

Overview on Novel Mucoadhesive Polymers

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Abstract—Mucoadhesive drug-delivery systems have emerged as an important area of interest in pharmaceutical research because of their potential to improve drug absorption and enhance therapeutic efficacy. These systems are designed to adhere to the mucosal lining of the gastrointestinal tract and other mucous membranes, allowing the dosage form to remain at the site of absorption for an extended period. Prolonged residence time helps maintain a higher local concentration of the drug, leading to improved bioavailability, reduced dosing frequency, and a lower risk of adverse side effects. A wide range of natural and synthetic polymers are employed in the development of mucoadhesive formulations. These polymers play a crucial role in providing desirable characteristics such as strong adhesion, adequate swelling, flexibility, and biocompatibility, which are essential for effective mucoadhesion. Natural polymers are particularly attractive due to their safety, biodegradability, and minimal environmental impact, mucoadhesive drug-delivery systems offer a promising and patient friendly approach for drug bioavailability and compliance

Index Terms—Mucoadhesive drug delivery, mucosal adhesion polymers, natural polymers. Synthetic polymers, bioavailability, residence time, patient compliance, controlled drug.

I. INTRODUCTION

Mucoadhesion refers to the ability of natural or synthetic polymers to stick to a biological membrane and remain attached for an extended duration. The term polymer is derived from Greek words, where poly means “many” and meros means “units,” highlighting that polymers are large molecules composed of numerous repeating structural units held together by strong covalent bonds. In pharmaceutical drug-delivery systems, mucoadhesive polymers are especially valuable because they allow the dosage form to remain at the absorption site for a longer time. This extended contact with the mucosal surface

improves drug retention, enhances absorption, and ultimately leads to better therapeutic efficacy of the medication.[1]

Natural polymers are widely preferred in pharmaceutical formulations because they are cost-effective, safe, easily accessible, and largely non-toxic. An ideal natural polymer should be gentle on the mucosal membrane and should possess desirable properties such as good spread ability, efficient wetting, adequate swelling behavior, and biodegradability. Since these polymers are obtained from living sources like plants and animals, they are generally well tolerated and produce minimal harmful effects on both the human body and the environment. On the other hand, synthetic polymers are created through chemical manufacturing processes and may be associated with certain drawbacks. Their production and use can sometimes lead to unwanted effects on human health as well as environmental concerns.[2]

In pharmaceutical sciences, polymers are commonly classified into three main categories. Natural polymers originate from plant or animal sources. Synthetic polymers are prepared in laboratories through polymerization or chemical reactions. Semi-synthetic polymers are derived from natural polymers that have been chemically modified to enhance specific characteristics.

This review article is intended to clarify the fundamental concepts of muco-adhesion, outline the different types of polymers used in mucoadhesive drug-delivery systems, and highlight the importance of natural polymers along with the factors that influence their performance.[3]

II. WHAT IS MUCOADHESION

Mucoadhesion describes the ability of drug molecules or polymeric materials to attach to the mucous layer that lines various biological tissues. These mucoadhesive drug-delivery systems have become increasingly important in pharmaceutical research because they help the drug stay at the site of administration for an extended period and maintain a strong concentration Application difference across the epithelial barrier. As a result, the drug remains in close contact with the tissue, which improves its absorption and enhances therapeutic effectiveness.[4] Typically, mucoadhesive formulations are prepared using one or more hydrophilic polymers along with the active pharmaceutical ingredient. [5,6]

Need of Mucoadhesion

Oral administration is the most widely used route for delivering drugs, and oral controlled-release systems are commonly developed to provide a sustained and controlled effect of the active ingredient. Despite their popularity, these systems have several drawbacks, including first-pass metabolism in the liver, degradation of drugs by digestive enzymes, and swallowing difficulties, particularly in children and elderly patients.

When compared with conventional oral controlled-release systems, mucoadhesive drug-delivery systems offer distinct advantages. They help the dosage form remain at the site of absorption for a longer period, allow targeted delivery to specific tissues, and ensure close and continuous contact with the absorptive mucosal surface. Moreover, mucoadhesive formulations are highly effective in treating localized conditions at mucosal sites, as they reduce the required drug dose and limit unwanted systemic side effects.

Mucoadhesive dosage forms mainly rely on water-soluble polymers that act as adhesive agents. When these polymers are applied in a dry form, they absorb moisture from the mucosal surface, swell, and establish strong interactions with the mucus layer. This improves adhesion and significantly extends the retention time of the formulation on the mucosa. Consequently, the drug remains in contact with the target tissue for a longer duration, resulting in enhanced absorption and improved therapeutic effectiveness.

