Chapter 1

CONTENTS:

1.1. The oral mucosa as a site for delivery
1.1.1. Anatomy, physiology and properties of the oral mucosa
1.1.2. Permeability
1.1.3. Various transmucosal routes of drug delivery

1.2. Soft Palate
   1.2.1. Anatomy and physiology
   1.2.2. Histology and vascular supply
   1.2.3. Soft palate mucosal structure and its suitability
   1.2.4. Mucus secretion in goblet cells from human soft palate
   1.2.5. Muscles and nerves of soft palate

1.3. Mucus
   1.3.1. Dynamic properties of mucus
      1.3.2.1. Mucus is secreted continuously
      1.3.2.2. Mucus forms and maintains and adherent unstirred layer

1.4. Prerequisites for successful oro-mucosal drug delivery system
   1.4.1. Formulation factor and design
   1.4.2. Mucoadhesive agents
   1.4.3. Penetration enhancers
      1.4.3.1. Mechanisms of action of penetration enhancer
1.5. Various transmucosal dosage forms

1.5.1. Non-attached drug delivery systems

1.5.2. Immobilised drug delivery systems

1.6. Absorption pathways

1.6.1. Intracellular route

1.6.2. Intercellular route

1.7. Experimental methodology for palatal permeation studies

1.8. Advantages and disadvantages of oro-soft palatal platform drug delivery system

1.8.1. Advantages

1.8.2. Limitations

1.9. Possibilities for future research

1.10. References
Introduction

For systemic delivery, the oral route has been the preferred route of administration for many systemically active drugs, when administered active drugs, however, many therapeutic agents have been reported subjected to extensive presystemic elimination by gastrointestinal degradation and or hepatic metabolism results in low systemic bioavailability, short duration of therapeutic activity, and/or formation of inactive or toxic metabolites. In the exploration of oral controlled release drug administration, one encounters three areas of potential challenge.

1- Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment(2).

2- Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for prolonged period of time to maximize the delivery of a drug dose.

3- Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Therefore the delivery of drugs via the absorptive mucosa in various easily accessible body cavities, like the ocular, nasal, buccal, rectal and vaginal mucosae has the advantage of bypassing the hepato-gastrointestinal first-pass elimination associated with oral administration. Because of the dual biophysical and biochemical nature of these mucosal membranes drugs with hydrophilic and/or lipophilic characteristics can be readily absorbed. In addition, mucosal membranes, particularly the soft palate, also be useful sites with good accessibility for easy application of drug delivery systems, especially for those with bio(muco)adhesive properties offer the potential for a absorption of drug. With the development of mucosal delivery systems having controlled drug release characteristics, the mucosal routes can be exploited for the noninvasive systemic delivery of organic- and peptide- based drugs, with rapid absorption as well as sustained drug action.
1.1. The oral mucosa as a site for delivery

1.1.1. Anatomy, physiology and properties of the oral mucosa

The anatomy and physiology of the oral mucosa have been extensively reviewed in several publications [1-8]. Nevertheless, a brief overview in this chapter is essential. The oral mucosa is composed of an outermost layer of stratified squamous epithelium, intermediate layer, lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium [9]. The basement membrane forms a distinctive layer between the connective tissues and the epithelium. It provides the required adherence between the epithelium and the underlying connective tissues, and functions as a mechanical support for the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa. Although knowledge of the properties of the absorbing membrane is essential for the successful utilisation of the oral cavity as a site for drug delivery, it is not the purpose of this paper to document in detail the composition and structural features of the oral mucosa. For a comprehensive review on the structure and biochemistry of the oral epithelium are illustrated by Squier et al. [10,11] and on its biochemistry to Gerson et al. [12]. It is important to realise, however, that from a drug delivery point of view the oral cavity is rather a complex area. Oral epithelium consists of a stratified squamous epithelium. Oral mucosa can be categorized into sublingual, gingival, buccal and palatal mucosa through which oral transmucosal drug delivery can be achieved. Gingiva and hard palate are keratinised areas, whereas buccal and sublingual areas are non-keratinised. Oral mucosa is covered largely by stratified squamous epithelium that functions much like skin, acting as a barrier to potentially dangerous substances. Due to the thin layer of epidermis, lack of a keratinized layer, and significantly greater vascular system, however, it is better permeated by comparable substances that have a lower depot effect than skin. A gel-like secretion known as mucus, which contains mostly water-insoluble glycoproteins, covers the entire oral cavity. Mucus is bound to the apical cell surface and acts as a protective layer to the cells below [13]. It is also a visco-elastic
hydrogel, and primarily consists of 1–5% of the above-mentioned water insoluble glycoproteins, 95–99% water, and several other components in small quantities, such as proteins, enzymes, electrolytes, and nucleic acids. This composition can vary based on the origin of the mucus secretion in the body [14-15].

1.1.2. Permeability
The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa there is considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa. The permeability coefficient of a drug is a measure of the ease with which the drug can permeate a membrane. The permeability coefficient is a function of the membrane thickness (i.e., inverse to its thickness) degree of keratinisation of these tissues, and the physicochemical properties of the drug (e.g., molecular weight, size, lipophilicity). Drug permeability appears to be highest in the sublingual area and lowest at the gingival site [16]. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called ‘membrane coating granules’ (MCG) [4, 17]. When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200μm of the superficial layer. In both keratinized and non-keratinized epithelia, the limit of penetration coincided with the level where the MCGs could be seen adjacent to the superficial plasma membranes of the epithelial cells. Since same result was obtained in both keratinized and non-keratinized epithelia, keratinization by itself is not expected to play a significant role in the barrier function [18]. The components of the MCGs in keratinized and non-keratinized epithelia are different; however The MCGs of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinized epithelium contains MCGs that are non-lamellar. The MCG lipids of keratinized epithelia include sphingomyelin, glucosylceramides, ceramides, and other nonpolar lipids, however for non-keratinized epithelia, the major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids [19]. Apart from the MCGs, the basement membrane may present some resistance to
permeation as well, however the outer epithelium is still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules. The low permeability coefficients of drugs through oral mucosa represent the major problem which must be overcome for the successful development of the oral cavity as a site for drug delivery. Various other advantages shown in figure (1)

