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Mucoadhesive Drug Delivery Systems- An Overview

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ABSTRACT

The term mucoadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the layer of surface of a biological membrane and the natural or synthetic polymer, which allows the polymer to the adhere the surface of that membrane for an extended as well prolonged period of time. Since the last four decades, the conception of mucoadhesion has achieved aimportant precious interest in the various fields of pharmaceutics. There are many advantages of mucoadhesive buccal drug delivery system that made this is a novel drug delivery system for the local as well as systemic delivery of various drugs. The main advantage of this route for drug delivery is that, the delivery by this route by passes the first pass metabolism of various drugs that are liable to their hepatic first pass metabolism .This review provides the brief knowledge about the oral mucosal drug delivery by discussing briefly the structural feature of mucosa, mechanism of mucoadhesion, various theories of mucoadhesion, general consideration in design of mucoadhesive buccal dosage forms, permeation enhances and the various evaluation methods along with the literature Survey of the buccal mucoadhesive drug delivery System.(1)

Keywords: Mucoadhesion, Polyacrylic Acid, Bioadhesion, Bioavilability, Films, Permeation Enhancers, Polymers.

1.0 Introduction

Mucoadhesive drug delivery system are drug delivery system which utilize the property of bio adhesion of certain polymers which becomes adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time .mucoadhesion may be describes because the kingdom where on substances adheres to every different for prolong time frame with the assist of interfacial forces .when this type of substances is organic in natural the manner is refer to as bio adhesion .mucoadhesion is the manner of binding a fabric to the mucosal layer of the frame. Utilizing herbal and artificial polymer, muccoadhesivedrug delivery is the way of managed drug released which lets for intimates contact between the polymers and the target tissue. Mucoadhesive drug delivery system are delivery system are delivery system which makes use of the assets of bio adhesion of positive polymers which grow to be adhesive on hydration and subsequently are able used for targeted delivery of the drug to particular region of body for prolong time period. The concept of mucoadhesion becomes introduced with inside the control released drug delivery within the early 1980s. eight control released system provides continuous drug released at a predetermine rate. In recent years'considerable interest has been shown in the use of bio adhesive polymers and copolymers in controlled drug delivery.(2) This interest is due to the following potential applications of bio adhesive drug delivery system:

1) Adhesion to specific site of the body, such as the oral and nasal cavities, resulting in an enhanced drug bioavailability.
2) The formation of an optimum contact with the adhesion surface, increasing drug absorption.
3) The prolonging of the residence time of the dosage of within ten gastrointestinal tracts. this would reduce the need for multiple dosing, resulting better patient compliance.

The biological surface can be epithelial tissue or the mucus coat on the surface a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Mucoadhesion should not be confused with bio adhesion; in bio adhesion, the polymer Is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used. (3)

The effect of a drug can now be reinforced as a result of the development of new release systems. Controlled release consists of techniques that make the active chemical agents available for a target, providing an adequate release rate and duration to produce the desired effect. The main controlled drug delivery systems currently available include matrices, pellets, floating systems, liposomes, microemulsions, liquid crystals, solid dispersions, nanosuspensions, transdermal systems, cyclodextrin inclusion complexes, osmotic pumps and bioadhesive systems. The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier (Hägerström, 2003). On the other hand, adhesion of preparations onto mucous membrane can be impaired by the mucociliary clearance system. This clearance, a natural defense mechanism of the body against the deposition of impurities onto the mucous membrane, can also remove the preparation. Thus, by using bioadhesive molecules, it is possible to retain the preparation at the action site and to direct the drug to a specific site or tissue. Other

features associated with the development of controlled drug delivery systems using bioadhesive molecules include a decrease in drug administration frequency and an increase in patient compliance to the therapy (Woodley, 2001). Therefore, a bioadhesive system controlling drug release could improve the treatment of diseases, helping to maintain an effective concentration of the drug at the action site.Mucous membrane is the main administration site for bioadhesive systems, although the need for new bioadhesive formulations for dermal administration has also been reported when prolonged cutaneous action is desired. A prolonged effect upon the dermal administration of creams, solutions, and lotions is unexpected, since such preparations can be easily removed from the skin by moisture, temperature, and physical movements. Although studies on the mechanisms involved in mucoadhesion and the development of novel mucoadhesive systems and polymers have evolved over the last twenty years, mucoadhesion is not yet fully understood. Quantitative and qualitative techniques are still treated separately. The aim of this study was to systematically review the mechanisms and theories involving mucoadhesion, as well as to describe the methods and polymers most used in mucoadhesive systems for drug delivery.(4)

Advantages of Mucoadhesive Drug Delivery System: -

1)Drugs shows bypass first pass metabolism then it increases bioavailability.

