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Review Article

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Advanced and Recent Emerging Trends in Insulin Drug Delivery Systems

Avinash M*, Suryaprabha M, Sreekanth N, Dineshreddy B, BabuRao Ch

Donbosco PG College of Pharmacy, 5thmile, Pulladigunta, Kornepadu (v), Vatticherukuru (m), Guntur, Andhra Pradesh, India

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Corresponding Author: Dr. Avinash. M*, Donbosco P.G College of Pharmacy, 5thmile, Pulladigunta, Kornepadu (v), Vatticherukuru (m), Guntur, Andhra Pradesh, India

Abstract

In today's era, insulin delivery by alternative route is an area of current interest in the design of drug delivery system. Most of the global pharmaceutical companies are showing encouraging progress in their attempts to develop alternative insulin delivery technologies. For most patients with type 1 diabetes, the tedious part of the treatment is to tolerate needle after needle, both for glucose measurement and to deliver insulin. The introduction of insulin therapy years ago has saved the lives of millions of patients with diabetes. The development of technologies in the last decade have brought to limelight the strategies that hold some promise in turning non-injectable insulin delivery from theory to reality. A rigorous research effort has been undertaken worldwide to replace the authentic subcutaneous route by a more accurate and non-invasive route. Considerable progress has been made to achieve new milestones for effective treatment of diabetes. Peroral, nasal, and pulmonary administration has demonstrated good potential for treatment of diabetes. In addition, transmucosal, buccal, ocular, rectal, and vaginal routes of insulin have also shown to decrease serum glucose concentrations. The transdermal route using various technologies also exhibits success in delivering insulin.

Keywords: Insulin, Glucose, Diabetes, Drug Delivery Methods.

Introduction

Insulin was first discovered by Bating Best in 1921and its crystalline form was first observed in 1926. The demand for novel drug delivery technologies is ever increasing. These drug delivery technologies can be broadly classified into four principle routes like oral, transdermal, inhalation and parenteral. The main goal for the delivery of any drug therapy is oral administration with once or twice daily dosing. However, there are large numbers of therapies, particularly protein-based, gene-based; vaccine-based that cannot be delivered by this route for example insulin, growth hormones and other similar biologics[1]. Insulin is a hormone secreted from the β cells of the islets of Langerhans, specific groups of cells in the pancreas. Insulin is a protein consisting of two polypeptide chains, one of 21 amino acid residues and the other of 30, joined by two disulfide bridges. Deficiency of insulin causes diabetes.

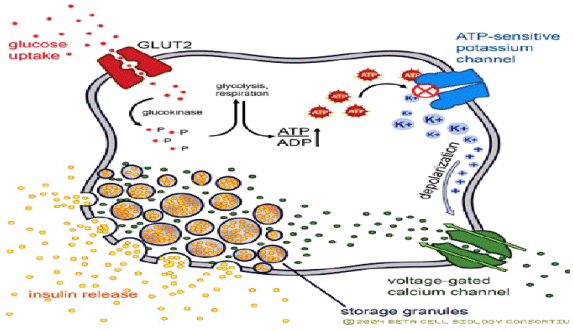
Synthesis and Release of Insulin:

It was released from the endocrine part of pancreas i.e. islets of langerhans.

History and Types of Disease:

About 40% of people with diabetes rely on insulin to maintain control of their blood glucose levels. Patients with Type-1 diabetes are completely dependent on insulin injections. For patients with Type-2 diabetes, which comprises 90% of the world's diagnosed cases of diabetes, about one-third of them rely on insulin as part of their regimen for controlling their blood glucose levels. Normal blood sugar is around 90 to 120mg/dL.

Release of insulin from pancreas



The disease diabetes is of two types mainly diabetes mellitus & diabetes insipidus. It is one of the

major spread diseases in the world.

Drug Delivery Systems:

There are different types of drug delivery systems are involved depending upon the route of administration of insulin. Demand for novel drug delivery systems is increasing.

A) Oral Route
B) Route
C) Inhalation
D) Parental Route
E) Ocular Route

Apart from these types there are few methods are used n delivery systems. They are:

- Insulin pump
- Gene therapy
- Islet cell transplantation

Factors Influencing Blood Glucose And Free Insulin Levels Following Insulin Delivery:

In addition to the delivery system, a wide range of other factors influence blood glucose and free insulin levels following insulin delivery. These include:

(1)Delivery site (inter- and intra-site variations):

- A primary influence, responsible for large variations in insulin absorption, even between the commonly-used sites, which patients are recommended to rotate sites between successive insulin deliveries.
- Insulin delivered in the abdomen is absorbed 86% faster than that delivered in the thigh and 30% faster than in the arm[2].
- This variation in absorptions directly affects blood glucose [3]levels, with 29% lower post-prandial blood glucose levels for deliveries in the abdomen compared with the thigh.
- Duration of insulin action varies with delivery site.