Figure-1 Oral transmucosal technology which favours its suitability for mucoadhesive drug delivery systems

1.1.3. Various transmucosal routes of drug delivery

Drugs for systemic medication are administered traditionally and routinely by oral and by parenteral routes. Although generally convenient, both routes have a number of disadvantages, especially for the delivery of peptides and proteins, a class of drugs that has been rapidly emerging over the last decades [20]. Orally administered drugs are exposed to harsh environment of the gastrointestinal tract, potential chemical and enzymatic degradation [21]. After gastrointestinal absorption the drug has to pass the liver, where, dependent on the nature of the drug, extensive first pass metabolism can take place with subsequent rapid clearance from the blood stream [22]. Low permeability across the gastrointestinal mucosa is also often encountered for
macromolecular drugs [23]. Parenteral administration avoids drug degradation in the gastrointestinal tract and hepatic first pass clearance but due to pain or discomfort during injection, patient compliance is poor, particularly if multiple daily injections are required as e.g. in the insulin therapy [24-25]. Also injection related side effects like tissue necrosis and thrombophlebitis lead to low patient acceptability. In addition, administration by injection requires trained personnel which add to the relatively high costs of parenteral medication.

1.2. Soft Palate

1.2.1. Anatomy and physiology
The soft palate is a mobile flap suspended from the posterior border of the hard palate, sloping down the back between the oral and nasal parts of the pharynx. The soft palate (or velum, or muscular palate) is the soft tissue constituting the back of the roof of the mouth [26]. The soft palate is distinguished from the hard palate at the front of the mouth in that it does not contain bone and boundary between the hard and soft palate is readily palpable and may be distinguished by a change in color, the soft palate being a darker red with a yellowish tint. Soft palate is a thick fold of mucosa enclosing an aponeurosis, muscular tissue, vessels nerves, lymphoid tissue, mucous glands and two small pits, the fovea palatine, one on each side of the midline are present. They represents the orifices of ducts from some of the minor mucous glands of the palate. The anterior (oral) surface of the soft palate is concave, and has a median raphe [27-28]. The posterior aspect is convex and continuous with nasal floor, the anterio-superior border is attached to posterior margin of the hard palate and the sides blend with the pharyngeal wall. The anterior third of the soft palate contains little muscle and consists mainly of the palatine aponeurosis. This region is less mobile and more horizontal than the rest of the soft palate and is the chief area acted upon by tensor veli palatini. When the mouth is opened wide, this raphae raises a fold of mucosa that marks internally the posterior boundary of the cheek, and is an important landmark for an inferior alveolar nerve block.
1.2.2. Histology and vascular supply

Typical adult soft palate consist of several major tissue layers including [29] the oral aspect which is glandular with a zone of adipose tissue located somewhat laterally;[30] two middle layers are muscular with the more inferior layer consisting mainly of transverse levator veli palatini fibers and the overlying longitudinal layer of musculus uvulae fibres [31] a supero-anterior layer consisting of the tensor veli palatini tendon; and [32] a postero-inferior layer consisting of a mixture of tissue that is primarily glandular. The oral mucosa consists of stratified squamous epithelium with a basement membrane that is reinforced with a dense meshwork of elastic fibers. The nasal mucosa consists of pseudo-stratified ciliated columnar epithelium anteriorly and stratified squamous epithelium postero-inferiorly. The mucous membrane on the oral surface of the soft palate is highly vascularized. The papillae of the connective tissue are few and short the stratified squamous epithelium is non-keratinized, the lamina propria shows distinctive layer of elastic fibres separating it from the submucous. The latter is relatively loose and contains an almost continuous layer of mucous glands. Typical oral mucosa is continuous around the free border of the soft palate for a variable distance and is then replaced by nasal mucosa with its pseudo-stratified, ciliated columnar epithelium [33-34]. Oral side epithelium of the soft palate is covered consistently and uniformly with non-keratinized stratified squamous epithelium of about 20-30 cell layers thick and therefore apparently well suited to withstand abrasive forces. The posterior portion is better adapted for withstanding the abrasion encountered in velopharangeal contacts during valving. The squamous epithelium on the nasal surface of the velum is thinner (less than 20 cell layer thick) compared to its counterparts on its oral surface (generally greater than 20 cell layers). The oral aspects of the palate, especially the anterior half is well endowed with seromucous glands, and to a lesser degree with fatty tissues. The glands function to aid in moisturizing the oral cavity to facilitate the passage of food even though the secretions from these glands accounts for a relatively small amount of saliva (750 ml) secreted daily [35]. Adipose tissues are well defined in a layer beneath the seromucous gland. The oral glandular and adipose tissue appear to be a substantial inertial constraint to overcome in palatal elevation. The substantial amount of adipose tissue probably provides some
relief and protection to underlying tissues from pressure generated by the preparation and propulsion of the bolus during mastication and swallowing. The sub-epithelial elastic fibers, which is the most dense in the anterior half of the velum may facilitate deformation of the oral surface of the soft palate resulting from bolus transport and then help to restore velar shape after passage of the bolus. Also, the elastic fibres provide a potential mechanism for lowering the palate during the speech and may help to keep the nasopharangeal airway during sleep. The nasal aspects of the palate contains glandular and adipose tissues but much less than the oral aspect thus the nasal aspect is moistened which may aid in cleansing and filtering of inhaled air. These glandular secretion may serve as a glandular lubricant to reduce frictional forces during velopharangeal valving as the velum slides up and down the pharyngeal walls.

The arterial supply of the soft palate is usually derived from the ascending palatine branch of the facial artery and the greater palatine branch of maxillary artery. The blood supply by the facial artery to the palatal region is 0.89 ml/min/100 cm². Sometimes this is replaced or supplemented by a branch of ascending pharyngeal artery which descends forwards between the superior border of the superior constrictor and levator veli palatines, and accompanies the latter to the soft palate. The veins of the soft palate usually drain to the pterygoid venous plexus. The secretomotor supply to most of the mucosa of the soft palate travels via the lesser palatine nerve also contains sensory fibres including those supplying to taste buds in the oral surface of the soft palate, which travel through the pterygopalatine ganglion without synapsing to access the greater petrosal nerve. Postganglionic secretomotor parasympathetic fibres may pass to posterior parts of soft palate from otic ganglion [36].

