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RECENT ADVANCES IN BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEMS: DEVELOPMENT, APPLICATIONS AND CHALLENGES

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Abstract

Buccal mucoadhesive drug delivery systems have sparked a lot of attention in recent years because they promise to increase drug bioavailability, improve therapeutic outcomes, and offer patient-friendly alternatives to traditional administration methods. These approaches take advantage of the buccal mucosa's unique qualities, including substantial vascularization, bypass of first-pass metabolism, and ease of access. This study examines recent advancements in buccal mucoadhesive drug delivery systems, focusing on innovative formulation strategies, novel polymers, and cutting-edge technologies such as nanocarriers and 3D-printed dosage forms. The utilization of novel materials such as mucoadhesive hydrogels, nanoparticles, and stimuli-responsive systems has significantly improved the precision and efficacy of medicine administration. Pain management, cardiovascular problems, and localized oral infection therapy are among the most important applications. Future possibilities include using smart technologies and personalized medicine to improve buccal medicinal administration and expand its therapeutic efficacy.

Keywords

Buccal mucoadhesive drug delivery, Controlled drug release, Bioadhesive polymers, Drug absorption enhancement, Applications in therapeutics.

Introduction

In recent years, there has been an increased emphasis on creating novel drug delivery systems to improve the efficacy of medicinal therapies. Mucoadhesive systems are promising because they can cling to the mucosal surfaces of the oral cavity, allowing for extended contact with the underlying tissues. (1)The "fixing" of two surfaces to one another is the simplest definition of adhesion. The setting in which the process takes place determines the several terminological subgroups of adhesion. When two materials, at least one of which is biological, are kept together for extended periods by interfacial forces, this is known as bio-adhesion.(2) Developing a drug delivery system that targets different absorptive mucosa, such as the ocular, nasal, pulmonary, buccal, vaginal, etc., by using a mucoadhesive polymer that adheres to related tissue or the tissue's

surface coating has gained attention in recent years. This drug delivery method is known as the mucoadhesive drug delivery system. The buccal area of the mouth cavity is a desirable site for administering the preferred medication. The administration of a desired medication via the buccal mucosal lining of the mouth cavity is known as buccal drug delivery. (3) The oral administration of some medication groups, particularly peptides and proteins, is prohibited due to hepatic first-pass metabolism and GI tract enzymatic breakdown. Transmucosal drug delivery methods have potential benefits, including bypassing the first-pass effect, avoiding presystemic clearance in the GI tract, and depending on the substance, having a superior enzymatic flora for drug absorption.(4) The oral cavity allows for self-medication, and if toxicity occurs, the medicine should be removed immediately from the buccal cavity. The buccal mucosa is less permeable than the sublingual location, making it a better alternative for prolonged drug administration.(5) Buccal drug delivery provides an effective medication administration method, offering systemic and localized therapeutic effects. Mucoadhesion has drawn attention in the past 20 years due to its potential for localized drug delivery by maintaining a dose form at the site of action. Many mucoadhesive devices, such as tablets, films, patches, discs, strips, ointments, and gels, have been developed recently.(6)

Mucoadhesive Drug Delivery

Mucoadhesion is a suitable interaction between the interface within a pharmacological dosage form and a mucosal membrane.(7) The mucoadhesive drug delivery system is gaining popularity for local and systemic medication delivery due to its approachability, avoidance of first-pass metabolism, large blood supply, safety, and improved patient acceptability and treatment. Mucoadhesion occurs when the mucus layer interacts with a bio-adhesive polymer that covers bodily tissues. This process involves wetting, absorption, and interpenetration of the biopolymer chains.(8) Mucoadhesive medication delivery systems rely on the bioadhesive properties of water-soluble polymers. When hydrated, these polymers become sticky and can deliver drugs to specific body areas for an extended period.

Drug distribution through oral cavity membranes is classified into the following categories:

1. Sublingual Delivery: Drugs enter the body through the mouth's mucosal membrane.
2. Buccal Delivery: Drugs enter the systemic circulation through the mucosal barrier by being placed between the cheek and gums.
3. Local Delivery: Drugs are administered in the oral cavity.(9)

Advantages of Mucoadhesive Buccal Drug Administration (6,8,10)

1. It has a greater surface area and a more abundant blood supply.
2. It avoids the hepatic first-pass metabolism, increasing bioavailability.
3. The dosage form is simple to administer and allows for quick termination of therapy during emergencies.
4. Improved patient compliance.
5. It works with a passive system of medication absorption that requires no activation.
6. Drug action begins quickly and continues for an extended period.
7. Easy administration of drugs to unconscious patients.
8. Saliva can dissolve drugs due to its water concentration.

