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"ADVANCEMENTS AND INSIGHTS INTO MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEMS: FORMULATION, MECHANISMS AND EVALUATION"

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Abstract: This comprehensive overview delves into the realm of mucoadhesive buccal drug delivery systems, highlighting their significance, mechanisms, components, and evaluation methodologies. Buccal drug delivery stands as a promising alternative, offering localized and systemic effects with enhanced patient compliance. The review encapsulates the significance of mucoadhesion, emphasizing the role of the buccal mucosa due to its high permeability and blood supply. It investigates the mucoadhesive mechanisms, elucidating the contact and consolidation stages, supported by various theoretical frameworks. Detailed insights into the composition and physiology of mucous membranes enrich the understanding of drug-mucosa interactions. The role of penetration enhancers in augmenting drug absorption is outlined, discussing their mechanisms and categorization. Factors impacting mucoadhesion, including polymer characteristics, environmental factors, and physiological influences, are meticulously analyzed. The review elaborates on the basic components essential in designing buccal drug delivery systems, delineating the role of drug substances, bioadhesive polymers, backing membranes, plasticizers, and permeation enhancers. Furthermore, it categorizes these systems into solid, semi-solid, and liquid dosage forms, providing a comprehensive landscape of available formulations. Evaluation methodologies for these dosage forms, spanning in vitro and in vivo techniques, are discussed in detail. This includes methods to study buccal absorption, mucoadhesive strength, and various experimental techniques such as rheological studies, fluorescence probes, and gamma scintigraphy. Insights into the key advantages and disadvantages of these systems offer a balanced perspective. In conclusion, this review serves as a comprehensive guide, providing a detailed understanding of mucoadhesive buccal drug delivery systems, their mechanisms, components, evaluation techniques, and associated advantages and limitations.

Keywords: Buccal mucosa, Gastric pH, Mucoadhesion, Penetration Enhancer

Introduction

Drug distribution via the oral route is mostly preferred and offers more benefits than other methods [1]. The traditional way of delivering drugs is painless and comfortable for patients, gives accurate dosages, and is easy to remove without causing a lot of pain. It also has better stability, patient compliance, uniform and

sustained drug release, and, most importantly, simple and inexpensive ways of preparation that can be done using a variety of commonly available biocompatible polymers [2]. Oral administration of drugs has been the subject of research for both local and systemic purposes. Conditions such as gingivitis, oral candidosis, oral lesions, dental caries, and xerostoma can be treated with local therapy, while the drug can be delivered into the bloodstream through systemic delivery without influencing the pH or digestion enzymes in the middle gastrointestinal tract. In comparison to the oral route, a relatively quick onset of action is possible. Additionally, the dosage can be removed if the patient need arises to stop the therapy [3]. The lining of the lips and cheeks, or buccal mucosa, is an appropriate site for delivering drugs.

The buccal mucosa is used to give medications because it has a lot of blood flow and is easy for medicines to pass through. Because the buccal mucosa also makes it hard for drugs to be absorbed, penetration enhancers are used to help the drug get through the mucosa and make the drug more bioavailable [4]. This method of drug delivery allows drugs to skip the liver and digestive tract metabolism. However, while designing a formulation, it's important to consider things like saliva, surface area limitations, and patient comfort into account. Most of the time, bioadhesive polymers with multiple hydrogen bonding groups are used as hydrophilic macromolecules in buccal drug distribution to keep a formulation in place. There have been advancements made in second-generation bioadhesives, such as the creation of new or modified polymers that facilitate improved adhesion and/or drug delivery.When two things adhere together and at least one of them is a mucous surface, this is called mucoadhesion. In the last few decades, mucosal drug delivery has gotten a lot of attention. It is possible to make mucoadhesive dosage forms that release drugs at a controlled rate for better therapeutic results by letting them stay at the application site for longer [5].