1.2.3. Soft palate mucosal structure and its suitability

Surrounding the oral epithelial cells is a thin layer of mucus, which plays a major role in cell-to-cell adhesion and oral lubrication, as well as mucoadhesion of mucoadhesive drug delivery systems [37]. The soft palatal mucosa composed of stratum squamous epithelial cells, thickness about 100-200 μm consists of a non-keratinized epithelial tissue with absence of acrylamides with small amounts of lipids like cholesterol and glycosyl ceramides. The permeability of oral soft palatal mucosa is about 4-4000 times
more than the skin and the thickness of palatal mucosa (158-224µm) is intermediate between sublingual (111 µm) and buccal (594 µm) [38]. The mucosal pH of all oromucosal sites was ranged from 6.24 ± 0.05 to 7.36 ± 0.06 and mean pH values in the palate (7.34 ± 0.38), buccal mucosa (6.28 ± 0.36) and the lingua (6.8 ± 0.26). The data obtained regarding different mucosal pH values may aid in exploring the optimal site for specific drug delivery since the palatal pH value (7.34 ± 0.38) is much more nearer to the pH value of blood as compare to the other oromucosal (buccal, sublingual) site and it also contain the lowest salivary secretion measured by Periotron method [39] emphasizing a major role in maintenance of suitable microenvironment because the salivary system is a powerful buffering system [40] usually capable of maintaining a stable intraoral pH. The residual amounts of saliva on the oral mucosal tissues in the morning and afternoon were almost identical. The residual salivary thickness ranged from a low of 0.16 ± 0.03 to a high of 0.58 ± 0.05 in lingual region; corresponding values for buccal ranged between 0.44± 0.06 to 1.13 ±0.05 and 0.03±0.003mm on soft palate [38] Fortunately the enzyme activity is relatively low in the palatal mucosa comparatively with other mucosal area of the oral cavity. Therefore the palatal mucosa is better site for oro-mucosal absorption to explore drug delivery in controlled and systemic manner.

1.2.4. Mucus secretion in goblet cells from human soft palate

In crypt goblet cells, acetylcholine-esserine induces rapid fusion of apical mucous granule membranes with the luminal plasma membrane (detectable by 2 min), followed by sequential, tandem fission of the pentalaminar, fused areas of adjacent mucous granule membranes. These events first involve the most central apical mucous granules that are then propagated to include peripheral granules, and finally spread toward the most basal granules, by 60 min, most crypt cells are nearly depleted. The apical membrane, although greatly amplified by these events, remains intact, and intracellular mucous granules do not coalesce with each other. During rapid secretion membrane-limited tags of cytoplasm are observed attached to the cavitated apical cell surface. These long, thin extensions of redundant apical membrane are rapidly lost, apparently by being shed into the crypt lumen. The glandular layer constitutes the
greatest bulk of the human soft palate and is composed of individual compound
tubulo-acinar salivary glands. Connective tissue partitions of the submucosa divide the
glandular layer into lobules of irregular shapes and sizes. Glands are interwoven and
bound firmly together by a connective tissue stroma rich in elastic fibers. The
secretory units consist of elongated, branched, and sometimes convoluted tubules
lined by a single layer of pyramidal mucous cells [41]. Mucous secretion by acini is
supplemented to some degree by mucous acinar cells, which were found as epithelial
components of all ducts except the main excretory ducts, suggesting a diffuse
distribution of progenitor cells. Some mucous acini communicate with highly
convoluted intercalated ducts which occupy partially isolated positions within inter-
and intralobular connective tissue septa. These ducts follow the connective tissue
septa and eventually join the main duct system [39].

1.2.5. Muscles and nerves of soft palate

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Action</th>
<th>Nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levator veli palatini</td>
<td>Deglutition</td>
<td>Vagus</td>
</tr>
<tr>
<td>Tensor veli palatini</td>
<td>Deglutition</td>
<td>Mandibular nerve</td>
</tr>
<tr>
<td>Palatoglossus</td>
<td>Respiration</td>
<td>Vagus</td>
</tr>
<tr>
<td>Palatopharyngeus</td>
<td>Respiration</td>
<td>Vagus</td>
</tr>
<tr>
<td>Musculus uvulae</td>
<td>Moves Uvula</td>
<td>Vagus</td>
</tr>
</tbody>
</table>

1.3. Mucus

1.3.2. Physical properties of mucus

A typical mucus sample is, by mass, 90–95% water. The remaining mass consists of
glycoprotein fibers, oligosaccharides, lipids, migrating or sloughed cell and cell
contents, enzymes, antibodies, DNA and electrolytes. In addition to commensals
microorganisms, which are non-pathogenic and tolerated by the host, the mucus gel
also plays host to a constant stream of foreign species ranging from dust and reactive
chemicals, to invading bacteria and viruses. The thickness of the mucus barrier is dependent on its location. Gastrointestinal mucus is reported to be 50–600 μm in the stomach and 15–450 μm in intestine and colon. A number of excellent reviews on the properties and function of mucus have been published [40–43]. The three-dimensional structure of mucus gel is sustained by a network of randomly interwoven flexible protein fibers called mucin. Convection is also inhibited by formation of a lipid-rich mucin layer at the surface of the gel [44]. Since there is little fluid movement within the gel, solutes are thought to penetrate purely by diffusion. The physical size and arrangement of mucin fibers contribute significantly to the kinetics of the diffusion process. A major structural component of mucus, mucin fibers are polydisperse molecules of 2–40 mDa MW and 0.5–10 μm in length, with a linear topography [45]. Mucin fibers consist of 80% proteoglycans that are attached to the primary backbone in clusters, resulting in a flexible fiber with diameter 3–10 nm (backbone glycosylation is 0.5–5 nm from the fiber core with length 50–200 nm) with persistence length 1–15 nm depending on glycosylation and charge [46-47].

