# The Principle of Mucoadhesion, Classifications of Mucoadhesive Polymers, Applications and Methods of Evaluation: A review Article

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**Abstract:**

Mucoadhesion is the attachment of two surfaces one of them is a mucous membrane while the other is a drug delivery system (DDS). In recent years, the pharmaceutical properties of mucoadhesion have aroused interest because mucoadhesion may be a solution for bioavailability difficulties and problems caused by the pharmaceutical dosage form remaining at its absorption site for an unacceptably short amount of time. It's been a significant problem for pharmaceutical scientists to enhance localized medication delivery or to introduce 'difficult' molecules (proteins and oligonucleotides) into the blood stream. Mucoadhesive methods maintain intimate connection with mucous membrane which is the absorption site, allowing medication to be delivered at the site of action, increasing local and systemic bioavailability. Spreading the residence duration of the dosage form at a specific location and regulating drug release from a dosage form are also beneficial for attaining a regulated plasma level of the medication and improving bioavailability. The current review study discusses Mucoadhesion, Mucoadhesive polymers and their application in the design of various natures of Mucoadhesive drug delivery systems (DDS).

**Key words:** Mucoadhesion**,** mucous membrane**,** Mucoadhesive polymers.

## مبدأ الالتصاق المخاطي, تصانيف البوليمرات الملتصقة بالاغشية المخاطية, تطبيقاتها و طرق تقيمها: مقالة مراجعة

**الخلاصة:**

يحدث الالتصاق المخاطي بين سطحين ، أحدهما عبارة عن غشاء مخاطي والآخر عبارة عن نظام توصيل الدواء. أثارت الجوانب الصيدلانية للالتصاق المخاطي اهتمامًا في السنوات الحالية لأن الالتصاق المخاطي قد يكون حلاً لمشكلات التوافر البيولوجي والمشاكل التي تنتج عن فترة بقاء قصيرة جدًا لشكل الجرعة الصيدلانية في موقع الامتصاص. لقد كان تحديًا كبيرًا لعلماء الأدوية من أجل تحسين توصيل الأدوية الموضعية أو توصيل الجزيئات "الصعبة" (البروتينات وأوليغونوكليوتيدات) في الدورة الدموية الجهازية. تظل أنظمة اللصق المخاطي على اتصال وثيق بنسيج الامتصاص ، الغشاء المخاطي ، مما يسمح بإطلاق الدواء في موقع التأثير مما يؤدي إلى زيادة التوافر البيولوجي (التأثيرات الموضعية والعامة). كما أن تمديد فترة بقاء الجرعات في موقع معين والتحكم في إطلاق الدواء من الجرعات مفيد أيضًا في تحقيق مستوى البلازما متحكم به بالإضافة إلى تعزيز

التوافر البيولوجي. تصف المراجعة الحالية الالتصاق المخاطي والبوليمرات اللاصقة للمخاط واستخدام هذه البوليمرات في تصميم أنواع مختلفة من أنظمة توصيل الدواء الملتصق مخاطيا.

**الكلمات المفتاحية**: الالتصاق المخاطي، الغشاء المخاطي ، البوليمرات الملتصقة بللأغشية المخاطية.

## Introduction

The adhesive phenomenon has been investigated in many domains and is described as the long-term binding of two materials when they come into touch with each other [1]. If one of the components (at least) that participated in the adhesive phenomenon is from biologic origin, it is known as bio adhesion, and when the biologic substance is a mucous surface, it is known as Mucoadhesion [2].The intensity as well as the nature for interfacial forces participated in development plus maintenance of Mucoadhesion have been the subject of much research for as a minimum in the last three decades. Specifically, the importance of the delivery system for Mucoadhesive drug could be converted for enhancement of the bioavailability of drugs, conservation of molecules that are unstable besides the capability for extended release of drugs production, each in direct or indirect manner associated to the increasing of the in-situ residence plus near interaction with mucosal lining tissues [3].As a result of the current surge in nanotechnology and Nano DDS with the expansion of suitable Nano tools, novel methods and concerns in the area of Mucoadhesion have been emerged.In this study, several polymers that have recently been utilized to design and develop drug delivery systems are reviewed, with a focus on the mechanism of Mucoadhesion exerted by each polymer[4].