Mechanisms of Mucoadhesion

Mucoadhesion takes place through two main steps,

- 1) Contact stage
- 2) Consolidation stage.

1) Contact stage:

During the contact stage, the mucoadhesive formulation comes into direct contact with the mucosal surface. At this point, the formulation spreads across the mucus membrane and starts to swell. This spreading and swelling help the dosage form establish close and effective contact with the mucus layer, which is necessary for proper adhesion.

2) Consolidation stage

In the consolidation stage, the presence of moisture activates the mucoadhesive material. Water from the mucosal surface softens and plasticizes the polymer, making the polymer chains more flexible and freer to move. This allows the mucoadhesive molecules to form bonds with the mucus layer through weak interactions such as hydrogen bonds and van der Waals forces. These interactions strengthen the adhesion and ensure that the formulation remains attached to the mucosal surface for a prolonged period. [8,9]

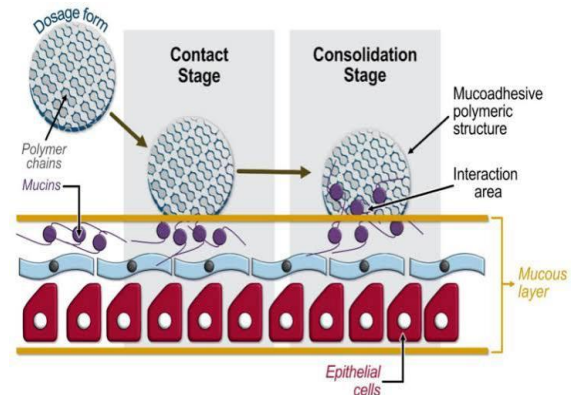


Fig.1: Mechanisms of mucoadhesionMucus membrane

III. MUCUS MEMBRANE

Mucous membranes, or mucosae, are moist tissues that line many internal cavities of the body, especially those of the gastrointestinal and respiratory systems. These membranes are mainly composed of two layers: an outer epithelial layer and an underlying connective

tissue layer called the lamina propria. The epithelial surface is usually covered by a thin coating of mucus, which gives the mucosa its soft, moist, and slippery character.

The type of epithelium present in mucous membranes depends on their location in the body. In organs such as the stomach, small and large intestines, and bronchi, the epithelium consists of a single cell layer. In contrast, areas like the esophagus, vagina, and cornea are lined with multilayered or stratified epithelium. In single-layered epithelia, mucus is produced and secreted directly onto the surface by specialized cells known as goblet cells. In stratified epithelia, mucus is generally supplied by nearby or associated secretory glands, such as the salivary glands, which release mucus onto the epithelial surface.

Mucus can appear either as a gel layer tightly bound to the mucosal surface or as a soluble or suspended material within the lumen. It is mainly composed of water, along with mucin glycoproteins, lipids, and inorganic salts. Water makes up more than 95% of the total weight of mucus, which explains its highly hydrated nature. Among its components, mucin glycoproteins are the most important, as they give mucus its gel-like structure, cohesive strength, and adhesive properties. The thickness of the mucus layer varies widely depending on the site. In the stomach, it may range from about 50 to 450 μm , whereas in the oral cavity it is much thinner and often less than 1 μm . Mucus performs two essential biological functions: protection and lubrication. It forms a protective barrier that guards the underlying epithelial tissue against mechanical damage, harmful chemicals, and microbial invasion. At the same time, it reduces friction and allows smooth movement over mucosal surfaces.

Mucous membranes are derived from ectodermal tissue and line cavities that are exposed to both the external environment and internal organs. They play an important role in key physiological processes, including absorption and secretion. In many tissues, continuous mucus secretion is vital for preserving the structural integrity and protective function of the mucosa. A clear understanding of mucoadhesion requires detailed knowledge of the structure and composition of the mucus layer. Mucus is a viscoelastic, gel-like network that is highly hydrated,

consisting mainly of water (up to 95% by weight), along with smaller amounts of glycoproteins, inorganic salts, carbohydrates, and lipids.

