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A Review On Buccal Mucoadhesive Drug Delivery System

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ABSTRACT:

The buccal region of the oral mucosa offers an effective pathway for systemic drug delivery. Medications administered through the oral mucosal layer bypass the gastrointestinal tract, which often has a high first-pass metabolism and can degrade drugs. The buccal drug delivery system allows for direct absorption into the systemic circulation, enabling painless administration, rapid enzymatic action, high bioavailability, and reduced liver metabolism. However, oral drug delivery routes are often limited by significant presystemic metabolism, which can lead to drug breakdown in acidic environments due to poor absorption. Buccal delivery is an appealing option because it allows for easy administration through the buccal mucosal membrane lining the oral cavity. This review paper provides a comprehensive overview of the oral mucosa, mucoadhesion, factors influencing the process, assessment methodologies, and strategies for overcoming challenges in formulating buccal drug delivery systems.

KEYWORDS: Drug delivery, Buccal mucosa, Bucoadhesion, Mucoadhesion, Bio adhesive polymers.

I. INTRODUCTION:

Over the past 40 years, the concept of mucoadhesion has gained significant traction in the pharmaceutical field, primarily due to its ability to extend the residence time of bioadhesive dosage forms and enable controlled drug release through various mucosal routes. Mucoadhesive drug delivery systems have been shown to enhance the bioavailability of numerous drugs. The development of sustained, extended, and prolonged release formulations has been greatly facilitated by the use of various mucoadhesive polymers, which have garnered significant interest in recent decades.

These polymers, whether natural or synthetic, adhere to mucosal surfaces, allowing for greater absorption and improved bioavailability of the administered dosage forms. This increased effectiveness is due to the large surface area and high blood flow in mucosal cavities. Moreover, drug delivery via mucosal membranes offers several advantages over other routes, such as bypassing hepatic first-pass metabolism and avoiding degradation by gastrointestinal enzymes and intestinal flora.

The selection of appropriate mucoadhesive polymers is critical to achieving the desired adhesive strength in dosage forms. In recent years, the use of these polymers has been widely recognized as an essential strategy for prolonging the residence time of drug delivery systems and enhancing localized effects on various mucosal membranes in the body.

The potential candidates for drug delivery using mucoadhesive dosage forms include several sites such as the oral cavity, gastrointestinal tract, nasal passages, eyes, vaginal area, and rectum. A brief comparison of these sites for drug delivery was discussed, with the buccal route emerging as particularly suitable for administering pharmaceutical agents through mucoadhesive polymers. This suitability is attributed to the relatively static and smooth surface of the buccal mucosa, which allows for the placement of various mucoadhesive dosage forms like films, tablets, gels, ointments, and patches. Drugs that have a short biological half-life, poor solubility and permeability, are susceptible to enzymatic degradation, or require sustained release may be ideal candidates for delivery via the oral cavity.

Another significant site for mucoadhesive formulations is the nasal route, which offers a large surface area of approximately 150-200 cm^2. However, the presence of foreign particles can enhance the activity of the mucociliary layer, resulting in a residence time of only 15-30 minutes for particles in the nasal mucosa. Employing various mucoadhesive formulations can extend the drug's residence time in this area. Additionally, topical drug delivery to the eye remains a crucial route for treating various ocular disorders.

To effectively deliver therapeutic agents to the eye, various dosage forms such as eye drops, ointments, gels, and ocular inserts can be utilized. However, the eye’s protective mechanisms, including reflex lachrymation, drainage, and blinking, often result in poor bioavailability of many drugs as they are quickly removed from the eye’s surface. This challenge can be addressed by using mucoadhesive polymers such as poloxamer, methyl cellulose, PVP, CAP, PAMAM, and thiolated PAA, which help the drug remain in contact with the eye longer.

Mucoadhesive dosage forms are also used for drug delivery through rectal and vaginal routes, which offer several advantages such as avoiding pain, preventing tissue damage, bypassing first-pass metabolism, and reducing hepatic side effects common with parenteral administration. Polymers such as gelatin, mucin, poloxamer, and polycarbophil are commonly used for drug delivery via these routes. Various formulations for rectal and vaginal administration include creams, ointments, in-situ gels, emulgels, and tablets.

Advantages of the Mucoadhesive Drug Delivery System:

- Buccal drug delivery offers a relatively rapid onset of action compared to other non-oral routes, leading to higher patient acceptability.
- Improved patient compliance is achieved due to the easy application of dosage forms, as opposed to injections, which can be painful.
- The mucosal membranes are highly vascularized, making the administration and removal of the dosage form convenient.
- Sustained drug delivery can be achieved using mucoadhesive polymers of sustained release (SR) grades.
- The high degree of perfusion allows for faster drug absorption.
- Side effects associated with oral administration, such as nausea and vomiting, can be completely avoided.
- Mucoadhesive drug delivery is well-suited for use in unconscious or less cooperative patients.
- Drugs with poor bioavailability via the oral route can have their bioavailability enhanced through mucoadhesive delivery systems.

