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Review on Buccal Drug Delivery Systems

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Abstract

Buccal drug delivery systems represent a promising frontier in pharmaceutical technology, offering a non-invasive route for drug administration that bypasses the gastrointestinal tract and hepatic first-pass metabolism. This method leverages the buccal mucosa's rich vascularization and permeability to enhance drug bioavailability. Recent advancements have focused on developing mucoadhesive films, tablets, and patches that ensure prolonged contact with the mucosal surface, improving drug absorption and patient compliance. Future innovations are expected to incorporate nanotechnology and bioadhesive polymers to further optimize drug release profiles and therapeutic efficacy. Additionally, the integration of smart drug delivery systems, capable of responding to physiological conditions, holds significant potential for personalized medicine. As research progresses, buccal drug delivery systems are poised to become a cornerstone in the administration of biologics and other complex therapeutics, addressing challenges such as enzymatic degradation and poor solubility.

Introduction

In 1947, dental adhesive powder and gum tragacanth were used to attach penicillin to the oral mucosa, introducing bioadhesive medication delivery formulations. The use of mucoadhesive drug delivery systems for the administration of medicinal medicines has grown in popularity in recent years. Reduced bioavailability, GI intolerance, irregular and unpredictable absorption, or pre-systemic clearance of other possible routes of administration are some of the reasons why some medications are ineffective.

The study of mucosal medication delivery has accelerated due to recent advancements in drug delivery. These channels include the nasal, pulmonary, buccal, ocular, and oral routes, among others [1,2].

The pharmaceutical sector has attracted a lot of attention and is now a significant player in the healthcare sector. The pharmaceutical industry's developments have significantly improved the quality of life by aiding in the treatment of illness.[3]

In order to increase the potential of authorized medication products or get beyond the limitations of the oral route, scientists and researchers working in the drug development sectors have been concentrating on alternative methods of administration over time. Despite being the preferred method of medication administration, oral administration has many drawbacks, such as hepatic first pass metabolism, local gastrointestinal toxicity, and GI tract enzymatic degradation.

Because it offers the potential to prevent either drug degradation by gastrointestinal contents or hepatic first-pass inactivation, pharmaceutical aspects of mucoadhesion have attracted a lot of attention recently. The mucoadhesive drug delivery system includes the following:

1. Systems for buccal medication delivery
2. Drug delivery methods that are sublingual
3. Drug delivery methods for the rectal area
4. Systems for vaginal medication administration

5. Drug delivery methods for the eyes
6. Systems for delivering drugs via the nose

One of the naturally occurring polymers that finds extensive application is chitosan. Glucosamine and nacetyl glucosamine, which are also found in mammalian tissue, make up chitosan. This polymer is biocompatible, biodegradable, and nontoxic. This polymer is taken into consideration due to its capacity to produce both films and matrixes. In addition to its permeation-enhancing qualities, chitosan is utilized as an enzyme inhibitor [4].

It is well established that mucoadhesion lengthens and intensifies the contact between a mucosal surface and a drug-containing polymer. It is thought that the device's mucoadhesive properties can lengthen the drug's half-life in the body. The direct drug absorption and the reduction in excretion rate work together to increase the medication's bioavailability. Lower API concentrations and fewer doses may be required to have the intended therapeutic effect because to increased residence duration and adhesion.[5]

Characteristics of an Ideal Buccoadhesive System

1. The following qualities should be included in the perfect buccal adhesive system:
2. Sufficient mechanical strength and rapid adhesion to the buccal mucosa.

The controlled release of drugs.

