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Mucosal Drug Delivery Systems: An Overview

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ABSTRACT

Bioadhesion is an interfacial phenomenon in which two materials are present, at least one of the materials is biological and are held together by methods of interfacial powers. At the point when this associated natural framework is mucus it is known as mucoadhesion. Mucoadhesion is an intricate procedure. In this paper various speculations like theories, advantages, disadvantages and factors are discussed with latest to clarify the mechanisms included. The goal of the investigation is to clarify the diverse components engaged with mucoadhesion and different variables influencing mucoadhesion.

Keywords: Mucoadhesion, Theories of mucoadhesion, Factors, Evaluation

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Introduction:

Adhesion is a term which refers to fixing or union of two opposing tissue surfaces. According to the physicist it is defined as "the molecular force of attraction in the area of contact between unlike bodies that acts to hold them together"[1]. Bio-adhesion is a term which can be defined as fixing or binding of two materials, in which one material is of biological origin. So simply it is adhesion of excipients or synthetic materials with biological tissues. The two materials, both can be biological materials. For example, sticking or attachment of microbes to gut, it may be either symbiotic or infectious[2].

If an adhesion occurs on surface of mucosal lining it is known as muco-adhesion. The mucosal layer is very much essential as it is semipermeable barrier and helps in exchange of nutrients gases while being impermeable to most bacteria and pathogens[3]. For example, In an earthworm the mucosal layer acts as permeable barrier for oxygen and carbon-dioxide but still protects it against the entry of other chemicals present in soil. The mucosal layer provides a distinct opportunity for sustained drug delivery.

In bio-adhesion the materials are held together for extended periods of time with the help of interfacial forces which consist of valency forces, interlocking forces or both[3]. In muco-adhesion the bonds involve secondary forces such as hydrogen bond or van der waals force. Of them covalent bonds lead to permanent adhesion, it is formed by chemical reaction of the polymer and the substrate. One should not get confused between muco-adhesion and bio-adhesion. In bio-adhesion the polymer is attached to biological membrane (lipid bilayer, mucosa layer). If polymer is attached to the mucous membrane, then the term muco-adhesion is used[3].

Based on phenomenological observation bio-adhesions are classified into 3 types[4]

Type 1: Adhesion between two biological phases without involvement of artificial material. For example: Cell fusion, platelet aggregation and wound healing.

Type 2: Adhesion of biological phase on to an artificial substrate (like culture dishes, metals, woods etc)

Type 3: Adhesion of artificial substance on to a biological substrate. For example, Adhesion of polymers to skin, Adhesion of polymeric hydrogels to soft tissues.

Mucosal drug delivery system includes the following systems[6]

- Buccal delivery system
- Sublingual delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system
- Gastro intestinal delivery system

Mechanism: M

echanism of muco-adhesion is not completely clear. This is a complex process. The mucoadhesive must distribute over the substrate to begin a close contact and increase surface contact. This approach or contact causes attractive and repulsive force[7]. Repulsive forces are caused due to osmotic pressure effects which is a result of interpenetration of the electrical double layers, steric effects and electro static interactions if the surfaces and particles are having opposite charges. The relative magnitude of the above-mentioned opposing forces will change depending on the nature of the particle, The aqueous environment and the distance between the particle and the surface area. For stronger adsorption to take place, Particles must overcome a repulsive barrier (potential energy barrier)[1].

Generally, two stages in mucoadhesive process supports the mechanism of interaction between mucoadhesive materials and a mucus membrane. These two stages are the contact stage and the consolidation stage[1].

The contact stage: An intimate contact is established between the mucoadhesive and mucous membrane. This contact is established when mucoadhesive and mucus membrane come together. It is a wetting or swelling phenomena[1].

The consolidation stage: during this stage various physicochemical interactions occur to harden and strengthen the adhesive point, resulting in prolonged adhesion. Simply presence of moisture activates the mucoadhesive materials and they are linked up by Van der Waals and Hydrogen bonds.

The following two theories can further explain this process. First theory is called diffusion theory. According to this theory the mucoadhesive material molecules interact with glycoproteins of mucus by means of inter penetrations of their chains and build secondary bonds[1]. Second theory is called as dehydration theory. It proposes that when a material which is capable of rapid gelation (solidification by freezing) in an aqueous environment is brought into contact with second gel, water movement occurs between gels until equilibrium is obtained[8]. This theory explains that Mucoadhesion occurs in matter of seconds.