a. Mechanism of Mucoadhesion:

Mucoadhesion is an interfacial phenomenon where two materials, one of which is typically a synthetic substance like a mucoadhesive polymer and the other is the mucin layer of the mucosal tissue, are held together through interfacial forces of attraction. A "mucoadhesive" refers to a synthetic material that can interact with a mucus membrane, allowing it to adhere to the membrane or keep them bound together for an extended period. The process of mucoadhesion generally occurs in two stages:

1. **Contact Stage:** In this initial stage, when the mucoadhesive material comes into contact with the mucus membrane, intimate wetting occurs between the mucoadhesive and the mucosal surface, facilitated by the mucus present in the membrane.
2. **Consolidation Stage:** In this stage, various physicochemical forces of attraction enable the mucoadhesive material to bond with the mucus membrane, leading to long-lasting mucoadhesion. Once these two stages are complete, the process of mucoadhesion is considered to be finalized.

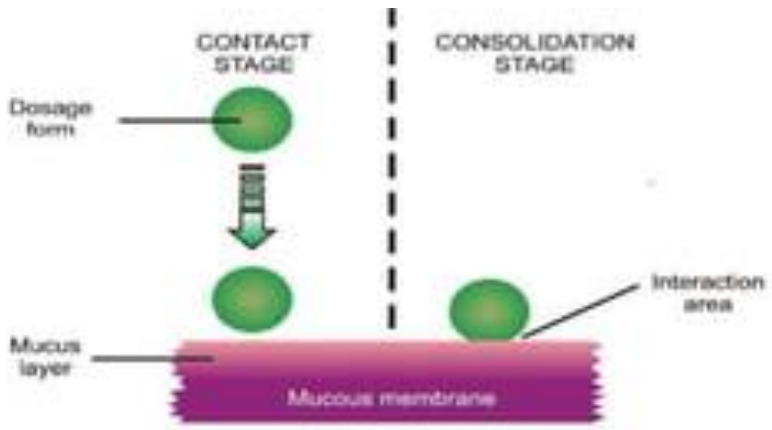

Figure 1: Mechanism of mucoadhesion

b. Mucoadhesion Theories:

While the chemical and physical foundations of mucoadhesion are not yet fully understood, six classical theories have been developed, adapted from research on the behavior of various materials and polymer-polymer adhesion, to explain this phenomenon.

1. Electronic Theory:

The electronic theory suggests that both mucoadhesive materials and biological tissues carry opposite electrical charges. When these materials come into contact, electron transfer occurs, creating a double electronic layer at the interface. The strength of the mucoadhesion is determined by the attractive forces within this electronic double layer.

2. Adsorption Theory:

According to the adsorption theory, mucoadhesion is achieved through secondary chemical interactions between the mucoadhesive device and the mucus. These interactions may include van der Waals forces, hydrogen bonds, electrostatic attractions, or hydrophobic interactions. For instance, hydrogen bonds, which are common in polymers with carboxyl groups, play a significant role in adhesion. Although these individual forces are relatively weak, the accumulation of a large number of interactions can lead to strong overall adhesion.

3. Wetting Theory:

Wetting theory applies to liquid systems that have an affinity for a surface, allowing them to spread across it. This affinity can be determined by measuring the contact angle, where a lower contact angle indicates a greater affinity. For optimal spreadability, the contact angle should be close to or equal to zero.

The spreadability coefficient, SABS_{AB}SAB, is calculated using the difference between the surface energies γB and γA and the interfacial energy γAB, as shown in Equation (1):

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB} \quad \text{(Equation 1)}$$

The greater relative to the interfacial energy, the adhesion work, WAW_AWA, increases. This means more energy is required to separate the two phases. The adhesion work is defined by Equation (2):

$$W_A = \gamma_B + \gamma_A - \gamma_{AB} \quad \text{(Equation 2)}$$

4. Diffusion Theory:

Diffusion theory describes the process where polymer and mucin chains interpenetrate to a sufficient depth, forming a semi-permanent adhesive bond. The adhesion force is believed to increase with the degree of penetration of the polymer chains. This penetration rate depends on several factors, including the diffusion coefficient, the flexibility and nature of the mucoadhesive chains, their mobility, and the contact time. According to the literature, the necessary depth of interpenetration for an effective bioadhesive bond ranges between 0.2 to 0.5 μm.

The interpenetration depth of polymer and mucin chains can be estimated using Equation (3):

$l=(t\cdot Db)^{1/2}$ (Equation 3)

where t is the contact time and DbD_bDb is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is achieved when the penetration depth is approximately equivalent to the polymer chain size.

For diffusion to occur, it is essential that the components involved have good mutual solubility, meaning the bioadhesive and the mucus should have similar chemical structures. The greater the structural similarity, the stronger the mucoadhesive bond.

