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| RESEARCH ARTICLE

New Dosage Form of Insulin: Review Article

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| ABSTRACT

Many patients with advanced type 2 diabetes mellitus (T2DM) and all patients with T1DM require insulin to keep blood glucose levels in the target range. The most common route of insulin administration is subcutaneous insulin injections. There are many ways to deliver insulin subcutaneously, such as vials and syringes, insulin pens, and insulin pumps. Though subcutaneous insulin delivery is the standard route of insulin administration, it is associated with injection pain, needle phobia, lipodystrophy, noncompliance, and peripheral hyperinsulinemia. Therefore, the need exists to deliver insulin in a minimally invasive or noninvasive way and in the most physiological way. Inhaled insulin was the first approved noninvasive and alternative way to deliver glucose, but it has been withdrawn from the market. Researchers are exploring technologies to enable noninvasive insulin delivery. Some of the routes for insulin administration that are under investigation are oral, buccal, nasal, peritoneal, and transdermal. This article has focused on different possible routes of insulin administration, their advantages and limitations, and the possible scope of the new drug development.

| KEYWORDS

Diabetes mellitus; inhaled insulin; insulin delivery; oral insulin; technology.

| ARTICLE INFORMATION

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1. Introduction

1.1 Definition of diabetes mellitus

Diabetes is a metabolic disorder characterized by increased glucose levels in the blood, with symptoms and signs of hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance, and sometimes ketonemia. It is caused by either impairment of insulin secretion and/or action resulting in dysregulation of glucose and lipid metabolism [Geremia, 2022].

Millions of people in the world are affected by diabetes. The International Diabetes Federation estimated that 366 million people had diabetes in 2011, and this number is expected to rise to 552 million by 2030 [IDF Diabetes Atlas, 2013].

1.2 Type of diabetes mellitus

Two major types of diabetes mellitus are as follows:

a. Type I, or insulin-dependent diabetes mellitus (IDDM)

This type is caused by β cell destruction in pancreatic islets; the majority of cases are autoimmune antibodies that destroy β cells, and these antibodies are detectable in blood, but some cases are idiopathic (no antibody is found). In all type 1 cases, circulating

insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition [Amish, 2011].

b. Type II, or non-insulin-dependent diabetes mellitus (NIDDM)

In this type, there is no loss or moderate reduction in β cell mass; insulin in circulation is low, normal, or even high; no anti-β-cell antibody is demonstrable; it has a high degree of genetic predisposition; and generally has a late onset [IDF Diabetes Atlas, 2013]. The majority of the cases have reduced sensitivity of peripheral tissues to insulin with a reduction in the number of insulin receptors [Tripathi, 2004].

1.3 Insulin

Insulin is a polypeptide anabolic hormone that is produced by islets of Langerhans (clusters of cells that are embedded in the exocrine portion of the pancreas). Insulin causes glucose uptake by the cells of different organs (like muscle, liver, fat cells, etc.) from the blood. It stores the glucose in muscle and liver as glycogen, an insulin hormone that plays a very important role in the use of fuels by tissues. Insulin is stored in the cytosol and released by exocytosis. The metabolism of insulin takes place through the enzyme insulinase. The half-life of insulin is approximately 6 minutes. Insulin secretion is increased by an increase in glucose, amino acids, and gastrointestinal hormones [Nitin, 2014].

1.4 Mechanisms of insulin's action

Insulin binds to specific, high-affinity receptors in the cell membranes of tissues [Richard, 2012]. These receptors are present in all the cells, but their density depends on the type of cell, with the maximum density being in hepatic cells and adipocytes.

The insulin receptor is a heterotetrameric glycoprotein consisting of two subunits, the alpha and the beta subunits. The extracellular alpha subunits have insulin binding sites. The beta subunits, which are transmembranous, have tyrosine kinase activity [Thota, 2023]. When insulin binds to the alpha subunits, it activates the tyrosine kinase activity in the beta subunit, which causes the translocation of glucose transporters from the cytoplasm to the cell's surface [Posner, 2017]. These glucose transporters allow the influx of glucose from the blood into the cell, thus reducing blood glucose levels [Jaldin-Fincati, 2017].

Insulin causes the following effects in the cell [Wilcox,2005]:

- Hepatic cells promote glycogenesis and inhibit gluconeogenesis.
- Adipocytes: Promotes lipogenesis, inhibits lipolysis
- Muscle cells: Promotes glycogenesis and protein synthesis. Inhibits protein catabolism
- Pancreatic beta cells: inhibits glucagon release
- Brain cells: involved in appetite regulation

So, in the absence of insulin, cells of different organs cannot take the glucose through the blood. In this condition, fat is used as an energy source. Any imbalance in the level of insulin causes diabetes mellitus.

