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Muco-adhesive buccal control delivery system

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Abstract

Mucoadhesive buccal drug delivery systems have drawn a lot of interest lately because of their potential to improve bioavailability and prolong drug retention at the site of absorption, both of which can lead to improved therapeutic outcomes. The principles of buccal medication administration are examined in this study, with a particular emphasis on mucoadhesion as a crucial mechanism that promotes steady and regulated drug release. The article explores the concepts of designing buccal formulations, such as tablets, films, and patches, as well as the anatomy and permeability of the buccal mucosa. It also discusses several kinds of mucoadhesive polymers. The advantages of buccal medication delivery—such as avoiding hepatic first-pass metabolism and enhancing patient compliance—are thoroughly examined. In addition, difficulties with drug permeability, formulation stability, and patient variability are explored, along with new developments in bioengineering and nanotechnology that are spurring innovation in this area. The analysis closes by outlining potential directions for the future and the contribution of mucoadhesive buccal systems to the creation of more effective and patient-friendly medication delivery techniques.

Keywords: Buccal Cavity; Films; Mucoadhesive; Future Direction

1. Introduction

Mucoadhesive meanthe adhesion to the mucosal layer. This preparation Stick to the mucosal membrane & slowly release the drugs from the formulation.it involves the interaction of dosages form with mucus layer causing increased. (mucus layer consists of mucosa epithelial surface and mucin molecules.) The residence site in dosage from at absorption site in order to attain extended release profile of a drug. Mucoadhesive drug delivery system is used to localize a delivery devices within the human to enhance the drugs absorption in the site specific mannar muvoadhesive polymer can adhere to the mucosa epithelial surface at the Target site.

Mucoadhesive drug delivery system classified various route:

- Buccal delivery system
- Sub-lingual delivery system
- Vaginal delivery system
- Rectal delivery system
- Ocular delivery system
- Nasal delivery system
- Gastrointestinal delivery system

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Various route are classified. Thickness varies from 40 to 300. General composition of mucus contain Water : 5% Glycoprotein & lipids : 0.5-5% Mineral salts: 1.0% Free protein-0.5-1%

The patient prefers the oral route over other drug delivery methods the most. According to what is currently known about the biochemical and physiological aspects of absorption and metabolism, many medications cannot be administered effectively by the traditional oral route because they undergo extensive presystemic clearance in the liver after administration. This frequently results in a lack of significant correlation between membrane permeability, absorption, and bioavailability [1].Buccal routes of drug delivery are superior to other drug administration methods in several ways, including bypassing the first pass effect and delivering the medication straight to the systemic circulation, as well as avoiding pre-systemic elimination within the gastrointestinal tract. Because of these characteristics, buccal medication delivery is a particularly desirable and practical site for systemic drug delivery.[2]

1.1. Designing

While designing mucoadhesive drug delivery system, following functional categories need to be considered as given below :

- Mucoadhesive polymer
- Penetration enhancer
- Enzyme inhibitors
- Mucoadhesive polymer

1.1.1. Mucoadhesive

Mucoadhesive qualities are promoted by polymer hydration and the resulting mucus cohesive characteristics.

- Swelling should encourage the flexibility of the polymer chain and the production of mucin and polymer chains together.
- In the presence of water, strongly cross-linked polymers swell while maintaining their structure.
- Low pH conditions are ideal for mucoadhesion.
- Strong spatial confirmation and viscosity
- The flexibility of the polymers encourages their interpenetration within the mucus network.

The polymer's chain length needs to be long enough to encourage interpenetration but not too long, as this can cause issues with diffusion.

Ideal polymer properties include

- Needs to be non-biodegradable and non-toxic from the GIT
- It must possess favourable qualities for spreading, wetting, swelling, and biodegradation.
- The ideal molecular weight.
- Mucous membrane that is non-irritating
- from a potent, non-violent both on the surface of epithelial cells
- The ability to write and swell

1.1.2. Penetration Enhancer:

- Penetration booster medicament to reach the systemic circulation and perform its function.
- Must be non-irritant and have a reversible impact.
- Polymers such as chitosan and its derivatives are known to have mucoadhesive characteristics.chitoson
- Promote paracellular transport of medicines across the mucosa.

1.1.3. Enzyme inhibitors

Enzymes improve drug absorption through the buccal mucosa, especially for high molecular weight molecules like peptides and proteins as well as medications like puromycin, bestatin, and aprotonin. Bile salts stabilise protein medicines by various

mechanisms that impact enzymatic activity, hence impeding conformational changes in proteins. When chitosin is chemically modified with EDTA, a polymer conjugate called chitoson is produced. EDTA has the potential to block metallopeptidase.