Disadvantages of Mucoadhesive Buccal Drug Administration (5,11,12)

1. Prolonged use of a medication with ulcerogenic properties.
2. Patient acceptability in terms of flavor, irritancy, and mouthfeel will be assessed.
3. The buccal membrane has lower permeability than the sublingual membrane.
4. It also has a smaller surface area.
5. Administering big doses of drugs is tricky.
6. Food and drink may be restricted.
7. The delivery system poses a danger of choking if swallowed involuntarily.
8. This method cannot deliver medications that are unstable at buccal pH.

Anatomy and Structure of the Oral Cavity

The oral cavity comprises two primary regions:

1. The outer oral vestibule, bordered by the lips and cheeks.
2. The main oral cavity, is enclosed by the hard and soft palates, the floor of the mouth, and the tonsillar area.

Physical Features of the Oral Cavity

The mucosal lining of the oral cavity is categorized based on its function into three distinct types:

1. Masticatory Mucosa: It includes the tissue surrounding the teeth and the hard palate. These areas are characterized by keratinized epithelium, providing resilience and protection.

2. Lining Mucosa: Found on the lips, inner cheeks, base of the mouth, the underside of the tongue, buccal mucosa, and the soft palate. These regions are covered with non-keratinised epithelium, allowing for flexibility and mobility.

3. Specialised Mucosa: Located on the tongue's upper surface (dorsum), this mucosa is highly keratinized and supports the tongue's specialized functions.(13)

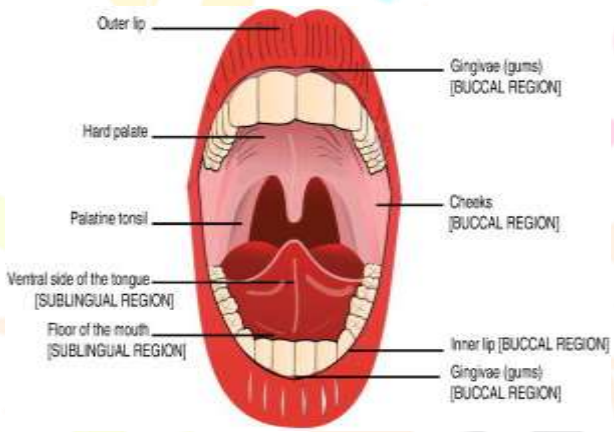

Fig. 1: Different anatomical regions of the buccal cavity (14)

Overview Of The Oral Mucosa

Structure

The oral mucosa comprises stratified squamous epithelium, a basement membrane, the lamina propria, and the submucosa. It is also home to various sensory receptors, including those responsible for taste located on the tongue. The epithelium of the buccal mucosa consists of approximately 40 to 50 cell layers, while the sublingual epithelium is relatively thinner.(15)

Permeability

The oral mucosa is generally considered a moderately permeable tissue, falling between the permeability of the epidermis and the intestinal lining. Studies suggest that the buccal mucosa's permeability is significantly higher than that of the skin, ranging from 4 to 4,000 times greater. Among the different regions of the oral mucosa, permeability varies, with sublingual mucosa being the most permeable, followed by buccal mucosa, and then palatal mucosa. These differences arise due to variations in tissue thickness and keratinization levels. The sublingual mucosa is thin and non-keratinized, the buccal mucosa is thicker but also non-keratinized, and the palatal mucosa is keratinized and of intermediate thickness.(16)

Functions of the mucus layer

1. The mucus layer serves several essential purposes.
2. Its hydrophobic properties make it highly protective.
3. It acts as a barrier, preventing the absorption of drugs and other substances into tissues.
4. Mucus has strong adhesive characteristics, allowing it to bind firmly to the epithelial cell surfaces and

form a continuous gel-like layer.
5. Due to digestion and bacterial activity, Goblet cells continuously secrete mucus to replenish the lost layer.
6. The mucus composition includes approximately 50% water, 0.5-5% glycolipids, 0.5-1% mineral salts, and 0.5-1% free proteins.(17)

Mucins and salivary composition

Mucins are secreted as large aggregates by prostaglandins, with molecular weights ranging from 1 to 10 million Da. These aggregates consist of monomers primarily connected through non-covalent interactions, though intermolecular disulfide bonds also contribute to their structure. The oligosaccharide side chains of mucins typically contain about 8–10 monosaccharide units, including L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, and sialic acid. The amino acids serine, threonine, and proline are also prominent in mucins.
Due to the presence of sialic acids and ester sulfates, mucus carries a negative charge at saliva's physiological pH, which ranges from 5.8 to 7.4. Saliva primarily comprises water (99.5%), proteins, glycoproteins, and electrolytes. It contains high levels of potassium (7× plasma), bicarbonate (3× plasma), calcium, phosphorus, chloride, thiocyanate, and urea, while sodium is present in lower concentrations (1/10× plasma).
The pH of saliva typically ranges from 5.6 to 7. Saliva also contains enzymes such as α-amylase, which breaks 1–4 glycosidic bonds in starch; lysozyme, which protects by digesting bacterial cell walls; and lingual lipase, which aids in fat digestion.(18)

