International Journal of Pharmaceutical Development & Technology

e ISSN - 2248 - 910X

www.ijpdt.com

Print ISSN - 2248 - 9096

RECENT TRENDS IN INSULIN DRUG DELIVERY SYSTEM

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ABSTRACT

The advanced methods of insulin delivery systems would gradually progress toward physiological insulin replacement and reduce the long-term complications of diabetes mellitus. Thus, a feasible alternative route for insulin delivery is likely to emerge in the future. This new millennium promises a revolutionary change in the delivery of insulin, which is not too far off for billions of sufferers who are reliant on subcutaneous administration. The approaches that seem to hold potential must be consolidated and converted to a working protocol. This review focused on various alternative delivery systems of insulin and each have their own set of favorable and unfavorable properties.

Keywords: Insulin delivery systems, Insulin, Diabetes mellitus, Hypoglycemia.

INTRODUCTION

Diabetes mellitus is chronic, progressive, systemic, disease characterized by the dysfunction of metabolism of fat, carbohydrates, protein, insulin, function and structure of blood vessels and nerves. Deficiency of effective insulin in the body causes the disease is called Diabetes mellitus. Insulin inhibits catabolic process such as breakdown of glycogen, fat and proteins. Overall effect of insulin is hypoglycemia. Insulin which alters the metabolism of lipids, carbohydrates and proteins results in hyperglycemia and glycosuria. The etiological classification of diabetes includes type 1 and type 2 diabetes. Type 1: It is characterized by destructive lesions of pancreatic β cells by an autoimmune mechanism. It can also be characterized when the β cells of the pancreatic islets of langerhan's are destroyed. It is insulin dependent diabetes mellitus. Type **2:** It is non-insulin dependent. It is characterized by a combination of decreased insulin secretion and sensitivity. Diabetes has traditionally utilized daily subcutaneous injection of human insulin. The development of novel noninvasive routes of insulin administration promises to further improve diabetes management. Many barriers to initiate insulin therapy include need for frequent insulin injection, fears that insulin injections will be painful and difficult to administer [1].

Insulin is a harmone central to regulating carbohydrates and fat metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle. Insulin stops the use of fat as an energy source by inhibiting the release of glucagon. With the exception of the metabolic disorder Diabetes mellitus and Metabolic syndrome, insulin is provided within the body in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic. When blood glucose levels fall below a certain level, the body begins to use stored sugar as an energy source through glycogenolysis, which breaks down the glycogen stored in the liver and muscles into glucose which can then be utilized as an energy source. As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). In addition, it has several other anabolic effects throughout the body [2].

Insulin received by

- Insulin should be considered in diabetics with significant complications like ischemic heart disease, CVA, peripheral artery disease, significant retinopathy, nephropathy and neuropathy, hepatic complications such as viral hepatitis.
- Any diabetic with an acute problem like several infection, injury, etc., should receive insulin

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- Diabetics with tuberculosis often do better with insulin.
- Any Type 2 patient who manifests ketosis for whatever reason.
- Diabetics undergoing most surgical procedures, especially those requiring general anesthesia, and where the patient will be on intravenous fluids for any significant period of time should be stabilized on insulin
- Pregnant diabetics, if not "tightly" controlled with diet alone must be managed with insulin [3].
- Any patient, even if optimally controlled with OHA's who shows evidence that may contraindicate the use of these oral agents, must be shifted to insulin.
- Many underweight patients and those with significant symptoms would do better with insulin therapy, possibly in combination with small doses of sulfonylurea.

Patients Who Should Preferably Use Human Insulin

- All patients who are on beef or porcine insulin and manifest resistance due to the presence of antibodies
- Patients requiring intermittent therapy, i.e. patients with gestational diabetes, those undergoing major surgery, patients with acute infections, etc., who otherwise may be controlled on diet, with or without OHA's, should use Human insulin
- Patients who require very large doses of beef or porcine insulin (>80 units/day), may benefit with changeover to human insulin**.**

TYPES OF INSULIN

Time-Activity Characteristics

Rapid acting

Insulin analogs have been developed by modifying the amino acid sequence of the insulin molecule. This modification alters the time characteristics of activity. The only insulin analog available in India is the rapid acting Lispro. It reaches the blood within 15 minutes after injection. It peaks 30 to 90 minutes later and may last as long as 4-5 hours.

Short acting

Short-acting (regular) insulin usually reaches the blood within 30 minutes after injection. It peaks 2 to 4 hours later and stays in the blood for about 4 to 8 hours.

Intermediate acting

Intermediate-acting (NPH and lente) insulin reach the blood 2 to 6 hours after injection. They peak 4 to 14 hours later and stay in the blood for about 14 to 20 hours.

