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Review Article

Buccal Patch: A New Avenue for Better Patient Compliance in Management of Diabetes Mellitus

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Abstract: Diabetes is a persistent metabolic condition that affects many individuals globally. To manage diabetes, patients need to take medication regularly, and the buccal patch has become a promising drug delivery option for this purpose. This review article highlights the potential of buccal patches as a novel approach to enhance patient compliance in treating diabetes mellitus. By exploring the advantages of buccal patches as a non-invasive drug delivery system, this article emphasizes their potential to improve medication adherence, thereby contributing to better management of diabetes mellitus. This article aims to evaluate the role of buccal patches in improving patient compliance in the treatment of diabetes mellitus. With the increasing global burden of diabetes, ensuring patient adherence to medication regimens is crucial for achieving optimal therapeutic outcomes. Traditional treatment methods often require frequent injections or oral administrations, which may lead to poor compliance due to various factors such as fear of injections, inconvenience, or forgetfulness. Reviewing the literature on buccal patches as an alternative drug delivery system, this article explores their advantages in enhancing patient compliance. Buccal patches adhere to the inner lining of the cheek, providing a convenient and non-invasive route of drug administration. This approach eliminates the need for injections and reduces the frequency of oral medication intake, improving patient acceptance and adherence to treatment regimens. Furthermore, this article highlights the potential of buccal patches in delivering medications directly into the systemic circulation through the highly vascularized oral mucosa. By bypassing first-pass metabolism in the liver, buccal patches can achieve higher drug concentrations and improve therapeutic effects. Presenting the benefits of buccal patches for diabetes treatment encourages further research and development. So, the conclusion of this article is to promote awareness among healthcare professionals and patients about the potential of buccal patches as a patient-friendly approach to enhance compliance in the management of diabetes mellitus.

Keywords: Diabetes Mellitus, Challenges, Buccal Drug Delivery, Oral Mucosa, Buccal Patch.

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1. INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by the chronic inability to regulate blood glucose levels effectively, resulting in elevated sugar levels in the bloodstream, known as hyperglycemia.[1] This medical condition arises from inadequate insulin production or the body's reduced sensitivity to this crucial hormone. Insulin is responsible for regulating the absorption and utilization of glucose by the cells within the body. If left untreated or inadequately managed, diabetes mellitus can lead to various complications, and it is a multifaceted and intricate condition. The pathophysiology of diabetes mellitus involves a complex interplay of various factors, including genetics, lifestyle, and environmental factors.[2] Hyperglycaemia is a prominent feature of diabetes mellitus, indicating abnormally high blood glucose levels. This condition arises due to the body's impaired capacity to regulate blood glucose levels effectively. Under normal physiological circumstances, consuming carbohydrate-rich food initiates the breakdown of glucose, which enters the bloodstream. In response to elevated blood glucose levels, the pancreas releases insulin, a hormone that stimulates cells in the body to absorb glucose from the blood and utilize it for energy or store it for future use.[3]

Fig 1. Diabetes is a metabolic disorder with different types.[4]

I. Prediabetes is characterized by higher blood glucose levels than normal that have not reached the threshold for a diabetes diagnosis. It is an early warning sign for the potential development of type 2 diabetes and is associated with an increased risk of various health complications. However, through lifestyle modifications and, in some cases, medication, individuals with prediabetes can reduce their risk of progressing to diabetes and improve their overall health.[5]

II. Type 1 diabetes, also known as insulin-dependent diabetes mellitus (IDDM). It used to be called juvenile-onset diabetes because it often begins in childhood. The immune system mistakenly attacks and destroys the pancreas's beta cells responsible for insulin production. As a result, the pancreas fails to generate adequate insulin, leading to the inability to regulate blood glucose levels and hyperglycemia.[6]

III. Type 2 diabetes, also referred to as non-insulin-dependent diabetes mellitus (NIDDM), the primary cause of hyperglycemia is insulin resistance. Insulin resistance arises when cells become less sensitive to insulin, prompting the pancreas to produce more insulin to compensate. However, over time, the pancreas may become overworked and incapable of producing sufficient insulin, resulting in hyperglycemia.[7]

IV. Gestational diabetes is a form of diabetes that occurs during pregnancy. It is characterized by high blood glucose levels that develop or are first detected during pregnancy in women who previously did not have diabetes. Gestational diabetes affects many pregnant women and can have implications for both the mother's and the baby's health. During pregnancy, the placenta produces hormones that can interfere with the action of insulin, the hormone responsible for regulating blood sugar levels. As a result, the body may require additional insulin to maintain normal blood glucose levels. When the pancreas cannot produce enough insulin to meet this increased demand, gestational diabetes develops.[8]

V. Other specific types- Monogenic diabetes (Monogenic defects of β-cell function, Monogenic defects in insulin action), Diseases of the exocrine pancreas, Endocrine disorders, Drug- or chemical-induced Infections, Uncommon specific forms of immune-mediated diabetes, Other genetic syndromes, sometimes associated with diabetes.[9]

Table 1. Drug Delivery Options Available for the Treatment of Diabetes Mellitus		
1	**Oral medications**	Multiple oral medications are accessible for the treatment of type 2 diabetes, which encompasses metformin, sulfonylureas, and DPP-4 inhibitors. These medications enhance insulin sensitivity or stimulate insulin production within the pancreas.[10]
2	**Injectable insulin**	The conventional approach for administering insulin involves subcutaneous injection, where insulin is delivered beneath the skin using a syringe or an insulin pen. Injectable insulin brands like Humulin and Novolog are commonly used for this purpose.[11]
3	**Insulin pumps**	Insulin pumps are compact, battery-operated devices designed to be worn externally, delivering insulin through a catheter inserted beneath the skin. Prominent examples of insulin pumps include Medtronic Mini Med and Tandem Diabetes Care t: slim X2.[11]
4	**Transdermal patches**	Transdermal patches are specialized adhesive patches affixed to the skin and designed to deliver medication directly into the bloodstream. It is important to note that no transdermal patches are approved by the FDA specifically for insulin delivery. However, transdermal patches are currently accessible for glucose monitoring, exemplified by the Freestyle Libre system.[12]

Table 1 shows the treatment of diabetes mellitus involves various drug delivery options. These options aim to effectively manage blood glucose levels and mitigate the symptoms of the disease. Common drug delivery methods for diabetes treatment include oral medications, insulin injections, insulin pumps, and inhalable insulin. These drug delivery options provide flexibility in managing diabetes and cater to individual patient needs and preferences.

Table 2. Pharmacological Agents for Glycaemic Control		
S.No	**Class**	**Agents**
1	Sulfonylureas	Glimepiride, Glipizide, Glyburide
2	Biguanide	Metformin
3	Thiazolidinediones	Rosiglitazone, Pioglitazone
4	Dipeptidyl peptidase-4 (DPP-4) inhibitors	Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin, Aloglptin
5	Sodium-glucose transporter (SGLT) 2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin
6	GLP-1 agonist	Liraglutide, Exenatide, Dulaglutide
7	Insulin	Types of Insulin: Short-acting insulins include Regular insulin (Humulin R, Novolin R), intermediate-acting insulins include NPH (Neutral Protamine Hagedorn), and long-acting insulins include Insulin glargine (Lantus), Insulin detemir (Levemir), and Insulin degludec (Tresiba). For rapid-acting insulins, there are options such as Humalog (Lispro), Novolog (Aspart), and Glulisine (Apidra).

Table 2 shows that Pharmacological agents play a crucial role in achieving glycaemic control in managing diabetes mellitus. These agents are medications designed to regulate blood glucose levels and improve overall glycemic control. Some commonly used pharmacological agents for glycaemic control include metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin.[13,14]

1.1   Challenges in Diabetes Management

Managing diabetes presents numerous challenges that individuals face in their day-to-day lives. These challenges can arise due to the chronic nature of the disease and its impact on various aspects of their well-being. Here are some common challenges encountered in diabetes management:

A. Blood glucose control: Achieving and maintaining optimal blood glucose levels is a central challenge in diabetes management. Balancing blood sugar throughout the day is complex, as factors such as diet, physical activity, stress, illness, and medication adherence can significantly influence glucose levels. It requires regular monitoring, adjusting medication doses, and lifestyle modifications to keep blood sugar within target ranges.[15]

B. Dietary considerations: Nutrition plays a crucial role in diabetes management, but making dietary changes and adhering to a specific meal plan can be difficult. Personal food preferences, cultural influences, social situations, and emotional eating can challenge consistently following a balanced and appropriate diet. Striking a balance between blood sugar control, nutritional needs, and enjoyment of food can be an ongoing struggle.[16]

C. Physical activity: Regular exercise is beneficial for managing diabetes as it improves insulin sensitivity, aids in weight management, and promotes overall well-being. However, incorporating exercise into daily routines can be challenging due to time constraints, physical limitations, and motivational barriers. Balancing blood glucose levels during physical activity and adjusting medication or carbohydrate intake adds additional complexity.[17]

D. Medication adherence: Diabetes management often involves taking oral antidiabetic drugs or insulin injections. Adhering to prescribed medication regimens can be challenging for various reasons, including forgetfulness, complex dosing schedules, fear of side effects, cost limitations, and the need for regular refills. Inconsistent medication adherence can lead to fluctuations in blood sugar levels and hinder effective diabetes management.[18]

E. Emotional and psychological aspects: Living with diabetes can have a significant emotional and psychological impact. Managing a chronic condition, coping with self-care stress, fear of complications, and the constant need to make decisions about food, exercise, and medications can lead to emotional distress, anxiety, and depression. Diabetes-related burnout, characterized by exhaustion and frustration, can also occur, making it difficult to sustain self-management practices.[19]

F. Support and education: Effective diabetes management often requires ongoing education and support. Individuals with diabetes may face challenges accessing adequate healthcare resources, diabetes education programs, and support networks. Limited knowledge, insufficient self-management skills, and a lack of social support can hinder optimal diabetes management and increase the risk of complications.[20]

G. Coexisting health conditions: Many individuals with diabetes have comorbidities such as hypertension, dyslipidemia, cardiovascular disease, or kidney disease. Managing multiple conditions simultaneously can be complex, necessitating coordination among healthcare providers, medication adjustments, and lifestyle modifications.[21]

1.2   Pharmacokinetic Challenges related to administration or dosage form

Administering medications for treating diabetes mellitus poses several pharmacokinetic challenges that can affect patient outcomes. One such challenge is the route of administration.

