Buccal Mucosa: a Gifted Choice for Systemic Drug Delivery

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Abstract

The main aim of pharmaceutical research is steadily shifted from the development of new chemical entities to the development of novel drug delivery system of existing drug molecule to maximize their effectiveness in terms of therapeutic action, patent protection, patient compliance and reduced adverse effects. In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal, etc. This system of drug delivery is called mucoadhesive drug delivery system. The buccal region of oral cavity is an attractive target for administration of drug of choice. Buccal drug delivery involves the administration of desired drug through the buccal mucosal lining of the oral cavity. Other than the common advantages of novel drug delivery systems, buccal mucosa has several specific advantages like, faster and richer blood flow, lesser thickness of the buccal mucosa and increased permeability, low enzymatic activity in the buccal mucosa and versatility in designing unidirectional release systems to overcome the first-pass metabolism and subsequent low bioavailability of the drug.

Keywords: Buccal mucosa, mucoadhesion, permeation enhancers, novel drug delivery, buccal adhesive polymers

Introduction

The goal of any drug delivery system is to deliver the therapeutic amount of drug to the proper site in the body. Therefore an ideal drug delivery system should deliver drug at a rate required by the needs of the body over a specified period of treatment. The two aspects that are most important to drug delivery are: Spatial placement Temporal delivery of a drug

Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed controlled release drug delivery system should be able to address and solve these problems [1].

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for achieving both systemic and local effects. For many drugs, conventional oral formulations provide clinically effective therapy, while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles, with an acceptable level of safety to the patient.

Depending on the drug to be delivered, oral drug delivery offers several advantages, such as [1]:

Patient acceptability Ease of administration Lower cost of manufacture and therapy

However, oral drug delivery also presents some disadvantages such as [1]:

Variability in the rate and extent of drug absorption Adverse effects on the GI tract Rapid first pass metabolism which needs higher dose to create the required effect

Unwanted effects due to intestinal motility, mucus barrier and presence of food

The gastro intestinal (GI) tract is the major route of drug delivery to the systemic circulation. However, for some drugs this route poses various problems. The GI tract is a hostile environment; containing enzymes, a range of pH conditions and varied composition. The blood from the GI tract goes directly to the liver. Thus drugs delivered through GI tract are susceptible to acid hydrolysis, extensive metabolism or are readily degraded in the...
Mucosal sites are considered the potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and buccal cavities) offer distinct advantages over per oral administration. These advantages include possible avoidance of first pass effects and presystemic elimination within the GI tract [2-15]. Many research groups have investigated the nasal cavity as a site for systemic drug delivery, but the potential irritation and irreversible damage to the ciliary action of nasal cavity on chronic application of nasal dosage forms make the nasal cavity less attractive route for drug delivery [2-4]. Even though the rectal, vaginal and ocular mucosa offers certain advantages, the poor patient acceptability associated with these sites render them reserved for local applications rather than systemic drug administration. Unlike the nasal cavity, however, drug delivery via the oral cavity is highly acceptable by patients. The oral mucosa is relatively permeable, has a rich blood supply, is robust and shows short recovery times after stress or damage [2-7]. Within oral cavity the two common regions for drug delivery are the sublingual mucosa (area beneath the tongue) and the buccal mucosa (inner lining of cheeks). Selecting one over the other is mainly based on anatomical and permeability properties of the various oral mucosal sites, desired residence time, and desired effects of the drug [2]. The sublingual route is by far the most widely studied. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs, and is convenient, accessible and generally well accepted. This route has been investigated clinically for delivery of substantial number of drugs. It is the route of choice for the administration of nitroglycerine, buprenorphine and nifedipine.

The aim of local drug delivery is to achieve drug release locally in the mouth and to provide uniform drug levels over entire area of oral cavity for a prolonged period of time. Local drug delivery to tissues of the oral cavity has a number of applications, including the treatment of toothache, periodontal disease, bacterial and fungal infections, aphthous and dental somatitis. Conventional formulations for local oral delivery are principally lozenges and mouthwashes that give high drug levels in the oral cavity, but only for a short time. It is feasible to design novel delivery systems that improve localization or retention of drug at the site of action [9-12,16,17].

