CHAPTER 1

Introduction, Literature
Survey and Objectives
INTRODUCTION, LITERATURE SURVEY AND OBJECTIVES

Oral administration of pharmaceutical compositions has some drawbacks. For instance, it is difficult to keep the medicament at the desired location so that it can be absorbed, distributed and metabolized easily. Accordingly, there has been much interest in the use of the mucosal lining of body cavities. Regions in the oral cavity where effective drug delivery can be achieved are buccal, sublingual, palatal and gingival. Buccal and sublingual sectors are the most commonly used routes for drug delivery and they may be used for the treatment of local or systemic diseases. The permeability of the oral mucosa is probably related to the physical characteristics of the tissues (Studzinska et al., 2009). The buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of controlled-release system which is well accepted by patients. 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 is relatively permeable, robust in comparison to the other mucosal tissues and is more tolerant to potential allergens which have a reduced tendency to irreversible irritation or damage. So, it has been largely investigate as a potential site for controlled drug delivery in various chronic systemic therapies. However, salivary production and composition may contribute to chemical modification of certain drugs. Moreover; involuntary swallowing can result in drug loss from the site of absorption. Furthermore, constant salivary scavenging within the oral cavity makes it very difficult for dosage forms to be retained for an extended period of time in order to facilitate absorption in this site. The relatively small absorption area and the barrier property of the buccal mucosa contribute to the inherent limitations of this delivery route (Puthli et al., 2009). Both the buccal and sublingual membranes offer advantages over other routes for administration. For example, drugs administered through the buccal and sublingual routes have a rapid onset of action and improved bioavailability of certain drugs. These routes can bypass the first-pass effect and exposure of the drugs to the gastrointestinal fluids. Additional advantages include easy access to the membrane sites so that the delivery system can be applied, localized, and removed easily. Further, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity. The palatal mucosa is intermediate in thickness and keratinized thus lessening its permeability. All of these
epithelia are coated with a layer of mucus (Shakya et al., 2009). Bioadhesive polymer can significantly improve the performance of many drugs, as they are having prolonged contact time with these tissues. These patient compliance controlled drug delivery products have improved drug bioavailability at suitable cost. Drug selection for oral transmucosal delivery is limited by the physicochemical properties of the drugs themselves. To be delivered transmucosally, drugs must have unique physicochemical properties, i.e. a proper balance between solubility and lipophilicity. Generally only a few milligrams of drug can cross the oral mucosa, even if the drug has a favourable profile for oral mucosal delivery (Giannola et al., 2007).

Since the early 1980s there has been renewed interest in the use of bioadhesive polymers to prolong contact time in the various mucosal routes of drug administration. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. Drug absorption through a mucosal surface is efficient because mucosal surfaces are usually rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation by gastrointestinal enzymes and first pass hepatic metabolism (Scholz et al., 2008).

1.1. Oral Transmucosal Drug Delivery

Within the oral cavity delivery of drug is classified into the categories. Due to its excellent accessibility and reasonable patient compliance oral mucosal cavity offers attractive route of drug administration. Within the oral mucosal cavity delivery of drug is classified into following categories:

(a) Sublingual delivery which is a systemic delivery of drug through the mucosal membrane lining the floor of the mouth

(b) Buccal delivery & local delivery, for the treatment of conditions of the oral cavity. The oral cavity is foremost part of digestive system of human body. It is also referred to as “buccal cavity”. It is accountable for various primary functions of body. The careful examination of various features of oral cavity can help in development of a suitable buccoadhesive drug delivery system (Khanna et al., 1998).

1.2. Oral Cavity

1.2.1. Components or structural features of oral cavity

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions.
• Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).
• Oral cavity proper, which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

Figure 1.1: Structure of Oral Cavity

1.2.2. Anatomical Features
The outer surface of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria overlying a submucousa containing blood vessels and nerves. The mucosa can be divided into three types (Ross and Wilson, 2001):
• 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.
All consists of a squamous stratified epithelium, many cell layers (40-50 for buccal mucosa) overlying a connective tissue, layer, the lamina propria. Intercellular connection in buccal tissue is characterized by desmosomes and tight junctions and the tissue is a somewhat leaky epithelium. The intercellular material between the superficial epithelial layers is extended by a unique organelle called “membrane coating granule”. It has been shown in rabbit keratinized epithelium that the lamella contents of the membrane-coating granules mix with existing material and form broad sheets in the intercellular spaces. These sheets are oriented parallel to the cell membrane and therefore may act as a barrier to permeability. Connective tissue papillae, which penetrate into the epithelia, give the basement membrane an enormous surface area compared to that of the surface of the epithelium (Amir et al., 2001).

1.2.3. Absorption pathways

Studies with microscopically visible tracers such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the intercellular spaces and that there is a barrier to penetration as a result of modifications to the intercellular substance in the superficial layers. However, rate of penetration varies depending on the physicochemical properties of the molecule and the type of tissue being traversed. This has led to the suggestion that materials uses one or more of the following routes simultaneously to cross the barrier region in the process of absorption, but one route is predominant over the other depending on the physicochemical properties of the diffusant (Hoogstraate et al., 1996 & Hao et al., 2003).
Passive diffusion

- Transcellular or intracellular route (crossing the cell membrane and entering the cell)
- Paracellular or intercellular route (passing between the cells)

Carrier mediated transport

Endocytosis

The flux of drug through the membrane under sink condition for paracellular route can be written as Eq. (1)

\[
J_p = \frac{D_p \varepsilon}{h_p} \times Cd
\]

Where, \(D_p\) is diffusion coefficient of the permeate in the intercellular spaces, \(h_p\) is the path length of the paracellular route, \(\varepsilon\) is the area fraction of the paracellular route and \(Cd\) is the donor drug concentration.

