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Significance and Advantages of Buccal Film for Diabetes Management: Biocompatibility and Safety Considerations

1. Mr. Surya Prakash 2. Mr. Pravin Kumar Sahu 3. Ms. Geetanjali sahu

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ABSTRACT: Buccal film technology has emerged as a promising approach for diabetes management due to its unique advantages over conventional dosage forms. This review paper explores the significance of buccal films in diabetes management, highlighting their benefits, challenges, and potential applications. Additionally, we delve into the biocompatibility and safety considerations associated with buccal films, addressing concerns related to patient acceptability and long-term use. The review emphasizes the need for further research and development to fully harness the potential of buccal films in revolutionizing diabetes treatment. Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder characterized by insulin resistance and impaired glucose regulation. The conventional oral antidiabetic medications for T2DM have limitations such as poor patient compliance, gastrointestinal side effects, and hepatic first-pass metabolism. Buccal film formulations have emerged as a promising alternative for the improved management of T2DM, offering direct drug absorption through the buccal mucosa, bypassing the gastrointestinal tract and hepatic metabolism. This review paper aims to discuss the development and evaluation of buccal film formulations for the effective and convenient treatment of T2DM, focusing on formulation strategies, drug candidates, evaluation techniques, patient compliance, and future perspectives.

Keywords: Buccal film, evaluation, diabetes management, drug delivery, biocompatibility, safety considerations.

I. INTRODUCTION

Diabetes mellitus is taken from the Greek word diabetes, meaning siphon - to pass through and the Latin word mellitus meaning sweet. A review of the history shows that the term "diabetes" was first used by Apollonius of Memphis around 250 to 300 BC. Ancient Greek, Indian, and Egyptian civilizations discovered the sweet nature of urine in this condition, and hence the propagation of the word Diabetes Mellitus came into being.[1] Diabetes is a chronic disease that develops when the pancreas either produces insufficient amounts of insulin or when the body uses its own insulin inefficiently. A hormone is insulinthat aids in blood sugar regulation. [2] Uncontrolled diabetes results in hyperglycemia, or high blood sugar, which over time seriously harms numerous bodily systems, including the blood vessels and neurons. [3]

Diabetes mellitus (DM) is a metabolic condition marked by unnecessarily high blood glucose levels. Type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes from endocrinopathies, steroid use, etc. are among the different types of DM. [4] Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) are the two primary subtypes of DM, and both are typically brought on by defects in insulin secretion (T1DM) and/or action (T2DM). T2DM is expected to affect middle-aged and older individuals who have chronic hyperglycemia as a result of poor lifestyle and nutritional choices, whereas T1DM is thought to manifest in children or teenagers. Since the pathophysiology of T1DM and T2DM is very diverse from one another, each type has a separate etiology, presentation, and course of treatment.[5]

1.1 Pathophysiology of diabetes mellitus

Several hormones work together to keep the body's level of glucose in equilibrium. However, insulin and glucagon, two hormones, dominate in the control of glucose homeostasis. Beta cells release insulin when the level of glucose increases. Insulin lowers blood glucose levels by either

a) Decreasing the liver's ability to produce glucose through the processes of glycogenolysis and gluconeogenesis, or

b) Boosting the absorption of glucose by the liver, muscles, and adipose tissue. [6]

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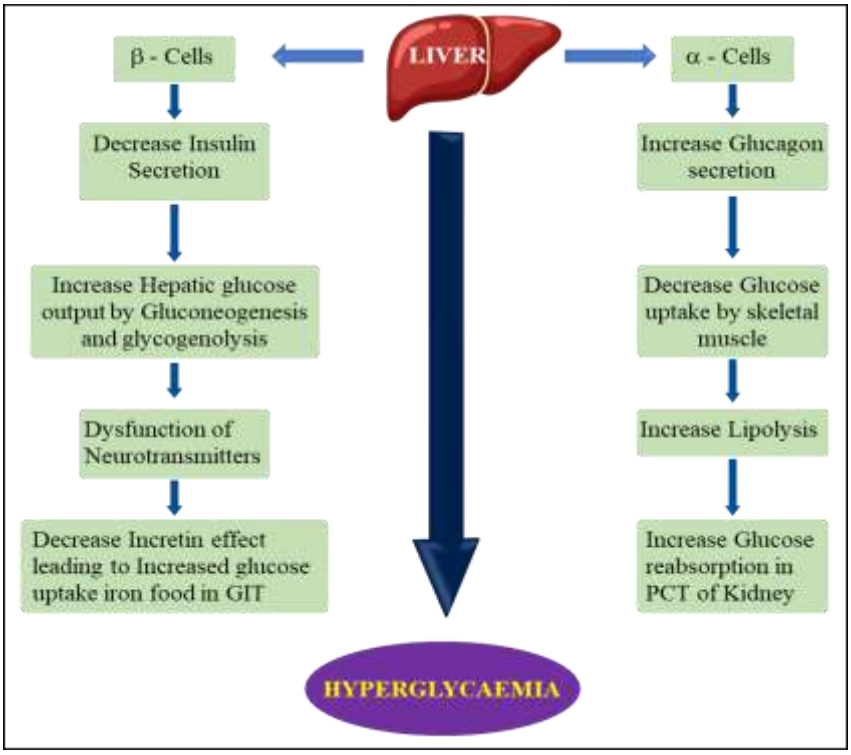