1.2. Why MDDS

- Mucoadhesive prolonge the residence time of the dosage from at the site if absorption
- MDDS provide rapid absorption and good availability due to is considerable surface area and high blood flow
- Intimate contact of the dosage from with the underlying absorption site
- Improve therapeutic performance of drug
- Rapid onset of action
- High drug loading capacity

1.3. Mechanism

The mechanism of mucoadhesive buccal drug delivery systems is based on the adhesion of a drug delivery device or formulation to the mucosal surface of the buccal cavity. This allows for the controlled and sustained release of therapeutic agents, providing prolonged contact time and improved drug absorption through the buccal mucosa. The mechanism involves three key stages: wetting, adhesion, and sustained drug release.[3,4,5]

1.3.1. Wetting and Swelling

When a mucoadhesive system is applied to the buccal mucosa, it first undergoes wetting by saliva. Hydrophilic polymers within the system absorb moisture, leading to swelling. This process exposes adhesive functional groups on the polymer, which then facilitate interaction with the mucosal surface.

1.3.2. Adhesion Mechanism

Mucoadhesion primarily involves the interaction between the polymer chains of the drug delivery system and the glycoproteins (mucins) present on the buccal mucosa. The adhesion is established through various mechanisms, including:

- Electrostatic Interactions: Ionic bonds or electrostatic forces between the positively charged mucin and negatively charged polymer groups.
- Hydrogen Bonding: Hydrogen bonds between hydroxyl, carboxyl, or amine groups in the polymer and the mucosal surface.
- Van der Waals Forces: Weak forces that contribute to adhesion on a molecular level.
- Physical Interlocking: The polymer chains may physically interpenetrate the mucosal tissue surface, enhancing the strength of the adhesion.

2. Controlled Drug Release

Once the mucoadhesive system adheres to the mucosal surface, drug release occurs over time. This controlled release can occur through:

- Diffusion: The drug diffuses out of the mucoadhesive matrix into the mucosa, allowing for absorption into systemic circulation or local treatment.
- Polymer Degradation: In some systems, drug release is also facilitated by the gradual breakdown of the polymer matrix, allowing sustained release of the active ingredient.

The buccal mucosa is highly vascularized, allowing for the rapid absorption of drugs into the bloodstream while bypassing first-pass metabolism in the liver. This leads to improved bioavailability and therapeutic efficacy, especially for drugs with poor oral absorption.

Theory of mucoadhesion

Their are five different theories,which explain are phenomenon.

- wettability theory
- Electronic theory
- Facture theory
- Adsorption theory
- Diffusion theory
-

2.1. Wettability theory

The Wetting Theory is applicable to liquid systems that exhibit a surface affinity in order to disperse over it. One method of measurement used to determine the affinity is the contact angle. As a general rule, the contact angle decreases with increasing affinity. In order to achieve sufficient speadability, the contact angle needs to be near or equal to zero. The spreadability coefficient is computed by subtracting the interfacial energy (γA) from the surface energy (γB). The formula is as follows: SAB = γB-γA – γAB larger adhesion work WA, or the energy required to separate the two phases, is proportional to larger interfacial energy in relation to individual surface energy.

WA= γA + γB – γAB.[6,7,8]

2.2. Electronic theory

The electronic theory is predicated on the fact that biological and mucoadhesive materials have opposing electrical charges. When two materials come into contact and a double electrical layer forms at the surface, an electron is transferred. Additionally, the mucoadhesive strength is dictated by the forces of attraction within the[5,6,7]

2.3. Facture theory

Fracture Theory: This is the most researched theory for measuring the mucoadhesion mechanism. This theory deals with the splitting of two surfaces following adhesion. G = (Eε./L) ½ represents the adhesive strength equivalent to fracture strength. Where: Young's Elasticity Modules, E- Fracture energy (ε) L: The critical crack length that occurs when two surfaces split apart.[6,7,8]

2.4. Adsorption theory

Adsorption theory: This theory states that the mucoadhesive substance sticks to the mucus by secondary chemical interactions including hydrogen bonds and vander Walls, as well as electrostatic attraction and hydrophobic interactions. For instance, the interfacial forces that are most common are hydrogen forces because the polymer contains carboxyl groups. [6,7,8]

2.5. Diffusion theory

The fundamental idea behind the diffusion hypothesis is that substances must sufficiently permeate one another to form a semi-permanent sticky bond. The cross-linking density and molecular weight affect the diffusion coefficient, whereas the diffusion coefficients of the two interacting polymers determine the penetration rate. Segment mobility, the bioadhesive polymer's elasticity, mucus glycoprotein, and the extended nature of both networks are additional parameters to take into account.[6,7,8]

