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Review

Recent Trends and Advances in Mucoadhesive Buccal Drug Delivery Systems

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Abstract:
Mucoadhesive buccal drug delivery systems have emerged as an effective alternative to conventional oral drug administration due to their ability to enhance drug bioavailability, prolong residence time, and bypass hepatic first-pass metabolism. The buccal route offers a non-invasive, patient-friendly platform for both local and systemic drug delivery, making it particularly suitable for drugs with poor gastrointestinal stability and extensive first-pass effect. This review highlights the fundamental concepts of bioadhesion and mucoadhesion, the anatomy and physiology of the oral mucosa, mechanisms and theories of mucoadhesion, formulation components, and factors influencing mucoadhesive performance. Various dosage forms including tablets, films, patches, gels, microspheres, and nanoparticles are discussed along with their evaluation parameters. Recent advances such as polymeric and surface-modified nanoparticles, hybrid carrier systems, 3D printing technology, smart drug delivery systems, mucoadhesive proteins and peptides, recombinant vaccine delivery approaches, and Quality by Design (QbD) applications have significantly improved the effectiveness of buccal drug delivery. Furthermore, therapeutic applications in cardiovascular diseases, inflammatory disorders, microbial infections, diabetes, migraine, and allergy management are reviewed. The article emphasizes the growing potential of mucoadhesive buccal systems in achieving targeted, controlled, and patient-compliant drug delivery and discusses future prospects for the delivery of proteins, peptides, and vaccines through the buccal mucosa.

Keywords: Mucoadhesion, Buccal Drug Delivery System, Bioadhesive Polymers, Buccal Mucosa, Mucoadhesive Patches

Introduction

DDS represents a promising technological advancement with extensive applications, engineered to release drugs in a controlled manner and at a predetermined rate and deliver them to specific tissues or cell types. Recent drug delivery systems, such as nanoparticles, molecularly imprinted polymers, and 3D printing technology, have emerged as cutting-edge research topics. DDS is a pivotal strategy for

achieving targeted and precise drug delivery. Table 1 succinctly introduces the challenges and solutions associated with drug molecular delivery. By leveraging multidisciplinary approaches, DDS is dedicated to the development of drug delivery systems and devices that can modulate the metabolism, potency, toxicity, immunogenicity, and biorecognition of drugs, thereby enhancing the microenvironment in which the drug operates and facilitating its uptake by the body (Vargason et al., 2021). Compared to conventional formulations, DDS offers several key advantages:

- enhanced drug stability and minimized degradation;
- optimized drug distribution, leading to increased target concentration, and reduced adverse reactions;
- precise drug localization, timing, and targeted release, such as breaking through the blood–brain barrier for drug delivery and
- decreased therapeutic dosage, reduced the toxicity, and elevated therapeutic index.

DDS not only delivers drugs to the affected area but also encompasses four core functions: drug targeting, controlled release, enhanced drug absorption and improved drug stability. These functions align with the most critical demands in clinical drug applications. The research on DDS spans multiple disciplines, intersecting and collaborating with each other. This review presents the latest research advancements in DDS from four perspectives:

- carrier-based and coupling-based targeted drug delivery systems
- intelligent drug delivery systems
- drug delivery devices, aligning with the primary objectives and methods of drug delivery systems Figure 1.

Table 1. The challenges and solutions to drug molecular delivery.

Drug Molecular	Challenges	Solutions
Protac (Proteolysis Targeting Chimeras)	High molecular weight, poor bioavailability, poor stability	Antibody drug conjugates (ADC) Three-dimensional printing(3DP) Transdermal preparation Implanted catheter
Peptides and Proteins	Immunogenicity, short half-life,	Polymeric nanoparticles (PNPs) Peptide drug conjugate (PDC) Implanted catheter
Anti-body	Toxicity, Immunogenicity,	Cell drug delivery systems Antibody drug conjugates (ADC) Implanted catheter
Nucleic acid	Extrahepatic delivery, Immunogenicity, Enzyme degradation,	Liposomal drug delivery systems Viral drug delivery systems Bioparticle drug delivery systems Coupling targeted drug delivery systems
Cell	Unstable drug characteristics, Poor tissue permeability	Liposomal drug delivery systems Polymeric nanoparticles (PNPs)