Fig.1: Pathophysiology of Type-II diabetes

II. CLASSIFICATION OF DIABETESMELLITUS

Diabetes is a long-lasting endocrine disorder, which is indicated by increased blood glucose levels due to insulin deficiency in the body [7]. Insulin and glucagon are the main hormones that control glucose homeostasis in the body. Rising blood glucose levels stimulate pancreatic β-cells to secrete insulin, resulting in decreased blood glucose levels. Low glucose levels affect pancreatic α-cell glucagon secretion and increase blood glucose levels [8]. Genetic predisposition, sedentary lifestyle and obesity are the three major risk factors for diabetes mellitus. **[9]**

2.1 Type-I diabetes mellitus

The manifestation of type-I diabetes affects nearly 5–10% of the whole diabetic population. The pathogenesis of this disease includes the devastation of β-cells by the instinctive and adaptive immune systems [7]. This is insulin-dependent and named "juvenile diabetes" because it occurs at a young age. It is treated with insulin only. Here, genetic predispositions are the primary cause of the occurrence of this disease. The patients suffering from type-I diabetes are prone to Graves' disease, celiac sprue, vitiligo, pernicious anemia, Addison's disease, Hashimoto's thyroiditis, myasthenia gravis, and autoimmune hepatitis. [10]

2.2 Type-II diabetes mellitus

Type-II diabetes mellitus (T2DM) is one of the most prevalent type of metabolic disorder across the globe, and the development of this disease is generally caused by the combination of two factors, namely, abnormal insulin secretion by the β-cells of the pancreatic and the inability of the tissues to respond to insulin. Worldwide, more than 90% of the diabetes mellitus cases are T2DM. The main drivers that lead to T2DM becoming an epidemic are high-calorie diets, sedentary lifestyles, obesity, and population aging. Also, patients with a previous medical history of dyslipidemia, hypertension, or any type of gestational diabetes mellitus have become more vulnerable to this disease. [11]

2.3 Latent Autoimmune Diabetes in adults (LADA)

This type of diabetes seen in the patients having autoantibodies which are reactive towards the islet antigens. Near about 10% of the type II diabetic patients are having at least one of this type of autoantibodies. It is an autoimmune disease

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that's why the patients shows both the immunological and genetic similarity with the type I diabetes but the distinguishing characterization are genetic susceptibility, T cell reactivity and autoantibody clustering. Due to the β-cell destruction and higher resistance of insulin the diabetes occurs at a very early stage in adults. The immunomodulator therapy is the only process which have some potential against this disease. [12]

2.4 Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus is a chronic hyperglycemia which occurs in the gestation period of pregnant women having previously undiagnosed diabetes. This type of hyperglycemia is generally occurring due to the dysfunction of β-cell of pancreas which results into weakening of glucose tolerance and resistance of insulin. [13] The main factors responsible are obesity and overweight due to maternity, higher age of maternity, previous personal or family history of any form of diabetes. There are various long-term risk factors associated with the GDM likely, cardiovascular diseases of both mother and the child, birth complications and irregular glucose metabolism. The basic treatment of GDM includes improvement of diet and physical activity. Insulin, glibenclamide and metformin are also used for regulating the hyperglycemia [14].

III. INSULIN

The development of insulin as a medicinal drug in 1921 signified a revolution in the treatment of diabetes mellitus, particularly Type 1. [15]

3.1 Oral insulin

It is widely known that the oral route of administering insulin is the most accommodating for patients. The bioavailability of a common oral formulation of insulin, according to Ansari et al., is less than 1%. This low oral bioavailability was shown to be caused by inactivation by proteolytic enzymes in the gastrointestinal tract and low intestinal membrane permeability. [16]

