BUCCAL DRUG DELIVERY SYSTEM: A REVIEW

Avani J. Ramani[1*], Dr. Kanu R. Patel[2] and Dr. Mukesh R. Patel[3]

[1]Department of Pharmaceutics, Shri B. M. Shah College of Pharmaceutical Education and Research, College Campus, Modasa -383315, Gujarat, India.

[2,3]Research Scholar, Gujarat Technological University, Gujarat.

*Correspondence for Author

Avani J. Ramani

Department of Pharmaceutics, Shri B. M. Shah College of Pharmaceutical Education and Research, College Campus, Modasa - 383315, Gujarat, India.

ABSTRACT

Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. Mucoadhesive are synthetic or natural polymer, which interact with the mucus.layer covering the mucosal epithelial surface, and mucin molecules constituting a major part of mucus. The concept of mucoadhesive as alters many investigator to the possibility that this polymer can be used over come physiological barrier in long-term drug delivery. Buccal mucosa is the preferred site for both systemic and local drug action. The mucosa has a rich blood supply and it relatively permeable. The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued. It is also possible to administer drugs to patients who unconscious and less co-operative. In buccal drug delivery systems mucoadhesion is the key element so various mucoadhesive polymers have been utilized in different dosages form. Various bioadhesive dosages form such as Chewing gum, tablets, Patches, Hydrogel, Thiolated tablets are discussed in this review article.

KEYWORDS: Buccal drug delivery, Bioadhesive polymers, Buccal Mucosa, permeation enhancers.

INTRODUCTION[1,3]

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as carriers. Amongst various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, this route presents some problems for a few drugs. The enzymes in the GI fluids, GIT-Ph conditions, the enzymes bound to GIT membranes are a few factors responsible for the bioavailability problems. The blood that drains the GIT carries the drug directly to the liver leading to first-pass metabolism resulting in poor bioavailability. The inherent problems associated with the drug, in some cases, can be solved by modifying the formulation or by changing the routes of administration. Parenteral, mucosal, and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs. In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via the buccal route, using bioadhesive dosage forms offers such a novel route of drug administration. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. Additionally, buccal drug delivery has high patient acceptability compared to other non-oral routes of drug administration. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route. Drug absorption through buccal mucosa is mainly by passive diffusion into the lipoidal membrane. After absorption, the drug is transported through facial vein which then drains into the general circulation via jugular vein, bypassing the liver and thereby sparing the drug from first-pass metabolism. Buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules.

Advantages of Buccal Drug Delivery Systems[1,2,4,7]

Drug administration via buccal mucosa offers several distinct advantages

- Ease of administration.
- Termination of therapy is easy.
- Permits localization of drug to the buccal cavity for a prolonged period of time.
- Can be administered to unconscious patients.
- Offers an excellent route, for the systemic delivery of drugs which undergo extensive firstpass metabolism or degradation in harsh gastrointestinal environment.

- A significant reduction in dose can be achieved thereby reducing dose related side effects.

- Drugs, which show poor bioavailability via the oral route, can be administered conveniently.

- It offers a passive system of drug absorption and does not require any activation.

- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in

- Systemic absorption is rapid as buccal mucosa is thin and highly perfused with blood.

- Provides an alternative route for the administration of various hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents etc.

- It allows the local modification of tissue permeability, inhibition of protease activity and reduction in immunogenic response. Thus, delivery of therapeutic agents like peptides, proteins and ionized species can be done easily.

Disadvantages of Buccal Drug Delivery Systems[1,2,4,7]

Drug administration via buccal mucosa has certain limitations

- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste or odour; can not be administered by this route.

- Drugs, which are unstable at buccal pH, cannot be administered by this route.

- Only drugs with small dose requirements can be administered.

- Drugs may get swallowed with saliva and loses the advantages of buccal route.

- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.

- Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

- Surface area available for absorption is less.

- The buccal mucosa is relatively less permeable than the small intestine, rectum, etc.

Permeability of drugs through buccal mucosa

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

1. Transcellular (intracellular, passing through the cell)

2. Paracellular (intercellular, passing around the cell).

Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules.

The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligo nucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancers may be required to overcome this. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also reduce stability. Disease states where the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such aslichen planus, pemphigus, viral infections and allergic reactions.

Mucus layer[3,4,5,7]

Anatomy of the oral mucosa

The mucosa that lines the oral cavity may be divided into three types, classified according to their functions.

1. **Masticatory mucosa:** Which includes the mucosa around the teeth and on the hard palate and these regions have keratinized epithelium.

2. **Lining mucosa:** Which covers the lips, cheeks, fornix, base of the oral cavity, lower part of tongue, buccal mucosa and the soft palate and these regions have non-keratinized epithelium.

3. Specialized mucosa: covering the dorsum of the tongue with highly keratinization. Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. Three distinctive layers of the oral mucosa are the epithelium, basement membrane and connective tissues. The oral cavity is lined with the epithelium, below which lies the supporting basement membrane. The basement membrane is, in turn, supported by connective tissues (fig. 1).

