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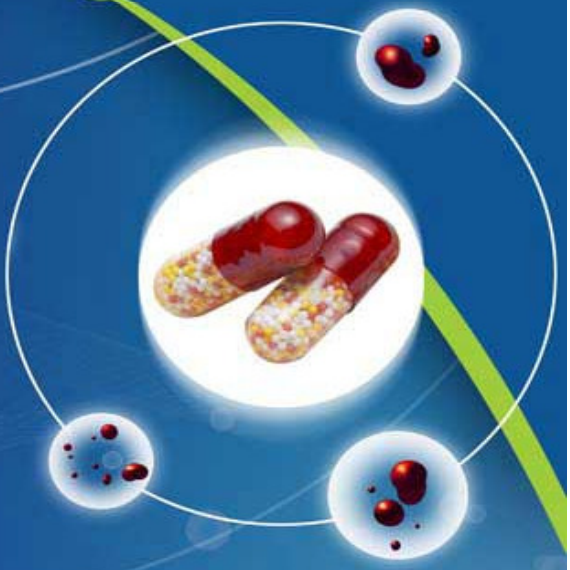

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Review Article

A REVIEW ON MUCOADHESIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Buccal controlled drug delivery system has been developed since the environment of the oral cavity provides potential sites for drug delivery. Within the oral mucosal cavity, the buccal region offers an adorable route of administration for systemic drug delivery. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily approachable site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. 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. The mucosa has a rich blood supply and it is relatively permeable. Buccal dosage forms will be reviewed with an emphasis on bioadhesive polymeric based delivery systems. The mucoadhesive interaction is explained in relation to the structural characteristics of mucosal tissues and the theories & properties of the polymers. Degree of mucoadhesion bonding is influenced by various polymer-based properties. The market share of transmucosal drug delivery systems has been increasing. This review will provide an insight into this route of drug delivery and the formulations that are, or can be, used, and it will also describe the challenges or possibilities of this route of administration. There is novel drug delivery system like buccal drug delivery system in which drug enters directly in systemic circulation thereby by passing the first pass effect.

Key Words: *Buccal controlled drug delivery, mucosa, transmucosal, mucoadhesion*

INTRODUCTION:

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time.

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[1-4] The adhesion of bacteria to the human gut may be attributed to the interaction of lectin-like structure (present on the cell surface of bacteria) and mucin (present in the biological tissues).[5-8] The bioadhesive polymers can be broadly classified into two groups, namely specific and nonspecific.[9] The specific bioadhesive polymers (e.g. fimbrin, lectins) have the ability to adhere to specific chemical structures within the biological molecules while the nonspecific bioadhesive polymers (e.g. polyacrylic acid, cyanoacrylates) have the capability to bind with both the cell surfaces and the mucosal layer. The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the

gums (gingival) and the inside of the cheeks (buccal). Buccal drug delivery has a number of advantages over peroral delivery. Mucoadhesive drug delivery systems are delivery systems which utilized the assets of bioadhesion of certain polymers which become adhesive on hydration and thus can be used for targeting a drug to exacting region of the body for extended period of time.

- Pharmaceutical aspects of mucoadhesion have been the subject of great significance during recent years because it provides the chance of avoiding either destruction by gastrointestinal contents or hepatic first- pass inactivation of drug.
- During the period of 1980s poly (acrylic acid), hydroxypropylcellulose, and sodium carboxymethylcellulose were extensively explored for the development of formulations having mucoadhesive properties.[10-12]After a lot of research, the researchers are of the view that a polymer will exhibit enough mucoadhesive property if it can form tough intermolecular hydrogen bonding with the mucosal layer, penetration of the polymer into the mucus network or tissue crevices, easy wetting of mucosal layer and high molecular weight of the polymer chain. The ideal distinctiveness of a mucoadhesive polymer matrix include the rapid adherence to the mucosal layer not including any change in the physical property of the delivery matrix, minimum interference to the release of the active agent, biodegradable without producing any toxic byproducts, inhibit the enzymes present at the delivery site and develop the penetration of the active agent (if the active agent is meant to be absorbed from the delivery site). [12]

Anatomy of the oral mucosa

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 epithelium, as a protective layer for the tissues beneath, is divided into (a) non-keratinized surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks,

