



Mucoadhesive Drug Delivery System- An Overview

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Abstract

Mucoadhesive drug delivery systems extend the residence time of the dosage form at the site of application or absorption. They facilitate an intimate touch of the dosage shape with the underlying absorption floor and accordingly enhance the healing overall performance of the drug. These structures continue to be in near touch with the absorption tissue, the mucous membrane, liberating the drug on the movement the site of action main to a bioavailability growth and each nearby and systemic effects. The principal benefit of this course for drug transport is that, the transport via way of means of this course via way of means of passes the primary pass metabolism of diverse capsules which are susceptible to their hepatic first pass metabolism. This assessment provide the short information approximately the oral mucosal drug transport via way of means of discussing in short the structural function of mucosa, mechanism of mucoadhesion, diverse theories of mucoadhesion, well-known attention in layout of mucoadhesive buccal dosage forms, permeation complements and the diverse assessment strategies at the side of the literature Survey of the mucoadhesive drug transport System.

Keywords

Mucoadhesive, mucous, transport, bioavailability, Mucoadhesion, polymer

Introduction

Since the early 1980s, the idea of mucoadhesion has won vast exciting pharmaceutical technology.[1] Adhesion may be described because the bond produced via way of touch among stress touchy adhesive and a floor. The American Society of Testing and Materials has described it because the country wherein surfaces are held collectively via way of interfacial forces, which may also encompass valence forces, interlocking motion or each. Mucoadhesive drug delivery structures lengthen the house time of the dosage shape on the web page of software or absorption. In latest years, many such mucoadhesive drug transport structures were advanced for oral, buccal, nasal, rectal and vaginal routes for each systemic and neighborhood effects.[2] Mucoadhesive drug transport structures are transport structures which make use of the assets of bioadhesion of positive polymers which come to be adhesive on hydration and as a result may be used for concentrated on a drug to a selected place of the frame for prolonged durations of time. Bioadhesion is an interfacial phenomenon wherein Two materials, at the least certainly considered one among that's organic, are Held collectively by interfacial forces. The attachment can be among an synthetic fabric and organic substrate, which includes adhesion among a polymer and a organic membrane. In the case of polymer connected to the mucin layer of a mucosal tissue, the term "mucoadhesion" is used[3]. The mucus membrane (additionally known as mucosa) is a wet tissue lining that covers the organs and cavities which includes the mouth, nose, eyelid, gut, and rectum. Leung and Robinson describe mucoadhesion because the interplay among a mucous floor and a artificial or herbal polymer. The polymer service containing healing fabric will adhere to the focused mucosa for an prolonged period, thereby growing its permeation and bioavailability. Many readers may also confuse the term "mucoadhesion" with "bioadhesion". In mucoadhesion, the polymer is connected to mucus floor (substrate), while in bioadhesion, the polymer is connected to the organic floor (it can be epithelial tissue or mucus coat at the floor of the tissue). Oral mucosal transport is in addition categorized into 3 categories:

- (i) sublingual transport, systemic transport of healing compounds via the mucosal floor of the mouth;
- (ii) buccal transport, management via the mucosal linings of cheeks (buccal mucosa)
- (iii) neighborhood transport, management via the oral cavity.

The buccal mucosa is broadly relevant for drug management, and sublingual transport is beneficial for the quick onset of healing motion (ex: sublingual nitroglycerin for the remedy of Angina pectoris) [4]. The mucoadhesion idea has attracted a good deal interest within side the pharmaceutical region and is efficiently used as a direction of management. Mucoadhesive drug transport structures may be brought via way of diverse routes:-

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system [5]

Rout Of Mucoadhesive Drug Delivery System.

1.Buccal Delivery System

Buccal delivery of medicine is one of the options to the oral direction of drug management, in particular to the ones capsules that go through first-by skip effect. The stratified squamous epithelium supported via way of means of a connective tissue lamina propria, that's found in buccal mucosa, become focused as a website for drug shipping numerous years ago. The buccal direction seems to provide some of benefits, like accurate accessibility, robustness of the epithelium, utilization of the dosage shape according with need, and relatively much less susceptibility to enzymatic activity. Hence, adhesive mucosal dosage paper work had been organized for oral shipping, with inside the shape of adhesive tablets, adhesive gels and adhesive patches. The permeation of hydrophilic drug via membrane is one of the essential proscribing elements for the improvement of bioadhesive buccal shipping devices.[6]

2.Oral Delivery System

An oral drug delivery device is accordingly believed to offer non-stop oral launch of the drug during the direction of its gastrointestinal (GI) transit. Oral management is the maximum famous and patient-compliant direction for drug shipping, alaven though it increases top notch demanding situations because of the involvement of the gastro-gut (GI) device and the drug bioavailability. Lipid-primarily based totally oral shipping structures investigated updated and emphasizes the contribution of every device aspect to the shipping performance, and the oral shipping course of lipids.[7]

3.Vaginal Delivery System

Vaginal delivery is an important route of drug administration for both local and systemic diseases. Vaginal delivery is an crucial direction of drug management for each neighborhood and systemic illnesses. The vaginal direction has a few benefits because of its massive floor area, wealthy blood supply, avoidance of the first-by skip effect, especially excessive permeability to many capsules and self-insertion. The conventional business preparations, including creams, foams, gels, irrigations and tablets, are regarded to

live with inside the vaginal hollow space for a especially quick time frame as a result of the self-cleansing motion of the vaginal tract, and regularly require a couple of day by day doses to make sure the favored healing effect. [8]

4.Rectal Delivery System

Rectal drug shipping refers back to the management of medication or medicines through the rectum for nearby or systemic effects. A sort of mucosal adhesive drug shipping gadget is a rectal drug shipping gadget. These structures offer mucoadhesion, i.e. the drug's attachment to the mucous membrane in conjunction with an powerful carrier .[9]

5. Nasal Delivery System

Nasal administration, popularly known as snorting, is a route of administration in which drugs are insufflated through the nose. In addition, the floor, the drug awareness and quantity, the bodily situation of the dosage shape and the placement of the top at some point of management all play a function with inside the drug absorption process – 1) Local used tablets for nasal drug shipping 2) systemic drug shipping 3) drug shipping from nostril to brain 4) nasal vaccine. [10]