Similarly, flux of drug through the membrane under sink condition for transcellular route can be written as Eq. (2).

\[
J_c = \frac{(1 - \varepsilon) D_c K_c}{h_c} \times Cd
\]

Where, \(K_c\) is partition coefficient between lipophilic cell membrane and the aqueous phase, \(D_c\) is the diffusion coefficient of the drug in the transcellular spaces and \(h_c\) is the path length of the transcellular route.

In very few cases absorption also takes place by the process of endocytosis where the drug molecules were engulfed by the cells. It is unlikely that active transport processes operate within the oral mucosa; however, it is believed that acidic stimulation of the salivary glands, with the accompanying vasodilatation, facilitates absorption and uptake into the circulatory system.

1.2.4. Biochemistry of oral mucosa

All the layers of the oral mucosal membranes contain a large amount of protein in the form of tonofilaments, consisting at least seven proteins called “keratins” with molecular sizes of 40-70 Kda. Both keratinized and non-keratinized tissues of varying thickness and composition are found in oral cavity. Keratinized and non-keratinized tissues occupy about 50% and 30% respectively of the total surface area of the mouth.
The difference between keratinized and non-keratinized epithelia is merely the difference in the molecular size of existing keratins. Cells of non-keratinized epithelia contain lower molecular weight protein while those in keratinized epithelia contain mainly higher-molecular weight keratins. The lipid content of the cells varies between tissues (Jain et al., 1997).

1.2.5. **Physiological aspects and functions of oral cavity**

The oral cavity is accountable for the following primary functions:

- As a portal for intake of food material and water.
- To bring chewing, mastication and mixing of food stuff.
- Lubrication of food material and formation of bolus.
- Identification of ingested material by taste buds of tongue.
- Initiation of carbohydrate and fat metabolism. Absorption of catabolic products thereafter metabolism.
- To aid in speech and breathing process.
- Slight antisepsis of ingested material and within oral cavity by saliva.

1.2.6. **Secretions of Oral Cavity** (Yamahara et al., 1990 & Kumar et al., 2004)

The secretions in the oral cavity include saliva, crevicular fluid and mucus.

1.2.7. **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. The flow rates of saliva depend upon the type of stimulus used, the time of day, the length of time glands had been stimulated, the age and sex of the individual and by their state of health. The average resting flow rate for whole saliva is 0.3 ml/ min (range 0.1-0.5 ml/min). For stimulated saliva the average flow rate is 1.7 ml/min (range 1.1 to 3.0 ml/min). 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:

- Modulation of oral flora
- 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
• Stimulation of epithelial proliferation
• Initiation of fat and starch digestion

The pH of whole saliva varies between 6.5 and 7.5. The main buffering system is the bicarbonate system; however, phosphate and protein buffers also play a minor role.

1.2.8. Crevicular Fluid
It is a fluid secreted from the gingival glands of oral cavity.

1.2.9. 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.

Mucus has two main functions:
• Protectant for biological membranes (exposed epithelia).
• Excellent lubricant.

1.3. Drug Delivery Via Oral Cavity
The oral cavity can be used for local and systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism, or for the administration of proteins and peptides (Amir et al., 2001). The two main-routes for administration with oral cavity are:

• Sublingual route
• Buccal route.

1.3.1. Drug Delivery via Sublingual Route
Sublingual administration implies systemic administration of drugs via the membranes that line the floor of the mouth and ventral surface of the tongue. A rapidly dissolving tablet is generally given by the sublingual route (Amir et al., 2001). The sublingual region suffers with one major drawback. The two major salivary glands (submandibular and sublingual glands) open their ducts in sublingual area to
release saliva. There is constant flushing of saliva in this region because of which it is
difficult to retain drugs and delivery system and build or maintain high concentration
of drug, in the sublingual region.

1.3.2. Drug delivery via buccal route
Buccal delivery refers to drug release which can occur when a dosage form is placed
in the outer vestibule between the buccal mucosa and gingiva (Sevdsenel et al., 2001).

Terminology
Various terms to be used in theoretical elucidation of buccal absorption are:

- Oral cavity mucosa: The membranes that line the oral cavity which include the
  sublingual, buccal mucosa, the gums (gingiva), the palatal mucosa and the labial
  mucosa.
- Buccal membrane: The membrane inside the mouth that lines the cheek.
- Buccal drug delivery system: A delivery system designed to deliver drugs
  systemically or locally via or to the buccal mucosa.
- Salivary pellicle: The components of saliva are adsorbed on to the surface of the oral
  mucosa to form a salivary pellicle. This pellicle coats all surfaces in the mouth and is
  a multilayered structure.

1.4. Buccal Absorption
Buccal administration involves systemic or local administration via or to the buccal
membrane (Yamahara et al., 1990 & Kumar et al., 2004).

1.4.1. Mechanism
Oral mucosal drug absorption occurs by passive diffusion of the nonionized species, a
process governed primarily by a concentration gradient, through the intercellular
spaces of the epithelium. An investigation showed, using a variety of organic drugs
from acids to bases, that the passive transfer of non-ionic species across the lipid
membrane of the buccal cavity was the primary transport mechanism. The buccal
mucosa has been said to behave predominately as a lipoidal barrier to the passage of
drugs; as is the case with many other mucosa and (within limits) the more lipophilic
(or less ionized) the drug molecule, the more readily it is absorbed. It has been
concluded that the passive diffuses in accordance with the pH partition theory of drug
absorption is the major route of drug absorption for most drugs. However, it has been
reported that certain molecules e.g., some sugars and vitamins may be transported by
a specialized transport system capable of saturation.
It has been proposed that the intercellular route, rather than the transcellular route, is the predominant route for drug absorption. Large hydrophilic molecules in particular are believed to be transported by the intercellular route and the presence of the contents of membrane-coating granules in the intercellular space may inhibit penetration in both keratinized and nonkeratinized mucosae.