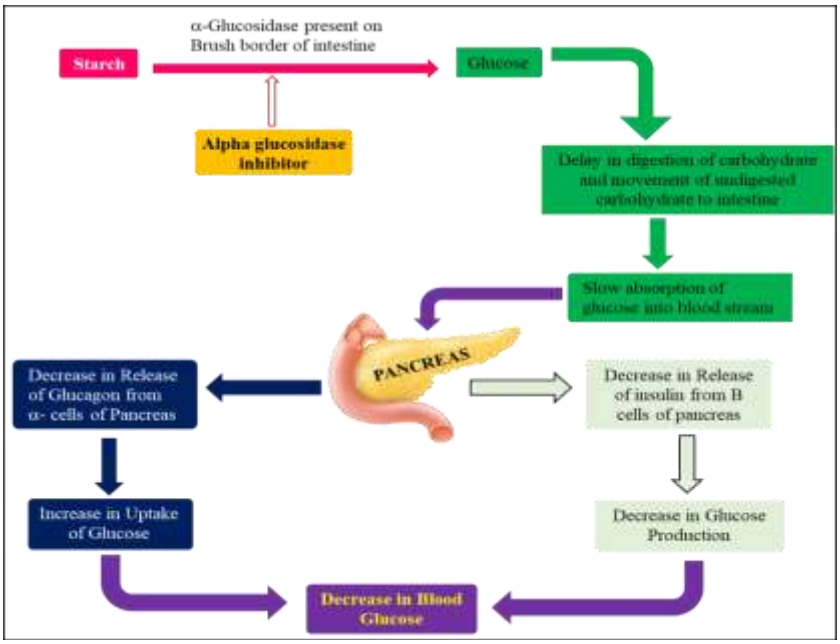

Fig. 2: Mechanism of action of Insulin

3.2 Transdermal insulin

Ahad et al. [17] in their review work on the delivery of insulin via skin route for the management of diabetes mellitus stated that effective insulin delivery through the skin is usually hindered by the intrinsic, protective properties of the intact skin. Accordingly, therapeutics with low molecular weight (<500 Da) can easily penetrate the skin, while the passive transport of protein drugs with higher molecular weight, such as insulin, is significantly restricted. It was however clarified that various approaches can now be explored to enhance the transport efficiency of insulin molecule across the skin to improve the drug delivery. [18]

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3.3 Buccal insulin

Comparable to oral insulin, buccal insulin has the advantage of avoiding gastrointestinal breakdown. Oral-lynTM, the first buccal insulin spray, was created as a liquid short acting insulin formulation that can be applied with Generex'sRapidMistTM metered dosage aerosol applicator. [17] It was reported in the work of Olorunsola et al. [18] Those early clinical trials were quite successful, but the companies involved in the development later found it difficult to agree to complete the phase three and phase four clinical trials. Oralazine, another buccal insulin, has been investigated in patients with type 2 diabetes. The pharmacodynamic and pharmacokinetic properties and clinical trials are also reviewed, as reported in the paper by Wei et al. [19]. This buccal insulin preparation was stated to be suitable for the treatment of postprandial hyperglycemia without risk of hypoglycemia. The research work by Rubin et al. [20] demonstrated the formulation of insulin as adjunctive therapy to oral hypoglycemic agents without success in subjects with type 2 diabetes. This work included the development of an oral film formulation of insulin. The dosage form was created using a soluble polymer that served to allow dissolution for 20 minutes and a hydrophilic bioadhesive polymer to ensure sustained drug release every 24 hours. The mucosal tissue was adhered by the thin film dosage form to allow efficient drug delivery. According to Mane et al. [21] Sustained or continuous release of buccal insulin is not harmful; And the side effects are not necessarily related to the administration and absorption of insulin, but to other excipients that are added to facilitate its absorption. In addition, since the cheek mucosa is more permeable and highly vascularized, but not keratinized, sustained drug release is facilitated.

IV. BUCCAL DRUG DELIVERY SYSTEM

As the mouth cavity offers prospective sites for medication delivery, the buccal controlled drug delivery system has been created. Acid hydrolysis and first pass metabolism are bypassed. Saliva production is a factor in how well drugs are released through the buccal film. The oral mucosa's mucin film provides a chance for the development of a mucoadhesive system, which stays at the absorption site for a long period through mucoadhesion. More of the medicine is absorbed thanks to close contact with the absorption membrane. With the proper dosage form design and composition, the medication is unaffected by the pH of the buccal cavity. It is possible to regulate and manage the buccal mucosa's permeability and local environment to allow for medication permeation.[22]