So, all patients with T1DM and many patients with long-standing T2DM require insulin therapy to achieve good glycemic control [U.K. prospective diabetes study 16, 1995].

The early insulins were derived from bovine and porcine pancreas and were associated with immunological reactions, lipodystrophy, and unpredictable insulin absorption from subcutaneous tissue. Hence, initial research focused on the purification of insulin [Shah, 2013]. In the last five decades, there has been marked progress in the development of insulins, such as rapid and long-acting insulin analogs [Shah, 2013].

1.5 Structure of the Insulin

The insulin molecule is a globular protein with a molecular weight of about 5,800 kD. It consists of 51 amino acids arranged in two chains, an A chain (21 amino acids) and a B chain (30 amino acids), that are linked by two disulfide bonds [Lawrence, 2011] (Figure 1).

Insulin exists as a monomer only at low concentrations, while it has a propensity to aggregate into stable dimers at higher concentrations in an aqueous solution at pH 2–8 and into hexamers in the presence of zinc ions. The hexamer, in which chain A constitutes much of the polar surface, is almost spherical in structure, with a diameter of 5 nm and a height of 3.5 nm. Polymerization of the hormone has major pharmacological implications [GUALANDI-SIGNORINI, 2001].

Proinsulin is the insulin precursor that is transported to the Golgi apparatus of the beta cell, where it is processed and packaged into granules. Proinsulin, a single-chain 86 amino acid peptide, is cleaved into insulin and C-peptide (a connecting peptide); both are secreted in equimolar portions from the beta cell upon stimulation from glucose and other insulin secretagogues. While C-peptide has no known physiologic function, it can be measured to provide an estimate of endogenous insulin secretion [Donnor, 2023].

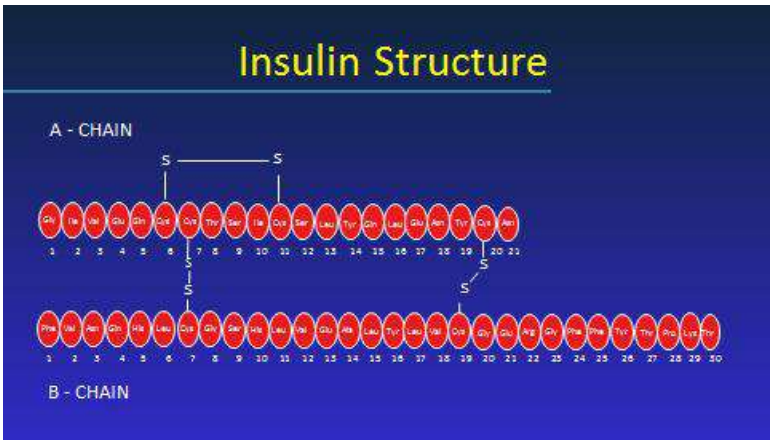

Figure 1: insulin structure

1.6 Administration

Insulin administration can be via subcutaneous, intravenous, and intramuscular routes. The route of administration usually depends on the patient's condition and setting.

The subcutaneous route is the most widespread route of administration and is preferred by most patients due to its ease of administration and convenience. Patients use the subcutaneous route in the form of insulin syringes, pens, and pumps. It is an effortless and convenient way for patients to self-administer [Thota, 2023].

Intravenous insulin is used in the hospital setting, especially when immediate and close monitoring of blood glucose levels is needed [Pérez, 2020]. It is used in patients with diabetic ketoacidosis, hyperosmolar hyperglycemic state, severe hyperkalemia, beta-blocker toxicity, and calcium channel toxicity. All of these cases require emergency treatment, and hence, intravenous insulin is used.

Intramuscular insulin use is rare and utilizes concentrated regular insulin. In 2014, the FDA approved an inhalable insulin formulation. It passes through the lungs and into the bloodstream and provides a rapid onset of action within 12 minutes. It can be taken by patients with diabetes type 1 and type 2 before meals. The insulin pump is a device that works like a natural pancreas. It replaces the need for long-acting insulin and continuously delivers small amounts of short-acting insulin to the body throughout the day.

2. A new dosage form of insulin

2.1. Insulin Patch Pump:

Continuous subcutaneous insulin infusion (CSII), more commonly referred to as insulin pump therapy, is one of the most notable advancements in diabetes technology in the past 50 years, and this technology advanced rapidly in an attempt to more closely mimic physiologic insulin secretion and help patients achieve tight glycemic control while minimizing the risk of hypoglycemia. [Berget, 2019].

