A Review on Mucoadhesive drug delivery system

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Abstract: Mucoadhesive drug delivery systems lengthen the dosage form's residence time at the site of absorption by interacting with mucin molecules and the mucus layer that covers the mucosal epithelial surface. The phenomena of interfacial molecular attractive forces in the layer of surface of a biological membrane and the natural or synthetic polymer, which permits the polymer to cling to the membrane's surface for an extended amount of time, is known as mucoadhesion. The mucoadhesive buccal drug delivery system has numerous benefits that make it a unique drug delivery method for both local and systemic administration of different medications. The primary benefit of using this route for drug administration is that it avoids the first pass metabolism of many medications, which are subject to their first pass metabolism in the liver.

Key words: Mucoadhesive, Mucoadhesion, Metabolism and Polymer

INTRODUCTION

For the majority of medicinal medicines, oral administration has been the most popular and favored method of administration to date. Oral administration has gained popularity because to its ease of administration, accuracy in dosing, economical manufacturing process, minimal sterility issues, adaptable dosage form design, and generally longer product shelf life.[1] [2] Mucoadhesive drug delivery systems work by utilizing the bioadhesion of specific polymers, which becomes sticky when hydrated. This allows the system to target a drug to a specific area of the body and deliver it there for a prolonged amount of timeMucoadhesion is the kingdom in which substances stick to one another for extended periods of time with the help of interfacial forces. This process is called "bio adhesion" when the substance in question is organic in nature. The process of adhering a cloth to the mucosal layer of the frame is known as mucoadhesion. Mucoadhesive drug delivery, which uses synthetic and natural polymers, is a controlled drug release method that allows the polymers to have close contact with the target tissue.

Mucoadhesive drug delivery systems leverage the capabilities of positive polymers' bioadhesion to become sticky during hydration. This allows for the prolonged, targeted administration of drugs to specific body regions. In the early 1980s, the idea of mucoadhesion is developed in relation to controlled release drug administration. Drug is continuously released at a predetermined rate thanks to the eight control released mechanism. Controlled medication delivery has shown a great deal of interest in the usage of copolymers and bio adhesive polymers in recent years. This interest is due to the following potential applications of bio adhesive drug delivery system:

a) Adhesion to particular bodily locations, like the nose and oral canals, which increases the drug's bioavailability.

b) The best possible contact with the adhesion surface is formed, enhancing drug absorption.

c) The dosage's extended residence period within ten gastrointestinal tracts. Better patient compliance would result from fewer doses being required. The biological surface can be epithelial tissue or the mucus coat on the surface a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Mucoadhesion should not be confused with bio adhesion; in bio adhesion, the polymer Is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used [3]

Advantages of Mucoadhesive Drug Delivery System:

1) Drugs that boost bioavailability first circumvent metabolism.
2) It is simple to deliver medication as therapy in an emergency.

3) Some medications that are unstable in the stomach's acidic environment can be delivered buccal.
4) Excellent accessibility and the ability to act quickly.
5) Quick absorption due to a high perfusion rate and enough blood supply.
6) Greater safety margin for strong medications as a result of improved plasma level control.
7) Maximum drug utilization allowing for a decrease in the total amount of medication given [4,5,6]

Disadvantages of Mucoadhesive Drug Delivery System:

1) The swelling and hydration of the bio adhesive polymers may cause the formulation's structural integrity to be compromised, and overhydration may result in the production of a slippery surface [4,5,6].
2) Drugs may be taken with saliva, in which case the buccal route's benefits would be lost.
3) It is not possible to deliver drugs that are not stable at buccal PH.
4) A small amount of necessary medication needs to be regulated.