2)Drug is easily administered of therapy in emergency condition.

3)Some drugs are not stable in acidic environment of stomach can be administered by buccal delivery.

4)Drug release for prolonged period of time.

5)In this system drug absorbed by passive diffusion.

6)Adaptability in actual state, shape, size & surface

- **Limitations of Mucoadhesive Drug Delivery System**:-

1)Drug which are not stable at buccal PH cannot be administered.

2)Drugs which have bitter taste or not pleasant taste or agood or bother mucosa can't be administered by this route.

3)Drug needed with little portion must be controlled.

4)Those medications which are consumed by inactive (5)

2.0 Historical Development of Mucoadhesive DDS's

since from the last 40 years the idea of mucoadhesion has supplied the awesome softwhere in prolonging the residence time as well as controlled realesed effect of various bioadhesive dosage forms through different mucosal routs .the formulation based on the mucoadhesive drug delivery system have shown enhanced the bioavailablity of many drug .Mucoadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mix with dental adhesive powder to apply penicillin to the oral mucosa. Over the year's various others polymers for examples sodium alginate, CMS, guar gum, HEC, andtragacanth have been found to exhibit mucoadhesiveproperties. during the 1980s polyacrilicacids, HPC and SCMC where widely explored for the development of formulation having mucoadhesive properties. since then the use of acrylate polymers for the developments of the mucoadhesion formulation has increased many folds. (6)

3.0 Anatomy & Physiology of Oral Mucosa

Oral mucosal locale is adhesive in nature and goes about as alubricant, whichis permitting the cells to move comparative with each other with less grating. There are four sites are as follows:

1)Buccal cavity

2)The sublingual area

3)The palate

4)Gingival region

It's utilized for drug organization. The utilized site for drug organization of the four locale referenced over that is the buccal cavity. The anatomicsite for drug organization between the cheek and gingival is known as the buccal mucosa. The oral cavity is made out of three layers. The primary layer is the delineated squamous Epithelium, under this layer is basement membrane film. The storm cellular layer overlies the lamina propriety and submucosa.The constitution of the epithelium inside the various locales of the oral cavity show divergence. The epithelium in the slot sense of taste, buccal and sublingual region isn't keratinized, subsequently not containing ceramides and acyl ceramides which are related with giving a boundary work. The mucosa of the buccal & sublingual locale has just modest quantities of ceramideand subsequently more porous. When contrasted with different locales of the oral cavity. A layer of bodily fluid is available on the outer layer of the cells. This assumes a significant part in cell to cell attachment, oralgrease just as mucoadhesion of mucoadhesive drug delivery frameworks. The buccal region has a field of smooth and somewhat stable surface, which is appropriate for arrangement of a retentive framework. For buccal drug delivery, grip to the oral mucosa licenses not just the

closeness of contact and the chance of further developed drug retention yet in addition the capacity of accomplish an ideal home time at the site of organization These qualities make the buccal mucosa as a more appropriate site for delayed foundational delivery of drugs.(7)