Mucous Membranes [6]:

The term "mucous membrane" describes the wet lining that occurs in many bodily cavities, such as those in the respiratory and gastrointestinal systems. The lamina propria is a connective tissue covering the epithelial layer that lies above a mucous layer in such structures. Structures having multilayered or stratified epithelia include cornea, vagina, and oesophagus. Structures having single-layered epithelia include the bronchi, small and large intestines, and the stomach. These either have specialized glands like salivary glands that release mucus onto the epithelial surface or are close to tissues that have them. The first group has goblet cells that make mucus and deposit it directly on the epithelium surfaces. It comes in two different forms: a gel layer that sticks to the mucosal surface and a form that dissolves in the lumen. The primary components of mucus gels are mucin glycoproteins, lipids, inorganic salts, and water, which accounts for almost 95% of its weight, indicating that it is a very hydrated system. Mucin glycoproteins are the most important structural component of mucous gel; they are responsible for the gel-like, cohesive, and sticky properties of the gel. In the stomach, the thickness of this mucus layer can be anywhere from 50 to 450 micrometers, whereas in the mouth cavity, it is less than 1 µ. Lubrication and protection are the two primary functions of mucus.

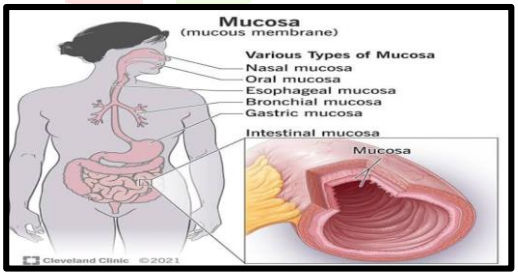

Fig 1.: Mucus Membrane

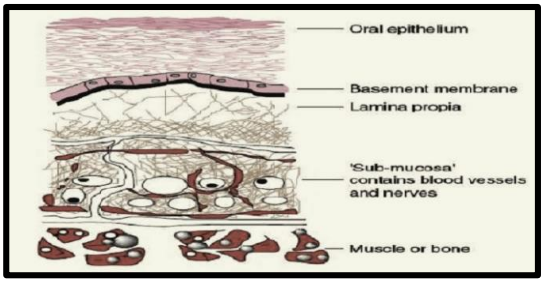

Fig 2.: Anatomy of Oral Mucosa

Mucus Composition:

The parotid gland, sublingual gland, and other salivary glands are the most common oral cavity glands that release oral mucus. Goblet cells or specific exocrine glands together with the mucus cells secrete the mucus, which is a translucent gel. [7]

Table 1: Composition of Mucus

Components	**Percentage**
Water	95%
Glycoproteins and Lipids	0.5-5%
Mineral Salts	1%
Free Salts	0.5-1%

Physiology Of Oral Mucosa:

Each of the following structures—the tongue, cheeks, lips, hard and soft palates, etc.—form the oral cavity. The shape of the different epithelia is what separates the skin from the oral mucosa through the GI tract lining [8]. The oral mucosa is an important route for the delivery of several drugs. It provides options for both local and systemic administration of drugs. The large surface area of mucous membranes in the mouth cavity allows for the full absorption of numerous drugs. The overall surface area of the mouth cavity, which is mucous membrane-lined, is close to 100 cm^2. The multi-layered epithelial tissues that make up the oral mucosal cavity are further covered by mucus. Inside the epithelial tissues, there is a basal membrane. The basement membrane contains a layer of connective tissues called the lamina propria. The mechanical support is provided by the lamina propria. The submucosal part goes on and is made up of different kinds of blood vessels and nerves from the brain and spinal cord. The submucosal area has the most blood vessels, which is important for effective drug absorption. When it comes to the human oral mucosa, there is both keratinized epithelium, which is in the gingiva and a part of the hard palate, and non-keratinized epithelium, which is on the surface of the soft palate, floor of mouth, lips, and cheek [9].

Buccal Mucosa as a Site for Drug Delivery:

Administering medication through the buccal and sublingual mucosa of the oral cavity, taking into consideration both the systemic and local therapeutic effects. The buccal mucosa, which refers to the inner lining of the lips and cheeks, is an appropriate site for the administration of drugs. The buccal mucosa is utilized as a site for drugs delivery due to its abundant blood supply and high permeability [10]. Bypassing the gastrointestinal tract and liver metabolism is possible with this method of drug delivery. But when designing a formulation, it's important to take into account things like saliva, surface area limitations and patient comfort. It has benefits like easy administration, avoiding first-pass metabolism, and direct access to systemic circulation.[11]

Fig 3: Buccal Route

Attractiveness of mucoadhesive drug delivery system [5].

- Allows the delivery system to be localized.
- Patients are well suited to taking medications orally.
- In comparison to other drug administration methods, patient compliance and acceptance are high.
- Prominent ability to quickly recover from local treatment.
- Permits the use of a variety of formulations, including mucoadhesive patches and ointments.