MECHANISM OF MUCOADHESION:

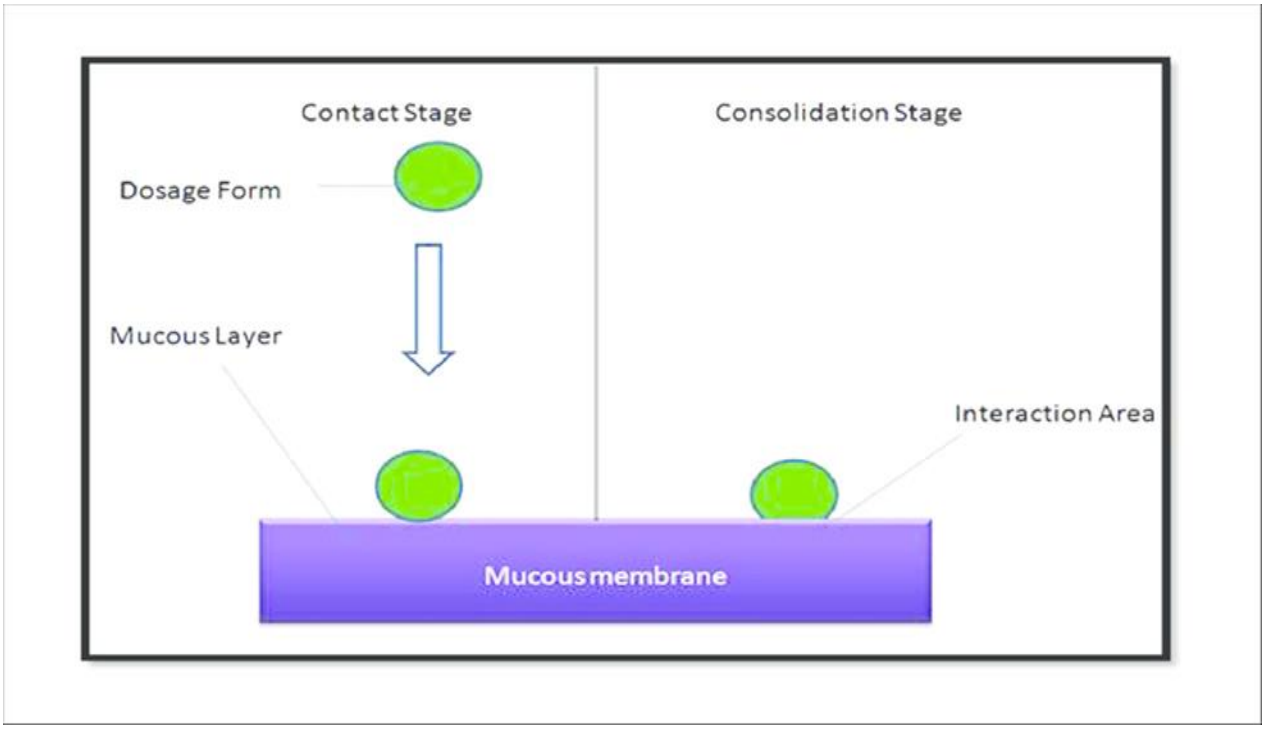
Mucoadhesion is a complex process involving wetting, adsorption, and interpenetration of polymer chains. Mucoadhesion is established in the following stages:

A. Contact Stage

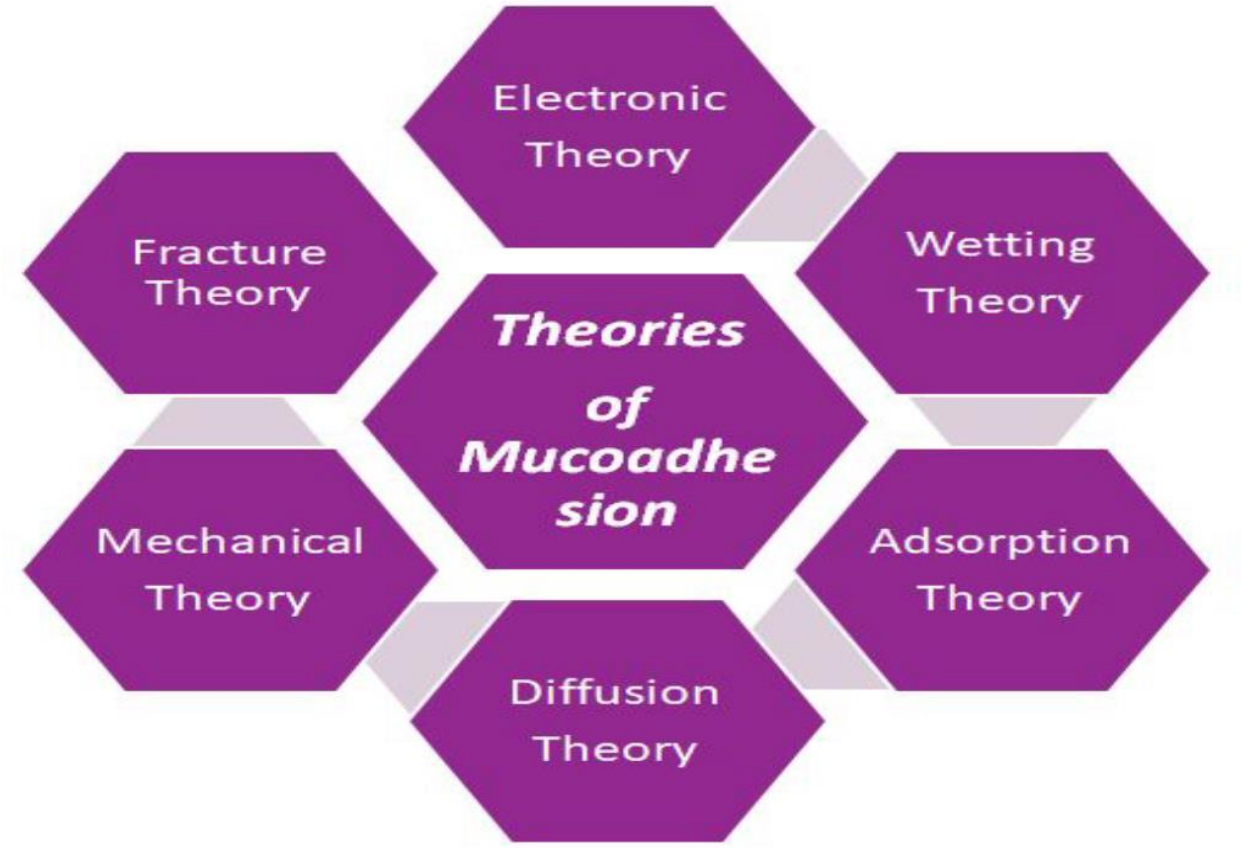
1) An intimate wetting between the mucoadhesive material and mucus membrane happens at this stage when the material comes into contact with the mucus membrane. The mucus found in the mucosal membrane is responsible for wetting the mucoadhesive.
2) Close physical contact between a membrane and a bio adhesive or mucoadhesive substance

B. Consolidation stage

1) The bioadhesive/mucoadhesive's penetration into the tissue underneath it or into the mucous membrane's surface (interpenetration). [7]
2) Using various physiochemical forces of attraction, including hydrogen bonds, electrostatic forces, and Vander Waals forces. Long-lasting mucoadhesion is the result of these pressures in the mucoadhesive substance joining with the mucus membrane. We refer to this phase as the consolidation stage. Following these two phases, mucoadhesion is finished. [8]



Theories of Mucoadhesion:



The ways in which mucoadhesive polymers adhere to the mucosal membrane are explained by these hypotheses. These hypotheses rely on the well-established theories of metallic sticky and polymers [10]. The phenomena is explained by six classical theories that have been altered based on research on polymer adherence and the performance of various materials.

a) Wetting Theory
b) Adsorption Theory
c) Diffusion Theory
d) Mechanical Theory
e) Fracture Theory