Advantages of buccal drug delivery

The main advantages of buccal drug delivery are avoidance of pre systemic elimination within the GI tract. Moreover that buccal mucosa has excellent accessibility and hence suitable for administration of retentive dosage forms. Also this will provide direct access to systemic circulation through the internal jugular vein by passes drugs from the hepatic first pass metabolism leading to higher bio availability. The buccal drug delivery provides low enzymatic activity, painless administration, easy drug withdrawal and versatility in designing as multi directional or unidirectional release systems for local or systemic action. Buccal mucosa has high patient acceptability compared to other non-oral routes of drug administration. Drugs which show poor bio availability via oral route can be administered through buccal mucosa. A drug which is not stable in the acidic environment (stomach) or in alkaline environment can be administered by this route and can be administered to unconscious patients [18-21]. Facility to include permeation enhancer, enzyme inhibitor or pH modifier in the formulation.

Disadvantages of buccal drug delivery

Drugs which are unstable at buccal pH cannot be administered. Only drugs with small dose requirement can be administered. The effect of salivary scavenging and accidental swallowing of delivery system, eating and drinking may become restricted. Drugs which irritate the mucosa or having a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route. Low permeability of the buccal membrane specifically when compared to the sublingual membrane and a smaller surface area [18-21].

Structure/ Histology of the Oral Mucosa

The total surface area of oral cavity with mucous membrane is 100 cm². The different areas in the oral cavity are, sublingual, cheeks, gingiva and the palatal mucosa and the lining of the lips. The oral mucosal tissue consists of a multi-layered epithelium covered with mucus. The basal lamina connects the epithelium to connective tissue layer, the lamina propria. The oral mucosa protects the body from external influences, such as the entry of potentially dangerous substances. The epithelium serves as the
mechanical barrier that protects underlying tissues, whereas the lamina propria acts as a mechanical support and also carries the blood vessels and nerves. Some regions of mucosa are keratinized and others are nonkeratinized. The nonkeratinized (flexible) regions, such as buccal mucosa, are more permeable than the keratinized (dehydrated, mechanically tough and chemically resistant) regions like mucosa of hard palate [3,5-7,10,12,13,15,22-24].

The epithelial lining differs in both composition (keratinized and nonkeratinized) and thickness in different regions of mouth. Therefore, drug absorption may vary from different sites in the oral cavity [6-12]. Histology of oral mucosa is shown in Figure 1. The oral mucosa tissue consists of a multilayered epithelium covered with mucus and consists of a stratum disstendum, stratum filamentosum, stratum suprabasale and stratum basael, below this lies a basal lamina. The basal lamina connects the epithelium to a connective tissue layer, the lamina propria. Below lamina propria lies submucosa. Epithelium serves as the mechanical barrier that protects underlying tissues where as lamina propria acts as a mechanical support and also carries blood vessels and nerves.

As cells of epithelium mature, small organelles, known as membrane coating granules, probably derived from the golgi complex appear in the prickle cell layer. In later stages of differentiation, they migrate towards the superficial part of the cell at the junction of the granular and cornified layers in the keratinized tissues; and in the deeper part of the superficial cell layer in the nonkeratinized tissue. The bounding membrane fuses with the cell membrane, and the contents of the granules are discharged into the intercellular space. During fusion, the bonding membrane of the granules is introduced into the plasma membrane of the epithelial cell. The extruded material, composed primarily of lipid is then organized into multiple stacked lipid sheets. Membrane coating granules of keratinized oral epithelium are ovoid, 0.1-0.3 μm in length and have high ratio of lipid to protein. The lipids include phospholipids, cholesterol esters, fatty acids, ceramides and several other natural lipids. In nonkeratinized epithelium, membrane coating granules have similar distribution within the epithelium and similar chemical composition to those of keratinized tissue. They are spherical, approximately 0.2 μm in diameter.