Mucoadhesive drug delivery system

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time.Bioadhesion is an integral phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces. In the case of polymer attached to mucin layer of a mucosal tissue, the term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, urogenital tract, the airways, the ear and eye. [13]

and(b) keratinized epithelium which is found in the hard palate and non-flexible regions of the oral cavity. The epithelial cells, originating from the basal cells, mature, change their shape, and increase in size while moving towards the surface. The thickness of buccal epithelium in humans, dogs, and rabbits has been determined to be approximately 500–800 μm. 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. The buccal epithelium is classified as a non-keratinized tissue. 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. 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. 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]

Overview of the Oral Mucosa

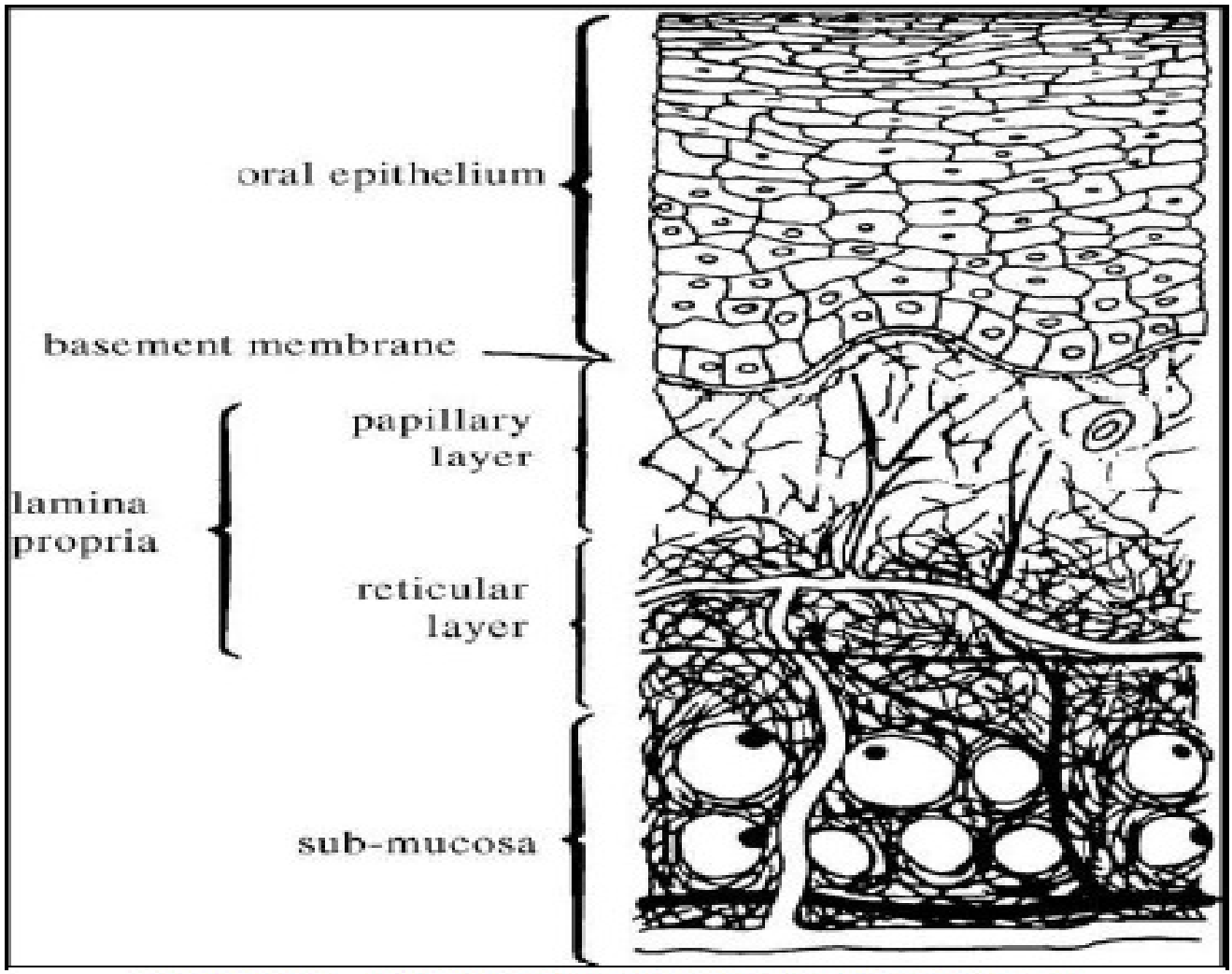

FIGURE 1: ANATOMY OF THE ORAL MUCOSA

Drug permeability through buccal mucosa

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

- Transcellular (intracellular, passing through the cell) and;
- 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. (Fig. 2)[15]

