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A comprehensive review on buccal drug delivery system

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Abstract
Buccal drug delivery has emerged as a promising and innovative approach for administering pharmaceutical agents, offering advantages such as bypassing hepatic first-pass metabolism, enhanced patient compliance, and the potential for controlled release. This research paper provides a thorough and systematic review of the current state-of-the-art in buccal drug delivery systems, encompassing various aspects of formulation development and delivery mechanisms. The review begins by elucidating the anatomical and physiological characteristics of the buccal mucosa, emphasizing its significance in drug absorption. Key formulation strategies, including mucoadhesive polymers, permeation enhancers are discussed in detail, shedding light on their impact on drug bioavailability and therapeutic efficacy. In conclusion, this comprehensive review provides valuable insights into the current landscape of buccal drug delivery systems, offering a roadmap for future research directions and the development of innovative therapeutic solutions. The integration of multidisciplinary approaches, collaboration between academia and industry, and a focus on personalized medicine are emphasized as key factors in advancing the field of buccal drug delivery.

Keywords: Buccal drug delivery, Mucoadhesion, mucoadhesive polymers, drug, first-pass effect

Introduction

The traditional oral route is ineffective for delivering many biotechnologically generated medications due to physiological and biochemical factors that affect their absorption and metabolism. Investigating alternate methods for the delivery of such medications was spurred by challenges related to parenteral delivery and low oral availability. Many tactics have been used to increase these medications' bioavailability. [1] As a result, buccal distribution of medications is an option for administering medications instead of orally, especially for medications that have a first-pass effect. [2] The buccal area of the mouth mucosal cavity is an appealing route of administration for regulated systemic medication delivery. The administration of medication via the mucosal membrane lining the cheeks is known as buccal delivery.[3] The buccal has considerable appeal for both local and systemic drug bioavailability due to its capacity to maintain a delivery system at a specific place for a longer duration of time.[4]

Mucosal drug delivery is being investigated more thoroughly due to recent advancements in drug delivery. Oral, buccal, ocular, nasal, and pulmonary routes are among them. Mucoadhesive drug delivery systems work by utilizing the bioadhesion of specific polymers, which becomes adhesive during hydration. This allows the delivery of drugs to specific body regions for prolonged periods of time. [5] Among the various systems of the mucoadhesive drug delivery system are: [6]

- Buccal drug delivery systems.
- Sublingual drug delivery systems.
- Rectal drug delivery systems.
- Vaginal drug delivery systems.
- Ocular drug delivery systems.
- Nasal drug delivery systems.

Characteristics of Buccal Drug Delivery System

The ideal buccal adhesive system ought to have the following features

- Releases the drug in a regulated manner Adheres quickly to the buccal mucosa and has enough mechanical strength.
- Promotes the rate and degree of drug absorption.
- The patient should comply well.
- Must not impede basic bodily processes like speaking, eating, and drinking.
- Needs to achieve a one-way drug release that targets the mucosa.
- Must not promote the growth of secondary infections like dental caries.
- Have a large safety margin on a local and systemic level.
- Need to be able to withstand saliva's flushing effect. [7]

Advantages of Buccal Drug Delivery System:

- It has no first-pass hepatic impact and is highly vascularized, making it easier to administer and remove dose forms from.
- Easy to administer.
- In the gastrointestinal tract, there is no pre-systemic metabolism.
- Patient accessibility is simple.
- A large area of mucosa and smooth muscle that is suitable for applying retentive dose forms but is not very mobile.
- Steer clear of exposing the drugs to the digestive juices.
- Quicker cellular repair and localized area completion on the smooth surface of the buccal mucosa.
- Non-invasive method of administering medication.[8]

Disadvantages of Buccal Drug Delivery System

- Limited absorption area: Of the 170 cm^2 of oral cavity membrane surface area that is available for drug absorption, 50 cm^2 are made up of non-keratinized tissues, such as the buccal membrane.
- The rate and extent of drug absorption through the buccal mucosa are retarded by barriers like mucus, saliva, basement membrane, membrane coating granules, etc. Continuous saliva secretion (0.5-2 L/day) results in the subsequent dilution of the drug.
- There is a risk of choking if the delivery device is inadvertently swallowed.
- Saliva swallowing may also result in the drug becoming suspended or dissolved, which could cause the dosage form to be involuntarily removed. [9]

Limitation of Buccal Drug Delivery System

There are some restrictions when administering drugs through the buccal mucosa.