1.3.3. Dynamic properties of mucus

1.3.2.1. Mucus is secreted continuously

Mucus is secreted, and transported before being digested or shed. Nearly 10 l (2.5 gal) of mucus are secreted into the the GI tract each day. Most mucus is secreted into the GI and respiratory tracts, and most of this is digested and recycled. The rest is shed in feces, sputum, saliva, and nasal secretions, reproductive tract secretions, and tears. In the human GI tract, the mucus blanket is thickest in the stomach (180 μm; range 50–450 μm) and colon (110–160 μm). Small intestine, the thickness varies greatly depending on digestive activity. For instance, with a fibrous diet, the outer “sloppy” layer of mucus in the rat intestine can be wiped away by the movement of the chyme, but a firmly adherent inner layer of mucus still covers the epithelial surface [48]. In addition, a thin mucus coat is likely to adhere to ingested particles. In the stomach, mucus is secreted almost fast enough to prevent pepsin in the lumen from diffusing to the epithelial surface but not fast enough to prevent HCl, ethanol, and salts from reaching the epithelial surface. The mucus blanket is much thinner on most other
surfaces and the barrier motions opposing NP delivery are primarily due to the rate of mucus clearance or shedding. This is especially the case in the eyes where tear film is shed within a matter of seconds into the nasolacrimal ducts. The thickness of the mucus blanket is determined by the balance between the rate of secretion and rate of degradation and shedding. Toxic and irritating substances can greatly stimulate mucus secretion. Toxic and irritating substances can greatly stimulate mucus secretion, increasing the thickness of the mucus blanket while efficiently and rapidly moving the irritants away from the epithelium[49-51]. Secreting new mucus is markedly more efficient than simply washing the surface, because rinsing the surface fails to refresh the unstirred layer adhering to the epithelium. In contrast, by continuously secreting new mucus, the unstirred layer is continuously and rapidly replaced. Thus pathogens and drug-delivery nanoparticles must migrate upstream to reach the epithelium. Even in an absorptive epithelium such as the small intestine, where water is moving inward and being filtered through the mucus coat, nanoparticles must advance through a blanket of mucus gel that is moving outward if they are to reach the epithelial surface [52-53].

1.3.2.2. Mucus forms and maintains and adherent unstirred layer

A second, and often underappreciated dynamic property of mucus is its ability to maintain an unstirred layer of mucus adjacent to epithelial surfaces despite the vigorous shearing actions of eye blinks, swallowing, coughing, intestinal peristalsis, and copulation. Mucus does this by being a shear-thinning gel that forms a lubricating slippage plane between sliding surfaces. Mucus adheres to epithelial cells by as yet poorly understood mechanisms that probably involve both adhesive and entangling interactions with the cell-surface mucins that form the glycocalyx. As the mucus gel begins to be sheared between the two surfaces, adhesive contacts, and entanglements between mucin fibers, are drawn apart to form the slippage plane. The shear-thinning (non-Newtonian) property of mucus is the viscosity of mucus gels is shown as a function of the rate at which the gel is sheared. Viscosity is the force exerted per unit area of the sliding surface, F/A, divided by the shear rate. As can be seen in the log–log plot, the viscosity of a mucus gel decreases as shear rate increases: viscosity (shear rate)−0.85. In contrast, the viscosity of water (a Newtonian fluid) does not change.
with shear rate as shown by the horizontal line. The most consistent feature is the dependence on shear rate that probably results from decreasing adhesive interaction between mucin fibers as the shear rate increases. Unlike surfaces covered with water, mucus maintains a significant unstirred layer adjacent to each surfaces [54-55].

1.4. Prerequisites for successful oro-mucosal drug delivery system

An ideal orotransmucosal drug delivery system must meet several prerequisites to be successful. The first prerequisite to target a gastrointestinal site is that the behavior of the dosage form must be reproducible. The second prerequisite for a orotransmucosal drug delivery system is that it should rapidly attach to the mucosal surface and maintain a strong interaction to prevent displacement. Spontaneous adhesion of the system at the target site is critical and can be achieved through bioadhesion promoters that use tethered polymers [56]. Contact time should also be sufficiently long at the target site, normally longer than that needed for complete drug release. As hydrophilic bioadhesive polymers tend to lose adhesiveness upon hydration, restricted hydration and formation of a rigid gel network would be desirable for prolonged adhesion [57]. A short retention time, in relation to the drug release rate, will compromise bioavailability. The third prerequisite for a successful and effective orotransmucosal drug delivery system is that the bioadhesion performance should not be impacted by surrounding environmental pH. Studies have shown that the bioadhesiveness of polymers with ionizable groups are affected by surrounding pH. For example, polyacrylic acid is more bioadhesive when the majority of the carboxylic acid groups are in the ionized state. Polyanhydride-based hydrophobic bioadhesive polymers (e.g., Spheromers, Spherics, Mansfield, MA) undergo erosion that is mainly affected by the aqueous environment and not by pH of the surrounding medium. Studies have shown that as anhydride-based polymers degrade at the mucus surface, carboxylic acid groups are formed at the transected polymer chain ends, which generate a new polymer surface rich in carboxylic acid end groups. These hydrophilic functional groups then form hydrogen bonds with surrounding mucin strands that in turn penetrate the newly created surfaces. The result is the formation of both chemical and mechanical bonds. As the degradation process proceeds, a more porous surface rich
with carboxyl groups is created, allowing for even greater adhesion that is essential to the success of an oror transmucosal drug delivery system. In earlier studies, one family of rapidly degradable polyanhydrides produced bioadhesive interactions with rat small intestine tissue that were substantially stronger than all other polymers in this class [58]. The fact that these bioadhesive polymers are stable in the acidic environment of the stomach and eventually degrade at $\text{pH} \geq 7.4$, make them ideal for targeted delivery to the stomach and small intestine [59]. Another prerequisite for an ideal bioadhesive delivery system is that the bioadhesive and drug-release functions are independent of each other. Often, the bioadhesive polymer used in the dosage form is also used to regulate the release of drug. Generally, these formulations are made by mixing bioadhesive polymer and drug or by coating drug-loaded beads or tablets with the bioadhesive polymer. These approaches of using bioadhesive polymers to achieve both bioadhesion and drug-release functions have compromised results. An effective bioadhesive formulation must not cause local tissue irritation or long-term tissue toxicity as a result of the bioadhesive polymer or other absorption enhancers used to promote drug absorption. Also, if encapsulated bioadhesive nanoparticles or multiparticulates beads are used as the delivery system, the particles may have a tendency to form agglomerates because of the charge or hydration within the capsule. Accordingly, measures should be taken to keep these structures monodisperse to allow maximum interaction with the mucosal surface upon release from the capsule. Other desirable characteristics of a bioadhesive dosage include high drug loading, complete drug release, and convenient administration. Although the prerequisites described above apply to bioadhesive dosage forms, the potential impact of formulation excipients on the adhesive behavior of bioadhesive drug delivery systems and mucosal surfaces also should be carefully taken into account. For example, excipients containing hydroxyl groups could form hydrogen bonds with the hydrophilic functional group of bioadhesive polymers and, as a result, prevent their interaction with the mucosal surface [60]. In addition, hydrophobic lubricants (e.g., magnesium stearate and talc) tend to hinder the formation of strong bioadhesive bonds and thus reduce the bioadhesive strength significantly [61]. Structural breakdown of mucin has been observed by the addition of surfactants. A number of agents (e.g., tetracycline and progesterone) may alter the viscosity of mucus by altering its molecular
composition. Integrity of mucin layers is also disrupted in some disease states (e.g., inflammation and ulceration). Therefore, in developing a bioadhesive dosage form, drug and excipient characteristics as well as the presence of disease states need to be taken into account

