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BUCCAL DRUG DELIVERY SYSTEM

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1.Abstract

The buccal drug delivery system is a sophisticated and promising method for delivering medications for both local and systemic therapeutic effects via the buccal mucosa, the inner lining of the cheek. It provides an alternative to traditional oral drug delivery by lessening the effects of hepatic first-pass metabolism and gastrointestinal degradation for appropriate medications. This strategy may increase patient compliance, provide regulated medication release, improve drug bioavailability, and give a practical, non-invasive way to administer drugs. The buccal mucosa's morphology and physiology, drug absorption mechanisms, and the contribution of mucoadhesion to better drug delivery and retention are the main topics of this review. The interaction between mucoadhesive formulations and the mucosal surface is explained by a variety of mucoadhesion theories, such as electronic, adsorption, diffusion, wetting, mechanical, and fracture theories. The significance of natural, semisynthetic, and synthetic mucoadhesive polymers in creating successful buccal formulations is also highlighted in the review. The preparation techniques and formulation elements of various dosage forms, including buccal tablets, films, patches, gels, and wafers, are explained. Additionally, the functions of various excipients and permeation enhancers in enhancing drug transport via the buccal mucosa are investigated. Mucoadhesive strength, swelling index, surface pH, drug content, in vitro drug release, ex vivo permeability, stability, and other crucial evaluation parameters are also covered. Recent developments in nanotechnology, fast-dissolving films, nanocarriers, and three-dimensional printing have opened up new possibilities for designing patient-friendly dosage forms and enhancing medication delivery efficacy. However, during formulation creation, issues such salivary secretion, mucosal barrier characteristics, limited absorption area, formulation acceptability, and possible irritation must be taken into account. As a whole, The buccal drug delivery system is an important pharmaceutical strategy that may enhance patient convenience, medication bioavailability, and therapeutic efficacy. The creation of buccal drug delivery formulations that are safer, more effective, and clinically useful may be facilitated by more research and technical developments

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Keywords: Buccal drug delivery system, Buccal mucosa, Mucoadhesion, Mucoadhesive polymers, Buccal films, Permeation enhancers, Controlled drug rele

2.Introduction

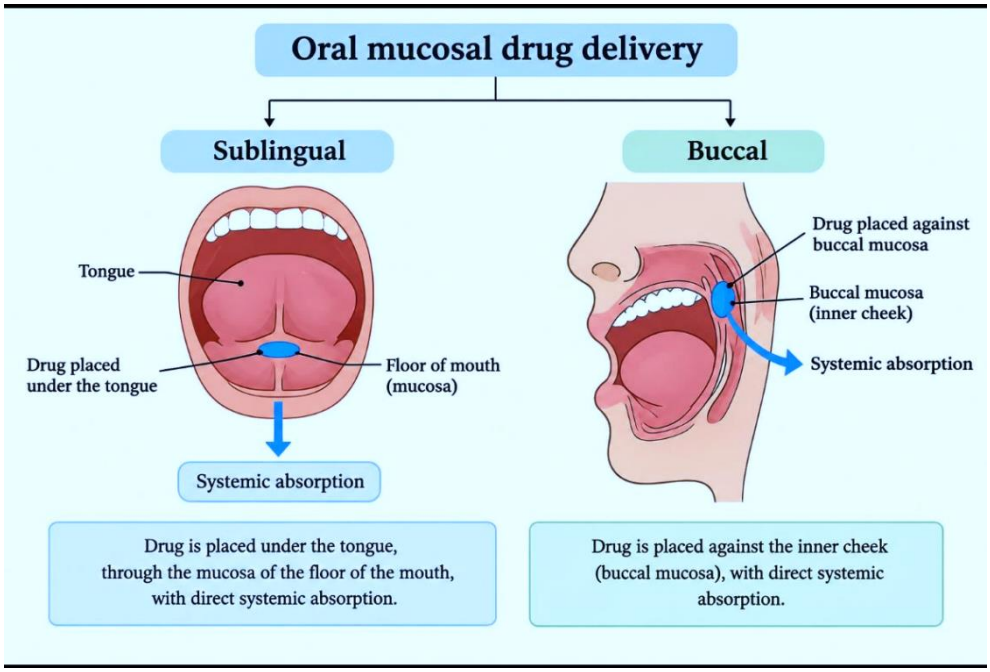
The most popular and recommended method of administering medications is orally. Compared to the majority of other drug delivery systems, it has a number of benefits, such as being patient-friendly, causing less pain, making self-medication simple, and enabling a flexible and controlled dosing schedule. (1)

While creating new drug molecules is costly and time-consuming, efforts have been made to improve the safety-efficacy ratio of "old" medications through a variety of techniques, including dose titration, individualized drug therapy, and therapeutic drug monitoring. Other extremely appealing approaches that have been actively studied include targeted delivery, slow delivery, and controlled rate medication delivery. (2)

For systemic action, transmucosal routes of drug delivery that is, the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities offer clear advantages over peroral administration. (3)