Mechanism of Mucoadhesion

It can be described using the two stages listed below:

Contact stage
During the contact stage, the mucoadhesive substance interacts with the mucous layer, causing the formulation to swell and spread across the membrane.

Consolidation stage
During the consolidation stage, moisture activates the mucoadhesive substance, plasticizing the system and allowing for separation and connection via weak Van der Waals and hydrogen bonds. (19)

Two theories are used to describe the consolidation steps:

Diffusion Theory
Mucoadhesive molecules interact with mucus glycoproteins, forming secondary connections by chain contact.

Dehydration theory
It states that when materials come into contact with mucus in an aqueous environment, they become jellified, and water is added to the dosage form due to concentration gradients until osmotic equilibrium is attained. This leads to an increased contact time between the formulation combination and the mucosal membrane. Adhesive contacts strengthen due to water flow rather than macromolecule interpenetration.(20)

Theories of Mucoadhesion

Mucoadhesion is a complex process with multiple ideas presented to explain the mechanics involved. Theories include mechanical interlocking, electrostatics, diffusion, interpenetration, adsorption, and fracture mechanisms.

1. Wetting Theory

The wetting theory applies to liquid systems that attract the surface and spread across it. This affinity can be determined using measurement techniques such as the contact angle. The general rule is that the smaller the contact angle, the stronger the affinity. For optimal spreadability, the contact angle should be close to zero. The spreadability coefficient (SAB) is calculated by subtracting surface energies (γB and γA) from interfacial energy (γAB), as illustrated in the equation below.
$SAB = \gamma B - \gamma A - \gamma AB$

This hypothesis highlights the importance of contact angle and minimizing surface and interfacial energy for successful mucoadhesion. (20)

2. Diffusion theory

Diffusion theory illustrates how polymer and mucin chains penetrate each other to form a semi-permanent sticky bond. The adhesion force between polymer chains is thought to grow with their penetration. The penetration rate is influenced by factors such as diffusion coefficient, mucoadhesive chain flexibility, mobility, and contact time. The research suggests that an effective bioadhesive binding requires interpenetration depths between 0.2-0.5 μm. The interpenetration depth of polymer and mucin chains can be determined using the equation below:

$l = (tDb)^{½}$

where t is the contact period and Db is the diffusion coefficient of the sticky substance in mucus.(21)

3. Fracture Theory

The mechanical measurement of mucoadhesion is commonly based on this idea. This analyses the force needed to separate two surfaces once adhesion is created. This force, Sm, is typically estimated in tests of resistance to rupture as the ratio of the maximal detachment force, F_m, and the entire surface area, A_0, engaged in the adhesive contacts.

$S_m = F_m/A_o$

This method is suitable for calculating rigid or semi-rigid bioadhesive compounds with polymer chains that do not penetrate the mucus layer. (21,22)

4. Electronic Theory

According to this theory, adhesion occurs through electron transfer between mucus and mucoadhesive molecules. Electronic structural variances cause system differences. Electron transfer between mucus and mucoadhesive forms a second layer of electric charges at the contact. This action generates attractive forces within the double layer. (23)

5. Adsorption theory

Adhesion occurs by surface interactions between the sticky polymer and mucus substrate, including both primary and secondary bonding. The chemisorption creates primary connections that cause adhesion through ionic, covalent, and metallic bonding, which is undesired owing to their permanence. (24) Secondary bonds form primarily by van der Waals forces, hydrophobic interactions, and hydrogen bonding. Although these connections need less energy to break, they are the most common type of surface interaction in mucoadhesion due to their semi-permanent nature. (25)

Factors Affecting Mucoadhesion:

A. Polymer-related factors

1. Hydrophilicity

Mucoadhesive polymers include multiple hydrophilic functional groups, including hydroxyl and carboxyl. These groups promote hydrogen bonding with the substrate and swelling in aqueous environments, resulting in maximum exposure of possible anchor sites. Swollen polymers have maximal chain distance, resulting in enhanced flexibility and efficient substrate penetration**.** (25)