5. Fracture Theory:

Fracture theory is one of the most widely used approaches in studying the mechanical measurement of mucoadhesion. It focuses on analyzing the force required to separate two surfaces after adhesion has been established. This force, denoted as SmS_mSm, is often determined during rupture resistance tests by calculating the ratio of the maximal detachment force, FmF_mFm, to the total surface area, A0A_0A0, involved in the adhesive interaction, as shown in Equation 4:

$$S_m = \frac{F_m}{A_0} \quad (4)$$

In a homogeneous, single-component system, the fracture force SfS_fSf, equivalent to the maximal rupture tensile strength SmS_mSm, is proportional to the fracture energy GcG_cGc, the Young's modulus EEE, and the critical breaking length ccc at the fracture site, as described by Equation 5:

$$S_f = \left(\frac{G_c E}{c}\right)^{1/2} \quad (5)$$

Fracture energy GcG_cGc can be derived from the reversible adhesion work WrW_rWr (the energy needed to create new fractured surfaces) and the irreversible adhesion work WiW_iWi (the work of plastic deformation caused by the removal of a proof tip until the adhesive bond is broken). Both of these values are expressed in units of fracture surface area AfA_fAf, as shown in Equation 6:

$$Gc=Wr+Wi\ldots\ldots\ldots\ldots 6)$$

The system's elastic modulus E is related to stress σ\sigma σ and strain ε\ varepsilon ε by Hooke's law.

A notable critique of this analysis is that it assumes the system under study has known physical dimensions and consists of a single, uniform material. Therefore, the derived relationships may not apply to the fracture site of a multi-component bioadhesive. In such cases, the equation should be modified to account for the elastic dimensions and moduli of each component. Additionally, it is important to note that adhesive failure is expected to occur at the bioadhesive interface. However, studies have shown that rupture rarely happens precisely at the surface; instead, it typically occurs near the surface or at the weakest point, which could be the interface itself, the mucus layer, or the hydrated region of the mucus.

Since fracture theory primarily focuses on the force required to separate the components, it does not consider the interpenetration or diffusion of polymer chains. Therefore, this theory is most suitable for calculating forces in rigid or semi-rigid bioadhesive materials, where polymer chains do not penetrate the mucus layer.

6. Mechanical theory:

Mechanical theory explains adhesion as the result of a mucoadhesive liquid filling the irregularities of a rough surface. This surface roughness increases the interfacial area available for interactions, which helps dissipate energy and plays a crucial role in the adhesion process. However, the mucoadhesion process may vary in different scenarios, making it difficult to describe with a single theory. All existing theories are important for identifying key variables in the process. The mechanisms that govern mucoadhesion depend on both the intrinsic properties of the formulation and the environment where it is applied. Intrinsic factors of the polymer include its molecular weight, concentration, and chain flexibility. For linear polymers, mucoadhesion generally increases with molecular weight, but this relationship may not hold for non-linear polymers.

Research has shown that more concentrated mucoadhesive dispersions remain on the mucous membrane longer, particularly in systems that form gels in situ. These systems spread easily when applied, as they behave like liquids, but gelify upon contact with the absorption site, preventing rapid removal. Chain flexibility is essential for effective interpenetration between the formulation and mucus. Environmental factors include pH, initial contact time, swelling, and physiological variations. pH can affect the formation of ionizable groups in polymers and charges on the mucus surface. The duration of contact between the

mucoadhesive and the mucus layer influences the extent of chain interpenetration. Excessive hydration can result in mucilage formation without effective adhesion. The thickness of the mucus layer varies, ranging from 50 to 450 μm in the stomach to less than 1 μm.

c. Factors Influencing Mucoadhesion:

- **Molecular Weight:**

  The mucoadhesive strength of a polymer increases with molecular weights greater than 100,000. There is a direct correlation between the mucoadhesive strength of polyoxyethylene polymers and their molecular weights, which typically ranges from 200,000 to 7,000,000.

- **Flexibility:**

  Mucoadhesion begins with the diffusion of polymer chains in the interfacial region. To achieve the necessary entanglement with mucus, the polymer chains must possess a significant degree of flexibility. The enhanced chain interpenetration can be attributed to the increased structural flexibility of the polymer when polyethylene glycol is incorporated. Generally, the mobility and flexibility of polymers are linked to their viscosities and diffusion coefficients, as higher flexibility leads to greater diffusion into the mucus network.

- **Cross-Linking Density:**

  The average pore size, the number and average molecular weight of the cross-linked polymers, and the cross-linking density are three crucial and interconnected structural parameters of a polymer network. As the cross-linking density increases, the rate at which water diffuses into the polymer network decreases. This results in insufficient swelling of the polymer and a reduced rate of interpenetration between the polymer and mucin.[12]

- **Hydrogen Bonding Capacity:**

  Hydrogen bonding plays a crucial role in the mucoadhesive properties of a polymer. Effective polymers must possess functional groups capable of forming hydrogen bonds, and the flexibility of the polymer enhances its potential for hydrogen bonding. Polymers like poly(vinyl alcohol), hydroxylated methacrylate, and poly(methacrylic acid), along with their copolymers, exhibit strong hydrogen bonding capabilities.

