A Review on Mucoadhesion – An Effective Method In Drug Delivery

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Abstract

By using a new drug delivery method, such as a mucoadhesive system, pharmacological effects can be improved. This technique maintains intimate contact with the mucus membrane, the absorption tissue, releasing the medication at the action site, improving both local and systemic effects. The mechanism of mucoadhesion is explained by various theories such as Electronic Theory, Wetting Theory, Adsorption Theory, Diffusion Theory, Mucoadhesive polymers can be used to achieve mucoadhesion. There are various polymers like cationic, anionic, non-ionic, but most common are cellulose derivatives, chitosan and alginates. This paper provides an overview of recent advancements in mucoadhesive drug delivery system processing techniques and polymers.

Key words: Mucoadhesion, Bioadhesion, Mucoadhesion Theories, Mucoadhesive polymers.

Introduction

Since The first 1980s, the thought of mucoadhesion has gained significant interest in pharmaceutical technology. Mucoadhesive drug delivery systems are delivery systems that utilize the property of bio-adhesion of sure polymer which become adhesive on association and therefore will be used for targeting a drug to a specific region of the body for extended periods of time. Bioadhesion may be outlined because the state within which two materials, a minimum of one among which is biological in nature, are maintained along for a chronic period of time by suggests that of surface forces. Oral drug administration is that the most well-liked and most typical route for drug delivery. Many blessings related to it include: it’s patient-friendly, painless, has the convenience of self-medication, and permits for a versatile and controlled dosing schedule compared to most different drug delivery systems. Though the oral route is preferred for administration of medication, it conjointly presents major disadvantages similar to 1st pass effect, canal catalyst degradation and delay between the time of administration and absorption, that is damaging within the case of drugs with fast onset requirements.

In latest years, mucosal drug transport has obtained massive interest for each nearby and systemic transport of therapeutics. Mucoadhesive drug transport structures are related with higher compliance fees due to painless administration, low enzymatic activity, easy accessibility and capacity to goal nearby disorders. Unlike oral administration, which provides harsh surroundings for healing proteins and peptides, mucosal course provides enormously mild and secure surroundings for the absorption of drugs. Mucoadhesion may be outlined as a state during which two components, of which one is of biological origin, are control along for extended periods of your time by the assistance of surface forces. Typically speaking, bioadhesion is an associate term which generally includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is employed once the bond is created with a membrane surface. Mucoadhesive drug delivery systems include the following:

- Buccal Delivery System
- Oral Delivery System
- Rectal Delivery System
- Vaginal Delivery System
- Nasal Delivery System
- Ocular Delivery System

Advantages Of Mucoadhesive Drug Delivery System

1. Mucoadhesive indefinite quantity forms are without delay localized within the region applied to enhance the bioavailability of drugs, as compared to traditional formulations. e.g., insulin, gentamicin, piribedit, vasopressin, testosterone and its esters, Dopamine.

2. These indefinite quantity forms additionally prolong the duration at the location of application and absorption.

3. The intimate contact of those formulations with the underlying absorption surface permits the modification of tissue porosity for absorption of macromolecules akin to peptides and proteins. Drug is shielded from degradation within the acidic surroundings in the GIT.

Disadvantages Of Mucoadhesive Drug Delivery System

1. Occurrence of native unhealthy effects because of prolonged contact of the drug possessing ulcerogenic property
2. One of the foremost limitations within the development of oral membrane delivery is that they lack of a decent model for in vitro screening to determine medication appropriate for such administration.

3. Patient satisfactoriness in terms of taste, irritant and mouth feel is to be checked\(^9\).

Mechanism Of Mucoadhesion
The mechanism of mucoadhesion is usually divided into two steps:
1. The Contact Stages
2. The Consolidation Stage
The primary stage is characterized by the contact between the mucoadhesive and the secretion membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer\(^2\).