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. It is penetrated by tall and conical shaped connective tissues. These tissues, which are also referred to as the

lamina propria, consist of collagen fibers, a supporting layer of connective tissues, blood vessels, and smooth muscles. The rich arterial blood supply to the oral mucosa is derived from the external carotid artery. The buccal artery, some terminal branches of the facial artery, the posterior alveolar artery, and the infra orbital artery are the major sources of blood supply to the lining of the cheek in the buccal cavity.[1]

Role of Saliva[7,11]

➢   Protective fluid for all tissues of the oral cavity.

➢   Continuous mineralization / demineralization of the tooth enamel.

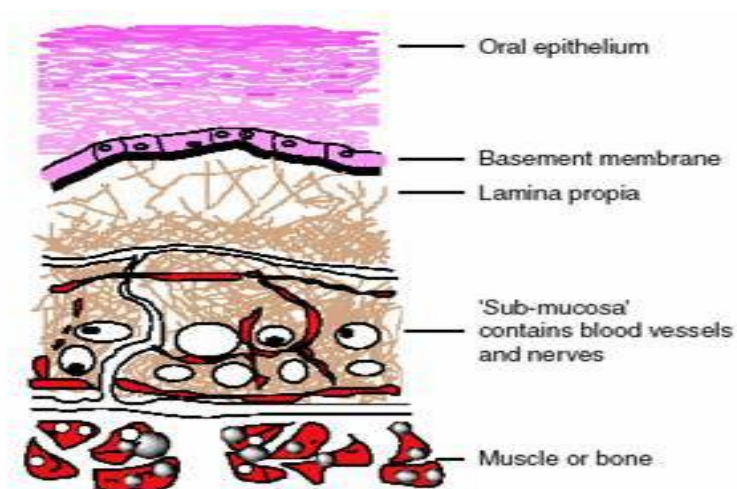➢   To hydrate oral mucosal dosage forms

Fig. 1 Structure of the human oral mucosa[13]

Role of Mucus[7,11]

➢   Made up of proteins and carbohydrates.

➢   Cell-cell adhesion.

➢   Lubrication.

➢   Bioadhesion of Mucoadhesive drug delivery system.

COMPOSITION OF MUCOUS MEMBRANE[5]

Component	Percentage
Water	95.00%
Glycoprotein and Lipids	0.5-5.0%
Mineral salts	0.5-1.0%
Free Proteins	0.5-1.0%

Saliva: The mucosal surface has a salivary coating estimated to be 70 μm thick, which act as unstirred layer. Saliva is composed of 99.5% water in addition to proteins, glycoproteins and

electrolytes. It is high in potassium (7×plasma), bicarbonate (3×plasma), calcium, phosphorous, chloride, thiocyanate and urea and low in Na (1/10×plasma). The normal pH of saliva is 5.6–7. Saliva contains enzymes namely α-amylase (breaks 1–4 glycosidic bonds), lysozyme (protective, digests bacterial cell walls) and lingual lipase (break down the fats).

Saliva serves multiple important functions

1) It moistens the mouth, initiates digestion and protects the teeth from decay.

2) It also controls bacterial flora of the oral cavity.

3) Because saliva is high in calcium and phosphate, it plays a role in mineralization of new teeth repair and precarious enamel lesions

4) It protects the teeth by forming "protective pellicle". This signifies a saliva protein coat on the teeth, which contains antibacterial compounds.

Stage of Mucoadhesion[6,9,14]

The Layer of mucoadhesion is generally divided into two steps:

(1) Contact stage and (2) Consolidation stage
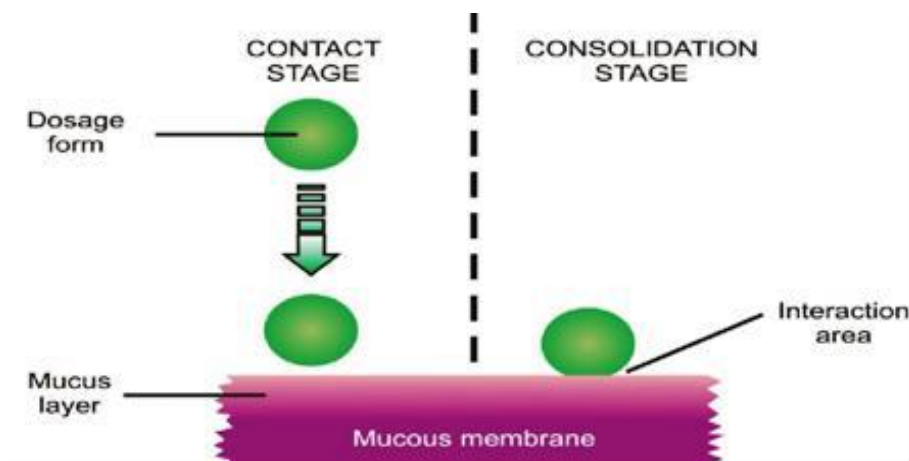
(Fig.2)

The contact stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over the membrane.

On the other hand, in the gastrointestinal tract direct formulation attachment over the mucous membrane is not feasible 11. In the consolidation step (fig. 2), the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the

mucoadhesive molecules to break free and to link up by weak Vander Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step 1) Diffusion theory, 2) Dehydration theory.