Mucins are a group of soluble glycoproteins that are primarily responsible for the gel-forming nature of mucus. Their high molecular weight, combined with their ability to form intermolecular disulfide bonds and hydrophobic interactions, enables them to create a complex three-dimensional network. Each mucin molecule is composed of a protein backbone, accounting for approximately 12–17% of its total weight, which is rich in the amino acids' serine, threonine, and proline. Attached to this backbone are numerous oligosaccharide side chains, mainly containing N-acetyl galactosamine, N-acetylglucosamine, galactose, and fructose, while the remaining regions are non-glycosylated. Most mucins carry an overall negative charge due to the presence of acidic sugar residues. These acidic groups have pKa values in the range of approximately 1.0 to 2.6, which means they remain fully ionized under normal physiological conditions. This negative charge plays a crucial role in maintaining mucus hydration, molecular expansion, and interactions with other substances, making it particularly important in the development and performance of mucoadhesive drug delivery systems.

Composition of mucus:

Oral mucus is produced by different glands in the oral cavity, including the sublingual, parotid, and other salivary glands. It is a transparent, thick, gel-like substance that helps in lubricating and protecting the tissues of the mouth. Mucus is mainly secreted by goblet cells and specialized exocrine glands, which are present together with mucus-producing cells in the oral mucosa.

Mucus is made mostly of water (around 95%), which makes it smooth, slippery, and gel-like. Because of this high-water content, mucus can easily spread over surfaces and keep them moist.

The remaining part of mucus contains small amounts of other important substances. Glycoproteins and lipids together make up about 0.5–1% of mucus and are responsible for its thickness and stickiness. Free proteins are present in low amounts, usually 0.5–5%, and help in protection and healing. Mineral salts,

which account for about 1%, help maintain the proper balance and stability of mucus

IV. MUCUS GLYCOPROTEINS (MUCINS)

Mucus contains special large molecules called mucus glycoproteins or mucins. These are very large proteins with sugar chains attached to them. This sugar chains help mucus stay sticky, flexible, and slippery, allowing it to protect and lubricate body surfaces.

The main sugars found In mucus are:

- N-acetyl-D-glucosamine
- N-acetyl-D-galactosamine
- L-fructose
- D-galactose
- Sialic acid

These sugars help maintain the thickness, structure, and protective function of mucus, enabling it to trap harmful particles and protect the underlying tissues

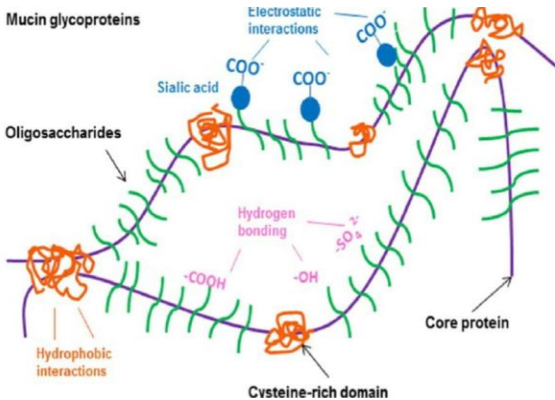


Fig.3 : Schematic structure of mucin glycoproteins and their potentially mucoadhesive elements

V. THEORIES OF MUCOADHESION

Mucoadhesion is a complex process, and researchers have proposed several theories to explain how mucoadhesive materials stick to mucosal surfaces. Each theory highlights a different aspect of the interaction between the polymer and the mucus layer. The main theories include the [10,11]