Advantages[7]:

- Extends the duration of residence time of the dosage form at the site of absorption and thereby increasing the bioavailability.
- Excellent penetrability and quick absorption because of enormous blood supply.
- Improved patient compliance and ease of drug administration.
- Faster onset of action due to mucosal surface.
- Painless intake of drug.
- As intimate contact forms between dosage forms and tissue, It results in high drug absorption at that tissue and improves the therapeutic performance of the drug.
- Drug is protected from dehydration in the acidic environment in GIT.

Disadvantages[3]:

- Prolonged contact of drug with mucosa layer may possess ulcerogenic property.
- Drug might dissolute due to continuous secretion of saliva.
- Some of these drugs may have bitter or unpleasant taste, odour and colour.
- Small dosage drugs only can be administered.
- Drugs which are absorbed by passive diffusion can be administered.
- Vaginal formulations may leak or interfere with sexual intercourse and may be contraindicated in pregnancy.
- Ocular formulations cause uneasiness and blurring.
- Nasal formulations may stimulate sneezing which causes dislodging of formulation. It might also irritate the sensitive nasal mucosa.
- Major drawback- lack of good model for invitro screening to identify drugs suitable for oral mucosal delivery.

Theories[1]:

Numerous theories have been proposed to explain the complex process of Mucoadhesion. Each theory is equally important in describing Mucosdhesion process. There is a possibility that there will be initial wetting of mucus layer and next diffusion of adhesive polymer into mucus layer occurs causing the fracture in layers and causing electronic transfer or simple adsorption phenomenon which finally leads to Mucoadhesion. The contact angle and time of contact plays an important role in Mucoadhesive process.

Wetting Theory: This theory is possibly the oldest theory of adhesion primarily applicable to liquid or low viscosity mucoadhesive systems. The adhesion between two surfaces is caused by interfacial energy. This theory explains that binding agents penetrates the surface irregularities of substrate then hardens and anchors itself to the surface. The affinity between adhesive agent and substrate can be determined by measuring the contact angle with a general rule, lower the contact angle greater the affinity. This theory necessarily measures the spreadability of adhesive polymer on the substrate. So, to provide adequate spreadability the contact angle should be equal or close to zero.

Diffusion Theory: The process of diffusion occurs due to presence of concentration gradient, which drives the polymer chains of bio adhesive into the mucus network and the glycoprotein mucin chains into the bio adhesive matrix until an equilibrium penetration depth is attained. Sufficient depth of penetration creates a semi-permanent bond and this bind strength increases with enhancement in the degree of penetration. The degree of penetration depends on various factors which include diffusion coefficient, mobility, time of contact, temperature, crosslinking density and expansion capability of both networks.

The exact depth which is needed for good bio adhesion bond to form is unclear but according to AlurHHet.al.19999 it is estimated to be in the range of 0.2-0.5 micrometers. Reinhart and Peppas reported that the diffusion coefficient is decreased with increasing crosslinking density. Polymer mobility and interfacial penetration are also decreased on increased crosslinking.

Solubility parameter of adhesive and glycoprotein network palys an important role because it helps in predicting the interpenetration. More the structural similarity better is the Mucoadhesion bond as the structural similarity between the bio adhesive and the mucus promotes mutual solubility resulting in diffusion phenomena.

Fracture Theory: The name of the theory itself indicates breaking, this theory states that force is required to break the bond, to separate two surfaces after adhesion is established. Perhaps this is the most widely used and accepted theory on the mechanical measurement of Mucoadhesion. The work fracture has found to be greater when polymer network fibres are longer or if the degree of crosslinking is decreased within such a system. This theory varies from other theories because it is occurred with the force required to separate the two surfaces and it does not take into consideration of the interpenetration or diffusion of polymer chains.

Electronic Theory: This theory explains that electrons transfer occurs when a contact is established between adhesive polymer and mucus glycoprotein due to difference in electron structure which results in the formation of electrical double layer at the interface (the polymer and the substrate are held in contact due to presence of electrostatic forces of attraction). There is a controversy in accepting the theory due to a fact which states that electro static forces are much weaker forces to cause the bond of adhesion.

Adsorption Theory: Once an initial contact is made between polymer and substrate, The material adheres due to presence of surface acting forces. There area two type of chemical bonds result in these forces and they can be distinguished as following:

Primary bonds: These are very strong, and they include ionic, covalent and metallic bonds and this leads to adhesion called chemisorption which is undesirable as it forms permanent bonds.

