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## **An Exhaustive Review on Recent Advancement in Pharmaceutical Bioadhesive Used for Systemic Drug Delivery Through Oral Mucosa for Achieving Maximum Pharmacological Response and Effect**

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**Abstract:** As compared to both injectable and oral delivery, the buccal delivery is preferred to and advantageous for enhancement of bioavailability of drug. The mucosal surfaces are usually rich in blood supply and provide the means for rapid drug transport to the systemic circulation avoiding drug degradation in harsh gastric environment and first-pass hepatic metabolism. Besides, it can prolong absorption and residence time due to prolonged contact with absorption surface and with the site of application allowing once or twice daily dosing. A rapid onset of action with comfort and convenience in delivery of certain drugs has been observed. Many drugs have been tried with buccal route, a few are also available commercially. Clinical need should be significant and must be high enough to counterbalance the high cost associated with development of a buccal product. Buccal drug delivery assures four times the absorption rate from the skin. The review aims the development in the buccal adhesive drug delivery systems to provide basic principles to the young researchers which will be helpful in overcoming the difficulties associated with the formulation design.

**Key words:** Buccal drug delivery, mucoadhesive polymer, mucoadhesion, bioadhesion, buccal mucosa, buccal absorption

### **INTRODUCTION**

There are various route of drug administration and each route has its own limitations. (Hoogstraate and Wertz, 1998). Oral route for delivery of drug, although more convenient, causes major problems like hepatic first pass metabolism (Patel *et al.*, 2011a; Abdollahi *et al.*, 2003) degradation of drug in harsh gastrointestinal environment (Kulkarni and Desai, 2010) and poor bioavailability (Dharami and Shayeda, 2010; Jafar and Ali, 2011). This route shows inadequate and erratic absorption (Sudhakar *et al.*, 2006). Parenteral route for drug administration avoids this problem but it has also some drawback like pain at the site of administration, anaphylaxis and extravasation infection (Scholz *et al.*, 2008; Qureshi *et al.*, 2006), so oral cavity is selected for administration of macromolecules such as oligopeptides (Veuillez *et al.*, 2001), unstable proteins and polysaccharides (Gandhi *et al.*, 2011). Administration through oral cavity can be used as an attractive and alternative site for drug delivery which can facilitate particularly in overcoming deficiencies associated with frequent dosing (Wong *et al.*, 1999).

The oral mucosa is comparatively permeable and enriched with blood supply (Shojaei, 1998), it is

highly vascularized (Rossi *et al.*, 2005), vigorous and demonstrate short recovery time after stress or damage (Yamamoto *et al.*, 2001). For drug absorption the total surface area of membrane of oral cavity available is 100-170 cm<sup>2</sup> (Tayal and Jain, 2011; Miller *et al.*, 2005) of which 50 cm<sup>2</sup> represent buccal cavity consisting of liner mucosa (Lee *et al.*, 2000). The thickness of buccal epithelium is approximately 500-800 µm (Harris and Robinson, 1992).

Local therapy is used to treat condition such as gingivitis, oral candidiasis (infection by fungus *Candida albicans*), oral lesions (breaking of mucous membrane due to disease), dental carries (decaying of teeth), xerostomia (dryness of mouth due to lack of saliva), oral cancer, mucositis and neuropathic pain (Galati *et al.*, 2000; Smart, 2004; Pourhashemi *et al.*, 2007; Taliyan and Sharma, 2010).

For transmucosal drug delivery buccal and sublingual or floor of mouth (Hoogstraate *et al.*, 1996; Kowsalya *et al.*, 2011), areas are most commonly used route. Sublingual mucosa is more permeable, thinner with high blood flow than buccal mucosa. Due to its smooth and relatively immobile surface, the buccal mucosa offer sustained and controlled delivery of drug (Madhav *et al.*, 2009) and less permeability (Shakya *et al.*, 2011).

Flexible, elastic and soft patches are used for buccal delivery (Patel *et al.*, 2001; Patel and Poddar, 2009) for modified release dosage form (Parmar *et al.*, 2010). Compared to tablet buccal patches are of small size and with adequate thickness to provide better patient compliance (Morales and McConville, 2011).

#### **ADVANTAGES OF BUCCAL DRUG DELIVERY**

- As it bypasses the GIT and hepatic portal system, it protects the drug from degradation due to pH and various enzymes present in GIT. The bioavailability of orally administered drug is increased (Vinod *et al.*, 2010)
- Patient compliance is improved due to the elimination of associated pain with injections. Drugs can be administered to mentally ill, disabled and uncooperative, or unconscious or incapacitated patients conveniently (Miller *et al.*, 2005)
- Allows localization of the drug for a prolonged period of time as required for sustained and controlled drug delivery (Grabowski *et al.*, 1992; Trivedi *et al.*, 2011)
- Dose dependent side effects are reduced due to dose reduction
- Unlike other surfaces for transdermal drug delivery, mucosal surfaces exhibit a faster initiation and decline of delivery than other transdermal patches as it does not have stratum corneum, a major barrier layer for drug transport (Gupta *et al.*, 2011; Varshosaz *et al.*, 2006)
- Flexibility in physical state, shape, size and surface
- Low metabolic activity (Gangwar, 2011)
- Very rare incidents of nausea and vomiting have been reported (Mohammadi and Seyedi, 2008)
- Drugs with poor bioavailability and the drugs which are unstable at different pH can be administered conveniently by this route (Amarji *et al.*, 2007; Giri *et al.*, 2010a)
- Though, less permeable than the sublingual area, drugs can be rapidly absorbed into the venous system below the oral mucosa because it is well vascularized. Unlike rectal and transdermal route the drug dissolution is relatively large due to the presence of saliva (Patel *et al.*, 2011b)
- Due to over hydration, the structural integrity of the formulation may get disrupted leading to slippery surface and hydration of bioadhesive polymer (Jain, 2002; Shanker *et al.*, 2009)
- The area of absorptive membrane is relatively lesser. If the effective area for absorption is dictated by the dimensions of a delivery system, this area then becomes even smaller (Alur *et al.*, 2002)
- Drugs with large dose are difficult to be administered (Khairnar and Sayyad, 2010)
- Only those drugs which are absorbed by passive diffusion can be administered by this route
- Frequent dosing may be required for drugs intended for local action but may face rapid elimination due to the flushing action of saliva or the ingestion of food stuffs (Yousefzadeh *et al.*, 2006; Wani *et al.*, 2007)
- Low permeability of the buccal membrane, specifically when compared to the sublingual membrane (Peppas and Buri, 1985)

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

**Anatomy of oral mucosa:** The oral cavity comprises the lip, cheek, tongue, hard palate, soft palate and floor of mouth as shown in Fig. 1. The oral mucosa is divided into three distinctive layers which are outer epithelium, middle basement and inner connective tissues as shown in Fig. 2.

There are two parts of oral cavity; the space between teeth and cheeks or lips is outer oral vestibule while the space between teeth and pharynx is interior oral vestibule (Tortora, 2002). The outer layer of buccal mucosa is composed of approximately 40-50 layers of stratified squamous epithelial cells while the sublingual epithelium contains fewer layers (Gandhi and Robinson, 1988). This layer serves as protective covering for the tissue and acts as a barrier to the entry of foreign material (Ghosh and Pfister, 2005), like antigens, carcinogens, microbial toxins and enzymes from food and beverages. The middle layer, a basement membrane, is a continuous layer of extracellular material and forms a boundary between the basal layer of epithelium and connective tissue (Senthil *et al.*, 2007; Shojaei, 1998; Basu *et al.*, 2010). The epithelium in masticatory mucosa is keratinized and lining mucosa is non-keratinized. The lining mucosa contributes approximately 60%, the masticatory mucosa contributes 25% and the specialized mucosa occupies approximately 15% of the total surface area of oral mucosa lining in an adult human. As compared to masticatory mucosa, the lamina propria of

#### **LIMITATION OF BUCCAL DELIVERY**

- Drugs which are unstable at buccal pH (5.5-7) cannot be administered (Vyas and Khar, 2008)
- Restriction in eating and drinking may be required (Lalla and Gurnancy, 2002)