- 1) Wetting theory
- 2) Diffusion Theory
- 3) Mechanical theory

- 1) Electronic theory
- 2) Adsorption theory
- 3) Cohesive theory

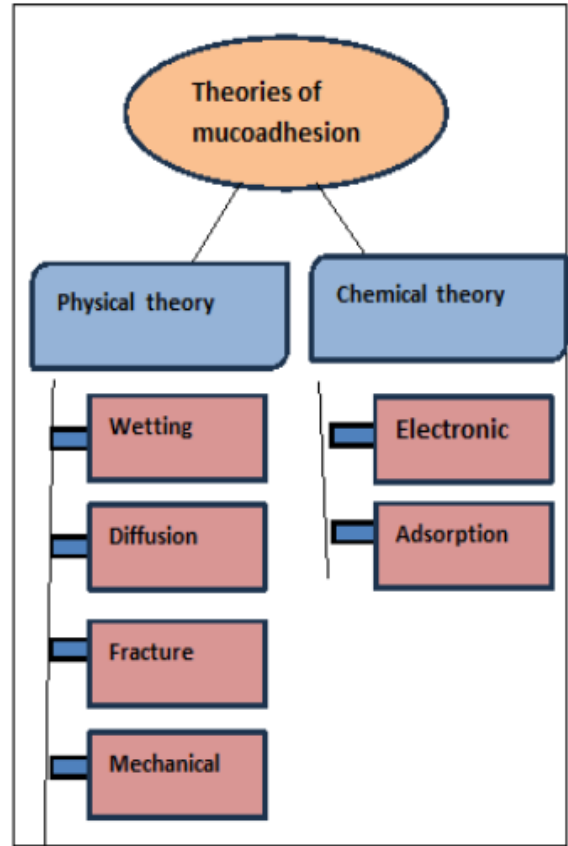


Fig.3 : Theories of mucoadhesion

1. Wetting Theory:

The wetting theory focuses on how well a liquid or semi-solid mucoadhesive can spread over the mucosal surface. If the formulation spreads easily (meaning it forms a small contact angle with the surface), it can stick better to the mucosa. In other words, better spreading leads to stronger adhesion.

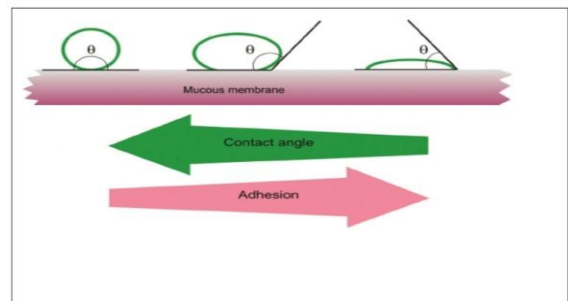


Fig.4: Diagram of wetting theory

2. Diffusion Theory:

The diffusion theory explains adhesion through the intermingling of polymer chains with the mucin in the mucus layer. When a mucoadhesive polymer touches the mucus, its chains move into the mucin network and get entangled, forming a stable, interconnected structure. This interlocking significantly improves the strength and durability of adhesion.

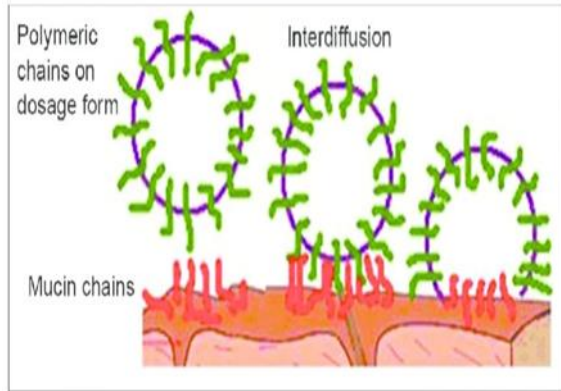


Fig.5: Diagram of Diffusion Theory

3. Mechanical Theory:

Adhesion happens when the adhesive penetrates tiny cracks and irregularities on a surface. Once it fills these spaces, it creates an interlocking network that holds the surfaces firmly together.

4. Electronic Theory:

This theory suggests that adhesion occurs because electrons are exchanged between the surfaces. This forms an electrical charge layer, generating attractive forces that help the surfaces cling to each other.

5. Adsorption Theory:

According to this idea, adhesion is driven by molecular forces, such as hydrogen bonding and Van der Waals forces, which naturally draw the surfaces together.

6. Cohesive Theory:

Here, adhesion is explained by the interactions among similar molecules within the adhesive itself, which helps it stick strongly and maintain its integrity on the surface

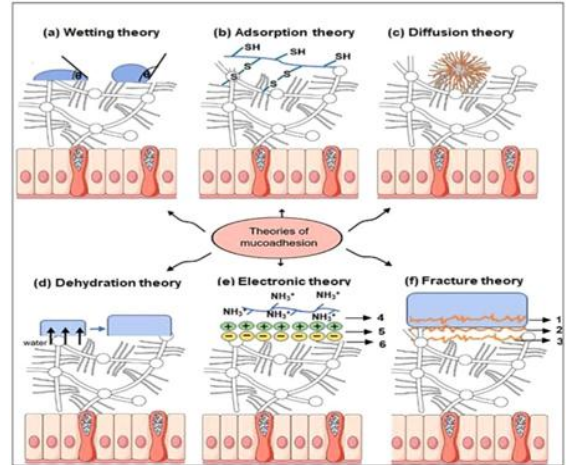


Fig.6 Theories of mucoadhesion

Characteristics of an Ideal Mucoadhesive Polymer

An ideal mucoadhesive polymer should be non-toxic and should not be absorbed from the gastrointestinal tract, so that it does not cause any systemic side effects after administration.

The polymer must be non-irritating to the mucosal membrane, as it remains in contact with mucosal tissues for an extended period. Irritation may cause discomfort or damage and reduce patient acceptability. It should be capable of forming strong non-covalent interactions, such as hydrogen bonds or electrostatic forces, with mucin and epithelial cell surfaces to ensure firm and prolonged adhesion.

