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Pharmaceutical Sciences **Review Article……!!!**

AN OVERVIEW OF BUCCAL MUCOADHESIVE DRUG DELIVERY METHODS

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ABSTRACT

Mucoadhesive buccal formulations have grown in importance in recent years when it comes to medicine delivery. Using buccal regions for drug delivery is a helpful strategy for both local and systemic medicines. It makes sure the drug stays in the body for a longer period of time, delays drug release, and allows close contact between the dosage form and the buccal cavity. First-pass metabolism in the liver and pre-systemic excretion in the digestive tract are avoided because the mucosa has adequate vascular and lymphatic drainage. Bucco-adhesive systems also offer the benefit of being affordable, simple to use, and quick to remove from the body. Mucoadhesive polymers are used to extend the dosage form's contact and residence periods with the mucous membranes in order to improve drugs delivery. The location is ideal for a retentive device and seems to be well-liked by the patient. With the right dosage form design and formulation, the mucosa's permeability and local environment may be controlled and maintained to facilitate drug absorption. This study emphasizes the mucoadhesive buccal drug delivery by briefly looking at the mechanisms and theories behind mucoadhesion, the anatomical characteristics of the oral mucosa, the elements of the buccal drug delivery system, and formulation strategies for buccal drug delivery.

INTRODUCTION:

The pharmaceutical sector has made significant strides in improving the quality of life by treating disease. As time goes on, scientists and researchers in the drug development fields are concentrating on alternative ways of administration to increase the potency of medicines that have already been authorized or to get beyond the limitations of the oral route. Drug delivery via the oral route is favoured, but it is also subject to various limitations, such as local GI toxicity, and GI tract enzymatic degradation, hepatic first pass metabolism. These difficulties have motivated researchers to take into account a variety of drug administration techniques, such as nasal, vaginal, rectal, pulmonary, buccal, ophthalmic, and transdermal. Transmucosal routes, which are made up of mucosal linings, provide strong possibilities and potential advantages over peroral administration for systemic drug delivery. One of such is the oral mucosa, which is possibly the most practical and favoured route for medication administration. The buccal, palatal, sublingual, and gingival areas of the oral cavity are the four possible sites for medication administration. In order to impact local or systemic pharmacological activities, buccal drug delivery particularly refers to the distribution of medications within or via the buccal mucosa.

Buccal formulations are inserted in the mouth between the upper gingival (gums) and cheek and line the inner cheek to address both local and systemic problems. A possible delivery method for hydrophilic, unstable and large proteins, polysaccharides and oligonucleotides as well as common, small pharmaceutical compounds is the buccal route. Drug release for an extended period of time, being able to administer medication to unconscious and trauma patients, the ability to avoid first pass metabolism, the ability to administer certain medications that are unstable in the acidic environment of the stomach, adaptability in physical therapy are just a few benefits of using buccoadhesive drug delivery. The buccal drug delivery system has some drawbacks, including the inability to administer medications that are unstable at buccal pH, the restriction of eating and drinking, the requirement for only small doses of drugs, and the inability to administer medications that have a bitter or unpleasant taste, an offensive odour, or that irritate the mucosa.

MUCOADHESION

The term "bio-adhesion" refers to the bonding of synthetic or biological macromolecules to living tissue. Mucoadhesion is the term for the bioadhesive contact that mostly happens with the mucus layer when it is applied to the mucosal epithelium.

Mechanism of mucoadhesion

The contact stage: The dosage form distributes, wets, and swells at the mucus surface, beginning contact between the polymer and the mucus/epithelium and leading to interdiffusion and interpenetration between the chains of the mucoadhesive and the network of mucous.

The consolidation stage: Ionic, hydrogen, covalent, and hydrophobic secondary chemical bonds may develop between the polymer chains and mucin molecules.

Theories of mucoadhesion

Adsorption theory:

According to the theory, when mucous and the mucoadhesive polymer first come into contact, primary and secondary covalent and non-covalent chemical interactions are created.