According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place the mucoadhesive device has features favouring both chemical and mechanical interactions. According to dehydration theory (**fig. 3**), materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. The difference in concentration gradient draws the water into the formulation until the osmotic balance is reached. This process leads to the mixture of formulation and mucus and can thus increase contact time with the mucous membrane. Therefore, it is the water motion that leads to the consolidation of the adhesive bond, and not the interpenetration of macromolecular chains. However, the dehydration theory is not applicable for solid formulation or highly hydrated form.
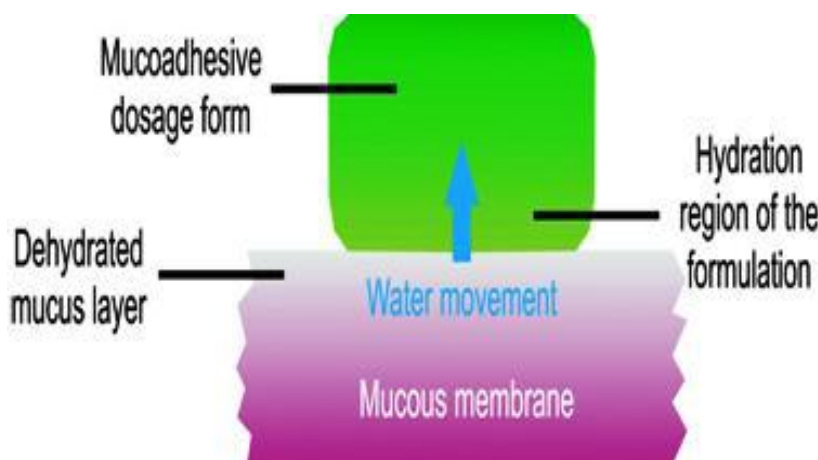

Fig. 3 Dehydration theory of mucoadhesion

MECHANISM OF MUCOADHESIVE[8, 6]

The mechanisms responsible in the formation of bioadhesive bonds are not fully known, however most research has described bioadhesive bond formation as a three step process.
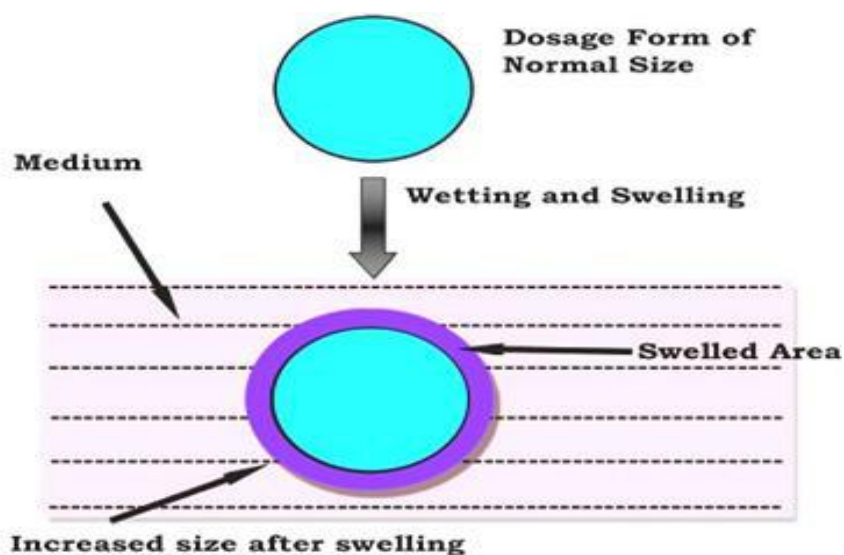
Step 1: Wetting and swelling of polymer

Step 2: Interpenetration between the polymer chains and the mucosal membrane.

**Step 3:** Formation of Chemical bonds between the entangled chains**.**

Step 1: In this step (**fig. 4**), when the polymer spreads over the surface of biological substrate or mucosal membrane, the wetting and swelling step occurs in order to develop an intimate contact with the substrate. By the help of the surface tension and forces that exist at the site of adsorption or contact, bioadhesive are able to adhere to or bond with biological tissues. Swellings of polymers occur because the components within the polymers have an affinity for water.

Step 2: The surface of mucosal membranes are composed of high molecular weight polymers known as glycoproteins. In this step (**fig. 5**) inter-diffusion and inter-penetration take place between the chains of mucoadhesive polymers and the mucous gel network creating a great area of contact. The strength of this bond depends on the degree of penetration between the two polymer groups. In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure.

Step 3*:* In this step (**fig. 6**), entanglement and formation of weak chemical bonds as well as secondary bonds between the polymer chains mucin molecule. The types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as Vander Waals interactions and hydrogen bonds. Both primary and secondary bonds are exploited in the manufacture of bioadhesive formulations in which strong adhesions between polymers are formed.