As a result, the use of insulin pumps has increased dramatically in the United States, from <7,000 users in 1990 to nearly 100,000 in 2000 and >350,000 today [McAdams, 2016]. The majority of insulin pump users have type 1 diabetes because they want improved glycemic control and a more flexible lifestyle than is afforded with multiple daily injection therapy, especially around meals and social situations [Alsaleh, 2012]. Also, many studies have demonstrated improved glycemic control and a reduction in hypoglycemia with insulin pumps in patients with type 1 diabetes [Burckhardt, 2018; Brorsson, 2015]. However, the use of insulin pump therapy for individuals with type 2 diabetes is increasing [Reznik, 2013].

The main advantage of the insulin pump is that it has no tubing and does not need an insulin infusion set (IIS). Also, these patch pumps improve quality of life, reduce diabetes-related distress, increase patient satisfaction, and are preferred by patients compared to conventional insulin pumps and multiple daily injection therapy (MDI) [Kulzer, 2022].

In addition, insulin pumps offer many advantages in managing unpredictable eating habits and low insulin requirements in the youngest children, suggesting that insulin pump therapy may be an ideal option for many young children with type 1 diabetes and their families [Weinzimer, 2006].

There are various patch pump insulins that are available or in development with major differences; for example, they can either deliver just basal insulin, bolus insulin, or both basal and bolus insulin [Heinemann, 2019].

The focus of the development of insulin patch pumps is either on the simplicity of the devices with a very easy operation or of patch pumps without tubing with the multiple options of modern insulin pumps for individual insulin dosing (e.g., variable basal rates, bolus options, bolus calculator). Generally, the different patch pumps can be divided into different categories according to restricted functionality and ease of use, additional features of the PP, and interoperability with other devices, especially regarding the possibility of being part of systems for automated insulin delivery [Kulzer, 2011].

2.2 simple mechanical patch pump:

The simple forms of pump patches are intended for insulin therapy for people with T2D and mainly aim to be easy to handle, easy to carry, small, and disposable.

Recent developments aim to replace insulin pen therapy with PPs that use relatively simple insulin dosing regimens. There are also options to deliver only the basal or bolus insulin via a pump patch to simplify insulin therapy. [Kulzer, 2011]

An example of a simple PP is the V-GO, which delivers a fixed amount of basal insulin over 24 hours and has a bolus button that permits up to 36 units of prandial insulin to be delivered in 2-unit increments per day. The V-GO is replaced daily. The Simplicity (CeQur; Luzern, Switzerland) PP holds up to 200 units of bolus insulin that are administered in 2-unit increments, while the CeQur's PaQ (later PaQ Total) has a reservoir of 330 units for 3 days of use and also allows different basal rates [Anhalt, 2010].

Figure 2 : V-Go by Valeritas and PAQ by CeQur

2.3 Full-Featured Devices

These are very flexible devices, fully capable of the most complex regimens of an insulin-using patient. They are generally electromechanical, a mechanical pump with an electronic controller, and are usually at least partially disposable. In some, the electronics are saved, whereas the pump and reservoir are disposable. The known device Omnipod is in its smaller third version and is available in the United States and Europe. The Cellnovo is approved and sold in Europe [Ginsberg, 2019].

2.4 Insulin Cream

The effect of insulin on wound healing has been reported in various animal wound models, including fracture wounds, skin ulcers, and incision wounds [Goenka, 2014]. Clinically, insulin efficacy in wound healing was reported in burn patients receiving allographs [Hrynyk, 2014]. Previous studies found that insulin accelerates non-diabetic wound healing by improving angiogenesis and epithelial remodeling [Apikoglu-Rabus, 2010]. Also, numerous studies reported the efficacy of insulin in wound healing.

Topical insulin improves wound healing by regulating oxidative and inflammatory responses. Insulin treatment decreases the levels of reactive oxygen species, which can induce deleterious effects on lipids, proteins, and DNA in burn wounds in rats [Dhall, 2015].

In addition, topical insulin induces early recruitment of neutrophils and exerts an anti-inflammatory effect in wounds by increasing the number of M2 macrophages and IL-10 levels to eliminate dead tissues [Chen, 2012]. In vitro, insulin facilitates chemotaxis and phagocytosis of macrophages, as well as the secretion of inflammatory mediators, by regulating MCP-1 expression at wound sites [Chen, 2012].

Moreover, topical application of insulin cream on skin wounds enhances keratinocyte migration, accelerates re-epithelialization, increases fibroblastic reaction, and improves collagen deposition and maturation, as evidenced by increased hydroxyproline levels [Liu, 2018].

In addition to regulating reepithelialization and inflammatory responses in wound tissues, insulin also exerts an angiogenic effect on wounds. Topical insulin increases the number of newly formed blood vessels in healing tissues [Dhall, 2015]. Furthermore, subcutaneous injection of insulin stimulates microvascular endothelial cell migration and endothelial tube formation. Recently, insulin cream has been successfully used to treat diabetic and non-diabetic wounds [Hrynyk-Hrynyk, 2012].