Diffusion Theory:

In accordance with this theory, the polymer chains and mucus mix deeply enough to form a semi-permanent adhesive bond. The exact depth to which polymer chains enter mucus is determined on the diffusion coefficient and the period of contact. This diffusion coefficient, in turn, is determined by the molecular weight difference between cross links and reduces dramatically as cross-linking density diminishes.

Wetting theory:

The wetting the theory explains how bioadhesive polymers spread on biological surfaces. The idea relates to liquid systems that have an attraction for the surface and spread across it. The contact angle between two surfaces is measured in this theory. In general, the affinity increases as the contact angle decreases. The contact angle should be zero or near to zero to give optimum spreadability. As a result, somewhat wettable polymers have been proven to have the best adherence to human endothelial cells.

Electronic theory:

According to this theory, electrons are transferred across the adhesive contact and adhering surface. This leads in the formation of an electrical double layer at the interface, as well as a series of attraction forces that keep the two layers in contact.

Mechanical theory:

According to this theory, adhesion happens when a mucoadhesive liquid fills the imperfections on a rough surface.

Fracture Theory:

Adhesion, according to Fracture theory, is related to the separation of two surfaces following adhesion. The fracture strength is equal to the adhesive strength as calculated by,

$G = (E\varepsilon. /L)$ ½

E= Young's module of elasticity, ε = Fracture energy, L= Critical crack length when two surfaces are separated.

ORAL MUCOSA

The three layers of the oral mucosa are the epithelium, the basement membrane, and the connective tissues. The top layer of oral mucosa contains the stratified squamous epithelium that is mucus-coated. There are approximately 40–50 cell layers in the epithelium. The epithelium, which develops from basal cells and acts as a barrier for the tissues below, matures, transforms into a different shape, and enlarges as it approaches the surface. The basement membrane creates a distinct layer that lies between the connective tissues and the epithelium. It provides the epithelium with a mechanical support and enables the epithelium to cling to the underlying connective tissues. Hard palate and gingivae mucosae are keratinized, whereas buccal, sublingual, and soft palate mucosae are not. Non-keratinized epithelia have a higher permeability than that of keratinized epithelia.

Three different kinds of mucosae make up the anatomy of the buccal site: The gingiva and the hard palate are covered by the masticatory mucosa, which has a thickness of 100–200 mm and makes up 25% of the entire oral mucosa. The lips, cheeks, soft palate, lower surface of the tongue, and oral cavity floor are all covered by the lining mucosa, which makes up 60% of the entire oral mucosa and measures 500–800 mm thick. The dorsum of the tongue is home to the specialized mucosa, which accounts about 15% of the oral mucosa overall and is involved in tasting. There are a few small salivary glands in the buccal area. A buccal mucosa has an average surface area of 100 cm^2 and encompasses the inside of the cheek as well as the region between the upper and lower lips.

The mucus that surrounds the buccal mucosa's epithelial cells is about 40 mm to 300 mm thick, negatively charged, and contains large glycoproteins called mucins, which are macromolecules with a molecular weight of 0.5 to 20 MDa and are used to lubricate, protect, and act as a wetting agent. 95% of mucins are made up of water, 1% mineral salts, 0.5–5% glycoproteins and lipids, and up to 1% free proteins. These support a pH range of 5.8–7.4 and largely contribute to saliva's viscoelastic properties.

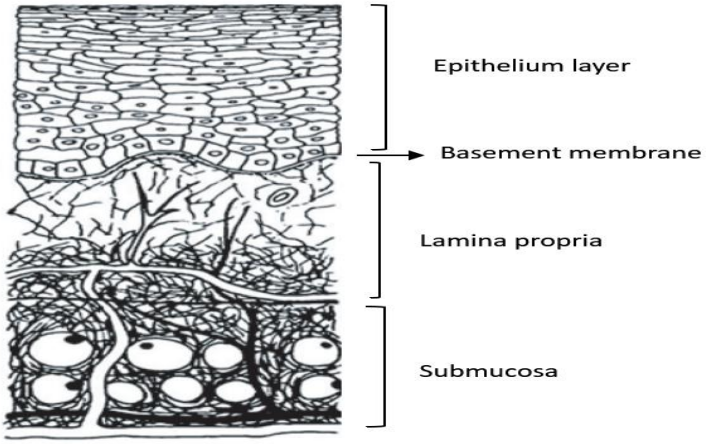

Fig. Structure of oral mucosa

COMPONENTS OF BUCCAL DRUG DELIVERY SYSTEM

The following functional agents should be included in formulations intended for buccal administration in order to meet the therapeutic requirements:

Drug substance:

One must choose whether the desired action is for quick or extended release and for local or systemic effect before designing a buccoadhesive drug delivery system. Pharmacokinetic parameters should be taken into consideration when choosing an appropriate medication for the construction of a buccoadhesive drug delivery system.

Following are the critical properties for candidature to Buccal Mucoadhesive Drug Delivery:

- Conventional single dose of drug should be low.
- For regulated drug delivery, medications with biological half-lives of 2 to 8 hours are suitable choices.
- When administered orally, the drug's Tmax exhibits broader oscillations or higher values.
- The medicine should not have a foul taste and be free of irritation, allergenicity, discoloration, or tooth erosion.
- When administered orally, the medication may exhibit first pass action or presystemic drug clearance.
- When a drug is administered orally, absorption should be passive.
- Drugs shouldn't harm the mouth cavity or natural microbial flora.

Mucoadhesive polymer:

Due to their accessibility and smooth, largely immobile surface, the buccal regions are excellent candidates for a bioadhesive system. The localization of pharmaceuticals in a specific area and the prolonged residence period of the formulation in the oral cavity are the main benefits of bioadhesive systems. Water-soluble and water-insoluble polymers that may expand and form a network when bonded together by a crosslinking agent make up mucoadhesive polymers. The

polymer can have enough polarity to allow mucus to wet it and enough fluidity to improve the mutual adsorption and penetration of the polymer and mucus. The production of slippery, nonadhesive mucilage due to excessive hydration may lower the adhesive strength or possibly cause the loss of adhesion. A polymer conformation that favours bioadhesion has functional groups like amines, hydroxyls, carboxyls, and amides accessible on its surface.

An ideal polymer for buccoadhesive drug delivery systems should have following Characteristics

- The polymer should be non-toxic, non-irritating, devoid of leachable contaminants, and absorbable by the mucous layer.
- Have some site specificity and adhere easily to wet tissue surface.
- Should make it simple to incorporate the medication into the formulation
- Should possess good qualities for solubility, swelling, spreading, wetting, and biodegradability.
- Must possess both liquid and dry bioadhesive qualities.
- Must not disintegrate while being stored or during the dosage form's shelf life.
- Should exhibit qualities that increase penetration and inhibit local enzymes.
- The distribution must be restricted and the molecular weight be high.
- Must be mechanically strong enough and attach to buccal mucosa fast.
- Should be adequately cross-linked but not to the point where bond forming groups are suppressed.
- Should have peel, tensile, and shear strengths in the bioadhesive range.
- Must not promote the growth of secondary infections such dental caries.
- Should have the necessary spatial conformation;
- Should have adhesively active groups.

Criteria	Categories	Example
Source	Natural	Agarose, Chitosan, Gelatin, Various gums (guar, xanthan, pectin, alginate).
	Synthetic	Cellulose derivatives- CMC, HEC, HPC, HPMC
		Polyacrylic acid derivative- CP, PC, PAA, Polymethacrylate, Copolymer of acrylic acid, PEG.
		Other- PVP, PVA, Polyoxyethylene, Thiolated polymer.
Potential bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen	Acrylates, Methacrylic acid, CO, PC, PVA

	Electrostatic interaction	Chitosan.
Charge	Cationic	Aminodextran, Chitosan, Trimethylated Chitosan
	Anionic	Chitosan, EDTA, CP, CMC, PAA, Pectin
	Non-ionic	Hydroxyethyl starch, HPC, PVP, PVA
Aqueous solubility	Water soluble	CP, HEC, HPC, HPMC, PAA, Sodium CMC
	Water Insoluble	Chitosan, EC, PC