A relationship between membrane coating granules and permeability has been established, thus, a greater volume of membrane coating granules is associated with a lower permeability [25]. Lipids including small amounts of ceramides, monohexosylceramides, cholesterol esters, cholesterol sulphate and fatty acids and a high proportion of phospholipids, triglycerides and cholesterol fill in the intercellular space of oral keratinized tissue.

In nonkeratinized regions, the chemical nature of the intercellular material is less well defined than that in the keratinized epithelium. Since the intercellular spaces of nonkeratinized epithelia appear to contain amorphous material, it is possible that the lipids within them are in a nonlamellar lipid phase, with only occasional short stacks of lipid lamellae. This may result in a barrier that is less efficient than that from, keratinized regions [25]. Saliva is the protective fluid for all the tissues of the buccal cavity and is necessary for oral health. Saliva protects soft tissues from abrasion by rough materials and certain chemicals. Upto 70% of total mucin found in saliva is contributed by minor salivary glands. Main role of salivary mucin is in the non-immune protection of the oral cavity by acting as a lubricant and as a selective permeability barrier against drying. Saliva is 99% water and contains organic and inorganic materials. The surface of the oral cavity is constantly bathed with a stream of saliva (approximately 1 to 1.2 lit per day). The pH of whole saliva varies between 6.2 - 7.5 [4,6,17].

Mucus is composed of mucins and inorganic salts suspended in water. Mucins are family of large, heavily glycosylated proteins composed of oligosaccharide chains attached to a protein core. Three quarters of the protein core are heavily glycosylated and impart a gel like characteristic to mucus. Mucins contain approximately 70-80% carbohydrate, 12-25% protein and up to 5% ester sulphate [21].

**Mucoadhesion**

Mucoadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment of a polymer is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion [26,27].

**Theories of Mucoadhesion**

Mucoadhesion is mainly occurring in three stages. Initially, an intimate contact between the mucoadhesive and 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, hydrophobic 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 [26,27];

- **Wetting theory**
- **Electronic theory**
- **Adsorption theory**
- **Diffusion theory**
- **Fracture theory**

**Wetting Theory**: This theory describes the adhesion of liquid or paste to a biological surface. The act of adhesion can be
expressed in terms of surface and interfacial tension (\(\gamma\)) being defined as the energy per \(cm^2\) released when an interface is formed. This theory proposes that, as a prerequisite for the development of adhesion, the liquid should have the ability to spread spontaneously onto a surface.

**Diffusion Theory:** As per diffusion theory inter diffusion of polymers chains across an adhesive interface causes adhesion and is driven by concentration gradient. 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 chemical structure are required for good mucoadhesion.

**Electronic theory:** In 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.

**Fracture Theory:** The fracture theory of adhesion is related to separation of two surfaces after adhesion.

**Adsorption Theory:** The adsorption theory proposes that hydrogen bonding and Vander waal’s forces are the main contributors to the adhesive interaction. According to this theory, after an initial contact of two surfaces the material will adhere because of surface forces acting between the atoms on the two surfaces. Weak interaction of Vanderwall 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 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 “mucoadhesion” may be more suitable to describe adhesion to the mucosal membrane of the oral cavity.

**Mucoadhesive Interaction**

**Chemical Bonds**

For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following way.

1. **Covalent bonds:** Like metallic bonds, covalent bonds are characterized by the electrons that are shared between the engaged atoms. Covalent bonds operate only over short interatomic distances (1-2x10^-10\(\mu m\)). They tend to decrease in strength with increasing bond-length and are oriented at well-defined angles. Unless chemical reactions take place, based on the formation, for example disulphide bridges, covalent bonds are unlikely to be important in bioadhesion processes under physiological conditions.

2. ** Ionic bonds:** In this case two oppositely charged ions attract each other via electrostatic interactions to form a strong bond (e.g. in a salt crystal).

3. **Hydrogen bonds:** Basically it is an electrostatic interaction that arises when a hydrogen atom bound to an electronegative atom, e.g., nitrogen, oxygen, or fluorine, interacts with another electronegative atom. The hydrogen can therefore be thought of as being shared and the bond formed is generally weaker than ionic or covalent bonds. The result is a dipolar molecule. The hydrogen atom has a partial positive charge and hence can interact with another highly electronegative atom in an adjacent molecule. This results in a stabilizing interaction that binds the two molecules together. The force is short range and highly directional.

