Review Article

A Comprehensive Review of Buccal Drug Delivery System

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ABSTRACT

Buccal drug delivery systems extend 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. Numerous medications can now be administered using this route thanks to its association with buccal drug delivery. The use of novel materials that may combine mucoadhesive, enzyme-inhibitory, and penetration-enhancing qualities is one way to get around the primary challenges that medications face when taken through the buccal route. Because it is simple to administer through the buccal mucosal membrane bordering the oral cavity, buccal administration is a desirable administrative route. Other barriers that must be taken into account are the oral cavity's efficient physiological clearance systems, which remove the formulation from the absorption site. The use of novel materials that may combine mucoadhesive, enzyme-inhibitory, and penetration-enhancing qualities, as well as the development of creative drug delivery systems that, in addition to enhancing patient compliance, promote a closer interaction between the drug and the absorption mucosa, are some of the strategies being investigated to get past such barriers. The most modern methods of drug delivery are transmucosal products. This article objectives potential, factors of bioadhesive & mucoadhesive, characterization parameters and basic concept of drug delivery.

Keywords: Buccal Delivery, Oral Mucosa, Mucoadhesion, Bio-adhesive Polymers.

1. INTRODUCTION

Buccal administration is one of the most effective medication administration techniques for both systemic and local pharmacological activities. The tissues that adhere to polymers, whether natural or manufactured, are referred to as bio-adhesion [1]. For prolonged, regulated drug distribution, the buccal mucosa provides a number of benefits. First-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided, and the mucosa is adequately supplied with both vascular and lymphatic drainage [2]. Investigating alternate routes for the delivery of such medications was prompted by challenges related to parenteral administration and low oral availability. To increase the bioavailability of these medications, a number of tactics have been used, such as reversible chemical changes, absorption enhancers, innovative formulation techniques, and additional enzyme inhibitor dosing. The buccal region of the oral cavity is a desirable target for the delivery of the medication of choice because it has great accessibility, a smooth muscular expanse, and relatively immobile mucosa compared to other transmucosal routes [3]. Both localized and systemic medications are administered through the oral cavity. However, oral administration of groups of drugs, especially proteins and peptides, is not advised due to disadvantages such enzyme breakdown and hepatic first pass metabolism inside the GI tract. Consequently, it is believed that the mucosal layer of absorption may be used as a site for drug administration [4]. Among these, medication administration to the oral cavity has garnered special interest because of its distinct physiological characteristics and potential for high patient compliance. There are two types of medication delivery within the oral mucosal cavity: (i) local delivery and (ii) systemic distribution through the buccal or sublingual mucosa. This review offers an overview of the developments in oral transmucosal delivery devices and looks at the physiological aspects of the oral cavity in relation to systemic drug delivery [5]. Cohesion is the propensity of similar or identical surfaces or particles to stick together, whereas adhesion is the inclination of dissimilar surfaces or particles to stick together [6]. The impact of the oral environment on medications should be taken into account when applying topical medications to the oral cavity. Drug delivery through the oral cavity is impacted by the intricate bacterial biofilm and its complex physical and chemical environment [7]. The drawbacks of traditional drug administration methods have prompted researchers to look for novel approaches. The fields of pharmaceutical and biopharmaceutical technology have advanced recently. One area that has seen substantial advancements and modifications is the systemic distribution of active pharmacological components (drugs) using innovative administration techniques [8]. The buccal membrane's limited permeability, particularly in comparison to the sublingual membrane, and its lower surface area are drawbacks to drug administration by this method. The buccal membrane and other non-keratinized tissues make up around 50 cm of the 170 cm of the oral cavity's membrane surface area that is available for drug absorption. Constant salivary flow (0.5–2 l/day) causes the medication to be diluted later [9]. Many fast-dissolving tablets are either very porous or naturally soft-molded matrices, or tablets compacted at very low dissolution/disintegration time. The delivery system is simply placed on a patient's tongue or any oral mucosal

tissue. Many of these tablets are soft, friable, and/or brittle (like the lyophilized dosage forms), and they frequently require specialized and costly packaging and processing [10]. Interfacial pressures hold two materials together when at least one of them is biological, a phenomenon known as bioadhesion [11]. Investigating the evidence about the existing formulations based on nanoparticles and their uses in the oral route of drug delivery was the goal of this investigation. To enable the effective use of these drugs, the study concentrated on various nanoparticulate formulations, stability, bioavailability, biocompatibility, toxicity, and morphology [12]. The buccal and sublingual mucosa serve as absorption sites for transmucosal medication delivery, which has two therapeutic objectives. Acute diseases are treated by using the sublingual procedure. It is typically used for drug delivery because of its high permeability across the mucosa. The buccal method is typically used when a continuous release of the active ingredient is required, as in the case of chronic diseases, but there are drawbacks to the sublingual procedure [13]. A medicine administered sublingually is placed beneath the tongue, whereas a substance administered buccally is placed between the cheek and gums. For medication administration, the buccal and sublingual routes are seen to be promising substitutes for the conventional oral route [14]. Regarding the requirement for dissolving and disintegration before medication absorption, the formulations vary. Additionally, until the drug has been absorbed, patients should refrain from eating, drinking, chewing, or swallowing [15]. The buccal epithelium turnover period has been estimated to be 5- 6 days, which is most likely indicative of the entire oral mucosa. The thickness of oral mucosa varies by place, with the buccal mucosa measuring 500-800µm and the hard and soft palates, floor of the mouth, ventral tongue, and gingiva measuring 100-200µm [16]. The oral delivery of certain drug classes is impeded by medication administrations, such as hepatic first-pass metabolism and GI enzymatic degradation. Because of this, the absorptive mucosae are considered as potential locations for drug administration. Methods of transmucosal medication delivery, including the mucosal linings of the nasal and rectal cavities [17]. The use of polymeric materials for medicinal applications is expanding quickly [18].