- This route cannot be used to administer medications that irritate the oral mucosa, taste bitter or unpleasant, or have an unpleasant odor.
- This method cannot be used to administer medications that are unstable at buccal pH.
- Only medications with low dosage requirements may be used.
- Drugs that are swallowed with saliva lose the benefits of the buccal route.
- Only medications that are absorbed through passive diffusion may be given via this method.
- It's possible for the patient to swallow the formulation.
- The formation of a slippery surface due to overhydration may occur, and the bio-adhesive polymers' swelling and hydration may compromise the formulation's structural integrity. [10]

Oral mucosal sites

Three types of drug delivery are distinguished within the oral mucosal cavity:

1. **Sublingual delivery:** This refers to the administration of the medication to the systemic circulation through the sublingual mucosa, which is the membrane that covers the floor of the mouth and the ventral surface of the tongue.
2. **Buccal delivery:** This refers to the administration of medication to the systemic circulation
3. **Local delivery:** Used to treat diseases of the mouth, mainly periodontal disease, fungal infections, and ulcers. The anatomical features, drug permeability, and duration of delivery system retention of these oral mucosal sites vary significantly from one another. [11]

Anatomy of oral cavity

The tongue, lips, cheeks, hard palate, soft palate, and floor of the mouth make up the oral cavity. The mucous membrane lining the oral cavity is comparatively thick, dense, multilayered, and highly vascularized. The soft palate, the floor of the mouth, the underside of the tongue, and the buccal and labial mucosa all of which typically have non-keratinized epithelium make up the mucous secreting region. The skin in the hard palate region is keratinized. The lips borders and the highly keratinized dorsal surface of the tongue comprise the specialized zone. The lingual, facial, and retromandibular veins drain blood from the oral mucosa. The veins avoid first pass metabolism because they open into the internal jugular vein. Since the stratum corneum might act as a barrier to the penetration of mucous membranes. Traditionally, the medications are applied to non-keratinized areas such as the sublingual and buccal areas. [12]

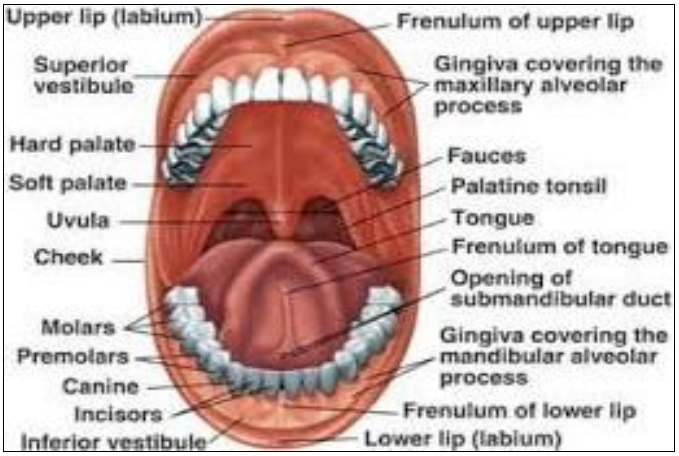

Fig 1: Structure of Oral cavity

Overview of the Oral Mucosa

A. Structure

The outermost layer of stratified epithelium makes up the oral mucosa. A basement membrane, a lamina propria, and the submucosa, the innermost layer, are located below. The epithelium resembles the rest of the body's stratified squamous epithelia. Its basal cell layer, which is mitotically active, progresses through several differentiating intermediate layers to reach the superficial layers, where cells are shed from the epithelium's surface. The sublingual Epithelium has slightly fewer cell layers than the buccal mucosa epithelium, which is roughly 40–50 cell layers thick. As the epithelial cells move from the basal layers to the superficial layers, they enlarge and flatten. It has been estimated that the buccal epithelium turnovers in 5–6 days, which is likely indicative of the oral mucosa turnover rate overall. The thickness of the oral mucosa varies based on the location: the gingival, floor of the mouth, ventral tongue, hard and soft palates, and gingiva measure between 100 and 200 μm. The buccal mucosa measures between 500 and 800 μm.

B. Role of Saliva
- Fluid that protects all of the oral cavity's tissues.
- Persistent mineralization of dental enamel.
- To hydrate dosage forms for oral mucosa.

C. Role of mucus
- Consists of both carbohydrates and proteins.
- Cell adhesion to cell.
- The lubricant.
- Mucoadhesive drug delivery system bioadhesion. [13, 14]

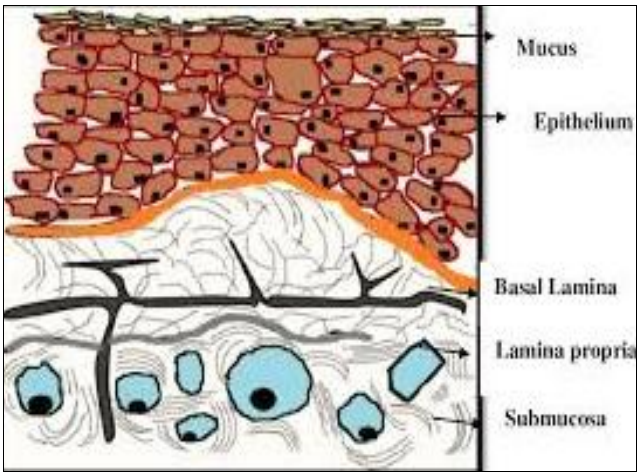

Fig 2: Structure of buccal mucosa

Factors affecting buccal absorption
Because there are numerous independent and interdependent factors that lower the absorbable concentration at the site of absorption, the oral cavity presents a complex environment for drug delivery.

1. Membrane factors
Include lamina propria, intercellular lipids of the epithelium, surface area available for absorption, mucus layer of the salivary pellicle, and degree of keratinization. The thickness of the absorptive membrane, lymphatic and blood supply, cell renewal, and enzyme content will also help to lower the quantity and rate at which the drug enters the systemic circulation.