## Mucous membranes

Mucous membranes (mucosae) are the moistened surfaces that line various walls of body cavities such as the respiratory tract and gastrointestinal tract [5]. The existence of an adhering sheet (mucous) which is extremely hydrated fluid that perform as a protectant film for fundamental tissues is one of the most typical aspects of mucosal surfaces. Variations in the histochemistry (for example the existence plus spreading of carbohydrate remains) or morphology (for example surface irregularity and folding) of mucosal faces for various areas in the body, also may affect polymer Mucoadhesion [6]. Furthermore, the temperature at these areas changes quite a little. Mucus can be thought of as the first line of defense against medication absorption, but it can also be thought to be one of the targeted site for drug delivery system since extended holding possibly will lead to increase the payloads for reaching the fundamental tissues under the mucosal membrane. The mucus is formed by mucosal cells which constantly released to the lumen of the cavities it coats before being lost or digested. The mucus consists mostly from water (90% or higher) plus mucins (more than 5 %), which are glycoproteins give the viscoelastic gel-like structure of this fluid, though additional constituents like electrolytes, proteins, lipids, enzymes,

immunoglobulins, nucleic acids, plus cells or may be cell remains are likewise visible [6].

**Theories of Mucoadhesion**

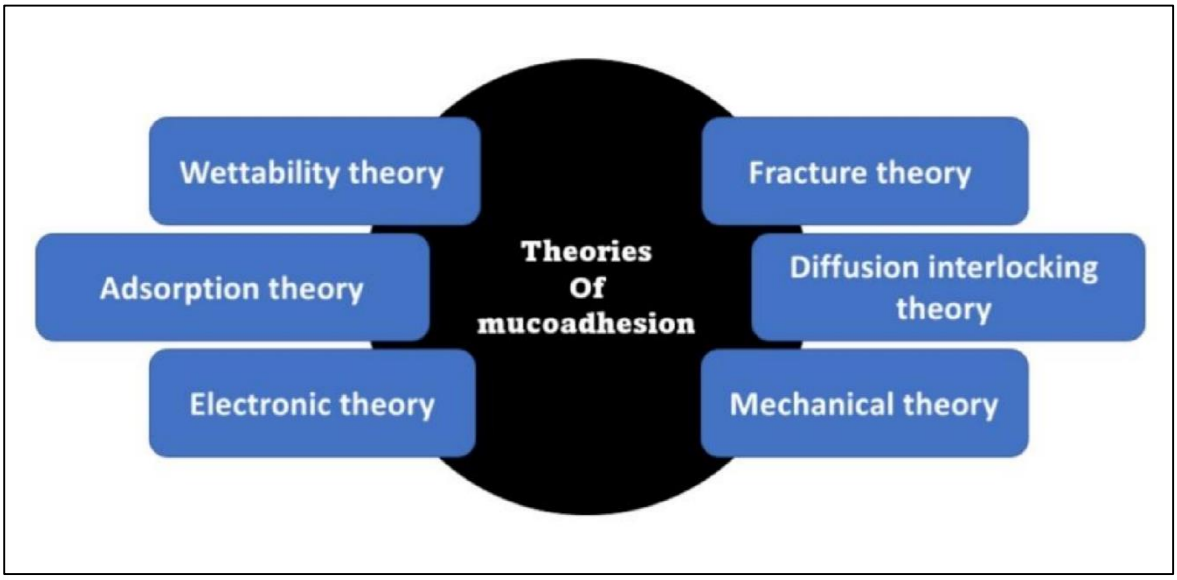


Figure1. Theories of Mucoadhesion

**a- Theory of wettability**

The wetting idea is most commonly used to Mucoadhesive systems that are liquid or have a low viscosity. This theory defines a Mucoadhesive polymer's ability to spread across biological surfaces, and therefore accounts for an active drug delivery system's spread ability. When the adhesive component gets into touch with the mucosa, it penetrates surface deformations, hardens, and adheres to the surfaces due to changes in surface and interfacial energy [7].

**b- Theory of adsorption**

For adhesive interactions, two types of chemical bonds have been established based on the adsorption hypothesis: hydrogen bonds and van der Waals' forces. After an initial contact, the Mucoadhesive material attaches to the inter-surfaces due to surface forces acting between the molecules of the two surfaces. According to the chemisorption theory, interaction across the contact occurs as a result of strong covalent bonding [7].