Many diabetes medications are available in oral form, but they may have variable absorption from the gastrointestinal tract. It can result in fluctuations in blood sugar levels and difficulties in achieving consistent therapeutic outcomes. Patients may experience challenges in maintaining stable glucose levels due to the unpredictable absorption of oral medications.[22] Additionally, some injectable diabetes medications, such as rapid-acting insulins, have a short half-life and require frequent dosing. It presents challenges for patients needing help to adhere to a strict dosing schedule.[23] Non-adherence to the prescribed dosing regimen can lead to fluctuations in blood sugar levels and compromise glycemic control. To ensure optimal treatment outcomes, healthcare providers must educate patients on the importance of proper administration and the potential consequences of missed or delayed doses.[24] Moreover, the timing of medication administration about food intake is crucial for certain diabetes medications. For example, GLP-1 receptor agonists may have reduced effectiveness with certain foods, especially high-fat meals. This interaction can compromise the therapeutic effects of the medication, leading to suboptimal glycaemic control.[25]

1.3 Pharmacodynamics Challenges related to administration or dosage form

Treating diabetes mellitus presents pharmacodynamic challenges related to administration that can impact patient outcomes. One significant challenge is the variability in individual patient responses to medications. Patients may exhibit different pharmacodynamic responses to the same medication, making it difficult to predict the optimal dosage and achieve desired glycaemic control. Personalized treatment plans and close monitoring of patient response are essential to adjust medication regimens and optimize therapy.[26] Another challenge is the potential for drug resistance or loss of efficacy over time. Some individuals with diabetes may develop resistance to certain medications, particularly in cases of long-term usage. It can result in decreased medication effectiveness and difficult in maintaining glycemic control. In such cases, healthcare providers must regularly reassess the patient's response to treatment and consider alternative medication options or combination therapies to overcome drug resistance and restore therapeutic efficacy.[27] Furthermore, the occurrence of adverse effects can pose challenges in the administration of diabetes medications. Some medications may have undesirable side effects impacting patient adherence and overall treatment success. For example, certain oral antidiabetic drugs may cause gastrointestinal disturbances or hypoglycaemic episodes. Patients may be reluctant to continue treatment if they experience these adverse effects, leading to suboptimal glycaemic control. Close monitoring, patient education, and proactive management of adverse effects are crucial to address these challenges and ensure patient comfort and adherence to the treatment regimen.[28] Thus, comorbidities and concurrent medications can also affect the pharmacodynamic response to diabetes medications. Patients with diabetes often have other medical conditions and may take multiple medications simultaneously. Drug interactions and the potential for additive or conflicting pharmacodynamic effects can complicate treatment. Healthcare providers must carefully evaluate potential drug interactions, consider individual patient factors, and adjust medication regimens to optimize treatment outcomes and minimize the risk of adverse events.[29]

2. Buccal Drug Delivery System

The buccal route of drug administration is considered an advantageous alternative among various administration methods, with oral administration being the most favored by patients. Within the oral mucosal cavity, the buccal region provides an appealing option for systemic drug delivery. Nonetheless, oral administration has limitations, such as hepatic first-pass metabolism and enzymatic degradation in the gastrointestinal (GI) tract, which restrict the use of certain drug classes, particularly peptides and proteins.[30] Buccal drug delivery overcomes these drawbacks and offers numerous benefits for systemic drug administration. These advantages include the potential avoidance of the first-pass effect and elimination in the GI tract before reaching systemic circulation.[31] The oral mucosal cavity becomes an attractive and feasible site for systemic drug delivery. Compared to other routes such as rectal, vaginal, sublingual, and nasal delivery, buccal drug delivery possesses advantages such as well-supplied blood circulation and relatively high permeability of the buccal mucosa.[32] The buccal mucosa, lining the inner cheek, allows for the placement of buccal formulations between the upper gingival (gums) and cheek, facilitating the treatment of local and systemic conditions. The buccal route exhibits potential for delivering large, hydrophilic, and unstable proteins, oligonucleotides, polysaccharides, and conventional small drug molecules.[33]

Table 3. Buccal Drug Delivery Dosage Forms		
1	Buccal Tablets	Buccal tablets are formulated as solid dosage forms intended to be positioned in the buccal pouch. Over time, these tablets gradually dissolve or disintegrate, enabling the release of medication for absorption through the oral mucosa.[34]
2	Buccal Patches	Thin and adhesive patches are used to adhere to the buccal mucosa, allowing drug delivery through the skin in this region. They are designed to release the medication gradually over a specific period.[35]
3	Buccal Gels	Buccal gels are semi-solid formulations in the form of dosage forms that are administered to the buccal mucosa using an applicator. When in contact with saliva, they acquire a gel-like consistency and gradually release the drug for absorption.[36]
4	Buccal Films	Buccal films refer to thin, flexible sheets applied to the buccal mucosa. Once placed, they adhere and dissolve, facilitating the absorption of the drug through the mucosal membrane.[37]
5	Buccal Sprays	These dosage forms administer medications by dispersing them as fine droplets that are sprayed onto the buccal mucosa. The drug is then absorbed through the oral mucosa.[38]

6	Buccal Lozenges	Buccal lozenges are solid formulations intended to be retained in the mouth, enabling the drug to dissolve and be absorbed through the buccal mucosa.[39]
7	Buccal Powders	These powder-based dosage forms are dry in nature and applied directly to the buccal mucosa. The drug is absorbed as the powder comes into contact with saliva.[40]
8	Buccal Nanoparticles	Nanoparticles loaded with drugs can be designed specifically for buccal drug delivery. These nanoparticles are administered as suspensions or gels, allowing controlled release and enhanced absorption.[41]

Table 3 shows the Buccal drug delivery dosage forms refer to medications designed to be administered through the buccal mucosa, which is the lining of the inner cheek. These dosage forms allow for the direct absorption of drugs into the systemic circulation through the rich network of blood vessels in the buccal region. Common buccal drug delivery dosage forms include buccal tablets, films, patches, and sprays.
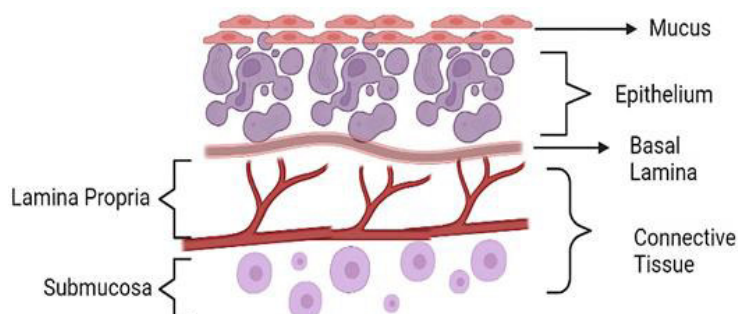

Fig 2: The buccal mucosa's structure comprises three layers: The epithelium comprises of stratified squamous cells; the lamina propria, a connective tissue layer with collagen and elastic Fibers; and the submucosa, containing adipose tissue and minor salivary glands. This tissue organization provides protection, support, and flexibility to the inner lining of the cheek.[42]

2.1 Oral Mucosa

The oral mucosa comprises a layered structure consisting of an outer layer of stratified epithelium supported by a basement membrane, lamina propria, and submucosa. The epithelium of the oral mucosa shares similarities with stratified squamous epithelia found in other parts of the body. It consists of a basal cell layer that actively divides and progresses through various intermediate layers of differentiation until reaching the superficial layers, where cells naturally shed from the surface of the epithelium.[43] In the buccal mucosa, the epithelium is approximately 40-50 cell layers thick, while the sublingual epithelium has a slightly lower number of layers. As cells move from the basal layers to the superficial layers, they increase in size and flatten. The turnover time for the buccal epithelium is around 5-6 days, which likely represents the overall turnover rate of the oral mucosa. The thickness of the oral mucosa varies depending on the specific site: the buccal mucosa measures between 500-800μm, while the mucosal thickness of the hard and soft palates, floor of the mouth, ventral tongue, and other areas ranges around 100-200μm.[44]
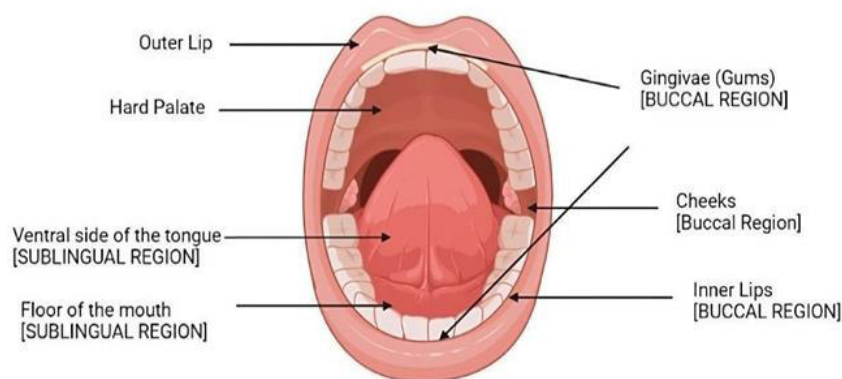

Fig 3. The anatomy of the oral cavity includes various structures such as the outer lips, hard palate, gingivae (gums), lips, and tongue.

These structures and their combinations contribute to the formation of distinct regions within the oral cavity, including the sublingual and buccal regions. The sublingual region refers to the area beneath the tongue, while the buccal region refers to the area within the cheeks. These regions play essential roles in various functions, such as speech, mastication (chewing), and the initiation of digestion.[45]

2.2 Oral Mucosal Sites

Drug delivery within the oral mucosal cavity can be categorized into three groups, delineated by the specific administration sites and intended therapeutic goals.