2. ADVANTAGES ORAL DOSE FORMS OVER ALTERNATIVE DOSAGE FORMS:

- Simplicity of administration.
- The right dosage.
- Self-medication
- Avoiding pain.
- Patient adherence [19].

They are used to administer drugs both locally and systemically in the oral cavity. Extended-release dose forms use this delivery method to enhance the medication's therapeutic efficacy. In the pharmaceutical sector, oral mucoadhesive drug delivery systems are becoming more and more popular. The most common mucosal dosage forms now on the market include chewing gum, ointment, cream, gel, spray, and tablet [20]. This technique is utilized to treat both systemic disorders and diseases that occur in the buccal cavity. The buccal mucosa's barrier qualities, residence time, and narrow absorption area are some of the restrictions. This review article explains the anatomy and physiology of the buccal cavity, as well as the obstacles and theories underlying the buccal system, drug delivery system formulation and design, and assessment of buccal cavity drug delivery [21]. Numerous chemical absorption enhancers and enzyme inhibitors have been used to facilitate therapeutic medication distribution through the oral mucosal route; these enhancers have been well investigated [22]. It is commonly known that medicinal chemicals absorbed from the oral mucosa allow the medicine to enter the systemic circulation directly, bypassing the gastrointestinal drug degradation and first-pass hepatic metabolism that are linked to peroral delivery [23]. The mucosal lining of the mouth, eye, vagina, rectum, and nasal cavity make up the transmucosal mode of drug transmission, which has advantages over oral systemic drug delivery systems. These characteristics include avoiding the pre-elimination of the drug in the GI tract and dependence on the drug's characteristics, avoiding the first-pass metabolism, and demonstrating improved enzymatic flora for drug absorption [24]. This idea will only work if the formulation offers adequate mucosal penetration and buccal retention. This study assessed mucoadhesive carrier systems that included propylene glycol as a penetration enhancer, mucoadhesive polymers (Hypromellose (HPMC), chitosan, and carbomer), and CBD-loaded silica (Aeroperl 300) carriers. They Extend the residence time of the dosage form at the absorption site, thus increasing the bioavailability and its therapeutic effect [25].

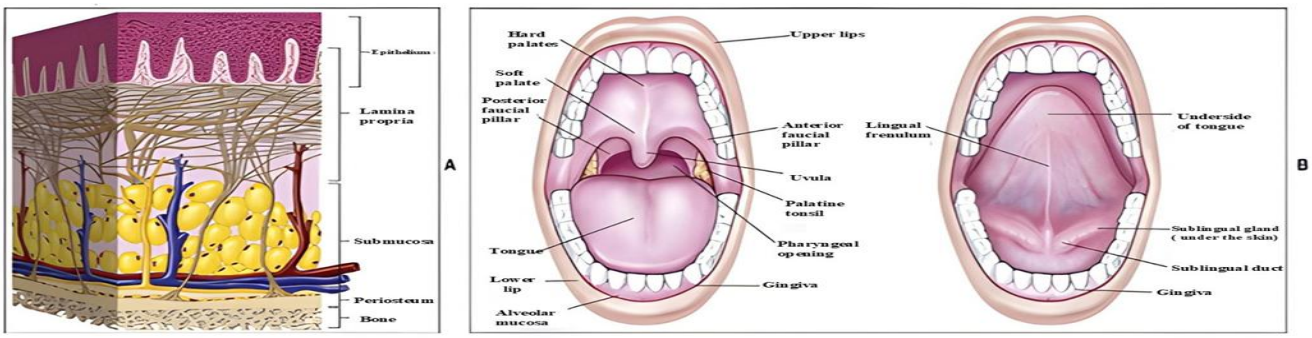

Figure 1: Anatomy of Oral Mucosa [2].