The polymer should adhere quickly to mucosal tissues and preferably show site-specific adhesion, which helps in localized drug delivery and minimizes drug loss.

It should be compatible with the incorporated drug, allowing easy formulation without affecting the drug's stability, release, or therapeutic effectiveness.

The polymer must exhibit good chemical and physical stability during storage and throughout the shelf life of the dosage form.

Finally, the polymer should be economical, so that the developed mucoadhesive dosage form remains affordable and commercially feasible (Patil et al., 2006). [13,14]

Classification of mucoadhesion Polymers: [15,16,17]

Mucoadhesive polymers can be broadly classified on the basis of their origin and nature. This classification helps in selecting suitable polymers for different pharmaceutical drug delivery systems.

A Classification Based on Origin:

1. Synthetic Mucoadhesive Polymers –

Synthetic mucoadhesive polymers are man-made polymers produced by chemical processes. They are widely used in pharmaceutical formulations because of their consistent quality, good stability, and predictable performance. These polymers can be easily modified to achieve desired drug release and adhesion properties.

Common examples include cellulose derivatives such as:

- 1) Hydroxypropyl methylcellulose (HPMC)
- 2) Methyl cellulose
- 3) Poly acrylic acid polymers
- 4) Carbopol
- 5) Poly hydroxyethyl methacrylate
- 6) Polyethylene oxide
- 7) Polyvinyl pyrrolidone
- 8) Poly (vinyl alcohol).

These polymers show excellent swelling ability, film-forming properties, and strong adhesion to mucosal surfaces, making them suitable for controlled and sustained drug delivery systems, such as buccal tablets, gels, and ocular formulations.

2. Natural Mucoadhesive Polymers –

Natural mucoadhesive polymers are obtained from plant, animal, or microbial sources. They are generally preferred due to their biocompatibility, biodegradability, and low toxicity. Because of their natural origin, they are well accepted by the body and cause minimal irritation.

Examples of natural mucoadhesive polymers include:

- 1) Tragacanth
- 2) Sodium alginate
- 3) Karaya gum
- 4) Guar gum
- 5) Xanthan gum
- 6) Soluble starch
- 7) Gelatin
- 8) Pectin
- 9) Chitosan.

These polymers are widely used in oral, buccal, nasal, and ocular drug delivery systems because they provide good adhesion to mucus and improve drug retention at the site of application.

VI. A CLASSIFICATION BASED ON NATURE

1. Hydrophilic Polymers –

Hydrophilic polymers are water-soluble polymers that readily absorb moisture when they come in contact with biological fluids. Upon hydration, formulations containing these polymers swell and form a gel-like structure, which allows close contact with the mucosal surface and improves mucoadhesion.

Common examples include:

- 1) Poloxamers
- 2) Hydroxypropyl methylcellulose
- 3) Methylcellulose
- 4) Polyvinyl alcohol
- 5) Polyvinyl pyrrolidone

These polymers are frequently used in buccal films, oral gels, and ocular formulations, where swelling and hydration play an important role in maintaining prolonged contact with the mucosa.

2. Polyelectrolytes:

Polyelectrolytes are polymers that carry positive or negative charges along their polymer chains. Due to these charges, they interact strongly with the mucus layer through electrostatic attractions, resulting in better mucoadhesion compared to non-ionic polymers.

For example:

Chitosan (positively charged) interacts with the negatively charged mucin present in mucus, leading to enhanced adhesion and increased residence time. Such polymers are particularly useful in nasal, buccal, and gastrointestinal drug delivery systems, where prolonged retention improves drug absorption.

3. Polysaccharides and Their Derivatives

Polysaccharides and their derivatives are widely used mucoadhesive polymers because of their natural origin, safety, and excellent swelling properties. These polymers can increase viscosity and form strong interactions with the mucus layer.

Examples include:

- 1) Chitosan
- 2) Methylcellulose
- 3) Hyaluronic acid
- 4) Hydroxypropyl cellulose
- 5) Xanthan gum
- 6) Gellan gum
- 7) Guar gum
- 8) Carrageenan.

They are especially valuable in ocular mucoadhesive drug delivery systems, as they enhance precorneal residence time, reduce drug loss due to tear drainage, and improve therapeutic effectiveness.