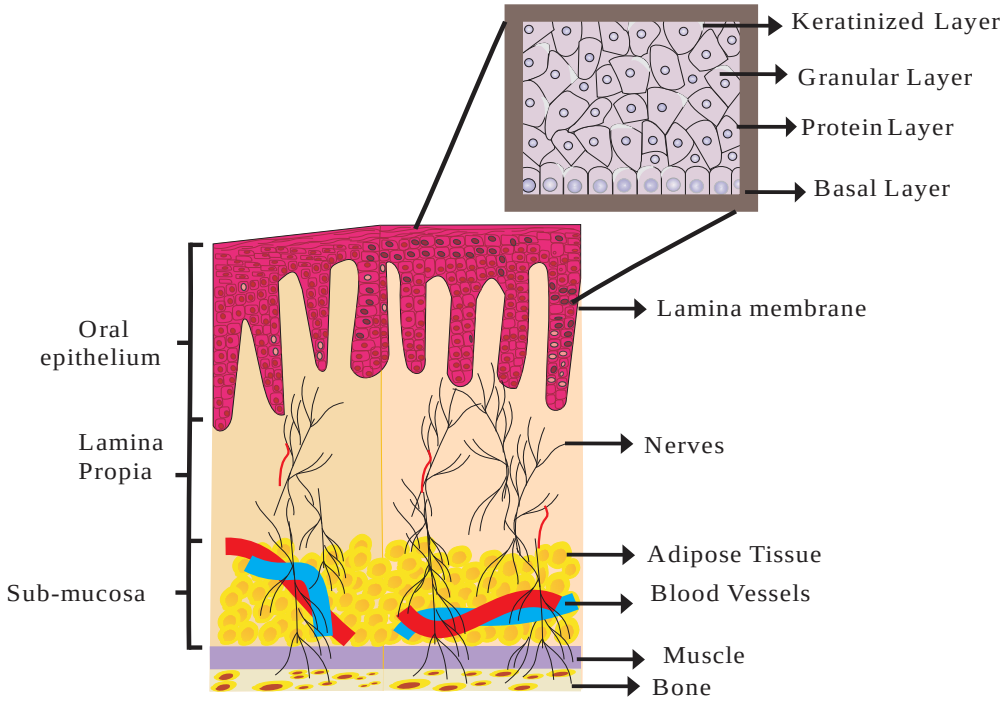

Fig. 3: Layers of the oral mucosa

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A. Tablets with buccal mucoadhesive

The buccal mucosa absorbs moisture from buccal mucoadhesive tablets, which are dry dosage forms. An illustration would be a double-layered tablet with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate) and an adhesive matrix layer made of HPC and polyacrylic acid. [23]

B. Films and Patches

Buccal patches are made of two laminates. First, an impermeable backing sheet is cast with an aqueous solution of the adhesive polymer before being cut into the required oval form. [23]

4.1 Methods of preparation of buccal drug delivery system

Buccal film formulation is mainly prepared by following three methods

4.1.1. Solvent Casting Method

In the solvent casting method, the required amount of polymer is added and dissolved in distilled water. A small amount of active pharmaceutical ingredient is added to this solution. Plasticizer is added to the suspension and shaken well. The solution is then poured into petri dishes and placed in a hot air oven to dry at 400°C. After drying, remove it from the petri dish by cutting it with a blade and keep it in a desiccator for 24 hours. From now on cut to the required size and shape. [24]

Steps Involved in the Solvent Casting Method

Step 1: Preparation of the casting solution

Step 2: Dilution of the Solution

Step 3 - Transfer the appropriate amount of dough to the mold

Step 4: Drying the foundry slurry

Step 5: Cut the final dosage form to contain the desired amount of medication.

4.1.2. Hot Melt Extrusion Method

In the hot melt extrusion method, a mixture of drug and other excipients is melted. It is then forced through the hole to obtain a more homogeneous material in various sizes such as granules, tablets or films. It is used for transdermal drug delivery systems.[25]

Steps Involved in the Hot Melt Extrusion Method

Step 1: the drug is mixed with the vehicles in solid form

Step 2: The heated extruder melts the mixture

Step 3 – Finally, the molten mix is formed into a film by the die

4.1.3. Direct Milling Method

This method is solvent free method. In this method, the drug and excipients are mixed directly by milling or kneading without the presence of liquid. Then the resulting material is rolled out on a non-stick coating to the required thickness. This method is generally preferred because there is no potential for residual solvent and no association with solvent-related health problems. [26]

4.1.4. Semisolid Casting Method

Semisolid casting is a commonly employed method for situations where acid-insoluble polymers are used. This technique involves creating a solution of a water-soluble film-forming polymer, which is then poured into a solution of an acid-insoluble polymer prepared in sodium or ammonium hydroxide. To achieve the desired gel mass, a plasticizer is introduced. The amount of plasticizer added significantly impacts the properties of the resulting gel mass. Subsequently, the gel mass is cast into films or ribbons using heat-controlled rollers or drums. It is essential to maintain the right balance between the acid-insoluble polymer and the film-forming polymer, typically at a ratio of 1:4, to achieve optimal results. The films produced through this method have a thickness ranging from 0.015 to 0.05 inches.[27]