4. **Van-Der-Waals bonds:** These are some of the weakest forms of interaction that arise from dipole-dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances. The attractive forces included in the Derjaguin and Landau, Verwey and Overbeek (DLVO) theory are normally termed vander waal’s forces and will arise in a number of ways. These may be further divided into the following three components:

   - **London dispersion forces:** These are also called as dispersion forces. These originate out of the electronic motions in paired molecules and give rise to attractive interactions. These forces involve the attraction between temporarily induced dipoles in non-polar molecules (often disappear within a second). This polarization can be induced either by a polar molecule or by the repulsion of negatively charged electron clouds in non-polar molecules. These results when two atoms belonging to different molecules are brought sufficiently close together. These interactions involve a force of about 0.5-1Kcal/mole. London Dispersion forces exist between all atoms.

   - **Dipole-dipole interactions:** These work in similar manner to ionic interactions, but are weaker because only partial charges are involved. These are due to attraction between polar groups. These have force of 1-7 Kcal/mole. Dipole-dipole interactions also come from partial charges another order of magnitude weaker.

   - **Debye type forces:** These are the interactions between permanent and induced dipoles. Permanent dipoles can induce a transient electric dipole in non-polar molecules and produce dipole induced dipole interactions. These interactions involve a force of about 1-3 Kcal/mole.

5. **Hydrophobic bonds:** Hydrophobic effect is another particularly important phenomenon with respect to bioadhesion, related to the presence of water. More accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non-polar groups are present in an aqueous solution. Water molecules adjacent to non-polar groups form hydrogen bonded structure, which lowers the system entropy. There is
therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect. The hydrophobic effect is usually described in the context of protein folding, protein-protein interactions, nucleic acid structure, and protein-small molecule interactions.

6. Disulfide bridging: A disulfide bond (SS-bond), also called a disulfide bridge, is a strong covalent bond between two sulfhydryl (-SH) groups. Oxidation of the thiol group yields a disulfide (S-S) bond. This bond is very important to the folding, structure, and function of proteins. Due to the formation of strong covalent bonds with mucus glycoproteins, thiomers show the strongest mucoadhesive properties of all so far tested polymeric excipients via thioldisulphide exchange reaction and an oxidation process.

7. Steric forces: Repulsive steric interaction or steric forces appear as the result of the increasing concentration of molecular segments that occurs when surfaces bearing for example bound macromolecules come close to each other and therefore considered to be important in biological systems. The maximum possible number of molecular contacts between an adhesive and its substrate may be greatly restricted by the steric aspects of molecular geometry [21,30-32].

**Mechanism of Mucoadhesion**

Generally in the study of adhesion, two steps have been identified to describe the interaction between mucoadhesive materials and a mucous membrane[7,33]. The stages in mucoadhesion are shown in Figure 2.

**Contact Stage:** An intimate contact or wetting occurs between the mucoadhesive polymer and mucous membrane. In some cases these two surfaces can be mechanically brought together, e.g. placing and holding a delivery system within the oral cavity, eye or vagina. In others the deposition of a particle is encouraged via the aerodynamics of the organ, e.g. within the nasal cavity or bronchi.

**Consolidation Stage:** Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion. Mucoadhesive materials adhere most strongly to solid dry surfaces as long as they are activated by the presence of moisture. Moisture will effectively plasticize the system allowing mucoadhesive molecules to become free, conform to the shape of the surface and bond predominantly by weaker vander Waal and hydrogen bonding (Figure 3).

There are essentially two theories as to how gel strengthening/consolidation occurs. One is based on a macromolecular interpenetration effect. In this theory, based largely on the diffusion theory for compatible polymeric systems. The mucoadhesive molecules interpenetrate and bond by secondary interactions with much glycoprotein (Figure 4).

The second theory is the dehydration theory when a material capable of rapid gelation in an aqueous environment is brought into contact with a second gel, water movement occurs between gels until equilibrium is achieved (Figure 5).