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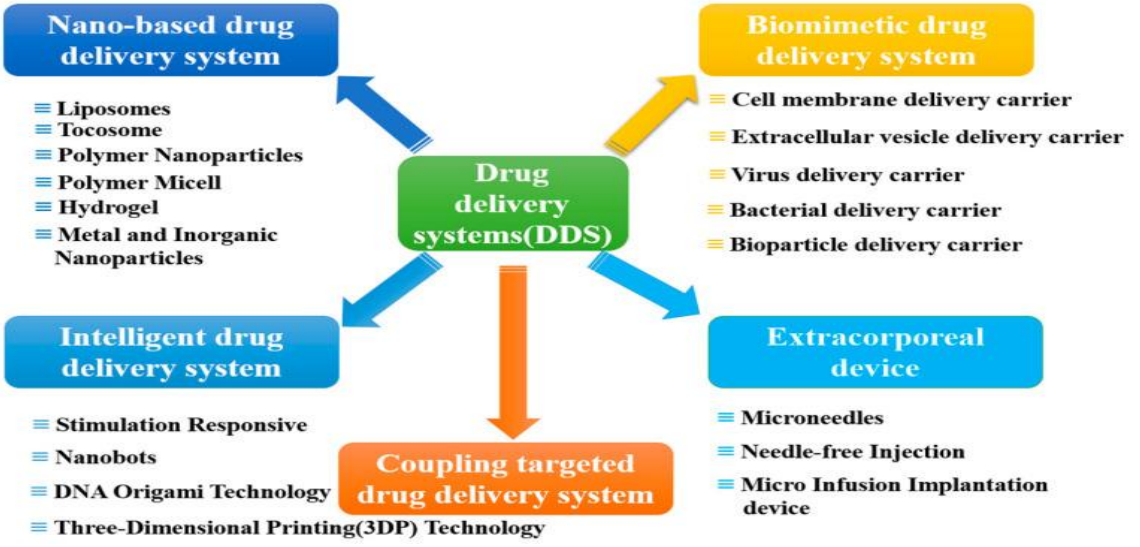


Fig. 1 Main types of drug delivery systems.

Concept of Bio adhesion/Mucoadhesion

Bio adhesion is a process characterised by interfacial molecular attracting interactions between the biological substrate surfaces and naturally or synthetically occurring polymers, allowing polymer to stick to the surface biological layers over a delayed period (Mukhopadhyay et al., n.d.) . Buccal dose forms are placed into the cheek and upper gums in the mouth to treat systemically and locally occurring diseases. For big, hydrophilic oligonucleotides, unstable proteins and tiny drug molecules, as well as polysaccharides the buccal route is one of the possible routes (Smart, 2005) **.** The mouth cavities are used to administer both systemic and localised drugs. However, due to drawbacks such as enzyme breakdown and hepatic first pass metabolism inside the GI tract, orally administered groups of medications, particularly proteins and peptides, is not recommended. Therefore, absorption mucosal layer is thought to be potentially for administrating sites for drugs. For local and systemic site of action for delivery of drug the oral cavities are seen to be useful. Localized therapies are used for treating disorders like oral candidiasis, dental caries, gingivitis, oral lesions, and xerostomia whereas systemically the delivery is seen for treating angina and asthma (Kurian Mathew, n.d.).

Delivery of drug via oral cavity membranes is sub-divided as following (Hearnden et al., 2012):

- **Buccal drug delivery systems** delivering drugs via mucosal membranes in blood stream by placing drug in between gums and the cheeks.
- **Sublingual drug delivery systems** delivering drugs via mucosal membranes that lined the flooring

of mouth inside the blood stream.

- **The local drug delivery systems** delivering drugs inside the oral cavities.