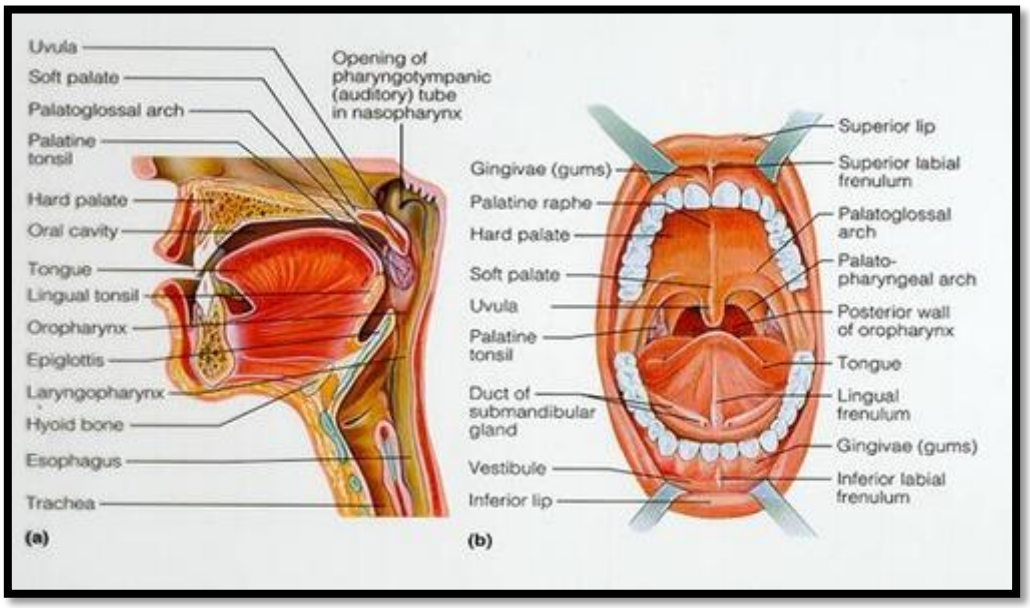


Figure 1: Overview of oral mucosa

Components and Structural Features of oral cavity

The oral mucosa is for the most part emitted by different organs of oral cavity that are sublingual organ, parotid organ and other salivary organs. The mucus is a clear gel discharged by goblet cell or by uncommon exocrine organs with the mucus cells. The components are given in figure 2**:**

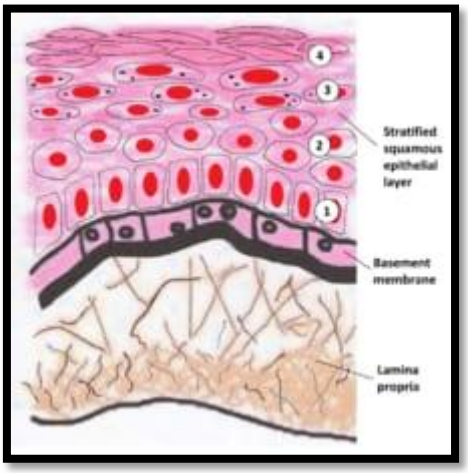


Figure 2: Composition of Mucus layer

Table 1 : Components of Mucus Layer

Components	**Percentage**
Water	95
Glycoproteins & lipids	0.5-5
Mineral salts	1
Free proteins	0.5-1

Mucus glycoproteins are the high molecular proteins that contain attached oligo- polysaccharide units. The mucus contains following oligosaccharide

units:

- L- fructose
- D-galactose
- N-acetyl –D-galactose
- Sialic acid

Functions of mucus: -

- Protective
- Lubrication
- Bio adhesion
- Cell –cell adhesion
- Barrier(8)

4.0 Mechanism of mucoadhesion

The two material in which one may be artificial such as mucoadhesive polymer and other may be mucin layer of the mucosal tissue are held together by means of interfacial force of attraction is known as mucoadhesion.

Mucoadhesive means artificial substance that is capable of interacting with mucus membrane and being retain on them or holding them together for extended or prolonged time. During the process of adhesion there have two stages identified are given below.