3. Promotes the pace and magnitude of medication absorption.
4. The patient should comply well.
5. Shouldn't interfere with everyday activities including eating, drinking, and chatting.
6. The medication should leak unidirectionally towards the mucosa.
7. Must not contribute to the development of dental caries or other secondary illnesses.
8. Have a large margin of safety on a systemic and local level.
9. Must be able to withstand the flushing effect of saliva.[6,7]

Advantages of Buccal Drug Delivery System

Drug administration via buccal mucosa offers several distinct advantages:

1. Compared to the other mucosal tissues, the buccal mucosa is robust, rich in blood supply, and somewhat permeable.
2. Avoid the first-pass effect and prevent the medications from coming into contact with the gastrointestinal tract.
3. Simple access to the membrane sites for the application, localization, and removal of the delivery system.
4. Since many medications have a longer duration of contact with the mucosa, they perform better.
5. High patient acceptance in contrast to alternative non-oral medication delivery methods.
6. Tolerance to possible sensitizers (in contrast to the skin and nasal mucosa).
7. A lower frequency of administration may result from a longer residence period and regulated API release.
8. API localization at the disease site may also result in significant cost savings and a decrease in dose-related adverse effects.
9. The formulation remains at the delivery site longer due to adhesion and close contact, increasing API bioavailability at lower API concentrations for the treatment of disease.
10. Buccal drug distribution avoids the harsh environmental variables that come with oral drug delivery.

11. It provides a passive drug absorption system that doesn't need to be activated.
    Unlike with rectal or transdermal methods, the presence of saliva guarantees a comparatively significant volume of water for drug dissolution.
12. Offers a different way to administer different hormones, steroids, narcotic analgesics, enzymes, cardiovascular medications, etc.
13. It permits local tissue permeability modification, protease activity inhibition, and immunogenic response decrease. As a result, it is simple to distribute therapeutic substances such proteins, peptides, and ionized species. [8,9,10]

Disadvantages of Buccal Drug Delivery System

The following are the primary obstacles to buccal administration:

1. Limited absorption area: of the 170 cm2 total surface area of the oral cavity's membranes that can be used for medication absorption, about 50 cm2 are made up of non-keratinized tissues, such as the buccal membrane.
2. The mucosa's barrier characteristics.
3. The medicine is subsequently diluted as a result of the constant salivary flow (0.5-2 l/day).
4. There is a risk of choking if the delivery system is involuntarily swallowed.
5. Saliva swallowing may also result in the loss of dissolved or suspended medication and, in the end, the involuntary removal of the dose form.[11,12]

Limitations of buccoadhesive drug delivery:

There are some limitations of buccal drug delivery system such as
It is impossible to deliver medications that are unstable at buccal pH.

1. This method cannot be used to administer medications that irritate the mucosa, have an offensive odor, or have a bitter or unpleasant taste.
2. Only a modest dose of the necessary drug can be given.
3. This is the only way to give medications that are absorbed by passive diffusion.
4. Restrictions may be placed on eating and drinking.[13]

Mechanism of Buccal Absorption:

Buccal drug absorption happens by the nonionized species' passive diffusion across the epithelium's intercellular gaps, which is mostly controlled by a concentration gradient. The main mode of transport for non-ionic species is passive movement over the buccal cavity's lipid membrane. Like many other mucosal membranes, the buccal mucosa has been described as a lipoidal barrier that prevents medications from passing through; the more lipophilic the drug molecule, the easier it is to be absorbed.
The first order rate process could provide a sufficient description of the kinetics of medication buccal absorption. Numerous possible obstacles to the absorption of drugs through the buccal region have been identified. Salivary secretion changes the concentration of the medication in the mouth, which in turn changes the buccal absorption kinetics from drug solution, as noted by Dearden and Tomlison (1971).[14]

Physiological factors affecting buccal bioavailability:

1. The epithelium's inherent permeability: The permeability of the oral mucosal epithelium lies in the

middle between that of the gut, which is highly specialized for an adsorptive function, and the skin epithelium, which is highly specialized for a barrier function. The buccal mucosa is less permeable than the sublingual mucosa within the oral cavity.