Mechanism Responsible for Mucoadhesion of Mucoadhesive Drug Delivery System:

It has been interesting to study mucoadhesion in the design of drug delivery methods in order to make medicines more bioavailable. This is done by giving the dosage form more time to stay in contact with the absorption surface below. A mucosal membrane and a drug delivery system stick together when their surfaces touch. This is called mucoadhesion. The mucous barrier lets the drug work where it's needed, and mucoadhesive systems stay in close contact with the tissue that absorbs it, making the drug more bioavailable and increasing its effects on both the local and systemic levels. To keep the drug's plasma level under control and to make it more bioavailable, it is very helpful to make the drug stay in one place for a longer time and control how it is released from the dosage form. It's still not clear how some macromolecules stick to the mucous tissue surface. The mucoadhesive has to permeate the substrate to maximize surface contact and create intimate contact. Because of this, its chains will be more likely to diffuse through the mucus. In order for a mucoadhesive to work, the adhesion forces must be stronger than the repulsion forces[12]. Dosage form composition and administration method may facilitate every stage. Consequently, the two phases that often establish mucoadhesion are the contact and consolidation stages.

During its long-term interaction with the mucus layer, the mucoadhesive goes through an initial stage of contact with the mucous membrane, followed by the formulation's swelling and spreading.

The mucoadhesive components are activated when there is moisture present during the consolidation process. In the presence of moisture, the solution becomes more flexible, which lets the mucoadhesive molecules separate and make weak hydrogen and van der Waals bonds.

There are two primary concepts that explain how consolidation works: diffusion theory and dehydration theory. Mucoadhesive molecules and mucus glycoproteins are said to associate with each other by forming secondary bonds and having their chains cross each other [13].

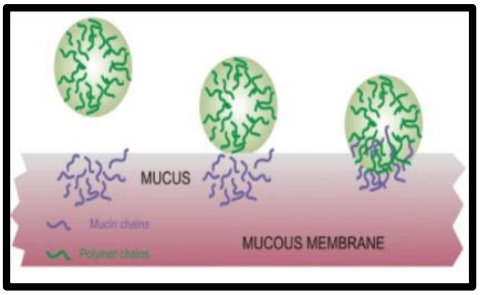

Fig 4: Two step method of mucoadhesion process

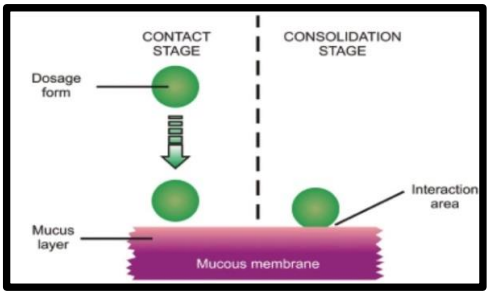

Fig 5: Mucoadhesion by Diffusion

Mucoadhesion Theories:

1. **Electronic Theory:** According to the electronic theory, the bio adhesive system and mucin surfaces have different electronic structures, which leads to achieving the goal of an electronic gradient. A difference in electrical structure causes the mucin surface and bioadhesive system to transmit electrons to one another when they come into contact. At the junction of the two surfaces, an electronic bi-layer forms as a result of this electron transfer. This interfacial bi-layer creates an attractive force at the intersection of two surfaces that could lead to successful mucoadhesion.[14]
2. **Adsorption Theory:** According to this concept, both primary and secondary chemical bonds play a role in the bio adhesive mechanism. The mucin-coated surface and the drug delivery system both have their own surface energy. Due to the surface energy, there are two different kinds of chemical bonds that form when they come into contact, which causes adhesion. Covalent bonds, which are primary chemical bonds and are strong by nature, result in permanent bonding, whereas secondary chemical bonds, which are weaker by nature and involve Vander Waals forces, hydrophobic interaction, and hydrogen bonding, result in semi-permanent bonds.[14]
3. **Mechanical Theory:** The contact between the two surfaces may be the source of this bond. It resembles the interlocking system in many ways. The five concepts of mucoadhesion listed below are based on the nature and strength of these two types of bindings [14].
4. **Wetting Theory:** The concept is supported by the mechanism of drug dosage form spreadability throughout the biological layer. This concept mostly applies to liquids or mucoadhesive systems with low viscosity. The concept states that the active ingredients enter the surface defects and harden them, which ultimately leads to mucoadhesion[15].
5. **Diffusion Theory:** As per this theory, the drug delivery system's polymeric chain and the mucus membrane's glycol protein chains form a mechanical link. The drug delivery system's polymeric chain is able to penetrate the glycoprotein network upon close contact of two surfaces. The theory says that the diffusion coefficient of the two polymeric chains has the most impact on bioadhesion. Additional factors that might impact how polymeric chains interact are temperature, cross-linking density, chain flexibility, and molecular weight. It is important that the bioadhesive material dissolves similarly to glycoprotein for good bioadhesion and mucoadhesion to work.[16]