2. Molecular weight

Polymers with molecular weights above 100,000 exhibit increased mucoadhesive strength. Polyoxyethylene polymers' mucoadhesive strength is directly proportional to their molecular weight, which ranges from 200,000 to 7,000,000. (26)

3. Flexibility of polymer chains

Mucoadhesion begins with the spread of polymer chains in the interfacial area. For effective entanglement with mucus, polymer chains must be flexible. Incorporating polyethylene glycol enhanced the polymer's structural flexibility, resulting in higher chain interpenetration. Polymer mobility and flexibility are linked to viscosity and diffusion coefficients. Higher flexibility leads to better diffusion into the mucus network. (27)

4. Cross-link density and swelling

A polymer network's structural considerations include pore size, cross-link density, and average molecular weight of cross-linked polymers. Flory's study suggests an inverse relationship between polymer swelling and cross-linking. As crosslinking density increases, polymer swelling reduces due to delayed water diffusion, which results in reduced mucin-polymer interpenetration rates**.** (28)

5. Concentration of active polymers

The optimal concentration of active polymers correlates with optimal bioadhesion. Concentrated systems have much lower adhesive strength. The Concentrated solutions cause coiled molecules to become solvent-poor, resulting in fewer interpenetration chains. (29)

B. Environmental Factors

1. pH

The pH of the polymer-substrate contact and saliva, as a dissolution solvent, impact the polymer's behavior. The pH of saliva ranges from 6.5 to 7.5, depending on flow velocity and measurement technique. The pH of the microenvironment can impact the ionization state and adhesion capabilities of a mucoadhesive polymer. (30)

2. Strength

To apply a solid bioadhesive system, a specific strength is required.

3. Initial contact time

Increased mucoadhesive strength leads to longer initial contact times.(31)

C. Physiological variables

1. Mucin turnover

Mucin turnover is significant for two reasons. The mucoadhesive's residence period on mucus layers is likely to be limited due to mucin turnover. Mucin turnover generates significant numbers of soluble mucin molecules**.** (32)

2. Diseased states

Mucus characteristics can change throughout several diseases, including common colds, gastric ulcers, ulcerative colitis, cystic fibrosis, female reproductive system infections, and eye inflammation. (33)

Classification of Mucoadhesive dosage forms

Tablets

Buccal tablets are small, flat, and oval, measuring around 5-8 mm in diameter. Mucoadhesive tablets provide comfortable drinking and speaking experiences, unlike traditional tablets. These are inserted on the mucosal surface to deliver drugs locally or systemically. These soften, attach to the mucosa, and remain in place until fully dissolved or released. Mucoadhesive tablets can be used for controlled-release drug administration, but adding mucoadhesive characteristics provides additional benefits. Its high surface-to-volume ratio allows for excellent medication absorption and bioavailability and closer contact with the mucous layer. Mucoadhesive tablets can be designed to stick to any mucosal tissue, including those discovered in the stomach, allowing for localized and systemic controlled medication release. Mucoadhesive buccal tablets are effective for treating candidiasis of the oral cavity, but their size and shape limit their widespread use. The drug delivery system must make close contact with the mucosal surface. (34)

Buccal Films

Mucoadhesive films offer more flexibility and comfort than adhesive tablets. Oral gels have a limited residence duration on the mucosa and are quickly washed away by saliva. Local distribution of films for oral disorders can reduce discomfort and improve treatment outcomes by protecting the wound surface. The perfect film should be flexible, elastic, and soft, but sturdy enough to endure tension from mouth movements. The product should have strong mucoadhesive properties to stay in the mouth for the intended period of action. If film swelling occurs, keep it to a minimum to minimize discomfort.(35)

Buccal patches

Buccal patches are made up of three layers an impermeable backing layer, a drug reservoir layer that releases the drug gradually, and a mucoadhesive surface for mucosal attachment. Patches can administer medications directly to mucosal membranes. They are similar to those used for transdermal medication administration. Patients are more likely to comply with them than with tablets because of their flexibility and minimal discomfort. They are more effective than creams and ointments because they deliver a precise amount of medication to the affected area. (36)

Lozenges

Lozenges can be used as an alternative to pills and capsules for individuals who cannot swallow. Lozenges can be used for systemic medication delivery; however, they are typically applied to the mouth or throat. Buccal lozenges, which are placed between the cheek and gums, are a popular alternative to sublingual lozenges due to their smaller size. The lozenge typically dissolves in 30 minutes, but patients can control the rate of disintegration and absorption by sucking on it until it dissolves. (37)