(2)Liver and kidney function[4]:

(3)Skin temperature and fat thickness at injection site[5]:

(4)Presence and degree of lipodystrophy:

- The prevalence of lipodystrophy in diabetic patients has been assessed at as high as 52%[6].

(5)Exercise:

- Absorption is affected in the region of an exercising muscle.

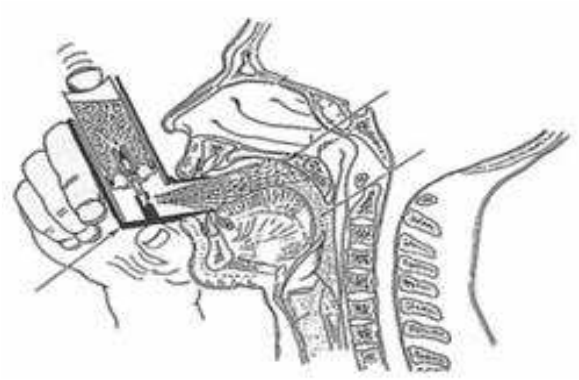
(6)Temperature of injected insulin:

- Insulin peak also occurs earlier when the insulin is stored in a fridge[7].

Modern Technologies for Insulin Delivery:

Insulin inhalers: Inhaled insulin appears to be a non-invasive, well-tolerated and liked modality of treatment with potential for both type-1 and 2 diabetes. Results of short-term studies indicate that glycemic control achieved with an inhaled insulin regimen is comparable with a subcutaneous insulin regimen in patients with type 1 and type-2 diabetes. It has been determined in patients with type 1 diabetes that improvement in overall patient satisfaction with inhaled insulin is rapid and sustainable compared with conventional subcutaneous insulin, and the reduced treatment burden has a positive impact on psychological well-being. Inhaled insulin greatly enhances patient satisfaction, quality of life and acceptance of intensive insulin therapy in a diabetic patient.

Insulin spray: The buccal route is another promising alternative for insulin delivery. With the buccal area having an abundant blood supply, it offers some advantages such as a means to deliver the acid labile insulin, and elimination of insulin destruction by first pass metabolism. The buccal spray formulation being developed by Generex Biotechnology, based in Toronto, delivers insulin to the buccal cavity as a fine spray using company 'rapidmist' device. The patient does not inhale with the buccal spray device; instead, the drug is sprayed onto the buccal mucosa. The high-speed spray allows the drug to be rapidly absorbed into the bloodstream. The deposition of the drug onto the buccal mucosa also allows the developers to bypass earlier concerns about any risks to lung tissue that have been raised regarding investigative inhaled insulin formulation[8].



Insulin pill: To adequately control postprandial glycemia, several daily injections of insulin are necessary. However, insulin therapy via subcutaneous or other parenteral route is known to result in peripheral hyperinsulinemia. In addition to the risk of hypoglycaemia, some studies have suggested that peripheral hyperinsulinemia may be associated with coronary artery disease, hypertension, dyslipidemia and weight gain[9].

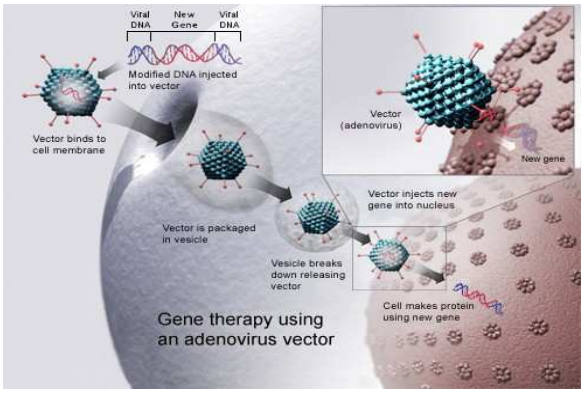
Transdermal Route: The Altea Therapeutics Passport System was the first product in development shown in US FDA clinical trials to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the skin. The PassPort™ System enables fast, controlled drug delivery without the pain of an injection or the possible complications associated with inhaled medications. It also avoids the first-pass gastro-intestinal and liver metabolism that occurs often after oral administration. It creates and effective, economical and patient-friendly delivery of insulin as well as the delivery of drugs for a wide variety of conditions[10].

Figure: The PassPort™ System is comprised of an applicator (on the left) and a reservoir patch; the latter is placed on the skin and provides for painless delivery of insulin.

The insulin transdermal patch maintains constant basal levels while avoiding skin depots of insulin common with subcutaneous injections. As a safety feature, if a patient begins to experience the hypoglycaemia associated with an inadvertent overdose of insulin, they may simply remove the insulin transdermal patch, thus immediately ending the influx of insulin[11].

Gene Therapy: Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. It derives its name from the idea that DNA can be used to supplement or alter genes within an individual's cells as a therapy to treat disease. The most common form of gene therapy involves using DNA that encodes a functional, therapeutic gene in order to replace a mutated gene. Other forms involve directly correcting a mutation, or using DNA that encodes a therapeutic protein drug (rather than a natural human gene) to provide treatment.

