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A Review on Insulin Drug Delivery Systems

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Abstract: *Diabetes Mellitus is a metabolic condition marked by elevated blood sugar levels, the presence of glucose in urine, and increased lipid levels. Currently, India holds the title of the diabetes capital of the world, with an estimated 35 million individuals affected by the condition. This number is projected to rise to 52 million by the year 2025. The two primary forms of diabetes mellitus are Insulin-Dependent Diabetes Mellitus (IDDM) and Non-Insulin-Dependent Diabetes Mellitus (NIDDM). Insulin, a protein hormone, is produced by clusters of cells known as islet cells within the pancreas. The discovery of insulin is credited to Frederick Banting and Charles Best. The hormone consists of 51 amino acids arranged in two chains: Chain A contains 21 amino acids, while Chain B comprises 30. Commonly utilized types of insulin include rapid-acting (such aspart or lispro), short-acting (regular insulin), long-acting (ultra Lente insulin), insulin glaring, and insulin detemir. Various insulin delivery systems are available, including syringes, insulin infusion pumps, jet injectors, and pens. Among these, the insulin syringe is the most widely used and cost-effective option. The insulin pump facilitates continuous subcutaneous insulin infusion therapy. A jet injector employs a high-pressure stream of the injection solution to penetrate the skin, eliminating the need for a needle. The pen is a reusable, prefilled device. Numerous insulin delivery devices are currently in development. This review aims to shed light on the role of insulin as a primary therapeutic agent for diabetes, tracing its historical significance to contemporary applications.*

Keywords: Diabetes mellitus; proteins and peptides; Insulin drug delivery systems

I. INTRODUCTION

Diabetes Mellitus is a metabolic condition marked by high blood sugar levels, the presence of sugar in urine, elevated lipid levels, a negative nitrogen balance, and occasionally, the presence of ketones in the blood. One common pathological change associated with this disorder is the thickening of the capillary basement membrane, along with an increase in the vessel wall matrix and cellular growth. These changes can lead to various vascular complications, including narrowing of blood vessels, early stages of arteriosclerosis, hardening of the glomerular capillaries, as well as issues like retinopathy, neuropathy, and peripheral vascular insufficiency.

Types of Diabetes Mellitus

Two major types of diabetes mellitus are as follows,

- Type I or Insulin dependent diabetes mellitus (IDDM)
- Type II or Non-insulin dependent diabetes mellitus(NIDDM)

Type I or Insulin dependent diabetes mellitus(IDDM)

Diabetes Mellitus is a metabolic condition marked by high blood sugar levels, the presence of sugar in urine, elevated lipid levels, a negative nitrogen balance, and occasionally, the presence of ketones in the blood. One common pathological change associated with this disorder is the thickening of the capillary basement membrane, along with an increase in the vessel wall matrix and cellular growth. These changes can lead to various vascular complications, including narrowing of blood vessels, early stages of arteriosclerosis, hardening of the glomerular capillaries, as well as issues like retinopathy, neuropathy, and peripheral vascular insufficiency.

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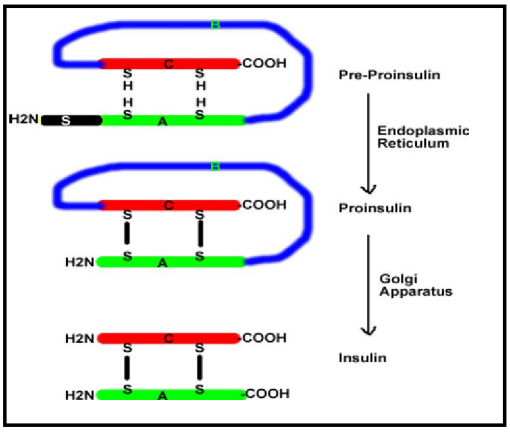
Type II or Non-insulin dependent diabetes mellitus(NIDDM)

Maturity onset diabetes mellitus is another name for this condition. In this type, there is either no loss or only a slight decrease in β cell mass. Insulin levels in the bloodstream can be low, normal, or even elevated, and there are no detectable anti-β-cell antibodies. It tends to have a strong genetic link and usually appears later in life. In fact, more than 90% of cases are classified as type 2 diabetes mellitus.

- There is an irregularity in the glucose receptors of β cells, causing them to react to elevated levels of glucose.
- Decreased sensitivity of peripheral tissues to insulin occurs due to a lower number of insulin receptors. Many individuals with hypertension may have high levels of insulin while maintaining normal blood sugar levels, indicating insulin resistance.