Gels and Ointments

Semisolid dose formulations, such as gels and ointments, provide facile dispersion throughout the oral mucosa. Semisolid dose forms may not provide accurate drug dosing like pills, patches, or films do. The use of mucoadhesive formulations has overcome the gel's poor retention at the application site. Mucoadhesive polymers such as sodium carboxymethylcellulose, carbopol, and hyaluronic acid can transition from liquid to semisolid. This shift increases viscosity, allowing for regulated and sustained medication release. Hydrogels are a promising option for buccal medication administration. Polymers in an aquatic environment entrap drug molecules and release them slowly through diffusion or erosion. (38–41)

Classification of Bioadhesive polymers used in the oral cavity (15,42,43)

Table 1: Bioadhesive polymers used in mucoadhesive formulations

Category	Sub-Category	Examples
A. Based on Source	Semi-Natural/Natural	Tragacanth, Agarose, Hyaluronic acid, Chitosan, Gelatin, Guar gum, Xanthan gum, Gellan gum, Carrageenan, Pectin, Sodium alginate
	Synthetic	Sodium carboxymethylcellulose, Polyvinylpyrrolidone, Polyvinyl alcohol, Hydroxypropyl Methyl Cellulose, Carbopol
B. Based on Aqueous Solubility	Water Soluble	Carbopol, Hydroxy Ethylcellulose, Hydroxy Propyl Cellulose, HPMC, PAA, etc.
	Water Insoluble	SCMC, Sodium alginate, HPMC, PVA, Carbopol, etc.
C. Based on the Force	Covalent	Cyanoacrylates
	Hydrogen Bond	Acrylates, Carbopol, PVA
	Electrostatic Interaction	Chitosan
D. Based on the Charge	Cationic	Aminodextrin, Chitosan, Trimethylated chitosan
	Anionic	Chitosan-EDTA, Carbopol, CMC, Pectin, PAA, PC, Sodium alginate, SCMC, Xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, PVA, PVP

Characteristics of the ideal mucoadhesive polymer (44)

1. Polymers and their degradation products should be non-toxic, non-irritating, and free of leachable contaminants.
2. Ideal qualities include spreadability, wetness, swelling, solubility, and biodegradability.
3. pH should be biocompatible and have good viscoelastic characteristics.
4. Adhere fast to the buccal mucosa and provide significant mechanical strength.
5. Must have peel, tensile, and shear strengths within the bioadhesive range.
6. Polymer should be readily available and reasonably priced.
7. Should exhibit bioadhesive characteristics in both dry and liquid states.
8. Proven ability to block enzymes locally and increase penetration.
9. Should have an appropriate shelf life.
10. Aim for optimum molecular weight.
11. Must have adhesively active groups.
12. Required spatial conformation.

Novel Drug Delivery Approaches:

Nanostructured Delivery Systems

1. Polymeric Nanoparticles

Polymeric nanoparticles have significantly improved the buccal medication delivery technique. Their modest size (10-1000 nm) and high surface area-to-volume ratio allow better drug penetration across biological membranes. These nanostructures have excellent cellular absorption and can easily cross biological barriers.

Polymeric materials offer fine control over medication release kinetics and customizable surface characteristics for targeted distribution. Using multiple polymer types might result in unique degradation profiles and release patterns, making them appropriate for various therapeutic purposes. (45)

2. Surface-Modified Nanoparticles

Surface treatment of nanoparticles with mucoadhesive polymers is an effective technique for improving buccal medication delivery. This technique increases drug absorption by boosting mucin layer adhesion and retention time in the buccal cavity. The selection of appropriate mucoadhesive polymers and modification procedures are crucial elements influencing the efficacy of these delivery systems. The customized surface qualities facilitate prolonged engagement with the buccal mucosa, resulting in sustained drug release and improved therapeutic efficacy.(46)

Advanced Carrier Systems

1. Microspheres and Microparticles

Microspheres and microparticles provide precise medication distribution with better stability during storage and administration. Microsphere formulations can be customized to meet specific pharmacological characteristics and therapeutic requirements. Compared to nanoparticles, their larger size allows for longer release profiles and effective mucoadhesion. Optimizing the manufacturing process allows for desirable particle size distributions and drug loading capabilities, making it appropriate for diverse therapeutic applications.(47)

2. Hybrid Delivery Systems

The advancement of hybrid systems that combine multiple types of carriers has shown significant benefits in enhancing drug delivery efficiency. By integrating the strengths of different transporters, these systems effectively address the limitations of individual components, leading to improved therapeutic outcomes. The strategic design of hybrid systems leverages the complementary features of various carriers, resulting in enhanced drug delivery performance, greater control over release profiles, and increased stability. This method has proven especially valuable in tackling complex therapeutic issues and boosting patient adherence to treatment regimens. (48)

