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Review Article

Advances in Mucoadhesive drug Delivery System: Enhancing Efficacy and Patient Compliance

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Abstract

The goal of mucoadhesive drug delivery systems (MDDS) is to improve drug delivery effectiveness by adhering to the body's mucosal tissues. The material used in this approach adheres to mucosal surfaces, including those in the mouth, gastrointestinal system, nasal passages, and vaginal walls. The most important goal is to extend the medication's residence duration at the absorption site in order to improve drug absorption and provide a more regulated and prolonged release. Mucoadhesion refers to the adhesion between two materials, one of which is biological, through interfacial forces over an extended period. This characteristic provides an effective solution to challenges in traditional drug delivery systems, such as avoiding first-pass metabolism and facilitating localized delivery of biomolecules, including proteins, peptides, and oligonucleotides. It holds significant promise for delivering compounds via routes like ocular, nasal, vaginal, and buccal administration This study addresses the introduction, benefits, drawbacks, mechanisms, and theories of mucoadhesion in addition to polymer categorization, mucoadhesive dosage forms, assessment, and factors affecting mucoadhesion and several kinds of mucoadhesive dosage forms.

Keywords: Mucoadhesion, Theories, Mucoadhesive Dosage Form, bio adhesion

1. Introduction:

A Mucoadhesive Drug Delivery System (MDDS) is a drug delivery method that employs mucoadhesive polymers that adhere to the mucus layer of the body's mucosal surfaces. This helps to extend the period that the medicine remains at the place of application, which may increase medication absorption and stability.[1] Bio adhesion is the phenomena that occurs when two materials, at least one of which is biological in nature, are kept together by interfacial forces for an extended length of time. When the sticky polymer comes into contact with the mucous membrane, the process is known as mucoadhesion. The accompanying delivery technique is known as a Mucoadhesive Drug Delivery method.[2] Mucoadhesive Drug Delivery System binds with the mucus layer that covers the mucous epithelium surface, and the mucin molecule enhances the dosage form's residence frequency at the site of absorption.[3]

Table 1: Components and Functions of the Mucoadhesive System

Term	Description
Mucoadhesive	A substance that tends to adhere to the mucosal surface.
Mucosa	The inner epithelial cell lining, covered with viscoelastic fluid.
Viscoelastic Fluid	A fluid covering the mucosa, secreted by goblet cells.
Composition of Fluid	Composed of water, mucin, proteins, lipids, mucopolysaccharides, and electrolytes.
Goblet Cells	Cells responsible for secreting the viscoelastic fluid.
Mucoadhesion	When a substance adheres to the biological mucosal layer.
Role of Mucosa	Provides protection and lubrication to the mucosal surface

Mucoadhesive Drug Delivery System is a category of Controlled Drug Delivery Systems. In which dosage forms may be developed to provide for raised retention at the site of purpose, resulting in a regulated rate of drug release and superior therapeutic effects. A mucoadhesive drug delivery system (MDDS) is a sophisticated technique for delivering medications to the target place of residence. In MDDS, the mucus membrane and polymer type are important factors in the mucoadhesion phenomenon.[5] Mucoadhesive drug delivery systems extend the dosage form's residence duration at the site where it is applied or absorbed. They make it easier for the dosage form to make contact with the underlying absorption surface, improving the drug's therapeutic effectiveness.[6] many mucoadhesive drug delivery methods have been created in recent years for both systemic and localized effects via oral, buccal, nasal, rectal, and vaginal rout Mucoadhesive systems have focused on a wide range of features.[7] It is a growing field with the purpose of creating novel devices and "intelligent" polymers, as well as developing new approaches to better understand the mucoadhesion phenomena.[1] With the right technology, delivery strategies, and polymer selection, the oral mucosa might be used future generations to treat a wide range of disorders, both mucosal and systemic, and the number of medications that can be administered via the mucosa could be significantly enhanced.[8] The mucoadhesion concept has sparked a lot of interest in the pharmaceutical sector and is being utilized successfully as a management strategy. Mucoadhesive drug carrier elements may be delivered by a variety of routes.