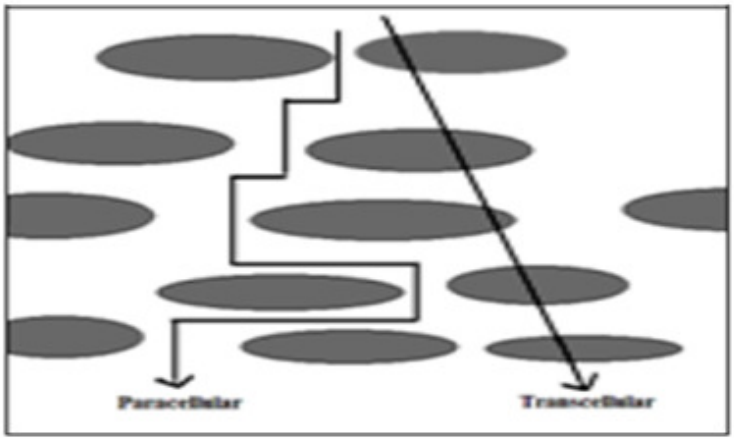

Figure 2: The paraceluar and transcelluar routes of transport have been designed to the buccal mucosa

Mechanism of Mucoadhesion

To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative. Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration, there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymerdiffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density. [16, 17, and 18]

Theories of Mucoadhesion

Theory	Mechanism of bioadhesion	Comments
Electronic theory	Attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material	Electrons transfer occurs between the two forming a double layer of electric charge at the Surface.
Wetting theory	Ability of bioadhesive polymer to spread and developintimate contact with the mucous membrane.	Spreading coefficient of polymers must be positive. Contact anglebetween polymer and cells must be near to zero.
Adsorption theory	Surface force resulting in chemical bonding.	Strong primary force: covalent bonds. Weak secondary forces:hydrogen bonds and van der Waal's forces.
Diffusion theory	Physical entanglement of mucin strands and flexible polymer chains.	For maximum diffusion and best adhesive strength, solubility parameters of the bioadhesive polymer and the mucusglycoproteins must be similar
Mechanical theory	Adhesion arises from an interlocking of liquid adhesive intoirregularities on the rough surface.	Rough surfaces provide an increased surface area available for interaction along with an enhanced viscoelastic and plasticdissipation of energy during joint failure, which are more importantin the adhesion process than a mechanical effect
Fracture theory	Analyses the maximum tensile stress developed duringattachment of the trans-mucosal DDS from the mucosalsurface.	Does not require physical entanglement of bioadhesive polymer chains and mucous strands, hence it is appropriate to study the bio-adhesion of hard polymers which lack flexible chains

Bioadhesive Polymers

Bioadhesive polymers have properties to get adhered to the biologicalmembrane and hence capable of prolonging the contact time of the drug with a body tissue. The use of bioadhesive polymers can significantly improve the performance of many drugs. This improvement ranges from better treatment of local pathologies to improved bioavailability and controlled release to enhance patient compliance. [19, 20]

Characteristics of Ideal Bioadhesive Polymers

- It should show bioadhesive properties in both dry and liquid state.
- It should possess an optimum molecular weight to the bio-adhesion.
- It should be able to accommodate both oil and water soluble drugs for the purpose of controlled drug delivery.
- It should demonstrate local enzyme inhibition and penetration enhancement properties.

- It should show specificity for attachment to an area or cellular site.
- It should show specificity and stimulate endocytosis.
- It should be inert and compatible with the environment.
- It should be easy and inexpensive to fabricate.
- It should have good mechanical strength.
- It should possess a wide margin of safety both locally and systemically.

Mucoadhesive buccal drug delivery systems

Drug delivery via the membranes of the oral cavity can be subdivided as Sub lingual delivery, buccal delivery and local delivery. These oral mucosal sites are at variance greatly from one another, on terms of anatomy, Permeability, to an applied drug, and their ability to maintain a drug delivery system for desired length of time. What aspects make the oral mucosa, mainly the buccal site rather attractive?