6.Ocular Delivery System

The eye is a complicated organ and specific each anatomically and physiologically. Novel technique drug may be hooked up at the cull-de sac or conjunctival hollow space of eye is called ODDS. [11] Ophthalmic method or instruction are specialised sterile instruction of dosage shape. Drug may be hooked up directly to the outside floor i.e. topical, administered interior i.e. intraocular or adjoining i.e. periocular to the attention. The one of the maximum exciting and tough challenge of ODDS is confronted via way of means of the prescribed drugs and researchers. [12]Ocular tablets are normally introduced domestically to the attention. Required drug loading, launch charge, and ocular retention time of drug shipping structures depend upon the potency, bioavailability, and clearance of the drug on the goal web page. [13]

Mucus Membrane

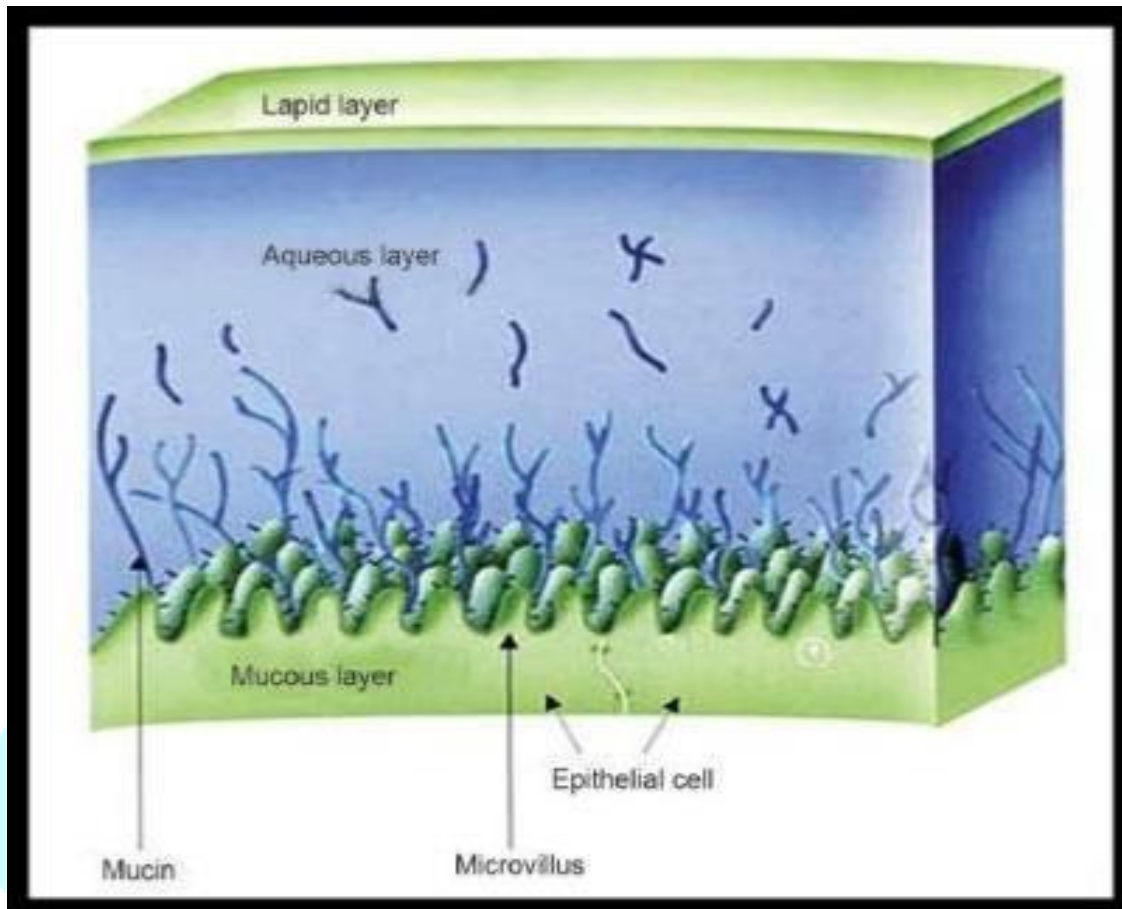


Figure 1: Mucous membrane structure

Mucus membranes (mucosae) are the wet Surfaces lining the partitions of diverse frame cavities along with the gastrointestinal and respiration tracts. They include a Connective tissue layer (the lamina propria) above that is an epithelial layer, the floor of that is made wet generally by the presence of a mucus layer. The epithelia can be both Single layered (e.g. the stomach, small and huge intestines And bronchi) or multi-layered/stratified (e.g. with inside the oesophagus, Vagina and cornea). The former incorporate goblet cells which Secrete mucus without delay onto the epithelial surfaces; the latter Contain, or are adjoining to tissues containing, specialised glands along with salivary glands that secrete mucus onto the epithelial floor. Mucus is gift both as a gel layer Adherent to the mucosal floor or as a luminal soluble or Suspended form. The primary additives of all mucus gels Are mucin glycoproteins, lipids, inorganic salts and water, the Latter accounting for greater than 95% in their weight, making Them a pretty hydrated machine. The primary capabilities of Mucus are that of safety and lubrication.[14]

Composition of mucus layer

The mucus includes glycoproteins, fats, salts and approximately 95% of water through mass, making it a pretty hydrophilic machine. [15,16] Mucus glycoproteins are excessive molecular weight proteins owning connected oligosaccharide devices containing, L-fructose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and Sialic acid. [17,18]

Functions of Mucus Layer:

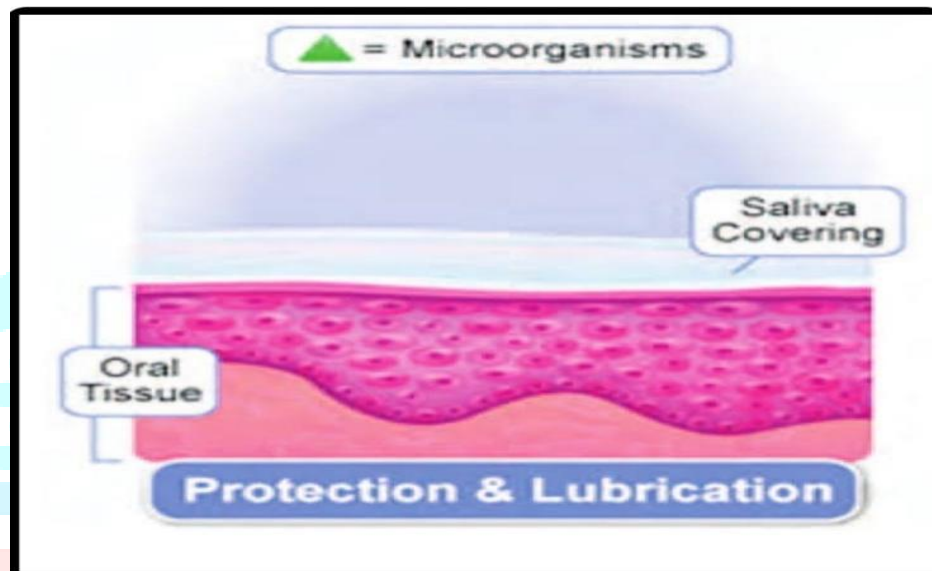
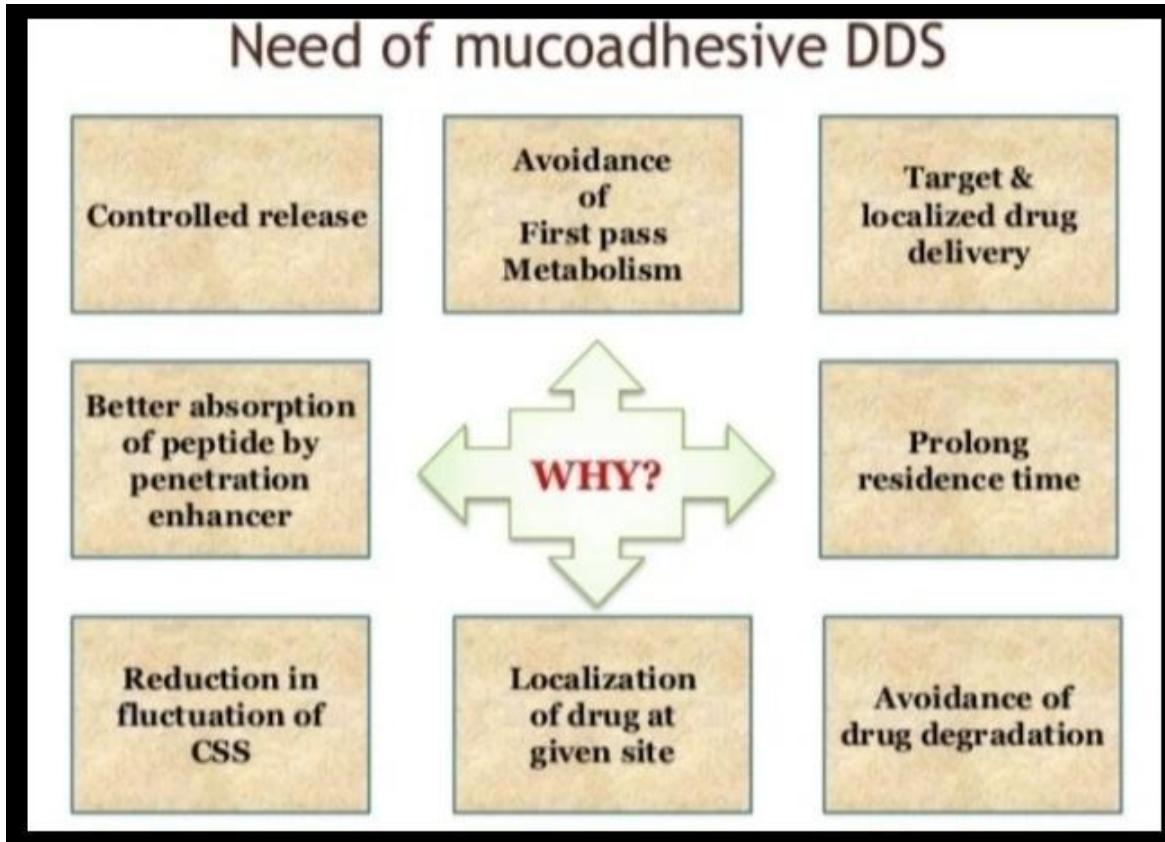


Figure 2.Function of Mucosa

- 1. Protective:** ensuing in particular from its Hydrophobicity.
- 2. Barrier:** The function of the mucus layer as a barrier In tissue absorption of the medication and impact The bioavailability.
- 3. Adhesion:** Mucus has robust adhesion Properties.
- 4. Lubrication:** It is to preserve the mucus from the Goblet molecular is vital to make amends for the Removal of the mucus layer because of digestion, Bacterial degradation and solubilisation of Mucin molecules.

Need of mucoadhesive drug delivery system



Flow Chart 1:Need of MDDS

Mechanism of mucoadhesion

The cloth wherein one can be synthetic along with mucoadhesive polymer and different can be mucin layer of the mucosal tissue are held collectively with the aid of interfacial pressure of enchantment is called mucoadhesion. Mucoadhesive approach synthetic substance this is able to interacting with mucus membrane and being maintain on them or preserving them collectively for prolonged or extended time. During the technique of adhesion there have degrees recognized are given below.

