

REVIEW ARTICLE

MUCOADHESION: A NOVELISTIC PLATFORM FOR DRUG DELIVERY SYSTEM

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Abstract:

The process of mucoadhesion involving a polymeric drug delivery system is a complex one that includes processes such as wetting, adsorption and interpenetration of polymer chains. The success and degree of mucoadhesion bonding is influenced by various polymer-based properties such as the degree of cross-linking, chain length and the presence of various functional groupings. Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for better therapeutic results. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects. Several in vitro and in vivo methodologies are proposed for studying its mechanisms. Oral mucoadhesivemicrocarriers were having potentiality for controlling and extending release profile so as to improve performance and patient compliance. The aim of this study was to review the mechanisms and theories involved in mucoadhesion, as well as to describe the most-used methodologies and polymers in mucoadhesive drug delivery system.

Keywords: mucoadhesion, bioadhesion, mechanism., evaluation techniques.

Introduction

BIOADHESION/MUCOADHESION

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for extended periods of time by the help of interfacial forces. Generally speaking, bioadhesion is a term which broadly includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used when the bond is formed with a mucosal surface[1].

Mucous Membranes

Mucous membranes (mucosae) are the moist surfaces, lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestine and bronchi) or multilayered/stratified (e.g. in the oesophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces, the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present as either a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form.

The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of its weight, making it a highly hydrated system. The mucinglycoproteins are the most important structure-forming component of the mucus gel, resulting in its characteristic gel-like, cohesive and adhesive properties. The thickness of this mucus layer varies on different mucosal surfaces, from 50 to 450 μm in the stomach, to less than 1 μm in the oral cavity. The major functions of mucus are that of protection and lubrication (they could be said to act as antiadherents) [2-3].

Composition of Mucus Layer

Mucus is translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. Mucus glycoproteins are high molecular proteins possessing attached oligosaccharide units containing the composition of mucus.

- a) L-fucose
- b) D-galactose
- c) N-acetyl-D-glucosamine
- d) N-acetyl-D-galactosamine
- e) Sialic acid [4].

FUNCTIONS OF MUCUS LAYER:

- ❖ Mucus layer is protective in nature because of its hydrophobicity.
- ❖ Mucus layer acts as a barrier in tissue absorption of drugs and other substrates.
- ❖ Mucus has strong adhesion properties and firmly binds to the epithelial cell surface as a continuous gel layer.
- ❖ An important role of mucus layer is to lubricate the mucosal membrane and keep it moist [5].

SITES FOR MUCOADHESIVE DRUG DELIVERY SYSTEM:

The common sites of application where mucoadhesive drug delivery systems have the ability to deliver pharmacologically active agents include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract. The current section of the review will give an overview of the above-mentioned delivery sites.

- ❖ The buccal cavity has a very limited surface area of around 50 cm^2 but the easy access to the site makes it a preferred location for delivering active agents. The site provides an opportunity to deliver pharmacologically active agents systemically by avoiding hepatic first-pass metabolism in addition to the local treatment of the oral lesions. The sublingual mucosa is relatively more permeable than the buccal mucosa (due to the presence of large number of smooth muscle and immobile mucosa), hence formulations for sublingual delivery are designed to release the active agent quickly while mucoadhesive

- ❖ formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery [6].
- ❖ Like buccal cavity, nasal cavity also provides a potential site for the development of formulations where mucoadhesive polymers can play an important role. The nasal mucosal layer has a surface area of around 150-200 cm^2 . The residence time of a particulate matter in the nasal mucosa varies between 15 and 30 min, which have been attributed to the increased activity of the mucociliary layer in the presence of foreign particulate matter [7].
- ❖ Ophthalmic mucoadhesives also is another area of interest. Due to the continuous formation of tears and blinking of eye lids there is a rapid removal of the active medicament from the ocular cavity, which results in the poor bioavailability of the active agents. This can be minimized by delivering the drugs using ocular insert or patches [8-10].
- ❖ The vaginal and the rectal lumen have also been explored for the delivery of the active agents both systemically and locally. The active agents meant for the systemic delivery by this route of administration bypasses the hepatic first-pass metabolism. Quite often the delivery systems suffer from migration within the vaginal/rectal lumen which might affect the delivery of the active agent to the specific location [11-13].
- ❖ Gastrointestinal tract is also a potential site which has been explored since long for the development of mucoadhesive based formulations. The modulation of the transit time of the delivery systems in a particular location of the gastrointestinal system by using mucoadhesive polymers has generated much interest among researchers around the world [14].

ADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

- ❖ prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- ❖ Excellent accessibility, rapid onset of action.
- ❖ Rapid absorption because of enormous blood supply and good blood flow rates
- ❖ Drug is protected from degradation in the acidic environment in the gut
- ❖ Improved patient compliance

DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

- ❖ occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property
- ❖ one of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.

- ❖ Patient acceptability in terms to taste, irritancy and mouth feel is to be checked[16].

MUCOADHESIVE DRUG DELIVERY SYSTEM IN ORAL CAVITY

Drug delivery via the membranes of the oral cavity can be subdivided as follows:

- ❖ **Sublingual delivery:** is systemic delivery of drug through the mucosal membranes lining the floor of the mouth.
- ❖ **Buccal delivery:** is drug administration through the mucosal membranes lining the cheeks.
- ❖ **Local delivery:** is drug delivery into the oral cavity[17]

MECHANISM OF MUCOADHESION:

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion[18]. A General Mechanism of mucoadhesion drug delivery system is show in Figure-

The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must be dominated. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water (Lee et al., 2000). Due to its relative complexity, it is likely that the process of mucoadhesion cannot be described by just one of these theories. Lee, Park, Robinson, 2000 had described the mechanism of mucoadhesion in four different approaches. These include:

- ❖ Dry or partially hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates administered into the nasal cavity).
- ❖ Fully hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates of many mucoadhesives that have hydrated in the luminal contents on delivery to the lower gastrointestinal tract).
- ❖ Dry or partially hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically tablets or patches in the oral cavity or vagina).
- ❖ Fully hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically aqueous semisolids or liquids administered into the esophagus or eye).

It is unlikely that the mucoadhesive process will be the same in each case (Chowdary and Srinivas, 2000). In

the study of adhesion, generally, two stages in the adhesive process supports the mechanism of interaction between mucoadhesive materials and a mucous membrane. Thus, the mechanism of mucoadhesion is generally divided in two stages, the contact stage and the consolidation stage.

Stage 1: Contact stage: An intimate contact (wetting) occurs between the mucoadhesive and mucus membrane. Stage 2: Consolidation stage: Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion[19].

THERIOS OF MUCOADHESION

Electronic theory

According to this theory, electron transfer occurs upon contact of adhesive polymer with a mucus glycoprotein network because of difference in their electronic structures. This results in the formation of electrical double layer at the interface e.g. Interaction between positively charged polymers chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provides an intimate contact between a dosage form and absorbing tissue.

Absorption theory

According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

Diffusion theory

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between crosslinking and decreases significantly as the cross linking density increases.

Wetting theory

The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

Cohesive theory

The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecules. Based on adhesion in which swollen mucoadhesive polymers

upon the above theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical(wetting, diffusion and cohesive theory).

Fracture theory

This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is established. This force S_m , is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, F_m , and the total surface area, A_0 , involved in the adhesive interaction (eq.1):

$$S_m = F_m / A_0 \dots\dots (1)$$

Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains.

Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on through surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions there by aiding dissipating energy and can be considered the most important phenomenon of the process[18].