A. Sublingual Delivery: Sublingual drug delivery entails the placement of medication under the tongue, enabling absorption through the sublingual mucosa situated on the tongue's ventral surface and the mouth's floor. This administration route facilitates direct absorption of the drug into the systemic circulation, bypassing the metabolism in the liver during the first-pass effect. Sublingual delivery is commonly used for medications that require rapid onset of action, such as nitro-glycerine for angina or certain medications for acute pain relief.[46]

B. Buccal Delivery: Buccal drug delivery refers to administering medications through the buccal mucosa, which lines the inner cheek. By utilizing this route, drugs are directly absorbed into the systemic circulation. The buccal mucosa presents advantageous characteristics, including a rich blood supply and a favorable level of permeability, facilitating efficient drug absorption. Buccal delivery can be employed for both local and systemic drug administration, depending on the specific formulation and properties of the drug. It offers the potential for controlled release and sustained drug delivery. Buccal delivery is frequently employed for drugs unsuitable for oral administration due to first-pass metabolism or enzymatic degradation within the gastrointestinal tract.[47]

C. Local Delivery: Local drug delivery pertains to the targeted administration of medications to treat oral cavity conditions. It includes the treatment of oral ulcers, fungal infections, and periodontal diseases. Local delivery may involve gels, mouthwashes, or topical formulations applied directly to the affected area within the oral cavity. The goal is to provide targeted treatment to the affected site while minimizing systemic exposure. Local drug delivery involves the precise administration of medications to treat conditions within the oral cavity.[48]

2.3 Mechanism of Buccal Absorption

The absorption of drugs through the buccal route occurs via passive diffusion of non-ionized compounds, predominantly driven by a concentration gradient across the intercellular gaps of the epithelium. The primary transport mechanism involves the passive diffusion of non-ionic species through the lipid membrane in the buccal cavity. Like other mucosal membranes, the buccal mucosa acts as a barrier to drug passage, and the lipophilicity of a drug enhances its absorption.[49] The rate of drug absorption through the buccal route can be accurately characterized as a first-order rate process. Numerous factors that impede buccal drug absorption have been identified. Dearden and Tomlinson (1971) observed that the kinetics of drug absorption in the buccal cavity are influenced by salivary secretion, which modifies the drug concentration in the oral cavity.[50]

2.4 Limitation Of Buccal Route

A. Limited absorption area. The buccal mucosa is a relatively small area, so only a limited amount of drug can be absorbed at a time.[51]

B. Small amount of liquid available for drug dissolution. The buccal cavity does not contain a lot of liquid, so drugs that need to be dissolved before they can be absorbed may not be well-suited for buccal administration.[52]

C. Taste. Some drugs have a strong or unpleasant taste, which can make them difficult to administer buccally.[53]

D. Irritation. Some drugs can irritate the buccal mucosa, which can make them uncomfortable to use.[54]

E. Accidental swallowing. Buccal tablets or films can be accidentally swallowed, leading to systemic side effects.[55]

3. Formulation and Design for Buccal Patch

A buccal patch is a specialized drug delivery system designed to administer medication through the buccal mucosa, the inner lining of the cheek, for direct absorption into the bloodstream. It is particularly useful for drugs with low oral bioavailability or those susceptible to degradation in the gastrointestinal tract. Buccal patches offer an efficient delivery route by bypassing the liver and gastrointestinal metabolism.[56] These patches are thin, flexible sheets that adhere to the buccal mucosa, releasing drugs directly into the systemic circulation via the oral mucosa. They represent an emerging and advantageous drug delivery method, surpassing conventional approaches like oral tablets, subcutaneous injections, and intravenous infusions.[57] The formulation of buccal patches involves critical considerations, including material selection, drug loading, and patch design. Typically, buccal patches comprise a backing layer, an adhesive layer, and a drug-containing layer. The backing layer, made of thin and flexible materials such as polyester, polyethylene, or polyvinyl chloride, supports and protects the drug layer from external factors. The adhesive layer ensures proper adherence to the buccal mucosa and may incorporate mucoadhesive polymers like carbopol, chitosan, and hydroxypropyl methylcellulose to enhance adhesion and prolong drug release.[58] The drug-containing layer contains the active pharmaceutical ingredient (API), which can be integrated into a polymer matrix, encapsulated in liposomes, or dispersed within a hydrogel. The selection of the drug delivery system depends on the drug's physicochemical properties and the desired release profile. Techniques such as solvent casting, hot melt extrusion, and freeze-drying are employed to prepare buccal patches. Buccal patches have been developed for various therapeutic purposes, including pain management, cardiovascular diseases, and central nervous system disorders.[59] They offer significant advantages regarding targeted drug delivery and improved therapeutic outcomes. The use of buccal patches for insulin delivery in treating diabetes has received considerable attention in recent years. Insulin buccal patches offer several advantages over traditional insulin delivery methods, such as subcutaneous injections, including reduced pain, improved patient compliance, and a more rapid onset of action. Several studies have investigated the use of buccal patches for insulin delivery in animal models and humans, with promising results.[60]

3.1 Benefits of Using Buccal Patch In The Treatment Of Diabetes Mellitus

Buccal patches have emerged as a highly promising drug delivery system in treating diabetes mellitus, offering distinct advantages compared to traditional tablets, injections, and other dosage forms. Using buccal patches eliminates the need for invasive procedures like injections or swallowing tablets, enhancing patient compliance. This non-invasive route of administration not only reduces patient discomfort but also eliminates the risk of needle-associated complications.[61] Additionally, buccal patches bypass the first-pass metabolism, enabling direct drug delivery to the bloodstream through the highly permeable buccal mucosa. This results in improved drug bioavailability and faster onset of action compared to oral

tablets.[62] Another advantage is the potential to minimize gastrointestinal side effects commonly associated with oral tablets, as buccal patches bypass the gastrointestinal tract.[63]Overall, using buccal patches in diabetes treatment offers convenient administration, enhanced drug absorption, and reduced side effects, making them a promising alternative to conventional tablets, injections, and other dosage forms.[64]

3.2   Selection of Suitable Polymer for Buccal Patch

The selection of the polymer for a buccal patch is a critical decision that impacts the performance and characteristics of the patch. Several factors need to be considered when choosing the appropriate polymer. Evaluating and selecting the polymer based on these criteria is crucial to ensure the buccal patch's safety, efficacy, and overall performance in delivering the intended drug through the buccal mucosa.

A. Biodegradability Ideal polymers for buccal patches should possess biodegradable properties to ensure their safe and efficient degradation in the body. Biodegradable polymers minimize the risk of long-term retention in the oral cavity and potential adverse effects. Biodegradation allows for the gradual release of the drug and facilitates the removal of the patch after use without residue or harm to the mucosal tissue.[65]

B. Permeability Enhancement Polymers used in buccal patches should possess permeability-enhancing properties to facilitate drug absorption through the buccal mucosa. These polymers improve the permeation of APIs by interacting with the mucosal membrane, opening tight junctions, and increasing paracellular transport. Enhanced permeability enables efficient drug delivery and ensures therapeutic efficacy.[66]

C. Compatibility with APIs Polymers employed in buccal patches must exhibit compatibility with a wide range of APIs to ensure the stability and integrity of the drug throughout the patch's shelf life. Compatibility between the polymer and the API prevents drug degradation, maintains the desired drug release profile, and preserves therapeutic efficacy. Polymer selection should consider the physicochemical properties and compatibility of the API to achieve optimal drug-polymer interactions.[67]

D. Safety Profile Safety is a critical aspect of polymer selection for buccal patches. Polymers should exhibit a favorable safety profile, including biocompatibility, non-toxicity, and non-irritation of the buccal mucosa. Biocompatible polymers minimize the risk of adverse reactions, tissue damage, or local irritation, ensuring patient comfort and acceptance of the buccal patch formulation.[68]

Table 4. Ideal Characteristics of a Drug for Buccal Patch		
1	**High lipophilicity**	It is preferable to use drugs with high lipophilicity for optimal drug delivery through a buccal patch. These drugs can easily permeate the lipid bilayer of the buccal mucosa, leading to enhanced drug absorption.[69]
2	**Low molecular weight**	The drug's molecular weight is more likely to be absorbed through the buccal mucosa. Smaller molecules have higher permeability and are less likely to be excluded by the tight junctions in the buccal mucosa.[70]
3	**Stability in Saliva**	The drug must possess chemical stability and resist enzymatic degradation by saliva, which can diminish its bioavailability. Drugs susceptible to degradation caused by pH, temperature, or enzymes require special attention to ensure stability.[71]
4	**Optimal solubility**	The drug should exhibit ideal solubility within the patch matrix to guarantee uniform dispersion and consistent release at an optimal rate.[72]
5	**Rapid onset of action**	The drug should have a rapid onset of action to provide quick relief to the patient.[73]
6	**Non-irritating**	The drug mustn't induce any irritation or inflammation within the oral cavity. It is because irritation can cause discomfort, and inflammation can affect the permeability of the buccal mucosa.[74]
7	**Prolonged release profile**	An ideal drug for buccal patch delivery should have a prolonged release profile, allowing for sustained drug delivery over some time.[75]
8	**High potency**	A highly potent drug necessitates a lower dosage to achieve the intended therapeutic outcome, thereby minimizing the quantity of drug needed for administration and potential adverse effects.[76]
	Safe and non-toxic	The drug must be safe and non-toxic for oral mucosa and the patient's overall health.[77]

Table 4 shows that certain ideal characteristics should be considered when designing a drug for buccal patch delivery to ensure optimal performance and efficacy. Considering these ideal characteristics helps select appropriate drugs for buccal patch delivery, ensuring optimal drug performance, patient compliance, and therapeutic outcomes.

3.3   Permeation/Penetration Enhancers Used In Buccal Patch

Permeation enhancers are agents that can permeate the skin and interact with various skin components, such as intracellular keratin and intercellular desmosomes, to increase the flux of drugs by temporarily reducing the resistance of the stratified epithelial barrier. These enhancers directly interact with the keratin in epithelial cells or disrupt the epithelium's intercellular lipids, proteins, and other components. They may enhance the drug's diffusion coefficient, increase its thermodynamic activity in the vehicle, and enhance its partitioning in the buccal epithelium.[78] Permeation enhancers are particularly beneficial for improving the transport of proteins, peptides, and hydrophilic, low-molecular-weight active compounds. Different absorption enhancers include surfactants, bile salts, fatty acids, complexing agents, polymers, cyclodextrins, and miscellaneous compounds like azone analogs. Although the combination of penetration enhancers generally leads to enhanced drug absorption, prolonged and excessive use of these agents may potentially cause local

inflammation or tissue injury. Therefore, when selecting penetration enhancers, it is essential to consider the physicochemical characteristics of the active compounds and ensure that the enhancers are nontoxic, physiologically compatible, non-irritating, pharmacologically inactive, and organoleptically inert. Many permeation enhancers demonstrate concentration-dependent effects, including pyrrolinones, alcohols, alkanols, sulfoxides, glycols, azones, and surfactants.[79]
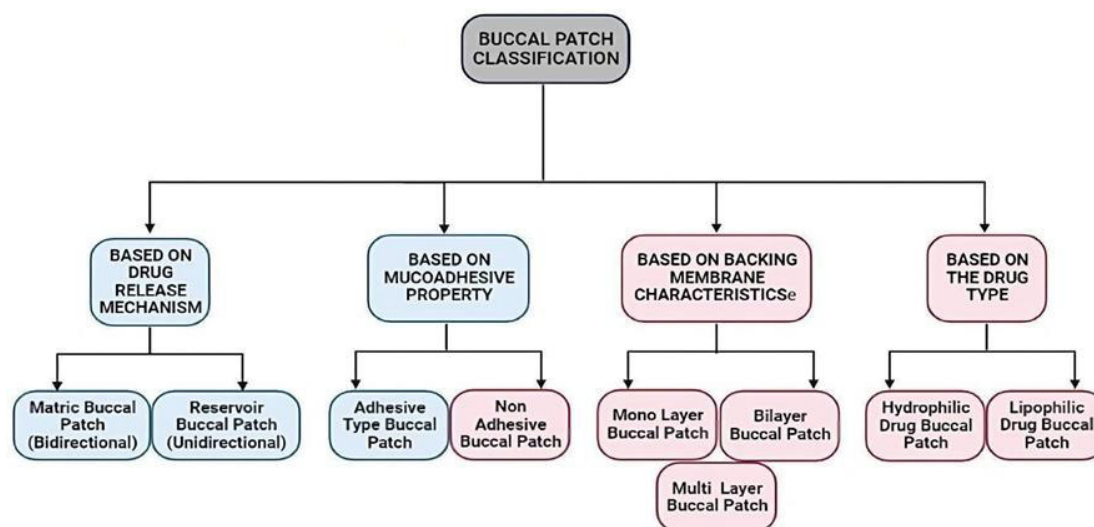
3.4   Classification of Buccal Patch

Fig 4. Buccal patches represent an innovative approach to drug delivery, specifically designed for the administration of drugs through the buccal mucosa with direct absorption into the systemic circulation.