1. Contact Stage
2. Consolidation degree

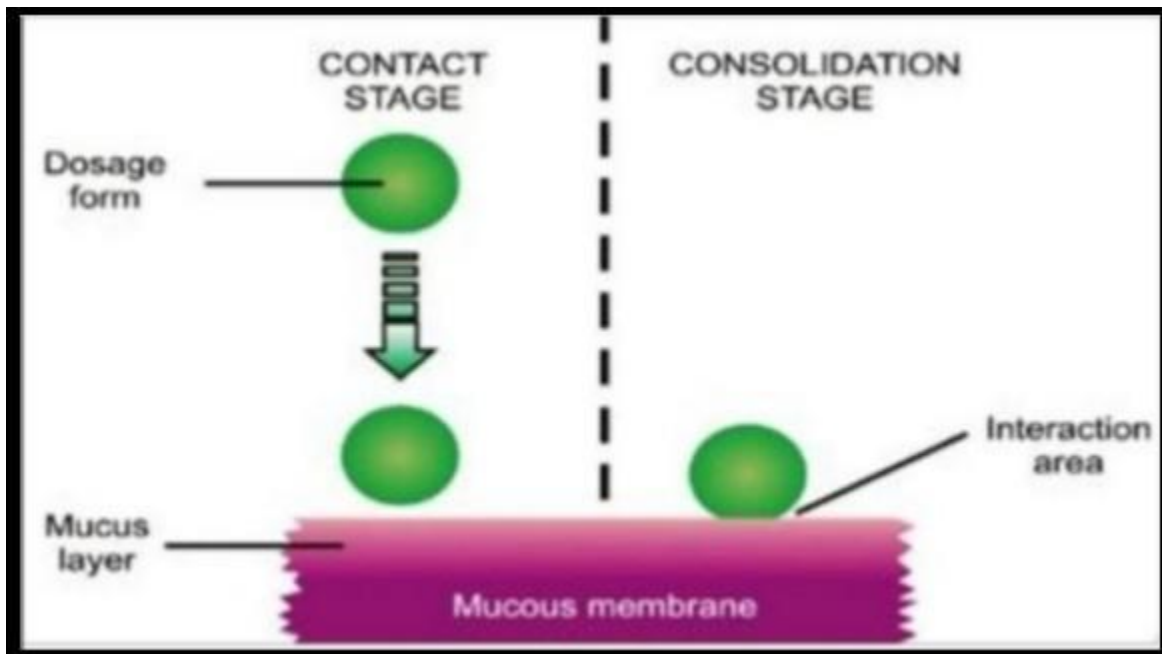


Figure No 3:Mechanism of mucoadhesion

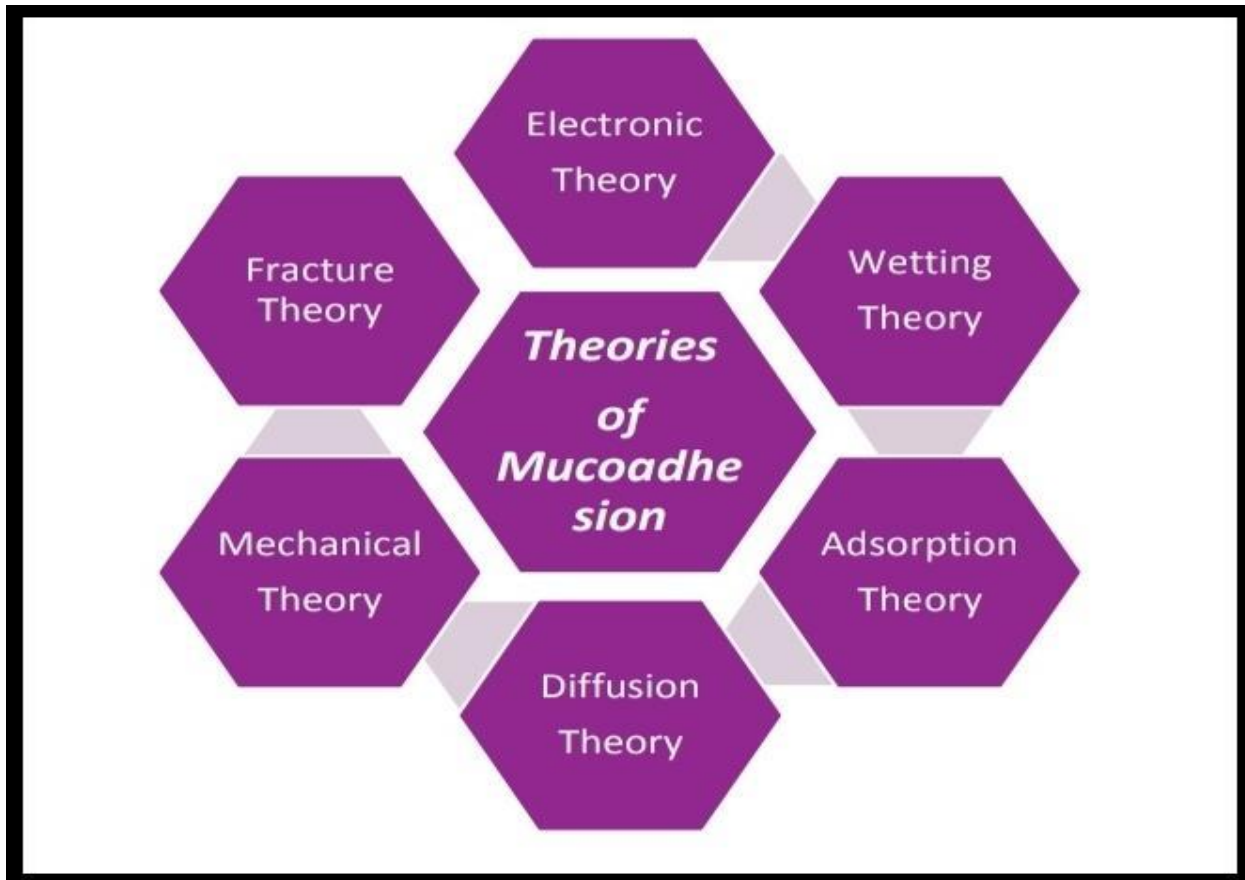
1.Contact Stage

During at this degree whilst the mucoadhesive cloth comes in touch with mucus membrane an intimate wetting happens among mucoadhesive and mucus membrane. This wetting of mucoadhesive is carried out through the mucus found in mucosal membrane.

2.Consolidation Stage

By approach of various physiochemical forces of enchantment along with Vander Waals forces, electrostatic forces and hydrogen bonding. This forces found in Mucoadhesive cloth receives be part of to the mucus membrane and ensuing in durable mucoadhesion. This degree is known as consolidation degree. After those degrees the technique of mucoadhesion completes.[19]

Theories of Mucoadhesion



Flow Chart 2: Theories of mucoadhesion

1)The Electronic Theory:

According to this concept electron switch takes place upon touch of an adhesive polymer and the mucus glycoprotein community due to variations in digital structure. This is proposed to bring about the formation of an digital double layer on the interface, with next adhesion because of appealing forces throughout the double layer