FACTOR AFFECTING MUCOADHESION

A. Polymer Related Factors

a. Molecular weight- The interpenetration of polymer molecules into the mucus layer is variable, for low molecular weight polymers penetration is more than high molecular weight polymers because entanglements are favored in high molecular weight polymers.

b. Concentration of active polymer- For solid dosage forms such as tablets, the higher the concentration of polymer, the stronger the bioadhesion force.

c. Spatial Conformation- Bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer.

d. Degree of Hydration- Another important factor affecting the mucoadhesive strength of polymeric components is the degree of hydration. In this respect many polymers will exhibit adhesive properties under conditions where the amount of water is limited. However in such a situation, adhesion is thought to be a result of a combination of capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface which act to dehydrate and strengthen the mucus layer. Although this kind of "sticking" has been referred to as mucoadhesion it is important to clearly distinguish such processes from "wet-on-wet"

attach to mucosal surfaces. Hydration is essential for the relaxation and interpenetration of polymer chains, excess hydration could lead to decreased mucoadhesion and/or retention due to the formation of slippery mucilage. In this situation cross linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect .

e. Chain flexibility of polymer- Chain flexibility is important for interpenetration and enlargement. As water-soluble polymers become more and more cross linked, the mobility of the individual polymer chain decreases, also as the cross linking density increases, the effective length of the chain which can penetrate into mucus decrease even further and mucoadhesive strength is reduced .

f. Functional Group Contribution- The attachment and bonding of bioadhesive polymers to biological substrates occurs mainly through interpenetration followed by secondary non-covalent bonding between substrates. Given that secondary bonding mainly arises due to hydrogen bond formation, it is well accepted that mucoadhesive polymers possessing hydrophilic functional such as, carboxyl (COOH), hydroxyl (OH), amide (NH₂) and sulphate groups (SO₄H) may be more favorable in formulating targeted drug delivery platforms. Typically, physical entanglements and secondary interactions (hydrogen bonds) contribute to the formation of a strengthened network; therefore polymers that exhibit a high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoprotein .

g. Swelling- The swelling characteristic is related to the polymer itself, and also to its environment. Interpenetration of chains is easier as polymer chains are disentangled and free of interactions. More the swelling of polymeric matrix higher the adhesion time of polymers.

B. Environmental – Related Factors

a. pH- pH influences the charge on the surface of both mucus and polymers. Mucus will have a different charge density depending on pH, because of difference in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion.

b. Applied strength- To place a solid bioadhesive system, it is necessary to apply a defined strength. Whichever the polymer may be the adhesion strength of those polymers increases with the increase in the applied strength.

c. Initial contact time- The initial contact time between decreases, reducing mucoadhesive strength.

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

d. Selection of the model substrate surface- The handling and treatment of biological substrates during the testing of mucoadhesive is an important factor, since physical and biological changes may occur in the mucus gels or tissues under the experimental conditions.

C. Physiological factors

Mucin turnover and disease state of mucus layer are physiological variables, which may affect bioadhesion[20].

POLYMER PROPERTIES DESIRABLE FOR MUCOADHESION

Functional group

The mucoadhesive polymer possessing hydrophilic functional group such as COOH, OH, NH₂, and SO₃H may be more favourable in formulating targeted drug delivery system. The functionalized polymer interact with mucus not only through physical entanglement but also through chemical bonds, resulting in formation of cross linked network. Example: Urea is well accepted hydrogen bonding disruptor which decreases mucoadhesiveness of mucin/pectin samples.

Degree of hydration

Hydration is essential for the relaxation and interpenetration of polymer chains. Excess of hydration could lead to decreased mucoadhesion and/or retention due to the formation of a slippery mucilage. In this situation cross-linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect.

Chain length

Chain length and its flexibility is critical for interpenetration and entanglement with the mucus gel. Increased chain mobility leads to increased inter diffusion and interpenetration of the polymer within the mucus network. Long polymer chains lose their ability to diffuse and interpenetrate through mucosal surfaces. Hence as the chain length decreases interpenetration increases.

Degree of cross linking

The chain mobility and resistance to dissolution is significantly influenced by the degree of cross-linking within a polymer system. Cross-linked hydrophilic polymers swell in the presence of water allowing them to retain their structure. High molecular weight linear hydrophilic polymers are swellable and readily dispersible. Cross-link density increases, chain mobility decreases and hence the effective chain length,

Polymer concentration

Polymer concentration is dependent on physical state of the delivery system, with differences between semisolid and solid-state dosage form. In the semisolid state, polymer concentration is low which reduces adhesion. Hence lower number of polymer chains are available for interpenetration with mucus. On the other hand, solid dosage forms such as buccal tablets exhibit increased adhesive strength as the mucoadhesive polymer concentration increases[21].