2. Environmental Factors
a. Saliva: Salivary pellicle or film is the term for the thin layer of saliva that covers the entire buccal mucosa. Salivary film has a thickness of 0.07 to 0.10 mm. The rate of buccal absorption is influenced by the film's thickness, composition, and movement.

b. Salivary glands
The buccal mucosa's deep or epithelial region contains the minor salivary glands. On the buccal mucosa's surface, they continuously secrete mucus. Mucus may act as a barrier to medication penetration even though it aids in the retention of mucoadhesive dosage forms.

c. Movement of buccal tissues
The oral cavity's buccal region moves less actively. When swallowing or eating, the dosage form should be kept in the buccal region for extended periods of time to accommodate tissue movements. This can be achieved by incorporating mucoadhesive polymers. [15]

Mucoadhesion/bioadhesion
The attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface is referred to as bioadhesion. [16] Two phases are involved in a basic mechanistic understanding of Mucoadhesion: (i) close contact (wetting or swelling phenomenon) between a bio-adhesive and a membrane, and (ii) penetration of the bio-adhesive into the tissue or into the mucus membrane surface. [17]

Theories of mucoadhesion
Though the molecular and physical underpinnings of mucoadhesion remain unclear, numerous theories have been proposed to explain the phenomenon. Six classical theories have been developed as a result of research on the adhesion between polymers and the performance of various materials. A major factor in mucoadhesion is the contact angle and duration of contact. The different theories of mucoadhesion are shown in Figure 1.

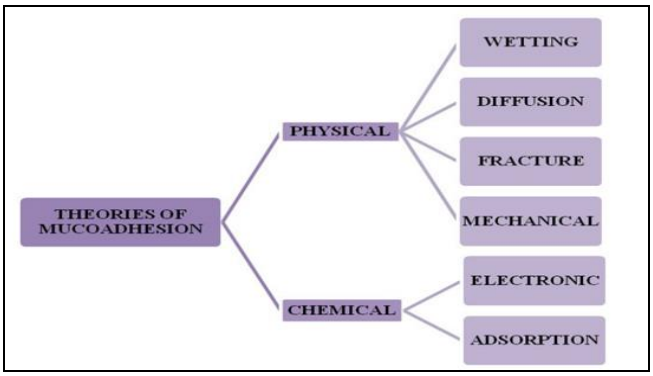

Fig 3: Theories of Mucoadhesion.

Electronic theory
The fact that biological and mucoadhesive materials have opposing electrical charges forms the basis of this theory. The mucoadhesive strength of these materials is determined by the attractive forces that form a double electronic layer at the interface as a result of the transfer of electrons between the materials.

Adsorption theory
According to this theory, when mucus and mucoadhesive polymer first come into contact, primary and secondary chemical bonds of both covalent and non-covalent types are formed. The formation of a secondary chemical bond is determined by the properties of the polymer. According to this theory, wander-walls, hydrogen bonds, and other associated forces are what cause the bio-adhesive systems to stick to the tissue.

Wetting theory
The bio-adhesive polymer's capacity to proliferate on biological surfaces is explained by the wetting theory. This theory is applicable to liquid systems that exhibit surface affinity and spread across it. Measuring the contact angle between two surfaces is the foundation of this theory. In general, the affinity increases with decreasing contact angle. In order to ensure sufficient spreadibility, the contact angle must be zero or nearly zero. It has been demonstrated that polymers that are moderately wettable have the best adhesion to human endothelial cells.

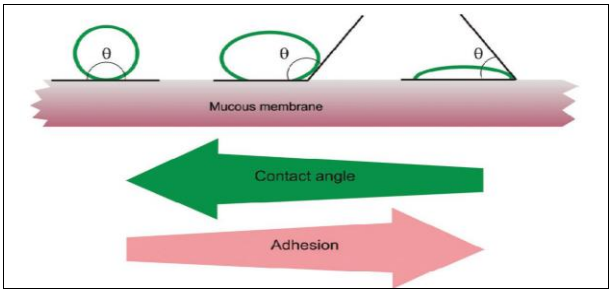

Fig 4: Schematic diagram showing influence of contact angle on bioadhesion

Diffusion theory

This theory states that a semi-permanent adhesive bond is formed when mucin and polymer chain penetrate each other to a sufficient depth. Diffusion coefficient, mucoadhesive chain flexibility and type, polymer chain mobility, and contact time all affect the degree of penetration. An effective bio-adhesive bond can only be formed at a depth of interpenetration between 0.2 and 0.5 µm. Good mutual solubility between the components is a prerequisite for diffusion to take place. The mucoadhesive bond is stronger when the structural resemblance between mucus and bio-adhesive is greater.

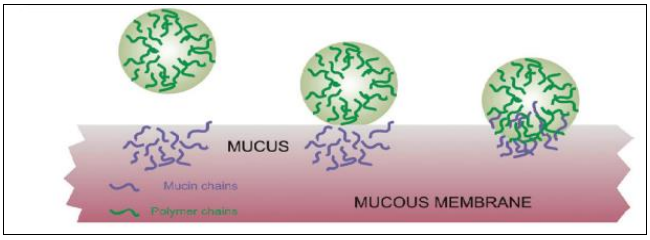

Fig 5: Secondary interactions resulting from inter-diffusion of polymer chains of bio-adhesive device and of mucus.