4. Cellulose and Its Derivatives –

Cellulose and its derivatives are among the most commonly used mucoadhesive polymers in pharmaceutical formulations. They possess good film-forming ability and surface-active properties, which help in maintaining prolonged contact with mucosal tissues. In ocular drug delivery, cellulose derivatives with lower surface activity are preferred to reduce eye irritation. Sodium carboxymethyl cellulose (NaCMC) is widely used due to its excellent ocular mucoadhesive properties.

In addition, cationic cellulose derivatives such as cationic hydroxyethyl cellulose are often combined with anionic polymers to develop sustained-release drug delivery systems, ensuring prolonged drug action.

Novel mucoadhesive polymers:

Novel mucoadhesive polymers are newly developed materials made either by improving already existing mucoadhesive polymers or by creating completely new polymer systems with better properties. These polymers are designed to stick more effectively to mucosal surfaces, stay at the site of application for a longer period, and improve the overall effectiveness of drug delivery.

Lectins

Lectins are naturally found proteins that are important in recognizing and interacting with cells. They belong to a varied group of proteins or glycoproteins that can specifically and reversibly bind to sugars present on the surface of cells. After attaching to mucosal cells, lectins may either remain on the cell surface or enter

the cell through a receptor-mediated process called endocytosis. Because of this property, lectin-based drug delivery systems provide two major advantages. They help the drug attach specifically to certain mucosal cells and also allow controlled delivery of large drug molecules by actively transporting them into the cells.

At first, lectins bind loosely and temporarily to the mucus layer. This reversible binding helps the drug delivery system move closer to the epithelial cell layer, which improves drug absorption.

Based on their structure, lectins are divided into three types:

1. Merolectins – contain only one carbohydrate-binding site
2. Hololectins – have two or more carbohydrate-binding sites
3. Chimerolectins – contain carbohydrate-binding sites along with other functional domains

Lectins are known to increase the attachment of drug-loaded microparticles to intestinal epithelial cells and improve drug penetration. For example, polystyrene microparticles coated with tomato lectin show strong and specific binding to enterocytes. Lectins are also widely researched for targeted cancer drug delivery, as tumor cells bind lectins more strongly than normal cells.[18]

Thiolated Polymers (Thiomers)

Thiolated polymers, also known as thiomers, are a special type of multifunctional polymers formed by chemically modifying existing polymers by adding thiol (–SH) groups. These polymers are water-loving (hydrophilic) and contain free thiol groups along their polymer chains.

Thiomers can form strong bonds within the same chain and between different polymer chains, called disulfide bonds. These bonds greatly improve the strength, cohesiveness, and stability of drug delivery systems such as matrix tablets. Thiomers show very strong mucoadhesive properties because they can form covalent bonds with mucus glycoproteins through thiol–disulfide exchange and oxidation reactions. Some commonly used thiolated polymers include chitosan-iminothiolane, poly (acrylic acid)-cysteine, chitosan-thioglycolic acid, alginate-cysteine, and sodium Carboxymethylcellulose-cysteine.[19]

Bioadhesive Nanopolymers as Drug Carriers

Nano medicine involves the use of very small, nanometre-sized particles to diagnose and treat diseases at the molecular level. Mucoadhesive Nanopolymers are especially useful in improving the effectiveness of topical drugs, particularly in eye drug delivery systems.

These tiny particles get trapped in the mucus layer of the eye and interact with mucin through their bioadhesive polymer chains. This interaction helps the drug stay for a longer time on the corneal surface, which improves drug absorption and results in a better therapeutic effect.[20]

Alginate–Polyethylene Glycol Acrylate (Alginate-PEGAc)

Alginate-PEGAc is a new type of mucoadhesive polymer formed by chemically linking alginate with acrylated polyethylene glycol (PEG). This polymer combines the easy gel-forming nature of alginate with the strong mucoadhesive properties of PEG. Its strong adhesion to mucus occurs because PEG chains can easily penetrate into the mucus layer, and the acrylate groups of the polymer form chemical bonds with sulfide groups present in mucin. Due to these properties, alginate-PEGAc has been widely used in the development of multifunctional biomaterials for various biomedical and biotechnological applications.[21]

Poloxomers

Poloxamers are special block copolymers that respond to changes in temperature. They remain liquid at room temperature but change into a gel at body temperature. This allows the gel to form directly at the site of application. Because of this property, poloxomers show better adhesion to mucosal surfaces and help the drug stay longer at the target site, which improves the overall effectiveness of drug delivery.

Pluronics and Their Combinations

Pluronics have been chemically combined with poly(acrylic acid) to improve their ability to stick to mucosal surfaces and to help the drug remain longer in the nasal cavity. Additionally, dihydroxyphenylalanine (DOPA), an amino acid found in mussel adhesive proteins, has been added to pluronics to further increase their adhesive strength.