(**Fig. 4**) **step 1: wetting and swelling of polymer interpenetration**
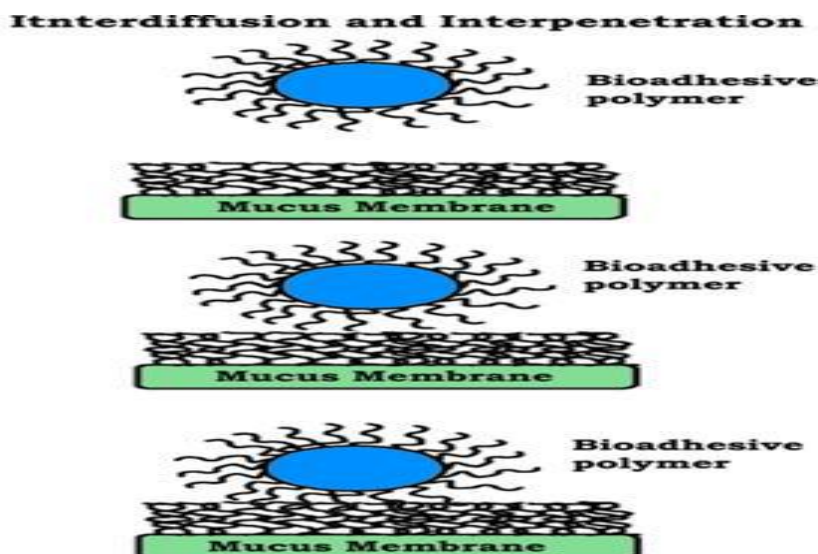
(Fig. 5)Step 2: Inter diffusion and of polymer and mucus
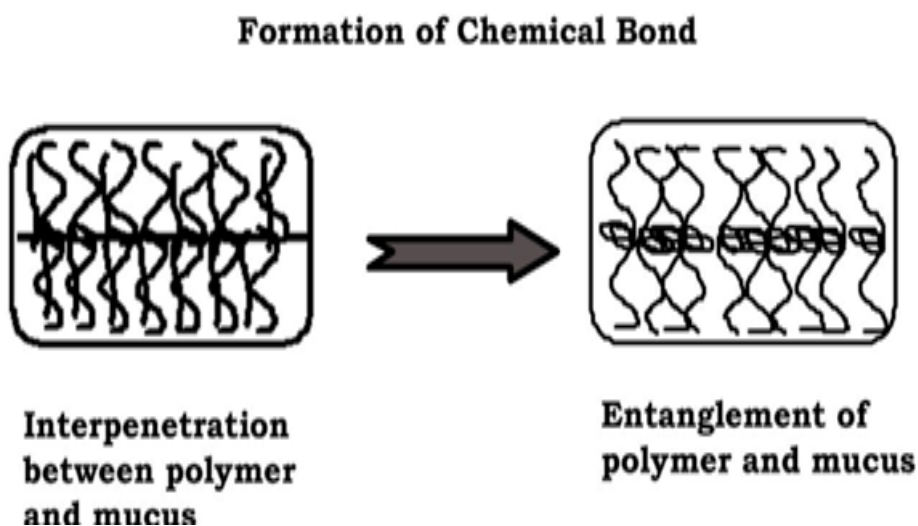
(Fig. 6)Step 3: Entanglement of polymer and mucus by chemical bonds

MUCOADHESION THEORIES[5,9]

Although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.

1) Electronic theory

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.

2). Adsorption theory

According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions. Such forces have been considered the most important in the adhesive interaction phenomenon because, although they are individually weak, a great number of interactions can result in an intense global adhesion.

3). Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (Fig 7). The contact angle should be equal or close to zero to provide adequate spreadability.
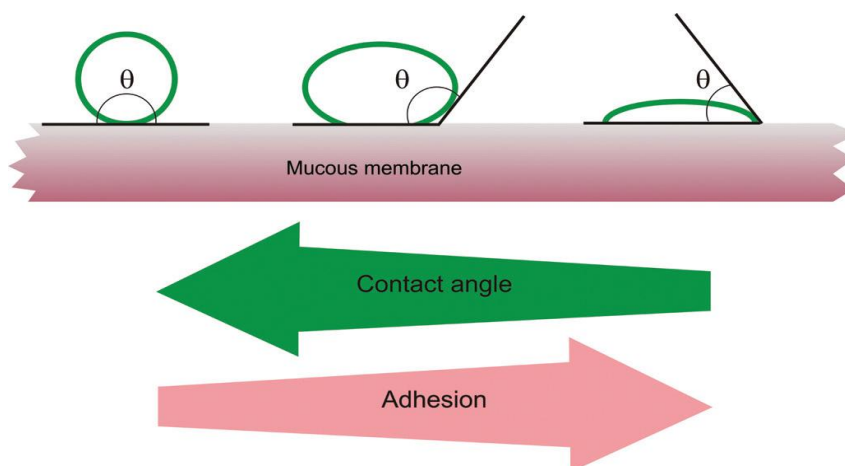
(Fig 7)– Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion.