MUCOADHESIVE POLYMERS[4].

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- ❖ Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- ❖ Polymers that adhere through nonspecific, non-covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- ❖ Polymers that bind to specific receptor site on the self surface.

A. Characteristics of an ideal mucoadhesive polymer

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

B. Molecular characteristics

- ❖ Strong hydrogen bonding groups (-OH, -COOH).
- ❖ Strong anionic charges.
- ❖ Sufficient flexibility to penetrate the mucus network or tissue crevices.
- ❖ Surface tension characteristics suitable for wetting mucus/mucosal tissue surface.
- ❖ High molecular weight.

bioadhesive polymers are classified as first generation and second generation. The older generation of mucoadhesive polymers, referred to as off-the shelf

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

A short list of mucoadhesive polymers is given below:

Synthetic polymers:

Cellulose derivatives (methylcellulose, ethyl cellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxyl propyl methylcellulose, sodium carboxy methylcellulose, Poly (acrylic acid) polymers (carbomers, polycarbophil), Poly (hydroxyethylmethacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol).

Natural polymers:

Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, Lectin, Soluble starch, Gelatin, Pectin, Chitosan.

Thiolated polymers:

The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly (acrylic acid) and chitosan) in addition to the paracellular uptake of the bioactive agents . Various thiolated polymers include chitosan–iminothiolane, poly(acrylic acid)–cysteine, poly(acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly(methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine [21].

Lectin-based polymers:

Lectins are proteins which have the ability to reversibly bind with specific sugar / carbohydrate residues and are found in both animal and plant kingdom in addition to various microorganisms . Many lectins have been found to be toxic and immunogenic which may lead to systemic anaphylaxis in susceptible individuals on subsequent exposure . The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-adhesive property and is being explored to develop targeted delivery systems. Lectins extracted from legumes have been widely explored for targeted delivery systems. The various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus*, soybean, peanut and *Lens culinaris*. The use of wheat germ agglutinin has been on the rise due to its least immunogenic reactions, amongst available lectins, in addition to its capability to bind to the intestinal and alveolar epithelium and hence could be used to design oral and aerosol delivery systems [21].

New generation of mucoadhesive polymers

In a recent mini-review by Lee et al. current

- use of pharmacoscintigraphy

polymers, lack specificity and targeting capability. They adhere to the mucus non-specifically, and suffer short retention times due to the turnover rate of the mucus. The chemical interactions between mucoadhesive polymers and the mucus or tissue surfaces are generally non-covalent in nature, and are classified as consisting mostly of hydrogen bonds, hydrophobic, and electrostatic interactions. However, newer polymers are capable of forming covalent bonds with the mucus and the underlying cell layers, and hence, exhibit improved chemical interactions. The new generation of mucoadhesives (with the exception of thiolated polymers) can adhere directly to the cell surface, rather than to mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers. We have chosen to focus on recently discovered bioadhesive polymers in this review. Examples of such are the incorporation of l-cysteine into thiolated polymers and the target-specific, lectin mediated adhesive polymers. These classes of polymers hold promise for the delivery of a wide variety of new drug molecules, particularly macromolecules, and create new possibilities for more specific drug–receptor interactions and improved targeted drug delivery.

METHODS OF EVALUATION OF MUCOADHESIVE POLYMERS

Mucoadhesive polymers and drug delivery systems can be evaluated by testing their adhesion strength by both in vitro and in vivo tests.

In vitro tests / ex vivo [22].

The importance is laid on the elucidation of the exact mechanisms of bioadhesion. These methods are

- 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
- mucoadhesiveness studies

In vivo methods [23].