Table 2. Details of bio adhesive formulations

Sr. No	Dosage form	Polymer used	Drug
1	Tablets	HPMCK100M, Carbopol 943P, Sodium CMC, chitosan	Acyclovir, Repaglinide, Propranolol, Lisinopril
2	Gel	Carbopol, Carbopol 974P, HPMC and Poloxamer 407, Chitosan	Metronidazole, Cidofovir, lidocaine, Itraconazole
3	Patch	Eudragit, Chitosan, NaCMC, HPMC	Tizanidine, Ketoprofen, Gentamicin
4	Microspheres	Carbopol, HPMC, Chitosan, Gelatine	Raloxifene, Berberine HCl, Acyclovir
5	Nanoparticles	Chitosan, Gelatine, Carbopol, HPMC	Clofazimine, Tenofovir, Neostigmine.

Advantages of bio adhesive drug delivery systems:

a) **Bioavailability enhancement:**
For bio adhesive formulation the residence time is more in comparison to conventional dosage forms so the drug is more available at the site of absorption leading to the enhancement of the bioavailability.

b) **Rapid onset of action:**
Bio adhesive formulations show the rapid onset of the pharmacological action in comparison to the conventional dosage forms.

c) **Protection from the acidic environment:**
The drug is matrixed into the polymeric system that protects from the acidic environment of the stomach.

Disadvantages/Drawbacks of the bio adhesive drug delivery system:

a. Ulcer development:
Due to the prolonged adhesiveness of the formulation, there may be chances of ulcer development at the site of application.

b. Lack of in vitro model:
So far there is no accurate in vitro model available to simulate the drug action in vivo.

c. Drug dilution:
Due to the continuous secretion of the saliva, there are great chances of drug dilution leading to the submissive therapeutic response.

d. Patient non-compliance:
Patient compliance is observed very less due to prolonged adhesion of the formulation at the site of action

Mechanisms For Bioadhesion (Palacio & Bhushan, 2012)**:**

Bio adhesion is an interfacial occurrence that occurs when two materials, in which any one should be biological, is kept intact together because of interfacial force. Adherence may occur between artificial materials & biologicals, like the adhesion of a

polymer-copolymer to a biological membrane. Bio adhesion is greatly influenced by the polymer's hydration. Some critically known degree of hydration is required for optimal bio adhesion. The active adhesion site may not fully be freed and ready for interacting if there is partial hydration. Polymer is bound to mucosal tissue consisting of mucin layers in the process of mucoadhesion. The mechanism of polymer–mucus interactions leading to mucoadhesion has been the subject of several theories. Hydrogen bonds between polymer chains dissociate during hydration. The interaction between the polymer and the water becomes stronger than between the polymer and the other polymer. Mucoadhesion is mainly classified into two stages as shown in Figure 2:

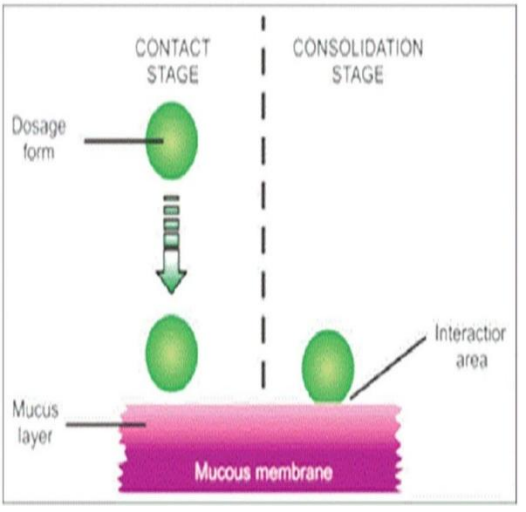


Fig. 2. Mechanism of bio adhesion showing contact stage and consolidation stage

Contact stage:

Both a fair wetting of the bio adhesive and the swelling of the bio adhesive cause close contact (wetting) between the mucus (membrane) and the mucoadhesive membrane.