Permeation enhancer:

Permeation enhancers are substances that aid in permeation through buccal mucosa. The drug's physicochemical qualities, administration site, vehicle type, and other excipients all affect the choice of enhancer and its efficacy. By enhancing cell membrane fluidity, removing structural intracellular and/or intercellular lipids, changing cellular proteins, or changing the structure and rheology of mucus, they are able to reduce the buccal mucosa's penetration barrier. The availability of protein, peptide, and nucleotide drugs is increasing as a result of the quick advancement of biotechnology. The majority of these drugs have low membrane-absorption properties, such as irregular shapes, large size with high molecular weight, various hydrophobicity, and delicate structures easily inactivated. Research on penetration enhancers is becoming increasingly relevant since many pharmaceuticals cannot penetrate membrane barriers in therapeutic quantities. These need to be non-irritating and have an impact that can be reversed; when the medication has been absorbed, the epithelium should regain its barrier function.

Category	Examples
Surfactants	Anionic: Sodium lauryl sulfate
	Cationic: Cetyl pyridinium chloride
	Nonionic: Poloxamer, Brij, Span, Myrj
Bile salts	Sodium glycol deoxycholate, Sodium glycocholate, Sodium tauro deoxycholate, Sodium tauro cholate
Fatty acids	Oleic acid, Caprylic acid, Lauric acid, Lyso phosphatidyl choline, Phosphatidyl choline
Cyclodextrins	α, β, γ, Cyclodextrin, methylated β –cyclodextrins
Chelators	EDTA, Citric acid, Sodium salicylate, Methoxy salicylates
Positively charged Polymers	Chitosan, Trimethyl chitosan
Cationic Compounds	Poly-L-arginine, L-lysine

Backing membrane:

The mucus membrane is the primary surface on which bioadhesive devices are attached. The backing membrane's materials have to be innocuous, impermeable to the drugs, and penetration-enhancing. The buccal bioadhesive patches' impermeable membrane avoids medication loss and improves patient compliance. Materials like Carbopol, HPMC, HPC, magnesium stearate, CMC, and polycarbophil are frequently used in backing membranes.

Enzyme Inhibitors:

The buccal mucosa has one of the lowest levels of enzyme activity among mucosal routes, and neither fast nor widespread drug inactivation occurs there. However, medications, especially peptide/protein drugs, can still be broken down by salivary and buccal mucosal enzymes. In the buccal epithelium, many proteolytic enzymes were discovered. Another method for enhancing medication buccal absorption through the use of enzyme inhibitors is the coadministration of medicines. Bestatin, Puromycin, Aprotinin, and certain bile salts are examples of enzyme inhibitors that stabilize protein drugs by a variety of ways, including changing the structure of peptides or proteins, modifying the activities of enzymes, and/or making the drug less susceptible to enzymatic breakdown.

FORMULATION APPROACHES OF BUCCOADHESIVE DRUG DELIVERY

The rate of buccal mucosal turnover, salivary secretion, mucus composition, degree of ionization, mechanism of absorption, dose, flavour, additives that interfere with salivary secretion, surface area needed for application, disease conditions that cause a change in buccal mucosa thickness, purpose of the dosage form, and drug interactions with mucin are to be taken into consideration.

Buccal tablets:

The dosage form for buccal drug delivery that has been studied the most frequently is the tablet. By using the direct compression approach, a number of bioadhesive buccal tablet formulations have been created for either local or systemic drug administration. They are intended to deliver the medication either in a single route by concentrating on the buccal mucosa or in several directions into the saliva. These are applied directly to the mucosal surface to administer drugs locally or systemically. These become softer, stick to the mucosa, and remain there until their dissolution or release is finished. To enable or achieve unidirectional release of the medication, water-impermeable materials, such as ethylcellulose, hydrogenated castor oil, etc., may be used either by compression or by spray coating covering all sides of the tablet apart from the one that is in contact with the buccal mucosa.

