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MODERN APPROACHES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

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ABSTRACT

The term bioadhesion commonly known as adhesion between two materials where at least one of the materials is from biological origin. In the case of bioadhesive drug delivery system, bioadhesion often refers to the adhesion between the excipients and biological tissue. When adhesion is restricted to mucous layer lining of the mucosal surface layer known as Mucoadhesion. For the purpose of drug delivery, the term bioadhesion is defined as the ability of the drug carrier system or the material to adhere to a biological tissue for extended period of time, leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, bioadhesive dosage forms have been used to target local disorders at the mucosal surface (e.g. mouth ulcer) to reduce the overall required and minimize side effect that may be caused by systemic administration of drugs.

KEYWORDS: Bioadhesion, Period of time, Drugconcentration, Bioavailability, Disorders, Mucosal surface.

1. INTRODUCTION

In the late of 20th century, the concept of mucoadhesion in drug delivery was introduced. Mucoadhesive Drug Delivery System is the best choice for hydrophilic high molecular weight drugs that cannot be easily administered. Mucoadhesive Drug Delivery System gives rapid absorption of drugs due to its high blood flow and preferable surface area. Mucoadhesive Drug Delivery System also prolong the residence time of the dosage form at the site of absorption. The use of various mucoadhesive polymers have achieved for the specific interest for formulation of sustained release dosage form. The delivery across the mucus membrane also provides various advantages over other delivery routes. For example, mucoadhesive drug delivery provides more advantages over controlled release system by virtual prolongation of drug in gastrointestinal tract. Mucoadhesive drug delivery system also severe both the purpose of sustain release and presence of dosage form at the site of action. For the particular mucoadhesive strength there are several kinds of mucoadhesive polymers for use. The use of various mucoadhesive polymers are used to improve the proper effects of drug delivery system on mucus membranesuch as chitosan, lectins etc. The different routes of mucoadhesive formulations are oral, gastrointestinal, nasal, ocular, vaginal and rectal. There are some pharmaceutical dosage form like films, gels and ointments are used for delivery of drug across mucosa. Films are used for this kind of delivery because an ideal film should be flexible, elastic and soft. For this nature, they can easily deliver drugs without breaking due to stress from mouth movements. On the other hand, Gels and ointments are more advantageous than films because they are easily dispersed throughout the mucosa for delivery of drug. An advantage of gel is that they can able to form a very good contact with mucus membrane and rapidly release drugs at their site of absorption. The rectal and vaginal formulations that can be used for delivery of drug are creams, ointments and gels. In this review, we describe in brief about mucoadhesive drug delivery system with its various advantages have a lot of potential for formulation of various dosage forms.

2. Promising Approaches of NDDS

a) A prolonged residence time at a site of absorption or action
b) A localization of the drug delivery system (DDS) at a given target site.
c) Increase in the drug concentration gradient due to the intestine contact of the particles with mucosal surface.
d) Possible by pass of first pass effect
e) Avoidance of presystemic elimination within GIT.

f) Depending on the particular drug, a better enzymatic flora for drug absorption.

g) Inclusion of penetration enhancers such as sodium glycocholate, sodium taurocholate and protease inhibitors in dosage form results in better absorption of peptides and proteins.

3. Mechanism and Chemistry of Mucoadhesion

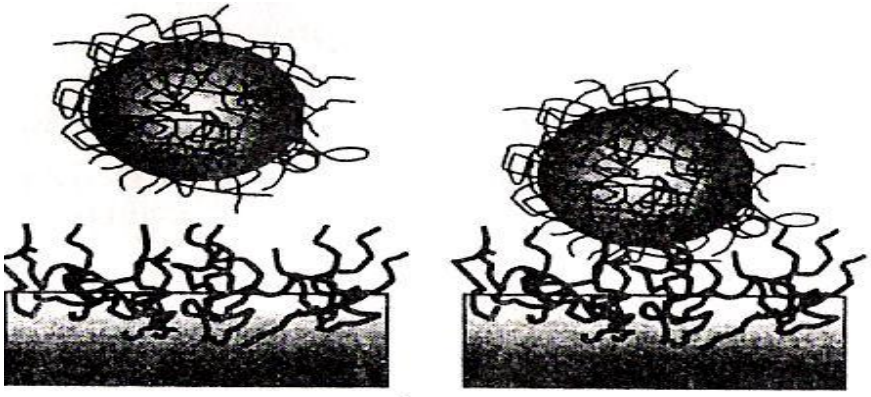
A. Chemical approaches

The process involved in the formation of bioadhesive bonds has been described in three steps –

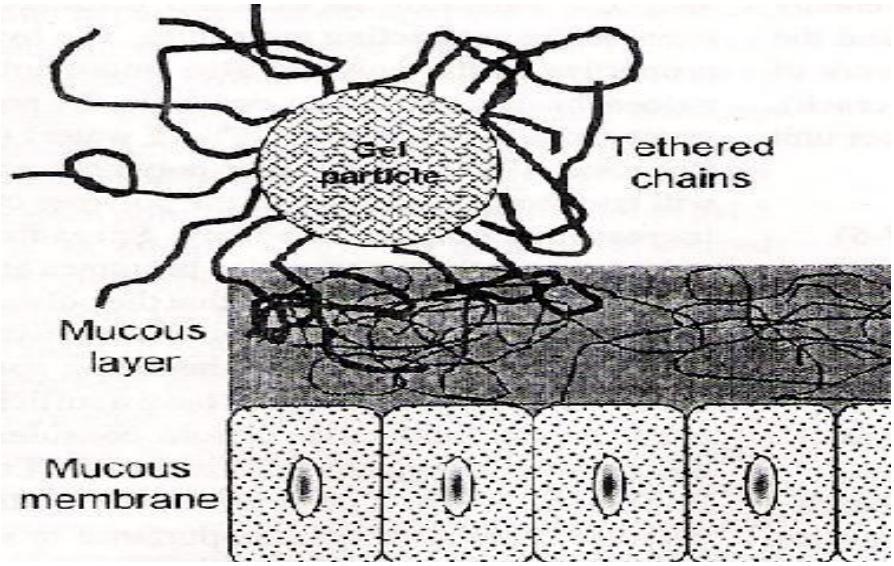
a) Wetting and swelling of polymer to permit intimate contact with biological tissue.

b) Interpenetration of bioadhesive polymer chain and entanglement of polymer and mucin chains.

c) Formation of weak chemical bonds between entangled chain.