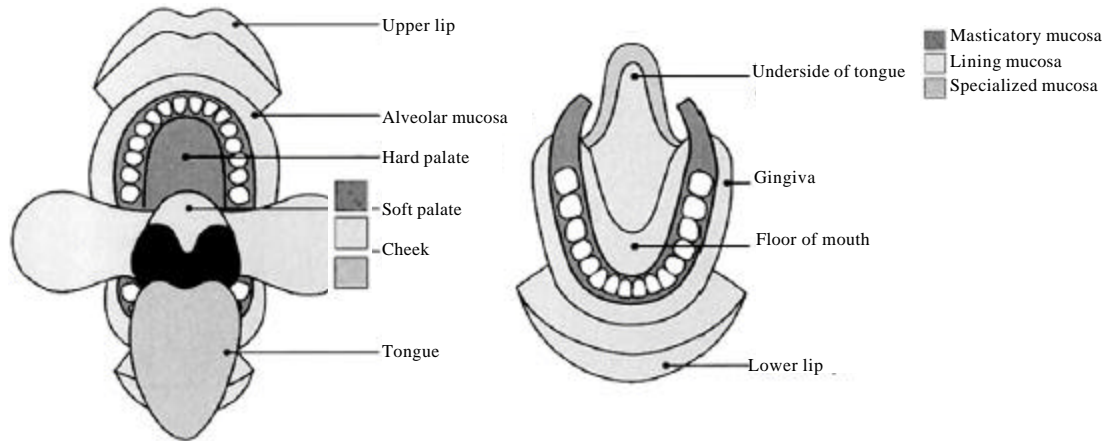


Fig. 1: Schematic representation of the different linings of mucosa in mouth (Patel *et al.*, 2011a)

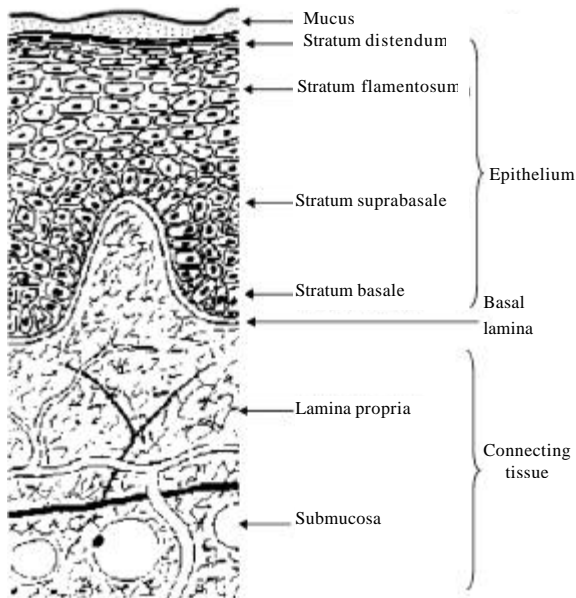


Fig. 2: Cross-section of buccal mucosa (Sudhakar *et al.*, 2006)

lining mucosa is lesser in thickness and elasticity. The specialized mucosa possesses well papillated surface both keratinized and non-keratinized (Collins and Dawes, 1987; Ahmed *et al.*, 2011).

**Biochemistry of oral mucosa:** The keratinized cell of epidermis of skin and masticatory mucosa of oral cavity is a barrier for drug permeability. In general, keratinized and non-keratinized epithelium of oral cavity occupies about 50% and 30%, respectively (Collins and Dawes, 1987). The composition and state of keratinization of oral mucosa is shown in Table 1.

### Secretion of oral cavity

**Saliva:** The physiological environment of the oral cavity in terms of pH, fluid volume and composition, depends on the secretion of saliva (Herrera *et al.*, 1988; Pajoumand *et al.*, 2003). There is a salivary coating over mucosal surface having thickness of about 70  $\mu\text{m}$ . This acts like a stagnant layer. Three major salivary glands- parotid, submandibular and sublingual and minor salivary or buccal glands situated in or immediately beneath the mucosa secrete the saliva (Slomiany *et al.*, 1996; Abdollahi *et al.*, 2003). The paired parotid glands, the major salivary glands, are located opposite to the maxillary first molars and the submandibular and sublingual glands as shown in Fig. 3 are located in the floor of the mouth. Minor salivary or buccal glands are found in the lower lip, tongue, palate, cheeks and pharynx (Humphrey and Russell, 2001). Watery secretion is produced by the parotid and submaxillary glands while the main viscous saliva with limited enzymatic activity is secreted by sublingual glands (Slomiany *et al.*, 1996; Herrera *et al.*, 1988). Except for the gums and the anterior part of the hard palate these glands are placed at every region of the mouth (Llena-Puy, 2006; Giradkar *et al.*, 2010).

There are several compounds in the saliva that control the mouth hemiparasites. The major constituent, about 99% is water with 1% organic and inorganic materials. The composition of the saliva depends mostly on the flow rate along with three other factors: the time of day, the type of stimulus and the degree of stimulation. Its pH varies from 5.5-7 depending on the flow rate. The concentrations of sodium and bicarbonate increase when flow of saliva increases resulting to an increase in the pH. Saliva imparts major effect on many activities like mastication, speech and tissue lubrication

Table 1: The composition and state of keratinisation of oral mucosa

State of keratinization	Tissue	Composition	Characteristic features	References
Non-keratinized	Buccal mucosa	It do not contain acylceramide with small amount of ceramide including Small amount of neutral but polar lipid. cholesterol sulphate and glucosyl ceramide are also present	These epithelia are more permeable to water	Squier <i>et al.</i> (1991) Squier and Wertz (1996)
	Sublingual mucosa			
Keratinized	Palatal mucosa	Neutral lipid like acylceramide Ceramide	These epithelia are relatively impermeable to water	Wertz and Squier (1991)
	Gingival mucosa			

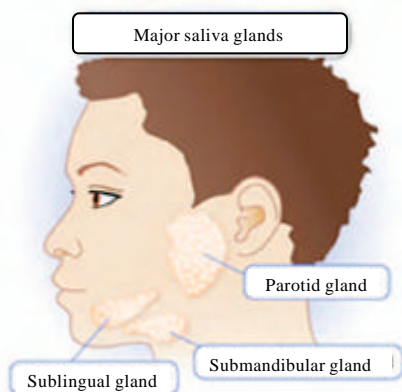


Fig. 3: Major salivary gland (Patricia *et al.*, 2008)

(Tabak *et al.*, 1982; Malekipour *et al.*, 2008; Rohaya *et al.*, 2010). Saliva contains a high molecular weight mucin called MG1 that attaches to the surface of the oral mucosa and maintains hydration, provides lubrication and concentrates protective molecules such as secretory immunoglobulins and also limits the attachment of microorganisms.

Salivary glands consists of acinar and ductal cells. Acinar cells, present in parotid gland, are responsible for production of serous secretion. Most of the  $\alpha$ -amylase is synthesized in this gland. The submandibular and sublingual glands produce mainly mucin while proline and histin are produced by parotid and submandibular glands. Mucous are essentially produced by the minor salivary glands (Nauntofte and Lagerlof, 2003; Saad *et al.*, 2005; Chatterjee, 1985).

Clinical diseases and prognostic monitoring on human saliva has a great potential (Jessie *et al.*, 2008). Saliva is complex mixture of fluids containing oral bacteria and food debris. The fluids along with gingival crevicular fluid come from the major and minor salivary glands. The average daily flow of whole saliva varies from 1-1.5 L depending on the health. The contributions of the salivary glands for usual flow are: 20% from parotid, 65% from submandibular, 7-8 % via sublingual and less than 10 % via humerous minor gland, shown in (Fig. 4) and when stimulated flow rate can increase by more than 50% of total salivary secretion (Edgar, 1990).