Recent trends

1. 3D Printing Technology Integration

Three-dimensional printing technology is transforming the development of buccal drug delivery systems by allowing the creation of customized dosage forms. This advanced manufacturing method ensures precise control over geometric shapes, drug distribution, and release profiles. It facilitates the production of complex, multi-layered structures and tailored formulations designed to meet individual therapeutic requirements. The ability to rapidly adjust design parameters makes this technology particularly valuable for personalized medicine and to promote the enhancement of drug delivery systems during the development process. (49)

2. Smart Delivery Systems

The attachment of biosensors into buccal drug delivery devices marks a substantial leap in therapeutic monitoring. These smart systems provide real-time information about drug release patterns, local pH levels, and other physiological data. The combination of responsive polymers and sensor technology enables adaptive drug release based on physiological cues. This sophisticated strategy for drug distribution improves therapeutic efficiency and patient monitoring, ultimately leading to better treatment outcomes. (50)

3. Mucoadhesive Proteins and Peptides

The discovery of novel mucoadhesive proteins and peptides has opened up new possibilities for targeted medication delivery. Biomolecular adhesives are more selective and biocompatible than traditional polymers.

Their capacity to connect with specific cellular receptors leads to more accurate targeting and improved therapeutic efficacy. Integrating these biological components improves medication absorption and residence time. (51)

4. Recombinant virus-based (RNA) vaccines

Replication-defective adenovirus vectors (rAdV) are commonly used to deliver antigens. Adenoviruses infect the airway epithelium and replicate in mucosal tissues of the respiratory system. These properties make these vectors appropriate for mucosal vaccination delivery. Sublingual immunization with rAdV, which encodes the conserved influenza nucleoprotein antigen or the soluble globular head of hemagglutinin, protects mice from influenza virus infection. Sublingual delivery of rAd5 vectors containing HIV proteins resulted in strong antigen-specific humoral (serum and mucosal IgG and IgA) and cellular (systemic and mucosal CTL) immune responses. (52)

5. Quality via Design Implementation

The application of Quality by Design (QbD) concepts has greatly aided product development and manufacturing processes. This methodical approach leads to a better understanding of important quality features and process factors. Establishing a design space helps maintain consistent product quality during scale-up operations. Implementing QbD principles improves manufacturing processes and reduces variability in product quality. (53)

Evaluation of Buccal tablets:-

1. Weight variation test

Twenty tablets were selected randomly and individually weighed in a single pan electronic balance, and the average weight was calculated using the following formula. (54)

$$\% \text{ Wt Variation} = \frac{\text{Weight of each tablet} - \text{Average weight of tablet}}{\text{Average weight of tablet}} \times 100$$

2. Thickness

The thickness of the tablet is a dimensional variable that affects the compression process. Tablet thickness was measured by using a Vernier calliper. (55)

3. Hardness

The hardness test of tablets is carried out by placing them between two anvils and applying force until they break. Several instruments assess tablet hardness, including the Monsanto tester, Strong-Cobb tester, Pfizer tester, Erweka tester, etc. (56)

4. Friability

Friability can be tested using tablet strength. The friability of tablets can be tested using a friabilator (Aarson). It's expressed as a percentage (%). The tablets are placed in a plastic chamber that rotates at 25 rpm for 4 minutes or up to 100 revolutions by dropping a tablet from a height of 6 inches in each revolution. Pre-weighed tablets were placed in the friabilator and subjected to 100 revolutions. The percentage loss is calculated by using following the formula. (57)

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

5. Content uniformity

Ten tablets will be accurately weighed and powdered in a glass pestle mortar. An accurately weighed amount equivalent to 5 mg of pure medication is taken, and the analysis is performed in triplicate. Filter and perform assay using UV-visible spectroscopy. (58)

6. Surface PH

The surface pH of tablet was assessed to determine any potential in vivo harmful effects. To avoid irritation of the buccal mucosa, the tablet's surface should have a neutral pH. The pills were immersed in 1.0 mL of distilled water in a custom-designed glass tube for 2 hours to allow swelling. Surface pH was then determined by placing the electrode directly on the tablet's surface and allowing it to stabilize for one minute. (59)

7. In-vitro drug release study

The USP dissolving device is utilized in the drug release study. It can be a rotating paddle type, in which the backing layer of the buccal tablet is glued to a glass disc and put at the bottom of the apparatus, or a revolving basket type. The dissolution investigation will be conducted using a suitable amount of phosphate buffer at pH 6.8, with samples taken at predetermined time intervals and replaced with fresh buffer medium. The samples are filtered, and a suitable dilution is created and analyzed by an UV spectrophotometer. (60)