1. Contact Stage
2. Consolidation Stage

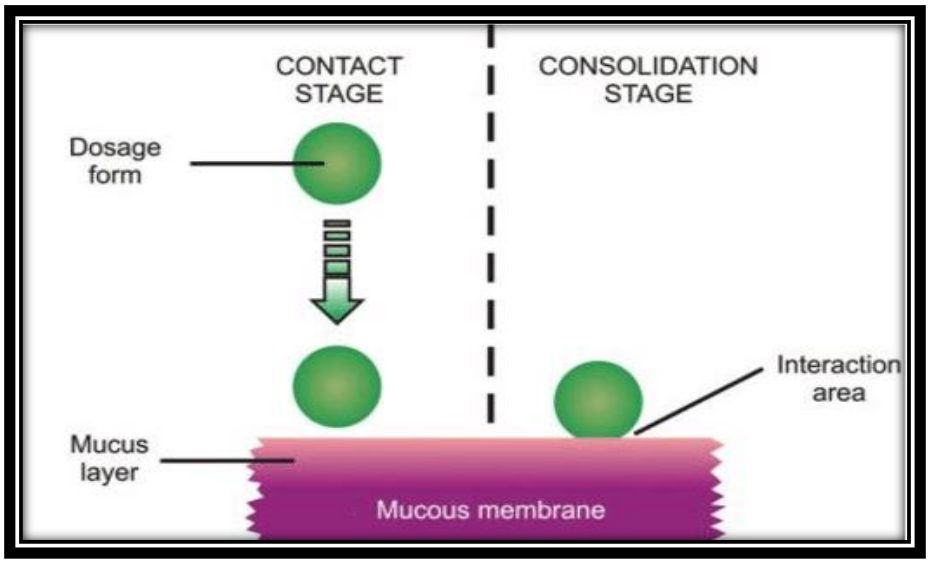


Figure 3: Mechanism of mucoadhesion

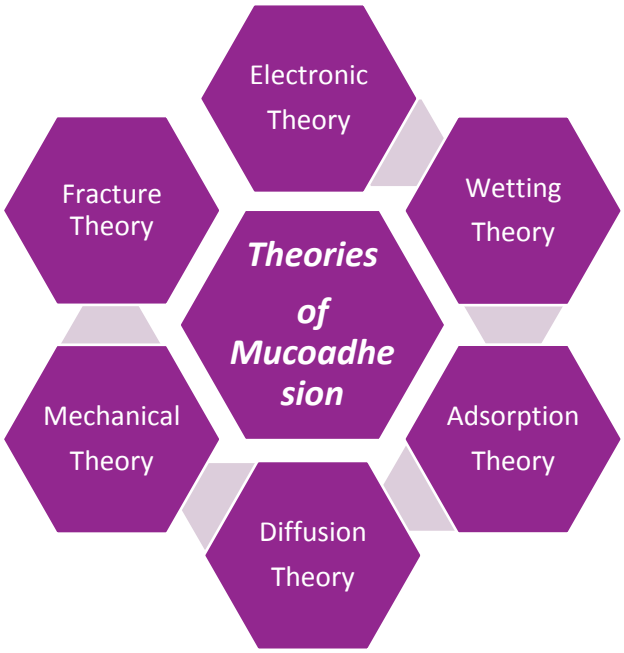
1) Contact Stage

During at this stage when the mucoadhesive material comes in contact with mucus membrane an intimate wetting occurs between mucoadhesive and mucus membrane. This wetting of mucoadhesive is done by the mucus present in mucosal membrane.

2) Consolidation Stage

By means of different physiochemical forces of attraction such as Vander Waals forces, electrostatic forces and hydrogen bonding. This forces present in mucoadhesive material gets join to the mucus membrane and resulting in long lasting mucoadhesion. This stage is called as consolidation stage. After these two stages the process of mucoadhesion completes.(9)

5.0 Theories of Mucoadhesion



Flow Chart 1: Theories of mucoadhesion

1)The Electronic theory:

According to this theory electron transfer occurs upon contact of an adhesive polymer and the mucus glycoprotein network because of differences in electronic structure. This is proposed to result in the formation of an electronic double layer at the interface, with subsequent adhesion due to attractive forces across the double layer.

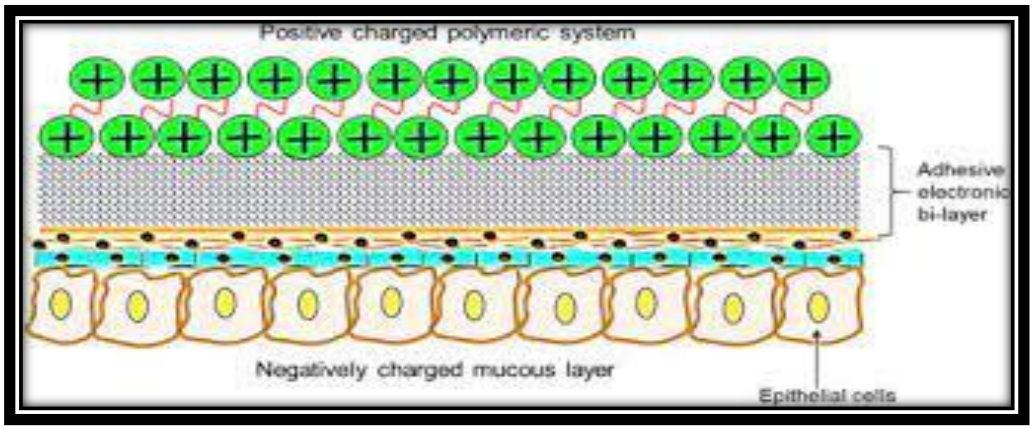


Figure 4: Electronic theory of mucoadhesion

2)The wetting Theory:

It is basically applied to liquid frameworks and things about surface and interfacial energies. It includes the capacity of a fluid to spread suddenly onto a surface as an essential for improvement of bond. The Affinity of liquid for a surface can be found using techniques such as contact angle geometry to measure the contact angle of the liquid on surface, with the general rule being that the lower the contact angle the greater the affinity of liquid to the solid.