3. Factor affecting on Mucoadhesion

- Flexibility: in the interracial area, mucoadhesion starts with polymer chain diffusion. Consequently, the polymer needs to be as flexible as possible to entangle with mucus as intended.
- Cross-linking density: A higher polymer cross-linking density influences swelling efficiency, which in turn influences swelling efficiency and lowers the attachment rate.
- Capacity for hydrogen bonding: Mucoadhesive polymers need functional groups in order to form hydrogen bonds with mucin and mucosa. Additionally, hydrogen bonding gives the polymer flexibility.
- Hydration: By exposing the bioadhesive site for hydrogen bonding/electrostatic interaction between the polymer and mucus network, wetting and swelling enable mechanical entanglement of the polymer.
- Concentration. As the polymer concentration decreases, the number of polymer interactive chains per unit volume of mucus will also drop. Consequently, the interaction between the polymer and mucus will become unstable.
- Applied strength: To position a solid mucoadhesive system, we have to apply a defined strength. Initial contact time: the mucoadhesive strength increases as the initial contact time increases

- PH: pH influences the charge on the surface of both mucus and the polymer Mucoadhesive Strength Contribution of Mucin Production. Mucin production is expected to limit residence on the mucus layers
- Diseased condition: physicochemical properties of mucus change during diseased states, such as common cold, gastric ulcer, ulcerative colitis, cystic fibrosis bacterial and fungal infection that may affect adhesion Generally, it is believed that a higher concentration of polymer would result in a longer penetrating chain length and better adhesion

In some cases, higher concentration of polymer do not enhance the mucoadhesive properties of the polymer molecular weight: medications with larger molecular weights have better mucoadhesive qualities.

3.1. Advantages:

Prolonged Residence Time Extended contact with mucosal surfaces promotes medication retention at the site of action, minimising the need for repeated dosing. Increases the bioavailability of medications, particularly those that degrade quickly in the body or are poorly absorbed through the gastrointestinal tract.

Localised Drug Delivery – Drugs can be delivered directly to certain mucosal tissues, allowing for focused therapy (e.g., nasal sprays, buccal tablets). – This reduces systemic adverse effects by focussing the medicine where it's most required. 3. Improved Drug Absorption – Longer engagement with mucosal surfaces leads to better absorption and avoids fast transit through the digestive system. Useful for medications with low oral bioavailability, such as peptides, proteins,and some vaccinations.

Improved Adherence and Compliance – Drugs can be released gradually, allowing patients to take medication less frequently. – Allows for a more constant therapeutic effect throughout time.

Avoidance of First-Pass Metabolism Mucoadhesive methods, such as buccal or sublingual tablets, bypass the liver's first-pass metabolism, increasing the bioavailability of medications that are heavily metabolised by the liver when taken orally.

Ease of Application and Patient Compliance: - These systems are often non-invasive and simple to use, enhancing patient comfort and compliance. There is no need for needles or intrusive procedures, making it ideal for those who prefer oral or nasal administration systems.

Suitable for a Broad Range of Drugs. Mucoadhesive systems can transport a variety of medications, including peptides, proteins, small molecules, and vaccines. They are ideal for drugs that are difficult to dissolve or sensitive to harsh circumstances, such as the acidic environment of the stomach. 8. Improved Drug Stability and Protection – Protects sensitive medications from breakdown caused by enzymes or pH changes in the GI tract.

3.2. Disadvantages

Limited medicament Loading Capacity: Mucoadhesive systems typically have a reduced surface area and can only hold a limited amount of medicament. This limits their usage for drugs that require high dosages.

Irritation or Discomfort: Bioadhesive polymers utilised in these systems may induce irritation, discomfort, or a feeling of a foreign object at the application site (e.g., mouth, nose, or gastrointestinal tract), leading to poor patient compliance.

Adhesion Variability – The mucosal environment (pH, moisture, mucin turnover) and patient-specific factors can impact the consistency of medication release and absorption. – Saliva or mucus flow might wash away the

Medicinal composition, lowering its potency. 4. Risk of Unintentional Swallowing or Dislodgement – Oral or buccal administration systems may cause dosage forms to be swallowed or dislodged, resulting in reduced therapeutic action or uneven absorption.

Enzymatic Degradation: Certain mucoadhesive delivery systems, particularly those utilised in the gastrointestinal tract, may experience enzymatic degradation, resulting in lower medication stability and bioavailability.

Hydrophobic medications have limited use in mucoadhesive systems, while hydrophilic drugs are often more suited. Hydrophobic medications may be difficult to incorporate into such systems, reducing the number of drugs that can be properly given.

Shorter Retention in Dynamic Environments: In areas with significant fluid turnover, such as the mouth and gastrointestinal tract, the system may not deliver prolonged drug release, necessitating frequent reapplication.

Complex Formulation and Manufacturing – Creating mucoadhesive formulations can be hard, requiring advanced processes to provide optimal adhesion, medication release, and stability. These technologies may also be more expensive to manufacture than conventional medication delivery systems. Overall, while mucoadhesive drug delivery systems have great potential, these drawbacks must be carefully considered during the formulation and design of the system.