8. ExVivo Mucoadhesion Strength

The mucoadhesion strength was determined using a modified balancing method. The equipment consists of a modified two-pan balance with a Teflon assembly that holds the tablet and is lowered onto another Teflon assembly with the buccal mucosa linked. Porcine buccal mucosa was used as the model membrane. The mucosa was kept in phosphate buffer (pH 7.4) at room temperature before use. The mucosal membrane was removed by eliminating the connective and adipose tissue. It was equilibrated in 0.2 molar phosphate buffer (pH 6.8) at 37±1°C for 30 minutes. The tablet was attached to the Teflon arm with cyanoacrylate adhesive and lowered onto the mucosa, maintained under a constant weight of 5 g for a 5-minute contact duration. Mucoadhesion strength was measured by the weight (g) required to remove the tablet from the membrane. (61)

9. Ex-Vivo Residence Time

The ex vivo residence time was assessed using a USP disintegration apparatus that had been customized locally. The disintegration medium comprised 800 ml of phosphate buffer at pH 6.8, maintained at a temperature of 37°C. Sheep buccal tissue was affixed to a glass slide using cyanoacrylate adhesive and positioned vertically in the apparatus. To hydrate the buccal tablet, 0.5 ml of phosphate buffer (pH 6.8) was applied to one side of the tablet before it was brought into contact with the mucosal surface. The glass slide, secured vertically, was operated so that the tablet alternated between full immersion in the buffer at the lowest position and re-emergence at the highest point. The duration required for the tablet to either erode or completely detach from the mucosal surface was recorded. (62)

10. Stability studies

Stability studies will be conducted on potential buccal pills for three months (90 days) at 40°C and 75±5% relative humidity. Tablets are stored in amber screw-capped bottles in a stability chamber at 40±1°C and 75±5% relative humidity. Samples will be taken monthly to estimate drug content. After three months, dissolution tests and drug content analyses will be conducted to evaluate drug release profiles and content. (58)

Recent developments in mucoadhesive drug delivery systems

Mucoadhesive polymers

Several types of polymers have been studied for their efficacy as mucoadhesive agents. Among these, polyacrylic acid (PAA) has shown substantial promise. To improve its characteristics, PAA is frequently copolymerized with polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP).

Delivery Devices

Various types of laminated devices have been created to permit long-term medication release. These gadgets can be divided into two primary types:

1. Monolithic Systems:

In these systems, the medication is either dissolved or evenly distributed throughout the polymer matrix. The overall release rate of the medication is determined mostly by its diffusion from the drug-polymer matrix.

2. Reservoir Systems:

These systems manage the rate of medication release by integrating a polymeric membrane that functions as a barrier to control diffusion.(63)

Applications of Buccal mucoadhesive drug delivery system

Cardiovascular diseases

Atenolol, a β-blocker, is commonly used to treat cardiovascular problems including excessive blood pressure, angina, arrhythmias, and heart attacks. Traditional atenolol tablets may cause changes in plasma concentrations, which could lead to adverse effects or reduced receptor-site activity. An oral controlled-release mucoadhesive tablet was developed to improve its efficacy in treating hypertension, with atenolol as the prototype medicine. This pill provides prolonged buccal delivery and sustained release over a longer period. (64,65). Carvedilol, a non-selective beta-adrenergic antagonist, is used to treat hypertension and stable angina pectoris. Mucoadhesive tablets of carvedilol have been developed for this purpose. This hydrophilic polymer formulation utilizes hydroxypropyl methylcellulose (HPMC K4M and K15M) and Carbopol 934 (CP 934) to provide controlled and zero-order release. Increased polymer concentration in formulations resulted in sustained carvedilol release, according to studies. The rapidly hydrating polymer effectively controlled the release of carvedilol from buccal tablets. (66)

Anti-inflammatory therapy

Inflammatory processes are a key cause of oral cavity illnesses. Topical application of nonsteroidal anti-inflammatory medications, such as flurbiprofen, flufenamic acid, and ibuprofen, can treat numerous oral cavity diseases, including gingivitis, periodontitis, stomatitis, and ulcers. Advantages include reduced therapeutic dose, localized drug delivery in target tissues, and fewer systemic side effects. (67,68)

Antimicrobial therapy

Traditional dose forms such as solutions, gels, suspensions, and mouthwashes are frequently unsuccessful in treating oral candidiasis because they are quickly removed from the oral cavity. A bilayer mucoadhesive tablet containing nystatin was formulated. The formulation enabled the quick release of nystatin from a lactose-based layer, followed by a regulated release from a polymeric layer over six hours. (69)