**c- Theory of electronic structure**

Surfaces with a variety of structural and electrical properties have a variety of electronic structures. Bonding occurs as a result of electron transfer between the polymeric system and the mucus membrane epithelium. As a result, a bi-layer of electrical charges is generated at the mucus and Mucoadhesive system contact.Finally, electrical double layer is in charge of creating an attractive force between the two surfaces [8].

**d- Fracture theory**

According to this hypothesis, the force required to separate two surfaces is proportional to the power of the adhesive connection. The force required to remove polymers from mucus is proportional to the sticky bonding strength of the polymers. As the polymer network strands lengthen or the degree of cross-linking within the system diminishes, the work fracture rises. [9].

**e- Diffusion interlocking theory**

According to this idea, mucoadhesive polymer chains permeate into the mucus layer's glycoprotein chain network in time-dependent manner.In this two-way diffusion process, the diffusion coefficients of both interacting polymers dictate the penetration rate. [10].

**f- The mechanical theory**

By this theory, adhesion occurs when a Mucoadhesive liquid fills defects in a rough surface. Moreover, such irregularity increases in the accessible interfacial area of interactions and may be regarded the most essential feature [11].

**Factors affecting Mucoadhesion**

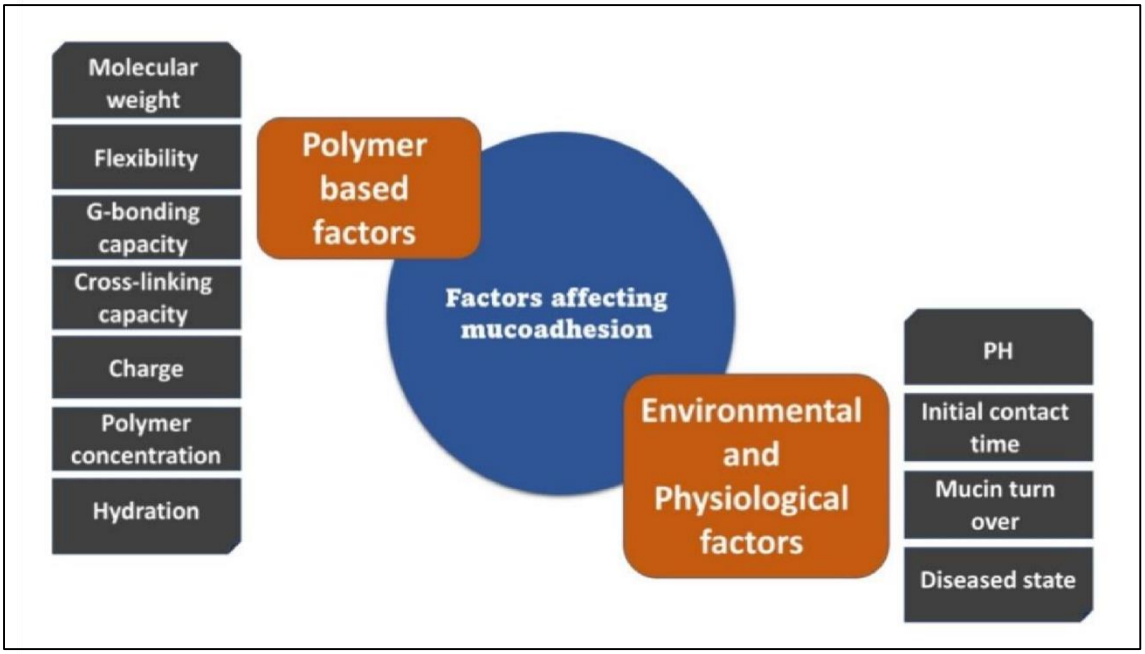


Figure 2. Factors affecting Mucoadhesion

A- Polymer based factors

1- Molecular weight: Several studies have shown that the ideal molecular weight for better bio-adhesion is dependent on the type of bio adhesive polymer used [12].

2- Flexibility: When polymer chains diffuse into the interfacial region, bio-adhesion occurs. To obtain the desired interaction with a mucous membrane, the polymer must have suitable flexibility [13].