Fracture theory

When it comes to the mechanical assessment of mucoadhesion, this is the most widely recognized theory. It provides a relationship between the forces needed to separate polymers from mucus and the adhesive bond strength of those polymers. It is discovered that when the degree of cross-linking is lower or the network strands are longer, the work fracture is greater.

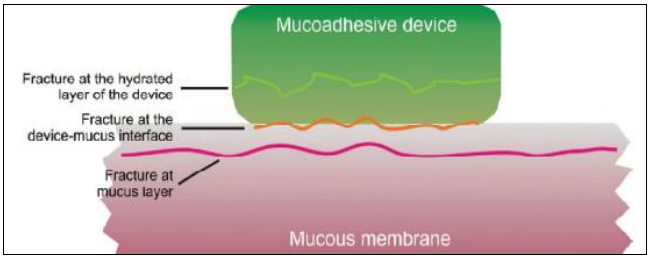

Fig 6: Regions where the mucoadhesive bond ruptures can occur.

Mechanical theory

This theory states that adhesion results from mucoadhesive liquid filling in irregularities on a rough surface. This roughness can be regarded as the most significant phenomenon of the process because it increases the interfacial area available to interactions, which helps dissipate energy. The phenomenon of mucoadhesion, which varies depending on the circumstances, cannot be fully explained by any one of these theories. To a certain extent, though, comprehending these mechanisms can aid in the creation of novel mucoadhesive products. [18, 12, 19]

Mechanism of mucoadhesion

We still don't fully understand how some macromolecules adhere to the surface of mucous tissue. There are forces of attraction and repulsion, and for mucoadhesion to work, the attraction forces need to be stronger. Thus, there are typically two steps in the mucoadhesion mechanism

- Contact stage.
- Consolidation stage.

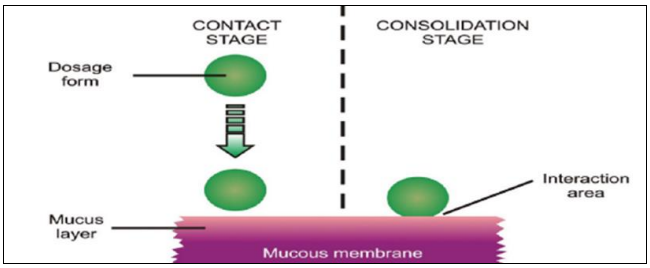

Fig 7: The two steps of the mucoadhesion process.

1. Contact stage

The point formulation starting the deep interaction with mucus layer is characterized by the mucoadhesive drug delivery systems, the interaction between the mucoadhesive and the mucous membrane, and the spreading and swelling of the mucoadhesive membrane.In these situations, mucoadhesion fluids in the organ cavity may be explained by Brownian motion or peristalsis, the motion of organic movement. Repulsive forces (osmotic friction, electrostatic repulsion, etc.) and attractive forces (van der Waals forces and electrostatic attraction) will come into contact with the particle if it reaches the mucous surface.

2. Consolidation stage

Mucoadhesive compounds, which are activated by humidity, are another characteristic of the consolidation stage. When the device gets moist, the mucoadhesive molecules loosen up and form weak van der Waals and hydrogen bond connections. Two theories explain the consolidation phase:

- Diffusion theory.
- Dehydration theory.

1. Diffusion theory

Mucoadhesive molecules and mucus glycoprotein interact through chain interpretation and secondary bond formation. Here, interactions between chemicals and mechanics are both present. Mucoadhesive properties, for instance, can be exhibited by molecules with hydrogen bond building groups (-OH, -COOH), anionic surface charge, high molecular weight, flexible chains, and surface-active properties that cause them to spread throughout the mucus layer.

2. Dehydration theory

When materials that easily gel in an aqueous environment come into contact with mucus, the difference in osmotic pressure can lead to dehydration. Water is drawn into the formulation until osmotic balance is reached by the gradient in concentration differences. This procedure creates a formulation and mucus mixture that lengthens the mucous

membrane's contact time. Dehydration theory, however, does not apply to highly hydrated forms or solid formulations. [20, 12]

Mechanism of Drug Transport

Drugs are primarily transported across the buccal mucosa by passive diffusion; carrier-mediated transport has been shown to play a minor part. Two paths of passive transport exist in the buccal mucosa:

- **Paracellular:** entails the movement of substances between cells via the intercellular space.
- **Transcellular:** It involves moving through and within cells. [21]

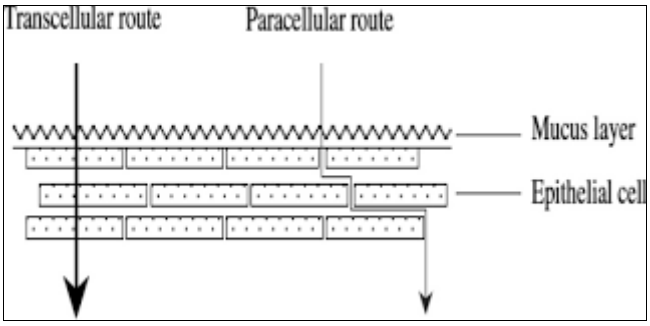

Fig 8: Mechanism of Drug Transport.