India is currently recognized as the diabetes capital of the world, with around 35 million people living with diabetes. This number is projected to rise to 52 million by 2025. Notably, one in five patients seeing a consulting physician and one in seven visiting a family doctor is diabetic. Given the concerning rise in diabetes cases in India, the World Health Organization (WHO) has officially designated the country as the Diabetic Capital of the world.

SYNTHESIS OF INSULIN



The Golgi complex initiates the process of converting proinsulin to insulin, which proceeds in the secretary granules and is almost finished at the moment of secretion. As a result, the blood contains equimolar levels of insulin and C peptide. While the biological purpose of the C peptide is unknown, it is a helpful indicator of insulin secretion that helps differentiate between individuals receiving insulin injections fraudulently and those who produce insulin spontaneously. In addition, β cells emit trace amounts of des-31, 32 Proinsulin and Proinsulin. This probably signifies either secretion via an alternative mechanism or exocytosis of granules, wherein the conversion of proinsulin to insulin is incomplete. Because proinsulin has a substantially longer half-life in the blood than insulin does, proinsulin and intermediates really make upto 20% of immunoreactive insulin in plasma.

Proinsulin is converted to insulin by two different Ca2+ dependent endopeptidases that are present in the granules of islet cells as well as in other neuroendocrine cells. These endopeptidases, PC2 and PC3, cut at Lys-Arg or Arg-Arg sequences and feature catalytic domains like those of subtilisin. PC2 selectively cleaves at the link between the C peptide and A chain. Additionally, PC3 cleaves preferentially at the A chain junction. Despite the existence of two more Endo proteases, PC2 and PC3 seem to be the primary enzymes involved in the conversion of proinsulin to insulin.

BIOSYNTHESIS OF INSULIN

The cells in the islet are linked by tight junctions that let small molecules move through, helping to coordinate the activity of cell groups. Arterioles flow into the islets and split into a capillary network that resembles a glomerulus in the core of the β-cells. From there, the capillaries extend to the edge of the islet and merge into collecting venules. Blood circulates within the islet, moving from the β-cells to the α and δ cells. This means that the β-cell acts as the main glucose sensor for the islet, while the other cell types likely experience higher levels of insulin. Insulin starts as a

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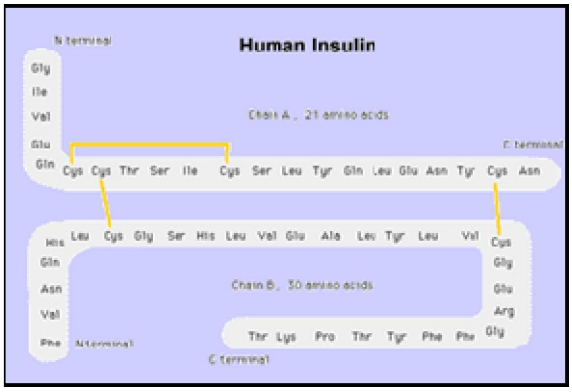
single-chain precursor where the A and B chains are linked by the C peptide. The first product of translation, preproinsulin, has a sequence of 24 mostly hydrophobic amino acids at the start of the B chain. This signal sequence is crucial for the new preproinsulin to associate with and enter the rough endoplasmic reticulum. It gets quickly cleaved, and thepro insulin is sent in small vesicles to the Golgi complex. There, proinsulin is packaged into secretory granules along with the enzyme that converts it into insulin.

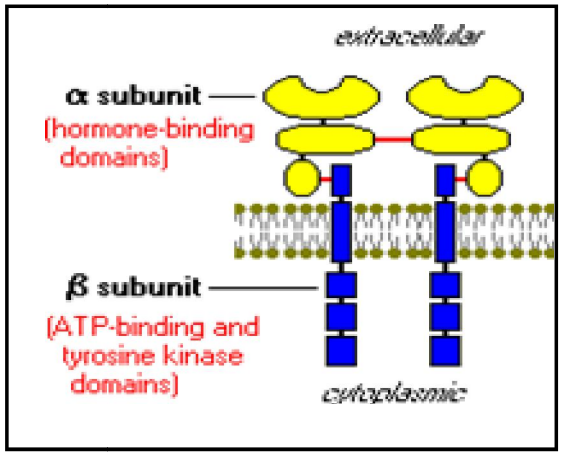
STRUCTURE OF INSULIN

About 6000 molecules make up the polypeptide insulin. Its two disulphide (-S-S-) bridges connect the 21 amino acid amino acid A-chain, which is acidic, and the 30 amino acid B-chain, which is basic. The "connecting" peptide (C-peptide), which is made up of 31 amino acids in humans, connects the A and B chains of proinsulin, the intermediate precursor of insulin within the pancreatic cells. There are 9000 molecules in one molecule of proinsulin. Although all forms of insulin have been synthesised, the majority of the supply now available comes from cows' pancreas (bovine).