The oral cavity is a desirable location for medication delivery because it is simple to administer and avoids first-pass metabolism and potential drug degradation in the gastrointestinal tract.[(4]

Drug distribution within the oral mucosal cavity can be broadly divided into two categories: (a) buccal delivery and (b) sublingual delivery, which involves systemic drug delivery via the mucosal membranes lining the floor of the mouth. The buccal mucosa is the most accessible of the different transmucosal pathways. [5]



Definition of buccal drug delivery system

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The term "buccal drug delivery" describes the administration of medications through the buccal mucosa in order to influence systemic and local pharmacological effects. (6)

The buccal mucosa is one of the many transmucosal channels that is most suited for the delivery of controlled release dosage forms because it is generally static, has a large area of smooth muscle, and is highly accessible. (7)

A buccal tablet is inserted and held in the buccal area, which is the space between the mandibular arch and the mouth mucosa, where it dissolves and enters the bloodstream. These two sites are better for drug absorption because they lack keratinized epithelia, unlike other buccal regions (such the hard palate, gingiva, or dorsal surface of the tongue).

Sublingual medicines dissolve in the tissue beneath the tongue and are absorbed into the bloodstream. (8)

Importance of buccal drug delivery system

- **Prevents first-pass metabolism**: By avoiding hepatic first-pass metabolism, medications taken through the buccal mucosa may have greater systemic availability.
- **Enhances bioavailability**: Drugs that are significantly metabolized in the liver or broken down in the gastrointestinal tract may have their bioavailability increased by buccal delivery.
- **Quick drug absorption**: Drugs can effectively reach the systemic circulation since the buccal mucosa is comparatively well vascularized
- **Controlled and sustained release:** Mucoadhesive buccal formulations have the ability to stay adhered to the mucosa while releasing the medication gradually.
- **Protection against gastrointestinal degradation**: Buccal administration may be advantageous for medications that are vulnerable to gastrointestinal enzymes or unstable in the stomach's acidic environment. [9]

Table 1.1: Different buccal dosage forms of BDDS

Dosage forms	**Structures**	**Release**	**Effect**	**Active ingredients**
Matrix tablets	Monolithic matrix	Sustained/bidirectional	Local/systemic	Local administration: metronidazole. Systemic administration: propanolol, timolol, metoclopramide, morphine sulphate, nitroglycerin, codein, insulin, calcitonin, glucagone-like peptide
	Coating matrix (coated on the outer side or on all but one faces)	Monodirectional	Systemic	
	Two-layer matrix	Bidirectional	Local (mainly)	
	Two-layer matrix coated with impermeable	Monodirectional	Systemic	

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	layer			
Patches	Laminated film with coating layer	Monodirectional	Local/systemic	Local administration: diclofenac, tannic acid, boric acid. Systemic administration: tyrotropin-releasing hormone, octreotide, oxytocin, buserelin, calcitonin, leuenkephalin
Lipophilic gels	Cubic and lamellar liquid crystalline phases of glyceryl monooleate	-	Systemic	Systemic administration: (D-Ala2, D-Leu5)enkephalin
Transfersomes	Phospholipid deformable vesicles	-	Systemic	Systemic administration: insulin

[10]]

3.Anatomy and physiology of buccal mucosa

The intricate network of tissues that lines the oral cavity is called the oral mucosa. It is made up of layers of tissue, including the basement membrane, stratified squamous epithelium, and supporting connective tissues. The oral mucosa includes the buccal mucosa together with the gingival and sublingual mucosa. It is the region with an average surface area of around 100 cm2 that is located within the cheek and between the gums and lower lips.[11]