3- Hydrogen bonding capacity: it has been established that excellent hydrogen bonding is essential for Mucoadhesion, and polymer flexibility is important for improving this capacity [14].

4- Cross-linking capacity: increasing the density of cross-linking lowers water transport into the polymer network, resulting in inadequate polymer swelling and, as a result, a drop in the rate of interpenetration

between the polymer and mucin, resulting in a decrease in Mucoadhesion [15].

5- Charge: When compared to anionic polymers, nonionic polymers have a lower degree of adhesion. Furthermore, some cationic polymers, such as chitosan, exhibit superior adherence, particularly in slightly alkaline or neutral environments [16].

6- Polymer concentration: a low concentration of polymer may result in an unstable contact between polymer and mucin; in general, a more concentrated polymer will result in longer penetration chain length and improved Mucoadhesion [17].

7- Hydration or swelling: polymer swelling is governed by the ionic strength, polymer concentration, and cross-linking density, plus the existence of water. Over hydration leads to wet slippery mucilage formation that prevent adhesion [18].

B-Environmental and physiological factors

8- pH: the site of administration pH affects the charge on the mucus surface besides some ionizable polymers. The degree of hydration of various polymers (e.g. polyacrylic acid) is affected by the pH of the medium [19].

9- Initial contact time: the swelling extent interpenetration of polymer chains is determined by the contact time of bio adhesive polymer and mucus layer. Furthermore, when the initial contact time increases, the bio adhesive's strength increases [20].

10- Mucin turn over: the duration of the bio adhesive's presence at the administration site is determined by the polymer's solubility in water and the rate of mucin turnover [21].

11- Diseased state: Mucus secretion from the mucus membrane is reduced in several disease states (e.g., Dry Mouth Syndrome). As a result, the amount of mucus available at the attachment point is insufficient to interact with the bio adhesive polymer [22].

**Advantages of Mucoadhesion**

- ✓ Mucoadhesive dosage forms give various advantages over other oral dosage forms and oral controlled release systems by prolonging the drug's residence time in the gastrointestinal tract or other mucous membranes [23].

- ✓ Targeting and localization of the dosage form at a certain site [24].
- ✓ Provide close contact between dosage form and the site of application or absorption [25].
- ✓ Drug compounds that are not suitable to oral administration, such as those that go through a lot of first-pass metabolism or acid degradation, may benefit from the application of dosage forms to mucosal surfaces [26].
- ✓ It has the ability to deliver controlled drug release (preferably unidirectional release) [27].

**Disadvantages of Mucoadhesion**

- ❖ Oral Mucoadhesive dosage forms containing ulcerative or irritating medications may cause local ulcerous effects due to prolonged contact.
- ❖ It is not ideal for high doses, and choking can occur if buccal patches or films are swallowed involuntarily.