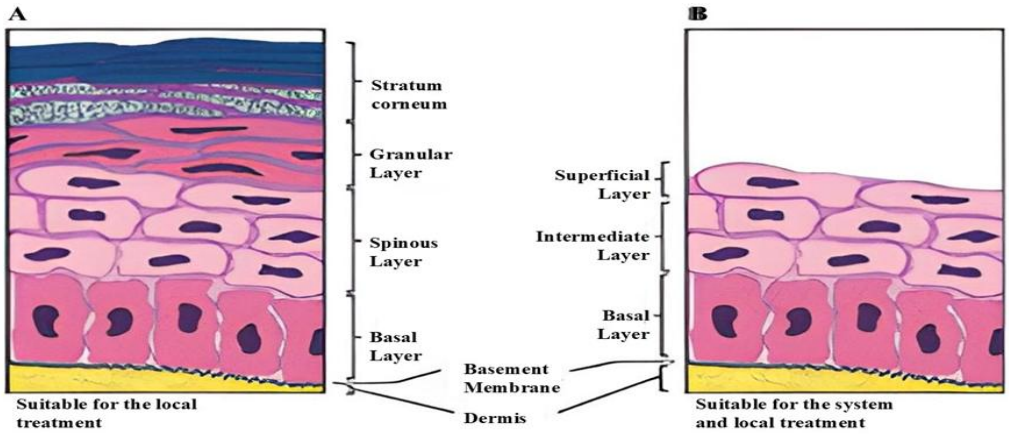

Figure 2: (A) The oral keratinized epithelium (B) non-keratinized epithelium [16].

3. OVERVIEW OF ORAL MUCOSA

Both keratinized and non-keratinized epithelium are present in the oral membrane cavity (Figure 2). Ceramides and acyl ceramides, which are mostly non-polar lipids, make up the keratinized mucosal epithelium, which is comparatively impervious to water. Therefore, it is appropriate for oral cavity local therapy [20].

The sabmucosa comes behind a basement membrane known as the lamina propria. It also has a lot of sensory receptors, such as the tongue's taste receptors. Collagen fibers make up the lamina propria, which is a layer of smooth muscles, blood vessels, and connective tissues. Either a single layer (stomach, small and large intestine, bronchi) or several layers (esophagus, vagina) make up the epithelium. Goblet cells, which are found in the top layer, secrete mucus components straight onto the surface of the epithelium. Mucus, a viscous, gelatinous secretion made up of glycoproteins, lipids, inorganic salts, and up to 95% water, gives tissues their wet surface [26]. Because of pre-systemic metabolism, administration by buccal or sublingual route can help prevent drug compound concentration. Systemic administration can negate the GIT's degradation and metabolism of the dose form [27]. An outermost layer of stratified squamous epithelium (about 40–50 layers thick), a lamina propria, and the submucosa as the innermost layer make up the oral mucosa. Site-specific variations in oral mucosal thickness include the buccal mucosa, which is 500–800 µm thick, and the hard and soft palates, floor of the mouth, ventral tongue, and gingival mucosa, which are approximately 100–200 µm thick [28].

3.1 Structure

The outermost layer of stratified squamous epithelium makes up the oral mucosa. The foundation membrane, lamina propria, and submucosa are the deepest layers that are visible below this. The buccal mucosa's epithelium has roughly 40–50 cell layers, whereas the sublingual epithelium has a somewhat lower number [2]. Based on different areas of the oral cavity, light microscopy shows multiple unique patterns of maturation in the human oral mucosa's epithelium [20]. The moist lining of the inner cheek, known as the buccal mucosa, is an essential component of the mucosal drug delivery system because it gives medications a direct path into the bloodstream. Drug adherence and absorption are significantly influenced by the structure and makeup of the buccal mucosa mucus layer. The composition and structure of the mucus layer of the buccal mucosa [29].

3.1.1 Structure of the Buccal Mucosa: [30]

1. Stratified squamous epithelium: A stratified squamous epithelium, including many layers of flat, densely packed cells, covers the buccal mucosa. This epithelium offers defence against environmental factors and mechanical harm.

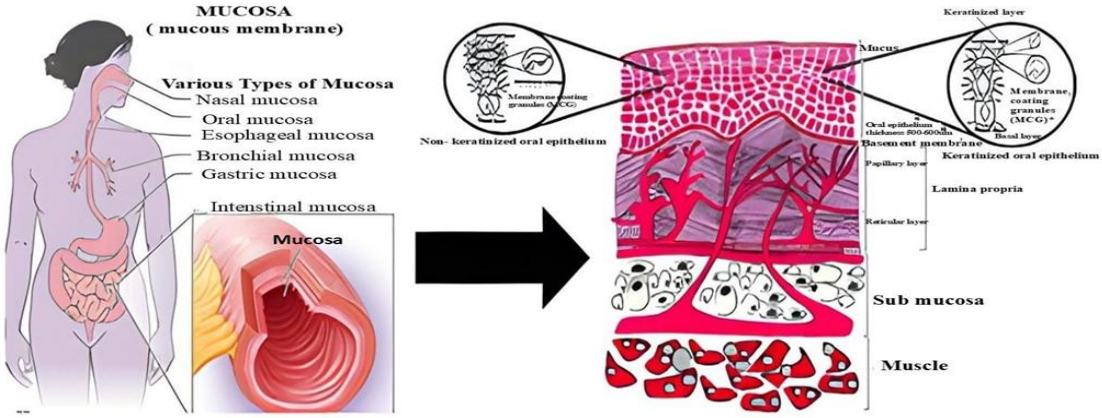

Figure 3: The Structure Representation of Mucosa Layer or Mucosa [30]

2. Basement membrane: This thin, cellular layer, which separates the stratified squamous epithelium from the underlying connective tissue, is located beneath the epithelium.