Interpenetration of Bioadhesive and Mucous Polymer Chains



B. Mechanism

Swelling is an affinity consequence of the affinity of polymeric components for water. Polymers swell because of an imbalance between the chemical potential of solvent within the polymer and that in the surrounding medium.[2] Thus solvent moves as a result of polymeric "osmotic pressure "until equilibrium is achieved and the internal and external chemical potentials are equivalent. For low- molecular weight hydrophilic polymers the equilibrium state is a solution; for high molecular weight crossed linked polymers it can be a water swollen gel. The extent and rate of swelling are affected by the degree of crsslinking and chain length. If the surrounding medium contains solute, the rate of swelling decreases, particularly if the solute is large and cannot enter the hydrogels network.

C. Theories

i) Electronic theory: - According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucous glycoprotein due to difference in their electronic structure. This results in formation of electrical double layer at the interface.

(ii) Adsorption theory: - After an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces.

(iii) Wetting theory: - Predominantly applicable to liquid bioadhesive systems. The thermodynamic work of adhesion is a function of surface tension of the surface in contact as well as interfacial tension.[1] The interfacial energy is responsible for the contact between the two surfaces and adhesive strength.

(iv) Fracture theory: - It attempts to relate the difficulty of separation of two surfaces after adhesion.

(v) Diffusion theory: - The polymer chains and mucus mix to a sufficient depth to create a semipermant adhesive bond.[1]

D. Environment related factors affecting mucoadhesion

(i) Ph

pH was found to have a significant effect on mucoadhesion.[3] pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on the pH because of the difference in the dissociation of the functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone. Robinsonet al. Observed that the pH of the medium is critical for the degree of hydration of highly cross linked polyacrylic acid polymers, increasing between pH 4 to pH 5, continuing to increase

slightly at pH 6- pH 7, and decreasing at more alkaline levels. This behavior was attributed to difference in the charge density at the different pH levels.

(ii) Applied strength

To place a solid bioadhesive system, it is necessary to apply a defined strength.[3] The adhesion strength increases with the applied strength or with the duration of its application, up to an optimum level.

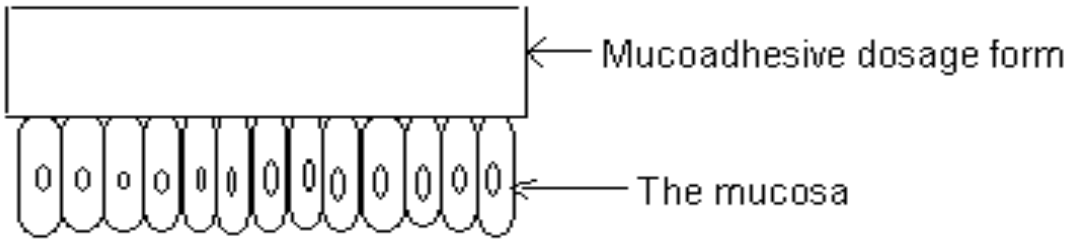
(iii) Initial contact time

The initial contact time between the mucoadhesives and the mucus layer determines the extent of swelling and the interpenetration of the polymer chains.[3] The mucoadhesive strength increases as the initial contact time increases.

(iv) Swelling

Interpenetration of chains is easier when polymer chains are disentangled and free of interactions.[3] When swelling is too great, a decrease in the bioadhesion occurs, such a phenomena must not occur too early, in order to lead to a sufficient time for action of the bioadhesive system. Two basic steps have been identified for mucoadhesion.

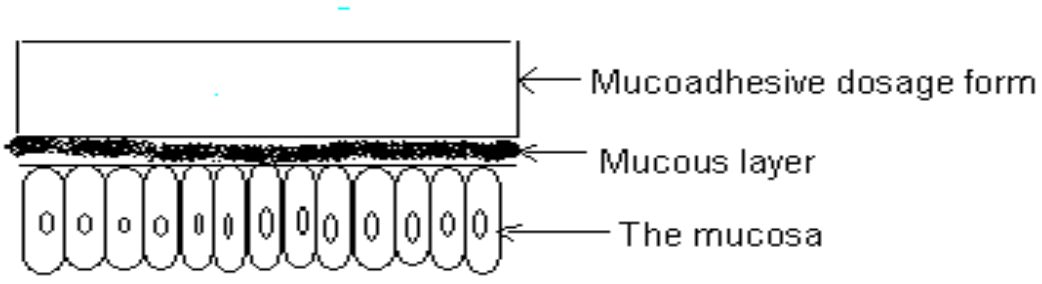
- **Contact stag-** An intimate contact is formed between the mucoadhesive and mucous membrane.