4.1.5. Solid Dispersion Extrusion

Solid dispersion extrusion is a specialized technique used to enhance the dissolution rate and bioavailability of poorly water-soluble drugs. It involves the dispersion of active pharmaceutical ingredients (APIs) in an inert carrier, typically a hydrophilic polymer, in a solid state. The aim is to improve the drug's solubility and dissolution characteristics, leading to better absorption and therapeutic outcomes. The process begins by dissolving the drug in a suitable liquid solvent to form a drug solution. Subsequently, this solution is incorporated into the melt of polyethylene glycol (PEG) at temperatures below 70°C. Importantly, the liquid solvent is not removed during this step, ensuring that the drug and polymer form a homogenous mixture.PEG is a commonly used hydrophilic polymer due to its excellent solubilizing properties and biocompatibility. Its ability to form hydrogen bonds with the drug and create amorphous structures contributes to enhanced drug solubility. The drug-polymer blend is then shaped into a film by passing it through dies, forming a solid dispersion film.[28]

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4.1.6. Rolling Method

In this method, a pre-mix is prepared, which serves as the base for the film. The pre-mix consists of a film-forming polymer, a polar solvent, a plasticizer, and other excipients, except for the active drug. The active drug is later added to the pre-mix in a separate container, referred to as the master batch. The master batch and the required quantity of the pre-mix are combined and blended for a specific time to ensure uniform distribution of the drug. The resulting mixture is then fed to a roller, where a metering roller controls the film's thickness and applies the mixture evenly onto the roller's surface. The film is formed and carried away by a support roller, which helps maintain the film's structural integrity during the process. To control the dosage of the film, a specific amount of the matrix is fed into a pan through a second metering pump. The metering roller determines the film's thickness, ensuring accuracy in the final product. After the film is formed, it is in a wet state and needs to be dried to achieve the desired consistency and stability. Controlled bottom drying is utilized to remove the moisture from the film. During the drying process, it is essential to avoid the presence of external air, as exposure to air could compromise the film's quality and properties. Once the film is thoroughly dried, it is cut into various sizes and shapes according to the intended use and dosage requirements. The cutting process ensures that the final product is ready for packaging and distribution.[28]

4.2 Benefits of buccal drug delivery system

When compared to the vaginal, rectal, and ocular routes of medication administration, the buccal route exhibits superior patient acceptance, increasing the patient's compliance with the therapy because it is more convenient and comfortable. The benefits of buccal delivery include avoiding significant drug degradation caused by the high enzyme content and acid environment present in the gastrointestinal tract when drugs are absorbed in the intestine and avoiding hepatic first-pass metabolism. These benefits are made possible by the good blood irrigation of the oral cavity. Additionally, the gastric emptying does not affect the rate of drug absorption when supplied via the buccal route Permeation enhancers may also be included in formulations for poorly absorbed medications to increase their systemic availability without permanently harming the mucosa. [29]

4.3 Drawbacks of buccal drug delivery system

Despite its benefits, the buccal delivery method has drawbacks and limitations that make it difficult to give drugs. Not all medications are appropriate for buccal distribution; for example, medications that are unstable at the oral pH, have an unpleasant taste or odour, or may trigger allergic reactions should be avoided. The pace of drug absorption and its disposal by involuntary ingestion of the delivery system and food or drinks may reduce the amount of drug absorbed, lowering the blood concentration, which might not be sufficient to have a therapeutic effect. [30]

The surface area, permeability coefficient, and drug concentration present in the oral mucosa surface mucosa surface all affect how quickly a drug is absorbed.

4.4 Advantages of Buccal Film for Diabetes Management

4.4.1 Enhanced Bioavailability

Buccal films enable direct drug delivery into the systemic circulation through the highly vascularized buccal mucosa, avoiding first-pass metabolism. This results in improved drug bioavailability and more predictable pharmacokinetics compared to oral dosage forms. [31]

4.4.2 Rapid Onset of Action

Buccal films provide faster drug absorption, resulting in quicker onset of action. This attribute is particularly valuable in managing postprandial hyperglycemia and emergency diabetes treatment. [32]

4.4.3 Improved Patient Compliance

The ease of administration and pleasant taste of buccal films enhances patient compliance, particularly in cases of paediatric and geriatric populations who may have difficulty swallowing tablets or capsules. [33]

4.4.4 Dose Flexibility

Buccal films can be tailored to deliver precise doses of antidiabetic agents, allowing for personalized treatment regimens and fine-tuning of drug delivery based on patient requirements. [34]

4.4.5 Reduced Side Effects

Targeted drug delivery through buccal films can minimize systemic exposure to drugs, potentially reducing the occurrence of adverse effects associated with conventional dosage forms. [35]

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V. THE ROLE OF INSULIN IN TYPE 2 DIABETES

Despite the introduction of various new oral agents and non-insulin therapies, individuals with established type 2 diabetes often experience a progressive decline in beta cell function, leading to difficulties in glycemic control. Consequently, many patients eventually require insulin treatment. Exogenous insulin is commonly administered subcutaneously with the aim of mimicking healthy pancreatic function. Basal insulin is used for long-acting coverage, while short-acting injections are given with meals to control postprandial glucose levels. However, currently available insulin preparations have certain limitations. Hypoglycemia and weight gain are well-known and concerning side effects associated with subcutaneous insulin administration. [36]