Other Novel Mucoadhesive Polymers

When ethyl hexyl acrylate is added to acrylic acid copolymers, the resulting polymers become more flexible and slightly water-repellent. This change slows down the rate at which the polymer absorbs water while still allowing good interaction with mucosal surfaces. As a result, these copolymers show stronger mucoadhesive properties compared to poly (acrylic acid) alone.

Similarly, glyceryl monooleate–water liquid crystalline systems have also shown good mucoadhesive behavior on different mucosal surfaces. However, their method of adhesion is different from that of traditional mucoadhesive polymers.[22]

Bacterial Adhesions

Some bacteria naturally attach to epithelial surfaces using structures called fimbriae, which are long, lectin-like protein projections present on the bacterial surface. For example, *Escherichia coli* attaches to intestinal epithelial cells through K99 fimbriae, and this attachment is an important step for toxin entry into the cells. This natural adhesion mechanism has been used in drug delivery systems to improve the attachment of bioadhesive microspheres to epithelial tissues. Another example is invasins, a membrane protein obtained from *Yersinia pseudotuberculosis*, which helps in enhancing the cellular uptake of polymeric nanospheres.

Amino Acid Sequences

Some specific amino acid sequences can naturally interact with matching regions on mucosal and cell surfaces. When these sequences are attached to drug-loaded microparticles, they help the particles bind more strongly to specific cell surface glycoproteins. Since these glycoproteins often change during disease conditions, this approach can be effectively used for targeted drug delivery to diseased tissues.

Antibodies

Antibodies can be developed to specifically recognize certain molecules present on mucosal surfaces. Because they have very high specificity and strong binding ability, antibodies are ideal for designing site-specific mucoadhesive drug delivery systems. This method is especially useful for targeting drugs directly to tumor tissues, helping improve treatment effectiveness while reducing unwanted effects.[24]

VII. FACTORS AFFECTING MUCOADHESION

Mucoadhesion depends on three major groups of factors:

1. polymer-related factors
2. environmental factors
3. physiological factors.

1. Polymer-Related Factors:

1. Molecular weight: The mucoadhesive ability of a polymer mainly depends on its molecular weight. Polymers having a molecular weight of 100,000 or above usually show better adhesion because their long chains can form stronger interactions with the mucus layer.

2. Polymer concentration: Maximum mucoadhesion occurs when the polymer is used at an optimum concentration. If the concentration becomes too high, polymer chains tend to coil and move away from the medium. As a result, fewer chains are available to interpenetrate with mucus, leading to reduced adhesive strength.

3. Flexibility of polymer chains: Flexible polymer chains can easily penetrate and entangle with the mucus layer, which improves adhesion. However, when water-soluble polymers are highly cross-linked, their mobility decreases. This reduced flexibility limits their penetration into mucus and lowers mucoadhesive strength.[25]

2. Environmental Factors:

1. Applied strength (pressure): Mucoadhesive strength increases when greater pressure is applied and when the contact is maintained for a longer time. Adequate pressure helps the polymer come into close contact with the mucus layer. In some cases, even polymers with weak natural affinity for mucin can show mucoadhesion if sufficient pressure is applied for enough time.

2. pH of the medium: The pH of the surrounding environment influences the electrical charges present on both the mucus surface and ionizable mucoadhesive polymers. Changes in pH affect the dissociation of functional groups in mucus and polymers, thereby altering their interaction. pH also

plays an important role in polymer hydration and swelling, which directly affects mucoadhesion.

3. Initial contact time: The duration of contact between the dosage form and the mucus layer is an important factor. A longer initial contact time allows the polymer to swell properly and enables deeper interpenetration of polymer chains into mucus, resulting in stronger mucoadhesion.

4. Swelling: Swelling of the polymer depends on factors such as polymer concentration, ionic strength, and availability of water. Controlled swelling improves adhesion by increasing surface contact. However, excessive swelling or over-hydration leads to the formation of a slippery gel, which reduces adhesive strength. [25,26]

3. Physiological Factors:

1. Mucin turnover: The mucus layer in our body is constantly being renewed. This natural replacement limits the time a mucoadhesive system can stay attached. Even polymers that stick strongly may eventually detach as the old mucus is shed and replaced by new mucus.