These patches can be categorized according to different factors, including the mechanism of drug release, mucoadhesive properties, and characteristics of the backing membrane.[80]

3.4.1   Based On Drug Release Mechanism

A. Buccal Patch designed for Bidirectional drug release

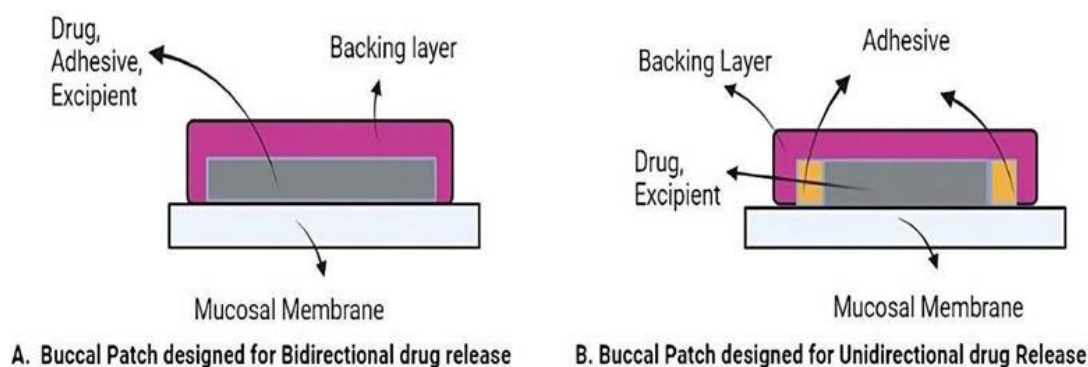B. Buccal Patch designed for Unidirectional drug Release

Fig 5. The classification of buccal patch based on the drug release mechanism is divided into two types: bidirectional drug release and unidirectional drug release, which are shown in Figures A and B, respectively.[81,82]

I) Matrix Buccal Patches (Bi-directional): Matrix Buccal Patches (Bi-directional) refer to a specific form of transmucosal drug delivery system utilized for the administration of medications through the buccal mucosa, encompassing the inner linings of the cheeks and gums situated within the oral cavity. These patches are equipped with an adhesive layer designed to securely attach to the buccal mucosa, facilitating the gradual release of the medication into the bloodstream using the mucosal tissue.[81] The bi-directional feature of the patches allows drug diffusion to occur in both directions, i.e., from the patch into the buccal mucosa and vice versa. The characteristic mentioned above improves the uptake of drugs. It allows for a controlled and prolonged release of the medication, leading to enhanced availability in the body and increased effectiveness in achieving the desired therapeutic outcomes. These patches are convenient to use,

do not require swallowing, and are ideal for drugs that have poor oral bioavailability or are sensitive to the digestive environment.[82]

II) Reservoir Buccal Patches (Uni-directional): The structure of these patches comprises a reservoir containing the drug, which is shielded by a backing layer and an adhesive layer for attachment to the buccal mucosa. The drug is discharged from the reservoir via a semi-permeable membrane in a one-way direction, specifically towards the buccal mucosa, and subsequently absorbed into the bloodstream through the mucosal tissue. This patch design ensures controlled and sustained drug release, enhancing therapeutic effectiveness and minimizing adverse reactions.[83] The drug is released from the reservoir through the membrane at a controlled rate. Reservoir buccal patches are suitable for delivering drugs with

high molecular weight or low solubility. They are more complex to manufacture than matrix buccal patches but offer greater control over drug release.[84]

3.4.2   Based On Mucoadhesive Properties

I) Adhesive-type buccal patches: The provided statement describes patches with a mucoadhesive component, allowing them to stick to the buccal mucosa and deliver medication directly into the bloodstream via the oral mucosa. The mucoadhesive layer can comprise various materials, including natural substances like chitosan, carbopol, hydroxypropyl methylcellulose, and synthetic polymers.[85]

II) Non-adhesive buccal patches: Non-adhesive buccal patches are innovative drug delivery systems that administer medication through the buccal mucosa without relying on mucoadhesive polymers. Instead, these patches employ a drug-containing matrix or reservoir applied to the buccal mucosa. The drug is gradually released from the patch via diffusion, passing through the buccal mucosa and entering the systemic circulation. [86] Non-adhesive buccal patches offer several advantages over adhesive buccal patches. First, they are more comfortable to use as they do not adhere to the buccal mucosa, which can cause discomfort and irritation. Second, they are easier to remove, and there is no risk of damage to the mucosal tissue upon removal. Third, these patches can be formulated to provide prolonged drug release, ensuring sustained medication delivery over an extended duration.[87]

3.4.3   There are several approaches to formulating non-adhesive buccal patches, including

Monolithic matrix systems: The patches consist of a matrix containing a medication formulated to release the medication through the buccal mucosa via diffusion gradually. The matrix can be composed of either natural or synthetic polymers, including polyvinyl alcohol, polyethylene oxide, and hydroxypropyl methylcellulose.[88]

Swellable and erodible systems: The patches are comprised of polymers that can swell and erode upon exposure to saliva, facilitating the release of the drug. These polymers include sodium carboxymethyl cellulose and hydroxypropyl cellulose.[89]

Osmotic systems: The patches consist of a reservoir containing the drug, which is encapsulated by a semipermeable membrane. Water from the saliva enters the reservoir, creating a pressure gradient that drives the drug through the membrane and into the buccal mucosa.[90]

Dissolving films: These are thin, flexible films composed of a drug-containing polymer matrix that dissolves upon contact with saliva, releasing the drug.[91]

3.4.4   Based On Backing Membrane Characteristics

I) Mono-layer buccal patches: The patches comprise a singular layer containing the drug matrix or reservoir. Mono-layer buccal patches serve as a specific drug delivery system to release the drug through the buccal mucosa. These patches consist of a single layer of material containing the drug, which is applied against the buccal mucosa. [92] The drug is gradually released from the patch by diffusing through the buccal mucosa and entering the systemic circulation. It offers several advantages over other types of buccal patches. First, they are easy to manufacture and can be made in large quantities. Second, they are thin and flexible, which makes them comfortable to wear. Third, they offer good adhesion to the buccal mucosa, which ensures efficient drug delivery.[93]

II) Bi-layer buccal patches: These patches consist of two layers, namely the drug-containing layer and the backing layer, which provides mechanical support to the patch. Bi-layer buccal patches are a specific drug delivery system characterized by two distinct layers: a layer containing the drug and an adhesive layer. The drug-containing layer is positioned on the buccal mucosa, while the adhesive layer ensures proper patch adhesion. The purpose of bi-layer buccal patches is to facilitate the release of the drug through the buccal mucosa, allowing it to enter the systemic circulation. The drug-containing layer of bi-layer buccal patches can be formulated using a range of substances, such as polymers, lipids, and hydrogels.[94] The adhesive layer is typically made from a pressure-sensitive adhesive, such as polyacrylate or silicone. The two layers are laminated together to form the final patch. Bi-layer buccal patches offer several advantages over other types of buccal patches. Firstly, bi-layer buccal patches offer improved adhesion to the buccal mucosa, ensuring effective drug delivery. Secondly, they can be formulated to enable controlled and sustained drug release over an extended duration. Thirdly, they can be specifically designed to release the drug at targeted locations within the oral cavity, thereby reducing potential side effects.[95] Numerous studies have highlighted the potential of bi-layer buccal patches in delivering a diverse range of medications, including antihypertensives, antidiabetics, and opioids. Moreover, these patches have also demonstrated efficacy in administering drugs to treat localized oral ailments like periodontitis.[96]

III) Multi-layer buccal patches: Multi-layer buccal patches represent a drug delivery system comprising more than two layers to facilitate medication transportation through the buccal mucosa and into the systemic circulation. Multi-layer buccal patches offer several advantages over other buccal patches, including better adhesion, controlled release, and targeted drug delivery. The drug-containing layers of multi-layer buccal patches can be formulated using various substances, such as polymers, lipids, and hydrogels. The adhesive layers provide the necessary adhesion to keep the patch in place. The multiple layers are laminated together to form the final patch. [97] Multi-layer buccal patches have been extensively utilized to administer diverse medications, including antihypertensives, antidiabetics, and opioids. They have also proven effective in delivering drugs for localized oral conditions like periodontitis. These patches offer the potential for controlled and prolonged release of drugs, as well as the ability to target specific areas within the oral cavity. A noteworthy study demonstrated the application of multi-layer buccal patches in insulin delivery. The patch encompassed a mucoadhesive layer, a drug-containing layer, and a backing layer.[98] The mucoadhesive layer of chitosan and hydroxypropyl methylcellulose exhibited excellent adhesion to the buccal mucosa. The drug-containing layer, comprising insulin, polyvinyl alcohol, and glycerine, facilitated the controlled insulin release over an extended duration. The backing layer, consisting of ethyl cellulose and polyvinyl alcohol, protected the drug-containing layer from external factors. The study demonstrated that the multi-layer buccal patch provided effective insulin delivery and maintained blood glucose levels in diabetic rats.[99]

