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ORAL INSULIN DELIVERY SYSTEM AND RECENT ADVANCES IN INSULIN DELIVERY

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ABSTRACT

Diabetes is and has remained one of the major lifelong (chronic) disease which may lead to various serious long-term complications viz. heart disease, stroke, kidney failure, foot ulcers and damage to the eyes. Since it is a lifelong disorder and the diabetics have to continue the medications throughout the life, it is imperative that the insulin administration must be feasible, and therefore the development of different approaches for insulin delivery is being studied. This review article covers all the most relevant insulin delivery methods under development, respective technology and clinical data available according to their status of development, the most important among them being the oral insulin delivery system.

Key words: Diabetes, Insulin, Drug delivery.

INTRODUCTION

Diabetes is a chronic lifelong disease which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia). There are basically two types of diabetes: type 1 and type 2.Type 1 diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin to properly control blood sugar levels. It occurs when the body's own immune system attacks and destroys beta cells in the pancreas that are responsible for creating the hormone insulin. Type 2 diabetes formerly called non-insulin-dependent diabetes is a disorder that is characterized by high blood glucose in the context of

insulin resistance and relative insulin deficiency. Type2 diabetes occurs when the pancreas doesn't make enough insulin or the cells of the body become resistant to insulin.

According to a report 347 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of fasting high blood sugar. [1-2] Studies have shown that good metabolic control prevents or delays these complications. Thus, the primary goal of treatment is to bring the elevated blood sugars down to a normal range, both to improve symptoms of diabetes as well as to prevent or delay diabetic complications. Achieving this goal requires a comprehensive, coordinated, patient-centered approach on the part of the health care system. [3]Traditionally, diabetes has been treated by regularly injecting the patients with insulin. The glucose level of the patient is monitored and when hyperglycaemia occurs insulin is injected by the subcutaneous route. The saline solution of insulin is gradually absorbed into the bloodstream via the dermal capillaries, where it reaches its maximum activity at 2 to 3 hours following injection. Certain slow-acting formulations of insulin such as Lente insulin show an even more prolonged effect. [4]

The major drawback associated with subcutaneous route is that it is painful and inconvenient for patients and it may also cause Lipoatrophy at injection sites. Chronic use of the same injection site increases the risk of Lipoatrophy. The fibrotic changes that occur at lipotrophic sites is believed to affect insulin absorption from lipoatrophic areas can result in difficulties in achieving ideal blood glucose control. Lipohypertrophy is the most common cutaneous complication of insulin therapy. Lipohypertrophy adverse effects diabetic control by causing erratic release of insulin into the systemic circulation. [5]

Research studies has been carried out for minimizing these effects and various new approaches for insulin delivery have been developed which includes nasal, pulmonary and oral ,aerosols, hydrogels, micro-capsules, dry powder inhalers, nanospheres, micro-needles, etc. [6]This article describes oral insulin as a approach for insulin delivery, status of oral insulin formulations and other advancements in insulin delivery.

Oral route for delivery of insulin: The oral route for insulin administration is of particular interest as in general oral drug administration results in less pain, greater convenience, higher compliance and reduced infection risk as compared to subcutaneous injections.[7] This would also lessen the incidence of peripheral hyperinsulinemia, which is associated with neuropathy, retinoendopathy, and so forth. An extensive amount of research has been carried

out to improve buccal absorption as it offers an excellent accessibility and a large area for absorption with little proteolytic activity. Some recent pharmacokinetics and pharmacodynamics studies on type 1 diabetic patients, have illustrated that the oral insulin spray showed peak insulin concentrations in relatively shorter time periods, a more rapid onset of action and faster run off as compared to regular subcutaneous insulin.[8] Some other studies on type 1 diabetic patients on multiple daily insulin injections and in insulin-treated type 2 diabetic patients showed that the oral insulin was effective in controlling postprandial glucose levels.[9]

However there are some major challenges associated with oral insulin delivery that includes enzymatic degradation of insulin, lack of insulin permeability through the GIT and dosage form stability issues. The successful oral delivery of insulin involves overcoming the barrier of enzymatic degradation, achieving epithelial permeability, and conserving the bioactivity of the drug during formulation processing. Pharmaceutical strategies have been proposed to maximize oral insulin bioavailability in insulin delivery systems, to overcome barriers, and to develop safe and effective therapies. [10-12]