The basic components of buccal bio-adhesive drug delivery system are

- Drug substance.
- Bio-adhesive polymers.
- Backing membrane.
- Penetration enhancers.

Drug substance

It is necessary to determine whether a local or systemic effect, as well as whether rapid or prolonged release, is the intended action before developing buccoadhesive drug delivery systems. Pharmacokinetic characteristics should be taken into consideration when choosing an appropriate drug for the design of buccoadhesive drug delivery systems.

The drug ought to possess the following features:

- The drug should be taken in small doses as a conventional single dose.
- Biological half-lives of two to eight hours make drugs suitable for controlled drug delivery.
- When taken orally, the drug's T_{max} exhibits larger fluctuations or higher values.
- Drugs taken orally may show signs of first pass effect or pre-systemic drug elimination.
- When a drug is taken orally, absorption should be passive. [22]

Bio-adhesive polymers

The choice and characterization of suitable bio-adhesive polymers for the formulation is the second stage in the creation of buccoadhesive dosage forms." In buccoadhesive drug delivery systems, bio-adhesive polymers are essential. Moreover, polymers are utilized in matrix devices, where a drug is embedded in a matrix of polymers that regulates the drug's release time. [5]

Ideal characteristics of bioadhesive polymer

- A robust non-covalent bond between the polymer and the mucin-epithelial surfaces is required.
- The polymer ought to stick to most tissues quickly and have some site-specificity.
- The polymer should facilitate the drug's easy incorporation and timely release.
- The mucous membrane shouldn't be irritated by polymer.
- Polymer shouldn't elicit an immune response.
- Polymers and the breakdown of them shouldn't enter the gastrointestinal tract (GIT) or, if they do, shouldn't be harmful to the host.
- The polymer needs to be cohesive in order to give the interlayer strength. [23]

Classification of various mucoadhesive polymers [24]

Table 1: Classification of various mucoadhesive polymers

Natural polymers	Synthetic polymers
▪ Tragacanth ▪ Sodium alginate ▪ Guar gum ▪ Xanthan gum ▪ Soluble starch ▪ Gelatin ▪ Chitosan	▪ Cellulose derivatives: (Methylcellulose, Ethyl cellulose, Hydroxy ethyl cellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose). ▪ Poly (Acrylic acid) polymers (Carbomers, Polycarbophil). ▪ Poly hydroxyl ethyl methylacrylate. ▪ Poly ethylene oxide. ▪ Poly vinyl pyrrolidone. ▪ Poly vinyl alcohol.

Backing membrane

The attachment of bioadhesive devices to the mucous membrane is significantly influenced by the backing membrane. The backing membrane's materials should be inert, impermeable to the medication, and enhancer of penetration. Better patient compliance and reduced medication loss are provided by the impermeable membrane found on buccal bioadhesive patches. Materials like carbopol, magnesium stearate, Hydroxyl propyl methylcellulose, Hydroxy propyl cellulose, Carboxy methylcellulose, polycarbophil, etc. are frequently used in backing membranes. [25]

Penetration enhancers

They are added to the pharmaceutical formulation in order to increase the rate at which the co-administrated drug's membrane permeates. They raise the bioavailability of medications with low membrane penetration without being toxic or harming the membrane. The ability to increase penetration depends on the drug's physiochemical properties, the type of vehicle, the site of administration, and whether they are used in combination or alone. [4]

Table 2: mucosal penetration enhancers and mechanisms of action.

Sr. No	Classification	Examples	Mechanism
a.	Surfactants	Anionic: Sodium lauryl, sodium lauryl Cationic: cetylpyridinium chloride Nonionic: poloxamer, brij, span, myrj, tween Bile salts: sodium gylcodeoxycholate, sodium glycocholate.	Perturbation of intercellular lipid, protein domain integrity

b.	Fatty acid	Oleic acid, ceprylic acid.	Increase fluidity of phospholipid domains
c.	Cyclodextrains	α, β, γ, cyclodextrin, methylated β –cyclodextrins.	Inclusion of membrane Compounds
d.	Chelators	Ethylenediamine teraacectic acid, sodium citrate.	Interfere with Ca Polyacrylates
e.	Positively charged polymers	Chitosan, trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
f.	Cationic compound	Poly-L-arginine, L-lysine.	Ionic interaction with negative charge on the mucosal surface

Buccal-adhesive dosage forms

- Tablets
- Patches/Films
- semisolids (ointments and gels)
- Buccal powders
- micro particles
- wafers

1. Tablets

Buccal tablets are oval-shaped, flat, and small, measuring about 5-8 mm in diameter and 2 mm in thickness. When saliva is present, they stick to the mucosal surface until the medication has completely released or dissolved. After a brief period of time, the patient is not aware that the tablet is in their mouth and can speak, drink, and eat without experiencing any discomfort.