2. Epithelium thickness: The oral epithelium's thickness varies significantly amongst oral cavity locales. The buccal mucosa has a thickness of between 500–800 μm.
3. Blood supply: Drug moieties that pass through the oral epithelium are easily absorbed into the systemic circulation because the oral cavity is served by a rich blood supply and lymphatic network in the lamina propria.
4. Metabolic activity: Drug components absorbed through the oral epithelium enter the bloodstream immediately, bypassing the liver's and the gut wall's first-pass metabolism action.
5. Saliva and mucus: Because of the salivary gland's activity, a stream of saliva—roughly 0.5–2L daily—continually washes the oral mucosal surfaces. Saliva exposure, especially in the sublingual region, can improve medication breakdown and hence raise bioavailability.
6. Retention of delivery system: As a result, it is well adapted to the application of retention delivery systems.The buccal mucosa is composed of a smooth, largely stationary surface.
7. Differences between species: Because of their highly keratinized epithelium, rodents are not ideal animal models for research on buccal medication delivery.
8. Transportation routes and methods: There are two primary ways for drugs to pass through the epithelium barrier: the paracellular route, which occurs between neighboring epithelial cells; and the transcellular route, which occurs across epithelial cells and can be accomplished by any of the following mechanisms: passive diffusion, carrier-mediated transport, and endocytic processes.[15]

Oral mucosal sites:

Drug distribution within the oral mucosal cavity is divided into three groups.

1. **Sublingual delivery**: this method involves delivering the medication to the systemic circulation through the sublingual mucosa, which is the membrane that separates the floor of the mouth from the ventral surface of the tongue.
2. **Buccal delivery**: is the process of delivering a medication to the systemic circulation through the buccal mucosa, or cheek lining.
3. **Local delivery**: for the management of oral cavity disorders, primarily periodontal disease, fungal infections, and ulcers. In terms of their anatomy, permeability to a drug, and capacity to hold a delivery system for the intended duration of time, these oral mucosal locations vary substantially from one another [16, 17].

Structure and Design of Buccal Dosage Form:

There are two types of buccal dosage forms:

1. Matrix type: This type of buccal patch combines medication, adhesive, and additives.
2. Reservoir type: A cavity for the medication and additives that are distinct from the adhesive is present in the buccal patch made with a reservoir system. To avoid medication loss, lessen patch distortion and disintegration in the mouth, and regulate the direction of drug distribution, an impermeable backing is used.

Composition of buccal patches:

A. **Active ingredient.**
B. **Polymers (adhesive layer**): HEC, HPC, polyvinyl pyrrolidone(PVP), polyvinyl alcohol (PVA), carbopol and other mucoadhesive polymers.
C. **Diluents**: Lactose DC is selected as diluents for its high aqueous solubility, its flavoring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. other example : microcrystalline starch and starch.
D. **Sweetening agents**: Sucralose, aspartame, Mannitol, etc.
E. **Flavoring agents**: Menthol, vanillin, clove oil, etc.
F. **Backing layer**: EC etc.
G. Penetration enhancer: Cyano acrylate, etc
H. **Plasticizers:** PEG-100, 400, propylene glycol, etc .[18]

Methods to increase drug delivery via buccal route:

Absorption enhancers: These substances have proven to be useful in delivering high molecular weight substances, including peptides, which typically have low buccal absorption rates. These could work in a variety of ways, including by making the cell membrane more fluid, removing intercellular or intracellular lipids, changing cellular proteins, or changing surface mucine.