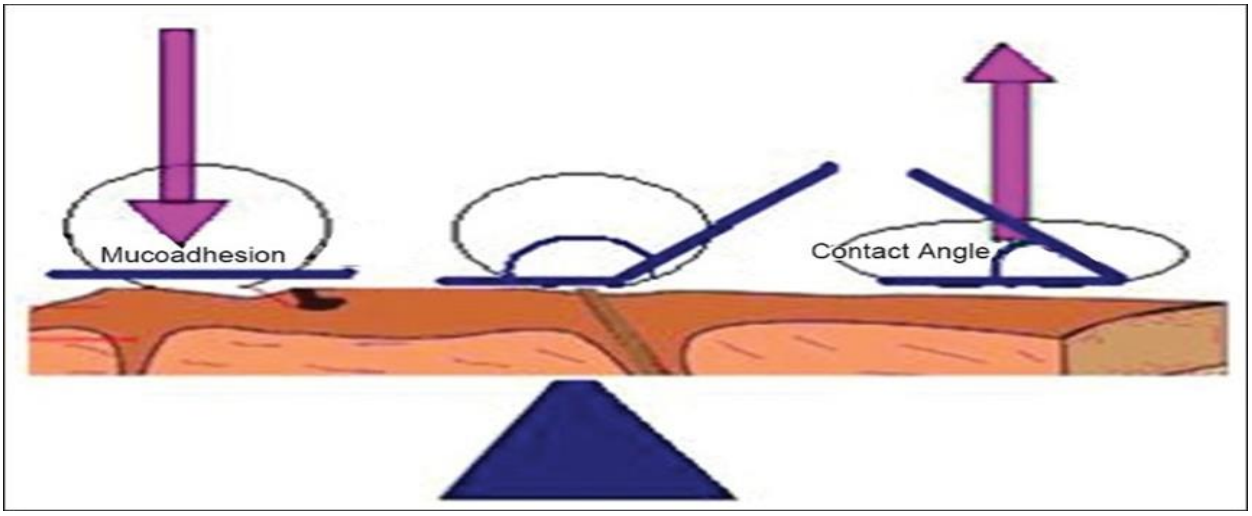
1.electronic theory

According to this idea, adhesion results from the transfer of electrons between the mucus and the mucoadhesive system, which is caused by variations in their electrical structures.[11] At the contact between mucus and mucoadhesive polymers, a double layer of electrical charges forms. [12] According to this idea, adhesion results from variations in the electronic structures of the mucus and the mucoadhesive system, which cause electron transfer to occur. A double layer of electrical charges forms at the mucus and mucoadhesive interface as a result of electron transfer between the mucus and the mucoadhesive. This process ultimately leads to the creation of attractive forces inside this double layer.[13]

2.Wetting theory

The liquid systems that present affinity to the surface in order to spread over it are covered by the wetting theory. The contact angle is one measurement method that can be used to determine this affinity. The basic norm is that affinity increases with decreasing contact angle.For proper spreadability, the contact angle needs to be equal to or nearly equal to zero. As shown in the equation below, the spreadability coefficient, SAB, can be computed from the difference between the interfacial energy γAB and the surface energies γB and γA. [14] According to this theory, achieving a good level of mucoadhesion requires a reduction in surface and interfacial energy as well as a contact angle.

$$SAB = \gamma B - \gamma A - \gamma AB$$



3.Adsorption theory:

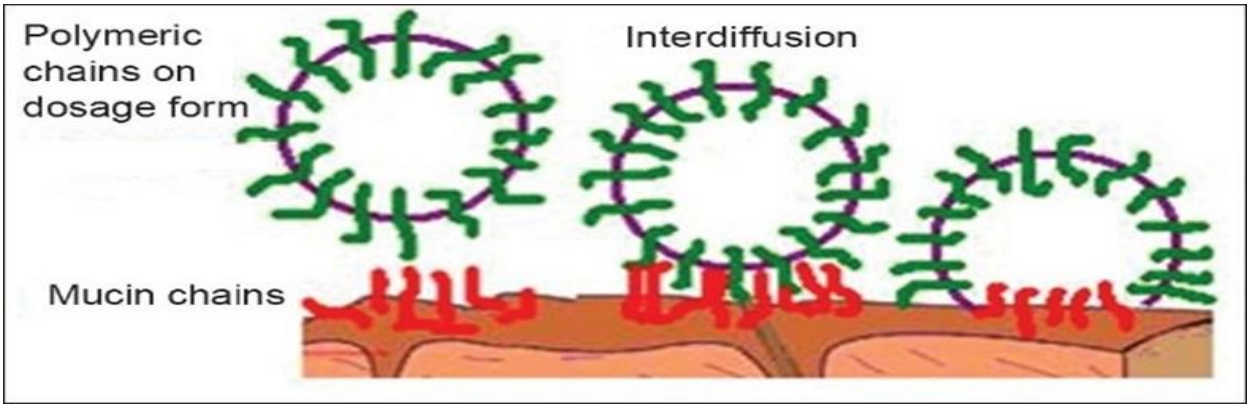
According to the chemisorption theory, contact occurs at the interface when strong covalent bonding is present. This hypothesis states that adhesive adhesion is based on Vander Waals forces and hydrogen bonding. There are two different kinds of chemical bonds: primary covalent bonds and secondary chemical bonds, which include hydrophobic, Vander Waals, and electrostatic interactions.The theory of adsorption Here adhesion results from different surface interactions (primary and secondary bonding) between the mucus substrate and the sticky polymer. Ionic, covalent, and metallic bonding from primary bonds resulting from chemisorptions cause adhesion, which is typically unwanted because of their permanence.[15] Hydrophobic interactions, hydrogen bonding, and van der Waals forces are the main causes of secondary bonds. Due to their semi-permanent bonding properties, these interactions are the most common type of surface interaction in mucoadhesion processes, even though they take less energy to "break."[16]

4.Diffusion theory:

Diffusion theory explains the occurrence of mucous polymer chains and bioadhesive polymer chains interpenetration and entanglement [17]. Diffusion theory explains how mucin and polymer chains interpenetrate deeply enough to form a semi-permanent sticky bond. According to theory, the degree of polymer chain penetration raises the adhesive force. [18] The interpenetration depth is represented by the formula l = (tDb) ½, where t is the contact time and Db is the mucoadhesive material's diffusion coefficient in the mucus. The mucoadhesive bond is better the higher the structural similarity. [19] Diffusion theory explains how mucin and polymer chains interpenetrate deeply enough to form a semi-permanent sticky bond. The degree of penetration of the polymer chains is thought to increase the adhesive force. The diffusion coefficient, the mucoadhesive chains' flexibility and nature, mobility, and contact time all affect this penetration rate. The research indicates that an effective bioadhesive bond can only be formed at a depth of interpenetration between 0.2 and 0.5 μm. The following formula can be used to measure the depth of polymer and mucin chain interpenetration:[20]

$$l = (tDb)^{1/2}$$

where Db is the mucoadhesive material's diffusion coefficient in the mucus and t is the contact time. When the depth of penetration is roughly equal to the polymer chain size, the adhesion strength of a polymer is obtained. It is crucial that the components involved have high mutual solubility—that is, that the mucus and the bioadhesive have similar chemical structures—for diffusion to take place. The mucoadhesive bond is better the higher the structural similarity.[20]



5.Mechanical theory:

When a mucoadhesive liquid fills in irregularities on a rough surface, adhesive connections are created. The potency of contacts is increased by irregularity because it increases the interfacial area. [21] The way these polymers adhere to mucosal surfaces is explained by the mechanical theory of mucoadhesive systems. Physical bonds are formed through molecular entanglement, hydrogen bonding, and van der Waals forces. Knowing these interactions makes it easier to create medical devices and medication delivery systems that guarantee sustained contact and regulated drug release at particular body locations.