5.1 Advancements in Insulin Delivery Technology

Despite significant advancements in oral drug therapy for the management of diabetes mellitus, injectable insulin remains the mainstay treatment due to the low bioavailability of orally administered drugs, primarily attributed to first-pass metabolism and degradation by gastrointestinal enzymes [37]. While parenteral insulin administration is effective, it comes with several limitations. Firstly, frequent insulin injections can lead to lower patient compliance due to the pain and discomfort experienced at the injection site. The ultimate objective of subcutaneous insulin therapy is to mimic normal physiological insulin levels to achieve normoglycemia. However, this goal is not always successfully met, mainly because of the altered absorption of insulin [38]. Additionally, the frequent injections can cause lipohypertrophy, a condition where fat tissue accumulates on the skin's surface, significantly delaying the absorption and reducing the bioavailability of insulin [39].

Lipohypertrophy can compromise the effectiveness of insulin therapy and negatively impact glycemic control. To address these challenges and improve insulin delivery, various efforts have been made to explore different routes of administration and the use of chemical and physical enhancers. The aim is to enhance the delivery of insulin while minimizing the discomfort and complications associated with frequent injections. By developing new formulations and delivery systems, researchers seek to improve the bioavailability and effectiveness of insulin therapy, allowing patients to achieve better glycemic control with reduced discomfort. Such advancements may lead to improved patient compliance and overall management of diabetes mellitus. [40]

5.2 Buccal Administration for Advancements in Insulin Delivery Technology

Buccal administration, as an alternative route for drug delivery, offers non-invasiveness and quick onset of action, similar to the nasal route. The buccal cavity provides a large and highly vascularized surface area, facilitating drug permeation into the systemic circulation [41]. This route shows promise, especially for delivering proteins, such as insulin, without the need for injectable agents [42]. there are some potential drawbacks to buccal administration. Leaving drugs in the buccal area for an extended period may cause discomfort for patients. Additionally, irritation to the buccal cavity can occur, which may lead to accidental swallowing of the drugs. Despite these limitations, the buccal route remains an attractive option for drug delivery due to its minimal invasiveness and potential to improve patient compliance. Careful formulation and design can address the challenges associated with buccal delivery and enhance the therapeutic benefits while minimizing adverse effects. [43] The buccal route has been explored as a potential method for administering insulin due to its advantages in providing direct access to the systemic circulation through the internal jugular vein, bypassing first-pass liver metabolism and gastrointestinal degradation. This leads to increased bioavailability of insulin, making it a promising alternative to traditional oral insulin delivery. Additionally, the buccal mucosa exhibits low enzymatic activity and good patient compliance, further supporting its use for insulin delivery [44].

However, it is essential to acknowledge that the buccal mucosa is not naturally designed for drug absorption, and different structures within the buccal cavity (cheek, sublingual, palate) may exhibit varying permeability to drugs. Saliva flow also poses a challenge as it can act as a barrier, limiting the retention of insulin in the buccal cavity. To enhance insulin stability and absorption, absorption enhancers and enzyme inhibitors are often incorporated into buccal insulin formulations. For instance, Oral-LynTM, a buccal insulin delivery system from Generex Biotechnology Corp., employs a spray device containing insulin and a combination of absorption enhancers to improve insulin absorption. However, it is

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important to note that only approximately 10% of the administered insulin is absorbed with this system [45]. While this is an improvement, further studies are necessary to assess the long-term mucosal tolerance to absorption enhancers and to confirm the safety of Oral-Lyn.

5.3 In vitro studies

In vitro studies on buccal delivery of insulin have yielded promising results using various strategies. The use of hydrophobic ion-pairing (HIP) nanocomplexes with bile salts showed improved permeation of insulin across buccal tissues. Elastic bilosomes with sodium glycodeoxycholate (SGDC) demonstrated effective insulin penetration. Insulin-phospholipid complexes (IPCs) with deformable nanovesicles showed higher deposition in the mucosa compared to conventional nanovesicles. Cell-penetrating peptide (CPP) conjugates enhanced insulin delivery, leading to sustained hypoglycemia. Chitosan-based electrospunfiber scaffold and nanoparticles improved insulin permeability. Thiolation of chitosan nanoparticles and amino acid addition in mucoadhesive buccal films also exhibited enhanced insulin permeation across buccal cells. These findings indicate that buccal film formulations hold great potential for improved management of Type 2 diabetes mellitus, offering enhanced drug permeation, sustained release, and enhanced patient compliance. Further research and development in this field can pave the way for innovative and effective treatments for diabetes management. [46]