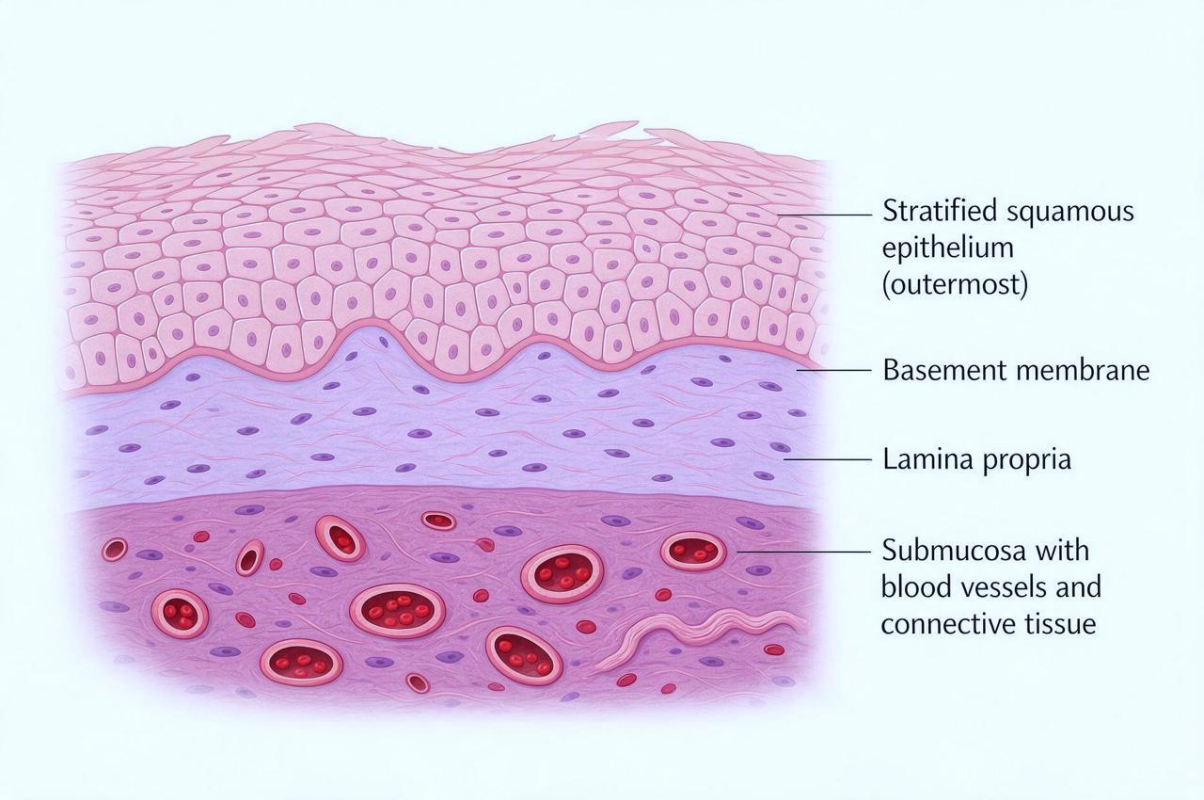
The outer epithelium and basement membrane make up the buccal mucosa. The outer buccal epithelium is composed of non-keratinized stratified squamous epithelium [12].

3.1 Location of buccal mucosa

The buccal mucosa, which is continuous with the mucosa of the upper and lower lips, is the mucosal lining of the inside of the cheek [13].

3.2 Structure of buccal mucosa

The oral mucosa is composed of three layers: the basement membrane, the connective tissue composed of the lamina propria and submucosa, and the topmost layer of stratified squamous epithelium. The buccal mucosa, which is four to four thousand times larger than the skin epidermis, has a higher permeability than the intestinal mucosa [14].



The buccal mucosa consists mainly of three structural component ;
1]Buccal epithelium
2]Basement membrane
3]Lamina propria
4]submucosa

1] Buccal epithelium

As the outermost layer of the buccal mucosa, the buccal epithelium acts as a barrier to keep the oral environment out.

A more flexible and elastic connective tissue supports the non-keratinized epithelium that lines the buccal and sublingual mucosa [15].

Tonofilament-like proteins and phospholipids make up the majority of its composition. From the outermost buccal surface, the epithelium's basal layer divides into replacement cells. Because of its architecture and lipid structure, the epithelium is thought to be the main obstacle to the majority of medicines' penetration during buccal administration. [12.]

2] Basement membrane

Connective tissue and the epithelial elementary layer surround the basement membrane. A sublayer of fibrous material, lamina Lucida (top amorphous layer), and lamina dense make up

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their trilaminar structure. The structure is strengthened by the collagen found in the lamina dense. In comparison to epithelium, they have a greater surface area. Therefore, by altering the diffusional path length, it prevents drug penetration or transport. They also serve a number of crucial purposes, such as adhering the epithelium to the underlying connective tissue, giving the epithelium mechanical strength, and bordering the passage of various macromolecules and cells. [16]

3]Lamina propria

The mucosal connective tissue is known as the lamina propria [17]. The papillary layer and the reticular layer are the two main compartments that make up the lamina propria. The epithelium is directly beneath the papillary layer. It has capillary loops and collagen fibers that are disorganized. The papillary layer contains nerve terminals, which can occasionally penetrate the epithelium. Collagen fiber bundles parallel to the mucosa's plane are seen in the lower reticular layer. Additionally, the lamina propria contains elastic fibers. Major and minor salivary glands, as well as sebaceous follicles, are found in the reticular layer. Sebaceous differentiation typically occurs in one or more lobes of the parotid, parietal, and sublingual glands, which are the main salivary glands [18].

4] Submucosa

All areas of the buccal cavity have submucosa, with the exception of the hard palate covered by masticatory mucosa and the connected gingiva, where the submucosa layer is absent and the lamina propria is directly joined to the underlying bone to form a mucoperiosteum

In certain places, the submucosa layer of the oral mucosa may contain ectopic sebaceous glands, also referred to as Fordyce granules. Fordyce granules have long been thought to be a normal variation, but new research indicates that those with elevated lipid profiles may have more of them. Therefore, it is not appropriate to ignore this clinical finding. They are primarily located on the labial and buccal mucosa. Their density is decreased by smoking and age [19].