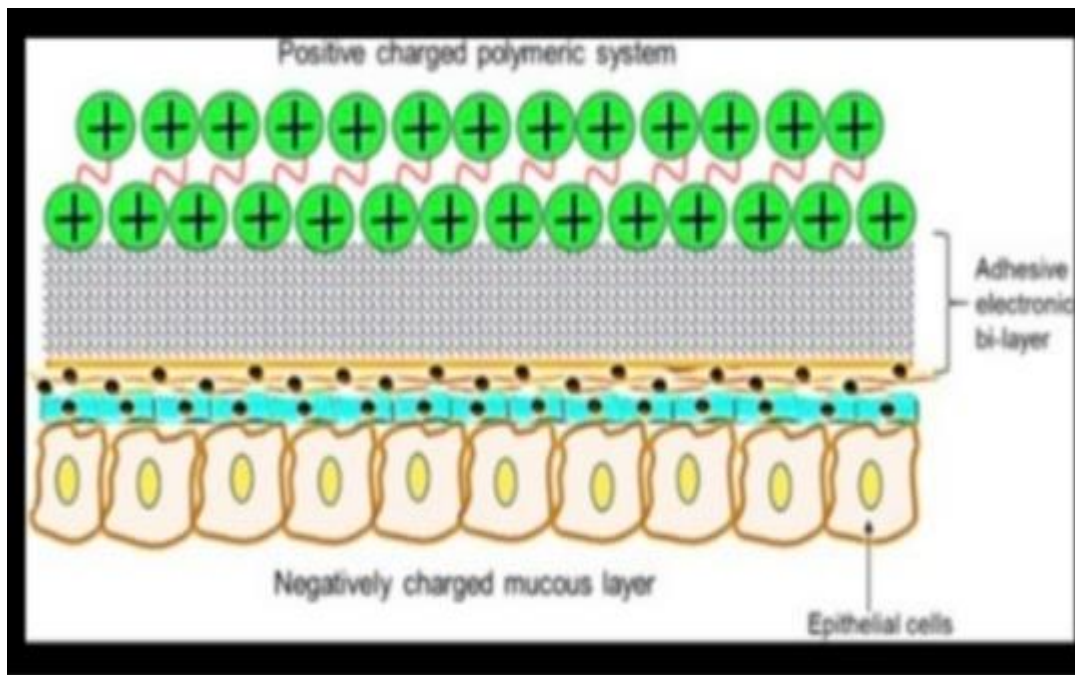


Figure No 4.Electronic concept of mucoadhesion

2)The wetting Theory:

It is largely implemented to liquid frameworks and matters approximately floor and interfacial energies. It consists of the potential of a fluid to unfold all at once onto a floor as an vital for development of bond. The Affinity of liquid for a floor may be observed the usage of strategies including touch attitude geometry to degree the touch attitude of the liquid on floor.

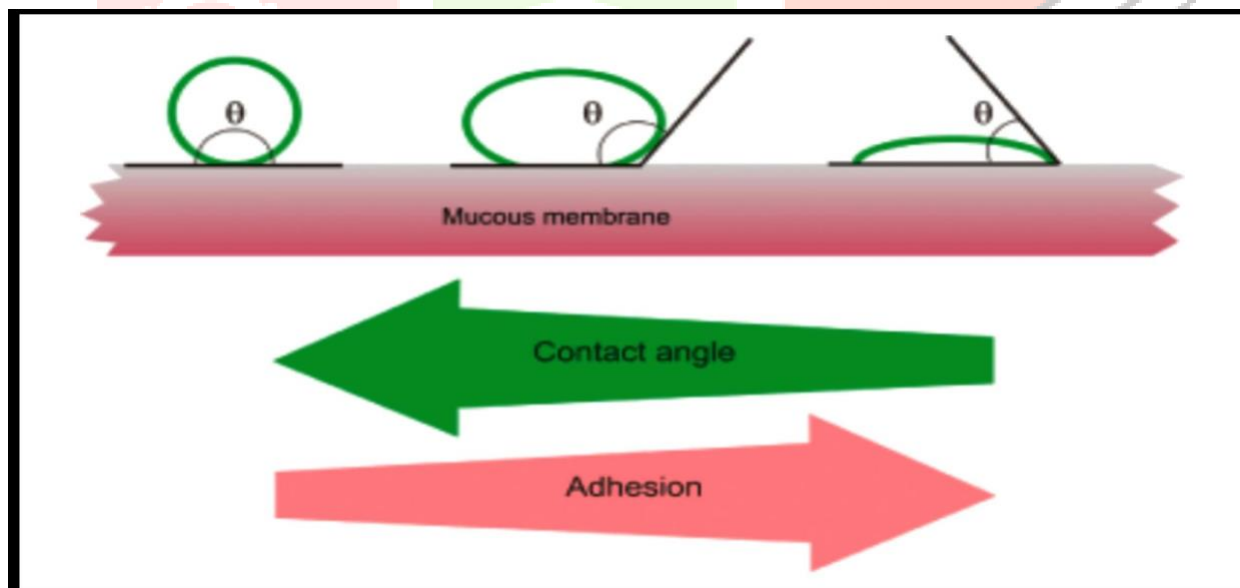


Figure No 5: Wetting concept of mucoadhesion

3)Adsorption Theory:

According to this concept the attachment of adhesive on the premise of hydrogen bonding and Vander Waals forces. Two kinds of chemical bonds including Primary covalent& secondary chemical bonds (consisting of electrostatic forces, Vander Waals forces & hydrophobic bonds).

4)The diffusion Theory:

According to this concept the polymer chain and mucus blend to good enough intensity to create semi everlasting adhesive bond. This method is pushed via way of means of Concentration gradient and is suffering from to be had molecular chain lengths and their mobility's. It relies upon at the fee of molecular weight among Cross hyperlinks and reduce appreciably because the go linking density decreases.

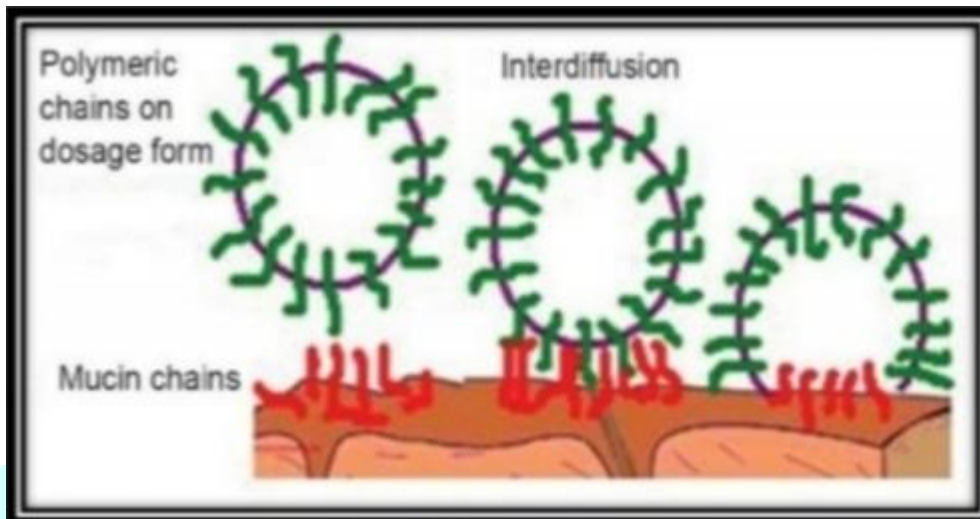


Figure No 6: Theory of Diffusion concept

5)The mechanical Theory:

This concept accepts that attachment emergency from an interlocking of fluid cement into anomalies on an ugly floor. However, tough floor Also affords on growth floor location to be had for interplay along side an more suitable viscoelastic and plastic dissipation of strength at some stage in joint failure, Which are notion to be greater vital with inside the adhesion method than a mechanical effect.