2.5 Insulin plaster

The insulin plaster is able to provide the same effective and safe glycemic control in adults with type 2 diabetes as standard insulin pens; however, studies on this subject are limited. Clinical examination is the mainstay for the diagnosis of peripheral neuropathy and prevention of foot problems, which is the main complication of diabetes [Boulton, 2005]. Sudomotor dysfunction develops early in the course of peripheral neuropathy [Hoeldtke, 2001]. Recently, a new test assessing sudomotor dysfunction, the indicator plaster neuropad (IPN), has been introduced for the diagnosis of peripheral neuropathy [Papanas, 2007]. The IPN has a high sensitivity for the diagnosis of peripheral neuropathy [38] and excellent reproducibility. Another advantage of the IPN is simplicity [Papanas, 2005].

2.6 Insulin gel

In a recent study, the development and evaluation of a novel composite microsphere delivery system composed of poly(acryloyl hydroxyethyl starch) (acryloyl derivatized HES; AcHES) (PLGA) and poly(D, L-lactide-co-glycolide) hydrogel using bovine insulin as a model therapeutic protein has been reported. The AcHES-PLGA composite microsphere system provides satisfactory in vitro and in vivo sustained release performance for a model protein, insulin, to achieve 10-day glucose suppression [Jiang, 2003]. Various bioadhesive polymers, such as polyacrylic acids (e.g., carbopol 934P, polymethyl methacrylate), are used in gel forms to prolong the residence time on the oral mucosa. The use of nasal bioadhesive gels blended with an appropriate chemical permeation enhancer might be used to provide enhanced bioavailability compared with oral delivery. [D'Souza, 2005]

So, when insulin is administered in a gel form with a penetration enhancer, it traverses the nasal mucosa and rapidly passes into the systemic circulation. Further, insulin gel delivered via nasal mucosa is a pleasant and painless alternative to injectable insulin. However, as the absorption is quite quick, using this form of insulin delivery may not be feasible for chronic patients in the long run [D'Souza, 2005].

2.7 Insulin Drop

Corneal epithelial erosions in diabetic animals appear to respond to topical insulin, according to some studies [Sassani, 2007].

One study found that insulin formulated as 1 U/mL eye drops and administered QID can be a quick, effective, safe, and affordable option for corneal epithelial defects. [Insulin eye drops for refractory corneal epithelial defects, 2022]

However, topical insulin experience for corneal ulcer treatment is limited, both in diabetics and non-diabetics [Bastion, 2013; Fai, 2017].

2.8 Insulin tablet

Insulin injections are associated with poor compliance, weight gain, risk of hypoglycemia, and adverse effects of systemic hyperinsulinemia. So, a search for oral insulin tablets that may closely mimic the physiological insulin secretions has always been there. [Chatterjee, 2019]
So, the most notable benefit of oral insulin is that the administration can be less painful than traditional insulin injections, as the injection area can become sensitive and inflamed over time.

In addition, oral insulin delivery also improves intake levels of the drug and reduces peripheral hyperinsulinemia, which is associated with neuropathy and retinopathy in other routes of administration [Khafagy, 2007].

Other advantages include improving compliance and reducing insulin exposure in the peripheral system so as to minimize the incidence of weight gain [Chen, 2008].

However, oral insulin delivery has been a persistent challenge because of the physicochemical properties, including the large molecular size and susceptibility to enzymatic degradation [Goldberg, 2003].

Oral tablets of insulin manufactured by recombinant DNA technology were successfully prepared to improve its bioavailability and to avoid hepatic first-pass metabolism and pre-systemic metabolism in the gastrointestinal tract. There were no possible interactions between the drug and polymers according to FTIR spectroscopy and the DSC study [Alkufi, 2024].

In comparison with gliclazide as a standard hypoglycaemic drug with insulin tablets, one study showed a lower biological half-life and duration of action than gliclazide, while insulin drug delivery systems showed less hypoglycemia and weight gain tendency [Alkufi, 2024].

In another comparison with glimepride (a second-generation sulfonylurea oral hypoglycemic drug), insulin tablets demonstrated less hypoglycemia and weight gain tendency than glimepride, but glimepride displayed a longer duration of action (12–24 h) and half-life (5 h) than insulin drug delivery systems [Ananya, 2011].

2.9 Powder Insulin

A novel drug delivery technique named powder needle injection (PNI) drew our interest. PNI uses high-speed gas flow to deliver vaccines or drugs in dry powder form to skin tissue without needles. It provides a promising approach for delivering biological drugs such as insulin with both high bioavailability due to its special aerodynamic properties and good compliance from patients due to its needle-free and pain-free advantages. The level of delivery efficiency it can reach is unknown [Ziegler, 2008].