Tablets that adhere to the mucosa have the ability to deliver drugs with controlled releases. Prior to direct compression, the drug may be prepared in specific physical states, such as microspheres, to obtain particular desired qualities, such as increased activity and longer drug release. Tablets with mucoadhesive characteristics provide added benefits. Due to a high surface-to-volume ratio and a facilitation of a much close contact with the mucous layer, it promotes effective absorption and increased bioavailability of the medications. The ability to target any mucosal tissue, including those in the stomach, using mucoadhesive tablets opens up the possibility of localized and also systemic controlled drug release. Patient acceptance (mouth feel, taste, and discomfort) and the inequitable dispersion of the medication within saliva for local treatment are potential drawbacks of buccal tablets. It is crucial to draw attention to the potential issues that young children and the elderly may encounter when using adhesive tablets, such as potential discomfort brought on by the material used on the mucosa and the potential for dosage separation from the mucosa, swallowing, and subsequent adherence to the oesophageal wall.

Buccal patches/ films:

Buccal patches are defined as laminates made of an impermeable backing layer, a reservoir layer that contains the drug and releases it gradually, and a surface that is mucoadhesive and allows for mucosal adhesion. Drugs can be directly administered to a mucosal membrane using patches. Due of their physical flexibility, which only slightly annoys the patient, they have higher patient compliance than tablets. The fact that they provide a precise amount of medication to the spot makes them superior than creams and ointments.

A buccal film should be soft, elastic, and flexible but sturdy enough to resist breaking under force from oral activity. It should also have strong mucoadhesion so that it can stay in the mouth for the required amount of time. Patches and films can be made using a variety of techniques, including direct milling, hot melt extrusion, semisolid casting, solvent casting, solid dispersion extrusion, etc.

Semisolid Preparations (Ointments and Gels):

Patient acceptance of bioadhesive gels and ointments is lower than that of solid bioadhesive dose forms. They are typically selected for local action when dose precision is less or not a concern because they do not have accurate dosing as a unit dosage form like tablets, patches, or films. Using steroidal gel locally, for instance, to treat mucosal ulcers. The use of mucoadhesive formulations has improved the gels' poor retention at the application site. Hyaluronic acid, sodium carboxymethylcellulose, Carbopol, and xanthan gum are a few mucoadhesive polymers that go through a phase shift from liquid to semisolid. This alteration increases viscosity, which

causes medications to release slowly and under control. Another interesting dosage type for buccal drug administration is hydrogel.

Bioadhesive lozenges:

Drugs that serve as antibiotics, corticosteroids, local anaesthetics, antimicrobials, and antifungals may be delivered topically in the mouth using bioadhesive lozenges. The brief residence duration at the site of absorption, which is dependent on formulation size and type and dissolves within 30 minutes, is a constraint of these bioadhesive lozenges. As a result, the total amount of the medication that may be administered is constrained. The initial medication release from lozenges in the oral cavity is considerable, but it quickly declines to subtherapeutic levels, necessitating additional doses. Patients often regulate how quickly or forcefully lozenges dissolve or disintegrate by sucking on them. Uncontrollable swallowing and medication loss through the GI system are caused by increased sucking and salivation. Therefore, absorption and bioavailability differences between and within individuals are often substantially larger for solid dose forms. Another significant obstacle to the effectiveness of such dose formulations is continuous saliva production. There is also a delayed release bioadhesive lozenge that may allow for a longer medication release period while improving patient compliance.

Buccal solution:

A viscous liquid known as buccal solution is applied to the buccal surface either as a protective coating or as a means of delivering medication to the buccal mucosal surface. These are offered as drug suspensions or solutions in appropriate vehicles. This kind of dosage form, used for local action, is marketed as antibacterial mouthwashes and mouth fresheners. The drawback of these liquid dose forms is that they can release relatively uncontrolled quantities of medication throughout the oral cavity and are not easily retained or targeted to the buccal mucosa. There are many other types of polymers used, but chitosan has the best ability for binding.