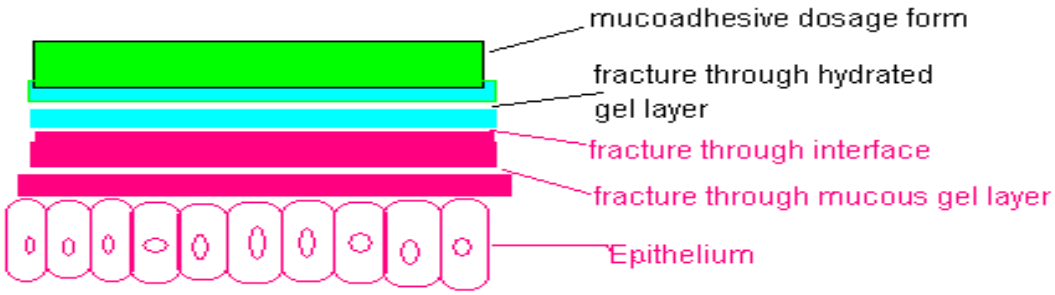


- **Consolidation stage**

It has been proposed that if strong or prolonged adhesion is required, with larger formulations exposed to stresses such as blinking or mouth movements, then a second " consolidation " stage is required. The mucoadhesive, the mucosa, and the interfacial region, consisting of mucous.

Adhesive joint failure may occur at weakest components of the joint. The strength of the adhesive joint will depend on the cohesive nature of the weakest region.





(Possible in Mucus Adhesive Failure)

To understand the above problem there is one theory of how this gel strengthening occurs.

- **Rheological synergic study**

The rheological synergy study suggests that as soon as mucus and mucoadhsive interpenetrate, they are likely to interact and form a surface gel layer that will substantially inhibit any further interpenetration.

The theory proposed that consolidation arises from the ability of dry or partially hydrated mucoadhesive materials to swell and hydrate mucous gel, and it is water movement rather macromolecular interpenetration.

E. Physico chemical factors

i. Composition and characteristic of mucous

a) Mucins are synthesized by the goblet cells and special exocrine glands
b) Mucin is of glycoprotein family, having mol.wt.1-40 dalton
c) Mucin network is negative because of

d) Presence of sialic acid which has pKa of 2.6

e) Presence of charged groups.

ii. Mucin turnover

The natural turnover of the mucin molecules from the mucus layer is important for at least two reasons, (a) The mucinturn over is expected to limit the residence time of mucoadhesive dosage form on the mucus layer. (b) Mucin turnover results in substantial amount of soluble mucin molecules. These mucin molecules interact with mucoadhesive before they have a chance to interact with the mucus layer.

iii. Disease states

The physiological properties of the mucus are known to change during disease conditions such as the common cold, gastric ulcers etc. The exact structural changes taking place in mucus under these conditions are not yet clearly understood.

iv. Physiological consideration

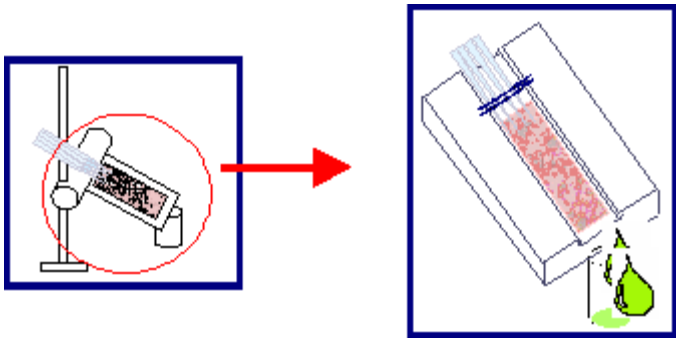
Membranes of internal tracts of the body are covered with a thick gel like structure known as mucin and mucin is synthesized by goblet cells and special exocrine glands with mucous cell acini. This bioadhesivemucin consists of highly hydrated, cross-linked, linear, flexible and random coil glycoprotein molecules with net negative charge. The cell surface membrane also possesses a net negative charge due to the presence of charged groups. Thus the binding of mucin to cell surfaces, which is a result of interaction between the two surfaces with same net charge, indicates that adhesive forces dominate the electrostatic repulsive forces between the two surfaces.

4. Evaluation of Mucoadhesive Drug Delivery System

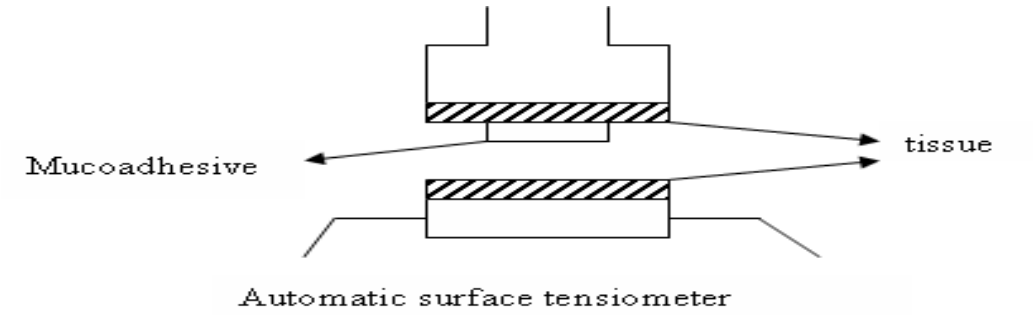
i. Measurement of residence time / retention time

Measured at site of application.

Provides quantitative information on mucoadhesive properties. The GI transit time of manymucoadhesives have been examined using radioisotopes e.g. 51Cr and the time dependent distribution of the radioactivity in the GIT is measured. As same, redionuclides such as 99mTc, 113mIn or 123I are used and their transit through the GIT is measured by γ scintigraphy.