Another technique for the delivery of insulin powder is that when formulated with an appropriate composition to produce adequate physical characteristics, the insulin powders exhibited excellent aerosolization properties for inhalation.

The present investigation focused on the physical characteristics and aerosolization performance of insulin dry powders for inhalation with different excipients [Sham, 2004].

Insulin powders were prepared by spray drying using excipients that are approved by the Food and Drug Administration for inhalation, such as lactose and mannitol materials such as trehalose and dextran that appear suitable for inhalation dry powders and amino acids that may improve the dispersibility of the powders, such as L-leucine, glycine, and threonine [Alkufi, 2023].

The physical characteristics of the powders (i.e., particle size, tapped density, morphology, moisture content, and moisture absorption) were determined.

3. Inhaled human insulin

Patients with diabetes show a reduction in pulmonary function with lower forced vital capacity and forced expiratory volume in one second. [Abd, 2023] Compared to oral delivery of insulin, the inhalation administration route still has a relatively faster onset of action due to the presence of alveoli in the lungs for systemic drug absorption. Insulin is also less susceptible to enzymatic degradation in the gastrointestinal tract.

They found that absorption of inhaled insulin in the alveoli varied significantly, especially for obese patients, smokers, and patients with asthma and chronic obstructive pulmonary disease (COPD). The variation in absorption was attributed to the reduction in alveoli surface area and the change in functional structure. They concluded that there were issues with inhaled insulin, which included patient compliance, lack of a safety profile for long-term use, and cost-effective-ness.[Skyler, 2008]

Recently, a new inhaled insulin powder product (Afrezzaâ) has entered the market. This product overcomes some of the barriers that contributed to the withdrawal of other inhaled insulins, such as Exubera [Alkufi, 2023].

The inhaler is less bulky than the previous product. It also mimics normal prandial insulin release with ideal glycaemic control. [Owayez n.d] Most importantly, the absorption of insulin is not altered in patients who smoke and with COPD. [Richardson, 2009]

However, a correct inhalation technique is required for optimal effect. [Alkufi, 2023] The long-term safety of this product for use in both T1DM and T2DM can only be established after it has been marketed for several years.

3.1 Insulin Suppository

The therapeutic use of insulin suppositories has potential clinical significance due to the higher concentrations achieved in the portal vein [Hosni, 1980], which are closer to physiological conditions than after other forms of administration.

The insulin response after rectal administration of insulin was positively correlated with the pre-stimulated glycemic level [YOSHIMITSU, 1984].

The rapid but short-acting effect of insulin suppositories refers to their use to provide meal-related insulin requirements when the basal insulin level has been ensured either by injection of a long-acting formulation or by means of an insulin pump device. However, it appears necessary to refine the suppository formula in order to achieve the best possible efficacy. [Hildebrandt, 1984]

3.2 Topical Insulin

In chronic diabetic wounds, there is an increased expression and activity of matrix metalloproteinases MMP8 and MMP9 that cause damage to several matrix proteins and growth factors needed in wound healing [Ågren, 2007].

Hyperglycemia is also associated with a decreased concentration of plasminogen urokinase activators and an increase in tissue plasminogen activator inhibitors that result in a disturbance of fibrinolysis and matrix deposition disorders, resulting in disturbed adhesion, motility, growth, and differentiation of cells involved in wound healing, causing the wounds to become chronic.

Hyperglycemia also triggers interference with the insulin signaling pathway through phosphorylation of insulin receptor substrate (IRS). This disruption of the signaling pathway is associated with a decrease in cell proliferation and differentiation activities [Lima, 2012]. So, it has been shown that topical insulin produced faster wound healing and minimal systemic side effects in some studies [Wang, 2022]. Despite that, topical insulin is still not widely used for chronic diabetic wound management.

Kargin et al. conducted a study on mice by dividing the sample into two groups, each of which consisted of 10 rats that were injured. The wound in the first group was given 0.3 IU of regular insulin, which was diluted with 20 µL of single-dose sterile water for 20 days. Meanwhile, normal saline was given to the control group of rat wounds. Wound closure rates were found to be higher in the first group on all days of the experiment. The period of complete wound closure is shorter in the first group, with a mean of 4 days [Kargin, 2015].

This study also found increased organized collagen fibrils on the epidermis and dermis layers of samples taken from the wounds of the insulin-given rats [Kargin, 2015]. Goenka et al. (2014) conducted a study with 50 samples of chronic wound patients with decubitus wounds, chronic postoperative wounds, and chronic diabetic wounds measuring less than 10 cm2. Patients were divided into four groups: diabetic patients, divided again into a group that was treated with topical insulin, and the other with normal saline. The non-diabetic groups were also divided again in the same fashion. This study showed a faster recovery in patients treated with topical insulin than without insulin. A similar result was found in either group, with diabetes mellitus or not.