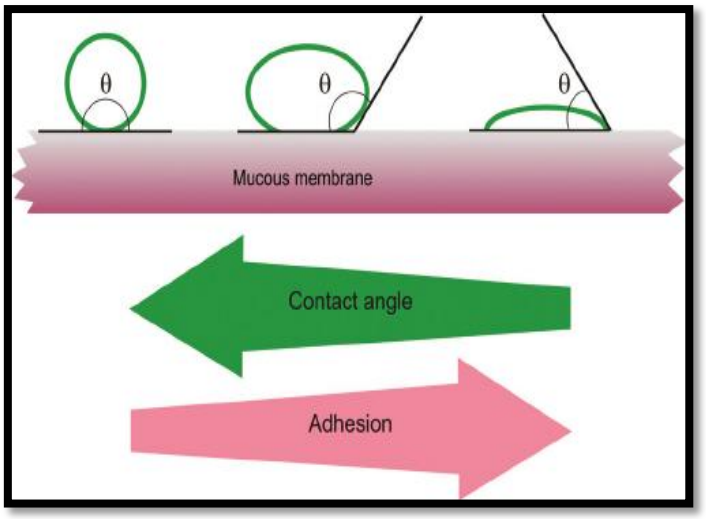


Figure 5: Wetting theory of mucoadhesion

3)Adsorption theory:

According to this theory the attachment of adhesive on the basis of hydrogen bonding and VanderWaalsforces. Two types of chemical bonds such as primary covalent& secondary chemical bonds (including electrostatic forces, VanderWaals forces & hydrophobic bonds).

4)**The diffusion theory**:

According to this theory the polymer chain and mucus mix to adequate depth to create semi permanent adhesive bond. This process is driven by concentration gradient and is affected by available molecular chain lengths and their mobility's. It depends on the value ofmolecular weight between cross links and decrease significantly as the cross linking density decreases.

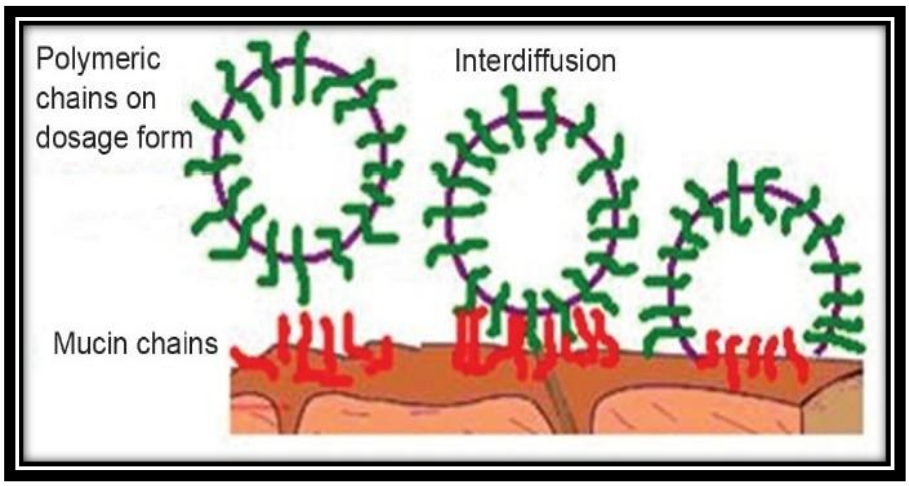


Figure 6: Theory of Diffusion theory

5)The mechanical theory:

This theory acceptsthat attachment emergency from an interlocking of fluid cement into anomalies on an unpleasant surface. However, rough surface also provides on increase surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.

6)The fracture theory:

According to this theory of adhesion is related to separation of two surface after adhesion. The fracture strength is equal to adhesive strength, it is given by,

$$G = \left(\frac{E\varepsilon}{L}\right)^{1/2} \ldots \text{(equation 1)}$$

Where,

E= Young's module of elasticity

ε= Fracture energy

L = Critical crack length when two surfaces are separated. (10)