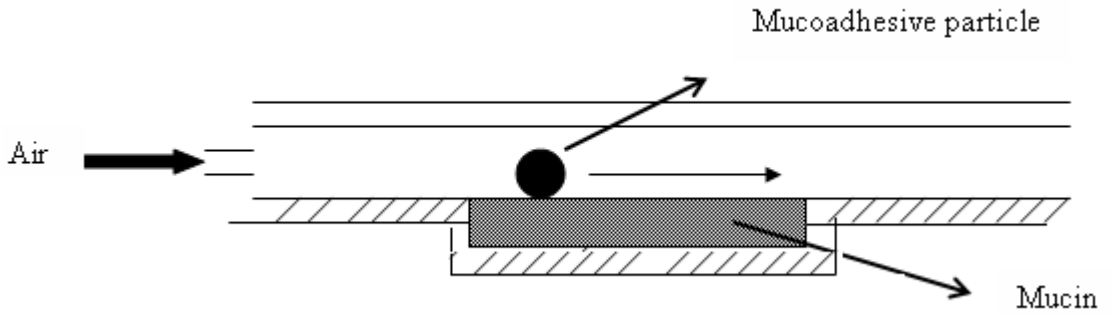


ii. Measurement of adhesive strength



In-vitro apparatus used to measure bioadhesive retention to a particular tissue.

Three different types of stress, tensile, shear and peel stress are measured. For simulation of actual application conditions, the ideal substrate would be the tissue to which the mucoadhesive system will be applied and the force required to separate mucoadhesives from mucosal tissue is measured using modified automatic surface tensiometer. The results from measuring tensile strength provides information regarding the effects of charge density, hydrophobicity and experimental conditions such as pH, ionic strength, mucolytic agents and applied pressure on bioadhesion.



The shear stress measures the force that causes mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. The shear mucoadhesive strength

is measured by flow channel method where force necessary for the detachment of a particle placed on the mucin gel was determined by passing humid air through the flow cell. The peel test involves the application of stress over a fine line at the edge rather than over the entire area of contact sites.

iii. Thumb test

Here, the adhesiveness is qualitatively measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. It provides useful information on mucoadhesive potential.

iv. Adhesion Number

With a mucoadhesive in the form of small particles, the adhesion number can be used as a parameter for Mucoadhesion. The adhesion number (Na) is, kiki**Na = (N/No)*100;** Where, No = total no. of applied particles, N = no. of particles attached to the substrate. It is assumed that as the adhesion strength increases, the adhesion number also increases.

v. Falling liquid film method

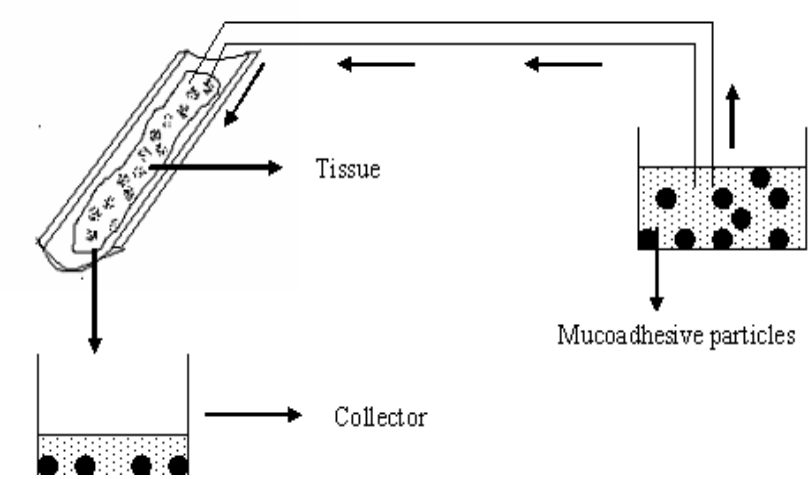
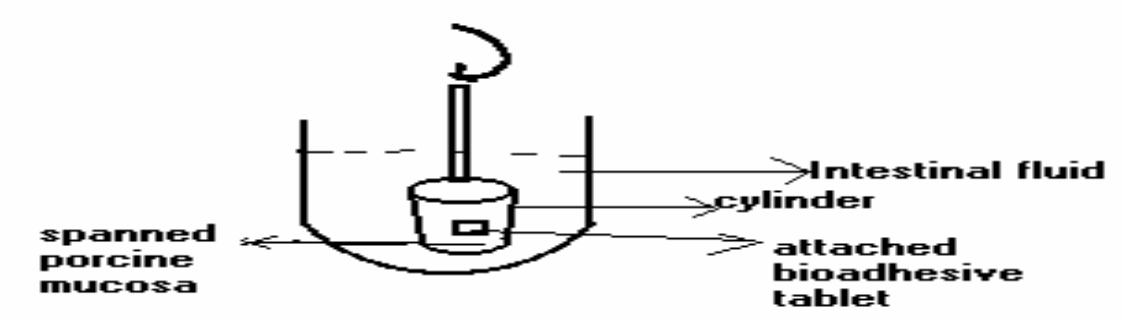


Figure: Small intestinal segments from rats were placed at an inclination on a tygon tube.

The adhesion of particles to this surface is measured by passing the particle suspension over the surface and by comparing the fraction of particles adhered to the tissue; the adhesion strength of different polymers can be determined.

vi. Membrane viscosity

The interaction between polymers and cell membranes was examined by labeling the cell membranes with fluorescent probes. The lipid bilayer and proteins of cell membranes were labeled with pyrene and fluorescein isothiocyanate. The fluorescence spectrum of pyrene and the fluorescence depolarization of fluorescein isothiocyanate were used to examine the change in membrane viscosity after interaction with polymer. Bernkop-schnurch and steininger et al. have established a new method to evaluate the binding to the mucosa as well as the cohesiveness of the tablet. The prepared tablets were attached to freshly excised intestinal porcine mucosa, which has been spanned on stainless steel cylinder (apparatus 4 cylinder, USP XXII).