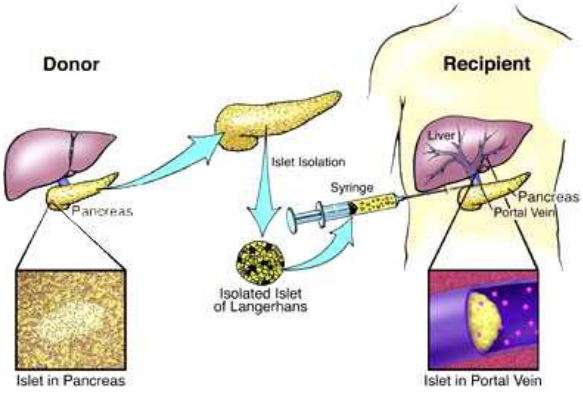
Gene therapy was first conceptualized in 1972, with the authors urging caution before commencing gene therapy studies in humans[12]. The first FDA-approved gene therapy experiment in the United States occurred in 1990, when Ashanti DeSilva was treated for ADA-SCID[13]. Since then, over 1,700 clinical trials have been conducted using a number of techniques for gene therapy[14].



Islet Cell Transplantation: Contrast to conventional insulin treatment, islet transplantation is far superior for achieving a constant normoglycaemic state and avoiding hypoglycaemic episodes. Insulin-producing beta cells are taken from a donor's pancreas and transferred into a person with diabetes. Once transplanted, the donor islets begin to make and release insulin, actively regulating the level of glucose in the blood[15].

Successful transplantation can provide the following benefits:

1. It can eliminate the need for frequent blood glucose measurements and the need for daily insulin injections. Although only a few are free of insulin injections a year after transplantation.
2. It can provide more flexibility with meal planning.
3. It can help protect against the serious long-term complications of diabetes, including heart disease, kidney disease, stroke and nerve and eye damage[16]

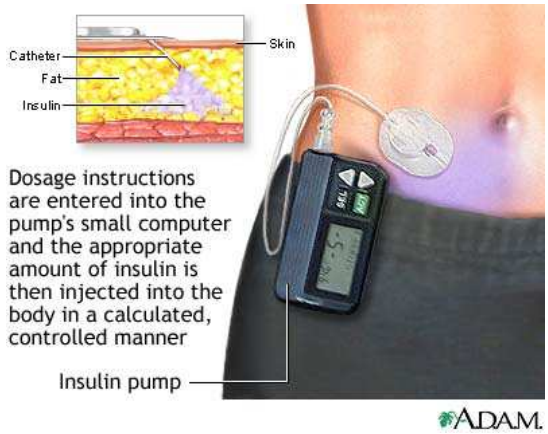


Insulin Pen Injectors: These are the one of major advances in the insulin delivery that has made self -injection easier made and convenient. These are smaller devices that consists of syringe and insulin cartridge and make use or smaller gauge needles that may result in painful injections Another advantage is that it is that desired dose of insulin is precisely selected.

Transfersome: When carriers are applied to administer macromolecules epicutaneously, the drugs must be associated with specifically designed vehicles in the form of highly deformable aggregates and applied on skin non-occlusively. As demonstrated, the application of insulin-laden transfersomes over 40sqcm would provide the daily basal insulin needs of a typical patient with type1 diabetes.Transfersomes mediated drug delivery through the skin is little affected by molecular size of carrier associated over the ingradient.

Dermosonics ha integrated microelectronics and the ultrasonic science into a skin pad called the U-strip™. It uses alternative ultrasonic waveforms to enlarge the pore diameter sufficiently for large molecules of insulin to procced through the skin ultimately reach the bloodstream.thw system consists of 4 parts: the Medi-Cap, Ultrasonic Applicator, the dose controller and the dose report of the physician.

The medi-cap and the tarnsdermal patch that holds the insulin, is applied to the skin. The ultrasonic applicator and the dose controller generate ultra sonic transmissions to dilate the pores and allow the large molecule drugs to enter the blood stream. It adjusts the rate and frequency to dose delivery and records the dose delivered and keeps this in memory for 60 days.



Conclusion

There is a long history of attempts to develop novel routes of insulin delivery that are both clinically effective and tolerable. The various approaches that have been studied to date have involved strategies that are designed to overcome the inherent barriers that exist for protein uptake across the skin, gastrointestinal tract, and nasal mucosa. Nevertheless, the “proof of concept” for many of these approaches appears to have been established. However, it does appear that the most clinically viable system to date may be pulmonary delivery. Two of the devices for pulmonary delivery are in phase III testing, and the results thus far demonstrate comparable efficacy to that of subcutaneous insulin. The pulmonary safety and tolerability data will need to be established before these devices are clinically available. Thus, 25 years after best hoped for and expected “more physiological methods for giving insulin,” systems are in place to achieve his hopes and expectations.

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