Approaches for oral insulin delivery

Absorption enhancers: Permeation enhancers improve the absorption of proteins by increasing their paracellular and trans-cellular transports. An increase in paracellular transport is mediated by modulating tight junctions of the cells, and an increase in transcellular transport is associated with an increase in the fluidity of the cell membrane. To improve the permeation of protein drugs through the intestinal wall, absorption enhancers have been used as formulation components, which include detergents, surfactants, bile salts, and Ca^{2+}chelating agents. [13, 14]

Enzyme inhibitors: One of main barriers in oral protein delivery is that proteins can be rapidly degraded by various proteolytic enzymes. To minimize degradation of proteins by various proteolytic enzymes, researchers have used trypsin or a-chymotrypsin inhibitors, such as pancreatic inhibitor [15], soybean trypsin inhibitor[15],camostat mesylate, [16] and aprotinin. [17]

Buccal Insulin: Insulin reaching the systemic circulation by absorption through the buccal mucosa is called buccal insulin. Buccal mucosa lines the inner cheek and buccal formulations are placed in the mouth between the upper gingivae (gums) and the cheek (sometimes

referred to as the buccal pouch) both for local and systemic delivery. The absorption potential of the buccal mucosa is influenced by molecular weight, hydrophilicity, electrostatic charge, conformation, stereospec- ificity, immunogenicity, solubility and partition coefficient of the peptides and proteins including insulin. [18] Researchers have investigated a variety of buccoadhesive formulations including gels, films, tablets, vesicles, nanoparticles, and sponges for this purpose as these are retained for a longer period of time within the buccal cavity.

Insulin spray: Pulmonary drug delivery systems offer an alternate and a better route of insulin administration as compared to other approaches. They are designed to be inhaled by patients in the form of drug dispersions where the active drug within the dispersion can reach the lung. They get readily absorbed through the alveoli directly into blood stream because of large surface area (~140 m2 in adults), high permeability,and vast vascularisation of the lung; and hence provide higher drug efficacy.[19] Insulin spray is another recent approach in delivering insulin through the buccal mucosa. Insulin buccal spray (IBS) was developed using soybean lecithin and propanediol as absorption enhancers. [20]

Oral insulin pills: Insulin administration in the form of a pill has always been an attractive concept in research. Due to numerous limitations of this mode of insulin administration, efficacy has been hard to demonstrate. Research is being focused on overcoming these limitations by stabilizing the degradation, improving the permeability, and adding absorption promoters to protect the insulin as it passes through the stomach.

Buccoadhesive Films: Buccoadhesive films have been recently developed for insulin delivery. These are preferred over mucoadhesive tablets owing to the comfort and flexibility offered by them. They circumvent the short residence time of gels and ointments. However, films must be adequately strong to withstand the breakage due to stress from mouth activities and also, there they must not swell extensively. [21]

Pelleted nanoparticles: Insulin loaded pelleted bioadhesive nanoparticles were developed as an alternative buccal delivery system for insulin. [22] Insulin was encapsulated in polyacrylamide nanoparticles prepared by emulsion internal phase evaporation method. These nanoparticles were pelleted in order to impart three-dimensional structural conformity and coherence. Pelletalization facilitated buccal application and adherence. In-vivo studies on diabetic rats showed a significant glucose lowering after 7h without any risk of

hypoglycemia. In another study, nanoparticle system of insulin (NSI) for buccal transmucosal delivery of insulin was prepared. [23]

Thiolated chitosan insulin tablets: Insulin-loaded thiolated chitosan microspheres let to more than 1.5-fold higher bioavailability and more than 7-fold higher pharmacological efficacy than unmodified chitosan microspheres**.** [24]

Current status of Oral insulin products

IN-105 (Oral Insulin)(Biocon , India): Biocon is developing IN-105 – a conjugated insulin molecule that is orally delivered and targeted towards liver which is a central organ in glucose metabolism. Biocon has successfully developed and scaled up the carefully selected formulation to give a consistent absorption from the GI tract. Currently Biocon is engaged in further clinical development of this molecule for global markets with help from Bristol-Myers Squibb, its partner for this program. Bristol-Myer Squibb will have an exclusive option to further develop and commercialize IN-105. [25]