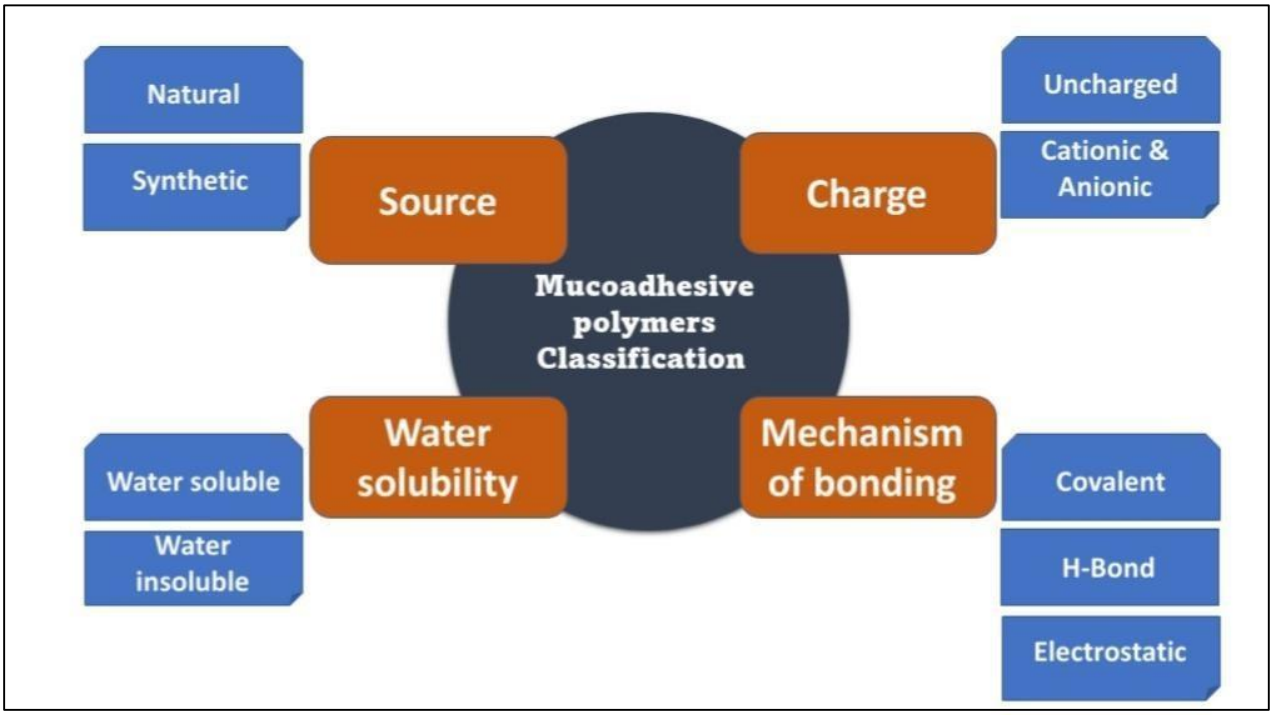


Figure 3 . An overview of Mucoadhesive polymers classification

**Mucoadhesive polymers**

A polymer is a lengthy molecule composed of structural and repeating units linked together via covalent connections. Polys, which means "many," and meros, which means "parts," are the Greek words that inspired the name [28]. A polymer is a substance made up of many small molecules called monomers linked together. Mucoadhesive polymers are swell able networks of water soluble plus water insoluble polymers joined by cross-linking agents. These polymers contain the proper polarity balance to allow for optimal mucous wetting, as well as the proper fluidity balance to allow for mutual adsorption plus interpenetration of mucous and polymer [29].

Table 1: Source-based classification of polymers

| **Natural polymers** | **Synthetic polymers** |
|---|---|
| Agarose | Poly meth acrylic acid |
| Chitosan | Cabopol |
| Gelatin | Polycarbophil |
| Hyaluronic acid | Poly acrylic acid |
| Pectin | PEG |
| Na alginate | Poly methacrylate |
| Carrageenan | |
| | **Others** |
| **Cellulose derivatives** | Poly Hydroxy ethylene |
| CMC | Polyvinyl alcohol (PVA) |
| Na CMC | PVP |
| Hydroxy ethyl Cellulose | |
| Hydroxy propyl Cellulose | |
| Methyl Cellulose | |

Table2: Polymer grouping by their water solubility

| **Water soluble** | **Water insoluble** |
|---|---|
| **Cellulose derivatives** | Poly meth acrylic acid |
| CMC | polycarbophil |
| Sodium CMC | Poly acrylic acid |
| Hydroxy ethyl Cellulose | Carbopol |
| HPC | PEG |
| MC (methyl cellulose) | Poly methacrylate |
| | Meth acrylic acid |
| **Others** | Ethyl hexyl acrylate |
| Polyhydroxy ethylene | |
| Polyvinyl alcohol (PVA) | |
| Polyvinyl pyrrolidine | |
| Thiolated Polymers | |

Table 3: Polymer classification by charges

| **Cataionic(+) polymers** | **Anionic(-) polymers** | **Nonionic** |
|---|---|---|
| Chitosan | CMC | Hydroxyethyl starch |
| Amino dextran | Carbopols | Hydroxypropyl Cellulose |
| | Polyacrylate | Polyethylene glycol |
| | Pectin | PVA |
| | | PVP |

Table4: Polymer grouping by bioadhesive forces

| **Covalent bond** | **Electrostatic Interaction** | **Hydrogen bonds** |
|---|---|---|
| Cyanoacrylate | Chitosan | Carbopol<br>Polycarbophiles<br>Acrylates<br>Poly vinyl alcohol |