3. Connective tissue: The buccal mucosa receives food and innervation from the blood vessels and nerves found in the connective tissue layer.

3.2 Permeability

In general, the oral mucosa is a type of relatively permeable epithelium that lies in between the intestines and epidermis. The buccal mucosa's permeability is thought to be 4–4000 times higher than the skin's. Due to the various forms and functions of the various oral mucosae, there are significant variations in permeability between various oral cavity regions, as seen by the large range in this reported value [2]. Protease inhibition, immunogenic response reduction, and local tissue permeability alteration are all made possible by it. This allows for the relative use of therapeutic agents such proteins, peptides, and ionized species [17]. Stronger skin permeability is encouraged by the integrated nano emulsion system's incorporation into the gel core [31].

3.2.1 Drug absorption through the oral mucosa can occur through the following routes:

i. Trans-cellular

ii. Para-cellular [1]

The oral mucosa's permeabilities decline in the following order: buccal greater than palatal, and sublingual greater than buccal. The sublingual mucosa is relatively thin and non-keratinized, the buccal mucosa is thicker and non-keratinized, and the palatal mucosa is intermediate in thickness but keratinized. This ranking order is based on the relative thickness and degree of keratinization of these tissues [16]. According to recent data, carrier-mediated transport has been found to have a minor part in the movement of medications across the buccal mucosa, whereas passive diffusion is the main route. There are two passive transport pathways in the buccal mucosa: one entails the transit of substances into and across cells (transcellular) and the other entails their movement via the intercellular space between cells (paracellular). Enzymatic breakdown is another factor that prevents drugs from passing through the buccal epithelium [26].

3.2.2 Role of Saliva:

A. Protective fluid for all mouth cavity tissues.

B. The tooth enamel's ongoing mineralization and demineralization.

C. To hydrate dosage formulations for oral mucosa.

3.2.3 Role of Mucus:

A. composed of carbs and proteins.

B. Adherence between cells.

C. Mucoadhesive drug delivery systems lubrication and bioadhesion [26].

3.3 Environment

Mucus, the intercellular ground substance that surrounds the cells of the oral epithelia, is primarily composed of protein and carbohydrate complexes [2]. provides the perfect setting for proteins and peptides that are sensitive to stomach contents and enzymes that aid in digestion [32]. For a long time, the active agent may be released continuously, cyclically, or in response to environmental stimuli or other outside occurrences. In any event, the goal of regulating medication delivery is to eliminate the possibility of both underdosing and overdose while achieving more effective therapy [33]. Buccal distribution of medications is an alternative for the traditional oral route of drug administration to overcome shortcomings such as high first pass metabolism and drug degradation in the harsh gastrointestinal environment [1]. The process might also be impacted by the surroundings in which adhesion takes place. The durability and efficacy of mucoadhesive and bioadhesive materials can be impacted by variables such pH, temperature, and the presence of enzymes [30].

4 POLYMER MOLECULAR WEIGHT

Several investigations have shown that bioadhesion peaks at a specific molecular weight. modest molecular weight polymers exhibit a modest range of expansion and a high range of interpenetration. Low range of interpenetration and high range of expansion are characteristics of high molecular weight polymers [8]. For instance, PEG with a molecular weight of 20,000 has low adhesive strength; PEG with a molecular weight of 200,000 is improved; and PEG with a molecular weight of 400,000 has exceptional adhesive qualities. The bioadhesiveness of linear polymers rises as the molecular weight does. This observation suggests two things: (a) entanglement is necessary for higher molecular weight polymers, and (b) interpenetration is more important for smaller molecular weight polymers. The trend for nonlinear structural adhesiveness is much different. The adhesive strength of PEG, which has a molecular weight of 200,000, is comparable to that of dextran, which has a molecular weight of 19,500,000. In contrast to the PEG conformation, the dextran helical shape may cover several adhesion-related groups, which could be the cause of the resemblance [6].

5 IDEAL CHARACTERISTICS OF BUCCAL DRUG DELIVERY SYSTEM

• The medications utilized in buccal drug delivery that are solely absorbed by the passive diffusion Citation process.

• The medications' molecular weight should be between 200 and 500 Daltons, and they should not smell.
• These that are hydrophilic and lipophilic can be appropriately added to buccal dosage forms.

• Buccal drug delivery devices are ideal for the tasteless and persistent pH medications [1].

• For a few hours, it should stay attached to the attachment site.

• The medicine should be released under strict surveillance.

• The medication release should be directed only toward the mucosa [2].

• The polymer should be inexpensive and widely accessible.

• Both in the liquid and dry states, it should exhibit bioadhesive qualities [3].

• Sufficient mechanical strength and rapid adhesion to the buccal mucosa.

• The controlled release of drugs.

• Promotes both the pace and volume of medication absorption.

• The patient should comply well [21].