- Because of easily accessibility it permits localization of the system.
- Since the patients are well modified to oral administration of drugs in general, patient recognition and compliance is expected to be good.
- Its ability to convalesce after local treatment is evident and hence allows a wide range of formulations to be used e.g. bioadhesive patches and ointments. [21, 22]

Advantages of mucoadhesive buccal drug delivery

- Drug administration via the oral mucosa offers a number of advantages
- Offers a superb route for the systemic delivery of drug which by passes first pass metabolism, thereby offering a greater bioavailability.
- Permits localization of the drug for a prolonged period of time.
- Easy administration and termination of therapy in emergency.
- Can be administered to comatose and trauma patients.
- Significant reduction in dose can be achieved, thereby reducing dose, dose dependent side effects, and eliminates peak valley profile.
- Drugs which are unstable in acidic environment of stomach or are destroyed by the enzymatic or alkaline environment of the intestine can be administered.
- It offers a passive system for drug absorption.
- It can be made unidirectional to assure buccal absorption.
- Flexibility in physical state, shape, size and surface.
- It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, careful uses of therapeutic agents like peptides, proteins and ionized species can be achieved.
- Maximized absorption rate due to intimate make contact with the absorbing membrane and decreased diffusion barriers.
- It satisfies a number of futures of the controlled release system.
- The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus build up beneath the applied dosage form.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- Rapid onset of action [22, 23].

Limitations of Buccal Drug Administration

- Drugs which are unstable at buccal pH cannot be administered.
- Eating and drinking may become restricted.
- There is an ever present possibility of the patient swallowing the dosage form.

- Over hydration may leads to slippery surface and structural integrity of the formulation mayget disrupted by this swelling and hydration of the bioadhesive polymers.
- Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor cannot be administered by this route.
- Only drug with small dose requirement can be administered.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Drugs contained in the swallowed saliva follow the pre-oral and advantages of buccal route are lost [8, 21].

An ideal mucoadhesive polymer has the following characteristics

- The polymer and its degradation products should be non-hazardous and should be non-absorbable from the gastrointestinal tract.
- It should be nonirritant to the mucous membrane.
- If possible form a strong non-covalent bond with the mucin-epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site-specificity.
- It should allow daily incorporation to the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of polymer should not be elevated so that the prepared dosage form remains competitive. [22, 23].

Molecular Characteristics

Investigations into polymers with various molecular characteristics conducted by many authors have led to a number of conclusions regarding the molecular characteristics required for mucoadhesion. The properties exhibited by a good mucoadhesive may be summarized as follows:

- Strong hydrogen bonding groups (-OH, -COOH).
- Sufficient flexibility to penetrate the mucus network or tissue crevices
- High molecular weight.
- Strong anionic charges

Surface tension characteristics suitable for wetting mucus/ mucosal tissue surface. [8, 24, 25]

Although an anionic nature is preferable for a good mucoadhesive, a range of nonionic molecules (e.g., cellulose derivatives) and some cationic (e.g., Chitosan) can be successfully used.

Method used to study bioadhesion

Several test methods have been reported for studying bioadhesion. These tests are important during the design and development of bioadhesion controlled released system as they guarantee compatibility, physical and mechanical stability, surface analysis and bioadhesion bond strength. The tests can be broadly classified into 2 major categories:

- **In-vitro / Ex-vivo methods:**

Most in-vitro methods were based on either tensile or shear stress. a. Modified balance or tensile testers. b. Wilhelm plate method (shear stress). c. Other in-vitro methods A number of other methods including thumb test method, adhesion weight method, flow channel method ,fluorescent probe method, falling liquid film method, colloidal gold staining method, have been used for the determination of bioadhesion.

- **In-vivo methods:**

Rathbone et al. has discussed several methods to study rate and extent of drug loss from human oral cavity. These include buccal absorption test, disks methods andperfusion cells. These methods have provided information on

mechanism by which drugs are transported across the oral cavity membranes**.** [26]

Factors Important To Mucoadhesion

The bioadhesive power of a polymer or of a progression of polymers is affected by the nature of the polymer and also by the nature of the surrounding media. Some factors are discussed below:

1. Polymer-Related Factors

(a) Molecular Weight:

The optimum molecular weight for most bioadhesion depends on the type of bioadhesive polymer at issue. It is usually implicit that the threshold required for successful bioadhesion is at least 100,000 molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has enhanced, and a PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for linear polymers imply two things:

- Interpretation is more critical for lower molecular weight polymers to be an excellent bioadhesive
- Entanglement is important for higher molecular weight polymers

Adhesiveness ofa nonlinear structure follows a quite different tendency. The adhesive strength of dextran, with a very high molecular weight of 19,500,000 is similar to that of PEG, with a molecular weight of 200,000. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are mainly responsible for adhesion, unlike the conformation of PEG.