Thereafter, the cylinder was placed in the dissolution apparatus according to the USP containing 100 mMTris-HCl buffered saline (TBS). The fully immersed cylinder was agitated with 250 rpm. The detachment, disintegration or erosion of tablet were observed and recorded within a time perio of 10h.

vii. In vivo evaluation methods

In vivo methods used for evaluation methods are based on administration of polymers to a laboratory animal and tracking their transit through the GI system. Administration methods include forced oral gavage, surgical stomach implantation and infusion through a loop placed in situ in the small intestine. Tracking generally followed with the help of X-ray studies, radio opaque markers and radioactive elements etc. For e.g. X- ray studies for monitoring GI transit time for bioadhesive tablet made of BaSO4 and radiolabelled microspheres and nanoparticles is.

viii. Mucoadhesive strength measurement

Here first tissue novel bioadhesive system (NBAS) is placed or adhered to the rabbit or porcine buccal mucosa. Whole assembly paced in the krebssolution. Then NBAS is clamped.

On other side, from the burette liquid is poured and amount of liquid required to detach the NBAS from tissue is measured and thus bioadhesive strength measured.

5. Factors Affecting Mucoadhesion

A) Polymer related factors

i. Molecular weight

There is certain molecular weight at which bioadhesion is at a maximum. The interpenetration of polymer molecules is favorable for low molecular weight polymers, whereas entanglements are favored for high molecular weight polymers. It seems that the bioadhesive forces increases with the molecular weight of the bioadhesive polymer up to 100000, and that beyond this level there is not much affect.

ii. Concentration of active polymer

Biomerker relates that there is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated systems, the adhesive strength drops significantly. In fact, in concentrated solutions, the coiled molecules become solvent-poor, and the chains available for interpenetration are not numerous. This result seems to be of interest only for more or less liquid bioadhesive forms.

iii. Degree of hydration

Depending on the degree of hydration adhesive properties are different. It is maximum at a certain degree of hydration. When the degree of hydration is high, adhesiveness is lost probably due to formation of slippery, non-adhesive mucilage in an environment of large amount of water at or near the interface.

iv. Charge on polymer

Mucosal surface is negatively charged. So positively charged polymer might facilitate the mucoadhesive process. Perhaps the initial step of mucoadhesion of a positively charged polymer to the biologic surface is through electrostatic attraction, followed by mechanical interlinking of polymer chains, vanderwaal forces, H bonds and other forces. Chitosan have bioadhesion due to electrostatic attraction between positively charged D- glucosamine residue of chitosan and negatively charged sialic acid residues.

v. Flexibility of polymer chain

Swelling is an affinity consequence of the affinity of polymeric components for water. Polymers swell because of an imbalance between the chemical potential of solvent within the polymer and that in the surrounding medium.

vi. Spatial confirmation

Spatial confirmation of a molecule is an important and useful factor for mucoadhesion because of proper mucoadhesiveproperty. The helical structure of dextran is a very good example of spatial confirmation because it may enclose many active groups containing adhesive property.

vii. Swelling

Swelling is an important factor for mucoadhesion. concentration and polymeric properties that are used in case of mucoadhesion must have proper effect on swelling. In case of polymetric materials those have high swelling index; decrease in mucoadhesion occurs for those materials.

viii. Presence of functional group

Non-invasive delivery of hydrophilic macromolecular drugs such as peptides, nucleic acids & polysaccharides is one of the major challenges in modern pharmaceutical technologies. Thiomers are thiolated polymers. Due to immobilization of thiol groups on well established polymers like chitosan & polyacrylic acid their permeation enhancement, enzyme inhibitory & mucoadhesive properties are improved. The immobilization of thiol groups on microparticles improves mucoadhesive properties.

B) Mucoadhesive polymers

They are water soluble and water insoluble polymers which are swellable networks jointed by crosslinking agents. Amucoadhesion promoting agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva. As understood earlier, that various physical and chemical exchanges can affect the polymer/ mucus adhesion, so as polymer should be carefully selected with the following properties in mind.

I. Characteristics of an ideal polymer

- Degradation products should be non toxic and non absorbable from G.I.T.
- Non irritant to mucous membrane.
- Form a strong non covalent bond with mucin epithelial cell surfaces.
- Should adhere quickly to moist tissue and should possess site specificity.
- Allow easy incorporation of the drug and offer no hindrance to its release.
- Polymer must not decompose on storage or during shelf life of dosage form.
- Cost effective.

II. Various polymers which are used

a. PAA derivatives carbomer-carbopolnoveon- polycarbophil

These are polymers of acrylic acid cross linked with polyalkenyl ethers or divinylglycol.[4] They are produced from primary polymer particles of about 2-6 micron diameter. Each primary particle exists as a network structure of polymer cahains interconnected by cross links. Carbopol polymers along with pemulen and noveon polymers are all cross linked.[5] They swell in water upto 1000 times their original volume to form a gel when exposed to a pH of 4.0 to 6.0 the glass transition temperature is about 105°C.

b. Chitosan

It is a cationic polymer (polysaccharide). It is produced by the deactivation of chitin.[6] Chitosan is gaining importance in the development of mucoadhesive drug delivery system because of its good biocompatibility, biodegradability and non toxicnature.[6] It binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Chitosan being linear provides greater polymer chain flexibility.

c. Thiolated Polymers

These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylatedgallan gum. The presence of the thiol group increases the residence time by promoting covalent bonds with the cystiene residues in mucus. The disulphide bonds may also alter the mechanism of drug release from the delivery system due to increased rigidity and cross linking.

d. Lectins

Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that

bind reversibly to specific carbohydrate residues. After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis. They hence allow a method for site specific and controlled drug delivery. The lectins have many advantages but they also have the disadvantage of being immunogenic.

e. Polyox WSR

Class of high molecular weight polyethylene molecular weight polyethylene oxide homo polymers having the following properties-Water soluble, Hydrophilic nature, High molecular weight, Functional group for hydrogen bonding, Biocompatible and non toxic, Can be formulated into tablets, films, gels, microcapsules, syrups.