3.3 Mucus layer

Mucous is the tissue layer that forms the sticky contact. Mucus is a viscous, transparent secretion that sticks to the mucosal epithelial surface as a thin, continuous gel blanket. In humans, this layer's average thickness ranges from roughly 50 to 450 μm. The equilibrium between the rates of secretion and breakdown and shedding determines the thickness of the mucous blanket, which varies depending on the place. In addition to serving as a lubricant that permits cells to move in relation to one another, this matrix may actually contribute to cell-cell attachment. [5]

3.4 Blood supply of buccal mucosa

From the posterior-inferior portion of the buccinator muscle, the facial artery and vein flow obliquely anteriorly toward the nose. The buccinator muscle is covered by the posterior superior alveolar (PSA) artery and vein, which enter it in the most posterior-superior corner. This artery connects to branches of the infraorbital artery. Alongside the buccal nerve, the buccal artery enters the posterior border of the muscle where it joins the superior constrictor pharyngeal muscle. The face vein or pterygoid plexus receives the rich venous plexus across the buccinator muscle. These vessels are extensively anastomosed with one another [20].

3.5 Salivary secretion

The oral cavity's primary and minor salivary glands secrete saliva. The parotid, submandibular, and sublingual glands are the three main pairs of salivary glands. The autonomic nerve system controls salivary secretion. Secretory cells produce fluid and release proteins as part of the secretion process. Water, electrolytes, proteins, and mucins make up the majority of saliva. It maintains the lubrication and moisture of the oral mucosa. Additionally, saliva facilitates speech, swallowing, and digestion. By preserving the oral environment and offering antibacterial activity, it also safeguards the oral tissues. Saliva is crucial for preserving the buccal mucosa's health and functionality. [21]

4. Drug absorption through buccal mucosa

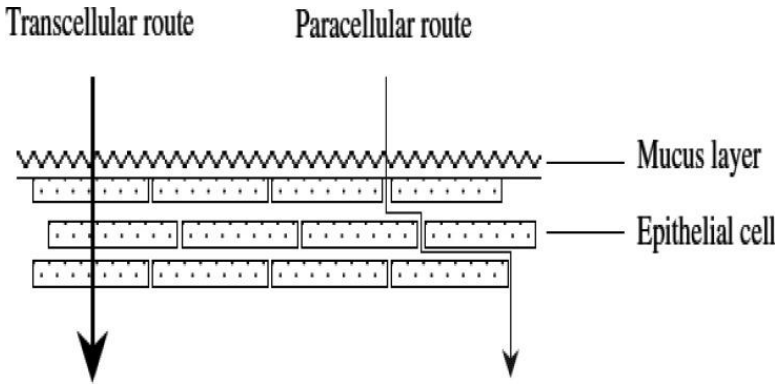
Both transcellular (intracellular) and paracellular (intercellular) transport mechanisms allow drugs to pass through the buccal epithelium.

Transcellular transport is a complicated process that mostly entails low-molecular-weight lipophilic substances with optimal lipophilicity (log P 1.6–3.3) passing through stratified epithelial membranes. [22]

Paracellular transport: This pathway allows small, low-molecular-weight hydrophilic substances to passively diffuse through the extracellular amphiphilic lipid matrix, which is a significant obstacle, especially for macromolecular hydrophilic compounds like peptides. [23].

The diffusant's molecular weight and lipid solubility have an impact on the buccal mucosa's absorption capacity. Certain medications are reported to be more readily absorbed through the buccal mucosa when the carrier pH is lowered and decreased by an increase in Ph [24].

Peptide medications are generally believed to pass past the buccal epithelium by passive diffusion via the paracellular pathway. It was recently found that medications containing a monocarboxylic acid residue could be transported from the oral mucosa into the systemic circulation through their carrier. [25]



5.Advantages of buccal drug delivery system ;-

1. Prevents first-pass metabolism: Drugs that are absorbed through the buccal mucosa may be more bioavailable because they can enter the systemic circulation without first going

through the liver.

2. Enhanced bioavailability: It could make medications that experience significant hepatic first-pass metabolism or gastrointestinal tract degradation more bioavailable.
3. Quick drug absorption: Because the buccal mucosa is comparatively well vascularized, medications with the right permeability can enter the bloodstream.
4. Non-invasive administration: It is a practical and patient-friendly method because it doesn't involve injections.

5. Simple access to the administration site: The buccal mucosa is easily accessible for both applying and, when appropriate, withdrawing the dose form. [9,23]

6. Mucoadhesion

Definition -

The attachment of two materials, at least one of which is a mucosal surface, is frequently referred to as mucoadhesion. (26)

6.1Theories of mucoadhesion

1. Wetting theory
2. Diffusion theory
3. Electronic theory
4. Adsorption theory
5. Fracture theory
6. Mechanical theory
7. Dehydration theory

1. Wetting theory

Liquid systems that exhibit affinity for the surface in order to spread over it are covered by the wetting theory. Measuring methods like the contact angle can be used to determine this affinity. Generally speaking, the affinity increases with decreasing contact angle. For sufficient spreadability, the contact angle must be equal to or near zero. As shown in the following equation, the spreadability coefficient, SAB, can be computed from the difference between the interfacial energy γAB and the surface energies γB and γA. In order to attain a high degree of mucoadhesion, this theory emphasizes the significance of contact angle and the decrease of surface and interfacial energy. [27]