Role of penetration enhancer and its mechanism:

Penetration enhancers may improve drug absorption through one or more potential routes. Table shows significant penetration enhancers along with their chemical category.

Table 2: Classification of Different Penetration Enhancer

Category	Penetration Enhancer
Cyclodextrins	Cyclodextrins Methylated- Cyclodextrin Hydroxypropyl cyclodextrin
Fatty Acids	Sodium Myristate, Oleic Acid, Lauric Acid, Propylene glycol, Sodium Laurate
Bile Salts	EDTA Sodium glycodeoxycholate, Sodium taurodeoxycholate, Sodium deoxycholate, Sodium glycocholate
Chelators	Sodium Citrate, Salicylates, Polyacrylates, EDTA
Vehicles and Adjuvant	Propylene Glycol, Ethanol
Surfactant	Sodium Lauryl Sulfate, Sucrose Laurate

Drugs are given with penetration enhancers that help the drug get into the buccal mucosa. Penetration enhancers may work in various ways depending on the chemicals they contain[17]. Nevertheless, the way that penetration enhancers work varies depending on the drug and the type of mucosal surface [18]. For penetration enhancers to work, they need to be safe, non-toxic, non-irritating to the buccal mucosa, therapeutically inert, non-allergic, and compatible with the drug and its ingredients [19]. The possible way that penetration enhancers work can be summed up as follows:

- By solubilizing intercellular lipids, drug transport via paracellular pathways is enhanced.
- Interaction with the lipid/protein membrane components of the cell membrane, thereby increasing membrane fluidity and promoting transcellular transport.
- Modification of mucus rheological characteristics, which results in a decrease in mucus layer viscosity and elasticity.
- Inhibition of the endo- and exopeptidase enzyme activity, which may prevent specific drug molecules from enzymatic breakdown.
- Increasing the thermodynamic activity of drugs causes more of them to move through the buccal barrier. [20]

Factors Affecting Mucoadhesion[21],[22],[23],[24] :

Table 3: Factors Affecting Mucodhesion

1. Polymer Related Factors	i. Molecular weight ii. Concentration of polymer iii. Swelling or Hydration iv. Charge v. Hydrogen Bonding Capacity
2. Environment Related factor	i. Moistening ii. Initial Contact Time iii. pH of polymer-substrate interface iv. Applied Strength
3. Physiological Factors	i. Tissue Movement ii. Concomitant Disease iii. Mucin Turnover iv. Diseased state v. Rate of renewal of mucosal cells

Advantages [25] :

- Simple administration and patient compliance.
- Rapid Disintegration Quick dissolving, dissolves in the mouth without water.
- Reduces the frequency of dose. It exhibits less side effects than other therapeutic dosage forms.
- This makes the drug more bioavailable by giving it more time to stay at the site of absorption.
- Improves bioavailability by keeping the dosage form at the site of absorption for longer.
- Easy to access to and starts acting rapidly. Quick absorption is possible in the presence of an abundant blood supply and healthy blood flow rates.
- The medication is protected from degradation in the acidic environment of the gastrointestinal tract.

Disadvantages [25][26]:

- The possibility of discomfort or irritation in the buccal cavity.
- Due to the little space accessible, there are limitations on size and formulation alternatives as well as difficulty in effective placement.
- The effectiveness of the medication may be impacted by individual differences in the rate of absorption.
- Choking fear as a result of the tablet's look.
- Localized ulceration caused by prolonged exposure to a material known to cause ulcers.
- One of the main challenges to developing oral mucosal delivery is the absence of a dependable model for in vitro screening to identify drugs that are appropriate for such medication administration.
- The ability of the patient to tolerate the taste and irritability.
- Eating and drinking are not allowed.