- use of radioisotopes
- use of gamma scintigraphy

- use of electron paramagnetic resonance(EPR) oximetry
- X ray studies
- Isolated loop technique

Shear stress method

The measurement of the shear stress gives a direct correlation to the adhesion strength. In a simple shear stress measurement based method smooth, polished plexi glass boxes were selected; one block was fixed with adhesive on a glass plate, which was fixed on leveled table. The level was adjusted with the spirit level. To the upper block, a thread was tied and the thread was 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 weight 17 gm was attached into which the weights can be added.

Detachment force measurements

The method involves the measurement of the bioadhesive force between the mucosal tissue and the polymer/dosage form attached to a metal wire and suspended into the microtensiometer. The mucosal tissue (usually rat jejunum) is used which is placed in the tissue chamber, this chamber is raised so as to make contact between the tissue and the test material. After a certain period (7 minutes for microspheres) the stage is lowered and the force of adhesion is measured. This apparatus measures the fracture strength (force per unit area required to break the adhesive bond) and deformation (distance required to move the stage before complete separation occurs).

Work of adhesion

This method is used to assess the tendency of mucoadhesive materials to adhere to the oesophagus. In this method, the intestine was removed from the sheep and kept in tyrode solution at 40°C. Segments of 6-7 cm long were cut from the intestine, the lower end tied to the glass tube of diameter 15 mm. The 6 mm paracetamol plane tablets, paracetamol tablets layered on one side with mucoadhesive polymer and the paracetamol in matrix tablets (2:1) ratio were prepared. A fine hole drilled in the tablets to be tested with fine needle in the centre. A thread was passed through it and tied around the tablet. The other end of the thread was tied to the glass rod suspended from the stand. To the other end of the glass rod, a pan was tied in which a beaker was placed. After inserting the tablet into GI segment and lightly pressing the GI segment with tablet by a forcep, the assembly was kept undisturbed for 30 mins to 1 hour. Then water was added to burette slowly drop by drop into the beaker. The amount of water required to pull out the tablet from the intestinal segment represents the force required to pull the tablet against adhesion.

$$F = 0.00981 \frac{w}{2}$$

w = amount of water.

In vitro drug release

These are performed in phosphate buffer pH 6.6, 150 ml at 37°C in a modified dissolution apparatus which consists of a 250 ml beaker and a glass rod attached with a grounded glass disk (2 cm diameter) as a donor tube. An adhesive cyanoacrylate polymer was attached to the glass disk. The donor tube was dipped into the medium and stirred at constant rpm. 5 ml aliquots were withdrawn at preset times (0.08, 0.16, 1, 2, 3, 4, 5, 6 hours), filtered through a 0.2 micron filter and absorbance measured at 290 nm.

GI transit using radiopaque technique

It involves the use of radio-opaque markers, e.g., barium sulfate, encapsulated in bioadhesive DDS to determine the effects of bioadhesive polymers on GI transit time³⁸. Faeces collection (using an automated faeces collection machine) and x-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility. Mucoadhesives labelled with Cr-51, Tc-99m, In-113m, or I-123 have been used to study the transit of the DDS in the GI tract^[24].

Fluorescent probe method

In this method the membrane lipid bilayered and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were mixed with the mucoadhesive agents and changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

Thumb test

The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. Although the thumb test may not be conclusive, it provides useful information on peel strength of the polymer^[21].

CONCLUSION

Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. It has to be noted that only a moist surface can bring the mucoadhesive nature of the dosage form. Mechanism of mucoadhesion is backed up by ionic bond, covalent bond, Vander Waal bond and hydrogen bond. Ionic and covalent bonds result in very strong mucoadhesive property. Mucoadhesion commences with wetting which is described as contact stage. In the consolidation stage lot of physiochemical interaction takes place. While considering a formulation development of mucoadhesive drug delivery dosage form, several physiological factors also have to be considered at the site of action. Several synthetic and natural polymers are considered to have