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

2. Diffusion theory

A sufficiently deep layer of chains may arise as a result of the polymer and mucus chains interpenetrating. Intimate contact between two polymers or two fragments of the same polymer is the diffusion mechanism. The polymer's molecules and the glycoproteinic network's dangling chains come into close contact during chain interpenetration. The concentration gradient causes the bioadhesive polymer chains to penetrate at rates that rely on the chemical potential gradient and the diffusion coefficient of a macromolecule through a cross-linked network. To achieve bioadhesion, the bioadhesive medium must also be well soluble in the mucus. As a result, the solubility characteristics of the glycoprotein and the bioadhesive medium should differ as little as feasible. The chemical structure of the bioadhesive medium must therefore resemble that of the glycoproteins. [28]

3 Electronic theory

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The foundation of electronic theory is the idea that biological and mucoadhesive materials have opposing electrical charges. As a result, when the two materials come into contact, electrons are transferred, creating a double electronic layer at the interface. The mucoadhesive strength is determined by the attractive forces within this electronic double layer [29].

4. Adsorption theory

The adsorption theory states that surface forces between the chemical structures at the two surfaces cause the materials to adhere after an initial contact. When polar molecules or groups are present, they reorient at the interface. When adhesion is very strong, chemisorption may take place. According to the theory, adherence to tissue results from the combined action of one or more secondary forces, such as hydrogen bonds, hydrophobic bonds, and van der Waals forces [26].

5, Fracture theory

This hypothesis explains the force needed to separate two surfaces following adhesion. The following formula shows that the fracture strength is equal to the adhesive strength. Tensile apparatus research on bioadhesion benefits from this hypothesis

$$\sigma = (E \times \varepsilon/L)1/2$$

where L is the critical crack length, σ is the fracture strength, e is the fracture energy, and E is the young modulus of elasticity [30].

6.Mechanical theory

According to mechanical theory, mucoadhesion happens when a polymer gets into the buccal mucosa's folds, pores, and abnormalities. Physical interlocking is created as the polymer covers the mucosal surface. The dose form's ability to interface with the mucosal surface aids in its retention. Adhesion is influenced by the degree of hydration, polymer flexibility, and surface roughness. It might promote extended drug release and lengthen the buccal formulations' residence time. In [31]

7. Dehydration theory

According to dehydration theory, the transfer of water from the mucus layer into the hydrophilic polymer causes mucoadhesion. A dry or partially hydrated polymer absorbs water from the mucosal surface when it comes into contact with the mucosa. The mucus layer becomes dehydrated as a result of this water transport, which also encourages tight contact between the polymer and mucosa. Adhesion between the two surfaces is strengthened by the intimate contact that results. The polymer's ability to absorb water and its hydration characteristics determine the degree of adhesion. (31)

6.2 Mechanism of mucoadhesion

These interactions, which take place in three consecutive stages—the contact, interpenetration, and consolidation stages—are essential to the development of a mucoadhesive joint, which is a link between a mucoadhesive material and a mucosal membrane [32].

Contact stage: When a mucoadhesive material is placed or held in close proximity to the mucosal surface, or when the mucoadhesive is adsorbed into the gastrointestinal tract, the mucoadhesive and mucosal epithelium come into close contact.

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Interpenetration stage: In this stage, the materials' physical condition and level of hydration are very important. Chain entanglements result from the diffusion of polymer chains into the mucus layer during the interpenetration stage

Consolidation stage: During this phase, the mucoadhesive joint is strengthened by mechanical and chemical interactions. Chemical ties include covalent bonds, hydrogen bonds, and electrostatic interactions, whereas mechanical bonds entail the physical tangling of polymer chains into the mucus layer. [33]

7. Mucoadhesive polymers

Mucoadhesive polymers are crucial to the buccal medication delivery system because they encourage adhesion between the drug formulation and the membrane of the buccal mucosa. These polymers aid in extending the formulation's residence duration at the application site and may enhance medication absorption and therapeutic efficacy. Mucoadhesion is caused by interactions between the mucin in the mucus layer and polymer chains. Polymer characteristics including molecular weight chain flexibility, hydration surface charge, and hydrogen bonding capacity affect the strength of adhesion. The production of buccal tablets, film patches, and other mucoadhesive compositions has been studied using natural, synthetic, and semi-synthetic polymers. In [34]

- **Classification**

A. Natural polymers

1. Chitosan
2. Sodium alginate
3. Pectin
4. Gelatin
5. Xanthan gum

B. Synthetic/Semi-synthetic polymers

1. Carbopol
2. Polycarbophil
3. Hydroxypropyl methylcellulose (HPMC)
4. Sodium carboxymethyl cellulose (Sodium CMC)
5. Polyvinylpyrrolidone (PVP) [3]

8.Types of buccal drug delivery system

Based on their physical properties, these systems are categorized as solid, semi-solid, and liquid dosage forms. The physiochemical characteristics of the medication, the intended release profile, the mucoadhesive qualities, and patient acceptability all influence the choice of an appropriate dose form.