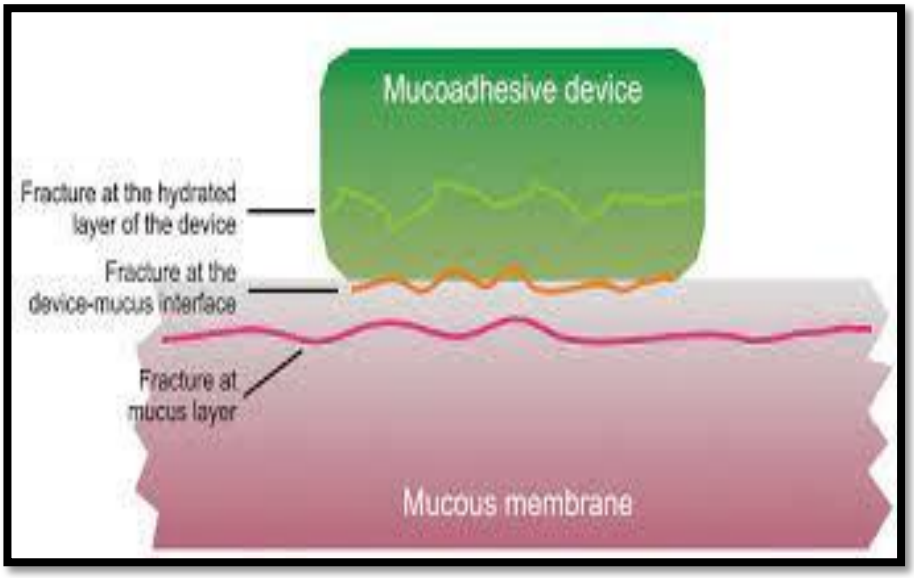


Figure 7: Fracture theory of mucoadhesion

6.0 Factors affecting mucoadhesion

1) **Molecular weight**

Be mucoadhesion strength of a mucoadhesive polymer mainlydepend on its molecular weight and polymeric linearity. Generally, for the linear polymers (e.g., Polyethylene glycol), the bio adhesive propertyarestraight away proportional to the molecular weight i.e., PEG-200000 having greatermucoadhesivestrength than that of PEG-20000. But in case of nonlinear polymer, the mucoadhesivestrength of polymer also canmoreover or may not be installed of its molecular weight. Is ismainlybecause of the reality the helical or coiled structures of such polymer also canmoreoverprotectsome of the adhesive group, which can bemainlyliable for the adhesive property.

2) **Concentration of polymer**

Be interest of a mucoadhesive polymer is a great sized issue of identifying its mucoadhesiveelectricity. Here is a maximumbeneficialinterest for a mucoadhesive polymer in which it produces the maximum mucoadhesion. For a fewfairlytargeted polymeric systems, beyond the maximumbeneficialdiploma of polymer, the mucoadhesiveelectricity of polymer starts off advanced to give waynotablybecause of the realitythe eye of polymer molecules starts of advanceddeveloping over the molecular interest of the liquid medium in order that there`s no similarly chain formation amongst liquid medium and polymer. As anquitend result of this, the polymer particlesremain separated from liquid medium, due to this the mucoadhesiveelectricity of that polymer starts off advanced fallen down.

3) **Flexibility of polymer chains**

A more the strength of the mucoadhesive chain motives the more di ̧union into the mucus network of buccal cavity. Is effects in stepped forward mucoadhesion. Be flexibility of polymer chain decreases with growth in the eye of polymer. For anpowerful bio adhesion, the polymer chain want to selectively problem into the mucus layer.

4) **Spatial confirmation**

The mucoadhesiveelectricity of a polymer is moreoverrelyingat the conformation or spatial affiliation of polymers i.e., helical or linear. Be polymers showing linear conformation having the greatermucoadhesiveelectricity as have a look at to the polymers showing helical conformation. Because, the helical conformation of polymer also canmoreoverguardnumerouslively groups, which might beat theentireanswerable for mucoadhesion, for this reasonreducing the mucoadhesiveelectricity of the polymer.(11)

5) **Swelling or hydration:**

The proper hydration of mucoadhesive polymer is essential for the popularmucoadhesive strength. With boom in hydration the pore duration of polymer will growth which consequencestriggered mobility and advanced interpenetration.

6) Hydrogen bonding capacity

Hydrogen bonding is every othervitalproblem for mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers need to have sensiblegroups which is probably capon a function to form hydrogen bonds. Ability to form hydrogen bonds is due to the presence of (COOH, OH etc.,). Flexibility of the polymer is vital to decorate its hydrogen bonding potential. Polymers which incorporates polyvinyl alcohol, hydroxylase methacrylate and poly (meth acrylic acid) in addition to all their co-polymers are having well hydrogen bonding capacity.

7) Cross linking density

The pass linking density of the polymer determines its higher molecular weight. Be byskip linking density indicates the extensivesort ofnot unusualplace molecular weight of the byskipconnected polymer, which determines the not unusualplace pore period. When the byskip linking density of polymer is higher, it reduces the pore period of polymer chain which ends up inreduced diffusion of water into the polymer network. It reducedeffects with within thedecreased penetration of polymer into the mucin and finally decreases the mucoadhesive strength.