Generex: Oral-Lyn™: Oral-Lyn is an oral spray formulation of human insulin indicated for the treatment of type 1 and 2 diabetes. It is being developed by Canadian company Generex Biotechnology. In September, 2009, the US Food and Drug Administration (FDA) approved Oral-Lyn under its treatment investigational new drug programme. Generex's Oral-Lyn is a liquid formulation of human insulin that is sprayed into the mouth using its proprietary RapidMist device. In the mouth the insulin is absorbed via the buccal mucosa, an area with a rich vasculature. Generex believes that Oral-Lyn will provide an effective alternative to prandial insulin injections and improve patient compliance with insulin therapy. [26]

Exubera - Inhaled Insulin: The product of a joint development programme between Aventis and Pfizer, Exubera is an inhaled short-acting insulin preparation indicated for the treatment of type 1 and type2 diabetes. In adult type 1 diabetics, Exubera was indicated for use in combination with long- or intermediate-acting insulin, while in type 2 adult patients it could be used in patients requiring insulin therapy and in those not adequately controlled on oral anti-diabetic medications alone. Clinical trials suggest Exubera is effective. Over 2,000 patients have so far received Exubera in clinical trials worldwide, some for as long as five years. Results from the phase III clinical trials suggest that Exubera may be as effective as injected insulin and superior to oral agents in lowering blood glucose in patients with diabetes. [27]

Pluronic F-127 Gel : Pluronic F-127 (PF-127) is a non-ionic poly (ethyleneoxide) 100-poly (propylene) 65- poly (ethylene) 100 triblock copolymer which exhibits a unique property of reversible thermal gelation at concentrations of 20% or more in aqueous solution.[28] Furthermore, its bioadhesive nature, low toxicity and weak immunogenic property make it a suitable polymeric system for controlled mucosal drug delivery.[29] Insulin bearing PF-127 gels were formulated using the unsaturated fatty acids, such as oleic acid, eicosapentaenoic acid (EPA), and docosahexanoic acid (DHA).[30]

Advances in insulin delivery

Dipeptidyl Peptidase-IV Inhibitors: DPP-4 inhibitors work by blocking the action of DPP-4, an enzyme which destroys the hormone incretin. Incretins help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed. These hormones are released throughout the day and levels are increased at meal times. [31]

Medications in the DPP-4 inhibitor family: Sitagliptin; Sitagliptin + Metformin; Vildagliptin; Saxagliptin; Linagliptin; Alogliptin ; Alogliptin + Metformin.

Sitagliptin: In October 2006, sitagliptin became the first DPP-IV inhibitor to gain FDA approval for the treatment of type 2 diabetes. Sitagliptin tablets are commercially available as 100-mg (beige), 50-mg (light beige), and 25-mg (pink) tablets.[32]Sitagliptin is also available in a combination product with metformin in doses of 50 mg sitagliptin/500 mg metformin and 50 mg sitagliptin/1,000 mg metformin.

Clinical trials have demonstrated that sitagliptin is safe and efficacious for the management of hyperglycemia in type 2 diabetes. One phase III trial demonstrated that sitagliptin administered in 100-mg and 200-mg daily doses reduced hemoglobin A1c (A1C) levels by 0.79 and 0.94%, respectively, at 24 weeks. These differences were statistically significant when compared to placebo ($P < 0.001$). [33]

SGLT2 inhibitors: Sodium-glucose co transporter 2(SGLT2) inhibitors are a new class of diabetic medications used for the treatment of type 2 diabetes. They have been studied alone and with other medications including metformin, sulfonylureas and pioglitazone. SGLT2 is a protein that facilitates glucose reabsorption in the kidney. They block the reabsorption of glucose in the Kidney, increase glucose excretion and lower blood glucose levels. [34]

Medications in the SGLT2 inhibitor family: Dapagliflozin, Canagliflozin, Empagliflozin

Insulin Pens: Insulin pens are a very useful way to transport insulin in a discrete way, allowing you to administer insulin on the move .Insulin pens are either disposable one-shot devices or they have replaceable cartridges of insulin. The tip of insulin pens includes a fine, short needle and diabetic patients can turn a dial to select the correct dosage.

Insulin Jet Injectors: Insulin jet injectors are a complex and relatively recent development in diabetes management. This type of device sends a fine spray of insulin through the skin using a high-pressure air current as opposed to a needle.

Insulin inhalers: Insulin inhalers convert a dose of dry insulin using compressed air, providing particles which may then be inhaled. The latest form of inhaled insulin to be approved in the United States is Afrezza. Researchers believe that these new insulin inhaling devices are becoming increasingly successful in the delivery of insulin and in the control of blood glucose levels.