1. Oral drug delivery system
2. Nasal drug delivery system
3. Ophthalmic drug delivery system
4. Vaginal drug delivery system
5. Buccal and sublingual drug delivery system.[9]

The oral mucosa has many properties which make it an attractive site for drug delivery but also provides several challenges for researchers investigating novel delivery techniques to overcome many different formulations including sprays, tablets, mouthwashes, gels, pastes and patches are presently used for delivery into and/or across the oral mucosa.[10] The use of various mucoadhesive polymers, such as chitosan and lectins, are utilized to increase the efficacy of drug delivery systems on mucus membranes. Mucoadhesive formulations may be administered by oral, digestive tract, nasal, ophthalmic, genital, or rectal routes. Some pharmaceutical dosage forms, such as films, gels, and creams and lotions, are used to transfer drugs across the mucosa.[11] Films are employed for this type of distribution since the perfect film is flexible, elastic, and soft. Given their nature, they may readily distribute medications without breaking owing to stress from mouth actions.[12] Gels and ointments, on the other hand, have an advantage over films, since they may be readily spreads throughout the mucosa for drug administration. Gels have the benefit of being able to make excellent contact with mucous membranes and quickly release medicines at the site of absorption. Creams, ointments, and gels may be used to administer drugs via the rectal and genital routes.[13] in this study, we will provide a quick overview of mucoadhesive drug delivery systems and their numerous benefits, which offer a lot of assurance for different dosage forms. This novel approach has been explored to provide prolonged drug delivery via the ophthalmic, buccal, gastrointestinal, vaginal and nasal routes.[14] The use of bio adheres has currently received a lot of interest in the field of soft tissue-based mucosal administration, and numerous formulations are currently commercially available or in development. Such technologies significantly enhance dosage form residence duration while also improving tissue intimacy, allowing the medication to be localized in a particular location. As a result, bio adhesion has the capacity to keep the dose form on the oral mucosa for a specific period of time.[15] The word "targeted drug delivery system" refers to a way of delivering a therapeutic dosage of pharmaceuticals to a particular location in the body in order to obtain the needed concentration of medicine.[16] A pharmaceutical may be focused toward an area of interest for a variety of reasons, including an unstable condition, a weak solubility, a short half-life, a large volume of dispersion, poor absorption, poor specificity, and a therapeutic index. The benefits of aimed drug delivery include raising the drug's therapeutic potency, limiting drug degradation, minimizing unwanted effects, and lowering the drug's unsafe dose.[17]

2. Advantages[18]

Prolongs the residence time of the dosage form at the site of absorption hence increase the bioavailability.

1. Quick beginning of action.
2. Reduced frequency of doses.
3. The drug resists breakdown in the acidic environment of the gastrointestinal tract.
4. Improved compliance by patients.
5. Compared to other non-oral methods, it has great patient acceptance.
6. Dosage forms are easier to apply and less unpleasant than injections, leading to higher patient compliance.
7. The mucosal membranes are highly vascularized, allowing for simple administration and removal of dose forms.
8. Side effects from oral delivery, such nausea and vomiting, may be fully avoided.
9. Mucoadhesive drug delivery is suitable for unconscious or uncooperative patients.
10. Mucoadhesive delivery devices may improve the bioavailability of drugs that are not well absorbed orally.
11. Targeting and localizing the dosage form to a certain place
12. High drug flow in absorbing tissues.
13. It demonstrates outstanding accessibility.

14. It demonstrates painless application.
15. It has minimal enzymatic activity and prevents first-pass metabolism.
16. Rapid absorption due to ample blood supply and high flow rates.
17. Enhance medication bioavailability by avoiding first pass metabolism.
18. The acidic environment of the gastrointestinal tract protects the drug from breakdown.
19. Mucosal surface provides quicker beginning of effect.

3. Disadvantages[19]

1. Evaluate patient acceptance for taste, irritancy, and mouth feel.

2. Topical ulcers may occur after prolonged exposure with a medication with ulcerogenic properties.

3. The absence of an appropriate in vitro screening model for oral mucosal distribution is a significant restriction in its development.