Consolidation stage:

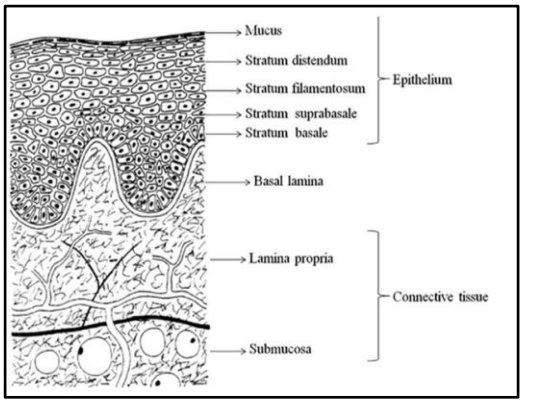
Physicochemical interactions include hydrogen bonding dispersion forces and hydrophobic interactions help to consolidate and increase the adhesive junction, resulting in longer adhesion.

Bio adhesive Drug delivery System into Oral Cavities (Reddy, Ksc, & Rao, n.d.)**:**

a. **Sublingual delivery**: This involves systemic medication distribution via mucus layer membrane that line the mouth's flooring.
b. **Buccal delivery**: The administration of drug is via the mucus layer membrane that line the cheeks (buccal mucosa)
c. **Local delivery:** The delivery of drug into the oral cavities.

Outline of the Oral Mucosa (Markiewicz, Margarone, Barbagli, & Scannapieco, 2007)**:**

Structure:



The outermost layer of the stratified epithelium makes up the oral mucosa. Underneath the skin, there is a foundation membrane, a lamina propria, and the submucosa, which is the inmost layering. The epithelia are identical to the stratified squamous epithelium seen throughout. It starts

with a mitotically active basal cellular layers and goes via several growing intermediate layer to superficial layer, here cell shed off the epithelial surfaces. The buccal mucosa epithelia have about 40-50 cellular layering's, while the sublingual epithelium has only a few. Epithelium related cells develop in sizing and flatten out as it progresses starting the basal up to the superficial layering's. The buccal epithelia turnover time seen to be expected to be 5- 6 days, which is likely indicative of the oral mucosal layer as entire structure. The buccal mucosa is 500-800m thick, while the mucosa thickening of soft and hard palate, the roof of the mouth, the ventral tongue, and also gingiva is 100-200m thick. Figure 3 depicts the architecture of the oral mucosa.

Fig. 3. Anatomy of the oral mucosa

A. **Saliva's Function**

1. A protecting fluids for the entire mouth cavity tissue.
2. A tooth enamel continues to mineralize.
3. To keep oral mucosal dosage forms hydrated.

B. **Mucus's Function**

1. Proteins and carbs are present.
2. Adhesion between cells.
3. Lubrication is third.

C. **Permeability**

1. The oral mucosa is a leaky epithelium that lies somewhere between the epidermis and the intestinal mucosa.
2. The buccal mucosa permeability is believed as 4-4000 times larger than skin. Overall, oral mucosa permeabilities decline in way of sublingual bigger than buccal, buccal bigger than palatal.
3. The sublingual mucosal layer is comparatively fine and non-keratinized, whereas the buccal mucosa layer is thick and non-keratinized, and the palate mucosa is average in thickness but keratinized.

Buccal Dosage Structure and Design (R. J. Reddy, Anjum, & Hussain, n.d.)

1. **Matrix type**: It has a mixture of medications, adhesives, and additives.
2. **Reservoir type**: It has a cavity for the medicine and additives that is distinct from the adhesive. For controlling the way of drug distribution, decrease patch deformed and the disintegration as in mouth, and avoid loss of drug, an impenetrable backing is used. Permeability of Drugs through Buccal Mucosa Absorption of drugs via the squamous stratified epithelium of the oral mucosal layer might be transcellular or intracellular (intracellular, passed inside the cell). Paracellular microorganisms (ii) (intercellular, passed around the cell). The major route of penetration over the buccal mucosa is the paracellular pathway via intercellular lipid formed by membrane-coating granules.

Buccal medication delivery system disadvantages:

- Limited absorption area: The oral cavity membranes, overall surface area is available for absorption of drug of 170cm^2 with non-keratinized tissue, like buccal membrane, accounts about ~50cm^2
- Absorption of drug via the mucosal layer is slowed by barriers such as mucus, saliva, basement membrane, membrane coating granules, and others.