6. Fracture theory.

most popular theory in research on mucoadhesion's mechanical measurement. It examines the amount of force needed to split two surfaces once adhesion is proven.The fracture theory does not account for the interpenetration or diffusion of polymer chains because it only considers the force needed to separate the components. As a result, it can be applied to calculations involving hard or semi-rigid bioadhesive materials, where the polymer chains are unable to pierce the mucous layer. [22, 23] It examines the amount of force required to split two surfaces once adhesion is proven. It has been discovered that longer polymer network fibers or a reduction in the degree of cross-linking within such a system result in greater work fractureThis theory aids in determining the fracture strength (σ) subsequent to the separation of two surfaces by relating it to the critical crack length (L), the fracture energy (ε), and the Young's modulus of elasticity (E) using the following equation. reveals areas where the mucoadhesive binding has broken. [24,25]

$$\sigma = \left(\frac{E \times \varepsilon}{L}\right)^{1/2}$$

Mucoadhesive Dosage Forms:

1.Tablets:

Tablets have an oval shape, are flat, and have a diameter of about 5 to 8 mm. [26] Mucoadhesive tablets, in contrast to traditional tablets, don't cause significant discomfort when speaking or drinking. They become softer, stick to the mucosa, and stay there until the disintegration and/or release process is finished. The combination of mucoadhesive properties with tablets offers additional benefits, such as efficient absorption and enhanced drug bioavailability due to a high surface to volume ratio and facilitated much more intimate contact with the mucus layer. Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery. Mucoadhesive tablets provide the option of both localized and systemic controlled drug release because they may be made to stick to any type of mucosal tissue, including the stomach mucosa. Mucoadhesive tablets are applied to the gastric epithelium's mucosal tissues in order to administer medications with a localized effect. Because they extend the medicine's release, decrease the frequency of drug administration, and increase patient compliance, mucoadhesive tablets are frequently utilized. Mucoadhesive tablets' primary flaw is their lack of physical flexibility, which makes it difficult for patients to comply with repeated, long-term use. [27–28]

2. Patches:

A mucoadhesive surface for mucosal attachment, an impermeable backing layer, and a drug-containing

reservoir layer from which the drug is released under regulated conditions make up a laminate known as a patch. Systems for applying patches resemble those used in transdermal medicine delivery. Adhesive patches are prepared using two techniques: solvent casting and direct milling. Using the solvent casting process, the drug and polymer solution is cast onto a backing layer sheet, and the solvent(s) are then allowed to evaporate to create the intermediate sheet from which patches are punched. The direct milling method involves mixing formulation ingredients uniformly, compressing them to the required thickness, and then cutting or punching out patches of a predefined size and shape. To regulate the direction of medication release, stop drug loss, and reduce device deformation and disintegration throughout the application time, an impermeable backing layer may also be used. [29, 30]

3.Gels and ointments:

Gels and ointments are examples of semisolid dose forms that have the benefit of easily dispersing throughout the oral mucosa. However, compared to tablets, patches, or films, drug dosing from semisolid dosage forms could not be as precise. The use of mucoadhesive formulations has helped to overcome poor gel retention at the application site. A phase transition from liquid to semisolid occurs in some mucoadhesive polymers, such as sodium carboxymethylcellulose, carbopol, hyaluronic acid, and xanthan gum [31, 32]. This alteration increases the viscosity, allowing for a controlled and prolonged release of medication. Another interesting dosage type for buccal medication administration is hydrogel. They are made of hydrated polymers in an aqueous solution that physically ensnared medicinal molecules for eventual gradual release by erosion or diffusion.33] Mucoadhesive gel application offers a prolonged duration of retention in the oral cavity, sufficient medication penetration, good efficacy, and patient acceptability. One of the main uses for adhesive gels is the local administration of medication to treat periodontitis, an infectious and inflammatory condition that results in pockets forming between the gum and the tooth and can ultimately lead to tooth loss. Mucoadhesive polymers have been proposed as potential therapeutic agents for periodontitis when combined with antibacterial formulations that are easily injected with a syringe into the periodontal pocket. [34–35]