4. Food and beverage consumption may be restricted.

4. Mucous Membrane

Mucous membranes (mucosae) are the moist areas that line the walls of many bodily cavities, including the gastro-intestinal and respiratory tracts. They are made up of a layer of connective tissue (the lamina propria) and an epithelial layer, with the top section generally wet owing to the presence of a mucus layer.[20] Epithelia may be single-layered (as in the stomach, small and large intestines, and bronchi) or multilayered/stratified (such as in the esophagus, vagina, and cornea).[21]

The former contain goblet cells which secrete mucus directly onto the epithelial surfaces, the latter contain, or are adjacent to tissues containing, and specialized glands such as salivary glands that secrete mucus onto the epithelial surface.[22] Mucus appears as either a gel layer adhering to the mucosal surface or as a soluble or suspended luminal substance. The primary components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter comprising more than 95% of it weights, making it a highly hydrated system.[23] The mucin glycoproteins are the most significant structure-forming constituent of the mucus gel, sending it its distinct gel-like, cohesive, and sticky qualities. The thickness of the mucus layer varies across mucosal surfaces, from 50 to 450 µm in the stomach to less than 1 µm in the mouth cavity. Mucus has two key functions, protection and lubrication.[24] Mucus membranes are ectodermal linings. It comprises an epithelial layer and an underlying lamina propria of loose connective tissue. Cavity linings that are exposed to both the external environment and the interior organs. The mucus membrane is involved in both absorption and discharge. Some mucus membranes produce mucus, which is a thick protective liquid. One of the main functions of mucus is to protect and lubricant.[25]

4.1 Composition of mucus:

Oral mucus is produced by a variety of glands in the oral cavity, including the sublingual gland, the parotid gland, and other salivary glands. The mucus is a transparent gel released by goblet cells or unique exocrine glands that coexist with mucus cells.[26]

Components	Percentage
Water	95%
Glycoproteins and lipids	0.5-5%
Mineral salts	1%
Free proteins	0.5-1%

Mucus glycoproteins are the high molecular proteins that contain attached oligosaccharide units. The mucus contains following oligosaccharide units [27]

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

4.2 Functions of mucus[28]

1. Protective: resulting mostly from its hydrophobicity.

2. Barrier: The mucus layer acts as a barrier in tissue absorption of the medicine, influencing bioavailability.

3. Adhesive: Mucus has strong adhesive properties.

4. Lubrication: It is necessary to maintain the mucus from the Goblet molecular in order to make up for the loss of the mucus layer due to digestion, bacterial deterioration, and mucin molecule Solubilization.

5. Mechanism of mucoadhesion: [28]

The two materials, in which one may be artificial, such as mucoadhesive polymer, and other may be mucin, layer of the mucosal tissue, is held together by means of interfacial force of attraction is known as mucoadhesion. [2] Mucoadhesive means artificial substance that is capable of interacting with mucus membrane and being retained on them or holding them together for extended or prolonged time. During the process of adhesion, there are two stages identified, which are given below.

5.1 Contact Stage:

Whenever the mucous adhesive substance comes into interaction with the mucosal membrane, they are intimately moist. The mucus in the mucous membrane is responsible for soaking the mucoadhesive.[27]

5.2 Consolidation Stage

Using various physiochemical forces of attraction such as Vander Waals forces, electrostatic forces, and bonding with hydrogen. These forces contained in mucoadhesive substance adhere to the mucus membrane, resulting in long-term mucoadhesion. This period is known as the consolidation phase. Following these two steps, the mucoadhesion mechanism is completed.[29]

6. Theories of Mucoadhesion[30]

Mucoadhesion is a complex phenomenon, and several ideas have been presented to explain its process. These hypotheses, given in Table, are relevant for understanding the adherence of mucoadhesive polymers to biological membranes. Adsorption theory, which describes the chemical connection between mucoadhesive polymer and mucin, is one of the most thoroughly investigated ideas. On the other hand, electron theory clarifies the significance of charge in adhesion. Though one may expect that each of these ideas would be applied independently, however, all hypotheses are engaged throughout the mucoadhesion phase.