**The Removal Mechanism:** Adhesive failure will normally occur at the weakest component of the joint. For weaker adhesives this would be the mucoadhesive mucus interface, for stronger adhesives this would initially be the mucus layer, but later may be the hydrating mucoadhesive material [33,34]. The mucoadhesive joint failure is shown in Figure 6.

On application of a constant tensile stress to compacts of mucoadhesive polymers, joint failure occurs due to the adhesive failure of the swelling polymer for all but the weakest adhesives. The strength and durability of the adhesive joint will therefore depend on the cohesive nature of the weakest region. The mucoadhesive polymer in an aqueous environment can over hydrate to form slippery mucilage, which is readily removed. Controlling the rate and extent of hydration is required to produce prolonged adhesion, and strategies such as cross-linking.

**Buccal Muco Adhesive Dosage Forms**

Several buccal adhesive delivery devices were developed at the laboratory scale by many researchers either for local or systemic actions. They are broadly classified into

- Solid buccal adhesive dosage forms
- Semi-solid buccal adhesive dosage forms
- Liquid buccal adhesive dosage forms

**Solid buccal adhesive formulations**

**Tablets:** Several bioadhesive tablet formulations were developed in recent years either for local or systemic drug delivery. Tablets that are placed directly onto the mucosal surface have been demonstrated to be excellent bioadhesive formulations. However, size is a limitation for tablets due to the requirement for the dosage form to have intimate contact with the mucosal surface. These tablets adhere to the buccal mucosa in presence of saliva. They are designed to release the drug either unidirectionally targeting buccal mucosa or multidirectionally in to the saliva.

**Micro particles:** Bioadhesive microparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a larger mucosal surface area. In addition, they can also be delivered to less accessible sites including the GI tract and upper nasal cavity. The small size of microparticles compared with tablets means that they are less likely to cause local irritation at the site of adhesion and the uncomfortable sensation of a foreign object within the oral cavity is reduced.

**Semi solids:** Bromberg et al, described a conceptually novel periodontal drug delivery system that is intended for the treatment of microbial infections associated with periodontitis. The delivery system is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers.

**Lozenges:** Bioadhesive lozenges may be used for the delivery of drugs that act topically within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. Conventional lozenges produce a high initial release of drug in the oral cavity, which rapidly declines to subtherapeutic levels, thus multiple daily dosing is required. A slow release bioadhesive lozenge offers the potential for prolonged drug release with improved patient compliance.
Semi-solid dosage forms

**Gels:** Gel forming bioadhesive polymers include cross linked polyacrylic acid that has been used to adhere to mucosal surfaces for extended periods of time and provide controlled release of drugs. Gels have been widely used in the delivery of drugs to the oral cavity. Advantages of gel formulations include their ability to form intimate contact with the mucosal membrane and their rapid release of drug at the absorption site. A limitation of gel formulations lies on their inability to deliver a measured dose of drug to the site. In general, bioadhesive ointments, gels and powders have less patient acceptability than solid adhesive dosage forms, and most are used only for localized drug therapy within the oral cavity. This has been used for the local application of steroids for the treatment of mucosal ulceration.

**Patches / films:** It is simple erodible and nonerodible adhesive films or laminated films in the size range of 1-16 cm². These can be designed to provide either unidirectional or bidirectional release of the drug. They must also be flexible and may be ellipsoid in shape to fit comfortably onto the center of the buccal mucosa. Laminated patches/films consisting of a mucosal-adhesive drug reservoir attached to an inert backing can be developed to achieve unidirectional release of drug acting systemically. An oral mucoadhesive film, prepared by a casting procedure, containing a polymer and the active drug can be developed for local therapy within the oral cavity. Buccal adhesive films are already in use commercially for example, Zilactin used for the therapy of canker sores, cold sores and lip sores.

Liquid dosage forms

Viscous liquids may be used to coat buccal surface either as protectants or as drug vehicles for delivery to the mucosal surface. Traditionally, pharmaceutically acceptable polymers were used to enhance the viscosity of products to aid their retention in the oral cavity. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain NaCMC as bioadhesive polymer [21].