- Drug dilution occurs as a result of continuous saliva secretion (0.5-2 L/day).
- The higher risk to getting chocked if the swallowing of drug is involuntary, is a worry.
- If the saliva is swallowed it may result into the loss of suspended or dissolved medications, also the unintentional the dosage form removal.

Formulation Components of Mucoadhesive Drug Delivery System:

It consists of the following components.

a) **Drug or Active pharmaceutical ingredient (API):**

The selection of the API is very critical in this drug delivery system. The API is decided based on physicochemical properties, dose, and type of the formulation to be developed. The drugs which have higher first-pass metabolism are considered an ideal candidate for the oral mucoadhesive drug delivery system.

b) **Mucoadhesive polymers:**

Different polymers are seen to be used for mucoadhesion in formulations. These polymers are classified as follows. Table 2 represents the classification of the polymers.

Table 2. Types of mucoadhesive polymers that are employed in oral cavity

Sr. No.	Type of polymer	Example
1	Natural	Xanthan gum, pectin, sodium alginate, agarose
2	Synthetic/Semisynthetic	Hydroxypropyl methylcellulose, thiolate chitosan, sodium carboxymethylcellulose (CMC), polyacrylic acid, polycarbophil
3	Cationic	Chitosan, amino dextran,
4	Anionic	Pectin, Carboxymethyl cellulose, polyacrylic acid
5	Nonionic	Polyethylene oxide, polyvinyl alcohol, PVP
6	Water-soluble	Hydroxyethylcellulose, sodium alginate, hydroxypropyl cellulose (HPC)

Characteristics of the ideal mucoadhesive polymers:

- It should be inert and should not cause any chemical or physical interaction with the biological system
- It should be biocompatible
- The by-products of the polymer should also be nontoxic and absorbable through the mucosal lining
- It should be economical and easily available
- It should not get decomposed upon storage or over the shelf-life period
- It should have sufficient capacity to adhere to the biological tissues
- It should have mucoadhesion property in dry as well as wet condition
- It should have a wetting, swelling, solubilising property in a biological system

c) Permeation enhancers:

Permeation enhancers are added to the pharmaceuticals to boost the penetration rates of the membrane of the co-administered drug. Increment in drug bioavailability with low membranal penetration either of producing toxicity or harming the membrane. The potential to improve penetration is dependent on whether used in combination or separately, the physiochemical properties of the medication, the type of the vehicle, and administering location. Table 3 summarises the various permeation enhancers used in the oral mucoadhesive drug delivery system.

Table 3. Classification of permeation enhancers

Sr. No	Type	Example	Mechanism of action
1	Chelators	Sodium citrate, EDTA	Interact with Calcium

2	Fatty acids	Oleic acid, ceprylic acid	Enhances the fluidity of the phospholipids
3	Cyclodextrins	μ, β cyclodextrins	Inclusion complex
4	Cationic polymers	Chitosan, Trimethyl chitosan	Interaction with a negative charge on the cell membrane
5	Surfactants	Cationic	cetylpyridiniu m chloride
		Anionic	Sodium lauryl sulfate
		Nonionic	Tween, Span, Myrj, Poloxamer

Factors affecting mucoadhesion (Boddupalli, Mohammed, Nath A., & Banji, 2010)**:**

- **Polymer-related factors**: Numerous qualities or properties of the active polymers are important in mucoadhesion. Concentration, polymer, swelling, specific confirmation, molecular weight, and polymer chain flexibility are all factors that may influence mucoadhesion.
- **Environmental factors**: mucoadhesion may influenced by the pH of the polymer-substrate interface, first contact time and functional strength.
- **Physiological variables:** Mucin turnover and status of diseases are vital physiological factors influencing mucoadhesion.

Some factors that affect mucoadhesion in the oral cavity

A. Polymeric Factors (Sharma, Singh, Kumar, & Singh, 2012)

a. Molecular weight:

In linear polymers, the bio-adhesiveness improves as the molecular weight increases. The optimal molecular weight for maximal mucoadhesion varies depending on the tissue and the kind of mucoadhesive polymer. High molecular weight polymers enhance physical entanglement, while lowering molecular weight polymer permeate the mucosal layer easier.