Medicated chewing gum:

Chewing on a piece of medicated gum releases a large amount of the medicine, demonstrating local activity in the mouth. Additionally, it may demonstrate systemic circulation-based absorption. There is medical chewing gum for use in nicotine replacement therapy. The same goes for caffeine-containing chewing gums. It is absorbed much more quickly, and its bioavailability was on track with the formulation used in capsules.

Bioadhesive Micro/nanoparticles:

The benefit of particles is that they are often tiny and more likely to be accepted by patients. Due to their high surface-to-volume ratio, tight interaction with the mucus layer, and accurate targeting of medications to the absorption site, they provide advantages including effective

absorption and increased bioavailability of pharmaceuticals. These are often administered as aerosols, mixed into pastes or ointments, or supplied as an aqueous solution. The positively charged surfactant trapped on the particle surface is responsible for the nanoparticles' bioadhesive characteristics.

CONCLUSION

Buccal adhesive systems provide a plethora of benefits, including ease of administration and removal, retentivity, minimal enzyme activity, affordability, and high patient compliance. Buccal drug delivery is an area that shows promise for further study with the goal of systemic distribution of poorly absorbed medications as well as a practical and alluring substitute for non-invasive delivery of potent peptide and protein therapeutic molecules.

Additionally, buccal adhesive dose forms have been utilized to treat local conditions at the mucosal surface (such as mouth ulcers), to lower the overall dosage necessary and reduce any potential negative effects from systemic medication delivery. The development of safe and efficient buccal permeation and absorption boosters is essential for the development of buccal medication delivery systems in the future. World-wide research and development on mucoadhesive buccal medication delivery systems is still ongoing. The development of vaccines and the delivery of peptides and tiny proteins make up the future of bucco-adhesive drug delivery systems.

REFERENCE

1. Fonseca-Santos B, Chorilli M. An overview of polymeric dosage forms in buccal drug delivery: State of art, design of formulations and their in vivo performance evaluation. Materials Science and Engineering: C. 2018 May 1;86:129-43.
2. Srivastava N, Monga MG. Current status of buccal drug delivery system: a review. Journal of Drug Delivery and Therapeutics. 2015 Jan 13;5(1):34-40.
3. Gupta S, Das S, Singh A, Ghosh S. A Brief Review on Bucco-adhesive Drug Delivery System. Journal of Drug Delivery and Therapeutics. 2021 Aug 15;11(4-S):231-5..
4. Chaudhari VA, Sarode SM, Sathe BS, Vadnere GP. MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM: A REVIEW. Pharma Science Monitor. 2014 Apr 1;5(2).
5. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. Journal of biomedical research. 2014 Mar;28(2):81.
6. Reddy PC, Chaitanya KS, Rao YM. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU Journal of Pharmaceutical Sciences. 2011;19(6):385.

7. Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A, Pandey J, Parajuli-Baral K. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon. 2021 Mar 1;7(3).
8. Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. European Journal of Pharmaceutics and Biopharmaceutics. 2011 Feb 1;77(2):187-99.
9. Koyi PK, Khan AB. Buccal patches: a review. International Journal of Pharmaceutical Sciences and Research. 2013 Jan 1;4(1):83.
10. Amasya G, Karavana SY, Şen T, Baloğlu E, Tarımcı N. Bioadhesive and mechanical properties of triamcinolone acetonide buccal gels. Turk J Pharm Sci. 2012 Apr 1;9(1):1-2.
11. Rossi S, Sandri G, Caramella CM. Buccal drug delivery: a challenge already won?. Drug Discovery Today: Technologies. 2005 Mar 1;2(1):59-65.
12. Rao NR, Shravani B, Reddy MS. Overview on buccal drug delivery systems. Journal of pharmaceutical sciences and research. 2013 Apr 1;5(4):80.
13. Hao J, Heng PW. Buccal delivery systems. Drug development and industrial pharmacy. 2003 Jan 1;29(8):821-32.
14. Verma S, Kaul M, Rawat A, Saini S. An overview on buccal drug delivery system. International journal of pharmaceutical sciences and research. 2011 Jun 1;2(6):1303.