4. Films:

Given their flexibility and comfort, mucoadhesive films might be a better option than adhesive tablets. Furthermore, they can avoid the oral gels' comparatively brief duration on the mucosa, as saliva readily washes and removes them. Additionally, when oral disorders are treated locally, the films aid in protecting the surface of the wound, which lessens discomfort and improves the efficacy of the treatment. A perfect film would be soft, elastic, and flexible, but also sturdy enough to resist breaking under the pressure of mouth movements. To stay in the mouth for the intended amount of time, it must also have strong mucoadhesive propertiesIf there is any film swelling, it should not be too severe to avoid pain.[36]

Mucoadhesive Drug Delivery Systems:

1.Sublingual Drug Delivery:

Mucoadhesive Polymers: Because of their adhesive qualities, polymers such as chitosan, hydroxypropyl methylcellulose (HPMC), and derivatives of polyacrylic acid are frequently utilized.

Improved Drug Absorption: Drugs can enter the bloodstream quickly and take effect quickly thanks to the highly vascularized sublingual mucosa.

Sustained Release: Over time, therapeutic levels can be maintained by controlled medication release provided by mucoadhesive systems.[37]

Advantages of Sublingual Mucoadhesive Drug Delivery:

Rapid Onset of Action: Quick absorption due to the rich blood supply under the tongue.

Avoiding First-Pass Metabolism: Direct entry into systemic circulation can increase drug bioavailability.

Improved Patient Compliance: Ease of administration compared to oral tablets or injections.

Applications:

Cardiovascular Medications: Nitroglycerin for angina, allowing rapid relief by sublingual administration.

Analgesics: Pain relief medications for quick action, such as opioids or certain NSAIDs.

Hormonal Therapy: Some hormone replacement therapies or medications like estradiol can be administered sublingually. [38]

Challenges and Considerations:

Taste and Palatability: Ensuring patient acceptance due to the taste of the formulation.

Uniformity of Absorption: Ensuring consistent absorption across the sublingual mucosa.
Dosage Form Design: Formulating the drug into a suitable mucoadhesive system for sublingual application.
Future Developments:
Nanotechnology: Utilizing nanoparticles for targeted drug delivery and improved bioavailability.
Novel Polymers: Exploring newer polymers with enhanced mucoadhesive properties and biocompatibility.
Evaluation of Sublingual Mucoadhesive Systems:
In Vitro Studies: Testing mucoadhesive properties, drug release kinetics, and stability.
In Vivo Studies: Assessing pharmacokinetics, bioavailability, and efficacy in animal models and human trials.

2.buccal drug delivery system:

Mucoadhesive buccal delivery is the process of delivering the right medications through the mouth cavity's buccal mucosal membrane with the right carriers. Several bucoadhesive delivery systems, such as films, wafers, tablets, and gels, have been created recently to treat a variety of pathological disorders. [39] Due to their ability to form strong intermolecular hydrogen bonds with the mucosal layer and display good mucoadhesive properties, mask the taste of therapeutics, have controlled drug release patterns, good viscoelastic properties, and are biodegradable, polysaccharides such as guar gum, xanthum gum, chitosan, alginate, cellulose, carrageenan, and their derivatives, etc., are considered potential carriers to realize both mucosal and transmucosal drug administration [40]. A lot of research has been done on polymeric nanoparticles for medication delivery that adheres to the buccal mucosa. Enhanced drug diffusion across the buccal mucosa is another feature of nanoparticles, which makes them particularly useful for oral transmucosal delivery of high molecular weight medications for systemic treatments. [41] Lower efficiency occurs when medication intended for buccal administration is diluted in saliva and enters the oral cavity. In order to improve efficacy, the design of a unidirectional buccal patch has recently been examined [42]. Despite the great potential, there are certain difficulties associated with buccal medication delivery. These include the relatively limited absorptive surface of the drug, bitter or unpleasant taste, and difficulty administering medicines that are unstable at buccal pH.