Higher molecular weight polymers will not wet as fast as lower molecular weight polymers, exposing free groups for substrate contact. Low molecular weight polymers, on the other hand, disintegrate fast.

b. Active polymer concentration:

The type of dosage form has an impact on this element. The higher the polymer content in a solid dosage form, the stronger the mucoadhesion. However, when using a liquid dose form, maximal mucoadhesion is achieved when an appropriate polymer concentration is used to induce the highest degree of bio adhesion.

c. Polymer chain flexibility:

This is required for growth and interpenetration. If water-soluble polymers are cross-linked, the individual polymer chains reduce in mobility, reducing the effective length of the chain that show penetration of the mucosal layers and therefore lowering bio adhesive strength.

d. Spatial Conformation:

A molecule's spatial confirmation is also a significant aspect. Despite its enormous molecular weight of 19,500,000, dextran's has the same adhesive strength as polyethylene glycol (molecular weight 200,000). The PEG polymers, having linear

conformation, dextran's helical shape can hide many active groups that are adhesive and reason for adhesion.

e. **Cross-Linking Density:**
Water migration into the polymer networking reduces as cross-linking density is seen to increase, resulting in insufficient polymers to swell and a reduced rate of interpenetration is seen in mucin and polymer. As per Flory, the degree of swelling at equilibrium has inverse proportion to degree of cross-linking, which is a common property of a polymer.

Hydrogen Bonding Capacity: It's another important aspect of polymeric mucoadhesion. It has been stated that for occurrence of mucoadhesion, desirable polymers should create hydrogen bonds and have functional groups. It was discovered that the polymer's flexibility is critical for improving hydrogen bonding potential. Polymers with high hydrogen bonding capability include hydroxylated methacrylate, polymethacrylic acid, polyvinyl alcohol, as well as all of their copolymers.

f. **Charge sign of polymer:**
This is a crucial component of bio adhesion. Non-ionic polymer has a low degree of adhesion comparing the anionic polymer. One of the essential features for mucoadhesion, according to Peppas and Buri, is a significant anionic charge on the polymer. Several cationic high-molecular-weight polymers, in a neutral or slightly alkaline media, like chitosan, is found to have good adhesion capabilities.

g. **Hydration (Swelling):**
Swelling of Polymer allows mechanical entanglement and expose the bio adhesive sites for hydrogen bonding and/or electrostatic interaction in both the polymer and the mucosal system. Though, optimal swelling and bio attachment need a certain level of hydration of the mucoadhesive polymer.

B. Environment Related Factors (Roy, Pal, Anis, Pramanik, & Prabhakar, 2009)

a. Applied Strength:
The adhesion strength of any polymer rises with application of strength or the length of its applicability. The depth of interpenetration can be affected by the initial pressure application to the mucoadhesive tissue contact point. Polymers become mucoadhesive when exposed to high pressure for a long time, even though they have no favourable interacting with mucin.

b. pH:
pH has a big impact on the charge of the surface of mucus and polymers. As there is a difference functional groups dissociation of amino acids and the moiety of carbohydrate of the polypeptide backbone, mucus is seen to have varying density charge that depends on the pH. It's also worth noting that the degree of hydration of cross-linked polyacrylic acid is influenced by the medium pH, with hydration increasing from pH 4 to 7 and later decreasing when alkalinity rises.

c. Initial Contact Time:
The level of swelling and interpenetration of the bio adhesive

polymer chain is determined during the first contact period between the bio adhesive and mucus layers. Furthermore, as the initial contact time rises, so does the bio adhesive strength.

C. Physiological Variables (Bagan et al., 2012)

a. **Mucin Turnover:** The mucoadhesive residence period on the mucus layer is limited by mucin turnover. Mucoadhesive are removed from the surface because of mucin turnover, regardless of mucoadhesive strength. Mucin turnover produces a large number of soluble mucin molecules. Before they may engage with the mucus layer, these molecules interact with the mucoadhesive.

b. **States of disease:** If they are utilised in a sick state, the mucoadhesive property must be assessed. Mucus' physicochemical qualities alter with illness, such as bacterial and fungal infections, the common cold, and so forth.

