight of the film. Mostly used saliva stimulating agents are citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid.<sup>[24]</sup>

**7. Flavoring agents:** The flavoring agents are very important in case of oral dissolving systems. Up to 10% w/w flavors are added in the buccal film formulations. The flavoring agent used in the formulation depends upon the type of drug to be incorporated in the formulation. For example, in products used for gastric related ailments like indigestion mint flavor is generally added. The choice of flavors changes from individual to individual. It was observed that age plays an important role in the taste liking. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. The oral disintegrating formulation by a patient is accepted depending on the initial flavor quality, which can be observed in first few seconds after consumption of the product and the after taste of the formulation which lasts for at least about 10 min. Flavoring agents are selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers.<sup>[27]</sup>

**8. Coloring Agent:** In buccal film pigments such as titanium dioxide or FD&C approved coloring agents are used. These must be in the concentration not exceeding 1% w/w.<sup>[26]</sup>

#### **Methods of preparation of buccal patches/ films**

**1. Solvent casting:** In this method, water soluble polymers are dissolved to form a homogenous solution. Active pharmaceutical ingredients and other ingredients are dissolved in aqueous solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry. It has advantages like better physical properties and more flexible, excellent uniformity of thickness, easy and low cost processing.

**2. Direct milling:** In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

**3. Hot melt extrusion of films:** In hot melt extrusion blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogeneous material in different

shapes such as granules, tablets, or films. Hot melt extrusion has been used for the manufacture of controlled release matrix tablets, pellets and granules, as well as oral disintegrating films.<sup>[14, 28]</sup>

### Evaluation of Buccal Films

**1. Physical appearance and surface texture:** It is done by visual inspection and evaluation of texture by feeling or touching.<sup>[2]</sup>

**2. Thickness:** Screw gauge or calibrated digital vernier calipers can be used to measure the thickness of the film. The thickness of each film was measured at five different locations i.e., centre and four corners. Thickness is represented as a mean  $\pm$  S.D. of five replicate determinations.<sup>[24]</sup>

**3. Tensile strength:** The tensile strength (psi) is the property of the film that requires a load to cause load deformation failure of film. The maximum stress applied to a point of the strip specimen to breaks is called the tensile strength. It is calculated as: the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below :

$$\text{Tensile strength} = \frac{\text{Load at breakage}}{\text{Strip thickness} \times \text{Strip width}} \quad [24]$$

**4. Swelling study:** The original weight and diameter of the patch was calculated. Then the samples were kept on the surface of agar plate and allowed to swell and stored in an incubator maintained at 37 °C. Increase in the weight and diameter of the patches were determined at the preset time intervals (1–5 h). The percent swelling, %S, was calculated using the following equation:

$$\%S = (X_t - X_o / X_o) \times 100$$

Where,  $X_t$  = the weight or diameter of the swollen patch after time  $t$ ,

$X_o$  = the original patch weight or diameter at zero time. <sup>[23]</sup>

**5. Surface pH:** For determining the surface pH agar plate is used. In this method, the film is placed on the surface of 1.5% w/v agar gel. Then pH paper (pH range 1-11) is placed on the films. The change in the color of pH paper is observed and reported.<sup>[29]</sup>

**6. Folding endurance:** The film of 1 cm<sup>2</sup> is taken. folding endurance is determined by folding the film repeatedly at the same place till it break. The film should fold more than 200 times without breaking. The experiments are performed in 3 films, and average values are taken.<sup>[16]</sup>

**7. Drug content:** Drug content is determined by dissolving each film of dimension 1 cm<sup>2</sup> in 10 ml solvent. The solution is filtered with Whatman filter paper (0.45 µm). The filtrate is evaporated and drug residue is dissolved in 100 ml phosphate buffer of pH 6.8. 5 ml of the above solution is diluted with phosphate buffer (pH 6.8) up to 20 ml and filtered through a 0.45-µm Whatman filter paper. The absorbance is measured using a UV Spectrophotometer at an appropriate wavelength using pH 6.8 phosphate buffer as blank. The experiments are performed in triplicate, and average values are taken.<sup>[16]</sup>

**8. Percentage moisture loss:** This test is carried out to check the integrity of films at dry condition. A film of 1 cm<sup>2</sup> diameter is cut out, and accurately weighed. It is then kept in desiccators containing fused anhydrous calcium chloride. After 72 hours, the films are removed and again weighed. The same procedure is repeated for atleast 3 films. Average percentage moisture loss of three films is taken. Percentage moisture loss can be calculated by the following formula:

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad [16]$$

**9. Water absorption capacity test:** Agar plates are prepared in simulated saliva (2.38 g Na<sub>2</sub>HPO<sub>4</sub>, 0.19 gKH<sub>2</sub>PO<sub>4</sub>, and 8 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.7). Circular Patches, of surface area 2.3 cm<sup>2</sup> are allowed to swell on the surface of the prepared patch and kept in an incubator that was maintained at 37°C ± 0.5°C., Samples are weighed (wet weight) at various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours) and then left for drying for 7 days in a desiccators over anhydrous calcium chloride at room temperature. Then the final constant weights are recorded. Water uptake (%) is calculated using the following equation:

$$\text{Percentage Water uptake} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad [30]$$

**10. In-vitro release study:** In-vitro release study can be done using Franz diffusion cell. The dissolution medium consists of phosphate buffer of pH 6.8 maintained in a temperature at 37°C ± 0.5°C. The parchment paper was soaked in phosphate buffer pH 6.8 for 1h and then air-dried and then mounted between the donor and receptor compartment. The film is then placed on it. Both the compartments were clamped together. The phosphate buffer pH 6.8 was filled in the receptor compartment and stirred using magnetic stirrer. Samples were

withdrawn at different time intervals and replaced with an equal volume of buffer. The samples were analyzed in UV spectrometer at appropriate wavelength. [30]

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