The spreadability coefficient, *SAB*, can be calculated from the difference between the surface energies *γB* and *γA* and the interfacial energy *γAB*, as indicated in equation (1).

$$S_{AB} = \gamma B - \gamma A - \gamma AB \qquad (1)$$

The greater the individual surface energy of mucus and device in relation to the interfacial energy, the greater the adhesion work, *WA*, i.e. the greater the energy needed to separate the two phases.

$$W_{AB} = \gamma B + \gamma A - \gamma AB \qquad (2)$$

4). Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond (Fig 8). It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. According to the literature, the depth of in-terpenetration required to produce an efficient bioadhesive bond lies in the range 0.2-0.5 μm. This interpenetration depth of polymer and mucin chains can be estimated by equation 3.

$$l = (tD_b)^{1/2} \qquad\qquad (3)$$

where t is the contact time, and Db is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures.
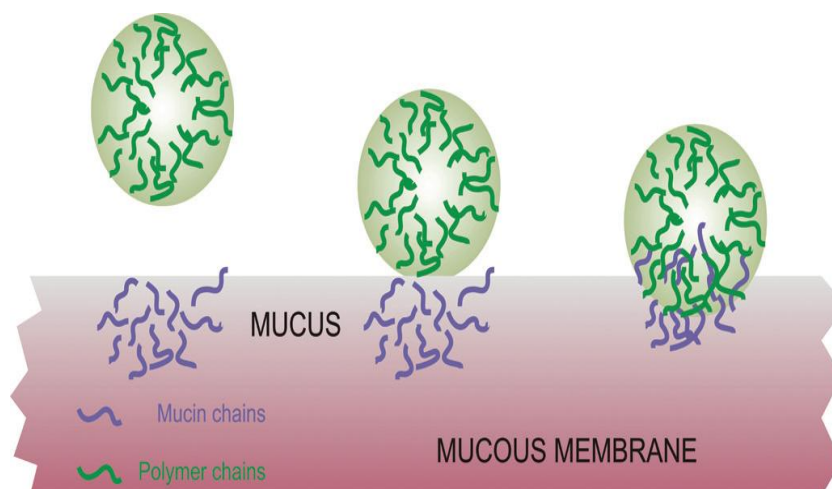
(FIG.8)– Secondary interactions resulting from inter diffusion of polymer chains of bioadhesive device and of mucus.

5).Fracture theory

This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is established. This force, *sm*, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, *Fm*, and the total surface area, *A0*, involved in the adhesive interaction (equation 4).

$$S_m = F_m/Ao \qquad\qquad (4)$$

In a single component uniform system, the fracture force, *sj*, which is equivalent to the maximal rupture tensile strength, *sm*, is proportional to the fracture energy (*gc*), for Young's module (*E*) and to the critical breaking length (*c*) for the fracture site, as described in equation 5.

$$\mathbf{S_f \sim |[g_c E/C]|^{1/2}} \qquad (5)$$

Fracture energy (*gc*) can be obtained from the reversible adhesion work, *Wr* (energy required to produce new fractured surfaces), and the irreversible adhesion work, *Wi* (work of plastic deformation provoked by the removal of a proof tip until the disruption of the adhesive bond), and both values are expressed as units of fracture surface (*Af*).

$$\mathbf{G_c = W_r + W_i} \quad (6)$$

The elastic module of the system (*E*) is related to the stress (*s*) and to the shear (*e*) by Hooke's law.

$$\mathbf{E = [\sigma/\varepsilon]_{\varepsilon\to0} = |[F/A_0 / \Delta l/l_0]|_{\Delta l \to 0}} \qquad (7)$$

In equation 7, the stress is the ratio between force (*F*) and area (*A0*), and shear is given by the ratio between the variation of system thickness (D*l*) and the original thickness (*l0*).

A criticism of this analysis is that the system under investigation must have known physical dimensions and should be constituted by a single and uniform material. In virtue of this, the relationship obtained cannot be applied to analyze the fracture site of a multiple component bioadhesive. In this case, the equation should be expanded to accommodate elastic dimensions and modules for each component. Besides, it must be considered that a failure of adhesion will occur at the bioadhesive interface. However, it has been demonstrated that the rupture rarely occurs at the surface, but near it or at the weakest point, which can be the interface itself, the mucus layer or the hydrated region of the mucus, as illustrated in Fig. 9.
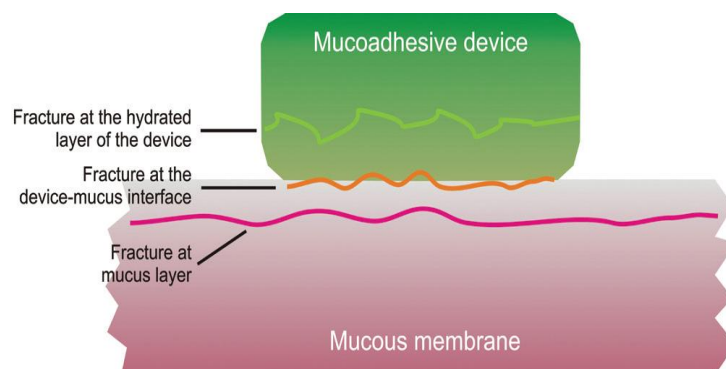

Fig. 9.Regions where the mucoadhesive bonds rupture can occur.

Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains. Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the polymer chains do not penetrate into the mucus layer.

6). Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process.

It is unlikely that the mucoadhesion process is the same for all cases and therefore it cannot be described by a single theory.

FACTOR AFFECTING MUCOADHESIVE[5, 10]

1. Polymer related factors.

i) Molecular weight.

ii) Concentration of active polymer.

iii) Flexibility of polymer chains.

iv) Spatial conformation.

v) Swelling.

2. Environment related factors

i) pH of polymer - substrate interface.

ii) Applied strength.

iii) Initial contact time.