1.4.1. Formulation factor and design

In the case of transmucosal administration, conventional dosage forms are not able to assure therapeutic drug levels on the mucosa and in the circulation. This is because of the physiological removal mechanisms of the oral cavity (washing effect of saliva and mechanical stress), which take the formulation away from the mucosa, resulting in a too short exposure time and unpredictable distribution of the drug on the site of action/absorption[62-63]. Factors known to affect the penetration of substances through the oral mucosa include the physical and chemical nature of the substance, such as its molecular weight; the degree of ionization at any particular pH (pK value); the relative solubility or partition coefficient in nonpolar and polar solvents; and the type of solvent or vehicle in which a drug is applied. In general, the smaller the molecule, the greater the concentration of un-ionized drug, and the presence of biphasic solubility with slight lipid preference provides optimum conditions for drug penetration. For highly hydrophilic drugs (log P <2), which also suffer from extensive presystemic elimination and require a rapid onset of action, orortransmucosal may offer advantages over oral administration. Compounds with favourable oil/water partition coefficients [40-2000] are readily absorbed through the oral mucosa. Since the mean pH of saliva is 6.0, adequate absorption through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base. Drug absorption through a mucosal surface is generally efficient because the stratum corneum epidermidis, the major barrier to absorption across the skin, is absent. Mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism [64]. The amount of drug absorbed depends on the following factors [65].

- Drug concentration
Vehicle of drug delivery
- Mucosal contact time
- Venous drainage of the mucosal tissues
- Degree of the drug's ionization and the pH of the absorption site
- Size of the drug molecule
- Relative lipid solubility

To obtain the therapeutic action, it is therefore necessary to prolong and improve the contact between the active substance and the mucosa. To fulfill the therapeutic requirements, formulations designed for palatal administration should contain the following functional agents: mucoadhesive agents, to maintain an intimate and prolonged contact of the formulation with the absorption site; penetration enhancers, to improve drug permeation across mucosa (transmucosal delivery) and enzyme inhibitors, to eventually protect the drug from the degradation by means of mucosal enzymes[66].

1.4.2. Mucoadhesive agents

Mucoadhesion may be defined as a state in which two materials, one of which is mucus or a mucous membrane, is held together for extended period of time [67]. For drug delivery purpose, the term mucoadhesion implies attachment of a drug carrier to a mucus coat at specific biological location [68] For mucoadhesion to occur, a succession of phenomenon, whose role depends on the nature of the mucoadhesive is required. The first stage involves an intimate contact between a mucoadhesive and a mucus/ mucus membrane, either from a good wetting of the mucoadhesive surface, or from the swelling of the mucoadhesive. In the second stage, after contact is established, penetration of the mucoadhesive into the crevices of the tissue surface or interpenetration of the chains of the mucoadhesive with those of the mucus takes place. Low chemical bonds can than settle [69-70]. On a molecular level, mucoadhesion can be explained based on molecular interactions for mucoadhesion to occur, the attractive interaction should be larger than non specific repulsion. Different situations for mucoadhesion are possible depending on the dosage form [71]. In the
case of dry or partially hydrated formulations, polymer hydration and swelling properties probably play the main role. The polymer hydration and consequently the mucus dehydration could cause an increase in mucous cohesive properties that promote mucoadhesion. Swelling should favour polymer chain flexibility and interpenetration between polymer and mucin chains. The spreading coefficient and the capability to form physical or chemical bonds with mucin (which results in a strengthening of the mucoadhesive interface) increase when fully hydrated dosage form (e.g. aqueous gels or liquids) are considered [72]. Their peculiarity lies in the mucoadhesion mechanism: such substances are able to recognize and bind some specific sugar residues on mucosal surface without altering the structure of the recognized ligand [73].

1.4.3. Penetration enhancers

Penetration enhancers are also required when a drug has to reach the systemic circulation to exert its action. These must be non-irritant and have a reversible effect: the epithelium should recover its barrier properties after the drug has been absorbed. The most common classes of penetration enhancers include fatty acids (that act by disrupting intercellular lipid packing), surfactants and, among these, bile salts (by extracting membrane protein or lipids, by membrane fluidization, by producing reverse micellization in the membrane and creating aqueous channels), azone (by creating a region of fluidity in intercellular lipids) and alcohols (by reorganizing the lipid domains and by changing protein conformation) [74,75]. Recently, chitosan and its derivatives, polymers already known for their mucoadhesive properties, have been shown to be the potential penetration enhancers for transmucosal (intestinal, nasal, buccal and vaginal) absorption of drugs [76-77]. Although the penetration enhancement properties of chitosan through mucosae (intestinal and nasal) are mainly owing to a transient widening of the tight junctions between the cells [78], the mechanism of penetration enhancement through the mucosa of the oral cavity has still to be clarified.
1.4.3.1. Mechanisms of action of penetration enhancer

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows [79,80]

➢ Changing mucus rheology: Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

➢ Increasing the fluidity of lipid bilayer membrane: The most accepted mechanism of drug absorption through mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.