Basic Components of Buccal Drug Delivery System:

1. **Drug Substance:** It is important to consider the pharmacokinetic properties of the pharmacological ingredient or API when making a selection. These characteristics should be present in the medicine:
   - A small dose (25 mg) of medication should be taken all at once.
   - The expected range for the biological half-life of the medication is 2–8 hours.
   - To bypass first pass metabolism, buccal medication administration might be utilized for drugs that are subject to it.[27]
2. **Bioadhesive Polymer:** Mucoadhesive strength, thickness, in-vitro release, and residence time of the drug delivery device are some of the factors that are determined by the application of bio adhesive polymer. In most cases, the desirable rate-controlling properties of polymers with a high molecular weight make them the preferable choice. A perfect polymer would have these characteristics for the best possible outcome:
   - It needs to be inert,
   - It need to be compatible with both the environment and drugs.
   - It should able to adhere quickly to the mucus membrane and stay there for the appropriate duration.[28]

The Classification of Bioadhesive Polymer are as follows:[29]

Table 4: Classification of Bioadhesive Polymers

Criteria	Categories	Examples
Source	Cellulose Derivatives [CMC, thiolated CMC, Sodium CMC, HEC, HPC, HPMC, MC]	Poly(acrylic acid) – based polymers[CP,PC,PAA polyacrylates, poly(methylvinylether-co-methacrylic acid), PVA, Thiolated CMC,HEC,HPC
	Semi Natural	Agarose, Chitosan, Elatine, Hyaluronic Acid, Various Gums (Gaur, Xanthan, Gellan, Carragenan, Pectin and Sodium Alginate)
Aqueous Solubility	Water Insoluble	Chitosan(soluble in dilute aqueous acids), EC,PC
	Water Soluble	CP, HEC, HPC (water below 38.8^{O}C), HPMC (cold water),PAA, Sodium CMC, Sodium Alginate
Charge	Anionic	Chitosan-EDTA, CP, CMC, Pectin, PAA, Sodium CMC, Sodium Alginate, PC, Xanthan gum
	Cationic	Aminodextran,(DEAE)-dextran, TMC, chitosan
	Non-Ionic	HPC, PVA, PVP, Poly(ethylene oxide), Scleroglucan, Hydroxyethyl starch

3. **Backing Membrane:** Formulation backing membranes should be impermeable to drug and mucus in order to prevent medication loss from all directions of the device. Materials used to make backing membranes should be inert, insoluble, or have a low water solubility. Ethyl cellulose, carbopol, sodium alginate, HPMC, polycarbophil, and other compounds are frequently utilized in backing membranes.[30]

4. **Plasticizers:** The delivery device's folding durability is enhanced using plasticizers. They give the dosing form enough flexibility to improve patient acceptance and compliance.
   Ex. PEG-400, PEG-600, dibutyl phthalate, propylene glycol, etc.
5. **Permeation Enhancers:** These are the chemicals or solutions that are used to help the drug get through the mucus layer from the device. Here are some of the ways that permeability enhancers work.
   Permeation works in four ways:
   - By making mucus less thick;
   - By making the lipid bilayer membrane more fluid;
   - By breaking through the metabolic barrier
   - By making drugs more thermodynamically active [31].

Classification of Buccal Adhesive Dosage Forms: [31],[32],[33],[34],[35],[36]

Table 5: Classification of Buccoadhesive Dosage Form

Solid Dosage Form	Buccal Tablet Bioadhesive Microsphere Bioadhesive Wafers Bioadhesive Lozenges
Semi Solid Dosage Form	Bioadhesive Patch/ Film Buccal gel and ointment Medicated chewing gum
Liquid Dosage Form	Solution Suspension

Evaluation of Buccal Mucoadhesive Dosage Forms:

Both in vitro and in vivo studies can be used to assess the adhesion strength of drug delivery systems and mucoadhesive polymers [37]. Bioadhesive drug delivery systems are subject to the same standard evaluation procedures as their conventional counterparts. These procedures include checking for characteristics such as tablet hardness, content uniformity, weight variation, thickness, in vitro dissolution, film endurance, hygroscopicity, gel and ointment viscosity, and the effect of aging [38].