MECHANISM OF ACTION

Insulin receptors are fixed in the plasma membrane, just as those for other protein hormones. Two alpha and two beta subunits connected by disulphide bonds make up the insulin receptor. Although the connected beta chains pass through the plasma membrane, the alpha chains are fully extracellular and include regions that bind insulin.



A tyrosine kinase is the insulin receptor. Stated differently, it serves as an enzyme that transfers phosphate groups from ATP to tyrosine residues on target intracellular proteins. Insulin-binding alpha subunits induce autophosphorylation in the beta subunits, which increases the receptor's catalytic activity. Following its activation, the receptor phosphorylates many intracellular proteins, changing their activity and triggering a biological response (Goldfine ID et al 2002). The receptor that the insulin targets is made up of two transmembrane β and two extracellular α subunits connected by

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disulphide linkages. The β subunits exhibit tyrosine protein kinase activity, whereas the α subunits include insulin binding sites.

Insulin aggregation and receptor internalisation are induced when insulin binds to α subunits, followed by released insulin molecules. The β subunit's tyrosine kinase activity is activated, leading to the autophosphorylation of its tyrosine residues. This, in turn, increases the subunit's ability to phosphorylate the tyrosine residues of insulin receptor substrate proteins (IRS1, IRS2). Insulin's fast metabolic activities are subsequently triggered or inhibited by a series of phosphorylation anddephosphorylation processes that follow a prescribed sequence.ByATP-dependently translocating the glucose transporters GLUT4 AND GLUT1 to the plasma membrane and by boosting their activity, insulin promotes glucose transport across cell membranes.

CURRENT INSULIN DELIVERY SYSTEMS

Syringes, insulin infusion pumps, jet injectors, and pens are the insulin delivery methods that are currently on the market for administering insulin.

- Insulin Jet injectors
- Insulin infusion pump
- Pens
- Syringes

Insulin Jet injectors :

A jet injector is a type of medical injectable syringe that was introduced in 1980. Rather of using a hypodermic needle to pierce the epidermis, it employs a high-pressure narrow stream of injection liquid.

Detailed Diagram of insulin jet injector

It is run with compressed air or gas, which can come from a tiny cylinder or built-in gas cartridge, or it can run off a pressure hose from a big cylinder. There are single-shot and multi-shot examples. These methods offer insulin delivery

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without the necessity for piercing the skin with a needle by applying force to a fluid under significant pressure through a tiny opening. Comparing the single component de-sign and dial-a-dosage operation to the traditional multi-component syringe and vial approach, the dose is regulated. The current generation of jet injectors can administer insulin in half-unit increments and have a dosage range of two to fifty units. Insulin delivered by the jet injector technique is quickly absorbed and carries no risk of subcutaneous infection. Jet injection therapy is linked to improved postprandial glycemia and decreased formation of anti-insulin antibodies (AIA) in cases of gestational diabetes.

Advantages:

- faster delivery of insulin to the bloodstream.
- may use less insulin
- doesn't use a needle

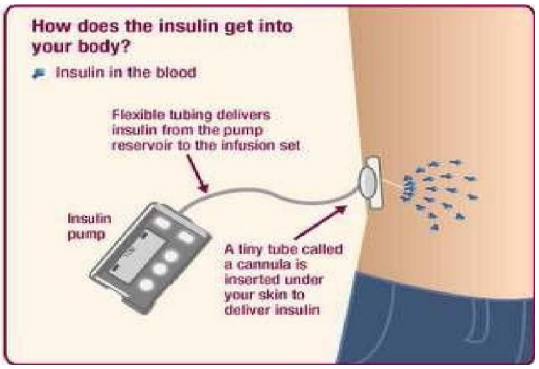
Disadvantages:

- The spray's force, which breaks the skin
- Compared to syringes, most users experience more discomfort while using injectors.
- It has the risks of incorrect dosage, skin damage or pain, and infection

Insulin Infusion Pumps :

INSULINE PUMP

Insulin pumps, also referred to as continuous subcutaneous insulin infusion therapy, are medical devices that are used to administer insulin for the treatment of diabetes mellitus.