➢ Acting on the components at tight junctions: Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

➢ By overcoming the enzymatic barrier: These act by inhibiting the various peptidases and proteases present within mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

➢ Increasing the thermodynamic activity of drugs: Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to increased thermodynamic activity resulting better absorption. Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface.

1.8. Various transmucosal dosage forms

The development and use of fast-dissolving tablet dosage forms in clinical practice have shown that administration of drugs via the oral mucosa was feasible. However, because of the aforementioned limitations of this type of dosage form, research in this
area has focused on the development of alternative oral mucosal drug delivery systems. Essentially, the research has revolved around developing strategies for prolonging the duration of the absorption process. This necessitates that the drug delivery system must ensure that the drug is released in a controlled manner and that a sufficiently high drug concentration is delivered to the mucosal surface. Two approaches are theoretically possible to achieve these aims: (a) the development of "non-attached" or "mobile" drug delivery systems that would be physically maintained within the oral cavity in contact with a mucosal surface by a conscious effort of the patient, and (b) the design of "immobilised" drug delivery systems that can be retained on the mucosal surface by the adhesive properties of the system itself [81-82].

1.8.1. Non-attached drug delivery systems

Three types of non-attached drug delivery systems can be indentified: (i) fast dissolving tablet dosage forms (which have been previously discussed), (ii) chewing gum formulations and (iii) microporous hollow fibers. In the case of chewing gum formulations, the main target mucosa for drug absorption is the sublingual mucosa, however, drug is released into saliva and its subsequent spreading may cause the drug to become absorbed across other mucosae of the oral cavity. Chewing gum formulations consist generally of a gum base of a cellulosic or acrylic polymer. The polymer is blended with sugars and the drug is incorporated. Drug release from chewable formulation is generally rapid but not as immediate as in the case for the fast-dissolving tablet delivery systems. A study by Chirstrup et al. [83] showed that about 57% of ascorbic acid incorporated in a chewable preparation was released after 5 min. This percentage was not significantly increased after 30 min of chewing. Similar trends were observed with noscapine derivatives [84]. However, in this case, the percentage released depended on the aqueous solubility of the incorporated compound. The percentages released was about 80%, 25% and 20% for the water soluble noscapine hydrochloride, the embonate salt and the poorly soluble noscapine base respectively. The release period can be extended by associating the drug with an ion-exchange resin. This principle has been used for the formulation of nicotine chewing gums (Nicorette®). Release was controlled by the rate and vigour of chewing.
and reached about 90% after 30 min of chewing [85-87]. Therefore, the patient can control the drug intake to match their needs. Clinical investigations with nicotine chewing gum have suggested that this product was indicated as an aid for giving up smoking. The bioavailability of different drugs incorporated into chewing gum formulations has been investigated. These drugs have included ascorbic acid [83], salicylamide [88], verapamil [89], noscapine [84] and nicotine [85]. In the case of methadone, it has been shown that there were no significant differences in the AUC of the plasma profiles obtained after administration of chewing gum or sublingual tablets [90]. Burnside et al. [91] reported the design of a microporous hollow fiber of polysulfone (molecular weight cutoff was 500 000 Da) intended for the delivery of histrelin, an LHRH agonist. This fibre is intended to be placed in the buccal cavity. Preliminary experiments showed that peptide delivery rates could be adjusted and prolonged for up to 6 h. However, the lack of intimate contact with the mucosa may be detrimental to peptide absorption because of possibility of enzymatic degradation in saliva. Despite some interesting results, non-attached oral mucosal drug delivery systems, including chewing gum formulations, have some drawbacks that are inherent within the design of the dosage form itself. These include: (i) drug is released into the saliva and disappears rapidly from the oral cavity because of involuntary swallowing; (ii) the concentration of drug in the oral cavity is decreased by continuous salivary dilution; (iii) drug is not protected from the physiological environment; (iv) drug release from chewing gum formulations has been shown to be strongly influenced by the way the patient sucks or chews the formulation [85,82,83]; and (v) administration of such dosage forms is restricted to short periods of time because the presence of the delivery system in the oral cavity is a handicap for drinking, eating and speaking. As a result of these limitations, controlled release of drug over long periods of time cannot be considered with such formulations.

1.5.2. Immobilised drug delivery systems

In recent years, oral mucosal drug delivery systems that are designed to remain in contact with the oral mucosa for prolonged periods have been a subject of growing interest. Such systems offer advantages over non attached systems. These include: (i)
the immobilisation allows an intimate contact to be developed between the drug dosage form and the mucosa; (ii) a high drug concentration can be maintained at the absorptive surface for a prolonged period of time; (iii) the dosage form can be immobilised specifically at any part of the mucosa: buccal, labial, sublingual, palatal or gingival mucosa; and (iv) the system itself can protect the drug from environmental degradation.