Based on studies conducted, topical insulin has a positive effect on multiple pathways, leading to enhanced wound healing.

Figure 3: The summary of topical insulin in wound healing. The application of topical insulin consists of local injection, insulin spray and cream, and a dressing delivery system. This study includes 15 animal studies and 10 clinical studies of topical insulin for wounds. The results exhibited that topical insulin can improve wound closure, reduce wound healing time, and improve wound remodeling through modifying inflammation, accelerating epithelialization, and neovascularization. No adverse systemic effects (hypoglycemia, hypokalemia, hypoaminoacidemia) and adverse local effects (infection, pain, allergenicity) were observed [Wang, 2020]

3.3 Oral Spray Insulin

Attempts to address some of the barriers associated with insulin therapy have led to the development of novel, non-injectable insulin formulations, the most promising of which has been the pulmonary route [Royle, 2004]. However, these formulations have not met with acceptable safety profiles or commercial success.

Because non-compliance with injected insulin therapy can lead to serious complications, the ease of use of this aerosolized spray formulation may increase patient acceptance and treatment compliance, thereby potentially reducing complications and improving the quality of life for patients with insulin-dependent diabetes [Paolo, 2010]. An alternative to injectable and inhaled insulin is a system that allows a liquid oral spray insulin formulation (Generex Oralin TM, Generex Biotechnology, Toronto, Ontario, Canada) to be delivered accurately into the mouths of patients via spray. Also, this system introduces a high-vvelocity fine-particle aerosol into the patient's mouth, thereby inducing a markedly increased deposition of the preparation over the regional mucosa, a deposition that is much larger than that observed with conventional technology [Guevara-Aguirre, 2004].

The active pharmaceutical ingredient in the oral insulin spray is recombinant human insulin that is present in a tasteless liquid aerosol mist formulation; however, the formulation behaves in a fashion more similar to the synthetic fast-acting insulin analogues (lispro, aspart, and glulisine) [Bernstein, 2008].

One spray of Generex Oralin delivers approximately 10 U of insulin to achieve absorption of approximately 1 U of insulin systemically [Generex Biotechnology Corporation, 2008].

The technology utilizes the formation of micro-fine micelles made from a combination of absorption enhancers that encapsulate and protect the insulin molecules for safe and effective delivery. The delivery device introduces a fine-particle aerosol at high velocity (~100 mph; 160 km/h) into the oropharyngeal cavity for local transmucosal absorption. The manually actuated mechanism incorporated into the device introduces the dose and standardized volume of the insulin formulation in relation to the patient's needs. Absorption is limited to the mouth, with no entry of the product into the lungs [Jhaveri, 2014]. Several studies conducted in subjects with type 1 and type 2 diabetes demonstrated very clearly that oral insulin has faster rapid absorption and metabolic control comparable to subcutaneously injected insulin [Guevara-Aguirre, 2003].

Guevara-Aguirre et al. found that oralin could be used as mealtime insulin in place of mealtime insulin injections in subjects with type 2 diabetes to regulate postprandial glucose levels.

3.4 Insulin spray-dried powder.

The successful development of an inhalable rapid represents a noninvasive alternative to multiple daily subcutaneous insulin injections and promises to change the management of diabetes. With advances in inhalers, there are now several insulin inhalations possible by devices and insulin systems at varying stages of clinical development, which in 2006 was the Exuberaformulation technology, one of which the U.G. Administration first inhaled insulin approved by the U.S. Food and Drug Administration (FDA) [Patton, 2004].

Spray human insulin Regular inhaled acting (Exubera®) is a rapid invasive treatment administered by oral inhalation before meals. It provides a nonalternative to multiple subcutaneous injections for the treatment of hyperglycemia in adult patients with type 1 and type 2 diabetes. analogs, Exubera acting insulin compared with subcutaneous rapid [Anthony,2007]. Control1C provides equivalent HbA.

Exubera® (insulin human [rDNA origin]) Inhalation Powder, developed by Pfizer Inc. in collaboration with Nektar Therapeutics, has received approval in both the US and the European Union for the control of hyperglycemia in adult patients with type 1 or type 2 diabetes. Exubera consists of a fine, drypackaged in unit doses of 1 or 3 mg for inhalation in blister packs, which are administered via a unique and reusable mechanical pulmonary inhaler [Rave, 2005].