3. Physiological factors

i) Mucin turns over

ii) Disease state

1. Polymer-Related Factors

i) Molecular weight

The optimum molecular weight for maximum bio-adhesion depends upon type of mucoadhesive polymer at concern. The threshold molecular weight required for successful bio-adhesion is at least 100,000. For example, polyethylene glycol (PEG), with a molecular

weight of 20,000 has little adhesive character, whereas PEG with 200,000 molecular weight has improved, and PEG with 400,000 has superior adhesive properties.

For linear polymers, the fact that mucoadhesiveness improves with increasing molecular weight implies two parameters: (1) Interpenetration is more critical for a low-molecular weight polymer to be a good mucoadhesive, and (2) Entanglement is important for high molecular-weight polymers.

ii) Concentration of active polymer

An optimum concentration for a mucoadhesive polymer is to produce maximum bioadhesion is to be determined. In highly concentrated system, adhesive strength drops significantly beyond the optimum level, however, the coiled molecules become separated from the medium the chain available for interpenetration becomes limited.

iii) Flexibility of polymer chains

Chain flexibility is critical for interpenetration and entanglement. As water soluble polymers become cross linked, the mobility of an individual polymer chain decreases. As the cross linking density increases and the effective length of the chain that can penetrate into the mucus layer decreases, which reduces mucoadhesive strength.

iv) Spatial conformation

Spatial conformation of a molecule is also important, besides molecular weight or chain length, despite a high molecular weight of 19,500,000 for dextrans, they have adhesive strength similar to that of PEG, with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation.

v) Swelling

Swelling characteristics are related to the mucoadhesive itself and its environment. Swelling depends on polymer concentration, ionic strength, and presence of water. During the dynamic process of bio-adhesion, maximum bio-adhesion. *In-vitro* occurs with optimum water content. Over hydration results in the formation of a wet slippery mucilage without adhesion.

2. Environment-Related Factors

i) pH of polymer–substrate interface

pH can influence the formal charge on the surface of the mucus as well as certain ionizable Mucoadhesive polymers. Mucus will have a different charge density depending on pH due to the difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Some studies had shown that the pH of the medium is important for the degree of hydration of cross-linked polyacrylic acid polymers, showing consistently increased hydration from pH 4 through pH 7, and then a decrease at alkaline pH levels.

ii) Applied strength

To place a solid mucoadhesive system, it is necessary to apply a defined strength. Depending on the type of polymer, poly (acrylic acid/ divinyl benzene) or carbopol, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum. The initial pressure applied to the mucoadhesive tissue at the contact site, can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with mucin.

iii) Initial contact time

Initial contact time between the mucoadhesive and mucus layer determines the extent of swelling and interpenetration of the mucoadhesive polymer chains. More Mucoadhesive strength increases as the initial contact time increases.

3. Physiological Factors

i) Mucin turnover

The natural turnover of mucin molecules from the mucus layer is important for at least two reasons. Firstly, the mucin turnover is expected to limit the residence time of the mucoadhesives on the mucus layer. No matter how high the mucoadhesive strength, they are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of mucoadhesive, but no information is available on this aspect. Secondly, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with mucoadhesives before they have chance to interact with the mucus layer. Surface fouling is unfavorable for mucoadhesion to the tissue surface. Mucin turnover may depend on the other factors such as the presence of food. The gastric mucosa accumulates secreted

mucin on the luminal surface of the tissue during the early stages of fasting. The accumulated mucin issue sequently released by freshly secreted acid or simply by the passage of ingested food; the exact turnover rate of the mucus layer remains to be determined.

ii) Disease state

The physiochemical properties of the mucus are known to change during disease conditions such as the common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial, and fungal infections of female reproductive tract, and inflammatory conditions of the eye. The exact structural changes taking place in mucus under these conditions are not clearly understood. If mucoadhesives are to be used in the disease states, the mucoadhesive property needs to be evaluated under the same condition.

BUCCAL MUCOADHESIVE POLYMERS[1,11,12,14]

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many, and meros meaning parts. Many Studies showed that addition of various polymers to Drug Delivery System, such as gums, increased the duration of attachment of the Medicinal Formulations to the mucous surface and increased the efficacy of antibiotic treatment. The development of the mucoadhesion theory and improvements in practical methods were accompanied by investigation of many polymers used in pharmaceuticals and new materials and their mixtures for the presence of mucoadhesive properties. The classification of mucoadhesive polymers and examples are presented in Table. 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.

Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes.
- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non-covalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface.

Ideal Characteristics of a Buccal Adhesive Polymer[12]

• Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.

• Should have good spreadability, wetting, swelling and 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 penetration enhancement properties.

• Should demonstrate acceptable shelf life.

• Should have optimum molecular weight.

• Should possess adhesively active groups

• Should have required spatial conformation.

• Should be sufficiently cross-linked but not to the degree of suppression of bond Forming groups.

• Should not aid in development of secondary infections such as dental caries.