5.4 In Vivostudies

Several studies have explored the use of different delivery systems for insulin across porcine buccal tissues and in in vivo models. SGDC-incorporated elastic liposomes (SGDC-EL) demonstrated enhanced insulin permeation compared to SC-incorporated elastic liposomes (SC-EL) due to SGDC's lipophilic and enhancing properties. A CAGE/CPVA insulin patch showed sustained hypoglycemia in rats without significant organ or tissue damage. Deformable vesicles, such as IPC-DNVs, exhibited sustained hypoglycemia and higher relative bioavailability compared to other formulations. Buccal films loaded with INS-CH-NPs demonstrated controlled insulin release and reduced blood glucose levels in rats. Overall, these studies show promising results for insulin delivery through buccal tissues, warranting further investigation on long-term safety and mechanisms of action. Notably, no observable irritation or alterations were reported in the studies conducted. [47]

5.5 Buccal Formulation strategies to improve the pharmacokinetics and bioavailability

The oral mucosa provides a direct route for drug absorption into the systemic circulation, bypassing first-pass metabolism, making buccal administration more convenient than other routes like subcutaneous, nasal, transdermal, vaginal, or pulmonary administration.[48] However, a significant challenge in buccal drug delivery is the low bioavailability of larger molecules, necessitating the use of various strategies such as absorption enhancers or enzyme inhibitors to improve their pharmacokinetics. Efforts have been made to develop effective buccal formulations for peptides, particularly insulin. However, some attempts, like an oromucosal spray and a dissolvable film with embedded gold nanoparticles, failed to reach the market due to low efficacy and variable pharmacokinetics. [49]

One technology, ArisCrown, was used for buccal administration of exenatide (ARG011), a peptide used in the treatment of diabetes. This technology utilizes biodegradable cyclic compounds (crowns) to selectively and reversibly mask peptide functional groups through non-covalent interactions. The modified peptide is then incorporated into a lipid formulation optimized to preserve the peptide's properties. [50] Preclinical studies with buccal exenatide in mice and monkeys showed promising results. In mice, buccal exenatide controlled blood glucose levels similarly to an intraperitoneal injection of unformulated peptide, and in monkeys, the buccal formulation of exenatide included in a buccal patchcontrolled blood glucose levels comparably to the subcutaneous formulation. Despite the positive outcomes, the development of this formulation was cancelled due to the closure of Arisgen SA, the company responsible for its development. [51]

5.6 Challenges and Considerations in Developing Buccal Films for Diabetes Management

5.6.1 Mucoadhesion

Ensuring optimal mucoadhesion to the buccal mucosa is critical for sustained drug release and effective drug absorption. Various polymer systems and formulations have been explored to achieve the desired mucoadhesive properties. [52]

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5.6.2 Drug Stability

Maintaining drug stability within the buccal film matrix during storage and handling is essential to preserve drug efficacy and bioavailability. [53]

5.6.3 Biocompatibility and Safety Considerations [54]

5.6.3.1 Irritation and Allergenicity

Buccal films should be designed to minimize mucosal irritation and the risk of allergic reactions. Selecting biocompatible polymers and excipients is vital to ensure the safety of long-term usage.

5.6.3.2 Toxicity and Metabolism

Thorough safety assessments, including in vitro and in vivo toxicity studies, are necessary to evaluate the metabolic fate of buccally delivered drugs.

5.6.3.3 Systemic Absorption

The potential for systemic drug absorption through the buccal route must be carefully evaluated to avoid unintended side effects.

5.7 Drug Candidates for Buccal Delivery

A range of antidiabetic drugs has been investigated for buccal delivery. This section will discuss the suitability of different drug candidates, including metformin, glipizide, pioglitazone, and others, for incorporation into buccal film formulations. Comparative studies on drug release profiles, bioavailability, and pharmacokinetics will be examined.

VI. EVALUATION TECHNIQUES

Robust evaluation techniques are crucial to assess the performance of buccal film formulations. This section will focus on the various evaluation parameters, including mechanical properties, drug release kinetics, mucoadhesion, in vitro drug permeation, stability, and in vivo pharmacokinetic studies, used to determine the effectiveness of these formulations.