1.4.2. Dynamics

The oral mucosal absorption of drugs could be adequately described by first order rate process. Several potential barriers to oral mucosa drug absorption have been identified. These include the mucus layer, keratinized layer, intercellular lipid of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply blood/lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation. Some time 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 Eq. (3):

\[
\frac{dm}{dt} = \frac{KC}{Vi + Vt}
\]

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.

1.5. 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.

1.5.1. Membrane Factors

This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium; basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation (Jain et al., 1997).

1.5.2. Environmental Factors

(a) Saliva: The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10
mm. The thickness, composition and movement of this film effects buccal absorption. (Kumar et al., 2004)

(b) **Salivary glands:** The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration (Edsman et al., 2005).

1.5.3. **Movement of oral tissues**

Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods while withstanding tissue movements during talking and if possible during eating food or swallowing.

1.6. **Advantages of Buccal Absorption**

The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation. Following buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect. Contact with the digestive fluids of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate (Khanna et al., 1998).

The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, which may be advantageous if the drug delivery system or other excipients reversibly damage or irritate the mucosa. Additionally, there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes (Amir et al., 2001).

The oral mucosa is routinely exposed to a multitude of different foreign compounds and physical insult. So it has evolved a robust membrane that is less prone to irreversible damage by drug, dosage form or additives used therein. Thus, it may be feasible to include permeation enhancers in the formulation to increase systemic availability of the drug without observing permanent damaging effects.

Additional advantages of the oral cavity as a site for systemic drug delivery include: sterile techniques are not required during manufacture or administration, the oral cavity contains teeth upon which drug delivery systems can be physically attached
using dental adhesives, the oral mucosa is low in enzyme activity and enzymatic degradation is relatively slow, hence, from the point of drug inactivation, the oral mucosal route would be preferred to the nasal or rectal routes (Rao et al., 1998).

1.7. Limitations In Buccal Absorption

(a) The area of absorptive membrane is relatively smaller. If the effective area for absorption was dictated by the dimensions of a delivery system, this area then becomes even smaller (Kumar et al., 2004).

(b) Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. Involuntary swallowing of saliva results in a major part of dissolved or suspended released drug being removed from the site of absorption. Furthermore, there is risk that the delivery system itself would be swallowed (Rao et al., 1998).

(c) Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allerginicity and adverse properties such as discoloration or erosion of the teeth may limit the drug candidate list for this route. In addition, the drug should not adversely effects the natural microbial flora of the oral cavity (Amir et al., 2001).

(d) Conventional type of buccal drug delivery systems did not allow the patient to concurrently eat, drink or in some cases, talk (Khanna et al., 1998).

(e) The permeability of the oral mucosa is not great compared to other mucosal membranes.

1.8. Buccal Dosage Forms

Buccal Dosage forms are meant to be placed between gingiva and cheek.

1.8.1. Conventional Dosage Form

The conventional type of buccal dosage forms are buccal tablets, troches and lozenges, and mouth washers. Buccal tablets are small, flat, oval tablets and are intended to be held between the cheek and the teeth or in the cheek pouch (buccal tablets). Progesterone tablets can be administered this way. These tablets should be designed not to disintegrate but to slowly dissolve, typically over a 15 to 30 minutes period to provide for effective absorption. Troches and lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat. These tablet forms are commonly used to treat sore throat or to control coughing in common cold. Lozenges (pastilles or cough drops), these two
classes of tablets are designed not to disintegrate in the mouth but to dissolve or slowly erode over a period of perhaps 30 minute or less. A mouth wash is an aqueous solution, which is most often used for its deodorant, refreshing or antiseptic effect on buccal mucosa (Nakhat et al., 2007 & Madgulkar et al., 2009).

1.8.2. Advanced Buccal Dosage Forms
The novel type buccal dosage forms include buccal adhesive tablets, patches, films, tapes, semisolids (ointments and gels) and powders.

1.8.3. Mucoadhesive Tablets
Buccal mucoadhesive tablets are dry dosage forms that move to be moistened prior to placing in contact with buccal mucosa. A double layer tablets, consisting of adhesive matrix layer of hydroxy propyl cellulose and poly (acrylic acid) with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate) have been reported (Giannola et al., 2007).

1.8.4. Patches, Tapes & Films
Buccal patches consists of two ply laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which was then cut to the required oval shape. A novel mucosal adhesive film called “Zilactin” consisting of an alcoholic solution of hydroxy propyl cellulose and three organic acids, forms a film which applied to the oral mucosal surface which can be retained in place for at least 4 hours, even where challenged with fluids (Baviskar et al., 2009, Pandit et al., 2001 & Cilurzo et al., 2008).

1.8.5. Semisolid Preparations (Ointments and Gels)
Bioadhesive gels or ointments have less patient acceptability than solid dosage adhesive forms, and most are used only for localized drug therapy within the oral cavity. One of the original oral mucosal-adhesive delivery systems “orabase” consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes (Khairnar et al. 2010 & Perioli et al. 2008).