Buccal Adhesive Polymers

The term buccal adhesive polymer covers a large, diverse group of molecules, including substances from natural origin to biodegradable grafted copolymers and thiolated polymers. Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and visco-elastic properties [21]. Polymers that can adhere to the mucin surface may be conveniently divided into three broad categories:

- Polymer that becomes sticky when placed in water and owe their bioadhesion to stickiness
- Polymers that adhere through non specific, non covalent interactions which are primarily electrostatic in nature
- Polymers that bind to specific receptor sites on the cell surface

Properties of ideal buccal adhesive polymers

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities
- Should have good spreadability, wetting, swelling, solubility and biodegradability properties. pH should be biocompatible and should possess good viscoelastic properties
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range
- Polymer must be easily available and its cost should not be high
- Should show bioadhesive properties in both dry and liquid state
- Should demonstrate local enzyme inhibition and permeation enhancement properties
- Should demonstrate acceptable shelf life
- Should have optimum molecular weight
- Should possess adhesively active groups
- Should have required spatial conformation
- Should not aid in development of secondary infections such as dental caries

Permeation Enhancers

Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Examination of permeation route for transbuccal delivery is important because it is fundamental to select the proper permeation enhancer to improve the drug permeability. Permeation enhancer is the limiting factor for many drugs in the development of buccal delivery devices. The selection of enhancer and its efficacy depends on the physico-chemical properties of the drug, site of administration, nature of the vehicle and other excipients. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. The permeation enhancers should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic. The different permeation enhancers available are, Chelators, surfactants, bile salts, fatty acids, non-surfactants (unsaturated cyclic ureas) and thiolated polymers [21, 36].

Upcoming Opportunities

Based on current understanding of biochemical and physiological aspects of absorption and metabolism of many biotechnologically produced drugs, they cannot be delivered effectively through the conventional oral route. The relatively recent evolution of recombinant DNA research and modern synthetic and biotechnological methodologies allow the biochemist and chemist to produce vast quantities of variety of peptides and proteins...
possessing better pharmacological efficacy. Because after oral administration many drugs are subjected to pre-systemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability. Difficulties associated with parenteral delivery and poor oral availability provided the impetus for exploring alternative routes for the delivery of such drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. In absence of external stimuli to facilitate absorption, use of these alternative routes has had limited success. Various strategies have been implemented to promote the bioavailability of these drugs, including supplemental administration of enzyme inhibitors, use of absorption enhancers, novel formulation strategies, and reversible chemical modifications. Buccal mucosa is a potential site for the delivery of drugs to the systemic circulation. A drug administered through the buccal mucosa enters directly the systemic circulation, thereby minimizing the first-pass hepatic metabolism and adverse gastro-intestinal effect. However, oral mucosal permeability of drugs is too low to allow plasma concentration to reach therapeutic levels.

Conclusions

Novel drug release through trans-mucosal and transdermal, would be of huge worth, because through such routes, the pain factor coupled with parenteral routes of drug administration can be totally eliminated. Buccal adhesive systems offer countless advantages in provisions of convenience, management and pulling out, retentivity, short enzymatic activity, cost effective and elevated enduring fulfilment. Mutually an economic and universal healthcare viewpoint, determining ways to formulate injectable medications is expensive and a number of time leads to grave harmful effects. Consequently various cost effective novel drug delivery formulations with improved bioavailability are essential.

References


Figure 1. Histology of oral mucosa

Figure 2. The stages in mucoadhesion (Reproduced from Carvalho et al.; Braz. J. Pharm. Sci. 2010 [8])
Figure 3. The three regions within a mucoadhesive joint Reproduced from -Smart JD, Adv Drug Delivery Rev. 1993 [6])

Figure 4. The interpenetration theory (Reproduced from Carvalho et al; Braz. J. Pharm. Sci.2010 [8])

Figure 5. The dehydration theory of mucoadhesion (Reproduced from Carvalho et al, Braz. J. Pharm. Sci.2010 [8])
Figure 6. The possible regions for mucoadhesive joint failure (Reproduced from Smart J.D, Adv Drug Delivery Rev. 1993 [6])