(b) Concentration of active polymers:

There is an optimum concentration of a bioadhesive polymer to produce maximum bioadhesion. In extremely concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

(c) Flexibility of polymer chains:

It is critical for interpenetration and entanglement. As water-soluble polymers become crosslinked, mobility of character polymer chains decrease and thus the valuable length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

(d) Spatial conformation:

Besides molecular weight or chain length, spatial conformation of a molecule is also prominent. In spite of a high molecular weight of 19,500,000 for dextrans, theyhave related adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily dependable for adhesion, unlike PEG polymers which have a linear conformation.

2. Environment Related Factors

(a) Applied strength:

To place a solid bioadhesive system, it is required to concern a defined strength. Whatever the polymer, poly(acrylic acid / vinyl benzene poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the period of its application, up to an optimum. the pressure initially applied to the mucoadhesive tissue contact site can influence 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 interaction with mucin.

(b) pH:

It can manipulate the formal charge on the surface of mucus as well as certain ionis capable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of efficient groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration of cross linked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then a reduce as alkalinity and ionic strength increases.

(c) Initial Contact Time:

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Bioadhesive strength increases as the initial contact time increases.

(d) Swelling:

It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration can result in the formation of slippery mucilage without adhesion.

3. Physiological Variables

a) Mucin Turnover:

The natural turnover of mucin molecules is important for as a minimum two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter, how high the adhesive strength, mucoadhesive are detached from the surface due to mucin turn over. Second, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with the mucoadhesive before they have a chance to act together with the mucus layer. Mucin turnover may depend on other factors such as presence of food.

b) Disease States:

The physiochemical properties of mucus are known to adjust during disease conditions such as common cold, gastric ulcers, and ulcerative colitis, bacterial and fungal infections of the female reproductive tract. [26]

Mechanism of Buccal Absorption Enhancer

The mechanism by which enhancers act are been unsuccessfully understood. Surfactants such as sodium lauryl sulphate interact at either the polar head groups or the hydrophilic tail regions of the molecules comprising the lipid bilayer disrupting the packing of the lipid molecules, increasing the fluidity of the bilayer and facilitating drug diffusion. Interaction of enhancers with the polar head groups may also cause or allow the hydrophilic regions of adjacent bilayers to take up more water and more apart, thus opening the Paracellular pathway. Non- ionic surfactants and long chain acids and alcohols also increase membrane components, thereby increasing the permeability. Agents such as DMSO, polyethylene glycol, and ethanol can, if present insufficient high concentrations in the delivery vehicle enter the aqueous phase of the stratum corneum and alter its solublizing properties, thereby attractive the partitioning of drugs from the vehicle into the skin. Mechanisms by which permeation enhancers are thought to improve mucosal absorption include the following: [27, 28]

- Overcoming the enzymatic barrier
- Increasing the thermodynamic activity of drugs
- Changing mucus rheology
- Affecting the components involved in the formation of intracellular junctions
- Increasing the thermodynamic activity of drugs.

Permeation enhancers

Permeation enhancers are substances added to pharmaceutical formulation in order to increases the membrane permeation rate or absorption rate of a co-administered drug. They are used to improve bioavailability of drugs with normally poor membrane permeation properties without damaging the membrane and causing toxicity. Enhancer efficacy depends on the physiochemical properties of the drug, administration site, nature of the vehicle and whether enhancer is used alone or in combination.

Categories and examples of membrane permeation enhancers

- Bile salts : Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium glycodeoxycholate,
- Surfactants : Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride,
- Fatty acids : Oleic acid, Capric acid, Lauric acid, Lauric acid/ propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholi
- Chelators: EDTA, Citricacid, Sodium salicylate, Methoxy salicylates
- Non-surfactants: Unsaturated cyclic ureas
- Inclusion complexes: Cyclodextrins
- Others: Aprotinin, Azone, Cyclodextrin, Dextran sulfate, Menthol, Polysorbate 80, Sulfoxides and various alkyl glycosides.

CONCLUSION

Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. It has to be noted that only a moist surface can bring the mucoadhesive nature of the dosage form. Mechanism of mucoadhesion is backed up by ionic bond, covalent bond, Vander Waal bond and hydrogen bond. Ionic and covalent bonds result in very strong mucoadhesive property. Mucoadhesion commence with wetting which is described as contact stage.In the consolidation stage lot of physiochemical interaction takes place. While considering a formulation development of mucoadhesive drug delivery dosage form, several physiological factors also has to be considered at the site of action. Several synthetic and natural polymers are considered to have complying properties of mucoadhesion. While performing gastro retentive mucoadhesive *in-vivo* tests, it should be proved that the dosage form is no more available in the stomach after the desired period.

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