3.4.5   Based On the Drug Type

I) Hydrophilic drug buccal patches: Hydrophilic drug buccal patches are a drug delivery system designed to deliver hydrophilic drugs through the buccal mucosa. These patches contain a polymer matrix containing the drug that is designed to adhere to the mucosal surface. Hydrophilic drugs have low permeability across biological membranes, so buccal patches are an attractive alternative route for their administration.[100] The polymer matrix employed in hydrophilic drug buccal patches can be derived from various materials, such as hydrogels, chitosan, and other polymers. Hydrogels possess remarkable hydrophilicity and can efficiently absorb significant amounts of water, which is crucial for optimal drug delivery. On the other hand, chitosan is a biodegradable, biocompatible, and mucoadhesive polymer with extensive application in buccal patch formulations owing to its exceptional mucoadhesive properties.[101] Hydrophilic drug buccal patches have been successfully utilized for administering diverse medications, including analgesics, antiemetics, and antihypertensives. One study demonstrated the potential of hydrophilic drug buccal patches for the delivery of metoprolol, an antihypertensive drug. The patch contained a hydrophilic polymer matrix containing metoprolol, hydroxypropyl methylcellulose, and polyvinyl alcohol. [102] The study demonstrated that the buccal patch provided effective delivery of metoprolol and maintained its therapeutic levels in the blood for an extended period. Another study evaluated the potential of hydrophilic drug buccal patches for delivering ondansetron, an antiemetic drug. The patch comprised a hydrophilic polymer matrix containing ondansetron, Carbopol, and chitosan.[103] The study demonstrated that the buccal patch provided sustained release of ondansetron and effectively controlled nausea and vomiting in chemotherapy patients. Hydrophilic drug buccal patches present a compelling alternative pathway for administering hydrophilic medications. Developing these patches requires careful consideration of the polymer matrix, drug formulation, and mucoadhesive properties to ensure effective drug delivery and patient compliance.[104]

II) Lipophilic drug buccal patches
Lipophilic drug buccal patches are a drug delivery system designed to deliver lipophilic drugs through the buccal mucosa. Lipophilic drugs have a high affinity for fat and are insoluble in water, which makes their delivery through conventional oral administration challenging. Buccal patches provide an alternative means of delivering lipophilic drugs, allowing them to bypass the gastrointestinal tract and avoid first-pass metabolism, thereby enhancing their bioavailability.[105] The polymer matrix utilized in lipophilic drug buccal patches can comprise diverse materials, such as ethyl cellulose, polyvinyl alcohol, and polyvinylpyrrolidone. These materials can incorporate lipophilic drugs into the patch, enabling their controlled release into the bloodstream. To enhance drug absorption, the patches may also contain permeation enhancers, such as menthol or eucalyptus oil.[106] Lipophilic drug buccal patches have found application in delivering various medications, encompassing hormones, sedatives, and antipsychotics. One study demonstrated the potential of lipophilic drug buccal patches for the delivery of clonazepam, a sedative drug. The patch contained a polymer matrix containing clonazepam, ethyl cellulose, and polyvinyl alcohol. The research showcased the efficacy of the buccal patch in delivering clonazepam, ensuring sustained therapeutic concentrations of the drug in the bloodstream for 8 hours. [107] Furthermore, another study examined the capability of lipophilic drug buccal patches in delivering testosterone, a hormone employed for hypogonadism treatment. The patch consisted of a polymer matrix containing testosterone and menthol.[108] The study demonstrated that the buccal patch provided effective delivery of testosterone and maintained its therapeutic levels in the blood for up to 12 hours.[109]
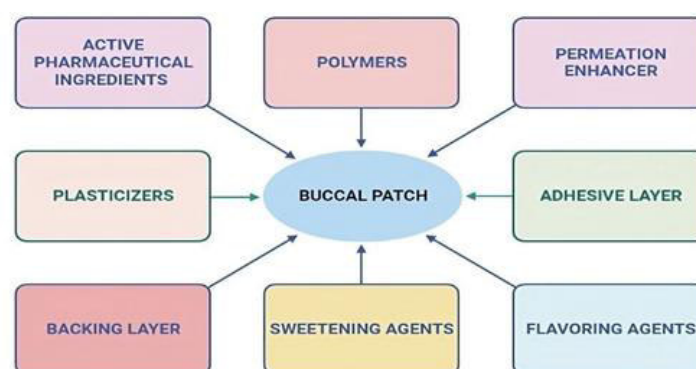
3.5   COMPOSITION OF BUCCAL PATCH

Fig 6. The composition of a buccal patch refers to the formulation components that make up the structure of the patch designed for buccal drug delivery.

The specific composition may vary depending on the drug being delivered and the desired properties of the patch. It's important to note that these components' specific composition and ratio can vary depending on the desired characteristics and objectives of the buccal patch formulation for effective drug delivery.[110]

A. API (Drug)- The active pharmaceutical ingredient intended to be delivered across the buccal mucosa.[110]

B. Polymer matrix- The polymer matrix is the backbone of the buccal patch and provides a platform for drug release. The most used polymers for buccal patches are hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose (NaCMC), and polyvinyl alcohol (PVA).[111]

C. Plasticizer- Plasticizers are added to the polymer matrix to improve the flexibility and elasticity of the patch. The most used plasticizers for buccal patches are glycerine, propylene glycol, and polyethylene glycol.[112]

D. Permeation enhancers - To enhance drug absorption through the buccal mucosa, permeation enhancers are utilized. Menthol, dimethyl sulfoxide (DMSO), and sodium Tauro deoxycholate are some of the commonly used examples of permeation enhancers.[113]

E. Backing layer - The backing layer is the outermost layer of the patch, which protects the patch from moisture, air, and other external factors.[114]

F. Adhesive layer- The adhesive layer is the layer that sticks the patch to the buccal mucosa. The most used adhesives for buccal patches are polyacrylic acid and polyvinylpyrrolidone.[115]

G. Sweeting & flavoring Agent- The use of flavoring and sweetening agents in buccal patches has gained significant attention due to their potential to improve patient acceptability and compliance.[116]

3.6 Methods of Preparation

I. Solvent Casting Method
The solvent casting method is a popular approach for creating buccal patches. This method entails dissolving a polymer and a plasticizer in a suitable solvent, resulting in a homogeneous solution poured onto a flat surface, such as a glass plate. The solvent evaporates, resulting in a thin film or membrane of the polymer-plasticizer blend. To incorporate the drug, the polymer membrane's surface can be coated with a drug solution or mixed with the polymer solution before casting. Subsequently, the film containing the drug is cut into the desired dimensions, and an adhesive layer is affixed to one side of the film. The patch is then ready for use. The solvent casting method allows for precise control over the composition and thickness of the buccal patch, and the resulting patch is flexible, durable, and comfortable to wear.[117]

II. Hot Melt Extrusion Method
The hot melt extrusion method is a manufacturing technique for producing buccal patches. In this method, a polymer matrix, drug, and other excipients are mixed and fed into an extruder, which melts the mixture and extrudes it through a die. After extrusion, the material is cooled, subsequently shaped, and sized accordingly to create the desired patch. Depending on the desired release profile, the patch may be coated with an adhesive layer on one or both sides. The hot melt extrusion method enables precise control over the composition and

properties of the buccal patch, such as drug release rate and adhesive strength. It is also a scalable and reproducible manufacturing process that can produce consistent quality buccal patches in large quantities.[118]

III. Freeze-drying Method
The freeze-drying method, also called lyophilization, is frequently used in formulating buccal patches. The procedure entails the dissolution of a polymer and a plasticizer in a solvent to generate a uniform solution. This solution is poured onto a flat surface or a Mold, such as a glass plate. The solvent is then removed by freezing the solution at a very low temperature and subjecting it to a vacuum, which causes the solvent to evaporate directly from the solid state. This process is known as sublimation. The resulting solid material is a porous, sponge-like structure that contains the polymer and plasticizer but no solvent. The drug is subsequently integrated into the solid material by mixing it with the polymer-plasticizer solution before freezing or impregnating it into the porous structure after freeze-drying. An adhesive layer is applied to one side of the patch and cut into the desired shape and size. Utilizing the freeze-drying technique makes it possible to manufacture buccal patches that exhibit elevated drug-loading capacity and enhanced stability. The resulting patch is highly porous, which facilitates drug release and absorption.[119]

3.7 Pharmacokinetics of A Buccal Patch

The pharmacokinetics of a buccal patch refers to the processes involved in the absorption, distribution, metabolism, and excretion of a drug following its administration through the buccal mucosa. This route of drug delivery offers several advantages, such as bypassing the gastrointestinal tract and hepatic first-pass metabolism. The drug diffuses through the mucosal tissues and enters the systemic circulation, where it can be distributed to target sites and undergo metabolism by enzymes.[120] The buccal mucosa also provides a relatively large surface area and good blood supply, facilitating drug absorption. Clearance of the drug from the body occurs through various elimination pathways, including renal excretion and metabolism by hepatic enzymes. The pharmacokinetic profile of a buccal patch, including the rate and extent of drug absorption, systemic availability, and elimination half-life, can be influenced by factors such as patch design, drug properties, and individual patient characteristics. Detailed studies and clinical trials are essential for a thorough understanding of the pharmacokinetics of specific buccal patch formulations.[121]
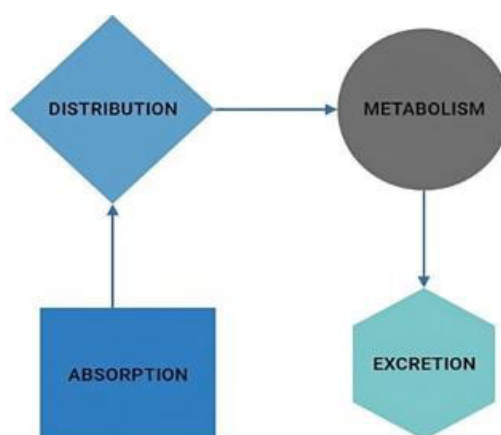

Fig 7. A buccal patch's pharmacokinetics encompasses drug absorption, distribution, metabolism, and excretion after its administration via the buccal mucosa.[120-121]

Absorption: The absorption of a drug from a buccal patch occurs through the buccal mucosa, which consists of an epithelial layer and a lamina propria. The drug diffuses across the epithelial layer and enters the blood vessels in the lamina propria, where it is transported to the systemic circulation.[122] The rate and extent of drug absorption from a buccal patch are influenced by various factors, including the drug's lipophilicity, molecular weight, solubility, and concentration within the patch.[123]