When a patient wears dentures, adhesive buccal tablets can be placed in any comfortable position between the lip and gum or on the palate, cheek mucosa, or other areas of the oral cavity. Specialized tablets with two layers have been developed to prevent drug loss from the top surface of the dosage form. In order to minimize drug leakage in the oral cavity and to promote unidirectional drug absorption, they are composed of an impermeable backing layer and a drug-loaded bioadhesive layer. Adhesive tablets containing a variety of medications for long-term treatment have been developed. These include morphine sulphate, nitroglycerin, codein, naltrexone, oxytocin, and lercanidipine. [26, 27]

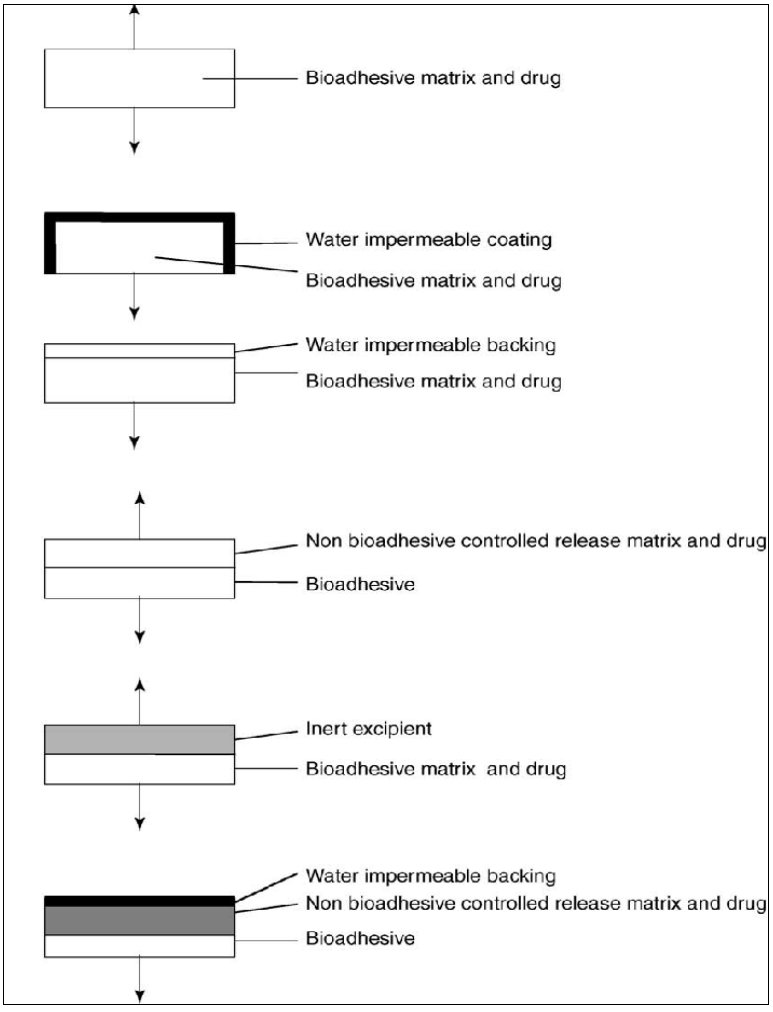

Fig 9: Schematic representation of different types of matrix tablets designed for buccal drug delivery system.

2. Adhesive Patches and Films

In order to provide a unidirectional flow of medication across the buccal mucosa, buccal bioadhesive patches are made of two-ply laminates or multilayered thin films that are round or oval in shape and primarily composed of an impermeable backing layer and a bioadhesive polymeric layer. Drug is added to an alcohol-based bioadhesive polymer solution to create buccal bioadhesive films.

- To increase bioavailability, isosorbid dinitrate is developed and characterized as a unidirectionally errodible buccal film.
- Salbutamol sulphate and terbutalin sulphate buccal film for asthma relief. Clindamycin buccoadhesive film used to treat pyorrhea. [28]

3. Adhesive Semi-Solid Systems (Gels, Ointments)

The benefit of semisolid dosage forms, like gels and ointments, is their easy dispersion across the oral mucosa. The accuracy of drug dosing using semisolid dosage forms may be inferior to that of tablets, patches, or films. Bioadhesive formulations have been used to overcome poor gel retention at the application site. A liquid phase transition occurs in a few bioadhesive polymers, such as xanthan gum, sodium carboxymethylcellulose, sodium carboxymethylcellulose, carbopol, hyaluronic acid, and HPMC. This alteration increases the viscosity, allowing for a controlled and prolonged release of medication. Carbopol and hydroxyl propyl cellulose were combined to create a highly viscous gel that could be applied topically to tissues for up to eight hours. [29]

4. Buccal powders

The reduction in diastolic blood pressure following the administration of nifedipine buccal film and tablets is achieved by spraying the buccal mucosa with buccal bio adhesive powders, which are a combination of drug and bio adhesive polymers. [30]

5. Micro particle

Tablets are not as advantageous as microparticles. Microspheres can be brought into close contact with a sizable mucosal surface thanks to their physical characteristics. The success of these microspheres is restricted by their brief residence time at the site of absorption. They can also be administered to less accessible locations like the GI tract and nasal cavity, and they cause less local irritation at the site of adhesion. [31]