6 FACTORS AFFECTING BIOADHESIVE / MUCOADHESIVE

Interfacial forces hold two materials together when at least one of them is biological, a process known as bioadhesion. The adhesion between a polymer or copolymer and a biological membrane is an example of an attachment that may occur between an artificial substance and a biological substrate. The term "mucoadhesion" is used when referring to a polymer that is affixed to the mucin layer of mucosal tissue [31]. Through interaction between the ionizable functional group and the charged mucin layer component, ionic polymers increase mucoadhesion and foster robust adhesiveness [34]. Since it describes the chemical interaction between mucoadhesive polymer and mucin, adsorption theory has been studied extensively among other hypotheses. However, the function of charge in adhesion is outlined by electron theory [35]. These are round or oval, single or multilayered thin films that are primarily composed of an impermeable layer and a bioadhesive polymeric layer to allow for a one-way drug flow across the buccal mucosa[36].

6.1 Polymer Related Factor

A very long molecule made up of recurring and structural units joined by covalent chemical bonds is referred to as a polymer [37]. Swelling properties and polymer hydration may be the primary factors. These polymers include carbopol, polyvinyl-pyrrolidone, polyvinyl alcohol, hydroxyethylcellulose, and hydroxypropylcellulose [1]. The bonding process involves the surfaces of the biological membrane, the adhesive surface, and the interfacial layer between the two surfaces. The molecular processes occurring in the interfacial layer are influenced by the properties of the membrane and polymer [14].

6.1.1 Molecular Flexibility

The flexibility of the polymer chain is essential for interpenetration and growth. Cross linking in water-soluble polymers reduces the mobility of individual polymer chains [8]. More diffusion into the buccal mucus network results from the mucoadhesive chain's increased flexibility. Mucoadhesion is boosted as a result. As the polymer concentration rises, the polymer chain's elasticity falls. The polymer chain must successfully diffuse into the mucous layer for bioadhesion to occur. The viscosity and diffusion coefficient of a polymer chain determine its flexibility [37].

6.1.2 Concentration of active polymer

In general, a higher concentrated polymer would result in a longer penetrating chain length and better mucoadhesion; a low concentration could induce an unstable contact between the polymer and mucin. Nevertheless, each polymer has a critical concentration over which the penetration of the polymer chain may be diminished [6]. It may cover up the formulation's unfavorable taste without adding any off-taste. Incompatible with high electrolyte and resorcinol concentrations, cationic polymers, and phenols [37]. Mucoadhesion requires the correct concentration of polymers. The strength of adhesion decreases when the concentration of the polymer exceeds the optimal concentration because the coiled molecules in the polymer separate from the medium, limiting the chain's availability for interpenetration. There are fewer penetrating polymer chains per unit volume and less interaction amongst the polymers in mucus when the concentration of polymers is lower [21].

6.1.3 Polymer Chain Length

The length of the polymer molecule must be sufficient [2]. Given the complexity and interpenetration, chain flexibility is crucial. Cross-linking between the water-soluble polymers and the substrate results in decreased mobility of the individual polymers, which in turn affects the strength of mucoadhesion and the penetration of the polymers into the mucus. As a result, the polymer chain has some flexibility to accomplish the entanglement. Their viscosity and diffusion coefficient are correlated with their mobility and flexibility[21].

6.2 Environment Related Factor

6.2.1 Applied Strength:

Interpenetration may be impacted if pressure is initially applied to the mucoadhesive tissue contact site. Even though the polymer doesn't have the ability to interact, it becomes mucoadhesive when strong pressure is applied [20].

6.2.2 Initial Contact Time:

The degree of swelling, interpenetration of polymers, and mucoadhesive strength are all impacted by the first contact time between the polymer and mucin [20]. The degree of swelling and the interpenetration of polymer chains are determined by the first contact period between the polymer and the mucous membrane. As the first contact time increases, so does the mucoadhesive strength [26].

6.2.3 Moistening:

Moistening produces a particle size that is appropriate for polymer penetration into mucin and offers the perfect conditions for the mucoadhesive polymer to disperse across the mucin surface [20].

6.2.4 pH:

The charge on the mucus and polymer surfaces is affected by pH. Because of variations in the dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone, mucus will have a varied chart density based on pH [2].

6.2.5 Hydrogen Bonding Capacity:

Hydrogen bonding is another important factor in mucoadhesion of polymers. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential. Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly (methacrylic acid), as well as all their copolymers, are polymers with good hydrogen bonding capacity [3].

6.2.6 Charge:

The connection between the polymer and mucus is unstable and there are few penetrating polymer chains per unit volume of mucus when the polymer concentration is too low. Generally speaking, the more concentrated polymer would produce stronger adhesion and a longer penetrating chain length. However, because of its highly coiled form, each polymer has a critical concentration over which it produces a bun disturbed state [3].

6.2.7 Hydration (swelling):

To improve the interpenetration process between the mucoadhesive polymer and mucin, hydration is necessary for the polymer to expand and form a suitable "macromolecular mesh" of enough size as well as to cause mobility in the polymer chains [2].

6.2.8 Cross-Linking Density:

Three crucial and interconnected structural parameters of a polymer network are the average pore size, the average molecular weight of the cross-linked polymers, and the crosslinking density [3].