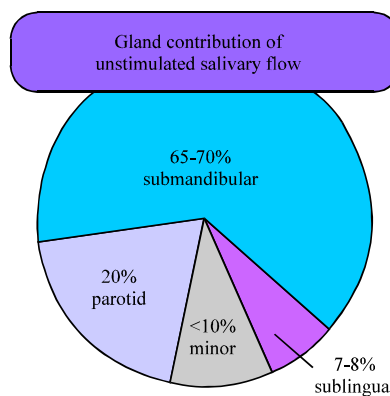


Fig. 4: Percentage contributions of the different salivary glands during unstimulated (Patricia *et al.*, 2008)

**Mucus:** The intercellular ground substance called mucus surrounds the epithelial cells of buccal mucosa varies in thickness ranging from 40-300  $\mu$ m (Allen *et al.*, 1984). Mucus, a translucent and viscid secretion, forms a thin, continuous gel cover over the mucosal epithelial surface like a blanket. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. Mucus consists of about 95% water and the major organic component in mucus is glycoproteins (Ehrhardt and Kim, 1995; Zakaria *et al.*, 2004).

The thickness of the mucus depends on its location (Marriot and Hughes, 1990). The thickness of the mucus blanket is controlled by the balance between the rate of secretion and the rate of degradation and shedding. Mucus secretion is greatly stimulated by toxic and irritating substances, the thickness of the mucus blanket is increased while the irritants go away from the epithelium efficiently and rapidly moving (Thomas and Moridani, 2009; Puchelle, 1987). The major and minor salivary glands secret mucus as part of saliva (Sangeetha *et al.*, 2010). Up to 70% of the total mucin found in saliva is secreted by the minor salivary glands (Rathbone *et al.*, 1994). The mucus network carries a negative charge at physiological pH due to the presence of sialic acid and sulfate residues which also play a role in mucoadhesion. At this pH mucus a strongly cohesive gel structure can be formed that will combine with the

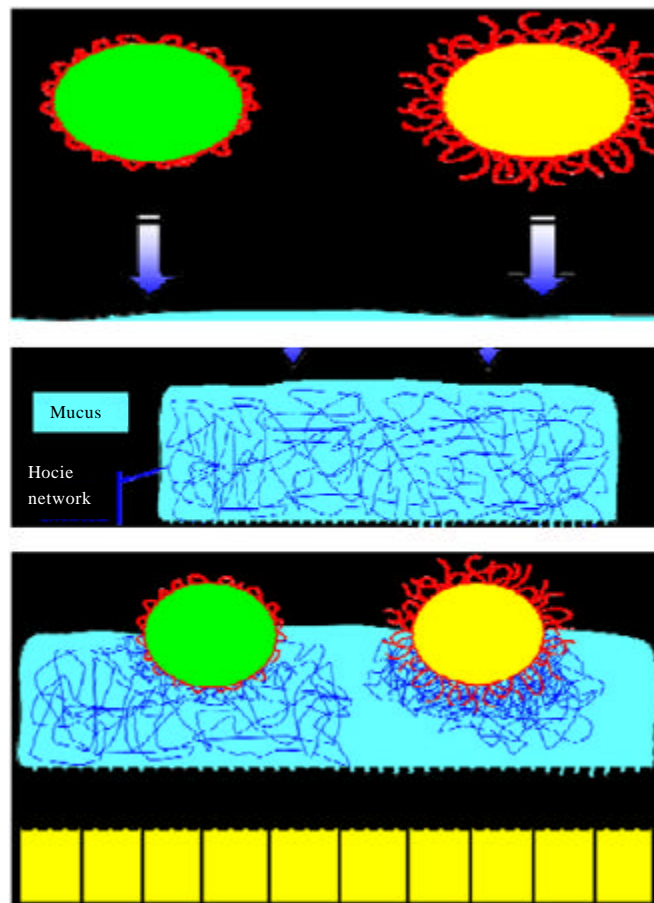


Fig. 5: Mucus interaction with drug delivery system (Madhav *et al.*, 2009)

epithelial cell surface as a gelatinous layer. The interaction of mucus with drug delivery system is shown as Fig. 5 (Gandhi and Robinson, 1988).

#### ORAL MUCOSA A BARRIER TO PERMEABILITY

The rate and extent of drug absorption through the buccal mucosa can be retarded by the saliva, mucus, membrane coating granules, basement membrane, etc., which also act as barriers (Gandhi and Robinson, 1988). The oral mucosa in general is a somewhat spongy epithelia intermediate between that of the epidermis and intestinal mucosa. It has been observed that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin (Galey *et al.*, 1976). However, this value is not absolute, there are considerable differences in permeability between different regions of the oral cavity due to difference in structures and functions of the different oral mucosa (Harris and Robinson, 1992;

Akhionbare and Ojehanon, 2007). In general, the permeability of the oral mucosa decreases in the order: sublingual<buccal<palatal (Harris and Robinson, 1992). The permeability coefficient has a direct relation with the membrane thickness (i.e., inverse to its thickness) degree of keratinisation of these tissues and with the physicochemical properties of the drug like molecular weight, size and lipophilicity. The characteristic features of oral mucosa are shown in Table 2 (Squic and Johnson, 1975).

Sublingual mucosa is relatively thin and non-keratinized, the buccal mucosa is thicker and non keratinized and the palatal mucosa is intermediate in thickness and is keratinized (Wertz and Squier, 1991). The permeability barrier property of the oral mucosa is mainly due to intercellular materials derived from the so called membrane coating granules (Gandhi and Robinson, 1994). Membrane coating granules are spherical or oval organelles with size range from 100-300 nm and are found in both keratinized and non-keratinized epithelia

Table 2: Characteristics features of oral mucosa

Characteristics	Tissue				References
	Buccal	Sublingual	Gingival	Palatal	
Nature of mucosa	NK	NK	K	K	Harris and Robinson (1992)
Thickness (micrometer)	500-800	100-200	100-200	100-200	Gandhi and Robinson (1994)
Turnover time (in days)	5-6	20	10	24	Harris and Robinson (1992)
Surface area (cm <sup>2</sup> ±SD)	50.2±2.9	26.5±4.2	----	20.1±1.9	Collins and Dawes (1987)
Permeability	Intermediate	Very good	Poor	Poor	De Vries <i>et al.</i> (1991)

NK: Non-keratinized, K: Keratinized

(Hayward, 1979). The membrane coating lipids granules of keratinized epithelia include sphingomyelin, glucosyl ceramide, ceramide and other non-polar lipid. However, for non-keratinized epithelia the major membrane coating granules are lipid components e.g., cholesterol ester, cholesterol and glycosphingolipids (Ganem-Quintanar *et al.*, 1997a). The membrane coating granules present on the basement membrane exhibit some resistance to permeation, however the outer epithelium is considered as rate limiting to mucosal penetration. The relatively large molecules cannot get excluded because of less dense structure of the basement membrane. (Slomiany *et al.*, 1996).

#### DRUG DELIVERY VIA THE ORAL MUCOSA

The function and detailed description of the oral mucosa is available elsewhere but only those details which are relevant to the oral mucosal delivery of drug have been included here. Lips, cheek (buccal), tongue, hard palate, soft palate and floor of mouth are the parts of oral cavity (Dawes, 2007; Al-Bassiouny, 2009). Buccal and sublingual areas are the most appropriate site for drug delivery and these may be used for the treatment of local (Chiappin *et al.*, 2007) disease like toothaches (Ishida *et al.*, 1982), periodontal disease (Collins *et al.*, 1989; Elkayam *et al.*, 1988), bacterial and fungal infections (Samaranayake and Ferguson, 1994), aphthous (Nagai and Machida, 1985) and dental stomatitis (Nagai, 1985) or systemic diseases. The surface area of oral mucosa, skin and gastrointestinal tract are about 200, 20000 and 350000 cm<sup>2</sup>, respectively. However, the oral mucosa is highly vascularized and therefore any drug diffusing into the oral mucosal membranes has direct access to the systemic circulation via capillaries and venous drainage (Squier and Wertz, 1993; Hakan *et al.*, 1990; El-Kamel *et al.*, 2007).

**Drug delivery via sublingual route:** The sublingual mucosa is generally well accepted because it is relatively permeable, gives rapid absorption, provide acceptable bioavailability of many drugs and is convenient. The sublingual route is capable of producing a rapid onset of action due to high permeability and rich blood supply which makes it appropriate for drugs with short delivery period (Squier and Wertz, 1996; Giri *et al.*, 2010b).