3.Nasal drug delivery:

Nasal administration of medication The nasal route offers a viable non-invasive substitute for systemic and local medication delivery, which can be difficult to administer or has poor bioavailabilities when taken orally. In contrast to the buccal mucosa, the nasal mucosa is highly vascularized and supports quick absorption. It is composed of a non-keratinized monolayer stratum corneum that is linked to many microvilli and has a surface area of around 160 cm^ [43]. Furthermore, it's thought that the nasal route provides improved medication delivery to the brain by providing near access to the blood-brain barrier Pridgen and associates revealed a patent for a mixture that includes mucoadhesive polymer from the group that includes chitosan and sodium alginate in amounts between 0.15 and 15% by weight of the mixture, and active agent chosen from the group that includes triamcinolone or acyclovir in amounts between 0.01 and 5% by weight of the mixture plus plasticizer. The invention states that the mucoadhesive composition offers a controlled release formulation meant to cure localized ailments such as fibromyalgia, radiation-induced mucositis, bacterial infection, pharyngitis, and aphthous stomatitis. When nasal secretions are present, the mucoadhesive polymers continuously grow, causing the formulation to progressively enlarge and release the medicines over a 120-minute period. Improved bioavailability, reduced first pass metabolism, and increased patient compliance are among the benefits of the discloser.

4.Vaginal drug delivery:

For both local (vaginitis brought on by different pathogens like bacteria, fungi, or viruses) and systemic (hormone replacement treatment, cervical cancer, ovulation inducing activities, and diabetic mellitus) drug delivery, the vaginal route presents a viable alternative. The therapeutic efficacy of medications is significantly increased by vaginal administration since it permits self-administration with little expert intervention and allows for regulated drug localization at the target region. Vaginal administration is a viable alternative for systemic distribution of low molecular weight medications due to its flexible and thin epithelium (200-300µm) and low level of protease, in addition to its capacity to bypass first pass metabolism [44]. According to recent findings, a particular

anomaly in the vaginal flora was linked to an increased risk of STIs, fungal infections, and UTIs. As a result, administering medication directly to the vaginal mucosa using formulations intended to adhere to and release drugs in the vaginal walls is known as vaginal drug delivery through mucoadhesive systems. These formulations, which include pills, gels, creams, and rings, adhere to the vaginal surface and release medication gradually over time. They help avoid hepatic metabolism, minimize adverse effects, and provide localized therapy. Challenges include vaginal environment variability, user comfort, and formulation design. Researchers work to develop more potent, better formulations for more focused treatment and better patient outcomes.

5.Ocular drug delivery:

Mucoadhesive drug delivery systems made of various polymeric materials are useful in boosting ocular bioavailability because they help to overcome the natural physiological and anatomical barriers of the eyes and increase precorneal residency. Above all, the hydrocolloid properties of polymeric carriers offer sufficient lubrication for simple application to the eye without impairing vision [45]. cyclosporine A as the therapeutically active substance, dextran as the bioadhesive material, polylactide as the hydrophobic material, and sodium citrate as the buffering agent are used in this mucoadhesive ocular drug delivery system to overcome issues with poor drug solubility, extend precorneal retention time on eye surfaces, and provide controlled drug release for improved therapeutic activity on target tissues. Similarly, produced controlled release mucoadhesive formulations that lengthen the drug's residence duration in the ocular mucosa can improve the treatments' ocular bioavailability, according to yet another patent report. Mucoadhesive formulation containing therapeutically active substance in an amount of approximately 0.025% to 0.25% by weight of the composition and 0.1 to 6.5% by weight of aqueous solution polycarbophil. When the composition was administered twice daily for two weeks, the results showed no discernible change in intraocular pressure when compared to the commercial formulation. After eye surgery, DuraSite® determined that the composition can be chosen. Compared to traditional dosage forms, thermo-responsive in situ gel has a number of benefits, such as simplicity of administration, prolonged drug release, strong stability, and biocompatibility properties.

CONCLUSION

This review gives a brief overview of mucoadhesive drug delivery systems by going over the Advantage, disadvantage, the mechanism of mucoadhesion, different theories of mucoadhesion, general factors to be taken into account when designing mucoadhesive buccal dosage forms, permeation enhancers, and different evaluation techniques in addition to the literature. An examination of the mucoadhesive buccal drug delivery system

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