C. Mechanism of Mucoadhesion (Smart, 2005; Chatterjee et al., 2017)

The mechanism by which some macromolecules adhere to the surface of mucous tissue is still unknown. The main factors for mucoadhesion are attraction and repulsion between the polymer and the mucus membrane. For effective mucoadhesion, the attraction force must be dominant. The processes of mucoadhesion may be broken down in two stages: contact & consolidation. The nature of the dose form and its administration technique might help with each phase. The first step of the contact stage, as shown in the diagram, is characterised by contact in between the mucosal membrane and the mucoadhesive by spread and swell of formulations, therefore establishing deep contacting the mucosal layer. In the presence of moisture, mucoadhesive molecules break away and connect via hydrogen bonds and weak van der Waals. Different hydrolysing enzymes, such as pepsin, trypsin, and chymotrypsin, contribute to the enzymatic activity of buccal mucosa, Different theories about the much addition are as follows:

a. Electronic Theory:

The electronic transfer, according to this theory, happens when a sticky polymer and mucosal glycoprotein network come into contact. Since variances in the electrical structures, this is the case. The forming electrical double layer at the contact is predicted as a result of this.

b. Adsorption Theory:

Adhesive attachment is based on hydrogen bonding and Vander Waal's forces, according to the adsorption hypothesis. According to this idea (figure 4), following first contacts in between the two surfaces, surficial forces act in the atoms into two surfaces induce the materials to adhere.

c. Wetting Theory:

The hypothesis is applicable to liquid system or low viscosity bio adhesives that develop an affinity for the surface and spread across it. Contact angle, which should be as equal to or near zero, can be used to determine this affinity. The work of adhesion, according to Dupre's equation, is:

$$Wa = YA + YB - YAB$$

The biological membranes and bio adhesive formulation are referred to as A and B, respectively. Cohesion work is performed by: $Wc = 2YA$ or

YB

d. Diffusion Theory: In this theory, mucus and polymer chains mix deeply enough to establish a semi-permanent adhesion bond whose penetrating action is determined by diffusion coefficient.

e. Fracture Theory: The relevant force necessary to remove or separate two surfaces following adhesion is known as the adhesion fracture theory. According to, the fracture strength is equal to the adhesive strength given by G = (Eε. /L) ½, Where: E- Young's modulus of elasticity, ε- Fracture energy, L- Critical crack length when two surfaces are separated.

All of these ideas do not provide a full picture of the mucoadhesion process. Mucoadhesion can be caused by a variety of hypotheses. When it comes to mucoadhesion, the wetting theory applies first (polymer gets wet with mucous layer and swells), then the electronic and adsorption theory applies (formation of bonds and electron transfer between the polymer and mucous), then the diffusion theory applies (interpenetration of proteins and polymers), and finally, the electronic and adsorption theory applies again (formation of bonds and electron transfer between the polymer and mucous) (formation of non-covalent and covalent bonds).

2. Evaluation Of Mucoadhesive Formulations [(Mishra, Kumar, & Kothiyal, 2012)**,** (Semalty, Semalty, & Nautiyal, n.d.)**,** (Fonseca-Santos & Chorilli, 2018)**]**

a. pH of surface:

The pH surface of the mucoadhesive formulation is measured to see whether there are any potential negative effects in vivo. The buccal patches are to be expanded for 2 hours at room temperature on an agar plate surface which is in contact with 1 ml of distilled water. To measure the pH, the swollen patch's surface is placed with the pH paper.

b. Measurements of thickness:

This test is applied for the mucoadhesive patch formulations. Each film's thickness is measured at five separate spots using an electronic digital micrometre (centre and four corners).

c. Folding Endurance:

It's determined manually. The patch is folded at the same location over and over until it ruptures or breaks. The patch's folding endurance is tested by folding one patch at similar location till its breaking or manually folding it up to 200 times, which is regarded as sufficient to disclose decent patch qualities. The folding endurance was determined by the number of folds necessary to fracture or break a patch.

d. Swelling Study:

Swelling causes weight gain. Buccal patches are independently weighed (W1) and put in 2 percent and for 37°C 1°C agar gel plates are incubated, and evaluated for physically occurring changes. To quantify the growth in the area, graph paper is placed beneath the Petri dish. Patches are taken from the gel plates at 3-hour intervals, & excess surface water using filter paper is removed carefully. The swollen patches are then again weighed (W2) and using the following formula swelling index (SI) was calculated.