6. Application of Mucoadhesive Drug Delivery System

The mucosal layer lines number of regions of the body including the GI tract, urogenital tract the airways, the ear, nose, eye etc., bioadhesive dosage forms have been used to target local disorders at the mucosal surface (e.g. mouth ulcer) to reduce the overall required and minimize side effect that may be caused by systemic administration of drugs. These represent the potential sites for the attachment of many bioadhesive systems and hence mucoadhesive drug delivery system include the following-

i. Solid bioadhesive formulations

a) Tablets
b) Bioadhesivemicroparticles
c) Bioadhesive inserts
d) Bioadhesive wafers
e) Lozenges

ii. Semisolid bioadhesive Formulations

a) Gels
b) Films

iii. Liquid bioadhesive formulations

a) Suspensions
b) Gel forming liquids

A. Buccal drug delivery

Oral cavity has rich blood supply and direct access to systemic circulation. The oral route is suitable for drugs which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver.

In oral cavity, buccal and gingival areas are associated with a smaller flow of saliva as compared to the sublingual region, thus the duration of adhesion of the delivery system would be longer at these areas than at the sublingual region.

i. Buccal absorption of drug

To penetrate the mucosa to a significant degree a drug should have relatively low molecular weight and exhibit biphasic solubility patterns, that is, be soluble in both the aqueous salivary fluid and lipid membrane barrier to show penetration.[7] High molecular weight muccopolysachrides such as heaperin and proteins such as insulin are not well absorbed.[8] A significant amount of drug should be un- ionized at salivary pH and the drug should also not bind strongly to the oral mucosa.

ii. Oral mucosa as site for drug delivery

Within the oral mucosal cavity, delivery of drugs is classified into three categories:

a. Sublingual delivery

Sublingual mucosa is relatively permeable due to the thin membrane and large veins, hence allow rapid absorption and acceptable bioavailability of many drugs. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets, and those consisting of soft gelatin capsules filled with liquid drug.[9]

b. Buccal delivery

Buccal mucosa is significantly less permeable than sublingual mucosa, which makes it more suitable for sustained drug delivery and is generally not able to provide the rapid absorption.[10] The buccal mucosa has an expanse of smooth muscle which makes it a more desirable region for retentive systems used for oral transmucosal drug delivery.

c. Local delivery

Local drug delivery is more permeable than others as it occurs over a defined period in a specified area. It is more advantageous than others because it can attain 100 folds higher

concentrations of an agent in sublingual sites. This drug delivery system is mainly suitable for delivery of antimicrobial drugs to reduces toxicity produced in systemic circulation.

iii. Advantages of Buccaladhesive drug delivery system

Good patient compliance.

Administration and termination of therapy is easy.

Due to lack of langerhans cells it is tolerant to potential allergens.

This route can administer drugs that are unstable in the acidic environment of the stomach or are destroyed at the enzymatic or alkaline environment of the intestine.

Permits localization of the drug to the oral cavity for prolonged period of time.

Offers an excellent route for systemic delivery of drugs having drawbacks of first pass metabolism, convenient for drugs that show poor bioavailability.

Significant dose reduction can be achieved.

The presence of saliva ensures relatively large amounts of water for drug dissolution unlike the rectal and transdermal routes.

Offers a passive system for drug absorption and does not require any activation.

Consist of non-keratinised epithelium resulting in somewhat more permeable tissue than the skin.

iv. Disadvantages of Buccaladhesive drug delivery system

- One of the major limitations with buccal drug delivery is the low flux, which results in low drug bioavailability. Drugs which irritate the mucosa or have bitter or unpleasant taste or an obnoxious odor or unstable at buccal pH cannot be administered by this route. Only drugs with small dose requirements and drugs that are absorbed by passive diffusion can be administered by this route. There is a possibility of patient swallowing the dosage form. Eating and drinking may become restricted. Over hydration may lead to formation of slippery surface. Swelling and hydration of the bioadhesive polymers may disrupt structural integrity of the formulation.

B. Gastrointestinal(G.I.T) drug delivery

i.G.I.T as a target for drug delivery

The target sites for bioadhesion in GIT are (a) The mucosal tissue. (b) The mucosal gel layer. The thickness of the mucin gel layer varies regionally throughout the GIT. There is a

continuous renewal of the mucosal layer by a turnover process, which limits the duration of mucoadhesion.[11]

The micro particles are attached to the mucosal layer through specific & non-specific interactions.