![Figure 1: structure of Mucus membrane](image1.jpg)

In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Wetness plasticizes the system, permitting the mucoadhesive molecules to interrupt free and to meet up by weak van der Waals and H bonds.

![Figure 2: The process of contact and consolidation](image2.jpg)
Essentially, there are 2 theories explaining the consolidation step:

a. The Diffusion Theory
b. The Dehydration Theory.

According to Diffusion Theory, the mucoadhesive molecules and also the glycoproteins of the secretion reciprocally move by means that of interpenetration of their chains and the building of secondary bonds. For this to require place, the mucoadhesive device has options pro each chemical associate degreed mechanical interactions. For example, molecules with element bonds building teams (–OH, –COOH), with an anionic surface charge, high molecular weight, versatile chains and active properties, which induct it unfold throughout the secretion layer, can gift mucoadhesive properties.

In keeping with Dehydration Theory, materials that are able to pronto gelify in a binary compound environment, once placed in reality with the mucus can cause its dehydration because of the distinction of diffusion pressure. The difference in concentration gradient attracts the water into the formulation till the osmotic balance is reached. This method results in the mixture of formulation and mucus, and may therefore increase contact time with the secretion membrane. Therefore, it's the water motion that results in the consolidation of the adhesive bond, and not the interpenetration of organic compound chains. However, the dehydration theory isn't applicable for solid formulations or extremely hydrous forms.

Mucoadhesion Theories

1. Electronic Theory
   The leptonic theory suggests that electron transfer happens upon contact of adhering surfaces due to variations in their electronic structure. This is often projected to lead to the formation of an electrical double layer at the interface, with future adhesion thanks to engaging forces.

2. Wetting Theory
   This Theory is applied to adhesive systems with low viscousness and high affinity to the substrate, permitting spontaneous scattering on the surface. The system-mucosa adhesion is simply Accepted, relating to the wettability and Spreadability of the liquid on the tissue layer surface. The liquid mucosa affinity happens thanks to the surface and free surface energy, which may be evaluated by variety of techniques, like the contact angle method. In this case, the low contact angle improves the association of polymers and permits an in-depth contact to be created between the mucoadhesive system and mucus, facilitating mucoadhesion. In general, bigger adherence happens once the contact angle is sort of zero. The interfacial/surface tension measure may be wont to predict scattering, so may also be used to measure mucoadhesion. Moreover, by decreasing interfacial/surface tension values, there's an improvement of the conditions for mucoadhesion.

3. Adsorption Theory
   This Theory describes the involvement of each form of chemical bond, that's, primary and secondary bond within the bio adhesion mechanism. Each of the surface that is glycoprotein and drug delivery system have their own surface energy. After they are available in contact, the adhesion happens thanks to the surface energy and leads to the formation of two sorts of attractive force. Primary chemical bond like valence bond, that is powerful in nature, so produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and element bonding, which are weak in nature, so produces a semi-permanent bond.

4. Diffusion Theory
   This Theory describes the involvement of a mechanical bond between the compound chain of drug delivery system and polymeric chain of secretion membrane, that is, glycol proteins. Once 2 surfaces are in intimate contact, the polymeric chain of the drug delivery system penetrates in to the conjugated protein network. In line with this theory, the bioadhesion primarily depends on the diffusion coefficient of each polymeric chains. The alternative factors that will influence the bury movement of polymeric chain are molecular weight, cross-linking density, chain flexibility and temperature to realize an honest bio adhesion, the bio adhesive medium ought to have the same solubility with conjugated protein leading to effective mucoadhesion.

5. Fracture Theory
   The fracture theory differs a touch from the opposite in this it relates the adhesive strength to the forces needed for the detachment of the two concerned surfaces when adhesion.

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<td>A. Polymer related factor</td>
<td>1. Molecular weight</td>
<td>Up to 1 0000 if molecular weight is increased then mucoadhesive force also increased, but beyond this level there is no effect.</td>
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Mucoadhesive Polymers
MDDS have been designed and developed using a large range of polymers, which are classified as cationic, anionic, non-ionic, thiolated polymers, and so on. Acrylate polymers are among the chemical groups that have been widely investigated for mucoadhesion. The most common are cellulose derivatives, chitosan, and alginates.