In the clinical studies of Afrezza, the inhaled insulin was shown to reduce incidence of severe hypoglycemia compared to rapid acting insulin injections.

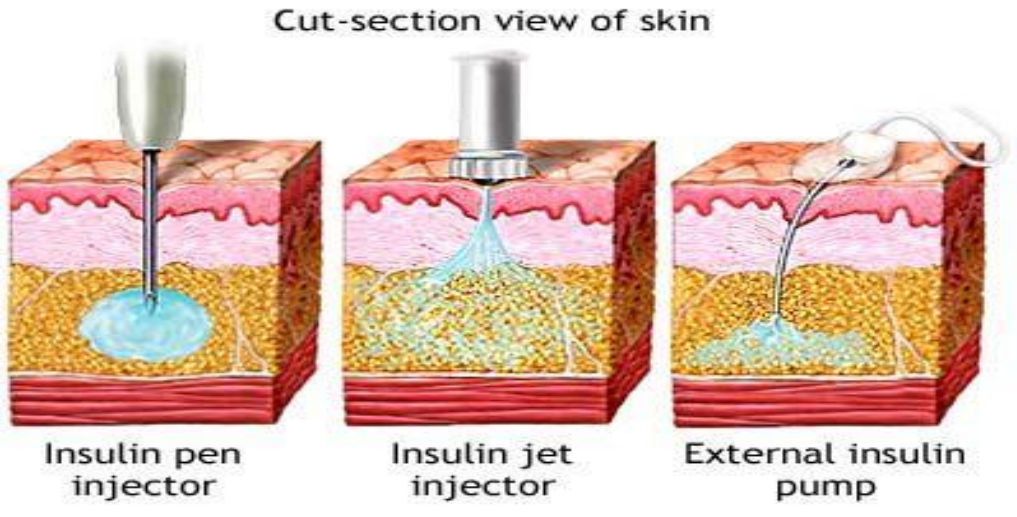

Figure1: Administration of insulin using Insulin pen injector, insulin jet injector and insulin pump[35]

Insulin pump: Insulin pumps are small devices of size of a pager that can be attached to our belt or placed in our pocket. They are made up of an insulin reservoir connected to a tube, ending in a cannula or catheter, which is inserted under the skin of our abdomen. They can be set to deliver insulin at a slow, continuous rate throughout the day, or to release larger

quantities at meal times or when blood sugar is high. The main advantage of a pump is that it closely mimics the slow but continual release of insulin by the pancreas.

Needle and syringe: A common way of administering is with the needle and syringe. Syringes come in range of capacities (1ml, 0.5ml, 0.3ml) with different needle types. Needles have very fine points and special coating to make injections pain free.

Future approaches

Gene Therapy: The gene therapy is developing rapidly as a result of advances in molecular biology. These studies define the potential of gene therapy in treatment of diabetes. Scientists have identified a gene called SHIP2 that appears to regulate insulin. Such findings make SHIP2 a potential gene therapy target for the treatment of type 2 diabetes aimed at improving the individual insulin regulation.

A protein that blocks the overgrowth of blood vessels in the eye is being studied as possible gene therapy for diabetic retinopathy. A recent study showed that treatment with the protein, called pigment epithelium-derived factor, or PEDF, prevented excessive new blood vessel formation in an animal model of retinopathy. It may also be used to treat macular degeneration. [36]

Artificial pancreas: Introduction of continuous glucose sensors [37] has led to development of the artificial pancreas, which made improved care possible. Closed-loop insulin delivery, also referred to as the artificial pancreas, is an emerging therapeutic approach for people with type 1 DM. In this closed-loop, blood glucose control is achieved using an algorithm, wireless communication of a continuous glucose monitor linked to insulin infusion pump that facilitates automated data transfer and delivers insulin, without the need for human intervention. The goal of closed-loop therapy is to achieve good glycemic control with the use of a control algorithm that directs insulin delivery according to glucose levels while reducing the risk of hypoglycemia.