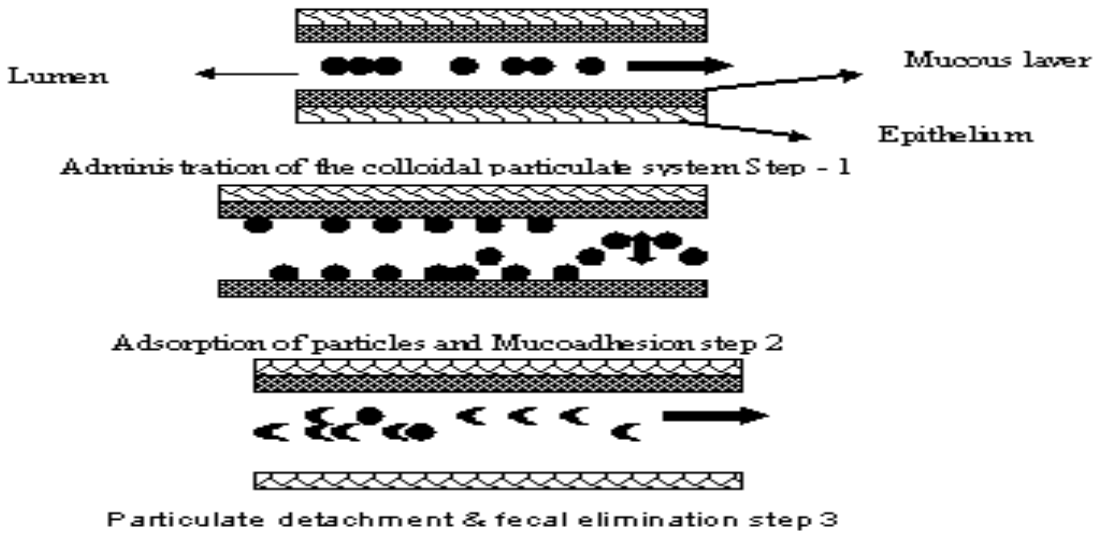
I. Non-specific bioadhesion

Non-specific bioadhesion with the intestinal membrane occurs through physiochemical interactions.

In the GIT, particles are directly mixed with liquid materials in the stomach, which is likely to strongly decrease the adhesiveness of such polymers because of the premature hydration of the polymer, which takes place before the contact with mucosal surface.

So the various approaches of GI bioadhesion of colloidal particles are based on the use of non-swellable, hydrophobic polymers.

In this case, adhesion is mainly due to inherent tendency of these small particles to develop intimate contacts with large mucosal surfaces.



Limitations of Non-specific bioadhesion

Only a fraction of the dosage form administered is absorbed while remaining part is subjected to direct fecal elimination. Due to unspecificity of the interactions, targeting to a specialized area of the mucosa with unmodified particles is unrealistic.

II. Specific adhesion

Specific adhesion is adhesion directly to surface of the cells of the mucosa and this involves specific ligand receptor interactions between complementary structures.

Ideally, the adhesion takes place when the dosage form reaches the desired site.

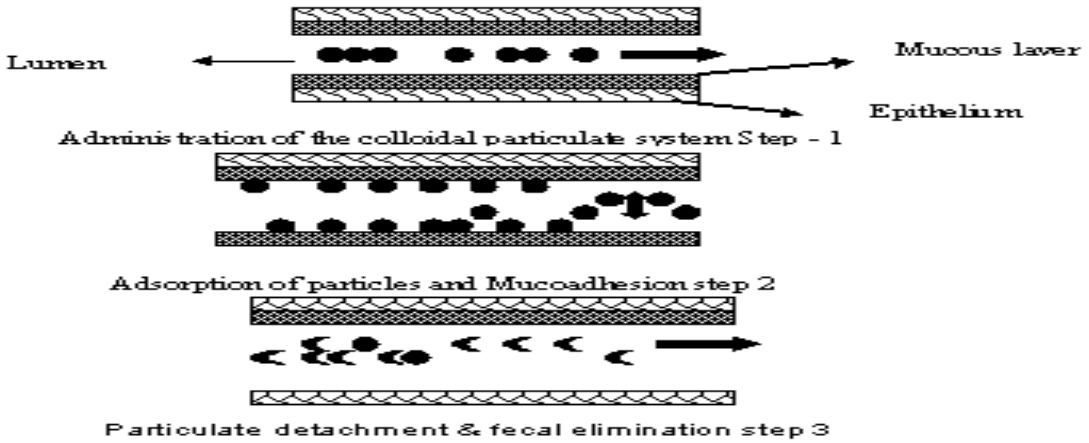
Different targets within GIT can be identified depending on the pharmaceutical applications. The targets are,

Mucosal glycoprotein, M-cells

Epithelial cells, Payer's patches or gut-associated lymphoid tissue etc.

Limitation of specific bioadhesion strategy

Specific bioadhesion strategy is likely to be limited in vivo by the limited capacity of the particles to diffuse through the mucous layer before reaching cell surfaces. The search of ligands exhibiting a sufficient specificity and lack of toxicity at the same time may be crucial task. A possible alteration or a blockage of the cell membrane functions and the immunogenicity of the ligand should be considered.



C. Nasal drug delivery system

The nasal mucosa allows effective absorption of a variety of lipophilic drug and hydrophilic drugs such as peptides and proteins.[12] The major difficulty in administering these drugs intra-nasally is their low bioavailability due to enzymatic degradation, mucociliary clearance and poor mucosal membrane permeability. This problems can be overcome by co-administering penetration enhancers or/and mucoadhesive substance. Chitosans are biodegradable high molecular weight cationic polysaccharide having mechanism of transport enhancement by transient opening of tight junction in nasal membrane and the property of

bioadhesion, enhance the nasal absorption in human volunteers of polypeptides and other polar drugs.