8.1 Solid buccal drug delivery system

Dosage forms intended to stay in contact with the buccal mucosa and release the medication at the application site are known as solid buccal drug delivery systems. Patches, films, and buccal tablets are the primary solid systems.

A] Buccal tablet –

Small, solid dose forms called buccal tablets are applied to the buccal mucosa to administer medication for either local or systemic activity. Mucoadhesive polymers are included in the formulation of these tablets to assist them stick to the mucosal surface. They might be made

for extended contact with the buccal mucosa and regulated medication release. However, pain, taste, irritation, and the potential for unintentional separation from the mucosal surface could restrict their use [3].

B] Buccal Films –

After being applied to the buccal mucosa, buccal films thin, flexible polymeric dosage forms release the medication. They can be made with the right excipients and mucoadhesive polymers.

These films offer close contact with the mucosal surface, high flexibility, and simplicity of administration. In comparison to many traditional solid dosage forms, they can be made to distribute drugs locally or systemically and may enhance patient comfort [35].

C] Buccal Patches-

Mucoadhesive dosage forms called buccal patches are made to adhere to the buccal mucosa and deliver medication over a predetermined amount of time. They typically consist of a mucoadhesive surface and a drug-containing layer; some formulations also include a backing layer to regulate the drug's release direction. [3)

8.2 Semi solid buccal drug delivery system

Gels and ointments are semisolid buccal drug delivery mechanisms These formulations are administered directly to the oral mucosa and can be used for local or systemic drug delivery. Their performance depends on viscosity, drug release, adhesion and resistance to removal by saliva. [5]

A] Buccal Gel

Buccal gels are semi-solid preparations containing the drug dispersed or dissolved in an appropriate gel base. Incorporation of mucoadhesive polymers can be done to improve adhesion to buccal mucosa. [3]

B] Buccal Ointments

Buccal ointments are semisolid preparations for application to the oral mucosal surface. They contain a drug incorporated into a suitable base and may be formulated with polymers to enhance adhesion.

These are useful for local application of drugs and can be kept in contact with the surface of the mucosa. However, due to saliva and movement in the oral cavity, accurate dosing and retention over time can be difficult. [5]

8.3 Liquid Buccal Drug Delivery Systems

Liquid buccal delivery systems for drugs are solutions, suspensions and sprays. These formulations are applied on oral mucosa and can be developed for local or systemic drug delivery. Its effectiveness is dependent upon the drug solubility, time of contact with the mucosa and the absorption characteristics. [3]

A] Buccal Solutions –

Buccal solutions are liquid preparations containing the drug dissolved in a suitable solvent or vehicle. They are applied to the oral mucosa to achieve the desired therapeutic effect [3]

B] Buccal Sprays –

Buccal sprays are liquid formulations that are sprayed over the oral mucosa. They might be made to deliver drugs locally or systemically and to be administered quickly. (36)

C] Buccal Suspensions:

Buccal suspensions are liquid preparations made up of finely divided drug particles scattered across an appropriate liquid medium. When the drug's solubility in the chosen vehicle is restricted, they might be taken into account. [3

9.Design of buccal drug delivery system

The purpose of a buccal drug delivery system (BDDS) is to apply a medication to the buccal mucosa, which is the inner cheek lining, in order to either release the medication locally or absorb it into the bloodstream. Strong mucoadhesion, controlled release, patient comfort, and saliva protection are its primary design objectives. [37]

Basic design components

The drug substance should be strong, stable in saliva, non-irritating, and able to penetrate the buccal mucosa. A 2 cm^2 system may give 10–20 mg/day on average. Mucoadhesive polymer: Increases residence time and offers adherence to the mucosal surface. Carbopol, chitosan, sodium alginate, hydroxypropyl methylcellulose (HPMC), and derivatives of polyacrylic acid are typical options.

Matrix or reservoir for drug release: regulates the drug's rate of release from the dose form. Reservoir methods put the medication in a different core or layer, whereas matrix systems distribute the drug evenly throughout the polymer.

Backing layer: A semi-permeable or impermeable outer layer that guides medication release toward the mucosa and stops drug loss into saliva.

Permeation enhancers are optional excipients that, particularly for big or less permeable medicines, accelerate drug transport over the buccal membrane.

The system should be compact, flat, and cozy. Patches are typically 1-3 cm^2 for patient tolerance, whereas buccal pills are typically 5-8 mm in diameter.

Enhance flexibility, mechanical strength, flavor, and patient acceptability with plasticizers, flavoring agents.Dimensions: The system must to be compact, level, and cozy. For adequate patient tolerance, buccal tablets typically have a diameter of 5–8 mm, whereas patches often have a diameter of 1-3 cm^2.

Enhance flexibilitlasticizers, fillers, sweeteners, and patient and [38].