Among all routes, the sublingual route is studied widely. There are two different design of sublingual dosage form, one composed of rapidly disintegrating tablets and the other consisting of soft gelatin capsules filled with liquid drug, such system before absorption to mucosa create a very high drug conc. in sublingual region (Ishida *et al.*, 1982). Generally, sublingual route is used for drug delivery in treatment of acute disorders, but due to washing of its surface by saliva and tongue activity it makes it difficult to keep the dosage form in contact for an extended period of time with mucosa (Chiappin *et al.*, 2007; Ryan *et al.*, 1997).

**Drug delivery via buccal route:** The buccal mucosa is less permeable than sublingual area and they generally do not provide rapid absorption as sublingual administration. Buccal mucosa is more fitted for sustained and controlled delivery application, delivery of less permeable molecules and peptide drugs because of immobile mucosa. (Aungst and Rogers, 1989; Singh *et al.*, 2011a). Both application and removal of a drug from buccal mucosal site are very convenient (Verma *et al.*, 2011). The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. The buccal mucosa for its permeability and robustness in comparison to other mucosal tissues, is more tolerant to potential allergens and has a reduced tendency to irreversible irritation or damage. So, it has been largely investigated as a potential site for controlled drug delivery in various chronic systemic therapies (Chiappin *et al.*, 2007).

#### BUCCAL ABSORPTION

**Mechanism:** In the oral mucosa both the hydrophilic and lipophilic regions are coexisting, for which there are two routes for drug transport, i.e., the paracellular and the transcellular routes. For hydrophilic compounds the paracellular route is the primary route, it is difficult for a hydrophilic compound to penetrate into the lipophilic cell membrane and thus, the intercellular space is the preferred route for drug transport. (Harris and Robinson, 1992; Shojaei and Li, 1997; Alur *et al.*, 2002; Lorenza *et al.*, 2008).

Lipophilic compounds would have low solubilities in the hydrophilic intercellular spaces and cytoplasm

(Peppas and Buri, 1985). The cell membrane, although, is relatively lipophilic in nature hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient (Harris and Robinson, 1992). Some of hydrophilic macromolecular therapeutic agents like polysaccharides, oligonucleotides, peptides, can be delivered as controlled delivery via buccal mucosa. To overcome low permeability the absorption enhancer may be required which can improve bioavailability of the high molecular weight drugs (Senel and Hincal, 2001; Lu and Low, 2002).

**Dynamic:** The first order rate process describes oral mucosal absorption of drugs adequately. Various potential barriers have been identified as obstacles to oral mucosa drug absorption. They mainly include mucus layer, keratinized layer, intercellular lipid of epithelium, basement membrane and lamina propria. The absorptive membrane thickness, blood supply/lymph drainage cell renewal and enzyme content helps in reduction of rate and amount of drug entering the systemic circulation.

The systemic circulation pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. They proposed a linear relationship between salivary secretion and time thus:

$$\frac{dM-KC}{dt} = ViVt$$

where, 'm' and 'C' are the mass and concentration of drug in mouth at time 't', Vi, the volume of solution put into mouth cavity and 'V' is salivary secretion rate (Kumar *et al.*, 2004).

#### FACTORS AFFECTING BUCCAL ABSORPTION

The oral cavity is a complex environment for drug delivery, as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.

#### Physicochemical factors affecting buccal absorption:

- **Size:** Smaller molecules (75-100 Da) generally exhibit rapid transport across the mucosa, with decreasing permeability as molecular size increases (Vaughan, 2003)
- **Partition coefficient:** When partition coefficient increase, permeability of drug through lipoidal membrane also increase

- **pH:** pH at the site of drug absorption can influence the partition coefficient. With increasing pH, the partition coefficient of acidic drugs decreases while that of basic drugs increases (Rao *et al.*, 1998)
- **Ionization of drug:** Both pKa and pH at the mucosal surface influence the ionization of a drug. Lipid solubility is exhibited appreciably only by the nonionized form of many weak acids and weak bases and thus the ability to cross lipoidal membranes (Ajazuddin, 2010)

#### Physiological factors affecting buccal absorption:

- Inherent permeability of the epithelium
- Thickness of epithelium (Swarbrick, 1999)
- Blood supply
- Metabolic activity
- Saliva and mucus
- Ability to retain delivery system
- Species differences
- Transport routes and mechanisms (Chatterjee, 1985)

#### MUCOADHESION/BIOADHESION

##### Definition

**Adhesion:** Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface (Jimenez *et al.*, 1993; Suryawanshi *et al.*, 2010).

**Mucoadhesion:** Mucoadhesion can be defined as the phenomenon of the attachment of natural or synthetic macromolecule to mucin layer of mucosal surface or epithelial surface. (Longer and Robinson, 1986; Laura *et al.*, 2009).

**Bioadhesion:** Bioadhesion is an Interfacial phenomenon in which two materials, at least one of which is biological nature are held together for extended periods of time by means of interfacial forces (Mathias and Hussain, 2010).

**Stages of mucoadhesion:** Dry or partially hydrated dosage form involve two basic steps in mucoadhesion shown in (Fig. 6). First step involve contact stage, where intimate contact is formed between the mucoadhesive and mucous membrane. The buccal patch is placed within the buccal cavity in contact with required mucosa and to the place to allow adhesion to occur. Second step involve consolidation stage where various physicochemical interaction occur to consolidate and strengthen the adhesive joint which prolongs adhesion (Smart, 2005; Omari *et al.*, 2012; Patel *et al.*, 2007a,b; Huang *et al.*, 2000).



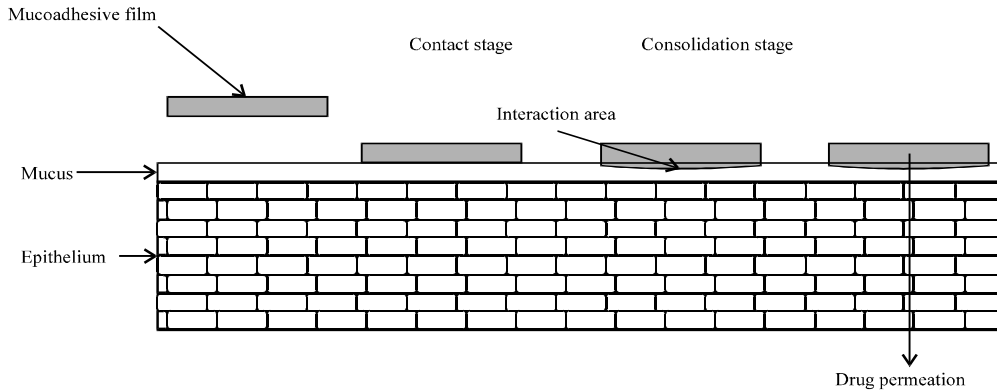


Fig. 6: Contact and consolidation stages of mucoadhesion (Morales and McConville, 2011)

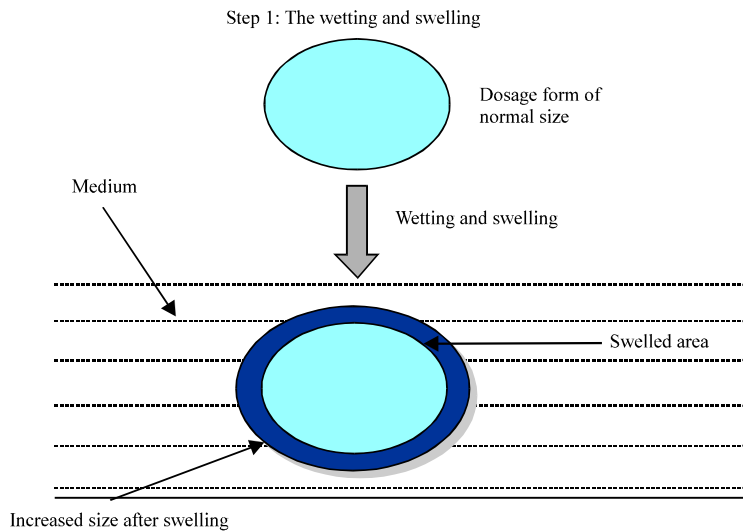


Fig. 7: Wetting and swelling of polymer (Aidoo and Sheila, 2009)