6)The fracture Theory:

According to this concept of adhesion is associated with separation of floor after adhesion. The fracture power is same to adhesive power, it's far Given via way of means of,

$$G=(E\varepsilon/L)^{1/2}\dots \text{(equation 1)}$$

E= Young's module of elasticity

ε = Fracture strength elasticity

L = Critical crack period while surfaces are separated.[20]

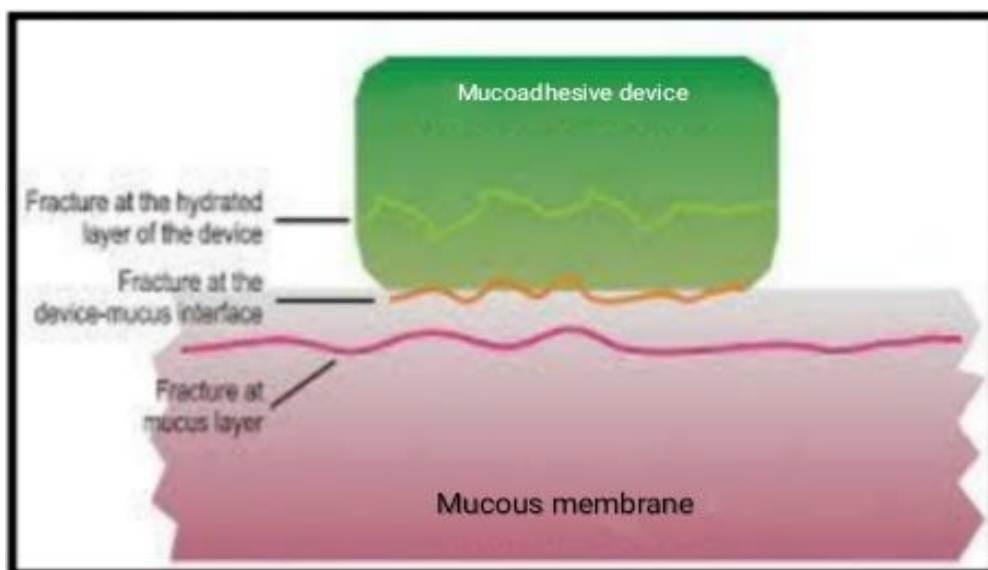


Figure No 7:Fracture principle of mucoadhesion

Mucoadhesive Polymers

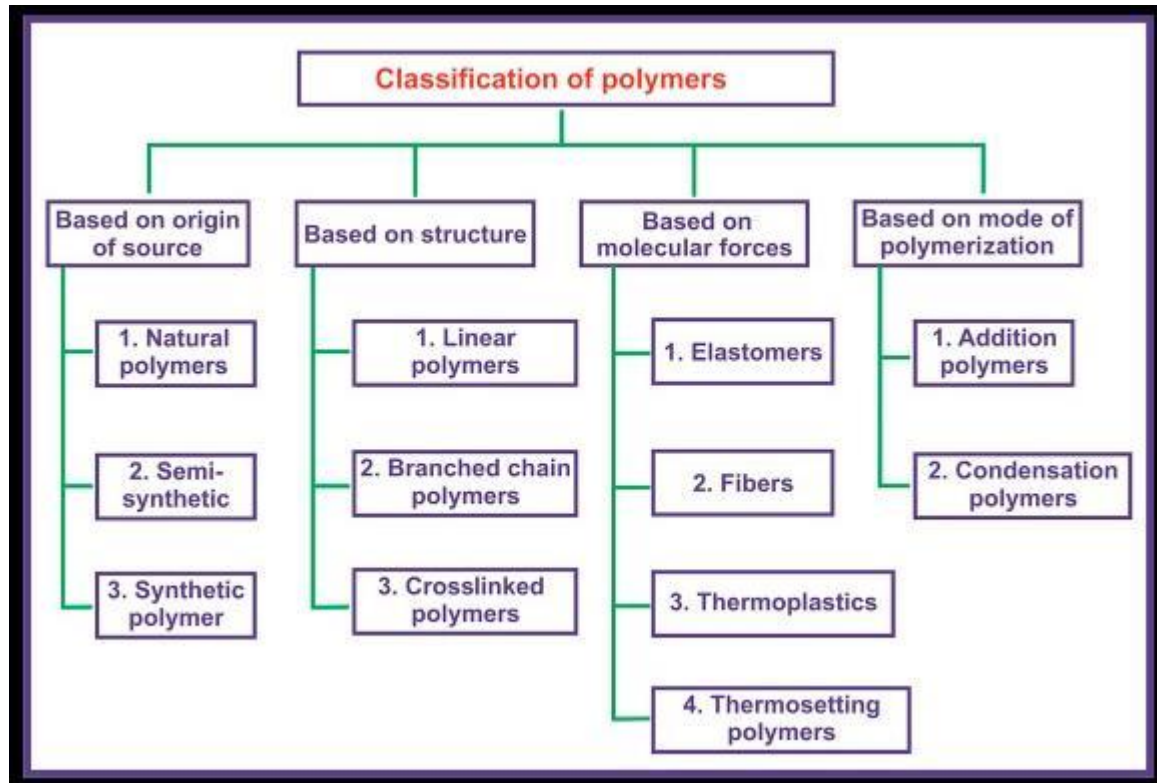
Ideal Characteristics of Mucoadhesive Polymers:

A mucoadhesion promoting agent or the polymer is delivered to the gadget which permits to promote the adhering of the active pharmaceutical detail to the oral mucosa. The agent may have such more houses like swelling with a purpose to promote the disintegration even as in contact with the saliva.

- 1) **Long chain polymers**-chain period must be prolonged Enough to promote the interpenetration and it want to now not be too prolonged that diffusion becomes a problem.
- 2) **Degree of by skip linking**- it influences chain mobility and resistance to dissolution. Highly by skip associated polymers swell in presence of water and keep their form.
- 3) **Concentration of the polymer**- an maximum beneficial interest is wanted to promote the mucoadhesive power. It is predicated upon but, on the dosage form.
- 4) **Charge and degree of ionization**- The effect of polymer rate on mucoadhesion grow to be actually tested by Freudl. Cationic chitosan HCl Showed marked adhesiveness even as compared to the control. The attachment of EDTA an anionic company prolonged the mucoadhesive power significantly. Hence the mucoadhesive power can be attributed as Anion>cation>non-ionic.
- 5) **Optimum hydration**- excessive hydration effects in decreased mucoadhesive power due to formation of a slippery mucilage.
- 6) **Optimum pH** – mucoadhesion is maximum beneficial at low pH conditions but at higher pH values a extrade with within the conformation takes area proper right into a rod like form making those more available

for inter diffusion and interpenetration. At very prolonged pH values, absolutely charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces. [21]

Classification of Mucoadhesive Polymer



Flow chart 3- Classification of Polymer

Based on origin of source

1.Natural Polymer – Polymers which can be isolated from natural materials are called natural polymers. E.g.: Cotton, silk, wool, rubber.