1.8.6. Powders
A hydroxpropyl cellulose containing powder are also used for the purpose of mucoadhesive drug delivery system that retain the drug on mucus membrane for a longer period of time and release the drug in a constant manner to maintain the drug concentration.
1.8.7. **Properties of an ideal buccal adhesive system**

(a) Polymer must be easily available and its cost should not be high.
(b) Should adhere to the site of attachment for a few hours
(c) Should show bioadhesive properties in both dry and liquid state
(d) Should release the drug in a controlled fashion
(e) Should provide drug release in an unidirectional way toward the mucosa
(f) Should facilitate the rate and extent of drug absorption
(g) Should not cause any irritation or inconvenience to the patient
(h) Should not aid in development of secondary infections such as dental caries.
(i) Should not interfere with the normal functions such as talking, drinking etc

1.8.8. **Commercial buccal adhesive drug delivery systems**

Some of the commercially available buccal adhesive formulations are (Jones et al., 1997 & Bandyopadhyay et al., 2006):

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Commercial Name</th>
<th>Bioadhesive polymer</th>
<th>Company</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Buccastem</td>
<td>PVP, Xanthum gum, Locust bean gum</td>
<td>Rickitt Benckiser</td>
<td>Tablet</td>
</tr>
<tr>
<td>2.</td>
<td>Suscard</td>
<td>HPMC</td>
<td>Forest</td>
<td>Tablet</td>
</tr>
<tr>
<td>3.</td>
<td>Gaviscon liquid</td>
<td>Sodium alginate</td>
<td>Rickitt Benckiser</td>
<td>Oral liquid</td>
</tr>
<tr>
<td>4.</td>
<td>Orabase</td>
<td>Pectin, gelatin</td>
<td>ConvaTech</td>
<td>Oral paste</td>
</tr>
<tr>
<td>5.</td>
<td>Corcodyl gel</td>
<td>HPMC</td>
<td>Glaxosmithkline</td>
<td>Oromucosal gel</td>
</tr>
<tr>
<td>6.</td>
<td>Corlan pellets</td>
<td>Acacia</td>
<td>Celltech</td>
<td>Oromucosal pellets</td>
</tr>
<tr>
<td>7.</td>
<td>Fentanyl Oralet</td>
<td>Sodium alginate</td>
<td>Lexicomp</td>
<td>Lozenge</td>
</tr>
<tr>
<td>8.</td>
<td>Miconazol Lauriad</td>
<td>Xanthum gum</td>
<td>Bioalliance</td>
<td>Tablet</td>
</tr>
<tr>
<td>9.</td>
<td>Zilactin</td>
<td>HPMC</td>
<td>Zila</td>
<td>Buccal film</td>
</tr>
<tr>
<td>10.</td>
<td>Luborant</td>
<td>Sodium CMC</td>
<td>Antigen</td>
<td>Artificial Saliva</td>
</tr>
<tr>
<td>11.</td>
<td>Tibozole</td>
<td>PVP, Xanthum gum</td>
<td>Tibotec</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

Table 1.1: Commercially available buccal adhesive formulations
1.9. Design Of Buccal Mucoadhesive Patches

1.9.1. Different Components of Buccal Mucoadhesive Patches

1.9.2. Profile of Each component (Jain et al., 1997)

1.9.2.1. Drug

The important drug properties that affect its diffusion through the patch as well as the buccal include molecular weight, chemical functionality and melting point. The selection of a suitable drug for design of buccal mucoadhesive drug delivery system should be based on pharmacokinetic properties. Following are the critical properties for candidature to buccal mucoadhesive drug delivery (Puratchikody et al. 2011).

• The conventional single dose of drug should be low.
• Through oral route, the drug may exhibit first pass effect or presystemic drug elimination. The fraction of oral bioavailability $F$ is low ($F<0.5$ in comparison to IV dose) and liver extraction ratio (ER) is high ($ER>0.7$).
• Drug absorption should be passive when given orally.
• The drug should not adversely affect the natural microbial flora or oral cavity.
• Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.
• The drug must be appreciably absorbed via buccal mucosa as evaluated by buccal absorption test.

1.9.2.2. Polymers

In buccal mucoadhesive patches, three different categories of polymers differing functionally are used. These are as follows (Madgulkar et al., 2009):

(a) Bioadhesive polymers.
(b) Polymers controlling rate of release of drug from matrix.
(c) Polymers used to prepare backing membrane.
(d) Plasticizer

1.9.2.2.1. Ideal characteristic of Polymer

1. Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
2. Should have good spreadability, wetting, swelling, solubility and biodegradability properties.
3. pH should be biocompatible and should possess good viscoelastic properties.
4. Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
5. Should possess peel, tensile and shear strengths at the bioadhesive range.
6. Polymer must be easily available and its cost should not be high.
7. Should show bioadhesive properties in both dry and liquid state.
8. Should demonstrate local enzyme inhibition and penetration enhancement properties.
9. Should demonstrate acceptable shelf life.
10. Should have optimum molecular weight.
11. Should possess adhesively active groups.
12. Should have required spatial conformation.
13. Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
14. Should not aid in development of secondary infections such as dental caries.

(a) **Bioadhesive polymers**: These are hydrophilic macromolecules that contain numerous hydrogen bond forming groups. These polymers become bioadhesive on hydration and are therefore called “wet adhesives”. The characteristic properties of ideal bioadhesive are (Gupta et al., 2011):
1. It should have good mucoadhesive property and at the same time it should be innocuous to buccal mucosa.
2. It should not chemically react with the drug and other excipients in formulation.
3. Molecular weight, glass transition temperature and chemical functionality of polymer must allow proper diffusion and release of drug.
4. It should be pharmacologically bland-free from irritancy, allergenicity, bad taste and adverse properties such as discoloration or erosion of teeth. Cost of polymer should not be excessive.
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Categories</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
<td>Seminatural/natural</td>
<td>Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate)</td>
</tr>
<tr>
<td></td>
<td>Synthetic</td>
<td>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(methylvinylether-co-methacrylic acid), poly(2- hydroxyethyl methacrylate), poly(acrylic acidco-thylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG] Others: polyoxyethylene, PVA, PVP, thiolated polymers</td>
</tr>
<tr>
<td><strong>Aqueous solubility</strong></td>
<td>Water-soluble</td>
<td>CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA,sodium CMC, sodium alginate</td>
</tr>
<tr>
<td></td>
<td>Water-insoluble</td>
<td>Chitosan (soluble in dilute aqueous acids), EC, PC</td>
</tr>
<tr>
<td><strong>Charge</strong></td>
<td>Cationic</td>
<td>Aminodextran, chitosan, (DEAE)-dextran, TMC</td>
</tr>
<tr>
<td></td>
<td>Anionic</td>
<td>Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum</td>
</tr>
<tr>
<td></td>
<td>Non-ionic</td>
<td>Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA,PVP, scleroglucan</td>
</tr>
<tr>
<td><strong>Potential</strong></td>
<td>Covalent</td>
<td>Cyanoacrylate</td>
</tr>
<tr>
<td></td>
<td>Hydrogen bond</td>
<td>Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA</td>
</tr>
<tr>
<td></td>
<td>Electrostatic</td>
<td>Chitosan (Gandhi et al., 2011)</td>
</tr>
</tbody>
</table>