1. Acrylic Acid Derivatives/Polyacrylate
Polyacrylate is a cross-linked polymer containing acrylic acid that has been substituted with divinyl glycol or polyalkenylether. Polycarbophil and carboram have been widely researched among the polyacrylates for the polymeric platform of MDDS. Carbomer grades containing non-residual benzene, such as 934P and 971P, have been extensively researched for their mucoadhesion properties. At a moderately higher pH, the functional carboxylic acid groups of carbomers become ionised (around 6.2). The resulting electrostatic repulsion forces the polymeric chain to uncoil. Mechanical entanglement and contact of polymers with mucus glycoproteins are promoted by such uncoiling. The presence of several carboxylic groups in carbomer results in a favourable macromolecular conformation and increases the accessibility of H bond forming groups.

Polycarbophil is water insoluble but has a high swelling capacity. It also found that polycarbophil improved H bonding with mucus glycoprotein following relaxing in the colon. This bonding improves adhesion by allowing the polymer to penetrate and interlink with the mucus network. Despite their remarkable mucoadhesive characteristics, polyacrylates swell when wet, causing patient discomfort. To counteract this disadvantage, methyl groups were substituted in polyacrylates, resulting in polymethacrylate or polymethyl methacrylate. After salification with sodium salt, polymethyl methacrylate (Eudragit® S100) showed no swelling and good bioadhesion. Erosion from the patch and tablets made from those methacrylate salts determined the drug release pattern.

Another modification of polyacrylate was thiolation or cysteine conjugation, which was done to improve bioadhesion. The carboxyl group of thiolated polycarbophil is neutralised with sodium hydroxide (NaOH) before covalent bonding with cysteine amino groups.

2. Cellulose Derivatives
Hydroxyl Propyl cellulose (HPC), Hydroxyl Propyl Methyl Cellulose (HPMC), Hydroxyl Ethyl Cellulose (HEC), and Carboxy Methyl Cellulose (CMC) are examples of cellulose derivatives as mucoadhesive polymers of the first generation. The formation of a H bond between the carboxylic acid group of cellulose polymers and the glycoprotein of mucin is the mechanism of adhesion. A stronger H bond causes the delivery system to attach to the mucous layer deeper and stronger.

HPMC are widely used for their mucoadhesive properties as well as their controlled release mechanism. It has been used to deliver a variety of drugs in a variety of dosage forms. CMC is superior to HPMC in terms of mucoadhesion. HPMC is a non-ionic polymer with no proton-donating carboxylic group, resulting in lower H bonding than CMC. CMC is an anionic polymer that produces more hydrogen bonding than non-ionic cellulose polymers. However, the nature of mucoadhesion is affected by the pH of the testing medium. Thiolated CMC made by cysteine conjugation had 1.6 times better mucoadhesion in the buccal cavity than non-thiolated CMC.
3. Chitosan
After cellulose, chitosan is the most abundant polysaccharide in the world among all mucoadhesive agents. It has been extensively studied in numerous scientific reports since the early 1980s. Chitosan, a cationic mucoadhesive agent, is a polysaccharide made from chitin after it has been deacetylated. This is a glucosamine and N-acetylglucosamine co-polymer. Chitosan is water insoluble but soluble in mild acid. Chitosan is a desirable polymeric component because of its biocompatibility, biodegradability, and low toxicity. Several processes are responsible for chitosan's mucoadhesion properties. Due to the presence of –OH and –NH2 groups, H bonding with mucin glycoprotein is a common mechanism. The mucoadhesion capability is additionally aided by the linear chitosan molecule's conformational flexibility. Both physiological factors and chitosan's physicochemical qualities influence its interaction with mucous and its mucoadhesive capabilities. The amount of chitosan adsorption of mucin increases as increasing mucin sialic acid. Because the amount of sialic acid in mucosal secretions varies, the force of chitosan adhesion to mucus varies as well, depending on the mucosa. Chitosan is employed in the creation of various mucoadhesive delivery systems. E.g., The use of chitosan nanoparticles to deliver cyclosporine A to the ocular mucosa improved medication delivery and increased drug permeability to the inner eye.