Evaluation of the design

• A well-planned buccal system is examined for:
• Residence time and mucoadhesive strength.
• Matrix erosion and the swelling index.
• Ex vivo penetration and in vitro drug release.
• pH, thickness, hardness, and mechanical strength of the surface.
• Toxicity, patient acceptance, and local irritation [39]

10.Permeation enhancer

Definition –

In buccal delivery, permeation enhancers are compounds added to a formulation to speed up a co-administered drug's absorption or permeation through the buccal epithelium. [40]

Need in buccal delivery-

• Enhancers for permeation are required to:
• Boost the flow of drugs via the buccal epithelium.

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• Increase poorly absorbed medications' bioavailability.
• Make hydrophilic medications and macromolecules deliverable.
• Mechanism: Lower the dosage needed to produce a therapeutic effect.
• Encourage quick action by using the buccal route [41].

Mechanism –

Buccal permeation enhancers primarily work by lowering the epithelium's barrier resistance. Lipid disruption: They solubilize, extract, or fluidize intercellular lipids, increasing both transcellular and paracellular transport. Protein/membrane interaction: They change membrane proteins and increase membrane fluidity. Tight-junction opening: Some agents temporarily widen intercellular spaces or open tight junctions, favoring paracellular transport. Mucus modification: They may decrease mucus viscosity or change its rheological characteristics, lowering the diffusion barrier.

11.Factors affecting buccal drug delivery system

A] Drug factors

Molecular size: Large molecules often have poor permeability, while smaller molecules diffuse through the buccal mucosa more readily.

Lipophilicity/partition coefficient: An ideal balance between aqueous solubility and lipid solubility is required for the medicine to partition from saliva into the lipophilic epithelium.

Solubility: Before the medication is taken, it must dissolve in saliva or mucous fluid.

pKa and ionization: The unionized proportion is determined by buccal pH, and unionized drugs typically penetrate more readily.

Stability: Saliva, enzymes, pH, and oral bacteria should not be able to break down the medication.

Dosage and potency: Due to the limited buccal absorption area, a suitably powerful medication is recommended.

Protein metabolism and binding: The amount of free medication available for absorption may be decreased by high binding or quick local metabolism [33].

B] Biological factors

Saliva flow and composition: Mucin, ions, enzymes, and viscosity influence adhesion and drug release; saliva dissolves the medication but also dilutes it and removes the dose form.

Mucus layer: Mucin can function as a diffusion barrier in addition to providing a surface for mucoadhesion.

Properties of the buccal membrane: Permeability is regulated by thickness, keratinization, intercellular lipids, and epithelial turnover.

Oral tissue movement: The formulation may come loose when you talk, chew, swallow, or move your cheeks.

.**Disease state and mucosal condition**: Permeability, saliva production, and retention might be affected by ulcers, inflammation, dry mouth, or infection. [43]

C] Formulation factors –

Mucoadhesive polymer: The length of time the dosage form stays affixed to the mucosa depends on its kind, molecular weight, concentration, swelling, hydration, charge, and chain flexibility.

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Drug loading: A high drug load may affect the release rate, decrease adhesion, or modify matrix structure.

Polymers that control release: HPMC, carbopol, sodium alginate, chitosan, and related polymers regulate erosion, swelling, and drug release.

Backing membrane: A backing layer guides drug release toward the mucosa while shielding the formulation from saliva.

Penetration enhancers: Mucosal permeability may be increased by bile salts, fatty acids, surfactants, chelators, ethanol, propylene glycol, and chitosan.

Flexibility, mechanical strength, comfort, and drug dispersion are all impacted by plasticizers and excipients.

Dosage-form design: Comfort and absorption are influenced by dimensions, shape, thickness, flexibility, surface area, and residence period. [44

12.Preparation methods –

12.1 Preparation of Buccal Tablets –

Solid dosage forms called buccal tablets stick to the buccal mucosa and release medication gradually. Typically, moist granulation or direct compression are used to prepare them.

A] Direct Compression Method –

For making buccal tablets, direct compression is the most straightforward and popular technique. This process does not require granulation; instead, the medication and all excipients are combined in the dry state and crushed straight into tablets. [45].

Procedure-

Weigh drug + polymer + excipients
↓
Dry mixing
↓
Add binder solution
↓
Form wet mass
↓
Pass through sieve → wet granules
↓
Drying
↓
Sizing of dried granules
↓
Add lubricant/glidant
↓
Compression into buccal tablets
↓
Packing

12.2 Preparation of Buccal Films

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Thin, flexible polymeric devices called buccal films stick to the buccal mucosa and release medication in a regulated way. Usually, hot-melt extrusion or solvent casting are used to prepare them.