Distribution: The distribution of a drug delivered via a buccal patch depends on its physicochemical properties, as well as the characteristics of the target tissues. The drug may be distributed to the systemic circulation, where it may bind to plasma proteins, or it may be distributed to specific organs or tissues where it exerts its pharmacological effects.[124] Factors such as the drug's tissue penetration, binding affinity, and elimination rate can also impact the rate and extent of distribution within the body.[125]

Metabolism: Following delivery via a buccal patch, drug metabolism can occur in the liver, involving enzymes like cytochrome P450. Additionally, the buccal mucosa can harbor enzymes contributing to drug metabolism.[126] The rate and extent of drug metabolism can be influenced by factors including the drug's metabolic stability, the activity of metabolic enzymes, and the drug concentration in the bloodstream.[127]

Excretion: Elimination of a drug delivered via a buccal patch primarily occurs through the kidneys, where the drug and its metabolites are excreted from the body.[128] The rate and extent of excretion can be influenced by factors including the drug's renal clearance, its concentration in the bloodstream, and the urine's pH level.[129]

3.8 Mechanism Action of A Buccal Patch

The drug in the patch diffuses into the buccal mucosa, which can be absorbed through the epithelial cells and enter the systemic circulation. The drug release from the buccal patch can occur through various mechanisms, depending on the patch design. Some patches use a reservoir system, where the drug is dissolved or suspended in a polymer matrix that slowly releases the drug over time. Other patches employ a matrix system, where the drug is dispersed uniformly throughout a polymer matrix, and the release occurs by diffusion or erosion of the matrix.[130] The release rate can be controlled by adjusting the properties of the polymer, such as its solubility or permeability. Once in the systemic circulation, the drug can be distributed to target tissues and exert pharmacological effects. The specific mechanism of action will depend on the drug's properties and intended therapeutic purpose. It may interact with specific receptors, enzymes, or cellular processes to produce the desired therapeutic response.[131]
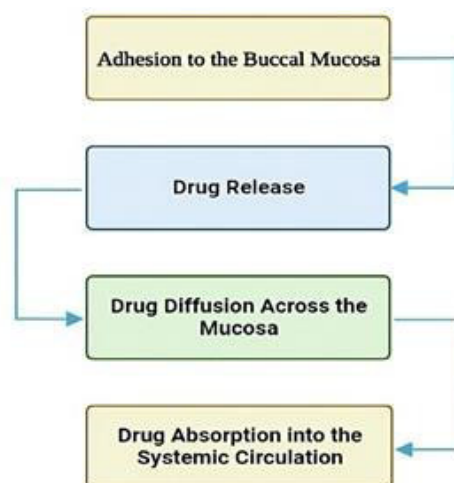

Fig 8. The mechanism of action of a buccal patch involves several steps, including adhesion to the buccal mucosa, drug release, drug diffusion across the mucosa, and drug absorption into the systemic circulation. [130-131]

Adhesion to the Buccal Mucosa- The initial stage in the mechanism of action of a buccal patch involves the attachment of the patch to the buccal mucosa. To achieve prolonged contact with the mucosa, pressure-sensitive adhesives are employed in the design of the patch. The adhesion of the patch to the buccal mucosa plays a vital role in drug delivery as it ensures that the drug remains in contact with the mucosa for an adequate duration, facilitating drug absorption.[132]

Drug Release- After the buccal patch adheres to the buccal mucosa, the drug is subsequently released from the patch. Various factors, such as the patch's composition, the drug's physicochemical properties, and the intended release rate, influence the control of drug release. Typically, the drug is embedded within a polymeric matrix, which governs the drug release rate. By adjusting the release rate, the drug's pharmacokinetic profile can be customized according to the desired outcome.[133]

Drug Diffusion Across the Mucosa- Following the release from the patch, the drug undergoes diffusion through the buccal mucosa. The buccal mucosa, known for its high vascularity and permeability, facilitates swift drug diffusion into the systemic circulation. Passive diffusion primarily propels drug diffusion, with the rate being influenced by various factors such as the drug's physicochemical properties, concentration within the patch, and the permeability of the buccal mucosa.[134]

Drug Absorption into the Systemic Circulation- The drug is absorbed into the systemic circulation upon diffusing across the buccal mucosa. Subsequently, the drug is transported through the blood vessels to its intended target site, where it manifests its pharmacological effect. The buccal route of drug administration presents numerous benefits, such as bypassing first-pass metabolism in the liver and facilitating prompt drug absorption into the systemic circulation.[135]

3.9　Advantages of Buccal Patch

A. Non-invasive delivery: Buccal patches offer a non-invasive approach to drug administration, which proves advantageous for individuals who may have reservations or limitations about injections or oral intake of medications.[136]

B. Avoidance of first-pass metabolism: Delivering drugs through the buccal mucosa allows them to bypass the liver's first-pass metabolism, increasing their bioavailability and efficacy.[137]

C. Consistent drug delivery: Buccal patches are designed to attain controlled and sustained drug release, ensuring consistent levels of the drug in the bloodstream for an extended period. This characteristic aids in maintaining steady plasma concentrations of the drug over a prolonged duration.[138]

D. Improved patient compliance: Since buccal patches are easy to use and require minimal effort, they may improve patient compliance with medication regimens.[139]

E. Fewer side effects: By bypassing the gastrointestinal tract and liver, buccal patches can reduce the likelihood of gastrointestinal side effects or drug interactions that may occur with oral medication.[140]

F. Faster onset of action: Drugs delivered via buccal patches can be absorbed more rapidly than oral drugs, resulting in a faster onset of action.[141]

G. Flexibility in dosing: Buccal patches offer the advantage of flexibility in dose delivery, as they can be designed to accommodate a wide range of drug doses. It makes them suitable for various therapeutic applications, from delivering low doses for hormone replacement therapy to higher doses for pain management. Moreover, these patches can be customized to achieve targeted drug release rates, offering precise control over the desired therapeutic effect. It makes them a promising drug delivery system for numerous medical conditions, including those that require frequent dosing or have a narrow therapeutic index.[142]

3.10　Disadvantages of Buccal Patch

A. Limited space: Buccal patches are typically small, limiting the amount of drug delivered at once. It may make them unsuitable for drugs that require high doses or have a large volume.[143]

B. Sensitivity of the mucosa: The buccal mucosa can be sensitive, and some patients may experience discomfort or irritation when using buccal patches. It can lead to reduced compliance with medication regimens.[144]

C. Adhesion issues: For effective drug delivery, buccal patches must adhere to the mucosa; however, achieving consistent and reliable adhesion may sometimes pose challenges. It can lead to inconsistent drug delivery or premature detachment.[145]

D. Difficulties in placement: Some patients may need help properly placing the buccal patch on the correct area of the mucosa, which can also lead to inconsistent drug delivery or reduced efficacy.[146]

E. Limited applications: While buccal patches are suitable for some drugs, they may not be appropriate for all therapeutic applications. It can limit their usefulness in certain clinical settings.[147]

4.　Evaluation Parameters Used For Buccal Patches

4.1　Physiochemical Evaluation

A. Surface pH
This parameter measures the pH of the patch surface in contact with the mucosa, which can affect drug release and irritation. One important parameter for evaluating the quality of buccal patches is the surface pH, which reflects the acidity or alkalinity of the patch surface. The surface pH of buccal patches plays a vital role as it influences drug stability, patient comfort, and the local conditions of the buccal mucosa. The surface pH can be measured using either a pH meter or pH paper. The patch is wetted with deionized water or buffer solution, and the pH of the surface is determined.[148] The surface pH of buccal patches usually falls within the range of 5.5 to 7.5, which closely aligns with the pH of the buccal mucosa. The surface pH of buccal patches holds significance as it can impact drug stability, influencing the degradation process of drug molecules. For example, some drugs are sensitive to acidic or alkaline conditions, and a patch with a pH outside the optimal range could cause degradation of the drug.[149] An acidic or alkaline patch could cause discomfort to the patient, leading to irritation or inflammation of the buccal mucosa.

B. Thickness measurement
Commonly utilized tools for determining buccal patch film density include digital vernier calipers with deviation or electronic micrometers. These instruments enable precise measurements and allow for density assessment at five specific points, encompassing the patch's center and four corners. Subsequently, an average value is calculated by considering these measurements.[150]

C. Weight uniformity/ weight variation
Evaluating weight uniformity or weight variation in buccal patches is a crucial aspect of quality control in pharmaceutical manufacturing. By employing techniques such as electronic balance, analytical balance, or automated systems, manufacturers can assess the consistency of drug content within the patches, ensuring reliable and predictable drug delivery. Adhering to established acceptance criteria for weight variation enhances patient safety, treatment efficacy, and regulatory compliance, ultimately contributing to the overall quality of buccal patch products.[151]

D. Folding endurance
Folding endurance is a crucial parameter determining the patch's ability to endure repeated folding without losing its integrity or breaking. The foldability of a patch refers to the number of times it can be folded in the same spot without experiencing breakage. This characteristic holds significant value in assessing the mechanical strength and resilience of buccal patches, as it reflects their capacity to endure handling and various stresses encountered during manufacturing, packaging, and transportation. A higher folding endurance indicates a stronger, more durable patch that is less likely to break or tear during use.[152] The folding endurance of buccal patches can be evaluated using different tests, including the Schopper, MIT, and Ross-Miles tests. These methods require the patch to be folded repeatedly along a single line until it

fractures, with the number of folds recorded as the folding endurance value. Various factors can affect the folding endurance of buccal patches, such as the quantity and type of polymer, drug concentration, patch thickness, and the manufacturing process. For example, increasing the polymer concentration or crosslinking can improve the patch's mechanical strength and folding endurance. Conversely, excessive drug loading or a thin patch may reduce the folding endurance and lead to patch failure.[153] Folding endurance is important for evaluating buccal patches' mechanical strength and durability. It reflects their ability to withstand handling and stresses during manufacturing, packaging, and transportation. Manufacturers should carefully consider the formulation and manufacturing process to optimize the folding endurance of buccal patches for safe and effective drug delivery.[154]

E. Thermal analysis study

Several thermal analysis techniques can be used in the evaluation of buccal patches:

Differential Scanning Calorimetry (DSC): Differential Scanning Calorimetry (DSC) is used to quantify the heat flow linked to phase transitions occurring in buccal patches, such as melting, crystallization, and glass transitions. Through DSC analysis, valuable insights can be obtained regarding the thermal stability of various components within the patch, including the active pharmaceutical ingredient (API) and the polymer matrix.