**Mechanism of mucoadhesion:** The mechanisms responsible in the formation of bioadhesive bonds are not fully known, however most research has described bioadhesive bond formation as a three step process:

- **Step 1:** Wetting and swelling of polymer
  - **Step 2:** Interpenetration between the polymer chains and the mucosal membrane (Varum *et al.*, 2008)
  - **Step 3:** Formation of Chemical bonds between the entangled chains (Smart, 2005)
- **Step 1:** The wetting and swelling step occurs when the polymer spreads over the surface of the biological substrate or mucosal membrane in order to develop an intimate contact with the substrate as shown in (Fig. 7) (Bhatt, 2009; Hagerstrom, 2003). Swelling of

polymers occur because the components within the polymers have an affinity for water (Aidoo and Sheila, 2009)

- **Step 2:** Glycoproteins the high molecular weight polymers composes the surface of mucosal membrane. A great area of contact shown between chains of mucoadhesive polymer and mucous gel network as shown in (Fig. 8) (Hagerstrom, 2003; Alexander *et al.*, 2011a; Sharma *et al.*, 2009)
- **Step 3:** This step include entanglement and formation of weak chemical bonds along with secondary bonds between the polymer chains. Primary bonds such as covalent bond and weaker secondary interactions such as Van der Waals interactions and hydrogen bonds are formed in mucin molecules which is also showed in (Fig. 9). Strong adhesion between

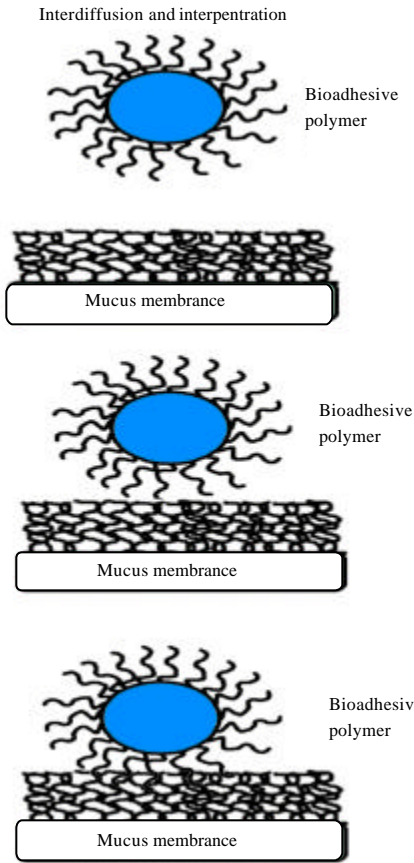


Fig. 8: Interdiffusion and interpenetration of polymer and mucus (Smart, 2005)

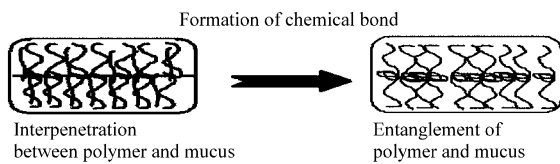


Fig. 9: Entanglement of Polymer and Mucus by Chemical bonds (Hagerstrom, 2003)

polymers is formed during the manufacturing of bioadhesive formulations as primary and secondary bonds are exploited (Hagerstrom, 2003; Alexander *et al.*, 2011b; Fasina *et al.*, 2007)

**Theories of mucoadhesion:** Mucoadhesion is described as a complex process and various other theories are explained to describe mechanisms are known but other numerous theories should be considered as supplement of mucus/substrate interaction. The diffusion theory of adhesion is shown in (Fig. 10) (Andrews *et al.*, 2009; Alexander *et al.*, 2011a; Sharma *et al.*, 2011):

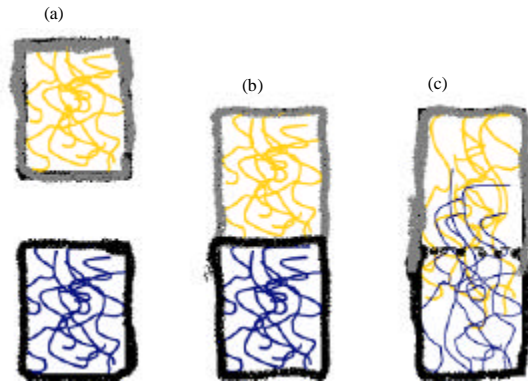


Fig. 10(a-c): The diffusion theory of adhesion, (a) Top (polymer) layer and bottom (mucus) layer before con-tact, (b) Top layer and bottom layer immediately after contact and (c) Top layer and bottom layer after contact (Punitha and Girish, 2010)

- Wettability theory
- The electronic theory
- The fracture theory
- The adsorption theory
- The diffusion-interlocking theory (Lee and Kellaway, 2000)

#### FACTOR WHICH AFFECT MUCOADHESION IN ORAL CAVITY

The bioadhesive power of a polymer or of a progression of polymers is affected by the nature of the polymer and also by the nature of the surrounding media.

##### Polymer related factor:

- Molecular weight (Chen and Cyr, 1970)
- Flexibility
- Hydrogen bonding capacity (Peppas and Buri, 1985)
- Cross linking density
- Charge (Lehr *et al.*, 1992)
- Concentration of active polymer (Khairnar *et al.*, 2009)
- Hydration (Swelling) (Gu *et al.*, 1998)

##### Environmental factor (Khar *et al.*, 1997):

- Applied strength
- pH
- Initial contact time

### Physiological variables

**Mucin turnover:** These molecules interact with the mucoadhesive before they have a chance to act together with the mucus layer. Mucin turnover may depend on presence of food.

**Disease states:** The physiochemical properties of mucus are known to adjust during disease conditions such as common cold, gastric ulcers and ulcerative colitis, bacterial and fungal infections of the female reproductive tract (Khar *et al.*, 1997; Rejaie, 2009).

### MUCOADHESIVE POLYMER USED IN ORAL CAVITY

#### Ideal characteristics of mucoadhesive polymer

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities (Mishra *et al.*, 1996)
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties
- The polymer and its degradation products should be non-hazardous and should be non absorbable from the mucus layer (Longer and Peppas, 1981)
- It should allow daily incorporation to the drug and offer no hindrance to its release (Jimenez *et al.*, 1993)
- Should not aid in development of secondary infections such as dental caries (Wise, 2000)

**Classification of mucoadhesive polymer:** (Savage, 1977).

In general, adhesive polymers can be classified as synthetic vs. natural, water-soluble vs. water insoluble and charged vs. uncharged polymers (Rao *et al.*, 2011). Examples of the recent polymers classified in these categories are listed in Table 3.

**New generation of mucoadhesive polymer:** In a recent mini-review current bioadhesive polymers are classified as first generation and second generation (Lee *et al.*, 2000). Newer polymers are capable of forming covalent bonds with the mucus and the underlying cell layers and hence, exhibit improved chemical interactions (Langoth *et al.*, 2003).

The new generation polymer are:

- Thiolated mucoadhesive polymers
- Target-specific, lectin-mediated bioadhesive polymers
- Bacterial adhesion
- Mucoadhesive polymers as enzyme inhibitors and permeation enhancers

### PERMEATION ENHANCER

Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers (Chattarajee and Walker, 1995). As most of the penetration enhancers were originally designed for purposes other than absorption enhancement, The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action (Shojaei,1998). The degree of enhancement depended on a number of factors, including the characteristics of the permeant, the composition of the delivery vehicle and whether the tissue was pretreated with enhancer (Ganem-Quintanar *et al.*, 1997b). In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers.

The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. Penetration enhancement to the buccal membrane is drug specific (Shojaei, 1998).