1. Experimental Methodologies for Buccal Absorption/ Permeability Study:

A. In Vitro Methods:

Nowadays, buccal tissues from animal models have been used in the majority of in vitro studies evaluating drug transport via buccal mucosa. Just before an experiment begins, animals are sacrificed. Isolation of the buccal mucosal membrane requires surgical separation of the mucosa from the oral cavity, meticulous removal of the underlying connective tissue, and subsequent processing. For the in vitro permeation tests, the membranes are placed between adjacent diffusion cells, and the buffers, usually Krebs buffer, are held at temperatures as low as 4°C. [36]

B. In Vivo Methods:

Another name for it is the buccal absorption test. The rate of drug absorption can be tracked using this method. As part of the procedure, human volunteers will spin a 25 mL test solution sample for a maximum of 15 minutes before releasing it. To find out how much medicine is absorbed, one needs to know how much drug is in the expelled volume. Saliva diluting the medicine and accidental swallowing of the sample solution are two potential downsides.

C. Experimental Animal Species:

The choice of animal for the experiment is an essential one. Depending on the tests to be run, researchers may prefer using animals for in vivo studies. The buccal mucosa of most animals is keratinized, while rabbits and pigs are the only mammals that have non-keratinized mucosa similar to human. Drug penetration studies generally use animals like monkeys, dogs, and pigs. [36]

D. In Vitro Release Study:

Researchers have created various equipment for mimicking in vivo situations, such as:

- Modified Keshary Chien Cell
- Beaker Method
- Interface Diffusion System

- Dissolution apparatus [36]

2. Methods to Study Mucoadhesive Strength:

A. In Vitro Evaluation:

Both in vitro and in vivo approaches can be used to evaluate the mucoadhesive strength of polymers.

i. Measurement of Tensile Strength: This method involves calculating the amount of force needed to rupture the bioadhesive bond between the mucus membrane and the bioadhesive polymer. The following formula can be used to calculate the buccal mucoadhesive device's tensile strength.

Force of adhesion (N) =Mucoadhesive strength × 9.81/1000

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

The following are some of the instruments used to test tensile strength:

- A tensile tester or a modified physical balance device
- William's Plate Method

ii. Measurement of Shear Strength: This method measures the shear stress that is delivered to the adhesive device to determine the mucoadhesive strength. Choose two boxes of smooth, polished glass for this technique, then use adhesive to attach one box to a glass plate on a flat surface. A thread is tied to the top block, which is then pulled through a pulley and down the block. The thread should extend 12 cm from the pulley. A 17 g pan and weights should be attached to the thread's bottom side. Thus, the weight needed to break the adhesion was correlated with the shear strength using an acceptable approach.[39]

B. Other In Vitro Methods:

i. Rheological Study:

An appropriate in vitro model that may accurately predict a mucoadhesive polymer's efficacy in vivo can be provided by the rheological data of polymer-mucus mixtures. The best way to find out how well a polymer sticks to mucus is to compare it to a monocomponent mucus/polymer system that is just as concentrated. The bioadhesive polymer and mucin chains interact chemically, undergo conformational changes, and interlock, changing how the two macromolecular species behave rheologically.[39]

ii. Colloidal Gold Staining Method:

This entirely novel in vitro method was created to check how well different hydrogels stick to mucoa. Stabilized red colloidal gold particles that are attached to mucin-gold conjugates are used in the method. When the mucoadhesive comes into touch with something, its surface turns red. The strength of the red color can be used to make quantitative comparisons of mucoadhesive properties.[39]

iii. Fluorescent Probe Method:

This technique involves using pyrine as a fluorescent probe to mark the lipid bilayer of cultivated human conjunctiva cells. When compared to a control cell, the fluorescence of this cell may alter if the polymer can cling to it and produce surface compression. Fluorescence intensity changes directly correlate with the amount of polymer binding. To find the density on adhesion, polymer charge, and charge sign, another probe can be utilized. A bioadhesive bond is supposedly defined by the molecular interaction between the polymer and mucus. [40]

C. In Vivo Methods of Evaluation:

i. Gamma Scintigraphy Techniques: The production of pharmaceutical dosage forms relies on this vital instrument. The non-intrusive collecting of information can be achieved with this strategy. This approach reveals information on the different sections of the gastrointestinal tract, where the drug is absorbed, when and where the dosage form dissolves, and how factors like illness and meal size affect the in vivo efficacy of the dosage form. The distribution and retention period of the mucoadhesive tablets are two significant factors that are investigated by this technique. A very helpful technique for determining the spreading, distribution, and clearance of given stomach mucoadhesive tablets is the combination of the sheep model and the gamma scintigraphy process.[36][39]

ii. GIT Transit using the Radio-Opaque Technique: This method uses radio opaque markers to measure the impact of the polymer on GI transit time. X-ray analysis and faecal testing are two noninvasive techniques that can yield enough information to examine GI residence duration. These are some examples of markers that are utilized for mucoadhesive drug delivery: Cr^{51},