Table 1.2: Mucoadhesive Polymers Used In The Oral Cavity
(b) **Polymers controlling rate of release of drug from buccal mucoadhesive patches**

The polymers which are insoluble in saliva or water can be used as efficient matrix systems through which rate of release of drug can be controlled as desired. Examples for this category include ethylcellulose and butyl rubber. Water-soluble polymers can be used for controlling rate of release in which, rate of polymer dissolution will be release rate determining step (Veillard et al., 1987).

(c) **Polymers used to prepare backing membrane**

The polymer whose solution can be casted into thin poreless uniform water impermeable film can be used to prepare backing membrane of patches. It should have good flexibility and high tensile strength and low water permeation. They should be stable on long storage maintaining there initial physical properties. The backing membrane can be of two types:

- A polymer solution casted into thin film. It is biodegradable in nature.
- A polyester laminated paper with polyethylene. It is not biodegradable.

The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The material used for the backing membrane must be inert and impermeable to drugs and penetration enhancers. The thickness of the backing membrane must be thin and should be around 75-100 microns. The most commonly used backing materials are polyester laminated paper with polyethylene. Other examples include cellophane, multiphor sheet and polyglassine paper.

(d) **Plasticizer**

These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. Examples of common plasticizers used are glycerol, propylene glycol, PEG 200, PEG 400, castor oil etc. Usually the percentage of polymer falls in the range of 10-50% of total polymer weight. The plasticizers help in release of the drug substance from the polymer base as well as act as penetration enhancers. The choice of the plasticizer depends upon the ability of plasticizer material to solvate the polymer and alters the polymer – polymer interactions. When used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity (Jain et al., 1997).
1.10. **Mucoadhesion/ Bioadhesion**: Bioadhesion is an interfacial phenomenon in which, two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as the adhesion between polymer and/or copolymer and a biological membrane. In the case of polymer attached to the mucin layer of mucosal tissue, the term “mucoadhesion” is employed.

1.10.1. **Theories of Bioadhesion/ Mucoadhesion**:

Mucoadhesion is proposed to occur in three stages. Initially, an intimate contact must form between the mucoadhesive and mucus (i.e., they must “wet” each other) then the mucus/ mucoadhesive macromolecules interpenetrate and finally the molecules interact with each other by secondary non-covalent bonds. The bonding occurs chiefly through both physical and chemical interactions. Physical or mechanical bonds result from entanglement of the adhesive material and the extended mucus chains. Secondary chemical bonds may be due to electrostatic interactions, hydrophonic interactions, hydrogen bonding and dispersion forces. Covalent bonding, such as occurs with cyanoacrylates, is also possible for mucoadhesion but is not yet common in pharmaceutical systems. Several theories of bioadhesion have been proposed to explain fundamental mechanism(s) of attachment. In a particular system one or more theories can equally well explain or contribute to the formation of bioadhesive bonds. Various theories propounded to explain mucoadhesion/ bioadhesion are (Lee et al., 2000):

**A. Wetting Theory**

This theory best describes the adhesion of liquid or paste to a biological surface. The work of adhesion can be expressed in terms of surface and interfacial tension \( \gamma \) being defined as the energy per cm² released when an interface is formed. Work of adhesion is given by:

\[
W_a = \gamma A + \gamma_b - \gamma B
\]

Where the subscript A and B refer to the biological membrane and the bioadhesive formulation respectively, the work of cohesion is given by:

\[
W_e = 2\gamma A = 2\gamma B
\]

For a bioadhesive material B spreading on a biological substrate A the spreading coefficient is given by:

\[
S_{B/A} = \gamma A - (\gamma B + \gamma AB)
\]
SB/A should be positive for a bioadhesive material to adhere to a biological membrane. For a bioadhesive liquid B adhering to a biological membrane A the contact angle is given by:

\[ \cos \theta = \frac{\gamma_A - \gamma_{AB}}{\gamma_B} \]

**B. Diffusion Theory**

According to this theory the polymer chains and the mucus co-mingle to a sufficient depth to create a semi-permanent adhesive bond. The polymer chains penetrate the mucus; the exact depth to which it penetrates to achieve sufficient mucoadhesion depends on diffusion coefficient, time of contact, and other experimental variables. The diffusion coefficient depends on molecular weight and decreases rapidly as the cross-linking density increases. The molecular weight, chain flexibility, expanded nature of both the mucoadhesive and substrates as well as similarity in chemicals structure are required for good mucoadhesion. The penetration depth is estimated as:

\[ L = (tDp)^{1/2} \]

Where L is the penetration depth, t is the time of contact and Dp is the diffusion coefficient.