Insulin Infusion Pumps Mechanism

The insulin reservoir inside the pump, which is disposable, along with the controls, processing module, and batteries. Disposable infusion set with an insulin reservoir interfaced to a cannula for subcutaneous insertion (beneath the skin) and a tubing system. When combined with blood glucose monitoring, an insulin pump can be used to provide intense insulin therapy as a substitute for numerous daily insulin injections using an insulin syringe or insulin pen. The

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physiology of regular insulin secretion can be replicated with continuous subcutaneous insulin infusion (CSII). In 1974, the market saw the introduction of the first CSII pump.

An insulin pump is normally made up of a reservoir filled with insulin (such as Velosulin® BR), a small battery-operated pump, and a computer chip that lets the patient regulate how much insulin is delivered. The pump can be adjusted to meet the individual needs of the patient and is intended to deliver an uninterrupted supply of insulin infusion 24/7. Through a tiny plastic tube called an infusion set, the pump administers the proper dosage of insulin to the body. Pump systems avoid the majority of factors, such as injection depth and site change, that impact the variability of subcutaneous injections. With these pumps, the subcutaneous catheter—which needs to be changed every two to three days—is connected to the insulin reservoir. Consequently, it is helpful for those who dislike needles because a needle insertion is only required once every three to four days. These fit neatly in a shirt pocket and are comparatively simpler to use than the older models. However, some patients might find it uncomfortable to wear a pump all the time or to remove the catheter before taking a bath or going swimming.

In particular, insulin pumps allow patients to receive insulin accurately and flexibly based on their unique needs, especially when travelling. Insulin microdoses (0.1 units) can be delivered consistently by a few of the infusion pumps currently on the markets

Advantages

- A lot of pump users believe that using a pump to blouse insulin is more covert and convenient than injecting it.
- It gives the individual greater autonomy, flexibility, and freedom in their day-to-day activities.
- More accurate insulin delivery than possible with a syringe is also made possible by insulin pumps.

Disadvantages

- A broken insulin pump could require multiple daily injections until a new pump is delivered.
- Insulin syringes are much less expensive than insulin pumps, cartridges, and infusion sets.
- If the pump user does not receive enough fast acting insulin for several hours, they may experience an episode of diabetic ketoacidosis. If the pump battery gets low, this may occur.

Insulin Pens:

The insulin container and the syringe are combined into a single modular unit, which makes pen devices unique. Carrying syringes and insulin is no longer an inconvenience thanks to insulin pens. Novo Nordisk released the first insulin pen (NovoPen®) in 1987. Since then, numerous pens in a range of styles and forms have become available. Pens are mostly divided into two categories: reusable pens and prefilled ones. In the former scenario, before using an insulin cartridge, the patient must load it. Whichever pen is used, it can hold cartridges that contain 1.5 ml to 3 ml of U100/ml insulin. The various pen device manufacturers have different processes for changing an insulin cartridge using reusable pens. For type 2 patients, prefilled devices are widely accepted as part of their bedtime insulin regimen. Numerous benefits come with reusable insulin pens, including their flexibility to carry a three- to five-day supply and their durability, which eliminates the need for cartridge refrigeration. The refilled insulin pens weigh less and are more compact in size. The smallest and finest disposable insulin needles are the reason they produce the least amount of pain.

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They are also quick and simple to use as They are regarded as discrete and have a fountain pen-like appearance. The pen device manufacturers advise separating the needle and attaching it only when needed. According to a study, recycling insulin pen needles can lessen the environmental impact of diabetes without causing deformity or discomfort. Pencil needles come in a range of gauges (from 29 to 31), and lengths (8 mm to 12.7 mm)—the gauge number indicating how small the needle bore is. The gadgets may improve glycemic control and provide greater flexibility in lifestyle choices. A lot of pens from the latest generation can give type 2 patients 60 U at once. Over 50% of patients receiving insulin use pens in France, one country where insulin pens have gained significant popularity.

Advantages

- Compared to a traditional vial and syringe, more portable and convenient.
- More precise dosages each time
- The size and weight of insulin pens are lower.

Disadvantages

- Pens are typically limited to full or half unit dosing, in contrast to traditional syringes. Moreover, mixing two different types of insulin in one pen is not allowed.

INSULINE SYRINGES:

Among all the delivery devices, this is the most widely utilised and environmentally friendly. It is made up of insulin syringes and a vial or tiny bottle. Because they are thin and short, the syringe needles cause less pain. Coated needles, which further lessen pain, are the result of recent advancements. Gradations on the syringes assist in drawing the proper insulin dosage. The gauge, length, and capacity of the needle are the three characteristics that define insulin syringes. There are many different sizes and styles available from the syringe manufacturers. Many factors, including the chemical makeup of the material used to make syringes and the syringe capacity, must be taken into account when choosing the right syringe.