The design of immobilised oral mucosal drug delivery systems is rather sophisticated because it is necessary to impart two specific properties to the delivery system (i): immobilisation and (ii) controlled-release behaviour. Such a combination of different properties within a single system can be achieved by the use of polymers. Immobilisation on the mucosa can be achieved by bioadhesion or mucoadhesion. Development of mucoadhesive drug delivery systems intended for oral administration have been the subject of intensive research recently. This concept has been applied to different types of delivery systems including sustained release tablets, semi-solid dosage forms, films, patches, and secondarily, powders [94] and microspheres [95]. Adhesive tablets consist of either monolithic, partially coated or multilayered matrices [96]. Monolithic tablets are easy to manufacture by conventional techniques. They provide the possibility of holding large amounts of drug which can be co-formulated with an absorption (penetration) enhancer if necessary. A partial coating of monolithic tablets has been proposed, consisting of a protection of every face of the tablet which is not in contact with the mucosa [97]. Such systems impose unidirectional drug release and avoid drug release into the saliva fluids. Multilayered tablets allow a variety of geometrical arrangements. In the case of bilayered tablets, drug release can be rendered almost unidirectional. The drug can be incorporated in the adhesive layer immediately adjacent to the mucosal surface and protected from environment by an upper inert layer facing into the oral cavity. Alternatively, the drug can be incorporated into the upper non-adhesive layer. In this case, drug is released into the environment of the oral cavity. Much attention has been paid to adhesive characteristics of tablets [98-105]. The use of cellulosic or acrylic polymers generally offers almost immediate, high adhesion performances for prolonged periods of time, even when drug content is high. Factors influencing the drug release from bioadhesive tablets are the same as those encountered in hydrophilic
matrices and include the nature of the polymer, the drug/polymer ratio, the swelling kinetics of the system. Various drugs intended for systemic activity have been incorporated in bioadhesive tablets including propranolol [104-106], timolol [107], metronidazole [110], metoclopramide [118], insulin [119], nitroglycerine [120], codeine phosphate [117] and morphine sulfate [121]. The limitations of adhesive tablets include (i) the small surface area of contact with the mucosa, (ii) their lack of flexibility, (iii) high drug release rates, which are required for some drugs, can hardly be obtained, and (iv) the extent and frequency of contact may cause irritation following chronic application of such systems on the buccal or sublingual mucosa. This latter limitation needs to be investigated more fully. To overcome some of the drawbacks of mucoadhesive tablets, flexible, adhesive films, laminated adhesive patches and bioflexidisk etc which cover a high surface area of mucosa have been developed. Polymers that can be used for the development of mucosal patches are cellulose derivatives (e.g. methylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose), natural gums (guar gum, Karaya gum, agarose), and polyacrylates including poly(acrylic acid), poly(methacrylic acid), poly(vinylpyrrolidone), poly(ethylene glycol), gelatine. These polymers exhibit mucoadhesive properties in the presence of water. Polyacrylic-based hydrogels have been extensively studied. Kellaway et al. [112-114] prepared hydrogels by reacting polyacrylic acid with sucrose, glycerol or a non-ionic surfactant for the delivery of oxytocin. De Vries et al. investigated the physicochemical determinants of the bioadhesive properties of copolymer hydrogels made of acrylic acid and butyl acrylate in various molar ratios [115-116]. Yang et al. [117] prepared polyetherurethane hydrogels which had high loading capacities and release profiles over periods of 12 h for heparin. Cassidy et al. [118] investigated the buccal delivery of diclofenac sodium by means of a hydroxyethyl methacrylatebased copolymer hydrogel. Drug loaded adhesive films can be prepared quite easily by using adhesive polymers. Kurosaki et al. [119] reported the use of a simple film of hydroxypropylcellulose for the delivery of propranolol. Rodu et al. [120] prepared a simple film by complexing hydroxypropylcellulose with tannic and boric acid. Adhesive patches can be designed either for uni-directional release into the mucosa or for bi-directional release into the mucosa as well as into the oral cavity [121]. The adhesive part of the system can be
used as a drug carrier or as a simple adhesive for the retention of a drug-loaded non-adhesive layer on the mucosa. In this respect, a peripheral adhesive ring is feasible. The use of an impermeable backing layer will maximise the drug concentration gradient and prolong adhesion because the system is protected from saliva. Poly(acrylic acid)-based patches have been used successfully for the delivery of opioid analgesics [122]. Bioavailability ranged from 35% to 50% in dog, compared to the oral bioavailability which was less than 5%. Veillard et al. [123] developed a patch in conjunction with 3M-Riker consisting of a rate-limiting membrane, a polycarbophil adhesive layer and an impermeable backing. Finally, Merkle et al. [121,124,125] investigated a number of polymers and different geometries for the design of patches for the delivery of different peptides, such as protirelin and octreotide. Studies on octreotide illustrate some of the drawbacks of such systems. Relative bioavailabilities of octreotide in rats of different patches ranged between 17% and 24% when compared to buccal administration of an aqueous solution. Such a result suggests that retardation in the drug release occurred because of insufficient diffusion of the drug throughout the adhesive layer. Such a phenomenon is not likely to favour drug absorption of such products. Therefore, a recent approach consisted of the combination of a fast-dissolving unit and a bioadhesive part in the same controlled-delivery system [126].

1.6. Absorption pathways

1.6.1. Intracellular route

Despite the fact that the surface area available for absorption is considerably greater for the intracellular route, it is a path offering considerable diffusional resistance with the drug alternatively crossing the aqueous and lipid phases of the epithelial cells. There are a few reports in the literature suggesting that drugs penetrate oral epithelium via the intracellular route. Seigel and co-workers [127-129] determined the permeability of canine and rabbit lingual frenula and the ventral surface of the tongue of rats of a number of structurally unrelated compounds. These workers proposed that compounds exhibiting a partition coefficient less than water and a molar volume of
less than 80 cm$^3$. The existence of specialised transport mechanisms for certain drugs [130-138] may suggest that such compounds cross the oral mucosa via an intracellular route since it would be likely that the carriers involved in these specialised transport processes exist within the cells of the epithelium.

### 1.6.2. Intercellular route

The intercellular route involves passage between the cells through the intercellular lipid material of the intercellular spaces. This pathway is a tortuous one, requiring the epithelium to have a sufficiently open matrix and the drug to have an appreciable affinity for, and diffusivity in, the intercellular fluids [139]. In contrast to the intracellular route the area available for transfer is small. However, it appears to be the predominant route for most compounds of pharmacologic interest [140-141].