i. Liquid Bioadhesive Technology

A range of studies has been performed with liquid bioadhesive formulations of variable viscosity. Pennigton et al. has shown that an increase in viscosity of a solution by means of the bioadhesive material hydroxypropylmethyl cellulose results in a prolonged clearance time from the nasal cavity.[13]

ii. Self- Gelling Bioadhesive System

A problem may be encountered in therapeutic use with application of the bioadhesive liquid gel system in the nasal cavity, especially if a high concentration of the polymer is used. The formulations are not likely to be readily delivered using a normal nasal spray device but rather will have to be applied with the means of a tube. To overcome this problem, bioadhesive formulation that gel upon interaction with the nasal mucosacalled environmentally responsive polymers have been exploited for nasal drug delivery.[14]

iii. Bioadhesive Powder System

The bioadhesive agents studied in combination with the freeze-dried insulin includes crystalline cellulose, hydroxy propyl cellulose and Corbopol 934. All formulations tested gave significant decrease in the plasma glucose levels when administered nasally to dog and rabbit models**.**

iv. Bioadhesive Microsphere System

- Illum et al first suggested the use of the bioadhesive microspheres.
- These microspheres swell when they come in contact with the nasal mucosa to form a gel and control the rate of clearance from the nasal cavity, thereby giving poorly absorbed drugs sufficient time to absorb from the nasal mucosa.[15]

D. Ocular bioadhesive drug delivery system

i. Hydrogels

Hydrogels-sodium hyaluronate and carbomer are the two hydrogels, providing considerable bioadhesive nature. Artificial tears for the treatment of dry eye (e.g. Viscotear®, Novartis) are the carbomer solutions that adhere on the surface of the eye providing a lubricated surface.

Carbopol is considered superior for sustained drug delivery in case of ocular drug delivery because it has similar features to mucin[16]. E.g. negative charge, expanded nature etc.

ii. Solid Formulations

Solid ophthalmic delivery devices are thin disks or small cylinders made with appropriate polymeric materials and fitting into the lower or upper conjuctival sac. Some inserts like now classical occusert can release the drug at a slow constant rate for one week.[17] So, mucoadhesivepolymers can be profitably used as constituents of inserts to achieve prolonged contact with the conjunctival sac and to alleviate the risk of expulsion from cul-de-sac.

iii. Particulate Drug Delivery systems

Liposomes, microspheres and nanoparticles – are manufactured with bioadhesive polymers to show controlled drug release properties.

E. Vaginal bioadhesive drug delivery system

Vaginal drug delivery offers many advantages; the avoidance of hepatic first-pass metabolism, a decrease in hepatic side effects and avoidance of pain, tissue damage, and infection commonly observed for parenteral drug delivery routes of administration. While the vagina provides a promising site for systemic drug delivery because of its large surface area, rich blood supply and high permeability, poor retention due to the selfcleansing action of the vaginal tract is often problematic.[18] However, residence times within the vagina tend to be much higher than at other absorption sites such as the rectum or intestinal mucosa. Another important consideration is the change in the vaginal membrane during the menstrual cycle and post-menopausal period. Typical bioadhesive polymers that have been in vaginal formulations include polycarbophil, hydroxypropylcellulose and polyacrylic acid.[19]

F. Oral drug delivery system

Oral mucosal drug delivery system is widely applicable as novel site for administration of drug for immediate and controlled release action by preventing first pass metabolism and enzymatic degradation due to GI microbial flora. Oral mucosal drug delivery system provides local and systemic action.

i. Chewing Gums

Gums are now considered pharmaceutical dosage forms, and have been used to deliver drugs for buccal absorption. These formulations consist of a gum base, which primarily consists of

resins, elastomers, waxes, and fats. Emulsifiers such as glycerol monostearate and lecithin are added to facilitate and enhance the uptake of saliva by the gum. Resin esters and polyvinyl acetate (PVA) are added to improve texture and decrease sticking of the gum to teeth.[20] Additives such as sweeteners, glycerol, and flavors can be added as desired. These chewing gums move about in the oral cavity, and the process of chewing mixes it with the saliva where the drug is rapidly released, partitioned, and then absorbed into the mucosal membrane. Thus, the solubility of the drug in saliva is an important factor in increasing the amount of drug released and absorbed.

ii. Lozenges

Lozenges can be used as an alternative dosage form to tablets and capsules when patients are unable to swallow. The use of lozenges has been reported for systemic drug delivery but it is more usual to see this dosage form used to bathe the oral cavity or the throat areas. While sublingual lozenges may be impractical due to their size, buccal lozenges have been extensively used, and are kept between the cheek and the gums.[21] Though the lozenge usually dissolves in about 30 min, the patient controls the rate of dissolution and absorption because the patient sucks on the lozenge until it dissolves.

iii. Buccal and Sublingual Tablets

These tablets are placed and held between the cheek and gum or the lip and gum (buccal) or under the tongue (sublingual) until they dissolve. Nitroglycerin tablets have been used extensively in the form of buccal and sublingual tablets for the fast onset and quick relief from angina.[22] Similarly isosorbidedinitrate is available in the form of sublingual tablets to be placed under the tongue or chewable tablets where the tablet has to be chewed in the mouth for 2 min before swallowing, and the drug is absorbed through the oral mucosa. Other formulations that have been used are nifedipine, sublingual misoprostol for labor induction, methyl testosterone, buprenorphine, and selegiline for monoamine oxidase-B inhibition.

iv. Hydrogels

Hydrogels are three-dimensional, hydrophilic, polymeric networks that can take up large amounts of water or other biological fluids. The networks consist of homopolymers or copolymers having physical or chemical cross-links that make them insoluble, which are responsible for the integrity of the network. Depending on their chemical side groups, hydrogels can be neutral or ionic. For a hydrogel to possess mucoadhesive properties, the

polymer chains have to be mobile to facilitate the interpenetration into the mucous layer and formation of bonds leading to mucoadhesion.

7. CONCLUSION

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. The various advantages of the oral mucoadhesivedrug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. With the appropriate technologies, delivery techniques and the choice of the polymer for the oral mucosa could, in the future, be utilized 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 muco-buccal 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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