8) Charge

Be bio adhesive property of ionic polymer is continuouslyhigher than the of non-ionic polymer. In independent or slightly alkaline medium, the cationic polymer indicatessuperiormucoadhesiveproperty. It has been hooked up that, cationic immoderate molecular weight polymer which incorporates chitosan very ownwell bio adhesive. (12)

❖ **Environment related factors**

➢ **pH of polymer-substrate interface**

The pH of polymer-mucin interface have to be identical as it's miles possible, because, the diٔTerence in pH amongthe 2structuresmight also additionallyeffectswithinside theswitch of pricebecause of the better pH gradient. Is might also additionally act the mucoadhesion.

➢ **Applied strength**

While setting a buccal mucoadhesive drug transport system, enoughelectricityhave to be implementedif you want toofferan awesome bio adhesive property. Even aleven though there aren't anyt anyappealing forces among polymer and mucus, then software of excessivestress for sunfficentlong term make the polymer come to be bio adhesive with mucus.

➢ **Initial contact time**

Greater the preliminarytouch time among themucoadhesive polymer and the mucus layer consequenceswithinside theaccelerated swelling in addition to interpenetration of the mucoadhesive polymer chain. Hence, will increase the mucoadhesion electricity of the polymer chain.

➢ **Moistening**

Moistening is needed to permit the mucoadhesivepolymer to unfold over the surface. It creates a community of polymer chains of enough pore size. Through those pores, the interpenetration of polymer and mucin molecules takes location that outcomes in growing the mobility of polymer chains for the right diffusion of mucoadhesive polymer in mucin layer.(13)

❖ **Physiological factors**

➢ **Mucin turnover:**

High mucin turnover isn'tuseful for the mucoadhesivebelongingsdue to following reasons: Be excessive mucin flip over limits the house time of bio adhesive polymer because it detaches from the mucin layer, although it has a very good bio adhesive belongings. High mucin flip over can also additionally produce soluble mucin molecule, for this reason molecule engage with the polymer earlier thanthey have interaction with mucin layer. Hence there'llnow no longer be enough mucoadhesion.

➢ **Disease state**

In a fewsickness states, the secretion of mucus from the mucus membrane receivesreduced (e.g., in Dry Mouth Syndrome and in antique age). So that there isn't alwayssunfficentquantity of mucus gifton theweb website online of attachment of mucoadhesive dosage form. Is may alsoresults inmistaken moistening and swelling of polymer. Due to which there may bereducedmucoadhesivepower of mucoadhesive dosage form.(14)

➢ **Rate of renewal of mucosal cells**

Rate of renewal of mucosal cells varies drastically from uniquesorts of mucosa. It limits the endurance of bio adhesive structures on mucosal surfaces.

➢ **Concomitant diseases**:

Concomitant sicknesses can regulate the physicochemical homes of mucous or its quantity (for example, hypo and hyper secretion of gastric juice), will increase in frame temperature, ulcer disease, colitis, tissue fibrosis allergic rhinitis, bacterial or fungal contamination and inflammation.(15)

- **Tissue movement**

Tissue motiontakes place on intake of liquid and food, speaking, peristalsis withinside the GIT and it impacts the mucoadhesivedevicemainly in case of gastro retentive dosage forms .

7.0 Mucoadhesive Dosage Forms

- **Tablet**

  Tablets are small, flat, and oval, with a diameter of about 5–eight mm. Unlike the traditionalpills, mucoadhesivepillspermit for consuming and talkingwith outprincipal discomfort. They soften, adhere to the mucosa, and are retained in functiontill dissolution and or launch is complete. Mucoadhesivepills, in general, have the capacityfor use for managedlaunch drug delivery, however coupling of mucoadhesivehousesto pill has extra advantages, for example, it givesgreen absorption and improved bioavailability of the medicine due aexcessivefloor to extent ratio and allowsa milesgreater intimate touch with the mucus layer. Mucoadhesivepillsmay betailor-madeto stick to any mucosal tissue along withthe onesdiscovered in stomach, as a resultproviding the opportunities of localized in addition to systemic managedlaunch of drugs.(16)