Thermogravimetric Analysis (TGA): TGA determines the thermal stability and composition of the buccal patch by measuring the weight change as a function of temperature. It helps in identifying the degradation temperature and evaluating the drug-polymer compatibility.[155]

Dynamic Mechanical Analysis (DMA): Dynamic Mechanical Analysis (DMA) is a method employed to evaluate the mechanical characteristics of buccal patches, including parameters like modulus, stiffness, and viscoelastic properties, as they vary with temperature. By utilizing DMA, valuable information regarding the mechanical behavior of the patch can be obtained, aiding in the assessment of its performance and suitability for drug delivery. It provides information on the patch's ability to withstand deformation and its potential for drug release upon application.[156]

Hot Stage Microscopy (HSM): HSM combines microscopy with controlled heating to observe the behavior of the buccal patch at elevated temperatures. It allows for the identification of melting, recrystallization, or changes in physical appearance, which can affect the drug release mechanism.[157]

F. Morphological Characterization

Analyzing morphological characteristics is essential in assessing buccal patches, as it offers valuable insights into the physical arrangement, surface attributes, and interrelationships present within the patch system. This characterization aids in understanding the structural properties and potential interactions within the patch, facilitating the evaluation of its performance and effectiveness in drug delivery. Researchers can assess the patch components' uniformity, integrity, and compatibility by studying the morphology, including the drug, polymer matrix, and additional excipients.[158] Here are some common techniques used for morphological characterization of buccal patches.

Scanning Electron Microscopy (SEM): SEM is extensively utilized for the high-resolution examination of the surface morphology of buccal patches. This technique allows for detailed observation and analysis of the patch's surface features at magnifications, providing valuable insights into its microstructure and topography. It enables the visualization of the patch structure, including the distribution of drug particles, polymer matrix, and any surface irregularities. SEM can provide information about the patch's porosity, roughness, and interfacial characteristics.[159]

Optical Microscopy: Optical microscopy is a versatile technique that allows observing buccal patches at lower magnifications. It provides a general overview of the patch's macroscopic appearance, including its shape, size, and homogeneity. Optical microscopy can identify any visible defects or inconsistencies in the patch formulation.[160]

Atomic Force Microscopy (AFM): AFM is a high-resolution imaging technique that provides detailed information about the topography and surface properties of buccal patches at the nanoscale level. The assessment of patch roughness, surface texture, and mechanical properties, along with the examination of interactions between the patch and buccal mucosa, can be facilitated using this method.[161]

Transmission Electron Microscopy (TEM): TEM, a highly effective imaging technique, enables the high-resolution visualization of the internal structure of buccal patches. Through this method, it becomes possible to gather insights regarding the dispersion of drug particles, polymer morphology, and any defects or non-uniformities in the patch.[162]

Confocal Laser Scanning Microscopy (CLSM): CLSM combines laser scanning microscopy with fluorescent labeling techniques to visualize specific components or interactions within buccal patches. It can be used to study the distribution of drug molecules, assess the permeation of drugs through the patch, or examine the release behavior of encapsulated materials.[163]

G. Drug content uniformity

This parameter measures the amount of drug in the patch and ensures that it meets the specified dosage. The evaluation of drug content is a critical parameter in ensuring the quality and efficacy of buccal patches. Evaluating drug content in buccal patches is critical to determining the amount of drug available for delivery to the systemic circulation. The drug content is evaluated based on several parameters, including loading, release, and permeation. The drug loading of a buccal patch refers to the quantity of drug included in the patch.[164] Multiple techniques are available for evaluating drug loading, including high-performance liquid chromatography (HPLC) and ultraviolet-visible (UV-Vis) spectroscopy. HPLC is frequently used for drug quantification as it is a highly accurate and precise method with high sensitivity. Determining drug loading in buccal patches can also be performed using UV-Vis spectroscopy, which is particularly useful for drugs exhibiting absorption at specific wavelengths. Drug release refers to the quantity of drug released from the buccal patch within a defined timeframe. The drug release rate is a critical parameter to determine the efficacy and safety of the buccal patch. The drug release is evaluated using various techniques, including dissolution testing, HPLC, and UV-Vis spectroscopy. Dissolution testing is a widely used method for assessing drug

release from buccal patches. HPLC and UV-Vis spectroscopy techniques are employed to determine drug release from buccal patches. Drug permeation refers to the movement of drugs from a buccal patch across the buccal mucosa and into the systemic circulation.[165] Accurately determining the drug permeation rate is crucial to evaluate the bioavailability of the drug. Various techniques, such as the Franz diffusion cell, HPLC, and UV-Vis spectroscopy, assess drug permeation from buccal patches. Among these techniques, the Franz diffusion cell is frequently used for drug permeation evaluation, and HPLC and UV-Vis spectroscopy are alternative methods for determining drug permeation from buccal patches.[166]

H. *Measurements of mechanical properties*

The elongation at break is measured using the Wilhelmy plate method on a specialized microprocessor-based tensile strength tester to assess the mechanical properties of buccal patches. A film clip with dimensions of 60 x 10 mm is prepared and positioned between two clamps, which are spaced 3 cm apart. The upper clamp securely holds the strip in place during the test, preventing any crushing, while the bottom clamp remains fixed, ensuring no movement occurs. The strip is subjected to a constant clamping rate of 2 mm per second until it reaches its breaking point. The force exerted on the film and its corresponding length are accurately recorded at the moment of breakage.[167]

$$Tensile \frac{strength\ at\ break\ (kg)}{Initial\ cross-sectional\ area\ of\ the\ sample\ (cm2)\ h}$$

Percentage elongation refers to the elongation and deformation experienced by the buccal patch when subjected to tensile stress. To assess the flexibility of the polymers, a texture analyzer is employed. The ductility value is calculated using the following formula.[168]

$$Percentage\ Elongation = \frac{Increase\ in\ length * 100}{Original\ length\ (cm2)}$$

I. *Swelling index study*

This parameter measures the degree of swelling of the patch in contact with saliva, which can affect drug release and adhesion. The swelling index is defined as the ratio of the increase in weight of the buccal patch after immersion in a liquid to its original weight. The swelling index of buccal patches provides important information about their swelling behavior, which is essential for determining their adhesion, drug release, and bioavailability. The swelling index is defined as the percentage increase in the weight of the patch after immersion in a swelling medium, usually simulated saliva or phosphate buffer solution, for a specific period. The swelling index is calculated using the following formula.[169]

$$Swelling\ index\ \% = \frac{Wt - Wo}{Wo} * 100$$

Here, the weight of the swollen patch after immersion in the swelling medium is represented as Wt, while Wo indicates the initial weight of the dry patch before immersion. The swelling index evaluation of buccal patches can be performed using various methods, such as gravimetric and thickness measurements. The gravimetric method involves measuring the weight of the patch before and after immersion in a liquid. In contrast, the thickness measurement method involves measuring the thickness of the patch before and after immersion in a liquid. The swelling index is calculated as the ratio of the increase in weight or thickness to the original weight or thickness.[170]

4.2   Ex - Vivo Evaluation

A. *Ex-vivo mucoadhesive strength*

The ex vivo evaluation of mucoadhesive strength in buccal patches involves the assessment of the adhesive characteristics between the patch and the buccal mucosa. This evaluation provides valuable insights into the patch's capability to adhere to the mucosal surface and withstand the forces encountered within the oral cavity. Several methods can be employed to evaluate mucoadhesive strength:

Texture Analyzer Method: A texture analyzer equipped with a probe (e.g., a cylinder or disc) is utilized to measure the force necessary for detaching the buccal patch from the mucosal tissue. The patch is applied to the mucosa, and the probe is pulled away at a specified speed. The highest force required to

detach the patch is documented as the mucoadhesive strength.[171]

Instron Method: An Instron testing machine commonly measures mucoadhesive strength. The buccal patch is affixed to the mucosal surface, and a controlled force is applied perpendicular to the patch-mucosa interface. The mucoadhesive strength is determined by recording the force needed to detach the patch.[172]

Rheological Method: A rheometer measures the adhesive force between the buccal patch and the mucosal tissue. The patch is attached to the rheometer, while the mucosa is fixed to a stationary platform. The rheometer applies a controlled strain or stress to measure the adhesive strength of the patch.[173]

Shear Method: The shear strength of the interaction between the buccal patch and mucosa is evaluated using a dedicated apparatus. This method involves positioning the patch between two parallel plates, with one plate connected to a movable platform. A shear force is applied, and the force needed to separate the patch from the mucosal surface is measured as the mucoadhesive strength.[174]

B. *Ex- vivo mucoadhesion time*

In the assessment of ex-vivo mucoadhesion duration, a customized USP disintegration apparatus (pH 6.2) breakdown method is utilized. Surgical scissors carefully separate The mucosal membrane from the underlying connective tissues.

Before stimulating saliva is applied, the mucosal membrane is rinsed with deionized water (pH 6.2). A porcine buccal mucosa sample with a diameter of 3 cm is affixed to a glass surface. One side of the buccal patch is moistened with artificial saliva (pH 6.2) using a fingertip and gently compressed for a few seconds. While the glass slab is allowed to move vertically up and down, the disintegration apparatus's vertical shaft remains fixed, cycling at a rate of 25 cycles per minute. The lower portion of the patch is coated with simulated saliva, while the upper portion remains unexposed to the liquid. The ex-vivo mucoadhesion duration is determined as the time taken until the patch completely detaches from the mucosal surface, losing its attachment.[175]

C. *Ex-vivo permeation studies*
It was conducted using a Franz diffusion cell at two different temperatures, namely 37°C and 5°C. The receptor compartment of the cell was filled with a phosphate solution containing a magnetic bead with a pH of 6.8. The system was clamped together after covering the mucosa with the buccal patch. A magnetic stirrer was employed to maintain hydraulic performance, running at a speed of 50 rpm within the chamber. Flow across the membrane was determined using formula-based calculations, where J represents the flow rate[176]

$$J = \frac{dQ}{A * dt}$$

Here, The slope of the stable portion of the curve is denoted as dQ/dt, while A represents the diffusion area in units of mg h-1 cm2.