Azone, fatty acids, bile salts, and surfactants like sodium dodecyl sulfate are the most often used absorption enhancers. Glyceryl mono oleates were reported to improve peptide absorption through a co-transport mechanism, while chitosan solutions/gels were also discovered to facilitate the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium.[19]

Prodrugs: Hussain et al. administered opioid agonists and antagonists in bitterless prodrug forms and discovered that the drug's bioavailability as a prodrug was low. When given to dogs through the buccal mucosa, the bitter medications naloxone and nalbuphine resulted in excessive salivation and swallowing. The medication consequently showed poor bioavailability. There were no side effects from administering nalbuphine and naloxone in prodrug form, and their bioavailability, which ranged from 35 to 50%, was noticeably better than their oral bioavailability, which is typically 5% or less. [19]

pH [19]: Shojaei et al. assessed the permeability of acyclovir at pH values between 3.3 and 8.8, as well as when sodium glycocholate, an absorption enhancer, was present. When compared to the midrange values (pH 4.1, 5.8, and 7.0), the flow and permeability coefficient increased at both pH extremes (pH 3.3 and 8.8), indicating that the in vitro permeability of acyclovir was pH dependent.

Patch Design[19]: A number of in vitro investigations into the kind and quantity of supporting materials as well as the drug release profile have demonstrated a relationship between the two. Additionally, single-layered and multi-layered patches had varied drug release patterns.

Basic components of buccal drud delivery system:

1. DRUG SUBSTANCE: Prior to developing mucoadhesive drug delivery systems, it is necessary to determine if a local or systemic effect and quick or extended release are the desired actions. Pharmacokinetic characteristics should guide the choice of an appropriate medication for the development of buccoadhesive drug delivery systems.

The following qualities should be present in the medication [20].

Traditionally, a single dose of the medication should be modest.

Medications with a biological half-life of two to eight hours provide excellent choices for regulated drug delivery.

When taken orally, the drug's Tmax exhibits larger fluctuations or higher values.

When taken orally, a drug may have a first pass effect or presystemic drug elimination. When taken orally, drug absorption should be passive.

2. BIOADHESIVE POLYMER: Choosing and characterizing the right bioadhesive polymers for the formulation is the first stage in creating buccoadhesive dosage forms. 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 [21]. The most varied class of polymers are bioadhesive ones, which offer significant advantages for patient care and therapy [22]. The core layer, also known as the rate governing layer, releases the medication into the mucous membrane.

Bioadhesive polymers that stick to the mucin/epithelial surface work well and greatly enhance oral medication administration [23].

3. BACKING MEMBRANE: The backing membrane is crucial to the bioadhesive devices' ability to adhere to the mucous membrane. The backing membrane's constituent materials ought to be inert, meaning they should not allow the medicine or penetration enhancer to pass through. Buccal bioadhesive patches with such an impermeable layer improve patient compliance and stop medication loss. Carbapol, magnesium stearate, HPMC, HPC, CMC, polycarbophil, and other compounds are frequently employed in backing membranes [24].

4. PERMEATION ENHANCERS: Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other Excipients.[24]

Table No. 1: Commercially Available Buccal Adhesive Formulations [25]**.**

Brand Name	Bioadhesive Polymer	Company	Dosage forms
Buccastem	PVP, Xanthum gum, Locust bean gum	Rickitt Benckiser	Tablet
Suscard	HPMC	Forest	Tablet
Gaviscon Liquid	Sodium alginate	Rickitt Benckiser	Oral liquid
Orabase	Pectin,gelatin	Orabase	Pectin,gelatin
Corcodyl gel	HPMC	Glaxosmithkline	Oromucosal Gel
Corlan pellets	Acacia	Celltech	Oromucosal Pellets
Luborant	Sodium CMC	Antigen	Artificial Saliva
Saliveze	Sodium CMC	Wyvem	Artificial Saliva
Aphtach	Hydroxypropyl cellulose Polyacrylic acid	Tejin Ltd	Tablet

Buccastem buccal	Xanthan gum	Reckitt	Tablet
Oralin – Gencrex	Unknown	Generex Biotechnology (Phase II trials)	Solution
Lauriad (Phase III trials)	Unknown	BioAlliance Pharma	Tablet
Striant SR buccal	Carbomer 934P Hypromellose Polycarbophil	Ardana Bioscience Ltd	Tablet
Suscard buccal	Hypromellose	Forest Laboratories	Tablet

Motheds of preparation the buccal DDSs :

Mucoadhesivebuccal patches can be prepared by the following methods:

A. **Solvent casting**: This process involves precisely weighing each ingredient before combining them in a mortar and pestle. The combination is then added to the solvent system that has the plasticizer in it. After that, the solution is moved to a petri dish. To enable the solvents to evaporate, the petri dish is covered by inverted funnels.