4. Alginates
Brown seaweed is used to make alginate, which is a natural and biodegradable anionic polymer. Because of its low toxicity and inexpensive cost, it has been widely explored in various research to make microparticles and beads with outstanding bioadhesive properties. The presence of a carboxylic acid group in alginate causes H bonding with the glycoprotein of mucin, resulting in good mucoadhesion. Alginate does not swell much at acidic pH, resulting in a lot of coiling of the polymeric chain. Uncoiling polymeric chains increases the likelihood of tangling with the mucous layer, resulting in increased mucoadhesion. As a result, alginate provides reduced mucoadhesion in acidic pH. Pharmaceutical researchers are increasingly combining alginate with other bioadhesive carriers to create drug delivery systems, such as the chitosan-alginate bead for vaginal delivery of chlorhexidine Di gluconate, and the jackfruit seed starch-alginate microsphere of metformin HCl. Low molecular weight alginate chains have been demonstrated to be more stiff than high molecular weight alginate chains. Low molecular weight alginate is less likely than high molecular weight alginate to bridge with mucin molecules, resulting in decreased bioadhesion.

5. Pectins
Pectin is a nontoxic heterogenous polysaccharide derived from citrus peel or apple pomace that is natural, biodegradable, and biocompatible. It consists of carboxyl-group-containing linear chains of (1→4)-linked D-galacturonic acid residues. The formation of a H bond with mucin and the electrostatic interaction between pectin and mucin molecule 200 have both been proposed as mechanisms for pectin's mucoadhesion. Direct compression was used to make the pectin buccal discs. Following DE, the discs were divided into two categories: low-DE (38 percent) pectin and high-DE (70 %) pectin. Low-DE pectin was discovered to have a higher mucoadhesion strength than high-DE pectin. It could be owing to the esterified pectin's lower molecular weight and the presence of methoxy groups. A reduced thermodynamic work of adhesion may result from a greater MW and the presence of hydrophobic moieties in pectin structure. Pectin thiolation was proven to have better mucoadhesion than regular pectin.

6. Hyaluronic Acid
Hyaluronic Acid (HA), a high molecular weight anionic biopolymer, is made up of alternating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine with a 14 interglycosidic bond. In nature, this is biodegradable and very biocompatible. The random coil structure in solution may be responsible for HA's bioadhesive property via tangling with the mucous layer. When compared to high molecular weight HA, low molecular weight HA formed superior mucoadhesion. The adhesion time sequence is as follows: HA > Thiolated HA > Pre-activated Thiolated HA.

The presence of disulphide bonds between thiolated HA and mucin glycoprotein is linked to stronger adherence than normal HA, where H bonding creation is the primary factor for adhesion.

Conclusion
Drug Delivery Systems created with the goal of enhancing patient compliance and convenience are more crucial than ever now. Therefore, there is a lot of work being done to create innovative dosage forms to meet the growing patient demand for more practical dosage forms. Applications for mucoadhesive drug delivery systems include the creation of novel mucoadhesives device design, mechanisms of mucoadhesion, and permeation improvement. Drug Delivery Methods using mucoadhesive dose forms include Nasal, Vaginal, Ophthalmic, and Rectal Routes in addition to the straightforward oral mucosal route. The hydrophilic, high molecular weight, anionic compounds like carbomers have received the most attention in research and acceptance as mucoadhesive polymers. Mucoadhesive systems may become more important in the creation of novel pharmaceuticals as a result of the massive influx of new compounds resulting from pharmacological research.

References