**Mechanism of permeation enhancer:** Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows:

- By changing mucus rheology in reducing the viscosity and/or elasticity of mucus layer
- By increasing fluidity of lipid bilayer
- By facilitating paracellular transport
- By passing the enzymetic barrier for peptides (Bernkop-Schnurch, 2005)
- By accelerating the thermodynamic activity of peptide drugs
- Alteration of partition coefficient is achieved by increasing the solubility of drug via some enhancer which leads to better absorption with increased thermodynamic activity (Rathbone and Tucker, 1993)
- By acting on the components at tight junctions (Siegel and Gordon, 1985)

#### Categories of permeation enhancer

**The categories and examples of various permeation enhancers:**

- **Bile salts:** sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate. sodium taurocholate

Table 3: Comparative study of buccal patch and buccal tablet

Drug	Solubility	Half life (h)	Bioavai lability (%)	Protein binding (%)	Oral dose buccal tablet	Amt. of drug loaded in buccal patch	Amt. of drug loaded in buccal tablet	Polymer used in tablet	% drug release for buccal tablet (h)	Polymer used in buccal patch	% drug release for buccal patch (h)	References
Salbutamol or Albuterol sulphate	Free soluble in water, slightly soluble in ethanol (95%) and in ether	1.6	50 %	10 %	For adult and children over 12 yr 2.4 mg 3-4 times per day if necessary the dose increase 8 mg 4 times per day.	10 mg	1.6	HPMC K-4M	4.5	PVP, Chito-san-PVA	7	Patel <i>et al.</i> (2009) Arya <i>et al.</i> (2011)
Carvedilol	Soluble in dimethyl sulfoxide, methanol, Ethanol methylene chloride, isopropranolol.	7-10	25-35	98 %	25 mg twice a day	6.25 mg	15 mg	Methyl-β Cyclo-dextrin	3	Chito-san and PVP	8	Hirekar and Kadam (2009)
Clotrima-zole	Free soluble in acetone, chloro-form, ethanol 95%, Metha-nol	2	--	--	90 %	10 mg	1.5 mg	HPMC-K-4M	1.15	Sodium CMC	8	Khanna <i>et al.</i> (1996)
Tizanidine HCL	Soluble in water, methanol, practically insoluble in acetone, chloroform and ethyl acetate.	2-3	34 - 40	30	2 mg TDS, max 24 mg per day	4.5 mg	4.43/ 0.9988 cm <sup>2</sup>	HPMC-K-4M	1.15	Sod. CMC	6	Shanker <i>et al.</i> (2009)
Metoprolol tartrate	Very soluble in water, free soluble in ethanol (95 %), chloroform and in dichloromethane, slightly soluble in acetone, practically insoluble in ether.	3-4	38 - 50	12	25/50/100 mg in tablet	50 mg	25 mg	Carbopol and HPMC-K-4M	8	PVP-K30	4	Raju <i>et al.</i> (2011)
Verapamil HCL	Free soluble in chloroform, soluble in, Sparingly soluble in ethanol(95%), practically insoluble in ether	2-8	20	90	40/80 mg in tablet	50 mg	50 mg	Hydroxy ethyl cellulose	8	PVP-K30	6	Chandira <i>et al.</i> (2009)
Propranolol HCL	Soluble in water and in ethanol (95%), slightly soluble in chloroform, practically insoluble in ether	3-4	15 - 23	More than 90%	Oral antiarrhythmic dose is 40-80 mg 2-4 times a day	160 mg	20 mg	HPMC-K-4M, SCMC	6	SCMC, CP-934	8	Patel <i>et al.</i> (2007b)

- **Chelators:** Disodium EDTA, citric acid, sodium salicylate, methoxy salicylates (Kurosaki *et al.*, 1989; Pramod and Lingappa, 2008)
- **Surfactants:** Sodium lauryl sulfate, polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxyethylene-20-cetyl ether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyl trimethyl ammonium bromide (Aungst, 1994)
- **Non-surfactants:** Unsaturated cyclic urea
- **Steroidal surfactants:** Sodium cholate
- **Fatty acids:** Oleic acid, capric acid, lauric acid, propylene glycol, cod liver oil methyl oleate, lysophosphatidylcholine, phosphatidylcholine (Hinton *et al.*, 2009)
- **Inclusion complexes:** Cyclodextrins
- **Thiolated polymers:** Chitosan-4-thiobutylamide, chitosan- 4-thiobutylamide/GSH, chitosan-cysteine, Poly (acrylic acid)-homocysteine, polycarboxiphil-cysteine, polycarboxiphil- cysteine/GSH, chitosan-4-thioethylamide/GSH, chitosan-4-thioglycolic acid
- **Others:** Aprotinin, azone, cyclodextrin, dextran sulfate, menthol, polysorbate 80, sulfoxides and various alkyl glycosides (Zhang *et al.*, 1994; Chen *et al.*, 2011)

**Buccal formulation:** In the past decades, different drug delivery systems intended for buccal administration have been developed, The size of the delivery system varies with the type of formulation, i.e., a buccal tablet may be approximately 5-8 mm in diameter, whereas a flexible buccal patch may be as large as 10-15 cm<sup>2</sup> in area. Mucoadhesive buccal patches with a surface area of 1-3 cm<sup>2</sup> are most acceptable. Comparative study of buccal patch and buccal tablet are shown in (Table 4). It has been estimated that the total amount of drug that can be delivered across the buccal mucosa from a 2 cm<sup>2</sup> system in 1 day is approximately 10-20 mg (Rathbone *et al.*, 1996; Chaudhary *et al.*, 2010).

**Matrix tablets/Bioadhesive buccal tablets:** Monolithic tablets in their simplest version consist of a mixture of drug with a swelling bioadhesive/sustained release polymer with a bidirectional release. They can be coated on the outer or on all sides but one face with water impermeable hydrophobic substances to allow an unidirectional drug release for systemic delivery (Rathbone *et al.*, 1996; Bose *et al.*, 2011). In case of bilayered tablets, drug can be incorporated in the adhesive layer which comes in contact with the mucosal surface. This drug containing mucoadhesive layer is then protected from the oral cavity environment by a second upper inert layer which faces into the oral cavity. Alternatively, the drug can be incorporated into the upper non adhesive layer to release the drug into the oral cavity. Various types of matrix tablets shown in (Fig. 11) (Gupta *et al.*, 2010; Chandira *et al.*, 2009).

**Semisolid preparations (ointments and gels):** Solid dosage adhesive forms are used widely than bioadhesive gels or ointments, because they are most used for localized drug therapy within oral cavity. “ORABASE” the original oral mucosal adhesive delivery system consist of finely ground pectin, gelatin and sodium carboxymethyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base. It can be maintained at the site of application for 15-150 min.

**Powders:** Yamamoto *et al.* (2001) described a hydroxypropyl cellulose and beclomethasone-dipropionate containing powder that was sprayed onto the oral mucosa of rats. A significant increase in the residence time relative to an oral solution was seen and 2.5% of beclomethasone was retained on buccal mucosa for over 4 h (Senel and Hincal, 2001; Ch’Ng *et al.*, 1985; Kaur and Kaur, 2011).

Table 4: Classification of polymers used in formulation of buccal patch (Savage, 1977)

Criteria	Categories	Examples
Source	Seminatural/natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate)
	Synthetic	Cellulose derivatives [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, Methyl hydroxyl ethyl cellulose] Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly(methyl vinyl ether-co-methacrylic acid), poly(2- hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexyl acrylate), poly(methacrylate), poly(alkyl cyanoacrylate), poly (isohexyl cyanoacrylate), poly(isobutyl cyanoa crylate), copolymer of acrylic acid and PEG] Others: polyoxyethylene, PVA, PVP, thiolated polymers
Aqueous Solubility	Water-soluble	CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium CMC, sodium alginate
Charge	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
	Cationic	Aminodextran, chitosan, (DEAE)-dextran, TMC
Aqueous Solubility	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan Potential Bioadhesive forces
	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
Electrostatic interaction	Electrostatic interaction	Chitosan

**Buccal patches:** The drawbacks of other dosage form are overcome by development of flexible adhesive patches. Transmucosal delivery patches include unique characteristic like rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug when the patch is removed. The less inter and intraindividual variability absorption profile is showed by a buccal patch

which it confined to the buccal area over which it is attached. List of commercial buccal patches for oral mucosal drug delivery are shown in (Table 5). In general patches with a dissolvable matrix, patches with a non-dissolvable backing and patches with a dissolved backing are the 3 categories for classification of oral mucosal patches (Dixit and Puthli, 2009; Alagusundaram *et al.*, 2009).