These are stored for 24 to 48 hours at 20 to 25 degrees Celsius, depending on the solvent system being utilized. Following the solvent's evaporation, a thin coating of the protective backing material is adhered to the coated release liner sheet to create a laminate that can be die-cut into the appropriate size and shape patches.

B. **Direct millin**g: No solvents are used in the production of these patches. Direct milling is used to mechanically combine the drug and excipients without the use of liquids.[26]

Different Buccal Mucoadhesive Dosage Forms:

The best candidate for creating such formulations is always constrained by a number of criteria, despite the fact that mucoadhesive buccal medication delivery has certain clear benefits. Size restriction is one of the crucial elements. The amount of drug moiety included should be relatively modest for an efficient and pleasant buccal drug delivery system; preferably, 25 mg or less is better suitable for buccal drug administration 2. A buccal drug delivery formulation of the medication with a short biological half-life can provide a regulated, extended, and sustained release of the drug from the intended dose form. Among the various forms of buccal drug delivery systems are buccal chewing gums, adhesive tablets, adhesive gels, sticky patches, adhesive ointments, and adhesive powders.

Buccal mucoadhesive films

Due to their adhesive properties, they are mostly transparent drug-loaded films meant to be inserted into the buccal mucosa. Because buccal films are more comfortable and flexible than other dose forms, they may be selected.

There are two varieties of mucoadhesive buccal patches.

a) Matrix-type drugs, adhesives, and additives are combined and subsequently shaped into patches.

b) The drug and additives of the reservoir type have to be kept apart. The release from the patch can be either unidirectional or bidirectional, depending on whether a backing membrane is present. [27]

Mucoadhesive buccal tablets

These resemble regular tablets except that they are mucoadhesive, meaning that they are kept between

the gums and cheeks rather than swallowed. The medium that comes from the places where these tablets are placed dissolves them adequately. However, to guarantee a steady and regulated release, the tablet's disintegration should be slowed. Such dosage formulations should be dissolved carefully to provide regulated dissolving. Therefore, there are no disintegrants in the sticky tablet. tablets designed to stick to the buccal cavity and become softer as a result of the mouth's constant production of saliva. This ensures that the entire drug is released into the systemic circulation through the buccal cavity's blood capillaries, avoiding the hepatic metabolism.

Dosage form for semi-solid buccal mucoadhesive

As semisolid dosage forms for mucoadhesive drug administration, gels and ointments advance important strategies over the oral mucosa. These systems' primary benefit is their malleable rheological nature, which allows for a longer residence duration when applied to the surface.

Chewing gum with buccal

Medicated chewing gum is very useful for nicotine replacement therapy and oral cavity treatment. Because of their adaptability and patient comfort, buccal patches are the finest mucoadhesive buccal medication administration method.

Microparticles

possess more benefits than tablets. Microspheres' physical characteristics allow them to come into close touch with a sizable mucosal surface. Their brief residence duration at the site of absorption limits the effectiveness of these microspheres, but they can also be administered to less accessible areas including the nasal cavity and GI tract, and they produce less local irritation at the site of adhesion.

Wafers

An innovative medication delivery device for periodontal disease. The purpose of this is to cure microbial infections. While the bulk layer is made up of matrix polymers, biodegradable polymers, and antibacterial agents, the surface layers have sticky qualities.