True closed-loop systems, that determine minute-to minute insulin delivery based on continuous glucose sensor data in real-time, have shown promise in small inpatient feasibility studies, using a variety of algorithmic and hormonal approaches. [38]

Edible vaccines for diabetes mellitus: Edible vaccines are those vaccines based on genetically engineered expression of an antigenic protein by an edible plant that trigger an

animal's immune response. In simpler words, they are simply sub-unit vaccines that are edible in nature. Here, the gene of interest is introduced into plants and then these altered plants are induced to manufacture the corresponding proteins. This process is known as transformation and the altered plants are called transgenic plants. [39]Initially thought to be useful only for preventing infectious diseases, it has also found application in prevention of autoimmune diseases, birth control, cancer therapy, etc. [40]

In the case of type1 diabetes, lymphocytes infiltrate the pancreatic islets and selectively destroy the insulin secreting beta cells. One strategy for vaccine development is to reduce the pathological lymphocytic infiltration by tolerisation.[41] Tolerization is defined as any mechanism by which a potentially injurious immune response is prevented, suppressed, or shifted to a non-injurious class of immune response. This process may involve clonal deletion, anergy (unresponsiveness), or active suppression of T cells by regulatory cytokines. Low doses of antigen tend to generate active suppression by TH2- produced regulatory cytokines, primarily TGF-, IL-4, and IL-10. High antigen doses may trigger an anergic response or result in clonal deletion of the auto reactive lymphocytes. Auto antigens given orally have been shown to induce tolerance in animal and human studies with promising results for type1 diabetes. [42]

Nanoparticle Vaccine: Researchers from the University of Calgary in Alberta have developed a vaccine that works well in mice. The researchers have developed a vaccine comprising of nanoparticles which are thousands times smaller than size of a cell. They coated the particles with type 1 diabetes-relevant peptides, or protein fragment that were bound to certain molecules that play a critical role in immune cell communication (called MHC molecules).

In the mice, the nanoparticle treatment expanded a type of regulatory T cell -- these cells ultimately suppressed the aggressive immune attack that destroys the insulin-producing beta cells of the pancreas. The researchers noted that the expanded cells shut down the immune attack by preventing auto reactive immune cells from being stimulated, either by the peptide contained in the vaccine or by any other diabetes autoantigen presented simultaneously by antigen-presenting cells. With the immune response that causes diabetes blocked, mice with type 1 diabetes regained normal blood sugars. [43]

Reverse Vaccine: Researchers at Stanford University are one step closer to discover a cure for Juvenile Diabetes by their "reverse vaccine" which shut down the part of the immune system that attack the insulin producing β- cells. The reverse vaccine uses an engineered plasmid—a small, circular piece of DNA that is separate from chromosomal DNA. The plasmid expresses proinsulin, the precursor of the hormone insulin. The reverse vaccine is an improvement over other proposed cures for Type 1 diabetes that involve immunosuppression, or a more general suppression of the immune response. [44]

GAD-alum/rhGAD65: GAD-alum/rhGAD65 is being developed by Diamyd Medical/Ortho-McNeil Janssen Pharmaceutical. This vaccine helps to preserve beta cell function amongst recent-onset type 1 diabetes mellitus and has also reached phase 3 clinical trial. The vaccine is injected subcutaneously.

CONCLUSION

Several attempts have been made to adopt various effective measures for the surveillance, prevention and control of diabetes and its complications, particularly in low and middle-income countries. In the attempt to make the diabetes treatment more acceptable, many alternative delivery systems and routes of insulin administration have been explored and many challenges are undertaken. Insulin delivery by alternative route is the area of current interest in the design of drug delivery system. In the endeavor to develop alternative insulin delivery technologies, most of the global pharmaceutical companies are showing encouraging progress. Oral delivery of insulin may significantly improve the quality of life of diabetes patients who routinely receive insulin by the subcutaneous route. In fact, compared with this administration route, oral delivery of insulin in diabetes treatment offers many advantages: higher patient compliance, rapid hepatic insulinization, and avoidance of peripheral hyperinsulinemia and other adverse effects such as possible hypoglycemia and weight gain. However, the oral delivery of insulin remains a challenge because its oral absorption is limited. The main barriers faced by insulin in the gastrointestinal tract are degradation by proteolytic enzymes and lack of transport across the intestinal epithelium. Several strategies to deliver insulin orally have been proposed, and some such products have been introduced lately.

The ultimate goal for the treatment of diabetes remains the development of a fully automated glucose controlling device. Although the search for alternative routes to subcutaneous insulin

administration has been relatively unsuccessful, recent approaches seem to hold potential for effective insulin therapy.

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