7 Basic concept of buccal drug delivery system

7.1 Drug Substance:

Prior to creating buccoadhesive drug delivery systems, it is necessary to determine if a local or systemic effect and quick or extended release are the desired outcomes. Pharmacokinetic characteristics should guide the choice of an appropriate medication for the development of buccoadhesive drug delivery systems [38].

• The drug's typical single dose should be modest.

• The best choices for regulated drug administration are medications with a biological half-life of two to eight hours.

• When taken orally, the drug's T max exhibits larger fluctuations or higher values.

• Drugs taken orally may have pre-systemic drug elimination or a first-pass impact.

• When used orally, the medicine should be absorbed passively [39].

7.2 Bio-adhesive Polymer

Choosing and characterizing the right bioadhesive polymers for the formulation is the first stage in creating buccoadhesive dosage forms [40]. This idea explains how bio-adhesive polymers can spread across biological surfaces. In this case, the two surfaces angle of contact is measured. The wettable polymers stick to epithelial surfaces the best [41]. In buccoadhesive medication delivery systems, bioadhesive polymers are essential. Additionally, polymers are employed in matrix devices, which control the length of drug release by embedding the drug in the polymer matrix. Bioadhesive polymers belong to the most varied class and offer significant advantages for patient care and therapy. The core layer or rate-controlling layer allows the medicine to enter the mucosal membrane. Bioadhesive polymers that stick to the mucin/epithelial surface work well and greatly enhance oral medication administration [42].

7.3 Ideal Characteristics of Buccal Drug Delivery [27]

• The polymer and its decomposing byproducts should be safe and free of poisons that drain out, they should also be well-hydrated, soluble, and biodegradable.

• The bio-adhesive set need to be solid and ductile.

• Local enzymes should have adhesively active groups if they exhibit penetration and inhibitory characteristics.

• The ideal molecular weights should be used.

• The acceptable shelf-life must be indicated.

• Confirmation in space is required.

• Needs to be an excellent bonding person.

• Must remain on the attachment site for a few hours.

• Dependent on the medication-controlled release.

• The drug's release into the mucosa should be unidirectional.

7.4 Criteria followed in polymer selection [28]

- It must be compatible with the biological cell.
- It must have a high molecular weight and a limited distribution.
- It must establish a strong non-covalent bond with the mucine/ epithelial surface.

7.5 Backing Membrane

When it comes to attaching bioadhesive devices to the mucous membrane, the backing membrane is crucial. Inert materials that are impermeable to the medication and penetration enhancer should be utilized as backing membranes [29]. Buccal bioadhesive patches with such an impermeable layer improve patient compliance and stop medication loss. Carbopol, magnesium stearate, HPMC,

HPC, CMC, polycarbophil, and other compounds are frequently utilized in backing membranes [20].

7.6 Penetration Enhancers

When a medication needs to enter the systemic circulation in order to work, penetration enhancers are also necessary. These tought to be non-irritating and reversible; once the medication has been absorbed, the epithelium should regain its barrier qualities. Fatty acids, surfactants, bile salts, azone, and alcohols are the most prevalent groups of buccal penetration enhancers [42]. Chemicals that may improve penetration include terpenes (like eucalyptus), fatty acids (like oleic acid), solvents (like ethanol), and surfactants (like Tween). Furthermore, bile salts, azone, polymers with the muc-oadhesion property, and currently chitosan and its derivatives have the ability to improve penetration. Chitosan is thought to have the potential to improve the penetration of hydrophilic macromolecular medications that are absorbed through the mucosa [43].

7.7 Bio-adhesives

Substances known as bioadhesives have the ability to engage with biological material and remain on it or hold it together for a long time. In addition to increasing the drug's intimacy and length of contact with the absorbing membrane, bioadhesive can be applied to any mucous or non-mucous membrane. Gelatin, sodium alginate, carbomers, polycarbophil, HPMC, HPC, and others are examples of bioadhesives that are frequently employed [2]. Putting the medication between the cheeks and gums to transport it through mucosal membranes in the bloodstream [4].

- The bioadhesion of biological layers without the use of synthetic materials. Two excellent examples are cell aggregation and diffusion.
- Cell adherence into culture dishes or adhesion to a range of materials, such as metals, woods, and other synthetic materials, are examples of bioadhesion.
- Artificial material attachment to biological substrates, such as polymer adhesion to soft tissues like skin [39].

8. Approaches of Buccal Drug Delivery System

8.1 Non-attached Drug Delivery System

Due to the local physiological environment, such as salivary flow and food and liquid consumption, non-attached drug delivery systems have numerous disadvantages [3]. This comprises chewing gum formulations, microporous hollow fibers, and dosage forms for fast-dissolving tablets. The nonattached drug delivery mechanism is significantly impacted by the local physiological environment, such as salivary flow and food and liquid consumption [2].

8.2 Bio-adhesive Drug Delivery Systems [3]

8.2.1 Solid Buccal Adhesive Dosage Forms

8.2.2 Semi-Solid Buccal Adhesive Dosage Forms

8.2.3 Liquid Buccal Adhesive Dosage Forms

8.2.1 Solid Buccal Adhesive Dosage Forms:

Dry formulations dehydrate the local mucosal surface to produce bio-adhesion [3].