Secondary forces: These are weaker, and they include Van der waal's forces, hydrogen bond and hydrophobic interactions. These are easily breakable with use of less energy. These are desirable as Mucoadhesion is a temporary event.

Factors Affecting Mucoadhesion[6]:

Physiological Factors:

Mucin Turnover: This is a critical parameter. This mucin turnover limits the residence time if the mucoadhesive on the mucus layer though the mucoadhesive strength is very high. It also results in production of soluble mucin molecules which interact with mucoadhesive before they have chance to interact with mucus layer. This phenomenon plays a role in body's immune system, It removes the pathogen which might have attached to mucus layer to prevent damage.

Disease State: The physicochemical properties of mucus change during disease conditions such as common cold, gastric ulcers, bacterial and fungal infections etc. The mucus undergoes structural change during these disease conditions, This alteration may affect the bio adhesive property.

Rate of Renewal of Mucoadhesive Cells: It varies enormously for different type of mucosa. Also limits the constancy of bio adhesive system.

Tissue Movement: It occurs during intake of liquid and food, speaking, peristalsis in the GIT and it affects the mucoadhesive system especially in case of gastro retentive dosage forms.

Concomitant Diseases: These are secondary illness developed due to primary illness and they can alter the physicochemical properties of mucus or its quantity (for example hypo and hyper secretion of gastric juice) increase in body temperature, ulcer disease, tissue fibrosis, inflammations etc.

Environmental Factors:

Ph of Polymer Substrate Interface: The pH has a significant effect on the surface of the mucus as well as the polymers. The mucus is more prevailed on the pH because of contrast in dissociation of the functional group on carbohydrate moiety and amino acids of peptide backbone, which may affect adhesion. The elevation of medium pH level plays a prominent role in degree of hydration, as the pH level is important for the degree of hydration for the crosslinked polycyclic acid. Consistently increased hydration from pH 4 to pH7 and then a decrease as alkalinity or ionic strength increase. But at higher pH, the chain is fully extended due to the electro static repulsion of the carboxyl ate anions.

Applied Strength: A solid mucoadhesive system can be achieved by engaging precise strength. Even though there are no attractive properties between polymer and mucus, application for high pressure for a long time make the polymer bio-adhesive with mucus. Hence the application of initial pressure can affect the depth of the interpenetration.

Initial Contact Time: The initial contact time between the mucoadhesives and mucus layer determines the extent of swelling and interpenetration of polymer chains. More the initial contact time, higher the bio-adhesive strength. The initial pressure at the initial contact time has hysteric effect on the performance of the system. Initial contact time directly effects the extent of swelling and diffusion of polymer chains.

Moistening: Moistening allows the mucoadhesive polymer to spread over the surface and creates a macromolecular network of required size for the interpenetration of polymer and mucin molecules, this will help in increase in the mobility of polymer chain. The critical level of hydration for mucoadhesive polymers is obtained by optimum swelling and bio-adhesion.

Swelling: Interpenetration is easier in chains when polymer chains are disentangled and free of interactions. Higher the swelling lower is the bio-adhesion. It should not occur too early as it need some time for the action of bio-adhesion. Swelling characteristic is related to polymer itself as well as to its environment.

Selection of Model Substrate Surface: As the physical and biological changes for mucus gels or tissues may occur during the experimental condition, The treatment and handling of the biological substrates is very critical.

Presence of Metal Ions: Interaction with charged group of polymers and mucous can result in significant decrease in number of interaction sites as well as the tightness of the mucoadhesive bonding.

Polymer Related Factors:

Molecular Weight: The interpenetration of polymer molecules is favorable for lower molecular weight polymer because higher molecular weights will not moisten or diffuse quickly and may cause entanglements.

Concentration of polymer: The Highly concentrated mucoadhesive contains greater number of functional groups to form molecular bonds so it improves mucoadhesion. If the concentration of polymer is too low then the interaction between polymer is small because the number of penetrating polymer chains per unit volume of mucus is small. An optimum concentration is present for mucoadhesive polymer to produce maximum bio adhesion. At high concentration beyond optimum level the adhesion strength drops significantly.

Flexibility of Polymer Chains: It is believed to be an important parameter for interpenetration and entanglement. For bio adhesions to be effective the polymer chain should effectively diffuse into mucus layer. To achieve this the polymer chain should have enough flexibility. This depends on viscosity and diffusion coefficient. To obtain greater diffusion into mucus network. The flexibility of polymer should be higher.

Spatial Conformation: Mucoadheison also relies on the conformation of polymer eg: helical or linear. Unlike PEG polymer which have linear conformation, The helical conformation of electrons may shield many active groups primarily responsible for adhesion.