Table 2: Theoretical Models Explaining Mucoadhesion Mechanisms

Theory	Comments
Diffusion Theory	It explains the diffusion of polymers towards the sticky surface. The diffusion process is driven by the concentration gradient at the applied surface The ability to penetrate of the mucoadhesive polymer relies on the diffusion coefficient.[31]
Electronic Theory	It explains the transfer of electrons across the applied surface. Adhesion is caused by variations in electrical distribution and attractive forces, This results in the creation of an electric double layer at the contact.[32]
Adsorption Theory	It proposes that forces (van der Waals forces, hydrogen bond, ionic bond, and covalent bond) at the surface are responsible for the adhesive contact formed between a mucoadhesive polymer and the mucosa.[33]
Wetting Theory	This is applicable to liquid systems. It discusses the capacity of the liquid system to spread across the applied surface.[33]
Fracture Theory	Defines the force needed to divide the two layers after adhesion is achieved. Measures the adherence of hard or semi-rigid mucoadhesive systems.[34]

7. Mucoadhesive Polymers:

The English word "polymer" is derived from the Greek words "poly" (meaning "many") and "meros," which means "parts or members." It refers to enormous molecules composed of repeating monomeric building parts. Natural polymers have been present on Earth since ancient times and are necessary for life. They are polymers that are either liquid or semisolid. Adhesives are typically made from polymers to create sticky compounds that bind surfaces together. Adhesive tapes, which blend polymers and adhesives, are an effective technique to connect things.[35]A polymer is an interesting substance or material composed of macromolecules, or large molecules. These macromolecules are known as polymers, and they include a significant number of repeated components.[36] Polymers are crucial and pervasive in our everyday lives owing to the variety of properties they possess. Polymers, whether synthetic or natural, are created by a process known as polymerization, in which several tiny molecules, or monomers, chemically link together to form as big macromolecules. [37]

The mixture of many tiny molecules, known as monomers, produces polymers, which are big molecules known as macromolecules. These smaller units go through a conversion process to become the large, complicated structures that are distinctive to polymers. Polymers are intriguing large molecule with a high molecular mass, also known as macromolecules. They are created by a process known as polymerization, which involves the complicated linking of several tiny molecules known as monomers.[38] The physical and chemical properties of the polymers used in the formulation influence how effectively solid dosage forms, implants, diffusion systems, transdermal patches, and particle systems perform. Pharmaceutical polymer sales represent a very modest. Fraction of the total polymer market. The Food and Drug Administration closely monitors these polymers' standards to ensure that their use has no unfavorable impacts.[39]

7.1 An ideal polymer has the following characteristics: [40]

1. Product degradation should not be harmful or absorbable from G.I.T.

2. Not irritating to mucous membranes.

3. Generate strong non-covalent bonds with mucin epithelial surfaces of cells.

4. Adhere fast to wet tissue and have site-specificity.

5. Ensure the medicine is easily absorbed and released.

6. The polymer must not disintegrate during preservation or shelf life of the dosage form.

7. Economical.

8. Factor Affecting of Mucoadhesive Drug Delivery System [4]

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

Table 3: Factors Affecting Mucoadhesion

Polymer - Related Factor	Environment Related Factor	Physiological Factor
1. Molecular weight	1. pH	1. Mucin turnover
2. Active polymer concentrations	2. Applying power	2. Disease states
3. Flexibility of polymer chains	3. First contact time	
4. Spatial conformation		

Table 4: Polymers used in mucoadhesive drug delivery system: [41]