2.Synthetic Polymer – Polymers which can be synthesized from low molecular weight compounds are called Synthetic Polymers. E.g.: Polyethylene, nylon, terylene.

3.Semisynthetic Polymers – These polymers are commonly derived from glaringly occurring polymers via chemical modification. E.g.: Rayon. [22]

Based on structure

1.Linear Polymer: Molecules form prolonged chains without branches.

2.Branched Polymer : Molecules having branch elements that be part of 3 or more segments.

3.Cross-Linked Polymer: It includes interconnections amongst chains.[23]

Based on molecular force

1.Elastomer: It is a polymer with very inclined intermolecular forces and Viscoelasticity. Thus, they're famously known as elastic polymers.E.g. Natural rubber Polyurethanes, Silicone, Neoprene.

2.Fibers:A “fibre” is defined as any product capable of being woven or otherwise made proper right into a material. It may be belief of due to the fact the smallest visible unit of material production ‘or’ a fibre can be defined as a pliable hair like strand that is very small in diameter close to its period

3.Thermoplastic: All the plastic materials which can be softened and melted via heating, but they set yet again even as cool are called thermoplastics.

4.Thermosetting polymer: Thermosetting plastics are polymers which can be semi-fluid in nature with low molecular masses. When heated, they start by skip-linking amongst polymer chains, therefore becoming difficult and infusible. They form a three-D form on the software program of heat. This reaction is irreversible in nature. The most common area example of a thermosetting polymer is that of Bakelite, that's applied in making electric powered insulation.

Based on mode of Polymerization

1.Additional Polymerization :Same type of monomers are without delay forwardly delivered. It is fast chain reaction having chemically activated. Each reaction devices up the situation for a few different to proceed.

It consists of 3 stages:

Initiation (Birth)

Propagation (Growth)

Termination (Death)

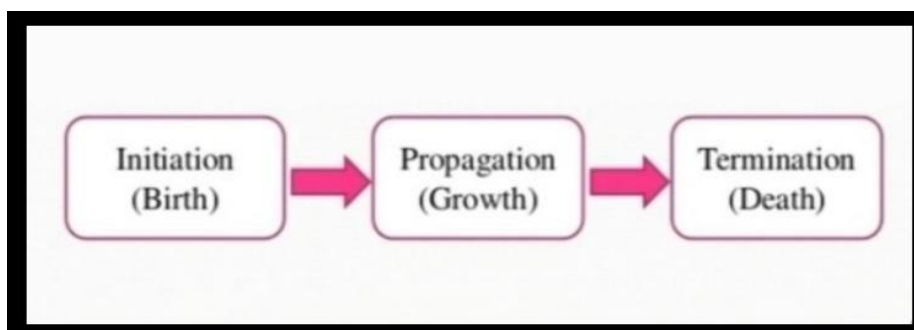
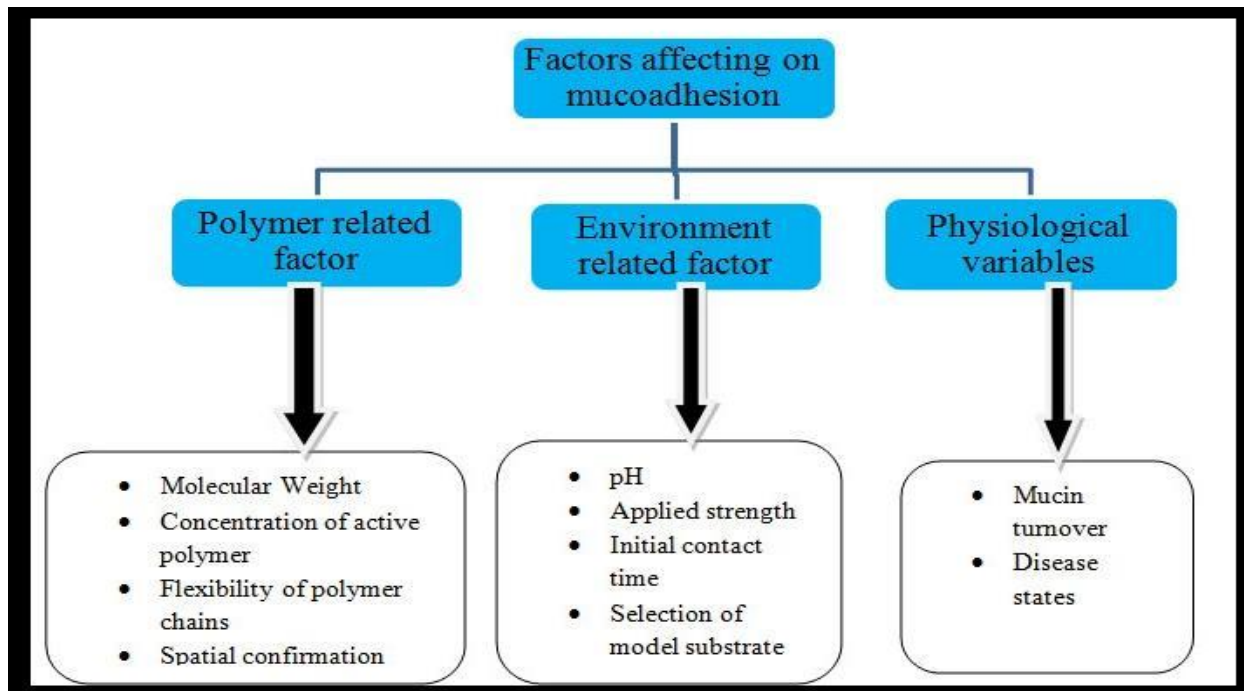


Figure No 8 : Additional Polymerization Stages

2. Condensation Polymerization :It consists of a polymerization reaction amongst monomers with the expulsion of a smooth via product. $A + B \rightarrow AB + \text{Simple via product}$. It consists of character chemical reaction amongst reactive By product is long-established and condensed out. This reaction is slower than more polymerization. Need reactive sensible groups

Factor Affecting of Mucoadhesive Drug Delivery System



Flow Chart 4 : Factors Affecting Mucoadhesion

A) Polymer related factors

1) Molecular weight- For a linear polymer, the bio adhesive belongings is right now proportional T the molecular weight. But in case of nonlinear polymer, the bio adhesiveness may or might not rely on molecular weight. The minimum molecular weight required for successful bioadhesion is at least one hundred,000.[24]

2) Concentration of active polymer- Optimum cognizance of active polymer is required. In remarkably centered system, beyond a positive most excellent level, the adhesive electricity Declines notably because of the truth the coiled molecules become separated from the medium so the duration of chain available for permeation become limited. When the attention of polymer might be very less, the huge kind of penetrating polymer chains consistent with unit amount of the mucous is small and the interaction amongst polymers and mucous turns into erratic.