- **Hydration:**

  For a mucoadhesive polymer to function effectively, it must undergo hydration to expand and form a sufficiently sized macromolecular mesh. This process also increases the mobility of polymer chains, which is essential for enhancing the interpenetration between the polymer and mucin. Polymer swelling facilitates mechanical entanglement by exposing bioadhesive sites for hydrogen bonding and/or electrostatic interactions with the mucus network. However, there is an optimal level of hydration required for the polymer to achieve the best swelling and mucoadhesion.

- **Charge:**

  The charge of a bioadhesive polymer significantly influences its mucoadhesive properties. Generally, nonionic polymers exhibit lower adhesion compared to anionic polymers. A strong anionic charge is essential for effective mucoadhesion. Certain cationic polymers also demonstrate excellent mucoadhesive properties, especially in neutral or slightly alkaline environments. High–molecular-weight cationic polymers, such as chitosan, have shown good adhesive qualities. Although the charge of the membrane plays a role in mucoadhesion, the pH of the membrane is more critical as it affects the ionization state of the polymers.

- **Concentration:**

  Polymer concentration is key to forming a strong adhesive bond with mucus. This can be attributed to the length of the polymer chains available to penetrate the mucus layer. When polymer concentration is too low, there are fewer penetrating chains per unit volume of mucus, resulting in weak polymer-mucus interactions. Typically, a more concentrated polymer leads to longer penetrating chains and stronger adhesion. However, each polymer has a critical concentration level, beyond which the polymer structure becomes highly coiled, reducing solvent accessibility and chain penetration. As a result, higher polymer concentrations do not always improve mucoadhesive properties and may even decrease them in some cases.

II. BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEM:

The mucoadhesive drug delivery system targeting the mucous membrane of the oral cavity can be divided into three types:

- Sublingual delivery
- Buccal delivery
- Local delivery

These oral sites offer a rich blood supply, facilitating enhanced drug absorption due to sufficient permeability. Among these three oral mucoadhesive drug delivery systems, buccal delivery is considered the most convenient. The buccal mucoadhesive drug delivery system has several advantages over other drug delivery methods, including:

- It can be utilized for both local and systemic delivery of various drugs.
- Buccal mucoadhesive dosage forms are easier to apply compared to other adhesive dosage forms.
- It offers increased patient compliance compared to injectable methods.
- It is the preferred system for the local treatment of drugs, leading to the development of a wide range of mucoadhesive formulations.

Limitations:

- Drugs with a bitter taste are unsuitable for this formulation.
- Drugs that irritate the oral mucosa, cause allergic reactions, or lead to tooth discoloration cannot be used.
- The presence of antimicrobial agents in the formulation may disrupt the natural microbial balance in the buccal cavity.
- Patients may experience discomfort while eating, drinking, or speaking.
- Only drugs that can be absorbed through passive diffusion are suitable for administration via the buccal route.
- Drugs that are unstable at buccal pH cannot be administered this way.
- Moisture-sensitive drugs may degrade due to saliva.

III. CHALLENGES OF THE BUCCAL DRUG DELIVERY SYSTEM:

- **Low Permeability**: The buccal membrane has lower permeability, especially when compared to the sublingual membrane, which can limit drug absorption.
- **Limited Surface Area**: The oral cavity offers a total surface area of approximately 170 cm^2 for drug absorption, with only about 50 cm^2 comprising non-keratinized tissues, including the buccal membrane. This smaller area restricts the absorption capacity.
- **Saliva Secretion**: The continuous production of saliva, ranging from 0.5 to 2 liters per day, can dilute the drug, reducing its effectiveness.
- **Drug Loss Due to Swallowing**: Swallowing saliva can result in the loss of dissolved or suspended drugs, potentially leading to the involuntary removal of the dosage form.

IV. OVERVIEW OF THE ORAL MUCOSA:

The oral mucosa serves as one of the most crucial pathways for drug delivery, supporting both systemic and local drug absorption. The oral cavity provides a large surface area of approximately 100 cm^2, lined with mucus membranes, which facilitates the complete absorption of various drugs. The different parts of the oral cavity include:

- The floor of the mouth (sublingual area)
- The buccal mucosa (cheeks)
- The gums (gingiva)
- The palatal mucosa
- The lining of the lips

The oral mucosal cavity is composed of multi-layered epithelial tissues covered by mucus. Beneath these epithelial tissues lies a basal membrane, followed by a layer of connective tissue known as the lamina propria, which provides mechanical support. Beyond the lamina propria is the submucosal layer, which

contains various blood vessels and nerves from the central nervous system. This submucosal layer offers high vascularity, allowing for the efficient absorption of drugs.

The human oral mucosa includes both keratinized epithelium (found in the gingiva and parts of the hard palate) and non-keratinized epithelium (found on the surface of the soft palate, floor of the mouth, lips, and cheeks). The oral mucosa primarily consists of three layers, as illustrated in Figure 2 [19].