Source Dependent Polymers	Aqueous solubility	Charge	Potential Bioadhesive Force
Natural polymers E.g. Agarose, gelatin, chitosan Various gums (guar, xanthan, pectin, and sodium alginate) Synthetic polymers E.g. Cellulose derivatives: CMC, Thiolated CMC, sodium CMC, HPMC, HPC, methyl hydroxyethyl cellulose. Poly (acrylic acid)-based polymers E.g., Polyacrylates, PAA, PC, Poly (methyl vinyl ether-coethyl hexyl acrylates), polyoxyethylene, PVP, PVA, thiolated polymers.	Water-soluble E.g., HEC, HPC, sodium CMC, Sodium alginate. HPMC flax seed. Chitosan is insoluble in water, but soluble in dilute aqueous acids.	Cationic charge E.g., Amino dextran, Chitosan trimethylated chitosan, dimethyl aminoethyl- dextran Anionic charge E.g., chitosan, EDTA, CP, CMC, Pectin, PAA, PC, sodium alginate, Sodium CMC, Xanthan gum	Covalent bonded polymers E.g., hydroxyethyl starch, HPC, PVA, PVP Hydrogen bond E.g., Acrylates, poly (methacrylic acid), CP, PC, PVA Electrostatic interactions E.g., Chitosan

9. Evaluation of Mucoadhesive Drug Delivery System:[42]

9.1 In vitro/ex vivo methods.

1. Methods determining tensile strength
2. Methods determining shear stress
3. Adhesion weight method
4. Fluorescent probe method
5. Flow channel method
6. Mechanical spectroscopic method
7. Falling liquid film method
8. Colloidal gold staining method
9. Viscometer method
10. Thumb method
11. Adhesion number
12. Electrical conductance
13. Swelling properties
14. *In vitro* drug release studies
15. Mucoretentability studies

9.2 In vivo methods

1. Use of radioisotopes
2. Use of gamma scintigraphy
3. Use of pharmacoscintigraphy
4. Use of electron paramagnetic resonance (EPR) oximetry
5. X - ray studies
6. Isolated loop technique

10. Mucoadhesive Dosage Form

10.1 Tablets

Tablets are tiny, flat, and round, with a thickness of around 5-8 mm. Unlike normal tablets, mucoadhesive pills enable you to drink and speak without pain. They

soften, cling to the mucosa, and remain in place until the disintegration and release is completed.

Mucoadhesive tablets, in general, have the ability to be used for controlled release drug delivery, however, coupling their adhesive characteristics to tablets has extra benefits, such as rapid absorption and improved bioavailability of drugs due to a large surface quantity proportion, as well as a greater level of contact with the mucus membrane. This mucoadhesive tablet enables patients to eat and talk comfortably while causing no itching, foul taste, or pain.[43]

10.2 Patches

Many various patch systems that attach to the oral mucosa and administer medications have been developed. Oro-adhesive patches can be divided into three types: patches having a dissolvable matrix used to deliver drugs to the mouth cavity. These patches function longer than solid versions like tablets and lozenges, permitting for continuous medication release in the treatment of oral yeast infections and mucous membrane inflammation [44]

10.3 Films

Mucoadhesive films may be preferable to adhesive tablets in both flexibility and comfort. Furthermore, they may avoid the relatively brief residence period of oral gels on the mucosa, which are readily washed away and disperses by saliva Thin strips of polymeric films, able to loading up to 20 mg of drugs, dissolve on the tongue in less than 30 seconds and deliver drugs (that can cross the permeability barrier) directly to the bloodstream for rapid treatment of conditions such as impotence, migraines, motion sickness, pain relief, and nausea.[45]

10.4 Gels and ointments

Semi-solid dosage formulations, such as gels and ointments, offer the benefit of being easily dispersed through the oral mucosa. However, medication dosing using semisolid dosage forms may be less precise than with tablets, patches, or films. The use of mucoadhesive formulations has overcome the gels' poor retention at the application site. Certain mucoadhesive polymers, such as sodium carboxymethylcellulose, carbopol, hyaluronic acid, and xanthan gum, change phase from liquid to semisolid.[46] this modification increases the viscosity, resulting in a more continuous and regulated release of medicines. Hydrogels are also a viable dose option for sublingual medication administration. Certain mucoadhesive polymers, such as sodium carboxymethylcellulose, carbopol, hyaluronic acid, and xanthan gum, change phase from liquid to semisolid. This modification increases the viscosity, resulting in a more continuous and regulated release of medicines. Hydrogels are also a viable dose option for sublingual medication administration.[47]

10.5 Sprays

Spray capable of transporting big molecules, such as insulin, over the oral mucosa. Glyceryl trinitrate is a tiny chemical that may be quickly given across the sublingual oral mucosa by spray for angina treatment. [48]