Swelling: Greater the swelling of polymeric matrix higher is the adhesion time. It depends on the concentration of polymer, ion strength and presence of water. This process permits mechanical entanglement by revealing the bio adhesive sites for hydrogen bonding or electrostatic interaction between polymer and mucus network.

Hydrogen Bonding Capacity: The hydrogen bonding is another important factor for Mucoadhesion of a polymer. For the process of Mucoadheison to occur the polymers must have functional groups which should be able to form hydrogen bonds.

Crosslinking Density: When the crosslinking density is greater, then the size of the pore becomes small and the diffusion of water into the polymeric networks occurs at lower rate thereby causing insufficient swelling of polymers which results in decreased penetration of polymer into the mucin. The degree of crosslinking significantly affects chain mobility and resistance to dissolution.

Charge: The bio adhesive nature of ionic polymer is always greater than that of nonionic polymer. Mucosal surface is negatively charged, So positively charged polymers might facilitate Mucoadhesion. In a neutral or slightly alkaline medium the cationic polymer shows higher level of mucoadhesive properties. It is proven that cationic high molecular weight polymer such as chitosan owns good bio adhesive property.

Evaluation Studies for Mucoadhesive Drug Delivery System

In vitro/ex vivo tests35-43

- Methods determining tensile strength
- Methods determining shear stress
- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Mechanical spectroscopic method
- Falling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Electrical conductance
- Swelling properties
- In vitro drug release studies
- Mucoretentability studies

In vivo methods

- Use of radioisotopes
- Use of gamma scintigraphy
- Use of pharmacoscintigraphy
- Use of electron paramagnetic resonance (EPR) oximetry
- X - ray studies
- Isolated loop technique

Methods determining tensile strength

In tensile and shear experiments, the stress is uniformly distributed over the adhesive joint, whereas in the peel strength stress is focused at the edge of the joint. Thus, tensile and shear measure the mechanical properties of the system, whereas peel strength measures the peeling force. Texture profile analyzer is a commercial instrument which is used to measure the force required to remove bioadhesive films from excised tissue in vitro. For this test, a piece of mucous membrane of an animal was taken and tested for the force required to take away the formulation from a model membrane which consists of disc composed of mucin. The texture analyzer, operating in tensile test mode and coupled with a sliding lower platform, was also used to determine peel strength of similar formulations. On a movable platform the animal skin was placed. On top of it the bioadhesive film was placed, which was later on pulled vertically to determine the peel strength.

Methods determining shear stress

The measurement of the shear stress gives a direct correlation to the adhesion strength. In a simple shear stress measurement based method two smooth, polished plexi glass boxes are selected; one block is fixed with adhesive Araldite® on a glass plate, which is fixed on leveled table. The level is adjusted with the spirit level. To the upper block, a thread is tied and the thread is passed down through a pulley, the length of the thread from the pulley to the pan was 12 cm. At the end of the thread a pan of fixed is attached. More weights can be added to it. A recent method involves the measurement of mucoadhesion by using a stainless steel rotating cylinder which is coated with freshly excised porcine intestinal mucosa to which polymer discs were attached. The cylinder is placed in a dissolution apparatus and rotated at 125 RPM. It is analysed every 30 mins for the attachment of the polymers discs.

Falling liquid film method

In this method the mucous membrane is placed in a stainless steel cylindrical tube, which has been longitudinally cut. This support is placed inclined in a cylindrical cell with a temperature controlled at 37º. An isotonic solution is pumped through the mucous membrane and collected in a beaker. Next, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a coulter counter. For semi-solid systems, the non-adhered mucoadhesive can be quantified by high performance liquid chromatography .This methodology allows the visualization of formation of liquid-crystalline mesophase on the mucous membrane after the flowing of the fluids and through analysis by means of polarized light microscopy.

Fluorescent probe method

In this method the membrane lipid bilayer and membrane proteins are labeled with pyrene and fluorescein isothiocyanate, respectively. The cells are mixed with the mucoadhesive agents and changes in fluorescence spectra

were monitored. This gives an indication of polymer binding and its influence on polymer adhesion.

Flow Channel method

The method was conducted in an attempt to understand structural requirements for bioadhesion in order to design improved bioadhesives polymers for oral use. The membrane lipid bilayer and membrane proteins were labeled with pyrene and fluorescence isothiocyanate, respectively. The cells were then mixed with candidate bioadhesives and the change in florescence spectra was monitored. This gave an indication of polymer binding and its influence on polymer adhesion.