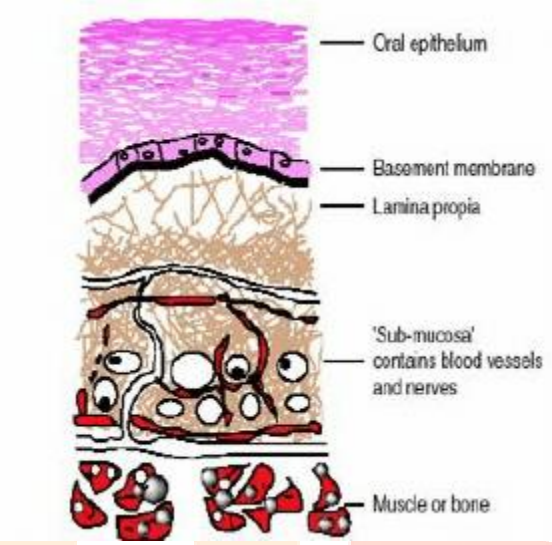

Figure 2: Anatomical structure of buccal route.

V. Mucus Composition:

Oral mucus is secreted by various glands within the oral cavity, including the sublingual gland, parotid gland, and other salivary glands. This mucus is a translucent gel produced by goblet cells or specialized exocrine glands containing mucus cells. The components of oral mucus are detailed in Table 1 below:

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

Table 1: Composition of mucus.

Mucus glycoproteins are large molecular proteins that have attached oligo-polysaccharide units. The following oligosaccharide units are present in mucus:

- L-fructose
- D-galactose
- N-acetyl-D-glucosamine

- N-acetyl-D-galactosamine
- Sialic acid

Functions of Mucus:

- Cell-cell adhesion
- Lubrication
- Bioadhesion
- Protection
- Barrier

VI. BUCCAL MUCOADHESIVE DOSAGE FORMS:

An ideal drug delivery system should ideally have two key properties:

1. **Spatial placement:** Targeting the drug to specific organs or tissues.
2. **Temporal delivery:** Controlling the rate at which the drug is released.

However, creating a perfect drug delivery system is challenging. This challenge has led to the development of sustained and controlled release systems. Despite these advancements, such systems still struggle to prevent drug loss due to hepatic first-pass metabolism or pre-systemic elimination (e.g., gastric, intestinal, or colonic degradation). To address these issues, various strategies have been explored to develop suitable dosage forms.

One promising approach is oral mucosal drug delivery. This physiological method has shown potential in formulating drugs into effective dosage forms with favorable therapeutic outcomes. Oral mucosal delivery of different drugs can be achieved using bioadhesive polymer systems.

VII. GENERAL CONSIDERATIONS IN DESIGNING DOSAGE FORMS:

Physiological Aspects:

Delivering drugs locally within the oral cavity is particularly challenging due to the constant flow of saliva and regular tissue movement. These factors reduce the residence time of drugs administered through this route. Buccal mucoadhesive formulations have been developed to address this issue. By using bioadhesive polymers, the residence time in the buccal mucosa can be extended, thereby improving drug absorption. Local absorption also helps reduce side effects compared to systemic delivery. Typically, a buccal delivery device should measure around 1-3 cm^2, with a daily drug dose not exceeding 25 mg. Ellipsoid or circular shapes are generally preferred for these devices.

Pathological Aspects:

The buccal mucosa's barrier function is primarily due to its epithelial tissue. However, the thickness of this tissue can be influenced by various diseases, potentially altering its barrier properties. Certain diseases or treatments may also affect mucus secretion rates, which in turn could impact the residence time of buccal delivery devices.

Pharmacological Aspects:

The design and formulation of a buccal dosage form depend on several factors, including the nature of delivery (local or systemic), the target site, and the mucosal area to be treated. Buccal delivery is often favored for systemic administration over local delivery.

Pharmaceutical Aspects:

Buccal drug delivery systems are typically used for drugs with poor water solubility. To enhance absorption through the buccal mucosa, the water solubility of the drug is often increased using solubility enhancement techniques, such as complexing with cyclodextrin. Optimizing the formulation's release and penetration characteristics is essential, as is considering the drug's organoleptic properties and those of the buccal dosage form. Excipients like plasticizers and penetration enhancers can improve the formulation's effectiveness and acceptability. Given the buccal mucosa's low permeability, various penetration enhancers, such as bile salts, fatty acids, and sodium lauryl sulfate, can be used. Enzyme inhibitors may also be included to prevent drug degradation by salivary enzymes, thereby improving bioavailability. Certain polymers, like carbopol and polycarbophil, can inhibit proteolytic enzymes such as trypsin and carboxypeptidases. The pH of the buccal delivery device is another important factor; it should be near neutral (saliva pH ranges from 6.6 to 7.4) to avoid mucosal irritation.

VIII. TYPES OF BUCCAL MUCOADHESIVE DOSAGE FORMS:

1. **Type I:** A single-layer dosage form that allows multidirectional drug release. However, it has the disadvantage of high drug loss due to swallowing.
2. **Type II:** A drug-loaded bioadhesive layer covered by an impermeable backing membrane, which only covers the side opposite the attachment site, preventing drug loss from the upper surface.
3. **Type III:** The drug-loaded mucoadhesive layer is completely covered by an impermeable membrane, except for the side that attaches to the target area, ensuring unidirectional drug flow and minimizing unwanted drug loss.