D. *Ex vivo bio adhesion test*
To perform adhesion tests, dissolution cells are utilized, which can involve techniques such as colloidal gold staining or fluorescence probes. In the case of evaluating adhesion on gingival mucosa, an open vial with a lip is employed to maintain a pH level of 6.8. A glass vial is positioned as close to the mucosa's surface as possible within a glass beaker to experiment. The beaker is filled with phosphate buffer at pH 6.8 and maintained at 37°C with a precision of 1°C. The buccal patch is affixed to a rubber stopper using cyanoacrylate adhesive. A two-pan balance evenly distributes a 5g weight between the pans. After removing the 5g weight from the left-side pan, the pan connected to the patch is placed on the mucosa. This process requires a face-to-face contact time of 5 minutes. The adhesive strength is determined by weighing the patch on the mucosal surface and dividing that weight by the weight of the patch itself.[177]

4.3   In vitro evaluation

A. In-vitro residence time

A modified USP dissolution test equipment is employed to ensure accurate measurements of this parameter. In this case,

a pH 6.8 phosphate buffer with a volume of 800mL is used as the experimental medium. The mucoadhesive patch is hydrated on one side using the phosphate buffer and positioned onto a glass slab. Subsequently, the patch is immersed in the buffer solution and raised to a position where it is fully exposed to the surrounding air with the help of a vertically mounted glass slab. The time taken for the patch to detach from the glass slab completely is recorded to determine the in-vitro residence duration.[178]

B. In-vitro drug release
Franz diffusion cells or Keshary Chien cells were employed to investigate the buccal patch profile, utilizing a dialysis membrane with a 0.45-pore size, such as a cellophane membrane. In the receptor compartment, which had a capacity of 16 ml, a phosphate buffer solution with a pH of 6.8 containing a magnetic bead was placed. A dialysis membrane was positioned between the donor and recipient chambers. A magnetic stirrer operating at 50 rpm maintained hydrodynamics within the system. At predetermined intervals, 1 ml samples were collected, and a UV spectrophotometer with a pH 6.8 phosphate buffer was utilized to determine the drug content. The flux value was calculated using the provided equation.[179]

$$flux = \frac{Amount\ of\ drug(mg)}{Time\ (hours)} * Area(cm2)$$

C. Stability study in human saliva
To evaluate the stability of the buccal patch, a study is carried out using human saliva. Human saliva is collected and distributed into individual Petri dishes containing five milliliters of saliva. The buccal patches are then placed into the dishes, and the plates are incubated at 37°C for six hours. Throughout the incubation period, the patches are visually inspected regularly to observe any color, shape, and pharmaceutical content alterations.[180]

5.   RECENT DEVELOPMENTS IN BUCCAL PATCH

Recently, buccal patches have garnered significant interest as a prospective drug delivery system, primarily due to their ability to address limitations associated with alternative routes of drug delivery. Recent progress in buccal patches has been concentrated on enhancing drug delivery efficacy, improving

the rate of drug release, and prolonging the duration of drug release.[181]

A. Development of mucoadhesive buccal patches:
Mucoadhesive polymers have significantly improved the adhesion and drug delivery efficiency of buccal patches. Buccal patches can be developed using synthetic and natural mucoadhesive polymers, such as chitosan, sodium alginate, polyvinylpyrrolidone, etc. These polymers aid in increasing the patch's retention time on the buccal mucosa, ensuring sustained drug delivery, and improving bioavailability.[182]

B. Nanoparticle-based buccal patches:
The utilization of nanoparticles as a drug delivery system has attracted considerable interest owing to their ability to accommodate a large drug payload, exhibit sustained release properties, and enhance bioavailability. As a result, researchers have explored the incorporation of nanoparticles into buccal patch

formulations to enhance drug delivery efficiency and optimize therapeutic outcomes. Nanoparticles such as liposomes, solid lipid nanoparticles, and polymeric nanoparticles have been integrated into buccal patches for various drugs, including anti-inflammatory agents, analgesics, and antiemetics.[183]

C. Combination buccal patches: The development of combination buccal patches incorporating two or more drugs has been explored to improve treatment outcomes and patient compliance. Simultaneous delivery of multiple drugs with diverse pharmacokinetic properties is possible with these patches, which can help achieve optimum drug concentrations and improve the overall therapeutic efficacy. Combination buccal patches have been developed for various indications, such as pain management, hormone replacement, and antihypertensive therapy.[184]

D. Buccal patches for pediatric use have been developed as an alternative to traditional oral medications. These patches provide a non-invasive drug delivery route that is more convenient and less painful than injections. Buccal patches have been developed for pediatric use for various drugs, such as antiemetics, antibiotics, and analgesics.[185]

E. Controlled drug release buccal patches: Controlled drug release buccal patches have been developed to improve drug delivery efficiency and ensure sustained drug release over an extended period. Controlled drug-release buccal patches can be formulated using technologies like osmotic pumps, ion exchange resins, and hydrogels. These patches have been developed for various drugs, including opioids, antihypertensives, and antipsychotics.[186]

S.no	Brand Name	Active Drug	Uses	Manufacturer
1	NicoDerm CQ	Nicotine	Stop Smoking	Pharma Intelligence UK Limited.
2	Anadrol-50	Androgen	Hormonal Agent	Thomson Healthcare
3	Fentora 800mcg	Fentanyl	Alleviating pain in individuals with cancer.	Merck Pharmaceutical
4	Breaky 400mcg	Fentanyl	Alleviating pain in individuals with cancer.	MEDA Pharma GmbH & Co. KG
5	Fentanyl MTX Patch	Fentanyl	Reduce Pain in Cancer Patients	Sandoz A Novartis Company

Table 5. Marketed Formulation of Buccal Patch[187]

Table 5 shows the information provided in the previous paragraph regarding the brand names, active drugs, uses, and manufacturers based on general knowledge and publicly available information. It is important to note that specific details and product information may vary, and it is always recommended to consult the relevant product labeling, healthcare professionals, and authoritative sources for accurate and up-to-date information regarding brand names, active drugs, uses, and manufacturers of pharmaceutical products.

Table 6. Patents of Buccal Patch

Patent Buccal Patch	Description	Applicant	Patent No.
Desmopressin buccal patch composition	Desmopressin is combined with a matrix to create a buccal patch designed to adhere to the mucosa in the mouth. This patch releases desmopressin into the bloodstream via transmucosal absorption.	East Riding Laboratories	US5298256A[188]
Transmucosal formulations of levosimendan	Levosimendan, or a pharmaceutically acceptable salt of levosimendan, can be administered to a patient via transmucosal routes, particularly targeting the oral or nasal mucosa. In this method, it is crucial to maintain continuous contact between a source of levosimendan and an intact mucous membrane for a substantial duration to administer levosimendan effectively. Furthermore, the transmucosal preparations of levosimendan are extensively described.	Orion Corporation	WO1999032 081A1[189]
Canker sore patch	A canker sore treatment patch comprising a mucoadhesive and protective layer has been developed. As detailed in the description, the protective layer is equipped with a pressure-sensitive adhesive layer.	Coloplast AS	US20110160 634A1[190]
Soft, adhesive, soluble oral patch	A soft and adherent oral patch designed for the topical administration of medicated substances incorporates a hydrophilic polymer that transforms into a liquid state in the mouth, aligning with human body temperatures. This particular polymer undergoes gelation slightly below the temperature of the oral cavity. The oral patches possess a mesh-	Halley Jaffrey.T	US20030124 178A1[191]

	like structure that gradually dissolves in saliva while maintaining a solid form within the mouth. The network's pores contain the hydrophilic polymer and the desired medicament. Creating the oral patch involves combining and hydrating the materials, subjecting them to a temperature just below boiling point, and cooling them to form a gel-like consistency.		
A Water-soluble pharmaceutical Patch with enhanced stability	A moisture-stabilized Oral Thin Patch, designed for the oral administration of an active component, is developed to maintain its structural integrity without sticking or curling when exposed to 70% relative humidity at 25°C for 2 minutes up to 2 hours. Additionally, a method for producing this Oral Thin Patch is disclosed, including various active ingredients such as pharmacological, nutraceutical, or cosmetic components.	Zim Laboratories Ltd.	WO2015083 181A3[192]

Table 6 shows the information provided in the previous paragraph regarding the patent buccal patches, their descriptions, applicants, and patent numbers based on publicly available information from various sources. It is important to note that patent details may vary, and it is recommended to consult official patent databases, legal resources, and authorized sources for accurate and up-to-date information regarding patent buccal patches, including their descriptions, applicants, and patent numbers.

6. Patient Compliance with Buccal Patch for The Management of Diabetes.

Patient compliance with buccal patches for treating diabetes is crucial for ensuring effective therapeutic outcomes. Compliance refers to the extent to which patients adhere to the prescribed medication regimen, including the proper application and duration of buccal patch usage. Maintaining high patient compliance is particularly important in managing chronic conditions like diabetes, as it directly impacts treatment efficacy and overall disease management.[193] Buccal patches offer several advantages that can improve patient compliance. Firstly, they provide a non-invasive and convenient route of drug administration, eliminating the need for injections or frequent oral dosing. This ease of use can positively influence patient acceptance and willingness to adhere to the prescribed therapy.[194] Additionally, buccal patches often offer controlled and sustained drug release, requiring less frequent application than conventional dosage forms. It reduced dosing frequency can simplify the treatment regimen and improve patient compliance. Furthermore, buccal patches may enhance patient compliance by minimizing the potential side effects of other administration routes. By avoiding gastrointestinal metabolism and bypassing the first-pass effect, buccal drug delivery can reduce the likelihood of systemic adverse effects, which may positively impact patient adherence to therapy.[195] To promote patient compliance with buccal patches for diabetes treatment, healthcare providers play a crucial role. Clear and comprehensive instructions on patch application, removal, and replacement should be provided to patients. Educating patients about the benefits of buccal patch therapy, potential side effects, and the importance of consistent adherence can also improve compliance. Additionally, regular follow-up appointments and open lines of communication with healthcare providers can support patients in addressing any concerns or challenges related to using buccal patches.[196]

7. CONCLUSION

In conclusion, the utilization of buccal patches presents a promising approach to the treatment of diabetes. These patches offer a range of advantages, including convenient administration, non-invasiveness, bypassing first-pass metabolism, and enhancing patient adherence. Preclinical and clinical studies have shown encouraging outcomes when using buccal patches for diabetes treatment, demonstrating improved drug delivery and enhanced glycaemic control in certain cases. Nevertheless, further investigation is necessary to optimize formulation techniques, address drug stability and permeability challenges, and establish the long-term safety and efficacy of buccal patches for managing diabetes. As formulation technology progresses and our understanding of the underlying mechanisms deepens, buccal patches hold substantial potential in revolutionizing diabetes treatment and contributing to better patient outcomes. Thus, buccal patches represent a promising and innovative drug delivery system for diabetes management, and future research in this field may unveil new possibilities for effective diabetes treatment in the coming years.

8. AUTHOR CONTRIBUTION STATEMENT

6. CONFLICT OF INTEREST

Conflict of interest declared none.

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