3) Flexibility of polymer chain- As water soluble polymer turns into flow related, the person polymer chain mobility drops and therefore the effective chain duration that can penetrate into the mucus layer reduces which decreases the mucoadhesive electricity. Flexibility is based upon on the viscosity and diffusion coefficient. Higher polymer flexibility motives greater diffusion into mucus network.[25]

4) Spatial conformation– Despite having immoderate molecular weight of about 2,00,00,000, the adhesive electricity of dextrin's is much like that of PEG whose molecular weight is one hundred times Lesser. The helical, in assessment to linear conformation of polymers, may cowl many active Groups, which are responsible for adhesion, therefore reducing the mucoadhesive electricity of the Polymer.

5) Swelling- Mucoadhesive polymer requires hydration to enlarge and form a proper Macromolecular mesh of desired duration and moreover to spark off mobility with in the polymer chain which will increase the entanglement way amongst polymer and mucin. Swelling is based upon on the Polymer cognizance, ionic electricity and the presence of water.[26]

6) Cross linking density– The not unusual place pore duration, the not unusual place huge range molecular weight of flow related polymers and the density of flow linking are three important and inter-related structural parameters of a polymer network. Higher the flow linking density, smaller is the pore duration simply so diffusion of water into the polymer network occurs at a slower rate, therefore there is an insufficient swelling of polymer resulting in reduced penetration of polymer into the mucin.

7) Hydrogen bonding capacity- The polymers should have useful agencies like carboxylic and hydroxyl agencies that can form hydrogen bonds. Polyvinyl alcohol, hydroxylated methacrylate and poly methacrylic acid and all their co-polymers are polymers with proper hydrogen bonding capacity.

8) Charge- The bioadhesive belongings of ionic polymer is continuously higher than that of non-ionic polymer. In independent or slightly alkaline medium, the cationic polymer like chitosan depicts Better mucoadhesive belongings.[27]

B) Environmental related

1) pH of polymer substrate interface- pH has an effect on the ground price of every mucus and polymers. The price density of mucus will vary counting on pH, because of version in dissociation of useful agencies on carbohydrate moiety and amino acids of the polypeptide backbone, which might also additionally have an effect on adhesion.[28]

2) Applied electricity- The strain first of all carried out to the mucoadhesive tissue contact net internet site on-line may have an impact at the depth of interpenetration. Polymers become mucoadhesive regardless of the truth that they do now not have attractive interactions with mucin if immoderate strain is carried out for the sufficiently prolonged Period of time.[29]

three) Initial contact time – Bioadhesive electricity is right now proportional to the initial contact time. It moreover determines the extent of swelling and interpenetration of polymers. It is not controllable for gastric systems.[30]

4) Moistening – Moistening allows the mucoadhesive polymer to spread over the ground and create a macromolecular network of sufficient duration for the penetration of polymer and mucin molecules to increase the mobility of polymer chains.[31,32]

5) Presence of steel ions – Combining with charged agencies of polymer and/or mucous can reduce the huge kind of interaction net web sites and the electricity of mucoadhesive bonding.[33,34]

C) Physiological factors

1) Mucin flip over – High mucin turnover which occurs regularly is not beneficial Because:

a. The immoderate mucin turnover limits the residence time of bioadhesive polymer as it detaches from the mucin layer, regardless of the truth that the polymer has a splendid bioadhesive belongings.

b. High mucin turn over may produce soluble mucin molecule, therefore molecule engage with the polymer, in advance than they interact with mucin layer. Hence there will now not be sufficient mucoadhesion.

2) Disease state- The physicochemical belongings of mucus may alter during some diseased state, collectively with common region cold, gastric ulcers, ulcerative colitis, bacterial and fungal infections etc.[35]

3) Renewal rate of mucosal cells– Renewal rate of mucosal cells differs considerably on the basis of varieties of mucosa. It limits the staying power of bioadhesive systems on mucosal surfaces.

Advantages of Mucoadhesive drug delivery system

- prolongs the house time of the dosage shape on the web page of absorption.
- Due to an multiplied house time it complements absorption and therefore the healing efficacy of the drug - Excellent accessibility .
- Rapid absorption due to full-size blood deliver and right blood float rates - growth in drug bioavailability because of first by skip metabolism avoidance.
- Drug is blanketed from degradation with inside the acidic surroundings with inside the git.
- Improved affected person compliance- ease of drug management - quicker onset of motion is finished because of mucosal floor.

Disadvantages of mucoadhesive drug delivery

- 1.Small mucosal surface for contact.
- 2.Lack of flexibility of dosage forms.
- 3.Difficult to achieve high drug release rates required for some drugs.
- 4.Extent & frequency of attachment may cause local irritation.

Application Mucoadhesive Drug Delivery System

- 1.Imaging: numerous cells, molecular lines, tissues and organs may be Imaged the use of radio labelled microspheres.
- 2.Release of proteins, hormones and peptides over prolonged length of time.
- 3.Targeting of drug at specific web page of motion.
- 4.Gene remedy with DNA plasmids and additionally shipping of insulin.
- 5.Topical porous microspheres.
- 6.Surface changed microspheres.

Conclusion

The phenomenon of mucoadhesion may be used as a version for the managed drug transport techniques for some of drug candidates. There is no any doubt that the oral direction is the maximum favoured and possibly maximum complicated direction of drug transport. .This review approximately the Mucoadhesive drug Delivery structures have programs from special angles, inclusive of improvement of novel Mucoadhesive, layout of the device, mechanisms of Mucoadhesion and permeation enhancement. With the inflow of a huge wide variety of recent drug molecules because of drug discovery, mucoadhesive drug transport will play a good extra crucial position in handing over those molecules. The buccal mucosa gives numerous blessings for managed drug transport for prolonged intervals of time. The use of Mucoadhesive polymers has made this transport machine of managed launch application.

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