6.1 Film weight and thickness

The weight of films (1x1 cm2) was measured using digital balance and the average weight was calculated. Thickness of each film was measured using Vernier caliper held at different positions on the films and the average was calculated. [55]

6.2 Mucoadhesive

Utilizing a 3% (w/v) mucin solution, mucoadhesive tests were conducted using mucoadhesion test equipment based on the double beam physical balance concept. On two various coverslips, ten microliters of mucin solution were applied. Each coverslip's reverse side was adhered using double-sided tape to the upper and lower surfaces of the balance's lefthand setup, respectively. On a coverslip that was present on the lower surface of the left side balance, 1x1 cm2 films were attached. The film covering the coverslip present on the lower surface came into contact with the coverslip present on the upper surface. This was accomplished by removing a 5 gram weight from the balance's right pan. The balance was maintained in this position for three minutes, after which weight was gradually applied to the right pan to cause the film to separate from the coverslip. The power needed to separate the film is equal to the surplus weight on the pan, or the total weight minus 5gm. In 'g', this provided the film its mucoadhesive strength. The average of three measurements was used to determine the maximum adhesive force.[56]

6.3 Folding endurance

The folding endurance of the films was determined by repeatedly folding each film at the same place until it broke or for a maximum of 300 times. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance. The mean value of three observations was calculated.[57]

6.4 Swelling

The samples were allowed to swell in phosphate buffer of pH 6.8 for 8 hours after the film weight was determined. By removing the film from the phosphate buffer and blotting it with filter paper to remove any excess water, the increase in film weight was measured at various time intervals.[58]

6.5 Thickness

The thickness of ten randomly selected films from every formulation batch was determined using a Vernier calliper [59]

6.6 Surface pH

In order to assess the potential consequences of irritation on the mucosa, the surface pH of the created buccal films was measured. The films were allowed to swell in 5 ml

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of pH 6.8 distilled water in tiny beakers, and the pH was then determined by putting an electrode in contact with the swollen films' surroundings. Three measurements' average pH was provided. [60]

6.7 Tensile Strength

A film strip measuring 2 x 2 cm2 that was devoid of air bubbles or other physical flaws was held between two clamps that were spaced 3 cm apart. To stop the film from being sliced by the grooves of the clamp, a cardboard was adhered to the clamp's surface using double-sided tape. The strips were pulled at the bottom clamp during measurement by putting weights in a pan until the film broke.[61]

$$\text{Tensile strength (kg/mm2)} = \frac{\text{Force at Break}}{\text{Initial cross sectional area of the film (mm2)}}$$

6.8 Weight Variation

An electronic balance was used to measure the weight of three randomly chosen films from each formulation batch. [62]

6.9 Percentage Elongation

A pulley system was used to draw the prepared film. To progressively raise the pulling power until the film was shattered, weights were gradually added to the pan The elongation was calculated by measuring the distance the pointer covered on the graph paper before the film broke.Formula (mm-2) was used to calculate the % elongation, as shown below.[63]

$$\text{Percent elongation} = \frac{L_1}{L_0} \times 100$$

6.10 Stability Study

A stability study was conducted at 40 °C and 75% RH in accordance with ICH guidelines. Aluminum foil, plastic tape, and butter paper were used to package each piece of the formulation films. The films' outward appearance, drug content, and in vitro drug release were assessed after one month.[64]

6.11Evaluation of mucoadhesion in vitro/ex vivo

To the extent that dosage forms are intended to be mucoadhesive, mucoadhesion is crucial. This is crucial for dosage forms designed for prolonged drug release because they require adherence (mucoadhesive strength) and retention times that are long enough to enable drug release over an extended period of time. Numerous techniques have been created to assess mucoadhesion in vitro, but only a few of them are applicable to mucoadhesive films; these techniques include atomic force microscopy and rheological evaluations for semi-solid preparations.[65]

VII. CHALLENGES AND FUTURE PERSPECTIVES

Despite the promising potential of buccal film formulations, there are challenges that need to be addressed. This section will address issues related to manufacturing scalability, regulatory considerations, and commercial viability. Additionally, future perspectives, such as personalized medicine approaches and combination therapies, will be discussed.

VIII. CONCLUSION

The development and evaluation of buccal film formulations for improved management of Type 2 diabetes mellitus show promising potential to overcome the limitations of conventional oral antidiabetic medications. The unique anatomy and physiology of the buccal mucosa enable efficient drug absorption, offering enhanced bioavailability and reduced gastrointestinal side effects.Formulation strategies involving mucoadhesive polymers, permeation enhancers, and other excipients play a crucial role in achieving controlled drug release and drug permeation. Several drug candidates, including metformin, glipizide, and pioglitazone, have been investigated for buccal delivery, showing encouraging results in in vitro and in vivo studies.Evaluation techniques have been established to assess the mechanical properties, drug release kinetics, mucoadhesion, and stability of buccal film formulations. These techniques aid in determining the effectiveness and performance of the formulations, ensuring their potential for successful clinical applications.The use of buccal film formulations offers numerous advantages, such as enhanced patient compliance, ease of administration, and reduced dosing frequency. These factors can positively impact patient adherence and therapeutic outcomes, addressing the challenges associated with T2DM management.However, there are challenges to be addressed, including manufacturing scalability, regulatory considerations, and commercial viability of these formulations. Despite these challenges, the future perspectives of buccal film formulations for T2DM management are promising, with opportunities for personalized medicine approaches and combination therapies.

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