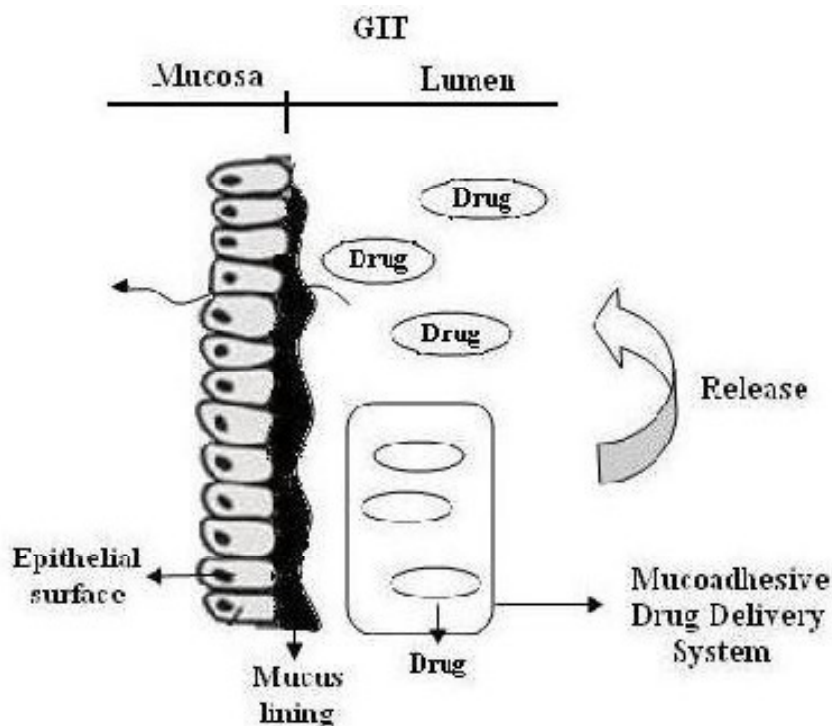


Fig: Mechanism of mucoadhesion[18].

complying properties of mucoadhesion.

CURRENT SCENARIO & FUTURE DEVELOPEMENTS IN MUCOADHESIVE DRUG DELIVERY SYSTEM

Currently mucoadhesivenanoparticulate systems were developed for the controlled and targeted delivery of drugs. Nanoparticles generally vary in size from 10-1000nm. Biodegradable nanoparticles have been used frequently as drug delivery vehicles due to its better encapsulation efficiency, control release and less toxic properties. They offer several advantages like enhanced biocompatibility, high drug/vaccine encapsulation, and improved release profiles for the drug. Synthetic nanoparticles typically feature hydrophobic, charged and/or hydrogen bonding surfaces and are, therefore, likely to be strongly mucoadhesive due to interactions with periodic exposed hydrophobic domains or negatively charged glycosylated segments along mucinfibers. The average pore size of viscoelastic mucus is around 150 ± 50 nm. Thus, mucoadhesivenanoprticles can easily penetrate in to the mucus and leads to the effective drug delivery at the target site. Commonly used materials for formulating nanoparticles are poly(lactide-co-glycolide) (PLGA) and Pluronics and chitosan. PEG coatings have been widely used in the development of polymeric drug carriers, including particles composed of biodegradable polyesters and polyanhydrides. PEG coatings reduce aggregation and enhance the blood circulation times of biodegradable nanoparticles designed for drug delivery. Nanoparticles size range up to 200 nm in diameter that are coated with a dense layer of non-mucoadhesive PEG polymers and mucoadhesive

polymer, chitosan composed drug carriers readily penetrate nasal mucus. The development of polymeric particles with improved mucus penetration capability should encourage the commercial development of new generations of nanoparticle based drug delivery systems. The use of mucoadhesivenanoparticles delivery system for peptide/poorly absorbable drugs is one of the areas that need to be explored in the future leads to enhancement of bioavailability and site specific targeting.

RECENT ADVANCEMENTS

Now scientists are developing mucoadhesive micro and nanoparticulate systems by using novel mucoadhesive polymers for better therapeutic results and site specific targeting with lesser side effects. 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 for delivery of narrow absorption window drugs at the target site to maximize their efficacy.

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