3.3. Method of evaluation

Some of the methods used to evaluate mucoadhesive drug delivery systems (MDDS) include those that are meant for determination and correlation with their adhesive ability, drug release pattern as well performance. The primary method for evaluation is given below:

Mucoadhesion Testing

3.3.1. In vitro methods

- Tensile Strength Measurement: Tells how much force is required to remove formulation from mucosal surface.
- Shear Strength Test: Determines the force needed for a mucoadhesive formulation to slide along a mucosal surface.
- Falling Sphere Method: mucoadhesion can be evaluated by measuring the time that a sphere coated with mucoahesive takes to detach from mucosal place.
- Wilhelmy Plate Method: This method uses a thin plate to measure the interactions of mucosal tissue with the metallic substrate.
- Wash-Off Method: The wash-off test assesses the mucoadhesive strength of a formulation to mucosal tissue by determining how much remains mucus surface after treatment with an aqueous medium.

3.3.2. Ex vivo methods

Mucosal Tissue Binding: Adhesion strength is commonly determined on animal mucosa (e.g., porcine buccal), where the system has been directly placed onto the tissue followed by applying force until detachment.

Perfusion Chambers: Mucosal surfaces were challenged with perfused liquid to measure mucsoadhesion time.

3.3.3. In vivo methods

Gamma scintigraphy: It is performed on live rabbits or human volunteers where mucoadhesive carriers are using in the form of a radiotracer and visualize at various retention times.

Fluorescent Labeling: The formulation is doped with fluorescent markers to determine retention by imaging.

3.3.4. Drug Release Studies

Object In Vitro Release Studies: These studies will investigatethe release kinetics ofthe drug from mucoadhesive formulation.

Common methods include:

- Franz Diffusion Cells: To simulate mucosal drug release and to absorb
- Dialysis Membrane Techniques: The concept here is the diffusion across a semi-permeable membrane from one compartment to another (drug release).
- Rotating Paddle Dissolution Apparatus: In this case, the dosage form is placed in a medium
- Suitable for dissolution and dissolution over time of mucoadhesive formulations as previously described.

Permeation Studies

In Vitro Permeation: Union of Franz diffusion cells with colonic mucosal tissue or synthetic membranes to determine the release and permeation mechanism through the mucus.

Example: Ex Vivo Models — Animal mucosal tissues (e.g. intestinal, buccal) are utilized to examine drug permeation. In Vivo Permeation:

Swelling Studies: Assesses the swelling behavior of mucoadhesive polymer in contact with mucus. This is most commonly achieved using dimensions or weight of the formulation post-exposure to an in vitro model mucosal medium.

Surface Analysis Electron Microscopy (SEM/TEM): To study the Surface topography of mucoadhesive drug delivery system.

AFM: Surface roughness and interaction forces at the micro- to nanoscale;

3.4. Bioadhesion Measurement

Texture Analyzer (measures bioadhesive strength; the mucoadhesive material is pressed against a piece of mucosal tissue, and results in how much force it takes to break that adhesive bond).

Contact Angle Measurement: To determine the surface wettability of mucoadhesive system, this is directly proportional to adhesivity on mucosal membranes.

3.4.1. Tissue Irritation Studies

Histological examination: Analysis of mucosal tissues exposed to the mucoadhesion system viewed under a microscope for possible irritation, inflammation or damage.

Mucoadhesive Compatibility tests: I n vitro or in vivo studies to evaluate the harmlessness of mucosal adhesive buit-up, on a mucosa.

3.4.2. Rheological Studies

The viscosity and mechanical properties of the mucoadhesive system are tested to determine how it behaves within a biological environment.

3.4.3. Mucoadhesive Retention Time

Assesses the retention time of mucoadhesive formulations on mucosal surfaces. This can be accessed from markers or imaging if in vivo; else one must perform these tests from samples sf human tissue further whether molecular pathways associated to metastases are pathway too.

4. Conclusion

Mucoadhesive buccal drug delivery systems present a promising approach for controlled and sustained release of medications, particularly for conditions requiring prolonged therapeutic effects or localized treatment. By adhering to the buccal mucosa, these systems provide several advantages, including enhanced drug bioavailability, avoidance of first-pass metabolism, and improved patient compliance, especially in populations such as pediatric, geriatric, and those with swallowing difficulties. Mucoadhesive buccal systems allow for targeted, sustained, and controlled drug release, leading to more consistent therapeutic outcomes.However, challenges such as formulation stability, patient comfort, and the potential for irritation or variability in mucosal adhesion still need to be addressed. Future advancements in polymer science, drug encapsulation techniques, and patient-centric designs are expected to enhance the effectiveness of these systems. Overall, mucoadhesive buccal delivery represents a valuable and innovative approach to improving drug administration and therapeutic efficacy across various clinical settings.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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