1. Buccal Tablet

Tablets have been the most commonly investigated dosage form for buccal drug delivery to date. Buccal tablets are small, flat and oval with a diameter of approximately 5–8 mm. Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek as well as between the lip and the gum [33].

2. Microparticles

The same benefits as tablets are provided by bioadhesive microparticles, but because of their physical characteristics, they can intimately contact a larger mucosal surface area. The discomfort of a foreign object in the oral cavity is lessened by the tiny size of microparticles, which makes them less likely to induce local irritation at the point of adhesion than tablets [3]. Usually administered as an aqueous suspension, they can also be applied as an aerosol or mixed into an ointment or paste. Microparticles can be supplied to less desirable areas, such as the upper nasal cavity and gastrointestinal tract (GIT), and they can intimately contact a larger mucosal surface area. Its diminutive size lessens the discomfort caused by the foreign items in the oral cavity as well as the local irritation at the adhesion site [13].

3. Wafers

Antimicrobial agents, biodegradable polymers, and matrix polymers make up the bulk layer of the delivery system, which is a composite wafer with surface layers that have sticky qualities [9]. The solvent evaporation process, which involves dissolving the polymeric material with or without plasticizer in a solvent or solvent mixture and dispersing the active ingredient, is the primary technique for creating polymeric films. After this solution is poured onto an appropriate substrate, the solvent is left to evaporate, leaving behind a solid polymeric film that contains the medication. Other methods including hot-melt extrusion and direct compression have also been used to create these kinds of dosage forms. These kinds of methods have the advantage of not using organic solvents, which makes them environmentally friendly [5].

4. Lozenges

Depending on the kind of excipients included to the dosage form, these solid dosage forms made by compressing powder mixtures can be applied to the oral mucosa and either dissolve or stick. They have the ability to deliver drugs in multiple directions to the mucosal surface or the oral cavity. As an alternative, an impermeable backing layer could be used in the dosage form to guarantee unidirectional drug delivery. The non-ubiquitous

distribution of the drug in saliva for local therapy and patient acceptance (mouth feel, taste, and discomfort) are potential drawbacks of buccal tablets [5].

These bioadhesive lozenzes brief residence period at the site of absorption, which varies depending on formulation size and type, limits the total amount of medicine that may be administered. They disintegrate in 30 minutes. The patient often controls the dissolution or disintegration of lozenges by sucking the unit as hard as possible. Uncontrolled swallowing and drug loss down the GI system are caused by increased salivation and sucking. As a result, the absorption and bioavailability of solid dose forms typically vary significantly more between and within individuals. Additionally, unidirectional drug release is not possible with these kinds of systems. Another significant obstacle to the effectiveness of such dose formulations is the continuous flow of saliva [28].

8.2.2 Semi-solid Buccal Adhesive Dosage Forms.

1. Gel

Upon instillation, this kind of formulation is liquid, but in response to stimuli like pH, ionic strength, or temperature, it passes through a phase transition to form a viscoelastic gel. When the pH rises, carbomers become more viscous. Poloxamers with Smart Hydrogel® (Adnaced Medical Solution) gel at body temperature [27]. Increased ionic strength causes gellan gum and alginate to develop, especially when Ca+2 ions are present. Currently, gel-forming formulations are employed for long-term ocular administration [19].

2. Buccal patches

Patches are laminates made up of a bioadhesive surface for mucosal adhesion, an impermeable backing layer, and a drug-containing reservoir layer from which the drug is delivered in a regulated manner. Buccal patch systems are comparable to transdermal drug delivery methods. Direct milling and solvent casting are two techniques used to create sticky patches. By casting the drug and polymer solution onto a backing layer sheet and then letting the solvent(s) drain, the solvent casting process creates the intermediate sheet from which patches are punched [43,44].

3. Buccal Films

A variety of ingredients, including polymer, plasticizer, medication, sweetener, and other required additions, are typically used to make buccal films. Mucoadhesive films made of polymers have been widely employed recently [45]. The most modern dosage form for buccal administration is a film. Because buccal films are more flexible and comfortable than sticky tablets, they might be chosen. Additionally, they can get beyond oral gels' brief duration of residence on the mucosa, which is readily eliminated by saliva. Additionally, when oral illnesses are delivered locally, the films also aid in protecting the surface of the wound, which lessens discomfort and improves the effectiveness of treatment. Despite its simplicity, the solvent casting method has several drawbacks, such as a lengthy production time, high costs, and environmental issues because of the solvents utilized [43].

8.2.3 Liquid Buccal Adhesive Dosage Forms

It is possible to apply viscous liquids to the buccal surface as protective coatings or as drug delivery vehicles to the mucosal surface. In the past, goods viscosity was increased using pharmaceutically acceptable polymers to help with retention in the oral cavity. Artificial saliva solutions that are kept on mucosal surfaces to provide lubrication are used to treat dry mouth. Sodium CMC is a bioadhesive polymer found in these solutions [3].