A] Solvent Casting Method-

The most popular technique for creating buccal films and patches is solvent casting. After dissolving or dispersing the medication, polymer, plasticizer, and other excipients in a solvent, the mixture is cast into a thin film, dried, and then cut to the desired size. [47]

Procedure

Weigh polymer + plasticizer + drug
↓
Dissolve/disperse in suitable solvent
↓
Stir to form uniform solution
↓
Remove air bubbles
↓
Cast into Petri dish/mold
↓
Drying (solvent evaporation)
↓
Peel the dried film
↓
Cut into required size
↓
Packing

B] Hot-Melt Extrusion Method –

The medication, polymer, and plasticizer are melted, combined, and extruded through a die to create a thin film using a solvent-free process called hot-melt extrusion. The active medication, plasticizer, and film-forming polymer are often necessary for a successful formulation. (47)

Procedure

Weigh drug + polymer + plasticizer
↓
Dry blending
↓
Feed into hot-melt extruder
↓
Heating and melting
↓
Extrusion through die
↓
Formation of thin film
↓

Cooling
↓
Cut into required size
↓
Packing

12.3 preparation of Buccal Gels

Buccal gels are semi-solid solutions that are mostly used locally to treat dry mouth, inflammation, fungal infections, and mouth ulcers. Before adding the medication and additional excipients, the gelling polymer is hydrated in water using the dispersion or hydration process. [48]

Procedure

Weigh gelling polymer
↓
Slowly add polymer to water with stirring
↓
Complete hydration → gel base
↓
Add drug with stirring
↓
Add preservative + flavor + pH adjuster
↓
Uniform mixing
↓
Deaeration/removal of air bubbles
↓
Fill into tubes
↓
Packing

13. Evaluation of buccal drug delivery system

13.1Mucoadhesion evaluation –

• The most crucial buccal-specific characteristic is mucoadhesion since oral movement and saliva can remove the dosage form before enough medication is absorbed.

• Mucoadhesive strength/peak detachment force: Indicates the amount of force needed to separate the formulation from excised buccal mucosa, which is typically the mucosa of goats, pigs, or cows.

• Mucoadhesion time/retention time: Indicates how long the system stays adhered in saliva-like conditions; longer retention typically results in better absorption.

• Ex vivo mucoadhesion: Prior to animal or human research, adhesive performance is estimated using recently removed mucosa.

• Erosion and swelling should be evaluated together since erosion might limit residence time and excessive edema may result in detachment.

13.2Drug-release evaluation

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• In vitro dissolution/release: Performed with a Franz diffusion cell, dissolution apparatus, or modified static method utilizing phosphate buffer or simulated saliva. It controls the amount of medication released over time.

• Ex vivo permeation study: Excised buccal mucosa, usually the goat cheek pouch or pig buccal mucosa, is used to evaluate drug permeability. This calculates the real mucosal transport.

• Flux and permeability coefficient: Determined using permeation data in order to forecast absorption potential and compare formulations.

• Release kinetics: To determine the release mechanism, release data are fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.

13.3 Biological and advanced evaluation

• Compatibility with permeation enhancers: While permeation enhancers may increase absorption, their safety and potential to cause mucosal irritation must be considered.

• Pharmacokinetic study: In vivo research evaluates the relationship between formulation design and bioavailability, AUC, and clinical performance; these

• Stability study: Assesses medication content, appearance, pH, mechanical characteristics, and release during storage at specific humidity and temperature levels.

• Histopathology and irritation: Crucial for high-strength or long-term formulations to prevent buccal mucosal damage. [3

14. Resent advances

Nanotechnology, QBD-based formulation design, and improved manufacturing have been the main topics of recent buccal delivery research. Mucoadhesive polymers, permeability enhancers, nanotechnology, and QBD are highlighted in a 2025 assessment as key approaches to enhancing the distribution of biologics and small pharmaceuticals.

Important developments consist of

Mucoadhesive nanocomposites: enhanced absorption and extended residency are combined by nanocarriers embedded in adhesive films or gels.

Fast-dissolving films and tablets: helpful in emergency situations where swallowing is challenging, as well as in children and the elderly.

Customized dose, shape, stacking, and release profiles are made possible via 3D printing.

High surface area and maybe better drug loading and release characteristics are provided by electrospun nanofibers.

Iontophoresis and microneedles are two physical methods designed to get beyond the buccal permeability barrier.

In-situ forming and thermosensitive systems enhance residency and may adjust to the oral environment. [49]

15.Conclusion

Because it avoids hepatic first-pass metabolism, improves medication bioavailability, and allows for regulated and prolonged drug release, the buccal drug delivery method is a prospective substitute for traditional oral drug delivery. Drug delivery for both local and systemic effects is made easy by the buccal mucosa. Mucoadhesive polymers are crucial for enhancing dosage form adherence and residence time at the buccal mucosal surface.

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Depending on the drug's characteristics and the intended therapeutic outcome, a variety of dosage forms, including buccal tablets, films, patches, gels, and sprays, can be created. Depending on the characteristics of the medication and the intended therapeutic outcome, a variety of dose forms, including buccal tablets, films, patches, gels, and sprays, can be created. To achieve efficient drug absorption and release, appropriate polymers, permeability enhancers, and formulation techniques must be chosen. Mucoadhesive strength and medication release evaluation For these formulations to be safe and effective, penetration, stability, and mucosal irritation are also crucial. Recent developments like 3D printing, electrospun nanofibers, and nanotechnology provide new
when there is a chance to enhance buccal medication distribution. However, issues including the buccal mucosa's permeability barrier, medication loss from saliva, and a small absorption region still exist. Overall, additional study and formulation development could enhance the buccal medication delivery system's efficacy, safety, and patient acceptability.

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