2. Disease state: The properties of mucus can change during various health conditions, such as the common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, or infections in the body. These changes can make mucus thicker, thinner, or alter its composition, which can affect how well a mucoadhesive system works.[27]

Evaluation of Mucoadhesive Dosage Forms: [28,29,30,31]

In vitro/ex vivo tests

Tensile strength

Shear stress

Fluorescent probe method

- Falling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Swelling properties
- Stability studies

In vivo methods

- Use of radio opaque markers
- Use of gamma scintigraphy
- Xray studies
- Isolated loop technique
- Use of electron paramagnetic resonance

The effectiveness of mucoadhesive dosage forms can be tested using in vitro (lab-based), ex vivo (using tissues), and in vivo (live organism) methods.

In Vitro / Ex Vivo Tests:

Tensile strength: This test measures the force needed to pull a mucoadhesive film away from a membrane of mucin.[28]

Shear stress: A stainless-steel rotating cylinder coated with freshly excised porcine intestinal mucosa is used. Polymer discs are attached to the mucosa, and the cylinder is rotated in a dissolution apparatus. Adhesion is measured by checking whether the discs stay attached at regular intervals.[29]

Fluorescent probe method: Components of the mucus membrane, like lipids and proteins, are labeled with fluorescent dyes. When mucoadhesive polymers are applied, changes in fluorescence indicate how well the polymer interacts with mucus.[30]

Swelling index: Swelling shows how much water the polymer absorbs and how much it expands. It is expressed as a percentage of weight gain:

$$\text{Swelling Index (S.I)} = \frac{W_t - W_o}{W_o}$$

Where,

S. I= Swelling index

W_t = Weight of tablet at time t

W_o= Weight of tablet before placing in the beaker [31]

Colloidal gold staining: Red colloidal gold particles attach to mucin molecules. When a bioadhesive hydrogel interacts with these mucin-gold complexes, a red color appears, showing adhesion.[33]

Viscometric method: The viscosity of a mucin solution is measured in the presence of polymers. Changes in viscosity indicate interaction between the polymer and mucus.[34]

Thumb method: Adhesiveness is assessed by how hard it is to pull the thumb away from the polymer, depending on the pressure applied and contact time.[33]

Adhesion number and stability studies: Adhesion can also be measured by repeated contact tests. Stability studies ensure that the formulation remains safe, effective, and stable throughout its shelf life.[33]

2.In Vivo Methods

Gamma scintigraphy: Gamma scintigraphy is a non-invasive imaging technique used to track the movement and behavior of mucoadhesive formulations in the gastrointestinal (GI) or respiratory tracts. In this method, the dosage form is radiolabeled using tracers like technetium-99m, indium-113m, or others. This allows researchers to study how the formulation spreads, deposits, moves, and clears in the body. For example, studies with radiolabeled HYAFF polymer tablets showed that dry powder formulations stayed longer in the stomach compared to pessaries. This demonstrates how gamma scintigraphy with animal models can effectively evaluate mucoadhesive retention. [35,36]

Gastrointestinal (GI) transit using radio-opaque markers: Mucoadhesive tablets can be labeled with barium sulfate or other radio-opaque markers to track their movement through the GI tract. X-ray imaging and feces collection are used to monitor the residence time of the tablet without affecting normal digestion. Similarly, radionuclides such as Cr-51, Tc-99m, In-113m, or I-123 are sometimes used to study tablet movement and retention in the digestive system, helping to evaluate the efficiency of mucoadhesive formulations.[33]

VIII. CONCLUSION

Mucoadhesive drug-delivery systems are a valuable and effective approach for improving the performance of pharmaceutical formulations. By attaching to the mucosal lining of the gastrointestinal tract and other mucous membranes, these systems help the dosage form stay at the site of absorption for a longer period. This prolonged contact allows better drug absorption, maintains a higher concentration of the drug at the target site, and leads to improved therapeutic results

while also reducing dosing frequency and unwanted side effects. Both natural and synthetic polymers play an essential role in the development of mucoadhesive systems. Among them, natural polymers are especially preferred due to their safety, biocompatibility, biodegradability, and minimal impact on the environment. A clear understanding of the mucoadhesion process, particularly the contact and consolidation stages, supports the rational design and optimization of effective mucoadhesive formulations. Modern evaluation methods, such as gamma scintigraphy, have significantly supported the advancement of mucoadhesive drug-delivery systems by allowing non-invasive monitoring of dosage-form movement and retention in the gastrointestinal tract. Overall, mucoadhesive drug-delivery systems provide an effective strategy for enhancing drug bioavailability, improving patient compliance, and achieving better therapeutic outcomes, making them an important focus in contemporary pharmaceutical research.

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