The pharmacokinetic profile of Exubera closely mimics the natural pattern of postprandial insulin secretion that is also achieved with rapid insulin analogs but not regular human insulin [acting subcutaneously]. Whereas regular insulin has a relatively slow onset of action and a prolonged duration of action when injected subcutaneously, resulting in sociated suboptimal control of postprandial hyperglycemia, Exubera is associated with an onset of action that is at least as fast as the subcutaneously injected rapid-acting insulin analog, insulin lispro [Ciofetta, 1999].

In addition to offering a rapid onset of action, the longer duration of action of Exubera relative to insulin lispro may be better suited to postprandial glucose control. Clinical studies have suggested that the duration of action of subcutaneously administered insulin analogs is too short to provide adequate postprandial control, as indicated by rising glucose levels post-absorption [Exubera, 2006].

The reason for the prolonged metabolic action of inhaled insulin relative to subcutaneously administered rapid-acting insulin analogs is unclear but may relate to the size-ddependent absorption and dissociation characteristics of inhaled insulin particles.

Exubera was indicated as combination therapy in patients with type 1 diabetes, to be used in conjunction with a longer-acting insulin [Oleck, 2016]. In patients with type 2 diabetes, Exubera could be used either as monotherapy or in combination with a longer-acting insulin or oral antidiabetic agents.

Contraindications included smokers and patients who had stopped smoking within the past 6 months. Because of an increased risk of hypoglycemia with smoking, patients who resumed smoking while on Exubera were advised to immediately discontinue using the product. Because of changes in pulmonary lung function affecting absorption of the drug and potentially leading to increased hypo- or hyperglycemia risk, Exubera was also contraindicated in patients with unstable or poorly controlled lung disease such as asthma or chronic obstructive pulmonary disease [Skyler, 2005].

Randomized clinical trials in patients with type 1 and type 2 diabetes have shown that Exubera achieves and maintains effective glycemic control administered regularly, which is comparable to subcutaneous NPH insulin [Heinemann, 2008].

However, Pfizer pulled Exubera from the market after it had only been on the market for a year (an unusual maneuver that reflects the very poor sales numbers). Recently, Eli Lilly announced that they would no longer be developing them. Eli Lilly's decision especially comes as a surprise to many since the company's last CEO made some strong statements right after Pfizer's decision to pull Exubera statements a few months ago over their confidence in their development and insulin inhalation in general. Not only did Eli Lilly have an attractive inhaler (much smaller and easier to use than Exubera), but they also had a sound clinical development program. Basically, this means that several billion dollars were spent on unsuccessful development, which is probably one of the largest product failures ever in the history of drug development [Modi, 2002]

Figure 4: Inhaled human insulin

4. Insulin Buccal Spray.

Limitations on controlling postprandial glucose levels with insulin, such as the wide range of insulin bioavailability, the risks of hypoglycemia, and the discomfort for the patients, have encouraged the study of alternative methods of insulin delivery [Palermo, 2012]. Also, non-compliance with injected insulin therapy causes a slowdown in the process of glycemic compensation; novel non-injectable insulin formulations have been developed. Oral spray insulin (Oralgen) provides insulin absorption via buccal mucosa [Oh, 1990].

The buccal mucosa offers excellent accessibility, a large area for absorption (~100–200 cm2) with little proteolytic activity, a lower risk of being traumatized, and relatively good permeability and perfusion [Shah, 2016]. Nevertheless, the structural integrity of the oral epithelium also confers a barrier to the access of drugs along with the continuous flow of saliva. So, buccal delivery of insulin has benefits similar to oral insulin, with the advantage of bypassing GI degradation [Palermo, 2011].

Several strategies have been tested to enhance buccal insulin absorption. Among them, absorption enhancers (such as surfactants, bile salts, chelators, or fatty acids), vehicles (with or without adjuvants) alone or in combination with protease inhibitors (aprotinin and sodium glycocholate), lipophilicity modification (e.g., by conjugation with polymers), bioadhesive delivery systems, or liposomal formulations associated or not with absorption enhancers, and enzyme inhibitors have been used [Oh, 1990].

Oralgen is a tasteless liquid formulation of micelle-creating and emulsifying agents combined with recombinant short-acting human insulin, the active pharmaceutical ingredient, and delivered into the oropharyngeal cavity by means of a propeller.

Oralgen provides insulin absorption via the buccal mucosa. The epithelial layer that guards the large surface area in direct contact with blood vessels forms a barrier for molecule absorption. This has always been one of the most important hurdles in producing insulin capable of penetrating the bloodstream without pricks [Kumria, 2011].

Another method for the delivery of insulin is fast-dissolving films, which are an alternative to oral tablets for rapid drug delivery [Bala, 2013]. The Monosol Rx (Pharm Film Drug Delivery Technology), in collaboration with Midatech Company, developed MidaformTM insulin, which is delivered by buccal route. No information is available on studies using this formulation.