Classification of mucoadhesive polymers[12]

Property used for classification	Example	
	Natural and modified natural polymers	**Synthetics**
Source	Agarose, Chitosan, Gelatin, Hyaluronic acid, Carrageenan, Pectin, Sodium alginate. **Cellulose derivatives** CMC, thiolated CMC, Na CMC, hydroxyl ethyl cellulose, HPC, HPMC, methylcellulose, Methyl hydroxyl ethyl cellulose.	**Polymers based on poly(meth)acrylic acid.** Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates, Copolymer of acrylic acid and PEG, Copolymer of methyl vinyl ether and Methacrylic acid, Poly-2-hydroxyethylmethacrylate, Copolymer of acrylic acid and Ethyl hexyl acrylate, Poly methacrylate, Poly alkyl cyanoacrylates:- Poly isobutyl cyanoacrylate, Poly isohexyl cyanoacrylate. **Others** Poly-N-2-hydroxypropylmethacrylamide,

	Water – Soluble	Water – insoluble
		Poly hydroxy ethylene, PVA, PVP, Thiolated polymers
Solubility in water	**Cellulose derivatives** CMC, Thiolated CMC, Na CMC, Hydroxy ethyl cellulose, HPC, HPMC, Methylcellulose, Methyl hydroxyl ethylcellulose. **Others** Poly-N-2-hydroxypropylmethacrylamide, Poly hydroxyl ethylene, PVA, PVP, Thiolated polymers. Ethyl cellulose, polycarbophil	**Polymers based on poly(meth)acrylic acid** Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates, Copolymer of acrylic acid and PEG, Copolymer of methyl vinyl ether and Methacrylic acid, Poly-2-hydroxy ethyl methacrylate, Copolymer of crylic acid and Ethyl hexyl acrylate, Poly methacrylate, Poly alkyl cyanoacrylates:- Poly isobutyl cyanoacrylate, Poly isohexyl cyanoacrylate.
	Cationic and Anionic	**Uncharged**
Charge	Amino dextran, dimethyl amino ethyl dextran, chitosan, quaternized chitosan Chitosan-EDTA, PAC, carbopol, polycar-bophil, pectin, sodium alginate, Na CMC, CMC	Hydroxy ethylated starch, HPC, PEG, PVA, PVP
Possible mechanism of formation of Bioadhesive bonds	Possible mechanism of formation of Bioadhesive Bonds	Cyanoacrylate Acrylates, carbopol, polycarbophil, PVA Chitosan
Notes. CMC = carboxy methyl cellulose; HPMC = hydroxyl propyl methyl cellulose; PEG = polyethylene glycol; PVA = polyvinyl alcohol; PVP = poly vinyl pyrrolidone; HEC = hydroxyl ethyl cellulose; HPC = hydroxyl propyl cellulose; PAA = poly acrylic acid; EDTA = ethylene diamine tetra acetate.		

Buccal Permeation Enhancer[14,16]

Penetration enhancers are the substances, which increase the buccal mucosal membrane permeation rate. Although most penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery. With the rapid development of biotechnology, more and more protein, peptide, and nucleotide drugs are becoming available, most of which have low membrane-absorption characteristics including.

- A large size with high molecular weight,
- Domains of different hydrophobicity,
- Irregular shapes, and
- Delicate structures easily inactivated.

These drugs are unable to cross membrane barriers in therapeutic amounts and thus research into penetration enhancers becomes ever more important.

Different permeation enhancers used in buccal drug delivery

Sr. no.	Permeation enhancer	Sr. no.	Permeation enhancer
1	Sodium EDTA	7	Polysorbate 80
2	23-lauryl ether,	8	Polyoxyethylene
3	Cetyl pyridinium chloride	9	Phosphatidylcholine
4	Azone	10	chitosan-cysteine
5	Cyclodextrine	11	Sodium glycocholate
6	Dextran sulphate	12	Sodium glycodeoxycholate

EVALUATION PARAMETER OF BUCCAL TABLETS DOSAGE FORM:[15,17]

➢ **Bulk density**

It is the ratio of total mass of powder to the bulk volume of powder. It was determined by pouring a weighed quantity of tablet blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume.

$$Db = M/ Vb$$

Here, M is the mass of powder: Vb is the bulk volume of the powder.

➢ **Tapped density**

It is the ratio of the total mass of the powder to the tapped volume of the powder. Accurately weighed amount of tablet blend poured in graduated cylinder and height is measured. Then cylinder was allowed to 100tap under its own weight onto a hard surface. The tapping was continued until no further change in height was noted.

$$Dt = M / Vt$$

Here, M is the mass of powder;

Vt is the tapped volume of the powder.

➢ **Carr's index**

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as Carr's compressibility index. It is indirectly related to the relative flow rate. Carr's compressibility index was determined by the given formula.

$$I = \frac{Dt - Db}{Dt} * 100$$

Here, Dt is the tapped density of the powder;

Db is the bulk density of the powder.

➤ **Hausner's ratio**

Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio was determined by the given formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Here, Dt is the tapped density; Db is the bulk density.

➤ **Angle of repose**

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug excipient blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}(h/r)$$

Here; **h** = Height of pile; **r** = Radius of pile; **θ** = Angle of repose.

2. Evaluation of Tablet

The tablets quality control tests following

➤ **Weight Variation**

According to I.P. procedure for uniformity of weight, twenty tablets are taken and their weight is determined individually and collectively on an electronic weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Average weight of Tablets (mg)	Maximum % deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

➤ **Thickness**

Thickness of tablets is determined using Vernier caliper. An average value is calculated by using tablets in triplicate and then the mean ± standard deviation values of thickness are notified.