**Permeation enhancers**

Permeation enhancers are chemicals that help medicines move through the mucosa more easily. Membrane penetration is a stumbling block in the development of Mucoadhesive drug delivery systems for a variety of medicines. The mucosal epithelium, particularly the buccal mucosa, is an extremely efficient barrier to medication absorption. Because of structural and functional differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition, and potential protein interactions, enhancer efficacy differs from one site to another [30]. They must be safe, nontoxic, nonirritant, non-allergic, chemically pharmacologically inactive [31]. Table 5: List of permeation enhancers [32].

| | |
|---|---|
| **Chelators** | Sodium salicylate, EDTA, Citric acid |
| **Surface active agents (SAA)** | Polyethylene, Polyethylene-9-lauryl ether<br>Polyethylene-20-cetyl ether, Benzalkonium-bromide |
| **Bile salts** | Na glycocholate, Na deoxycholate, Na taurocholate |
| **Fatty acids(FA)** | Oleic acid, capric acid, lauric acid, methyl oleate |
| **Non-surfactants** | Unsaturated cyclic ureas |
| **Inclusion-complexes** | B-Cyclodextrins |
| **Thilated polymers** | Chitosan cysteine plus chitosan-4-thiobutyl amide |
| **Others** | Aprotinin, azone, menthol,plus Sulfoxides |

Features of a perfect Mucoadhesive polymer

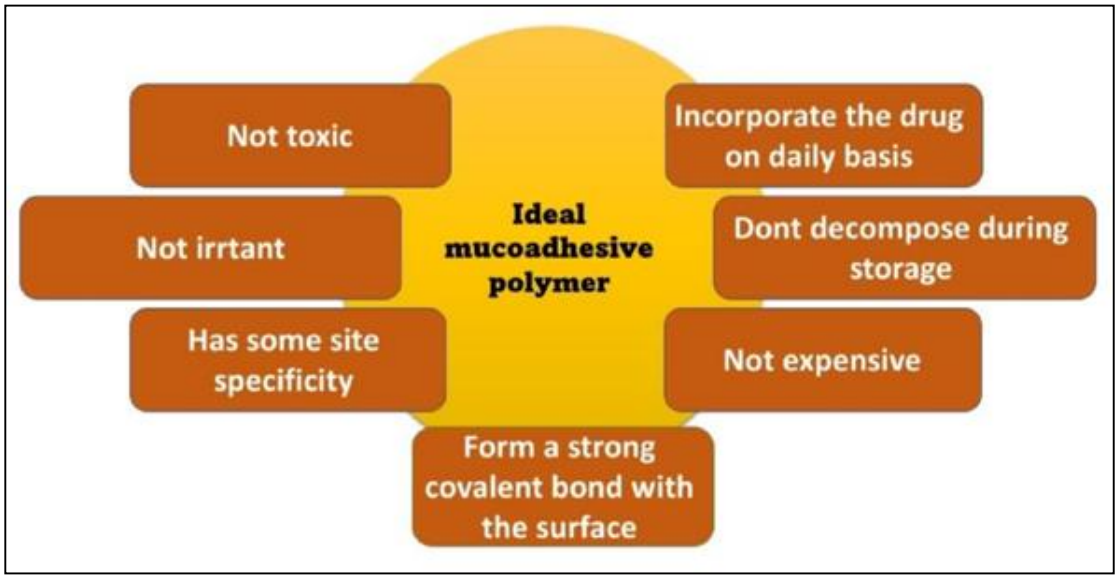


Figure 4: characteristics of ideal polymer

Ideal polymer should be:

- Neither the polymer nor its breakdown products should be harmful or absorbable through the gastrointestinal system.
- It must not irritate the mucous membranes.
- It should create a strong non covalent connection with the surfaces of mucinepithelial cells as much as possible.
- It should attach to most tissues fast and have some site-specificity.
- It should be able to integrate the medicine on a regular basis without interfering with the release of the drug.
- It should not disintegrate during storage.
- Not highly expensive.

**The polymer's molecular properties**

• Hydrogen bonding groups that are extremely strong

• High negative charges

• Flexible enough to enter the mucus system or tissue fissures.