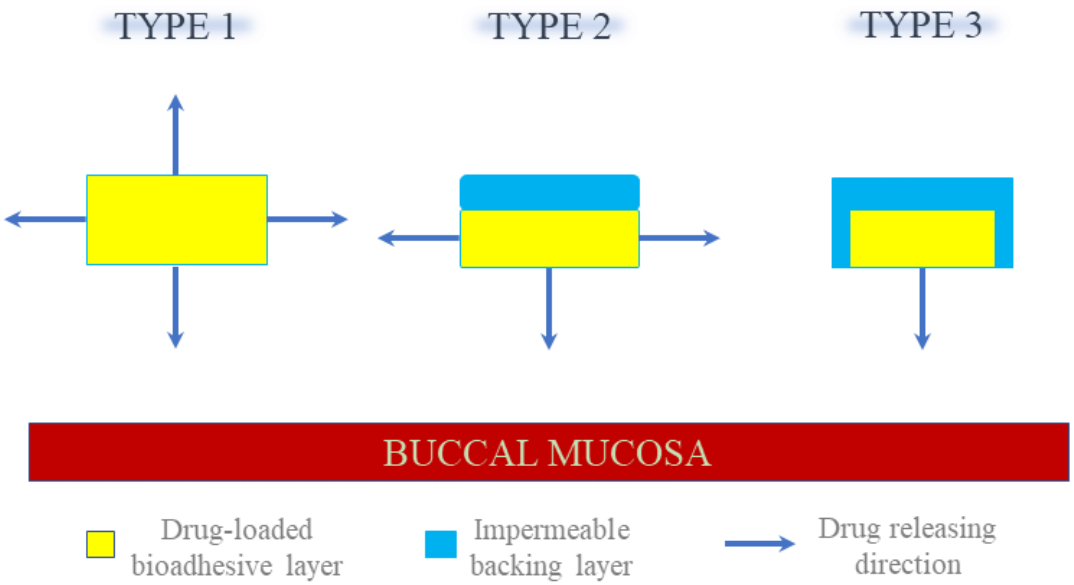

Figure:3 Types of buccal mucoadhesive dosage form.

IX. KEY COMPONENTS OF A BUCCAL DRUG DELIVERY SYSTEM:

Drug Substance:

When selecting an active pharmaceutical ingredient (API) for a buccal drug delivery system, its pharmacokinetic properties are crucial.

The ideal drug should possess the following characteristics:

Low Dose: The drug's single dose should be small, ideally ≤ 25 mg.

Short Biological Half-Life: The drug should have a short biological half-life, typically between 2 to 8 hours.

First-Pass Metabolism: Drugs that undergo significant first-pass metabolism are well-suited for buccal delivery, as this route can bypass the first-pass effect.

Bioadhesive Polymers:

The selection of bioadhesive polymers plays a crucial role in determining key parameters such as mucoadhesive strength, thickness, in-vitro drug release, and the residence time of the drug delivery system. Polymers with high molecular weight are generally preferred because they effectively control the release rate.

To achieve optimal results, an ideal polymer should possess the following characteristics:

- It should be inert.
- It should be compatible with both the environment and the drug.
- It should adhere quickly to the mucous membrane and maintain adhesion for the required duration.

Criteria	Categories	Examples
Source	Semi natural	Agarose, chitosan, elatine, Hyaluronic acid, Various gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate)
	Cellulose derivatives [CMC, thiolated CMC, Sodium CMC, HEC, HPC, HPMC, MC, MHEC]	Thiloated CMC, HEC, HPC, Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), PVA
Aqueous Solubility	Water-soluble	CP, HEC, HPC (water below 38.8°C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, (DEAE)-dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum

Backing Membrane:

The backing membrane used in formulations should be impermeable to both the drug and mucus to prevent unnecessary drug loss from all sides of the device. The materials selected for the backing membrane should be inert, insoluble, or have low water solubility. Common materials used for backing membranes include ethyl cellulose, carbopol, sodium alginate, HPMC, and polycarbophil.

Plasticizers:

Plasticizers are added to enhance the folding endurance of the delivery device, providing sufficient flexibility to the dosage form to improve patient acceptability and compliance. Common examples of plasticizers include PEG-400, PEG-600, dibutyl phthalate, and propylene glycol.

Permeation Enhancers:

Permeation enhancers are chemicals or liquids used to improve the drug's permeation from the device into the mucus membrane. They work through several mechanisms, including:

- Reducing the viscosity of mucus.
- Increasing the fluidity of the lipid bilayer membrane.
- Overcoming the enzymatic barrier.
- Increasing the thermodynamic activity of drugs.