- **Films**

  Mucoadhesivemoviescan bedesired over adhesive capsules in phrasesof flexibleness and comfort. In addition, they are able tostay away from the exceptionallybriefhouse time of oral gels at the mucosa, which can bewithout problems washed away and eliminatedwith the aid of using saliva. Moreover, withinside the case of neighborhoodtransport for oral diseases, the moviesadditionallyassistguard the wound surface, accordinglysupporting to lessen pain, and deal with the sicknessextra effectively. Anbestmovieneed to be flexible, elastic, and soft, butcorrectlysturdyto resist breakage because ofstrain from mouth movements. It need toadditionallyownprecisemucoadhesiveenergyif you want to be retained withinside the mouth for the preferredlength of action. Swelling of movie, if it occurs, need tonow no longer be too enormousif you want tosave youdiscomfort.(17)

- **Patches**

  Patches are laminates which include an impermeable backing layer, a drug-containing reservoir layer from which the drug is launched in a managed manner, and a mucoadhesivefloor for mucosal attachment. Patch structures are much likethe onesutilized in transdermal drug delivery. Two strategies used to put together adhesive patches consist of solvent casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is readyvia way of means of casting the answer of the drug and polymer(s) onto a backing layer sheet, and in the endpermitting the solvent(s) to evaporate. In the direct milling method, systemcomponents are homogeneously combined and compressed to the favored thickness, and patches of predetermined length and form are then reduce or punched out. An impermeable backing layer can also beimplementedto govern the course of drug release, save you drug loss, and limit deformation and disintegration of the toolin the course of the utility period.

- **Gels and ointments**

  Semisolid dosage paperwork, inclusive of gels and ointments, have the benefit of clean dispersion at some stage in the oral mucosa. However, drug dosing from semisolid dosage paperwork won't be as correct as from tablets, patches, or films. Poor retention of the gels on the web website online has been conquer with the aid of using the use of mucoadhesive formulations. Certain mucoadhesive polymers, for example, sodium carboxymethylcellulose, carbopol, hyaluronic acid and xanthan gum, go through a segment alternate from liquid to semisolid. This alternate complements the viscosity, which leads to sustained and managed launch of drugs. Hydrogels also are a promising dosage shape for buccal drug shipping. They are fashioned from polymers which might be hydrated in an aqueous surroundings and bodily entrap drug molecules for next gradual launch with the aid of using diffusion or erosion. The software of mucoadhesive gels gives an prolonged retention time withinside the oral cavity, ok drug penetration, in addition to excessive efficacy and affected person acceptability. A important software of adhesive gels is the nearby shipping of medicinal retailers for the remedy of periodontitis, that is an inflammatory and infectious disorder that reasons formation of wallet among the gum and the tooth, and might subsequently motive lack of teeth. It has been advised that mucoadhesive polymers is probably beneficial for periodontitis remedy whilst integrated in antimicrobial-containing formulations which might be effortlessly added into the periodontal pocket with a syringe. HPMC has been used as an adhesive ointment components. Additionally, a distinctly viscous gel become advanced from carpal and hydroxypropylcellulose for ointment dosage paperwork that might be maintained at the tissue for up to eight hours.(18)

7.0 Marketed Products

Table 2: Marketed Product of mucoadhesion drug delivery system

Brand name	Active ingredient	Bioadhesive polymer	Dosage form	Company
Aphtach	Triamcinolone acetonide	HPC, PAA	Tablet	Teijin Ltd
Buccastem	Prochlorperazine	Xanthan gum, Povidone, Locust bean gum	Tablet	Reckitt Benkiser Plc
Oralin–Generex	Insulin	Unknown	solution	Generex Biotechnology (Phase III trials)
Lauriad	Miconazole	Unknown	Tablet	BioAlliance Pharma (Phase III trials)
Striant SR	Testosterone	Carbomer 934P, Hypromellose, PC	Tablet	Ardana Bioscience Ltd
Suscard	Glyceryl trinitrate	Hypromellose	Tablet	Forest Laboratories

9.0 Discussion and Conclusion

This review provides the brief knowledge about the oral mucosal drug delivery by discussing briefly the structural feature of mucosa, mechanism of mucoadhesion, various theories of mucoadhesion, general consideration in design of mucoadhesive buccal dosage forms, permeation enhances and the various evaluation methods along with the literature Survey of the buccal mucoadhesive drug delivery System.This overview about the mucoadhesive dosage forms might be a useful tool for the efficient design of novel mucoadhesive drug delivery systems. Mucoadhesive drug delivery systems have applications from different angles, including development of novel mucoadhesives, design of the device, mechanisms of mucoadhesion and permeation enhancement. With the influx of a large number of new drug molecules due to drugdiscovery,mucoadhesive drug delivery will play an even more important role in delivering these molecules.

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