Antiemetics

Ondansetron hydrochloride is a 5HT3 serotonin antagonist used to prevent nausea and vomiting during emetogenic cancer treatment. (70) A buccal mucoadhesive tablet containing ondansetron was produced and

assessed. It used CP 934, sodium alginate, SCMC low viscosity, and HPMC 15cps as mucoadhesive polymers to impart adherence and ethyl cellulose as an impermeable backing layer. The medication stability in the optimized adhesive tablet was evaluated for 6 hours in natural human saliva. Both the medicine and the device remained stable. (71) Domperidone buccal bioadhesive hydrophilic matrix tablets were formulated with HPMC and Carbopol. Increased polymer content led to increased bioadhesive strength. A two-way ANOVA-based factorial investigation found that polymers significantly influenced the bioadhesive characteristics of compressed matrices. (72)

Hypoglycaemic agents

Hypoglycemic drugs such as glipizide and glibenclamide have lately received interest for their possible use in buccal administration. Due to its short biological half-life of roughly 3.4 hours, glipizide must be taken twice or thrice daily in doses ranging from 2.5 to 10 mg. Mucoadhesive buccal films containing glipizide were formulated utilizing the solvent casting method with polymers such as HPMC, SCMC, CP934P, and Eudragit RL-100. The study investigated the effects of glipizide on the swelling behavior and residence time of several mucoadhesive polymers. The results indicated that medicated films had a considerably higher swelling index than plain films. In addition, adding the water-insoluble medication increased the films' water absorption capability. These results indicate that the buccal route could efficiently deliver therapeutic dosages of glipizide. (73)

Antimigraine

Sumatriptan succinate, a 5-HT1 receptor agonist is used to treat migraines, was developed into mucoadhesive bilayered buccal patches for alternate drug delivery. Increasing the concentration of chitosan resulted in stronger mucoadhesive patches. The study found that chitosan concentration had a greater impact than PVP K30 concentration. Increased chitosan and PVP K-30 levels resulted in increased swelling of patches. Drug release increased with higher PVP K30 concentrations and decreased with lower chitosan concentrations. (74)

Antihistamine

Chlorpheniramine maleate (CPM) is an antihistamine H1 receptor antagonist used to treat a variety of allergies. (75) Using HEC as a water-soluble polymer in mucoadhesive buccal patches improves CPM bioavailability by bypassing first-pass metabolism. The study found that the dosage form was non-irritating and did not produce mucosal damage or irritation during buccal delivery. The optimized buccal patch had 1.46 times the bioavailability of the oral dosage form, resulting in a statistically significant difference. (76)

Future Scenarios and Challenges

Research in buccal drug delivery has seen significant progress and innovation over recent decades. The buccal mucosa offers substantial potential for the systemic delivery of inefficient drugs when taken orally and presents a viable, non-invasive alternative for administering potent peptide and protein therapeutics. Mucoadhesive drug delivery systems serve as versatile carriers for various pharmaceuticals. They can be tailored to adhere to different mucosal tissues, including those in the oral cavity, gastrointestinal tract, vagina, and eyes. An area of growing interest is the development of novel buccal adhesive delivery systems, which target the buccal mucosa while maintaining a protective local environment. Looking ahead, researchers anticipate a shift toward using these systems for delivering vaccines and small proteins or peptides. Microparticulate bioadhesive systems are particularly promising, as they not only protect therapeutic agents but also enhance absorption through prolonged contact with mucosal surfaces, facilitated by the bioadhesive properties. Bioadhesion is expected to play a pivotal role in developing non-parenteral protein formulations and vaccines designed to adhere to mucosal membranes and trigger localized immune responses.

Conclusion

In the current global scenario, scientists are creating buccal adhesive systems to improve the bioavailability of drugs that are ineffective or inefficient when taken orally. This entails modifying formulation strategies. Research is required to produce new mucoadhesive polymers that are biodegradable, biocompatible, non-toxic, attach to specific cells or mucosa, and act as enzyme inhibitors for successful protein and peptide delivery. The buccal mucosa provides a potential delivery route for drugs that must leave the gastrointestinal

tract due to breakdown by stomach pH, intestinal enzymes, or strong hepatic first-pass action. Injectable medications are expensive to administer and can frequently have serious side effects. As a result, cost-effective multiple-dose formulations with improved bioavailability are required. Parenteral medication administration can cause pain that can be entirely eradicated using increased drug delivery methods such as transmucosal and transdermal. Buccal mucoadhesive systems provide several advantages, including ease of administration, withdrawal, and accessibility, as well as limited enzymatic activity, low cost, and high patient compliance.

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