**C. Electronic theory**

According to this theory electron transfer occurs on contact of adhesive polymer and the mucus glycoprotein network because of difference in their electronic structure. This results in the formation of electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

**D. Fracture Theory**

This theory analyses the force required to separate two surfaces after adhesion. The maximum tensile stress produced during detachment of polymer and mucus membrane can be calculated as:

\[ S_m = \frac{F_m}{A} \]

Where Sm is the tensile stress, Fm & A are the maximum force of detachment and surface area involve in the adhesive interaction respectively.

**E. Adsorption Theory**

According to this theory after an initial contact of two surfaces the material will 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. From a drug delivery point of view the mechanism
of mucoadhesion appears best explained by a combination of diffusion and electronic theory, although other mechanisms may simultaneously be operative at minor level. It may also be more appropriate to restrict the term “mucoadhesion” to describing the adhesion of hydrated dosage forms to those mucus membranes having a substantial mucus layer. The term “bioadhesion” or “mucosal adhesion” may be more suitable to describe adhesion to the mucosal of the oral cavity.

1.11. Structure and Design of Buccal Dosage Form

Buccal Dosage form can be of two types (Mitra et al., 2002):

1. **Matrix type**: The buccal patch designed in a matrix configuration contains drug, adhesive and additives mixed together.

2. **Reservoir type**: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss. Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