6. Wafer

Wafers as BDDS essentially share the same primary characteristics as buccal films/patches, hydrogels, or sponges: flexibility, elasticity, softness, and mucoadhesivity. However, their advantages include reduced residual moisture and increased drug loading (for drugs with low solubility), resistance to mechanical removal, and the capacity to retain their swollen structure for an extended period of time, which improves drug absorption.65–71 Wafer formulations contain the following polysaccharides: chitosan, alginate, pectin, xanthan, carrageenan, and derivatives of cellulose. There are commercial wafers on the market, such as Wafermine™ and Wafesil™. [32]

Evaluation

The mucoadhesive strength and permeability of buccal adhesive drug delivery devices should be specifically assessed in addition to the standard evaluation tests, which include weight variation, friability, hardness, content uniformity, and *in vitro* dissolution for tablets; tensile strength, film endurance, hygroscopicity, etc. for films and patches; viscosity, effect of aging, etc. for gels and ointments. [33]

Preformulation evaluation

To assess the powder blend's flow ability, micrometrics properties such as bulk density, tapped density, angle of repose, compressibility index, and Hausner's ratio were measured. Drug solubility in a range of solvents, including ethanol, water, and pH 6.8 phosphate buffer. Drug identification was accomplished using FTIR, DSC, and UV spectroscopy. FTIR and DSC were used to conduct studies on the compatibility of drug excipients. [34]

Compatibility Studies

Liquid Fourier transform infrared was used to test the drug excipient compatibility. The procedure involved equal parts of drug and excipient, followed by the use of a NaCl cell to note the mixture's IR spectrum. After applying a small amount of the mixture to the sample cell and fitting it into the sample holder, the FTIR instrument was used to scan the spectra over the frequency range of 4000-400 cm-1 and perform spectral analysis. [35]

Bulk Density (Db)

It is the proportion of the powder's bulk volume to its total mass. Pouring the weighed powder which had been through standard sieve No. 20 into a measuring cylinder and noting the initial weight allowed for measurement. The bulk volume was the name given to this first volume. Using the following formula, the bulk density was computed from this. It is provided by and expressed in gm/ml. [36]

$Db = M/ Vb$

where M and Vb stand for the powder's mass and bulk volume, respectively.

Tapped Density (Dt)

It is the proportion of the powder's total mass to its tapped volume. The powder was tapped 300 times to determine the volume, and if there was a difference of less than 2% between the two volumes, the tapped volume was recorded. If the difference is greater than 2%, 500 taps are made, and the volume of each tap is recorded. In a bulk density apparatus, tapping was done until the difference between successive volumes was less than 2%.It is provided by and expressed in gm/ml. [36]

$Dt = M/ Vt$

Where,

M and Vt are mass of powder and tapped volume of the powder respectively.

Hausner Ratio

The following formula was used to get Hausner's ratio of granules. Good flowing properties are more evident in Hausner's ratios less than 1.25 than in higher values. Hausner's ratios, ranging from 1.25 to 1.6, indicate moderately fluid characteristics. Powders with a Hausner's ratio greater than 1.6 will be more cohesive. [37]

Hausner′ ratio = tapped density bulk density

Carr's Index

The following equation was then used to calculate Carr's Index. [38]

Carr's index = bulk density − tapped density/ bulk density × 100

Angle of repose

This represents the greatest angle that can exist between the powder or pile's surface and the horizontal plane. The funnel method was utilized to ascertain the angle of repose. The angle of repose can be used to calculate the frictional forces in the lost powder. The coefficient of friction between the particles equals the tangent of the angle of repose. [39]

$\theta = \tan\text{-}1 (h / r)$

Where,

θ is the angle of repose, h is the height in cm and r is the radius in cm.

Evalution of formulation

Thickness

Vernier calipers were used to determine the thickness of the buccal tablets. Each batch of ten tablets was tested, and the findings were averaged. [40]

Hardness

A hardness testing device (Monsanto type) was used to measure the tablets' hardness. [41]

Friability test

Roche friabilator (USP) was used to measure the friability of tablets for four minutes at 25 rpm. Twenty tablets were weighed both before and after the test was finished, and the following formula was used to determine friability [42].

Friability (%) = W1 – W2/ W1 X 100

Where,

W1 and W2 are weights of tablets before and after test respectively.