• Surface tension(ST) features appropriate to wet the surface of mucosal tissue

• It has a large molecular weight.

**Mucoadhesion Applications**

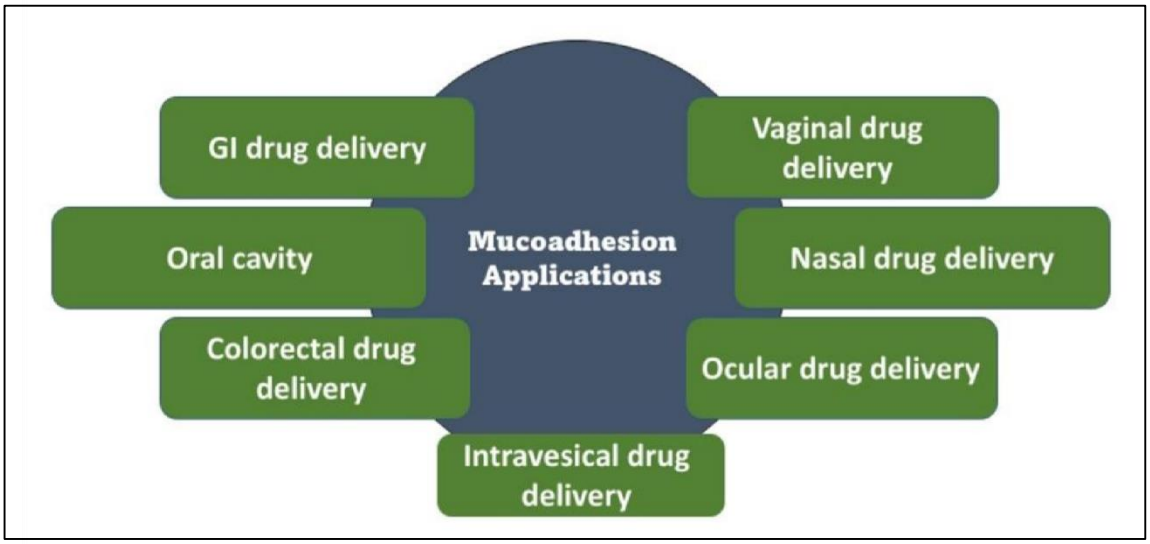


Figure 5: Mucoadhesion Applications

**A- Gastro-intestinal delivery**

The most widely used and well-accepted route of delivery of drug is oral administration. Furthermore, the gastrointestinal tract (GI) has a highly absorbent surface which has both local and systemic effects [33].

**B- In the oral cavity**

A mucous membrane covers the inside surface of the mouth cavity. Saliva secretion hydrates the mucus membrane and causes the enamel pellicle to form on the teeth, making it necessary for optimum dental health [34].

**C- Colorectal**

Subsequent to oral or rectal administration (e.g., suppository, enemas), colonic mucosa might be regarded an excellent location for drug delivery.

For example, because the colonic mucosa usually contains fewer digestive enzymes than the mucosa of the stomach or small intestine, it has less proteolytic activity [35].

**D- Vaginal drug delivery**

A mucous membrane covers the surface of the vaginal tract.

The mucin layer is made up of two kinds of mucins: cell-associated as well as secreted mucin, with the latter forming the outer layer. The mucin generated has a high turnover rate and has the ability to hold foreign particles, which are subsequently quickly removed. The vaginal tract can be utilized for both systemic and local medication administration, with local drug delivery being of particular relevance in treating fungal, bacterial, or viral diseases [36].

**E- Nasal drug delivery**

For transmucosal drug delivery, the nasal route has become a popular choice, especially for protein/peptide medications.The nasal mucosa is made up of epithelial cells with a lot of blood vessels, which allows for direct drug absorption into the systemic circulation via passive diffusion and a fast onset of pharmacological activity [37].

**F- Ocular drug delivery**

Drug administration to the eye is difficult due to physiological and anatomical limitations. One of them is overcoming physical and metabolic limitations. Tear production and blinking, and also the conjunctival lining, sclera and corneal connective tissue barriers, and blood retinal barriers, all constitute structural barriers on the retina's periphery [38].