Tc^{99m}, In^{113m}, or I^{123}.

iii. **Moisture Absorption Studies for Buccal Patches**: Determining the moisture absorption by buccal films or patches is necessary for the evaluation of drug release and absorption parameters. Agar in distilled water at a concentration of 5% w/v can be used to conduct experiments on moisture absorption. Petri dishes are used to allow the solution to solidify after being heated and transferred. Afterwards, select the six buccal patches with the accurate weight from every batch. After the agar had hardened, they were placed on top of the plate, and the incubator was turned up to 37°C. Recalculate the proportion of absorbed moisture by weighing all the patches and applying the following formula:

% Moisture absorbed=Initial weight–Final weight/Initial weight×100

iv. **Thickness:** At random, select five patches and measure their thickness using a screw gauge.

v. **Folding Endurance:** The folding capability of patches was assessed manually. Patch was folded at the same spot repeatedly till it ruptured. The folding endurance was determined by counting how many folds were necessary to shatter or break a patch.

vi. **Swelling Study of Tablet:** Tablets and other mucoadhesive dosage forms can swell when exposed to fluids, leading to an increase in both volume and weight. Particle hydration or capillary space saturation are two possible mechanisms by which particles absorb liquids. Liquid enters through pores in the particles and binds to big molecules, breaking the hydrogen bond and causing the particle to inflate. The mucoadhesive dose form allows for the calculation of swelling in terms of % weight gain. The mucoadhesive dosage form is adjusted and put in a beaker with 200 ml of buffer media as the method of dosage. The dose form is taken out of the beaker and weighed once more after each interval. Up to 8 hours are required for this process.

The Swlling Index Calculated by using formula:

Swelling Index = (Wt-Wo) / Wo

Where, Wt = Weight of dosage forn at time t

Wo = Weight of dosage form before placing in the beaker [39]

vii. **Surface pH Study:** The surface pH of the buccal tablets is tested to investigate the possibility of any in vivo adverse effects. This is because an acidic or alkaline pH may irritate the buccal mucosa. The approved technique is employed to determine the surface pH of a bioadhesive product, such as a tablet. For this, a glass electrode is also employed. The tablet is allowed to swell at room temperature by allowing it to come into contact with 1 mL of distilled water (pH 6.5 ± 0.05) for two hours. By placing the electrode in touch with the tablet's surface and letting it adapt for a minute, the pH is determined.[39]

viii. **Residence Time:** The in vitro residence period is most helpful for determining the mucoadhesive performance to be retained at the application site. With the help of modified disintegration equipment, this time can be measured. As a disintegration medium, an 800 ml solution of isotonic buffer with a pH of 6.75 can be utilized. A glass slide with a 3 cm long rabbit mucosa attached to it was positioned vertically on a side arm. When a mucoadhesive tablet was taken into mucosal contact, one surface was moistened with 15 ml of isotonic phosphate buffer solution. For total immersion, the glass slide was permitted to move up and down. The moment the tablet separates from the mucosal surface can then be noticed.[41]

Conclusion: Mucoadhesive buccal drug delivery systems present a promising avenue in drug delivery, offering advantages such as enhanced bioavailability, patient compliance, and localized therapy. Understanding the intricate mechanisms of mucoadhesion, the composition of mucous membranes, and the role of penetration enhancers is pivotal in formulating effective dosage systems.

The diverse components of buccal drug delivery systems—drug substances, bioadhesive polymers, backing membranes, plasticizers, and permeation enhancers—play crucial roles in their efficacy. However, alongside their advantages, these systems exhibit limitations concerning formulation, discomfort, and individual variability.

Evaluation methodologies spanning in vitro and in vivo techniques provide a holistic approach to assess these systems, aiding in their refinement and optimization. Further research into improving formulations, enhancing mucoadhesive properties, and addressing limitations will continue to advance the field, paving the way for more efficacious and patient-friendly drug delivery systems.

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