Swelling index

The extent of swelling can be measured in terms of % weight gain by the dosage form. The swelling index is calculated by using following formula.

$$\text{Swelling index (S.I)} = \frac{Wt - Wo}{Wo}$$

Where, S.I = Swelling index

Wt = Weight of tablet at time t

Wo = Weight of tablet before placing in the beaker

Colloidal gold staining method

Colloidal gold staining technique is proposed for the study of bioadhesion. The technique employs red colloidal gold particles, which are adsorbed on mucin molecules to form mucin–gold conjugates, which upon interaction with bioadhesives hydrogels develops a red color on the surface. This can be quantified by measuring either the intensity on the hydrogel surface or the conjugates at 525 nm.

Viscometric method

A simple viscometric method is used to quantify mucin–polymer bioadhesive bond strength. Viscosities of 15% w/v porcine gastric mucin dispersion in 0.1M HCl (pH 1) or 0.1M acetate buffer (pH 5.5) is measured with a Brookfield viscometer in the absence or presence of selected neutral, anionic, and cationic polymers. Viscosity components and the forces of bioadhesion are calculated.

Thumb method

This is a very simple test used for the qualitative determination of peel adhesive strength of the polymer. It is useful tool in the development of buccal adhesive delivery systems. The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time.

Adhesion number

Adhesion number for mucoadhesive microspheres is determined as the ratio of the number of particles attached to the substrate to the total number of applied particles, expressed as a percentage. The adhesion strength increases with an increase in the adhesion number.

Electrical conductance

The rotational viscometer was modified to determine electrical conductance of various semi-solid mucoadhesive ointments and was found that the electrical conductance was low in the presence of adhesive material.

Mucoadhesive Strength

Mucoadhesive strength of the dosage form can be measured on the modified physical balance.The apparatus consists of a modified double beam physical balance in which the right pan is replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A Teflon® block of fixed diameter and height is fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This is kept in beaker filled with buffer media 0.1N HCl pH 1.2, which is then placed below right side of the balance. Goat or rat stomach mucosa can be used as a model membrane and buffer media 0.1N HCl pH 1.2 can be used as moistening fluid. The one side of the dosage form is attached to the glass slide of the right arm of the balance and then the beaker is raised slowly until contact between goat mucosa and mucoadhesive dosage form is established. A preload of 10 g is placed on the slide for 5 min (preload time) to establish adhesion bonding between mucoadhesive dosage form and goat or rat stomach mucosa. The preload and preload time are kept constant. After the completion of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water is stopped when mucoadhesive dosage form is detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive dosage form from stomach mucosa is noted as mucoadhesive strength in grams.

$$\text{Force of adhesion (N)} = \frac{mucoadhesive\ strength \times 9.81}{1000}$$

$$\text{Bond strength (N/m}^2\text{)} = \frac{force\ of\ adhesion}{surface\ area\ of\ tablets}$$

Stability Studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. ICH guidelines can be followed in this regard.

Measurement of the Residence Time/In Vivo Techniques

Measurements of the residence time of mucoadhesive at the application site provide quantitative information on their mucoadhesive properties. The GI transit times of many mucoadhesive preparations have been examined using radioisotopes and the fluorescent labeling techniques.

Gamma Scintigraphy Technique

Distribution and retention time of the mucoadhesive tablets can be studied using the gamma scintigraphy technique. A study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium-labeled HYAFF tablets. Dimensions of the stomach part of the sheep can be outlined and imaged using labeled gellan gum, and the data collected are subsequently used to compare the distribution of radio labeled HYAFF formulations. The retention of mucoadhesive-radio labeled tablets based on HYAFF polymer was found to be more for the dry powder formulation than for the pessary formulation after 12 h of administration to stomach epithelium. The combination of the sheep model and the gamma scintigraphy method has been proved to be an extremely useful tool for evaluating the distribution, spreading, and clearance of administered stomach mucoadhesive tablets. Table 4 contains information about some commercially available mucoadhesive drug delivery systems.

Conclusion

The mucoadhesive drug delivery system is a very promising approach for delivering the drugs which have narrow

absorption window at the target site to maximize their usefulness. With the introduction of a large number of new drug molecules from drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules. Improvements in mucoadhesive based oral delivery and, in particular, the development of novel, highly-effective and mucosa compatible polymers, are creating new commercial and clinical opportunities.

Conflict of interest

The authors confirm that this article has no conflict of interest.

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