**G- Intra-vesical drug delivery**

The bladder is a hollow structure with many tissue layers. The layers that go from the luminal to the external surface are urothelial, detrusor muscle, and adventitia. The mucin layer's principal function might be more like an antimicrobial adhesion function than a barrier function. The mucin sheet might potentially play a role in stone formation and particle attachment to the urothelial [39].

**Evaluation of Mucoadhesive properties of Nano particulate systems**

**Indirect methods**

1- Mucin-particle technique

One of the earliest approaches reported to analyze Nano particle-mucin engagement relied on determining the quantity of nanoparticle or mucin which interacts with each other when disseminated in aqueous conditions.

One drawback of this technique is that the interaction between Nano particulates and larger amounts of mucin more than seen *in-vivo* might have a significant influence on Mucoadhesive function. [40].

2- Micro gravimetric methods

To determine Mucoadhesion of nanoparticles, the quantity of material adsorbed on mucin was quantified using a quartz crystal micro-balance.

This approach is based on the resonant frequencies of a quartz crystal changing as the mass of the crystal modifications. This powerful technique enables dynamic investigation in a liquid medium, offering important kinetic information regarding the Mucoadhesion process in Nano systems [41].

3- Atomic force microscopy(AFM)

AFM is a strong technology used to investigate the topography of diverse materials. The concept is straightforward: a probe scans a sample's surface at close range, detecting attraction and repulsion forces between molecules. Ultimate output of this process is usually three dimensional surface picture [42].

4-Optical techniques

These methods are based on how incident light changes on a surface immobilized substrate when it binds to the analytic (typically, a mucin film and nanoparticles are used in this situation.).

Svensson et al., work based on the Mucoadhesive contact between several Nano systems, for example chitosan-modified units (cubosomes) and mucin coated planes was evaluated using ellipsometry.

Surface plasmon resonance is another optical approach that has been employed successfully. [43].

5- Methods for tracking diffusion/particles

Diffusion measuring techniques of many sorts were used to determine the movement of various kinds of particles plus their interactions through biological aquatic system constituents (e.g., cell cytoplasm).When using genuine mucus or a mucin-containing simulant, the hindrance to the unimpeded diffusive motions of Nano systems can be used to infer Mucoadhesion. Real-time optical tracking techniques, particularly multiple particle tracking(MPT), were widely utilized for studying the inter action of various Nano systems with mucus/mucus mimicking fluids [44].

**Direct methods**

1-Cytoadhesion methods

In these investigations, the use of monolayers of the epithelial cell from investigated mucosa is common. These methods usually focus on cyto-adhesion and are conducted by protecting fluorescently tagged Nano particles with cells in culture and then assessing the rating of adherence utilizing fluorescent microscopy. [45].

2-*Ex-vivo* methods

For a long time, these approaches have been utilized to evaluate the Mucoadhesive properties of nanoparticles. Typically, studies are carried out using radiolabeled or fluorescently labeled nanoparticles, besides the retaining in mucosal tissue explants is investigated using constant or discontinuous wash by solutions (aqueous), which mimics physiological washing processes *in vivo* to some extent [46].

3- Administration in *vivo/ex vivo* analysis

These techniques entail giving Nano particulate systems to alive animals and assessing Mucoadhesion after sacrifice. Fluorescent or radioisotope-labeled Nano systems are either delivered directly to the specified mucosal tissue (e.g., in the vaginal or oral canals) or indirect in most situations (for example inhaled pulmonary delivered drugs or ingested by mouth for gastrointestinal delivery through mucosa). A number of methods may be utilized depending on the category of label used to track the Nano systems as well as mucosa processing. For example, after oral administration of fluorescently-labeled Nano systems to rodents, confocal microscopy of mucosal pieces or a fluorometric analyze next to fluorescent dye withdrawal from tissue have been used successfully to quantify the retaining of fluorescently labeled Nano systems in GIT including stomach and intestine [47].

4-*In-vivo* imaging

These approaches are the most appropriate in terms of real-world application of medication dose forms and delivery systems. In vivo imaging methods, when used with appropriately tagged nanoparticles, allow for the tracking of natural nanoparticle mobility with little interference. Ramteke et al., for example, used X-ray imaging and barium sulfate as a contrast agent to investigate the stomach retention of gliadin-based nanoparticles [48].

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