1.12. LITERATURE SURVEY ON BUCCAL DRUG DELIVERY

Bioadhesive films of fentanyl were developed using PVP K30 and PVP K 90 as polymers, for the delivery in buccal cavity. The in-vitro performance was done on pig oesophagus. Films were evaluated for the permeation of drug across the mucosa and effect of pH on it. Delivery of fentanyl was determined across full thickness mucosa and across heat separated epithelium. The influence of film pH was also investigated and it was found that fentanyl permeation increases with increasing pH (Jacques et al., 2007). Eight formulations of mucoadhesive buccal patches of aceclofenac were prepared, using gelatin, poly sodium CMC and poly vinyl alcohol by varying the
concentration of polymer. The evaluation was performed for weight variation, patch
thickness, entrapment efficiency, folding endurance, in-vitro drug release and stability
study. Formulation containing 6% aceclofenac, 4.5% gelatin, 5.5% poly sodium
CMC, 2.5% poly vinyl alcohol and distilled water up to 100%, release the drug 88.4%
in 8 hours (Baviskar et al., 2009). Mucoadhesive buccal tablets of Naltrexone HCl
were developed HCl by direct compression method using poly-octylcyanocrylate as
matrix. Franz diffusion cell was used for ex-vivo permeation study across porcine
buccal mucosa 800 µm; data was compared with in-vitro data previously obtained by
reconstituted human oral epithelium 100 µm in thickness. Release pattern was
Higuchian and there was no any sign of flogosis when evaluated histopathologically
(Giannola et al., 2007). Solvent casting technique was used for the preparation of
buccoadhesive delivery system of isosorbide. Carbopol 934P, PVP as mucoadhesive
polymers and propylene glycol, diethyl phthalate as plasticizers were used. Physical
characters, bioadhesive performance, and other parameters were evaluated. In the
carbopol films containing ratio of Eudragid RL100 and PVP in proportion of 1:2 &
2:1, respectively & both the plasticizers release rate was higher. The kinetics was zero
order and mechanism was diffusion controlled (Doijad et al., 2006). For the systemic
delivery of propranolol hydrochloride buccoadhesive films were prepared using
carbopol 934P, NaCMC and polycarbophil. The ex-vivo mucoadhesive study showed
that there was a correlation between concentration of polymer and mucoadhesivity.
The in-vivo study was carried out on oral mucosa of rabbit by inducing tachycardia
with the help of isoprenaline. The results of in-vivo study showed a correlation with
in-vitro study. Release pattern was zero order kinetics and the system was successful
to avoiding the first pass metabolism of the drug (Pandit et al., 2001). Mucoadhesive
microspheres of metoprolol tartarate were prepared using HPMC, Carbopol and
polycarbophil by ionic gelation technique. Rotating cylindrical method was used for
mucoadhesive strength studies. For mucoadhesive microspheres HPMC had greater
mucoadhesive properties than carbopol and polycarbophil. With the help of falling
film technique in vitro mucoadhesive strength was determined and compared with ex
vivo studies (Belgamwar et al., 2009). Mucoadhesive bilayered buccal tablets of
Atorvastatin calcium were developed using Carbopol 934P, Sodium CMC,
Hydroxyethyl cellulose and Sodium alginate along with ethyl cellulose as an
impermeable backing layer by direct compression method. In the buccal cavity no any
irritation was observed because the surface pH of all tablets was close to neutral pH
Principles of mucoadhesive drug delivery systems based on adhesion to biological surfaces that are covered by mucus were studied. The mucoadhesive drug delivery systems is one of the most important novel drug delivery systems with its various advantages and it has a lot of potential in formulating dosage forms for various chronic diseases (Tangri et al., 2011). A carvedilol-Methyl-β-cyclodextrin complex was prepared by kneading method and characterized by Fourier Transformation Infrared spectroscopy, Differential Scanning Calorimetry and powder X-Ray Diffractometry studies. The complex was incorporated into buccal tablet and evaluated for drug release, mucoadhesive strength and ex-vivo permeability. The bioavailability of buccal tablet was improved after incorporation of complexed carvedilol (Hirlekar et al., 2009). Direct compression method was used for the preparation of mucoadhesive buccal tablet of Domperidone using Carbopol 934P, Methocel K4M, Methocel E15LV and Chitosan. Mucoadhesive performance and in-vitro drug release was best in the tablet containing chitosan and Methocel K4M in ratio of 1:1. The release pattern from the tablet was Hixson Crowel release kinetics (Ganesh et al., 2008). Plain and medicated mucoadhesive patches of cetylpyridinium chloride (CPC) were prepared using polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC) and chitosan. Both plain and medicated patches were evaluated but when the CPC was added in the formulation the radial swelling was increased (Ismail et al., 2003). With the help of low dextrose equivalent as film forming material oral fast-dissolving films of maltodextrins were developed. This basic formulation was adapted to the main production technologies, casting and solvent evaporation or hot-melt extrusion, by adding sorbitan monoleate or cellulose microcrystalline (MCC), respectively. MCC decreased the film ductility and significantly affected the film disintegration time both in vitro and in vivo (Cilurzo et al., 2008). A simple; isocratic and sensitive high-performance liquid chromatographic (HPLC) method was developed and validated for the simultaneous analysis of marker compounds for the atenolol and lidocaine pathways during permeation enhancement studies across the buccal mucosa. After pre-treatment with glycodeoxycholate-Na an increase in the permeation of atenolol was observed by the application of this method, while the permeation of lidocaine did not change significantly (Jasti et al., 2008). By an investigation the ability of galantamine to permeate through the buccal epithelium using two permeation models was done. Firstly, in vitro permeation experiments were carried out using reconstituted human oral non-keratinised epithelium. Then results
were validated by ex vivo experiments using porcine buccal mucosa as membrane and Franz type diffusion cells as permeation model, the buccal mucosa does not block diffusion of galantamine (Caro et al., 2008). A complex omeprazole with cyclodextrins in the absence and in the presence of an alkali, L-arginine agent was prepared to check the effect of cyclodextrins on the buccal permeation. In vitro transbuccal permeation of omeprazole non-complexed and complexed with b-cyclodextrin and in presence of L-arginine was examined using freshly obtained porcine buccal mucosa, and in the complexed form the drug permeation was more (Veiga et al., 2009). For the measurement of mucoadhesion films of pectin and chitosan were formed. Mucoadhesive controlled release tablets of lercanidipine hydrochloride were developed by direct compression method using polyethylene oxide and HPMC individually or in combinations. The tablets containing only polyethylene oxide shows good mucoadhesion and depends on the concentration of polymer (Charde et al., 2008). Chitosan and pectin interpolymer complexes were used for the preparation of bioadhesive patches of carvedilol. Optimized patches demonstrated good in vitro & in vivo results, and significantly improve the bioavailability of drug (Kaur et al., 2011). A number of mucoadhesive polymers like thiolated polymers were used for the preparation of buccal drug delivery system. Discussion was also made about the anatomy of oral mucosa and mechanism of drug permeation, this route shows advantages over the others route for the delivery of a variety of drugs (Khairnar et al., 2010). Sustained release mucoadhesive tablets of flurbiprofen were prepared using chitosan as primary polymer and HPMC and sodium CMC as secondary polymer, and characterized the prepared tablet for weight variation, thickness, hardness, swelling index and in vitro drug release. Both the polymers showed synergistic effect on in vitro drug release (Darwish et al., 2009). Buccal patches of propranolol hydrochloride were prepared by solvent casting method using a natural bioadhesive polymer chitosan. For the enhancement of drug release different concentration of PVP K-30 also used (Patel et al., 2006). Investigation was made on the benefit of thiolated polymers by preparing buccal tablets and compared the disintegration time unmodified polymer and conjugated polymer. A complex of L-Cysteine by covalently attachment with polycarbophil mediated by carbodiimide was formed for the preparation of tablet. The tablets based on thiolated polycarbophil remained attached on mucosa (Schnurch et al., 2003). Based on poly ethyleneoxide (PEO) as bioadhesive sustained release platform and hydroxypropyl-β-cyclodextrin