Lozenges

Are used as topically within mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. In lozenges multiple daily dosing required because the release of drug in oral cavity is initially high and then rapidly decline.[28]

Buccal permeation enhancers:

Permeation enhancers are substances that help substances pass through the buccal mucosa. The physiochemical characteristics of the medication, the administration site, the kind of vehicle, and additional excipients all influence the choice and effectiveness of the enhancer. Despite avoiding hepatic first-pass metabolism and gastric breakdown, medications delivered orally have a comparatively low bioavailability. Co-administration of a permeation enhancer is crucial, especially for peptides. A variety of methods can be used to achieve improved absorption[29]. Co-administration of a permeation enhancer can improve medication absorption through tissue.

These substances can lower the barrier across the mucosa layer (by mimicking the desmosome

fluidization of intracellular liquids) or change the drug's characteristics (by forming complexes). [30]

Mechanism of action of permeation Buccal:

1. **Modifying mucus rheology**: This barrier can be broken by decreasing the viscosity of mucus and saliva.
2. **Making the membrane of lipid bilayers more fluid**:
   Interact with either protein or lipid packing components to disturb the intracellular lipid packing.
3. **Interacting with the components at tight junctions**: By blocking different peptidases and proteases found in the buccal mucosa, the enzymatic barrier is broken.
4. **Increasing the drug's thermodynamic activity**: Certain enhancers make the drug more soluble, which modifies the partition coefficient [31,32]

The future of buccal drug delivery systems

looks promising, with several advancements and trends shaping its development:

- Enhanced Permeability: Research is focusing on improving the permeability of the buccal mucosa to allow for better drug absorption. This includes the use of permeation enhancers and nanotechnology.[33]
- Mucoadhesive Polymers: The development of new mucoadhesive polymers is crucial. These polymers help the drug formulation adhere to the buccal mucosa, ensuring prolonged contact and better absorption.[33]
- Nanotechnology: Nanoparticles and nanocarriers are being explored to enhance the delivery and efficacy of drugs through the buccal route. These technologies can help in targeting specific sites within the oral cavity.[34]
- Biologics and Peptides: There is a growing interest in delivering biologics and peptides via the buccal route. This method can bypass the harsh gastrointestinal environment and first-pass metabolism, making it a viable option for these sensitive molecules.[34]
- Patient Compliance: Buccal drug delivery systems are being designed to improve patient compliance. This includes developing formulations that are easy to use, have a pleasant taste, and provide sustained release of the drug.[33]
- Treatment of Oral Infections: Specialized drug delivery systems are being developed for the prevention and treatment of oral infections. These systems aim to provide localized treatment, reducing systemic side effects and improving efficacy.[35]

Overall, the future of buccal drug delivery systems is geared towards making drug administration more efficient, patient-friendly, and effective for a wide range of therapeutic applications.

Conclusion

For prolonged, regulated drug distribution, the buccal mucosa provides a number of benefits. First-pass metabolism in the liver and presystemic elimination in the gastrointestinal tract are avoided, and the mucosa is adequately supplied with vascular and lymphatic drainage. The location seems to be agreeable to the patient and is ideal for a retentive device. Drug permeation can be accommodated by controlling and manipulating the mucosa's permeability and local environment with the proper dosage form design and formulation. In order to systemically distribute oral ineffective medications and provide a viable and appealing substitute for non-invasive delivery of strong peptide and protein therapeutic molecules,

buccal drug delivery is a potential field for further investigation.

Finding methods to give injectable drugs is expensive and can occasionally have major negative implications on health, both financially and globally. Therefore, there is a demand for low-cost, multi-dose formulations with improved bioavailability. Research on buccal medication administration has grown and advanced remarkably during the last few decades. Due to its many benefits, including as avoiding the liver's first pass metabolism and the gastrointestinal tract's pre-systemic clearance, the transmucosal route is growing in popularity. Buccal drug administration is a viable and alluring substitute for non-invasive delivery of strong peptide and protein therapeutic molecules, and it has significant potential for systemic delivery of oral ineffective medications.

However, a key element of a potential future in the field of buccal medication administration is the requirement for safe and efficient buccal permeation/absorption enhancers.

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