10.6 Pastes

Pastes have been used to administer antimicrobial agents for enhanced extraction socket healing after tooth extractions in HIV patients, as well as controlled release triclosan in oral care formulations. Pastes are also used to treat gingivitis by localizing and retaining slow-release antibiotics in the gingival crevices around dental. Liposomes have been investigated as drug delivery carriers both as a solution and in a paste formulation.[49]

11. Application of Mucoadhesive Drug Delivery System:[6]

Mucoadhesive forms of medication have been utilized to treat local problems at the mucosal surface, reducing the total necessary dose and reducing adverse effects associated with systemic therapeutic delivery. These are possible connection locations for numerous Mucoadhesive mechanisms; hence a mucoadhesive drug delivery system comprises the following.

11.1 Therapeutic Use Mucoadhesive Drug Delivery System

1. The oral medication administration method improves drug absorption and gastrointestinal tract residence duration.
2. Nasal drug delivery system allows for direct medication administration to the nasal mucosa for systemic or local effects.[50]
3. Improved ophthalmic medication delivery by extending ocular residence duration and increasing absorption.
4. Vaginal drug delivery system: Providing sustained release of drugs for the treatment of vaginal infections or contraception.[51]

11.2 General Application Mucoadhesive Drug Delivery System: [52]

1. Radio-labeled microspheres may be used to image various cells, molecular lines, tissues and organs.
2. Extended release of proteins, hormones, and peptides.
3. Targeting of drug at specific web page of motion.
4. DNA plasmid-based gene therapy, including insulin delivery.
5. Topical porous microspheres.
6. Surface changed microspheres.

12. Advances in Mucoadhesive Drug Delivery System:

Mucoadhesive drug delivery systems provide a potential solution for overcoming the limits of traditional drug delivery technologies and improving therapeutic effectiveness in a variety of medical applications. Continued research and innovation in the fields of polymers, nanotechnology, and formulation design are required to solve the limitations and maximize the

promise of mucoadhesive drug delivery systems in enhancing patient care and results.[53]

Nanotechnology in mucoadhesion

Nanotechnology mucoadhesive systems, such as nanopa rticles and nanogels, have intriguing prospects for target ed medication administration and improved mucosal ad herence.

1. **Bio adhesive hydrogels:** Innovations in biological adhesive hydrogels with customizable characteristics have the ability to regulate medication release and target particular tissues.[54]
2. **Combination therapies**: Mixing mucoadhesive systems with other drug delivery methods, such as nanoparticles or liposomes, may improve treatment effects.
3. **Personalized medicine:** Mucoadhesive preparations customized to the unique features of every person, including disease statuses and mucosal features, may maximize therapeutic benefit and reduce side effects.[55]

Conclusion:

Mucoadhesive dosage forms can be made to stay at the point of application for extended periods of time, allowing for regulated drug release and better outcomes for treatment. The most traditional and patient-preferred method is oral administration, since it is easy to consume. Similarly, patients have been drawn to mucoadhesive dosage forms because they are painless and easy to administer drugs. A wide range of topics were covered in the study of the mucoadhesive drug delivery system, ranging from straightforward oral mucosal distribution to the nasal, genital, occular, and rectal drug delivery systems. The development of innovative mucoadhesive materials, device design, and mucoadhesion mechanisms are only a few of the several uses for mucoadhesive drug delivery systems. These systems will become even more crucial in the medical field. The goal of developing mucoadhesive drug delivery systems is to better understand the several mechanisms underlying mucoadhesion and enhance the penetration of active agents. Through extending the residence duration at the distribution site, mucoadhesive polymers may offer a valuable tool to enhance the bioavailability of the active ingredient. Mucoadhesive polymers have been found to be particularly effectives in the buccal cavity, nasal cavity, genital lumen, and digestive system, among other areas. Overall, Mucoadhesive Drug Delivery System represents an advanced approach to optimizing drug delivery by taking advantage of the natural properties of mucosal cells to enhance therapeutic efficacy.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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