INSULINE SYRINGE

The first insulin syringes were big and heavy, with barrels that held long, large-bore needles and reusable glass plungers. These days, the market is filled with insulin injection syringes made of plastic that are inexpensive, disposable, and can be used with a wide range of microfine needles.

Advantages:

- It's affordable.
- Its use is simple, even for those with less education.
- Improved patient compliance results from these syringes' ease of use and comfort for the user.

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Disadvantages:

- It is awkward to use at gatherings or parties.
- When two types of insulin need to be mixed and taken, the process becomes a little more involved and time-consuming.
- Compared to other devices like insulin pens, using the syringe is more painful because the needles are slightly thicker.

FUTURE ASPECTS OF INSULIN DELIVERY SYSTEMS:

Provided below is a brief overview of some of the most well-known insulin delivery

Systems:

Insulin Inhalers

Because of their large surface area, the lungs are a prime target for drug delivery. One of the most promising alternatives to injection is pulmonary insulin, also known as inhaled insulin. Over fifty years has passed since the initial attempt to inhale insulin was made. Based on clinical experience, inhaled insulin may prove to be a useful treatment for diabetic patients, especially in the management of postprandial hyperglycemia. Exubera®, which contains powdered rapid-acting insulin, has been thoroughly studied in individuals with both type 1 and type 2 diabetes.

Human insulin is supplied in liquid form by the AERx® Insulin Diabetes Management System (AERx® iDMS).Based on preliminary data, patients who switched from insulin injections to inhalation systems demonstrated better glycaemic control, which is a sign of higher therapy compliance. Investigations are also being conducted on other pulmonary insulin delivery systems, such as Technosphere TM -insulin Med Tone® inhaler (Pharmaceutical Discovery Corp.), AIR® (Al-kermes, Eli Lilly), Spiros® (Dura Pharmaceuticals and Eli Lilly), and ProMaxx® (Epic Therapeutic-Baxter Healthcare Corporation). Regular insulin inhaled by humans absorbs more quickly than insulin injected subcutaneously. However, because pulmonary delivery of insulin involves some drug loss within the inhaler or mouth during inhalation, the efficiency of inhaled insulin is lower than that of subcutaneous injection. However, because pulmonary delivery of insulin involves some drug loss within the inhaler or mouth during inhalation, the efficiency of inhaled insulin is lower than that of subcutaneous injection. The Exubera® device is roughly 25 cm long, with a transparent chamber above that transforms the insulin powder into an aerosol cloud that can be inhaled and a base that can hold an envelope of insulin powder. The apparatus administers 1 and 3 mg doses of powdered insulin, or roughly 3 and 9 units, respectively. Particulate matter that is finely ground can clump together and make it challenging to breathe in, making precise dosage administration less likely. Many inhalers, like those used by some asthmatics, rely on the patient inhaling quickly in an attempt to break up the particles. However, effective treatment does not depend on the patient's ability to correct their breathing. In order to produce an insulin powder cloud that the patient can breathe in slowly and deeply to their lungs, where it dissolves into the blood stream, the inhaler uses compressed air moving at the speed of sound. According to clinical trials, the AERx® iDMS's inhaled insulin regulates blood glucose in a manner that is comparable to that of

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injected insulin, with respect to both absorption and onset of action. This means that it is recommended for dosing right before a meal.

Mouth Sprays

Mouth sprays are not the same as inhalers because they administer insulin via an aerosol spray. Instead of being absorbed through the lungs, insulin from mouth sprays is absorbed through the inside of the cheeks and the back of the mouth. Generex Biotechnology is developing two types of mouth spray: Rapid Mist and Orlin. One of the forms is fast-acting, while the other addresses the basal rate of insulin, which is the quantity of insulin needed to maintain stable blood sugar levels throughout the day.

Nasal Insulin

Due to the quick absorption of insulin through the nasal mucosa, nasal insulin application was thought to be a promising technique for a number of years. More significantly, the metabolic effect was too short-lived to be clinically useful, and the relative bioavailability was low, necessitating the use of absorption enhancers. Insulin delivered by nasal technique has been studied for up to three months, but the results have been disappointing thus far because only 10% to 20% of the dose is absorbed. Additional issues linked to nasal insulin include upper respiratory infections and nasal passage irritation. Even though this approach might work in the future, it is not the most promising one being researched.

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II. CONCLUSION

The syringe and insulin pen remain the most widely used insulin delivery devices, despite the enormous efforts made in developing other ones. Oral or inhaled insulin, however, will undoubtedly take the place of any other insulin dosage form if it helps to sustain the development of the hypoxia.

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