Patches with a dissolvable matrix shown in Fig. 12 are designed to release drug into the oral cavity. The mucoadhesive layer (either in drug matrix or attached to drug matrix) would prolong the duration of drug matrix in the oral cavity. Hence, in comparison to other dosage forms, these systems are longer acting and can potentially deliver more drug quantities. Patches with non-dissolvable backing shown in Fig. 13 are usually designed for systemic delivery. Since, they are closed systems and the formulations are protected from saliva, the drug concentrations are controlled and drug is continuously delivered for 10-15 h. The system include disadvantages as removal of backing by the patient after drug administration and use of only a small area. The entire patch get dissolved in oral cavity which have dissolvable backing. But these patches show shorter acting as compared to non-dissolvable backing membrane. Basically buccal patch consist of drug substance, bioadhesive polymer, plasticizers, backing membrane and permeation enhancer. The commonly used

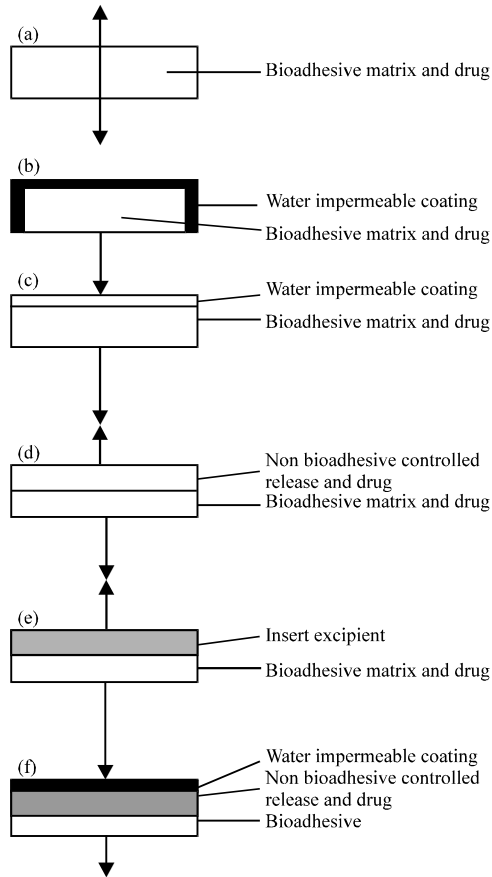


Fig. 11(a-f): Schematic representation of different matrix tablets for buccal delivery. Arrows indicate the direction of drug release (Rossi *et al.*, 2005)

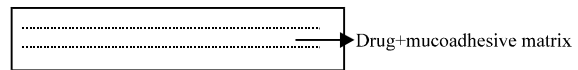


Fig. 12: Buccal patch with a dissolvable matrix (Veillard *et al.*, 1987)



Fig. 13: Buccal patch with a non dissolvable backing (Kurosaki *et al.*, 1989)

Table 5: List of commercial buccal patches for oral mucosal drug delivery

Product name/brand name	API (Active pharmaceutical ingredient)	Name of manufacturer	Strength (mg)	References
Triaminic	Dextromethorphan HBr	Novartis	7.5	Bhyan <i>et al.</i> (2011)
Triaminic	Diphenhydramine HCl	Novartis	12.5	
Theraflu	Dextromethorphan HBr	Novartis	15.0	
Gas-X	Simethicone	Novartis	62.5	
Sudafed	Phenylephrine HCl	Pfizer	10.0	
Benadryl	Diphenhydramine HCl	Pfizer	12.5	
Chloraseptic	Benzocaine Menthol	Prestige	3/3.0	
Suppress	Menthol	InnoZen	2.5	
Orajel	Menthol/Pectin	Del	2/30.0	
Listerine	Cool mint	Pfizer	--	
DentiPatch	Lidocaine	Noven Pharmaceuticals	46.1	
Onsolis	Fentanyl citrate	Media pharmaceutical	--	Pather <i>et al.</i> (2008)

Table 6: List of active pharmaceutical ingredients (Drugs) and polymer used in buccal patches

Drug	Category	Polymer	References
Felodipine	Antihypertensive (dihydropyridine derivative calcium channel blocker)	PVP, PVA	Martindale (2005)
Ondansetron Hydrochloride	Antiemetic (5HT-3 inhibitor)	HPMC	Vamshi <i>et al.</i> (2007) and Steven (2002)
Metoprolol tartrate	Selective $\beta$ -1 adrenergic antagonist	Poly (ethylacrylate methyl methacrylate) copolymer (Eudragit NE40D)	Robertson (1983) and Lanzara (2005)
Metoprolol succinate	Selective $\beta$ -1 adrenergic antagonist	PVP, PVA	Lehr <i>et al.</i> (1992)
Verapamil HCL	Calcium channel blocker and a class IV antiarrhythmic agent	Chitosan, PVP K-30	Patel <i>et al.</i> (2007b)
Atenolol	$\beta$ 1-receptor selective antagonist	Carbopol 934P, Sodium carboxymethyl cellulose and HPMC	Jug <i>et al.</i> (2009)
Clotrimazole	First line broad-spectrum antifungal agent	Sodium carboxymethylcellulose and carbopol 974P (CP 974P)	Ahuja <i>et al.</i> (1997) and Martin (1990)
Enalapril maleate	Antihypertensive and antianginal	Sodium CMC, HPMC, HEC and polyvinyl pyrrolidone K-90	Houghton (2002) and Singh <i>et al.</i> (2011a,b)
Carvedilol	Non selective $\beta$ -adrenergic blocking agent with $\alpha$ -1 blocking activity	Chitosan, PVP	Riikka <i>et al.</i> (2009) and Rejaie (2009)
Propranolol hydrochloride	Non-selective beta-adrenergic blocking agent.	Eudragit L-100, Polyvinylpyrrolidone K-30	Gampimol <i>et al.</i> (2002)
Metoprolol tartrate	selective $\beta$ -1 adrenergic antagonist	Chitosan, PVP K-30 and Ethyl Cellulose	Senel <i>et al.</i> (2000)
Sumatriptan succinate	HT1 receptor agonist used in the treatment of migraine	Ethyl cellulose, PVP	Ryan (1997)
Zolmitriptan	serotonin (5-HT1) agonist	NaCMC, HPMC, HEC, chitosan	Rao <i>et al.</i> (2011)
Lidocaine	Local anaesthetic	HPC, Methocel K-15 HPMC (PVA), hydroxyethyl cellulose (HEC) and chitosan	Repka <i>et al.</i> (2005)
Cetylpyridinium chloride	Quaternary antiseptic		Noha <i>et al.</i> (2003)
Oxybutynin HCl	Antispasmodic, anticholinergic agent	HPMCP, HPMCK4M, chitosan	Bose <i>et al.</i> (2011)
Fexofenadine HCl	H1 antagonist, is a potent antihistamine	HPMC, Carbopol 934, eudragit RS 100 and Ethylcellulose (EC), sodium alginate, carbopol 934, Na CMC, PVP, HPMC and PVP	Breier <i>et al.</i> (2005)
Methotrexate (MXT)	Anticancer	Carbopol 934 and HPMC	Satyabrata <i>et al.</i> (2010)
Miconazole nitrate	Antifungal		Vinod <i>et al.</i> (2010)
Famotidine	H2-receptor antagonist (also called H2-blocker) which decreases the amount of acid produced by the stomach	HPMC, sodium CMC, PVA	Kumar <i>et al.</i> (2010) and Ramchandran <i>et al.</i> (2011)
Lidocaine Hydrochloride	Local anaesthetic	HPMC E-15, NaCMC	Varshosaz <i>et al.</i> (2006)
Tizanidine Hydrochloride (TZH)	Skeletal muscle relaxant	NaCMC, Carbopol 934 (CP 934)	Giradkar <i>et al.</i> (2010)
Aceclofenac	NSAID posses good antiinflammatory, analgesics and anti-pyretic.	Poly-Sodium CMC and Polyvinyl Alcohol.	Kharinar <i>et al.</i> (2009) and Gupta <i>et al.</i> (2010)
Meloxicam	Non-steroidal anti-inflammatory drug is widely used in the treatment of rheumatoid arthritis	Chitosan, Carbopol 934p	Jafar <i>et al.</i> (2011)
Ibuprofen	NSAID	NaCMC, PVP	Luana <i>et al.</i> (2004) and Giri <i>et al.</i> (2010a,b)
Ranitidine	H2- antagonist	HPMC, PVP	Alagusundaram <i>et al.</i> (2009) and Ramchandran <i>et al.</i> (2011)
Risperidone	A benzisoxazole derivative, is a novel antipsychotic	Chitosan, HPMC, PVP, PVA	Bingi <i>et al.</i> (2010)
Pimozide	A diphenylbutylpiperidine derivative, an antipsychotic agent.	Carbopol 934 and hydroxypropylmethylcellulose (1.5 cps) (HPMC), Poly vinyl alcohol (PVA) and poly vinyl pyrrolidone, HPMC 47 cps	Basu <i>et al.</i> (2010)
Methotrexate	Anticancer	Ethyl cellulose	Choudhary <i>et al.</i> (2010)
Carvedilol	Non selective $\beta$ -adrenergic blocking agent with $\alpha$ -1 blocking activity	Chitosan	Kaur and Kaur (2011)
Triamcinolone Acetonide	A synthetic corticosteroid.	Carbopol 934 and (HPMC)	Singh <i>et al.</i> (2011a,b)
Tetracycline HCL	Broad-spectmm antibiotics	Carbopol 934, Carvacrol and ethyl cellulose.	Rana <i>et al.</i> (2011)

materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc. List of active pharmaceutical ingredients (Drugs) and polymer used in buccal patches are shown in Table 6. (Santos *et al.*, 1999; Satyabrata *et al.*, 2010; Ritthidej *et al.*, 2002; Kumar *et al.*, 2010).

**Innovative drug delivery systems:** Innovative drug delivery systems, such as lipophilic gel, buccal spray and phospholipid vesicles have been recently proposed to deliver peptides via the buccal route (Lee *et al.*, 2000; Senel *et al.*, 2000). A novel liquid aerosol formulation has been recently developed and it is now in clinical phase II

Table 7: Patents on buccal patches

Patent No.	Inventor	Comments
US 2011/0160634	Malcovati (2011)	An oral mucoadhesive patch were formulated in which the protective layer comprises pressure sensitive adhesive
US 7862802	Kim <i>et al.</i> (2011)	The present invention relates to a dry type tooth whitening patch in which peroxide is contained, as a teeth whitening agent, in a matrix type adhesive layer
US 2010/0239646	Nair (2010)	The inventor had designed the sublingual methotrexate patches
US 2010/0189770	Crutchley <i>et al.</i> (2010)	This invention relates to formulation of bioerodible patch which applied on mucosal or dermal surface of mammals
US 7579019	Tapolsky and Osborue (2009)	The formulator designed the device comprises an adhesive layer and a non-adhesive backing layer for providing localized drug delivery and protection to the treatment site
US 2009/0010997	Haley-Jeffrey (2009)	The invention relates to a lenticular medical patch is designed with a thin, tapered edge with multiple layers by passing a single sheet to increase the bioavailability of the drug
US 2008/0274164	Vollmer (2008)	The invention relates to a plaster composition for administering active agents by buccal patch through buccal cavity, lips or genitalia
US 7306812	Zhang (2007a)	The inventor design a patch consisting dissolvable backing layer for transmucosal drug delivery
US 7276246	Zhang (2007b)	The formulator designed a device comprising a water-dissolvable backing layer, an adhesive layer adjacent to at least a portion of the backing layer and an active layer that is circumscribed by the backing layer and adhesive layer
US 6592887	Zerbe <i>et al.</i> (2003)	This invention relates to a composition which contain therapeutic agents and/or breath freshening agents This formulation is generally used in oral cavity
US 6552024	Chen <i>et al.</i> (2003)	The present invention relates to designing of dissolving oral film which help administration of drug in pediatric and geriatric patient
US 6375963	Repka <i>et al.</i> (2002)	The present invention includes configuration of hot melt extruded film which contain a therapeutic agent and many other additives
US 6319510	Yates (2001)	In this invention formulator design a gum pad which applied on oral cavity and is used for treatment of systemic disorder
US 6210699	Acharya and Baker (2001)	Inventor formulate a mucoadhesive dosage form which can adhere easily on oral mucosa and provide sustained delivery of drug
US 6197331	Lerner <i>et al.</i> (2001)	This invention relates to formulation of sustained and controlled release pharmaceutical oral patch
US 6177096	Zerbe <i>et al.</i> (2001)	Invention relates to formulation of mucoadhesive dosage form by which we can deliver therapeutic and cosmetic agent

trials. This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth. Levels of drug in the mouth are dramatically increased compared with conventional technology. This oral aerosol formulation is rapidly absorbed through the buccal mucosal epithelium and it provides the plasma insulin levels necessary to control postprandial glucose rise in diabetic patients (Modi *et al.*, 2002). A number of advantages are included in this novel, pain free oral insulin formulation which also show rapid absorption, precise dosing control, a simple administration technique and bolus delivery of drug. The recently devised element for delivery of insulin in buccal cavity are phospholipids, deformable vesicles and transferosomes. These vesicles are prepared from surfactants, such as sodium cholate or sodium deoxycholate. They are similar to liposomes morphologically but they peculiarly respond to external stresses and their rapid shape transformation require low energy (Yang *et al.*, 2002; Khanna *et al.*, 1996).

**Recent invention in field of buccal patches:** Lots of work had been done in the field of bioadhesive drug delivery systems and the innovators had successfully patented their work with new modified systems. Some of the patents on this drug delivery have been reported in (Table 7) (Kim *et al.*, 2011).

## CONCLUSION

The ease of access and avoidance of the hepatic metabolism enable buccal drug delivery for being a potential alternative conventional oral drug delivery and parental administration which suffer from certain limitations. Almost 80% of the current commercially available formulations are limited to tablet. Oral buccal dosage forms will continue to be an exciting research focus for improving drug absorption especially for the new generation of the so called 'biologics', however, the palatability, irritancy and formulation retention at the site of application need to be considered during design of such formulation.

This article presents a summary of the investigations conducted by various researchers to explore the possibility of utilizing buccal drug delivery and their observations during last two to three decades. The authors expect that this article can be useful and ready reference to those who shall be interested to design, develop a buccal drug delivery system.

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**ABBREVIATION**

MCG	=	Membrane coating granules
cm	=	Centimeter
m	=	Mass
C	=	Concentration
t	=	Time
V	=	Volume
Da	=	Dalton
L	=	Litre
mm	=	Millimeter
mg	=	Milligram
E	=	Young's modules of elasticity
$\epsilon$	=	Fracture energy
L	=	Critical crack length
cal	=	Calorie
K	=	Kilo
EDTA	=	Ethylenediaminetetraacetic acid
h	=	Hour
kg	=	Kilogram
RH	=	Relative humidity
Wvt	=	Water vapour transmission
S	=	Surface area
rpm	=	Resolution per min
NK	=	Non-keratinized
K	=	Keratinized
SD	=	Standard deviation
HPMC	=	Hydroxy propyl methylcellulose
HPC	=	Hydroxy propyl cellulose
CMC	=	Carboxymethylcellulose
PVA	=	Polyvinylalcohol
PVP	=	Polyvinylpyrrolidone
CP	=	Carbopol
PEG	=	Polyethylene glycol
EC	=	Ethyl cellulose
HEC	=	Hydroxyethylcellulose
US	=	United state
cps	=	Centipoises
PC	=	Polycarbonate
DEAE	=	Diethylaminoethyl cellulose
TMC	=	Trimethylcellulose
PAA	=	Polyacrylic acid
CP	=	Conductive polymer

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