➤ **Tablet Hardness**

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage, transformation and handling before usage depends on its hardness. Hardness in case of MDTs is kept low to allow rapid disintegration in mouth. It is done by using hardness tester like Pfizer hardness tester or Monsanto tablet hardness tester.

➤ **Friability**

Friability is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. A preweighed tablet is placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for 4 minutes for 100 revolutions. At the end of test, tablets are reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} * 100$$

➤ **Content uniformity**

Ten tablets were weighed and powdered in a glass mortar. Quantity of powder equivalent weight was accurately weighed and transferred in a 100ml volumetric flask. In 100ml take 1 ml solution and Make volume in volumetric flask up to 100ml using 6.8 pH buffer, then take 1ml and make volume up to 10 ml then filter through whatman filter. The filtrate was suitably diluted and analyzed spectrophotometrically at 283nm against blank using UV visible spectrophotometer.

• **Surface pH**

The surface pH of the buccal tablets was determined in order to investigate the possibility of any in vivo side effects. An acidic or alkaline pH may cause irritation to the buccal mucosa. The method developed by Battenberg et al was used. A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (pH 6.8) for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min.

- **Mucoadhesion strength**

Mucoadhesion strength of the tablet was measured on a modified physical balance. The method in using sheep buccal mucosa as model mucosal membrane. Fresh sheep buccal mucosa was obtained from a local slaughter house and was used within 2 h of slaughtering. The mucosal membrane was washed with distilled water and then with phosphate buffer pH 6.8. A double beam physical balance was taken and to the left arm of balance a thick thread of suitable length was hanged and to the bottom side of thread a glass stopper with uniform surface was tied. The buccal mucosa was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker which was placed in a 500 ml beaker filled with phosphate buffer pH 6.8 kept at 37o C such that the buffer reaches the surface of mucosal membrane and keeps it moist. The buccal tablet was then stuck to glass stopper from one side membrane using an adhesive (Feviquick).

The two sides of the balance were made equal before the study, by keeping a weight on the right hand pan. A weight of 5 g was removed from the right hand pan, which lowered the glass stopper along with the tablet over the mucosal membrane with a weight of 5 g. The balance was kept in this position for 3 min. Then, the weights were increased on the right pan until tablet just separated from mucosal membrane. The excess weight on the right pan i.e. total weight minus 5 g was taken as a measure of the mucoadhesive strength. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with phosphate buffer and left for 5 minutes before placing a new tablet to get appropriate results for the formulation.

- **In vitro drug release study**

The dissolution of the buccal tablet was performed using USP type II (paddle method) dissolution apparatus using 900 ml of phosphate buffer pH 6.8 containing as the dissolution media, which was maintained at 37^0 c and stirred at 50 rpm. Aliquots of 10 ml of samples were withdrawn with a bulb pipette at different time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 hrs and replaced with equal withdrawal, filtered it through what man filter paper no. I. The samples were then analysed using UV spectrophotometer at 283 nm and the cumulative amount of drug released at various time intervals was calculated. The experiments for different formulations (F1 to F2) were conducted in triplicate and average values recorded.

➢ **Sweling index**

For conducting the swelling study, the tablet was weighed (Wo) and placed in a petri dish containing 5 ml of phosphate buffer (pH 6.8)for 10 hours. After that ,the tablets were taken out from the petri dish and excess water removed carefully by using filter paper and weighed again(Wt). The swelling index was calculated using the following formula.

$$SI= (Wt-Wo) / Wo \times 100$$

Where, SI= Sweling index, Wt= Weight of tablets after time(t), Wo= Weight of tablets before placing in petri dish.

List of Active Ingredients delivered via a buccal route[1,7]

Sr.No.	Active Ingredient	Sr.No.	Active Ingredient
1	Acitretin	11	Metronidazole
2	Acyclovir	12	Melatonin
3	Arecoline	13	Metoprolol tartrate
4	Buprenorpine	14	Morphine sulphate
5	Carbamazepine	15	Nalbuphine
6	Cetyl Pyridinium chloride	16	Nicotine
7	Chlorhexidine diacetate	17	Nifedipine
8	Chitosan	18	Omeprazole
9	Chlorpheniramine maleate	19	Oxytocin
10	Cyanocobalamin	20	Pentazocine

CONCLUSION

In conclusion, the oral mucosa's accessibility, high blood supply, by-pass of the hepatic first pass metabolism, quick recovery time after damage and permeability profile makes it an attractive and interesting area for topical drug delivery research. There are several challenges to overcome, which include the permeability barrier of the epithelium and enzymatic activity within the oral cavity which can degrade biological drugs. With the appropriate technologies and delivery techniques the oral mucosa could, in the future, be utilised for the treatment of many diseases both mucosal and systemic and the catalogue of drugs which can be delivered via the mucosa could be greatly increased. Further advances in mucobuccal adhesive technology and sustained local drug release also have the potential for reducing the systemic side effects from ingested or injected therapies, where an oral mucosal disease is the target of therapy.

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