4.1 Smart Insulin

Insulin replacement therapy (IRT) is essential for the treatment of type 1 diabetes mellitus and is often required by patients with late-stage type 2 diabetes. Advances in diabetes technologies have been broadly motivated by the aim to link the optimization of IRT [Ismail-Beigi, 2012]. During a typical 24-hour period, patients on insulin therapy often exhibit episodes of hyperglycemia [Campbell, 2015] because, unlike pancreatic secretion of insulin, standard pharmacological administration of insulin is not regulated by an endogenous feedback mechanism despite individualized dosing regimens [Nimri, 2020] and the broad use of engineered basal and rapid-acting insulin analogues [Vajo, 2001].

Blood glucose shifts outside the narrow blood sugar range that is classified as normal for blood glucose (4.4 = 6.7 mmol/L) are frequent despite strict adherence to dietary and lifestyle recommendations [Dandona, 2017].

The chronic health risks associated with elevated mean glycemia (microascular disease, renal disease, retinopathy, and neuropathy) and macrovare insidious relative to the dramatic presentation of acute metabolic decompensation (diabetic ketoacidosis in T1DM and hyperglycemic coma in T2DM) or the immediate signs and symptoms of hypoglycemia (adrenergic and neuroglycopenic effects leading to anxiety, tremulousness, and altered mental status leading in severe cases to coma [Cryer, 2003]) So, avoidance of hypoglycemia often limits individual hemoglobin A1c goals (an integrated indicator of mean glycemia over three months) and the rigor of current insulin treatment regimens [Rege, 2017].

The range of glucose-responsive ('smart') approaches to control hypoglycemia and prevention of hypoglycemia that are associated with treatment discuss the prospects for mechanism-based molecular design of intrinsic glucose-responsive insulin (GRI) analogues [Bakh, 2017]. Such delivery systems or insulin analogues seek to optimize hypoglycemia by the combined approaches of molecular design of new chemical entities and increased engineering controls to deliver insulin therapeutics. Like (broadly designated GRIs) would endogenous beta cells, such systems provide insulin activity proportionate to the metabolic state.

Accordingly, "smart insulin" systems (broadly designated glucose-responsive insulin; GRI) have attracted the attention of the research community for four decades [Zaykov, 2016]. Such systems are defined as a class of insulin-delivery devices or insulin formulations that provide insulin activity commensurate with the metabolic needs of the patient.

With this in mind, GRIs may be broadly classified as follows:

- Algorithm-based mechanical GRI systems [Halvorson, 2007] in accordance with the above definition
- Polymer-based systems in which insulin is encapsulated within a glucose-responsive polymeric matrix-based vesicle or hydrogel [Ravaine, 2008].
- Molecular GRI analog systems, which involve the introduction of a glucose-sensitive motif to the insulin molecule or its formulation, in either case, conferring glucose-responsive changes to the bioavailability or activity of the hormone [Hoeg-Jensen, 2005].

5. Pill Insulin

Oral insulin therapy holds multiple potential benefits; for example, it would be convenient for patients and would reduce peripheral hyperinsulinemia. While oral insulin preparations have been explored for many years in both animal models and patients, a promising formulation for clinical application has not yet been created. 1338 long-acting oral insulin preparation that was the subject of a recent phase II clinical trial could be an important stepping stone on this path. "Although the present formulation will not be taken forward, we have shown that insulin can be effectively administered orally to patients with T2 DM." In the blind, randomized controlled trial, 49 patients with T2 DM who were currently taking metformin or another oral antidiabetic drug were given either iGlar, a subcutaneously administered insulin preparation, or i338 tablets once daily in the morning for 8 weeks [Van-der-Klaauw, 2018]. At the end of the study, the authors assessed plasma glucose concentration in both groups and found that both treatments were equally efficacious at lowering blood glucose values measured at ten time points throughout the day [Van-der-Klaauw, 2018].

Despite these encouraging findings, the authors note that the total and within-patient variability of fasting blood glucose levels was higher in the i338 group than in the iGlar group.

"The potential benefits of oral basal insulin therapy versus other treatment options still need to be investigated in adequately powered, long-term clinical trials in various patient populations with diabetes mellitus, explains Halberg. "The findings of the present study, however, are likely to encourage the further development of oral insulin products [103].

6. Conclusion

There is a long history of research focusing on identifying a route of administration for insulin that is minimally or noninvasive, effective, safe, convenient, and cost-effective for patients. Each route and delivery method has its own potential advantages and disadvantages. However, if successful, alternative routes of administration could revolutionize the treatment of diabetes mellitus and help improve patients' quality of life.

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