HPβCD as modulator of drug release tablet dosage form of the poorly soluble drugs carvedilol (CAR) was prepared. The drug permeation through PEO was higher than the HPβCD tablets (Rotonda et al., 2006). Bi-laminated films & bilayered tablets were prepared by solvent casting method and direct compression method using chitosan and ethyl cellulose. Both the prepared films and tablets show a sustained release of drug (Lopez et al., 1998). Some authors were discussed about the buccal and oral administration of drugs which undergoes severe first pass metabolism through hydrogel. They claimed that hydrogel was an appropriate material for the buccal delivery system because of its mucoadhesiveness and sustained release properties (Machida et al., 1993). Transport of fluorescein isothiocyanate labelled dextran of different molecular weights as model compounds for peptides and proteins through buccal mucosa was characterized. Investigation was made on the penetration of these dextrans through buccal mucosa by measuring transbuccal fluxes and by analysing the distribution of the fluorescent probe in the epithelium (Junginger et al., 1999). In the buccal films prepared by different polymers like carbopol, sodium alginate and HPMC, the sodium alginate films exhibited greater bioadhesion and showed higher tensile strength and elasticity than carbopol films (Sklason et al., 2009). With the help of drug/cyclodextrin inclusion buccal bioadhesive films of atenolol were prepared. Freeze drying method was used for the preparation of complex in solid state. For the preparation of buccal drug delivery system complexes were incorporated into films (Jug et al., 2009). Nanoparticles were developed based on mucoadhesive system (diskettes), an alternative novel transmucosal (buccal) delivery of Fluoxetine hydrochloride by emulsion solvent evaporation method. The optimized formulation using 3² factorial designs indicated it is possible to develop a novel mucoadhesive system for buccal route that could be effectively maintain the drug release (Sapre et al., 2009). Investigation was made on the influence of different formulation parameters on the rheological and functional properties of emulgels, intended for the buccal administration of flurbiprofen. Analysis on the emulgel in term of size & morphology and also for in vitro release studies was performed, and the emulgels were able to remain on buccal mucosa for an average period of 1 h (Perioli et al., 2008). Monolayered multipolymeric films comprising of Propranolol HCl were prepared using Eudragit and Chitosan, by emulsification and casted by a new approach using a silicone-molded tray with individual wells. The study confirmed the potential of monolayered multipolymeric films as a promising candidate for buccal
delivery of propranolol (Govender et al., 2008). For the controlled release of piroxicam buccoadhesive controlled release tablets were prepared, and evaluated the tablets for their dissolution, swelling and mucoadhesive properties, the differences in release rates of piroxicam from the tablets could be attributed to the presence of the polymers and to cyclodextrin complexation (Jug et al., 2004). For the delivery through buccal route the fast dissolving film of salbutamol were prepared by solvent evaporation method using polyvinyl alcohol as polymers and glycerol as plasticizer. The concentration of polymer and plasticizer showed effect on mechanical properties and % drug release (Mashru et al., 2005). Two water soluble drugs diltiazem hydrochloride and metclopramide were used for the preparation of buccal mucoadhesive tablets. Effect of drug and dose on the mucoadhesive properties and in-vitro drug release was determined. An observation was performed on the effect of ageing, for 6 months at 40°C and 75% RH, there was no effect on mucoadhesive performance (Boraie et al., 2004). Relative bioavailability of Fentanyl effervescent buccal tablets (FEBT) with that of oral transmucosal fentanyl citrate (OTFC) was compared, the total systemic exposure was statistically similar between FEBT and OTFC (Darwish et al., 2006). Buccal administration of ibuprofen was done with the help of mucoadhesive patches using PVP as film forming polymer and NaCMC as mucoadhesive polymer. In-vitro results, revealed that the diffusion process was the main drug release studies mechanism and the Higuchi’s model provided the best fit (Perioli et al., 2004). The effect of formulation variables on the buccal absorption of the drug was determined by preparing the buccal tablets of nifedipine. Natural flax seed polymer was incorporated, and compared the bioavailability of drug per oral administration with buccal administration, the presence of natural flax seed polymer enhance of bioavailability due to increase in mucoadhesion (Vijayaraghavan et al., 2004). Mucoadhesive buccal patches of miconazole nitrate were prepared using NaCMC, chitosan, PVA, HEC and HPMC. The bioadhesion, swelling index, surface pH and in-vitro drug release was determined. The patches exhibited sustained release over mare than 5 hours (Ismail et al., 2003). Buccal patches of metoprolol tartrate were developed by using Eudragit NE40D, NaCMC and carbopol. The bioadhesion as well as the drug release was determined, on addition of hydrophilic polymers the drug release as well as the enhanced the bioadhesiveness was observed (Yuen et al., 1999). Bilayered buccoadhesive tablets of atenolol were formulated by direct compression method, using different mucoadhesive polymers such as carbopol, sodium alginate
and HPMC, to prepared tablets were evaluated for the different physicochemical and bioadhesive parameters. The preparation containing combination of carbopol and HPMC showed better bioadhesive strength (Pannier et al., 2011). Buccal films of losartan were prepared using HPMC, EC and Eudragit RS 100, and evaluated for mucoadhesive forces, thickness, weight, drug contents, and surface pH. The mucoadhesive force, swelling index, tensile strength and % elongation was higher in formulation containing HPMC (Koland et al., 2010). The advantages of buccal films over the dosage forms were explained. The films have improved patient compliance due to their small size and reduce thickness, compared to lozenges and tablets. The suitable method for the preparation of buccal films was solvent casting (McConville et al., 2011). HPMC E-15 and NaCMC alone or in combinations were used for the preparation of buccal patches of lidocaine hydrochloride by solvent casting technique. The prepared patches were evaluated for weight, thickness, surface pH, in-vitro drug release and in-vitro permeation. The optimized patch showed more than 80% drug release in 3 hrs (Parmar et al., 2011). A discussion was made about the mucoadhesion and buccal route of administration. Within the oral mucosal cavity, the buccal region offers an adorable route of administration for systemic drug delivery. The degree of mucoadhesion was calculated, the bonding was influenced by various polymer-based properties (Patel et al., 2011). It was found that major hindrance for the absorption of a drug taken orally was extensive first pass metabolism and this problem may be overcome by buccal transmucosal delivery which helps to bypass first-pass metabolism by allowing direct access to the systemic circulation through the internal jugular vein (Puratchikody et al., 2011). Fast dissolving buccal films, which dissolve or disintegrate instantly on the patient buccal mucosa which improved bioavailability with reducing dosing frequency to mouth plasma peak levels, and minimize adverse/side effects and also make it cost effective were developed (Mahajan et al., 2011). Buccal film of Rasagiline for intraoral delivery was prepared using carbopol P 940 and sodium alginate as mucoadhesive polymers. The prepared films were evaluated for surface pH, percentage moisture absorption, Percentage moisture loss, folding endurance and content uniformity. Carbopol has more pronounced effect than sodium alginate on the mucoadhesive strength (Bukka et al., 2010).
1.13. OBJECTIVE OF THE WORK

Present research aims at prepare and evaluate the mucoadhesive buccal device of cardiovascular drugs (Metoprolol succinate and Carvedilol) using Chitosan, NaCMC and PVA as polymer, to improve the bioavailability.

The main objectives of this work to:

- Perform preformulation studies of metoprolol succinate and carvedilol.
- Prepare the mucoadhesive buccal patches of metoprolol succinate and carvedilol using chitosan, NaCMC and PVA.
- Evaluate the prepared buccal patches for
  - Content uniformity,
  - Patch thickness,
  - Weight variation,
  - % swelling,
  - Folding endurance,
  - Residence time,
  - Mechanical properties,
  - Bioadhesion study,
  - In vitro permeation
  - Release study,
  - Pharmacodynamic study,
  - Pharmacokinetic study,
  - Effects of ageing on patches.
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