X. CLASSIFICATION OF BUCCAL ADHESIVE DOSAGE FORMS:

Solid Dosage Form

- **Buccal Tablet:**

Bioadhesive tablets are the most commonly preferred mucoadhesive devices for enhancing the bioavailability of drugs. These tablets can be manufactured using methods such as wet granulation or direct compression. For buccal drug delivery, the tablets are positioned in the buccal pouch, located beneath the muscles of the teeth. The mechanism of drug release from these tablets is primarily through erosion.

- **Bioadhesive Microspheres:**

Microspheres play a crucial role in novel drug delivery systems. These mucoadhesive microspheres are primarily utilized for targeted delivery to specific body cavities.

- **Bioadhesive Wafers:**

Bioadhesive wafers represent a newer dosage form for buccal drug delivery. They are applied in the periodontal region to treat infections associated with periodontitis.

- **Bioadhesive Lozenges:**

Bioadhesive lozenges are typically used for the delivery of drugs such as antimicrobials, corticosteroids, local anesthetics, antibiotics, and antifungals. These are applied topically in the buccal cavity.

Semisolid Dosage Forms:

- **Bioadhesive Patches/Films:**

Patches or films are often preferred over tablets due to their comfort and flexibility. These formulations are designed to ensure good contact between the bioadhesive and the mucosa. However, the thickness of the patch can be a limitation, as it may not allow for controlled drug release over an extended period. In the case of drug-containing reservoir layers, the drug can be released in a controlled manner. Patches and films are primarily used for local treatment of oral diseases. Various methods are used to formulate these patches or films, including solvent casting, hot melt extrusion, direct milling, semisolid casting, and solid dispersion extrusion, with solvent casting being the most popular and widely used method.

- **Buccal Gels and Ointments:**

Gels and ointments offer the advantage of dispersion, which has drawn attention. Unlike unit dosage forms like tablets, patches, or films, gels and ointments do not provide precise dosing, making them more suitable for local action where dose accuracy is not a primary concern.

Medicated Chewing Gum:

Medicated chewing gum is a dosage form that delivers drugs through chewing. This allows for a high concentration of the drug to be released for local action in the mouth, and it can also be absorbed into the systemic circulation. Examples include chewing gums used for nicotine replacement therapy and caffeine gums.

Liquid Dosage Forms:

Liquid dosage forms, such as solutions or suspensions of drugs in suitable vehicles, are commonly used for local drug delivery. Examples include mouthwashes and mouth fresheners. Various polymers are used in these formulations, with chitosan being notable for its superior binding capacity. Viscous liquid formulations are often preferred as they coat the buccal cavity, serving as either a vehicle or a protective agent.

XI. EXPERIMENTAL METHODOLOGIES FOR BUCCAL ABSORPTION / PERMEABILITY STUDIES:

In-vitro and Ex-vivo Methods of Evaluation:

In-vitro studies are utilized to assess the release, solubility, and dissolution characteristics of dosage forms. Ex-vivo studies, on the other hand, involve testing on animal tissues and membranes by preparing animal models. These tissues are obtained from freshly deceased animals and must be used within two hours of collection. The membranes are stored in ice-cold (4°C) Krebs buffer until they are mounted between diffusion cells for ex-vivo permeation experiments.

In-vivo Methods:

Also known as the buccal absorption test, this method measures drug absorption kinetics. The procedure involves human volunteers swirling a 25 ml sample of the test solution in their buccal cavity for up to 15 minutes, after which the solution is expelled. The amount of drug absorbed can be determined by calculating the amount of drug present in the expelled solution. Potential disadvantages include salivary dilution of the drug and accidental swallowing of the sample.

Experimental Animal Species:

The choice of animal species is crucial for in-vivo studies. Researchers select animals based on the specific tests being conducted. While most animals have keratinized buccal mucosa, rabbits and pigs possess non-keratinized mucosa similar to humans. Monkeys, dogs, and pigs are commonly used for drug permeation studies.

In-vitro Release Study:

To simulate in-vivo conditions, researchers have developed various apparatus, including:

- Beaker method
- Dissolution apparatus
- Interface diffusion system
- Modified Keshary Chien cell

XII. Methods to Study Mucoadhesive Strength

The characterization of polymers for their mucoadhesive properties can be assessed using both in vivo and in vitro techniques.

In Vitro Evaluation Techniques:

1. Measurement of Tensile Strength:

This method involves calculating the force required to break the bioadhesive bond between the mucus membrane and the bioadhesive polymer. The tensile strength of a buccal mucoadhesive device can be determined using the following formulas:

- **Force of adhesion (N) =** Mucoadhesive strength × 9.81 / 1000
- **Bond strength (N/m²) =** Force of adhesion (N) / Surface area of the tablet (m²)

Various instruments are employed for measuring tensile strength, including:

- Modified physical balance or tensile tester
- Wilhelmy Plate Technique

2. Measurement of Shear Strength:

This technique assesses the mucoadhesive strength by measuring the shear stress applied to the adhesive device. The process involves using two smooth, polished glass blocks. One block is fixed on a glass plate with adhesive on a leveled table, while the other block is attached to a thread that passes through a pulley. A 17 g pan with weights is attached to the bottom end of the thread. The shear strength is determined by correlating the weight required to break the adhesion.