SI = {(W2-W1)/W1} X 100

Due to water absorption and patch

swelling, the weight differential causes the weight to grow.

e. Study of thermal Analysis:

Using a differential scanning calorimeter (DSC) thermal analysis study is performed.

f. Morphological Characteristics:(Wang, Zuo, & Guo, 2021)

Using scanning electron microscope (SEM) morphological characters are studied

g. Test for water absorption capacity (Abruzzo, Cerchiara, Bigucci, Gallucci, & Luppi, 2015)**:**

Circular Patches with 2.3 cm^2 surface area and is allowable to swell on the agar plate surface with preparation of simulated saliva and incubated at 37°C 0.5°C in an incubator. Samples are weighed at different intervals (0.25, 0.5, 1, 2, 3, and 4 hours) and then dried in desiccators over anhydrous calcium chloride at RT for 7 days before the final constant weights are recorded.

Water Uptake (%) = {(Ww – Wf)/ Wf} X 100

Where, Ww is the wet weight and Wf is the final weight. Measurement of swelling of each film is done.

h. Measurement of mechanical properties:

A microprocessor-based advanced force gauze with a motorised test may be used to examine the mechanical characteristics of the patches. A tensile tester is used to evaluate the mechanical properties of the films (patches), which include elongation at break and tensile strength. The dimensions of a film strip of 60 x 10 mm and no evident flaws were cut and positioning was done between two clamps spaced by 3 cm. The bottom clamp stays fixed while the top clamp pulls the strips apart at a rate of 2 mm/sec till the strip breaks, keeping the patch in place during the test without crushing it. The force and elongated film are measured at the point where the strip breaks are recorded. The formula is used for calculating tensile strength and elongation at break values.

[T= (M X g) / (B X T)]

Where M is the mass in grams, g is the acceleration due to gravity (980 cm/sec^2), B is the specimen's width in centimetres, and T is specimen's thickness in centimetres. The force at break (kg) per initial cross-sectional area of the specimen is defined as tensile strength (kg/mm^2) (mm^2).

i. Stability study in human saliva:

The stability of optimal bi-layered and multi-layered patches can be tested using human saliva. Human saliva is taken from people aged 18 to 50 years old. Buccal patches containing 5ml of human saliva are put in separate Petri plates and baked for 6 hours at 37°C 0.2°C in a temperature-controlled oven. According to ICH requirements, all batches of films are subjected to a stability test.

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 (Gujjala et al., 2024).

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 (Hu et al., 2010).

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 (Vasir et al., 2003)

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 (Sarella & Mangam, 2024).

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 (Ventola, 2012).

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 (des et al., 2006).

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 (Kraan et al., 2014).

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 (Yu et al., 2014).

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 (Pandey, 2017).

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 (Singh et al., 2006; Adhikari et al., 2010). 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 (Yamsani et al., 2007).

Anti-inflammatory therapy

Inflammatory processes are a key cause of oral cavity illnesses. Topical application of nonsteroidal antiinflammatory 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 (Perioli et al., 2007; Mura et al., 2010).

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 lactosebased layer, followed by a regulated release from a polymeric layer over six hours (Llabot et al., 2002).

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 (Semalty et al., 2008).

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 (Shidhaye et al., 2008).

Antihistamine

Chlorpheniramine maleate (CPM) is an antihistamine H1 receptor antagonist used to treat a variety of allergies (Koch et al., 1998). 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 (Sekhar et al., 2008).

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, nontoxic, 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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