Weight Variation Test

To determine the weight deviation, 20 tablets of each formulation type were weighed separately on an electronic balance. The average weight of the tablets was then computed, and the weight of each tablet was compared to the average value. It also computes the percentage weight variation. [43]

Content uniformity

Using a glass mortar and pestle, ten tablets were chosen at random, triturated, and precisely weighed. A precise amount of triturated powder, equal to 20 mg of drug, was added to a 50 ml volumetric flask, dissolved in the least amount of methanol, and then filled to the brim with pH 6.8 phosphate buffer. then, samples were examined at 238 nm using a UV spectrophotometer. [44]

Surface pH Study

In order to prevent irritation of the buccal mucosa, the surface pH needs to be closed off to the pH of saliva. The pH range of saliva is 6.5 to 7.5. For two hours, the tablets were left to swell in one milliliter of distilled water. Next, a digital pH meter was used to measure the tablet's surface pH. Before reading the measurement, the pH electrode was positioned close to the tablet's surface and given a minute to acclimate. [45]

Swelling and erosion studies

Regarding buccal tablets Studies on swelling and erosion for buccal tablets were conducted using gravimetric analysis in phosphate buffer with a pH of 6.6. Using cyanoacrylate adhesive sealant, the tablets were affixed to glass supports that had been previously weighed. The tablet supports were submerged in phosphate buffer at 37 ◦ C. The devices were taken out of the media at prearranged intervals, weighed, and then excess water was blotted with tissue paper. Following the measurement of the wet weight, the tablets were dried at 40°C until their mass remained constant. The following formulas were used to determine erosion and the swelling index (S.I.) gravimetrically. [46]

Swelling index (%) = ws -wd /wd

Erosion (% mass loss) = Original weight – remaining dry weight/ Original weight×100

Where,

Wd and Ws are the weights of dry and swollen devices, respectively.

Bioadhesion strength

The Modified Physical Balance was used to gauge the buccal tablets' muco-adhesive strength. Porcine buccal membrane is used as a model mucosal membrane in this technique. After being cut into pieces, the fresh porcine buccal mucosa was cleaned with phosphate buffer (6.8). By placing an appropriate weight on the left-hand pan, the two pans were brought into balance. A section of the mucosa was attached to the beaker's surface and positioned beneath the right pan, which had been wetted with phosphate buffer (6.8). The tablet was adhered to the right pan's lower side like glue. Water (equivalent to weight) was gradually added to the previously weighed beaker, which was set on the left-hand pan, until the tablet separated from the mucosal surface. The mucoadhesive strength was determined by the weight necessary to separate the tablet from the mucosal surface. Three duplicates of the experiment were run, and the average value was determined. [47]

Force of adhesion (N) = (muco-adhesive strength/100) ×9.8

Bond strength (N/m^2) = Force of adhesion (N) / Surface area of tablet (m^2)

Bioadhesion time

Following the application of the buccal tablet on freshly cut goat buccal mucosa, the *In-Vitro* mucoadhesion time was measured. The fresh goat buccal mucosa was tied to the glass slide, and each tablet's mucoadhesive core side was moistened with one drop of phosphate buffer (pH 6.8) before being gently pasted to the mucosa for thirty seconds using the fingertip. After that, the glass slide was placed inside the beaker, which was maintained at 37 ± 1°C and contained 200 ml of pH 6.8 phosphate buffer. After two minutes, a slow stirring motion was used to replicate the environment of the buccal cavity, and tablet adhesion was observed for eight hours. The mucoadhesion time was measured as the amount of time it took for the tablet to separate from the goat buccal mucosa. [44]

***In-Vitro* drug release**

The drug release study employs the USP dissolving apparatus. It comes in two varieties: a rotating paddle type that requires attaching the buccal tablet backing layer to a glass disk with cyanoacrylate glue and placing the disk at the apparatus's bottom, or a rotating basket type. A suitable amount of phosphate buffer (pH 6.8) is needed for the dissolution study. Samples are removed and replaced with fresh buffer medium at pre-arranged intervals. An ultraviolet spectrophotometer analyzes the samples after they have been filtered and diluted appropriately. [48]

In vitro drug permeation

The *in vitro* drug permeation study of drugs through the buccal mucosa of sheep or rabbits is carried out at 37°C ± 0.2°C using a Keshary-Chien or Franz type glass diffusion cell. The donor and receptor compartments, where a new buccal mucosa was tied, are included. With the compartments clamped together, the buccal tablet's core side faced the mucosa. Phosphate buffer with a pH of 6.8 is put in the donor compartment, and a pH of 7.4 is put in the receptor compartment. By agitating the receptor compartment at 50 rpm with a magnetic bead, the hydrodynamics condition was preserved. One milliliter of sample can be taken out at prearranged intervals and tested with a UV spectrophotometer at an appropriate nm to determine the drug content. [49]

In-vivo mucoadhesion studies

For the studies, healthy human volunteers are gathered. The volunteers must apply for 30 seconds by pressing the buccal mucosa. Human volunteers are instructed to conclude any side effects from the film, such as taste, mucosal irritation, or dry mouth, and to carry on with their usual activities, with the exception of eating. [50]

Conclusion

In conclusion, this comprehensive review on buccal drug delivery systems illuminates the multifaceted landscape of a promising field that holds significant potential for revolutionizing drug administration. The exploration of formulation strategies, anatomical considerations, and recent technological advancements underscores the complexity and diversity inherent in buccal drug delivery. While buccal drug delivery offers advantages such as enhanced bioavailability, reduced first-pass metabolism, and improved patient compliance, challenges persist, including limited drug permeability, inter-individual variability, and regulatory intricacies. Despite these challenges, the field has witnessed remarkable progress in overcoming hurdles through innovative approaches such as mucoadhesive polymers, nanotechnology applications, and personalized medicine initiatives

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