9 Advantages of Buccoadhesive Drug Delivery

Using buccoadhesive drug delivery for drug administration has various benefits, including:

1. The medication is simple to administer, and it is possible to stop therapy in an emergency.

2. Extended duration of drug release.

3. Drugs can be given to traumatized and unconscious patients.

4. Drugs boost bioavailability by avoiding the first pass metabolism.

5. Buccal administration is an option for certain medications that are unstable in the stomach's acidic environment.

6. The passive diffusion method of drug absorption.

7. Adaptability in terms of surface, size, shape, and physical state.

8. Close contact with the absorbing membrane results in a maximum absorption rate.

9. Quick start to action [2].

10. Lower systemic toxicity, self-administration, and drug dosage [46].

10 Disadvantages of Buccoadhesive Drug Delivery

The buccal drug delivery technique has certain drawbacks, like:

1. It is impossible to deliver medications that are unstable at buccal pH.

2. This method cannot be used to administer medications that irritate the mucosa, have an unpleasant taste, or have an offensive odor.

3. Only a modest dose of the necessary drug can be given.

4. This is the only way to give medications that are absorbed by passive diffusion.

5. Restrictions may be placed on eating and drinking [2].

6. Its dose size is minimal since it increases the absorption of active components [47].

Table 1: BDDS Characterization of Parameters [49]

Sr. No.	Characterization Parameter	Method Used	Instrument	Used For Dosage Form
1.	Surface pH	Visual colour change	pH meter	Mucoadhesive tablet, Patch, tablet Fims
2.	Swelling index	Swelling of Tablet and patch in pH 6.4 phosphate buffer	Agar gel plates	Tablet films, wafers, Patches, films
3.	Morphology	Microscopy	Scanning Electron Microscopy (SEM)	Tablets, Patches, film
4.	Drug compatibility	Spectral analysis, Thermal analysis	Differential Scanning Calorimeter (DSC), X-ray Diffractometer (XRD), Fourier Transform infrared spectrometer (FTIR)	Films Tablets, Wafers, patches
5.	Folding endurance	constant folding at the same point	Manually folded	Patches, Films
6.	Thicknesses	Standard deviation	Electronic digital micrometer, vernier calipers, screw gauze	Films tablets, wafers, patches
7.	Water absorption capacity test	Agar plate technique	desiccator	Patches or film
8.	Mucoadhesive strength	Tensile strength	Texture analyzer	Films tablet, patches
9.	In-vitro drug release	Beaker method; Rotating peddle method; Dissolution method	Kesary chein cell; Franz diffusion cell	Tablets, Microspheres, patches or films
10.	Residence time	Disintegration	Modified disintegrator	Patches, film
11.	Mechanical properties	Wilhelmy plate technique	Modified tensile strength tester or micro process	Patches, film, buccal hydrogel
12.	Hardness	Crushing force	Monsanto hardness tester	Tablets, wafers
13.	Friability	weighing	Roche friabilator	tablets
14.	Drug content	Titration	Ultra violet (UV) spectrophotometer, Reverse-phase high performance liquid chromatography (RP HPLC)	Tablets, patches or films
15.	Flatness	Constriction	Vernier Calipers	Patches, films
16.	Contact angle	Optical tensiometer	Optical tensiometer	Films
17.	Bio-adhesive	Colloidal gold staining method, Florescence probe method	Dissolution cells	Patches, Films
18.	Water vapour transmission rate	Dressing method	Ovens	Patches, Films
19.	Drug entrapment	Assay	UV spectrophotometer	Films, Patches, Microspheres
20.	Transparency	Transmittance	UV spectrophotometer	Films
21.	Ex-vivo residence time	Disintegration test	Modified disintegration test apparatus	Patches, Films Tables
22.	Percentage moisture loss	Gravimetry method	Desiccator	Patches, Films

11 Limitation of Buccal Drug Administration

There are some restrictions when using the buccal route to take drugs:

• It can be challenging to administer medications with large dosages.

• The potential for patients to forget to consume the medications.

• Until the medication release is over, eating and drinking may be prohibited.

• For medications that are unstable at the pH of the buccal environment, this route is inappropriate.

• Medication that irritates the mucosa or has an unpleasant or bitter taste cannot be administered in this route.
• The surface area accessible for absorption is little [40].

• Prodrug development and screening limitations [48].

CONCLUSION

This review presents, oral administration of buccal doses forms, its structure, permeability & environment. The buccal drugs have different factors according to the bioadhesive and mucoadhesive dosage forms. Different types of formulations and parameters are used in it. There are solid buccal, semi-solid and liquid buccal dosages forms are prepared and used.

Mucoadhesive buccal patches have applications from various angles, including avoiding first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. The mucosa is well supplied with both vascular and lymphatic drainage, and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and seems to be acceptable to the patient. The permeability and the local environment of the mucosa can be controlled and manipulated to allow drug permeation. The Flash release wafer is promising due to the availability of modern technologies combined with well-built market acceptance.

Future possibilities for improvements in fast dissolving drug delivery system are bright. Pharmaceutical researchers may find this review useful in elucidating the potential of BDDS to resolve current drug delivery disputes over medication bioavailability, permeability, and absorption efficiency.

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