### 1.7. Experimental methodology for palatal permeation studies

Before a palatal drug delivery system can be formulated, palatal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. This study involve in vitro palatal permeation profile and absorption kinetics. Animals are sacrificed immediately before the start of an experiment. Palatal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the soft palate mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the in vitro permeation experiments. The most significant questions concerning the use of animal tissues as in vitro models in this manner are the viability and the integrity of the dissected tissue. How well the dissected tissue is preserved is an important issue which will directly affect the results and conclusion of the studies. The most meaningful method to assess tissue viability is the actual permeation experiment itself, if the drug permeability does not change during the time course of the study under the specific experimental conditions of pH and temperature, then the tissue is considered viable.
Table-1-Recently marketed and under research oral mucosal drug delivery systems [27,28,33,34,142, 143]

<table>
<thead>
<tr>
<th>Mucosa</th>
<th>Drug</th>
<th>Proprietary Name</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual</td>
<td>Nitroglycerin</td>
<td>Nitrostat</td>
<td>Tablet</td>
</tr>
<tr>
<td></td>
<td>Isosorbide dinitrate</td>
<td>Linitr spray</td>
<td>Spray</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>Suladrin</td>
<td>Bioadhesive tablet</td>
</tr>
<tr>
<td></td>
<td>Buprinnorphine</td>
<td>Sorbitrate</td>
<td>Chewable tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isocard spray</td>
<td>Spray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adalat</td>
<td>Tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tengerin</td>
<td>Tablet</td>
</tr>
<tr>
<td>Buccal</td>
<td>Prochloperazin</td>
<td>Buccastem</td>
<td>Bioadhesive</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>Tementill</td>
<td>Tablet</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>Nicorette</td>
<td>Solution</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>BEMA™ System</td>
<td>Chewing Gum</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>Elyzol®</td>
<td>Buccal adhesive</td>
</tr>
<tr>
<td></td>
<td>Peptides</td>
<td>Atridox®</td>
<td>Disk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hollow fibers</td>
</tr>
<tr>
<td>Gingival</td>
<td>Buprinnorphine</td>
<td>Cydot</td>
<td>Patch</td>
</tr>
<tr>
<td></td>
<td>Melatonin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft palatal</td>
<td>Amikacin</td>
<td>-</td>
<td>Smart Flexiplate</td>
</tr>
<tr>
<td></td>
<td>Gentamycin</td>
<td>-</td>
<td>Bioplate</td>
</tr>
</tbody>
</table>

1.8. Advantages and limitations of oro-soft palatal platform drug delivery system

1.8.1. Advantages

- Smooth surface of the soft palate and its good flexibility are prerequisites to prevent mechanical irritation and local discomfort.
- Accessibility of soft palate is very easy with the help of thumb the delivery device can be placed and Self administration is possible with this type of delivery system
Fortunately the enzyme activity is relatively low in the palatal mucosa comparative to other mucosal area of the oral cavity.

Adverse effects/ therapeutic failures frequently associated with intermittent dosing can also be avoided.

Soft palatal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug eg. Gastrointestinal irritating, low absorption, decomposition due to hepatic first pass metabolism, formation of metabolites that cause side effects, short-half life necessitating frequent dosing.

Daily lower dose of the drug is elicited via soft palatal route providing equivalent therapeutics effect in comparison with orally administered drug.

Simplified medication regimen leads to improved patient compliance and reduced inter and intra patient variability.

The drug input can be terminated at any point of time by removing the delivery system.

1.8.2. Limitations

- Relative impermeability and small surface area coupled with metabolism of some drugs are problematic for this route of delivery.
- Drugs which are not absorbed by passive diffusion cannot be administered.
- Unpleasant taste drug and odour cannot be administered.
- Irritating drugs to the mucosa cannot be applied.
- Drug unstable at oral pH cannot be administered.
- Involuntary swallowing of dosage form is possible.
- If the dosage form fails to adhere to the particular adhesive site the hazard of swallowing the delivery system is a concern.
- Swallowing of saliva can potentially lead to loss of dissolved or suspended drug if the dosage form is not protected by impermeable membrane.

1.9. Possibilities for future research

Colloidal dosage forms including liposomes, nanoparticles, and nanocapsules, are widely investigated as drug carriers for different purposes. However, only a few
studies have been devoted to investigate their potential in oral mucosal drug delivery. Looking at the potential of colloidal systems as oral mucosal delivery systems, various major features are of interest. First, the very large specific surface of those systems is likely to favour a large contact between the dosage form and the oral mucosa. Second, immobilisation of particles on the mucosal surface can be obtained by adsorption or adhesion phenomena. As a result, a high drug concentration in front at the oral mucosal surface might be obtained. Third, controlled release of drug is possible from such systems. Fourth entrapped drug can be protected from saliva, which is of importance for drugs subject to degradation in this fluid. Further studies are necessary for the assessment of the potential of colloidal systems in oral mucosal drug delivery. A few major limitations have been identified for these systems which would limit their application. Because of their limited loading capacities, they would be restricted to the delivery of potent drugs only. Despite their ability to interact strongly with mucosal surfaces, which favours drug delivery, interaction is not immediate and therefore the administration procedure should allow for a sufficient contact time between the colloidal particles and the mucosa.

Vaccination against debilitating infectious diseases has proven remarkable in prevention of these diseases and has contributed significantly to an increase in life expectancy, especially in children, in many parts of the world. In order to have adequate mucosal protection, there are several factors that can influence the effectiveness of vaccines. The most critical factor in mucosal vaccine effectiveness is the route of administration and potential for the antigen to be processed by the antigen-presenting immune cells, such as macrophages and dendritic cells. Presently, most vaccines are administered via the parenteral route or via other invasive routes. Invasive mode of vaccine administration can trigger the systemic immune response, but may not essentially provide adequate mucosal immune protection. On the other hand, effective mucosal vaccines will not only elicit superior local immune protection, but has been shown to trigger systemic response analogous as that of parenterally-delivered vaccine. As such, it is critically important to examine the development of mucosal vaccination strategies that can effectively trigger systemic as well as mucosal immunity [79]. Mucosal vaccines have currently been investigated using a broad spectrum of nanocarrier systems such as multiple emulsions, liposomes, polymeric
nanoparticles, dendrimers, ISCOMs etc. More importantly, mucosal delivery of nanocarrier antigens and vaccines can trigger immunization at different mucosal barriers which is body’s imperative first line defense in addition to systemic immune response. From the future perspective, development of vaccines using combined strategic approach like nanocarriers delivered by orosoft-palatal mucosal route. The soft-palatal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Palatal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules.
REFERENCES