3. Rheological Study: Rheological analysis of polymer–mucus mixtures provides a valuable in vitro model that can correlate with the in vivo performance of a mucoadhesive polymer. This method evaluates the mucoadhesive potential of polymers by comparing binary mucus/polymer blends with equally concentrated monocomponent mucus/polymer systems. The rheological behavior of these macromolecular species can be altered by chain interlocking and chemical interactions between the bioadhesive polymer and mucin chains.

4. Colloidal Gold Staining Method:

This novel in vitro method is used to compare the mucoadhesive properties of various hydrogels. Red colloidal gold particles, stabilized by partially or fully adsorbed mucin, are employed in this technique. The interaction with the mucoadhesive causes the surface to develop a red color. The intensity of this red color is measured to compare the mucoadhesive properties of different devices.

5. Fluorescent Probe Method:

In this technique, the lipid bilayer of cultured human conjunctiva cells is labeled with pyrene, a fluorescent probe. If a polymer adheres to these cells, it alters the fluorescence due to changes in surface compression compared to control cells. The degree of fluorescence change is directly proportional to the amount of polymer binding. Additional probes can be used to determine polymer charge, density of adhesion, and charge sign. This method is based on the molecular interaction between the polymer and mucus to determine the bioadhesive bond.

In Vivo Evaluation Methods:

Gamma Scintigraphy Techniques:

Gamma scintigraphy is a non-destructive method used to evaluate pharmaceutical dosage forms. It provides detailed information on various aspects of the gastrointestinal (GI) tract, including the site of drug absorption, the timing and location of dosage form disintegration, and the impact of diseases and food size on the biopharmaceutical characteristics of the dosage forms. This technique is particularly useful for studying the distribution and retention time of mucoadhesive tablets.

GIT Transit Using Radio-Opaque Technique:

This technique employs radio-opaque markers to assess the effect of polymers on GI transit time. Non-invasive methods, such as fecal examination and X-ray evaluation, can yield sufficient data on GI residence time. Examples of markers used for mucoadhesive drug delivery include Cr-51, Tc-99m, In-113m, and I-123.

Thickness:

Randomly select five different patches and measure their thickness using a screw gauge.

Folding Endurance:

Choose a patch and fold it repeatedly at the same point until it breaks. The number of folds required to rupture the patch is its folding endurance. The folding endurance of the buccal patch should exceed 150 folds.

Swelling Study for Tablets:

Accurately weigh the mucoadhesive dosage form and place it in a beaker with 200 ml of buffer media. Remove and weigh the dosage form at regular intervals up to 8 hours. Calculate the swelling index using the following formula:

Swelling Index (S.I.)=Wt−WoWo

Swelling Index (S.I.)=WoWt−Wo

where:

- WtW_tWt = Weight of the dosage form at time t
- WoW_oWo = Initial weight of the dry dosage form

Surface pH Study:

Measure the surface pH of the buccal dosage form to assess the potential for any in-vivo side effects due to acidic or basic pH. Use a glass electrode to determine the pH. Soak the dosage form in distilled water at room temperature for 2 hours to allow swelling, then measure the pH by placing the electrode in contact with the surface of the dosage form.

Residence Time:

To determine the residence time of the buccal dosage forms, use a modified disintegration apparatus. Prepare 800 ml of isotonic buffer solution with a pH of 6.75. Attach a 3 cm long piece of rabbit mucosa to a glass slide, which is then vertically positioned. Hydrate one surface of the mucoadhesive tablet with 15 ml of isotonic phosphate buffer solution, and place it in contact with the mucosal surface. Allow the glass slide to move up and down to ensure complete immersion. Record the time it takes for the tablet to detach from the mucosal surface.

XIII. Conclusion:

Buccal drug delivery offers numerous advantages, including ease of administration, accessibility, withdrawal, retention, high patient compliance, cost-effectiveness, and low enzymatic activity. This method can bypass first-pass metabolism in the liver and pre-systemic clearance in the gastrointestinal tract. The buccal site is ideal for retentive devices and is generally well-tolerated by patients. Another benefit is that the permeability of the mucosal layer can be managed and modified to enhance drug absorption with appropriate dosage form designs and formulations. Buccal drug administration holds promise as a non-invasive approach for delivering potent peptides and protein-based therapeutic agents, as well as for the systemic delivery of drugs that are ineffective when taken orally. However, absorption enhancers are crucial for the future of buccal drug delivery to ensure safer and more effective permeation.

Mucoadhesive systems may become increasingly important in developing new pharmaceuticals due to the large influx of novel compounds from pharmacological research. The buccal and sublingual routes offer significant potential and various formulation strategies due to their effectiveness, benefits, and ease of access through oral mucosal tissue, though current commercially available formulations are mostly limited to tablets and films. Consequently, the buccal mucosa presents several advantages for long-term controlled drug delivery and provides a suitable environment for systemic distribution.

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