Long acting

Long-acting (ultralente) insulin takes 6 to 14 hours to start working. It has no peak or a very small peak 10 to 16hours after injection. It stays in the blood between 20 and24 hours.

TRADITIONAL INSULIN DRUG DELIVERY SYSTEM

Insulin therapy via subcutaneous or other parentral route in diabetic patient is preferred but on continuous administration there may be chance of peripheral hyper insulinemia, formation of thrombus, inflammation and irritation at the site. Also patient suffering from needle phobia hesitate to take it [4].

The jet injector gun (fig: 8) and the Ped-o-jet is air-powered medical injector devices designed to administer vaccinations in an extremely efficient manner. Invented by Aaron Ismach. The jet injector is powered by electricity, while the Ped-o-jet version is powered by a foot pump and does not require electricity to administer the vaccines. These devices have various specialized nozzles for different medication densities and also permitted the efficient inoculation of animal populations as well. Care must be taken around high pressure sprays of this kind to avoid such injuries [5].

Devices Preferred By Children

In numerous surveys conducted by bioject, patients consistently prefer the Biojector 2000 over needle-and-syringe. Most patients fear the pain and discomfort of needle-based injections. However, Bioject does not claim that its systems are painless. Some medications and vaccines, for instance, can cause burning and stinging sensations because of their formulations, which are independent of the injection method. For highly needle-phobic patients, such as small children, the biojector has optional “Elephant EARS” which can help reduce anxiety.

VACCINE AGAINST DIABETES ON THE HORIZON

Scientists have developed the world's first drug that stops the destruction of pancreatic beta cells in humans. It thereby offers the possibility of preventing type 1diabetes in people at high risk and of halting its progress in people newly diagnosed with it. Israeli scientists have worked on this agent for more than a decade. To date, 200 patients in Israel, England, Hungary, Bulgaria and Germany have been successfully treated. Results published in a recent issue of *The Lancet* showed that three injections of the compound given within six months of diagnosis of type 1 diabetes successfully arrested the progression of the disease in newly diagnosed patients. After treatment, these patients produced insulin and required fewer insulin injections. They did not experience any harmful or major side effects. While this data looks promising, additional studies are under way to confirm its effectiveness and safety [6].

Insulin infusion pumps

Continuous subcutaneous insulin infusion (CSII) is a way to simulate the physiology of daily insulin secretion. The first CSII pump was introduced in the market in 1974. By design, an insulin pump typically consists of a reservoir filled with insulin (e.g., Velosulin®BR), a small battery operated pump and a computer chip that allows the patient to control the insulin delivery. The pump is designed to

provide a continuous supply of insulin infusion around the clock and can be adjusted as per the specific needs of the patient. Appropriate amounts of insulin are delivered into the body by the pump through a thin plastic tube known as an infusion set. Most of the factors that affect the variability of subcutaneous injections such as depth of injection and change of injection sites are avoided with pump systems. In these pumps, the insulin reservoir is connected to a subcutaneous catheter, which is changed every two to three days. Thus, advantageous for people who do not like injections as it is only necessary to insert a needle once every three to four days. Patient education by a healthcare team is a crucial component of successful insulin pump therapy [7].

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's 'rapidmist' device [8].

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.

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.

INSULIN ANALOGUE

Traditional insulin preparations such as NPH (Neutral Protamine Hagedom) insulin have duration of action 14 h and plasma insulin peak level 4-6 h after administration. As a consequence, NPH insulin may need to be administered up to three times daily in type 1 diabetic patients to provide sufficient insulin supply throughout the day.

Insulin complement

Apart from the new insulin, one new drug, Symylin, is ready to be launched by Gibard Pharma, San Diego. Symylin is a synthetic version of the human hormone amylin, which moderates the glucose lowering effect of insulin. Symylin has been designed to complement insulin action and has been shown to reduce blood glucose without causing an increase in hypoglycemic episodes.

Implantable insulin Pumps

An implantable insulin pump works the same way as an external insulin pump with two major differences: It is implanted just under the skin (usually in the abdominal area) and insulin is delivered into the peritoneal cavity not into the subcutaneous tissue.

Usinga special, highly concentrated insulin, implantable insulin pumps have to be refilled every 2 to 3 months depending on the insulin requirements of the patient. Currently, implantable insulin pumps are used in selected centre in some countries in Europe by specialist doctors.

Transdermal patches

The Altea Therapeutics Pass Port 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 Pass Port 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. 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 [6].

Islet cell transplant

In 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.

Successful transplantation can provide the following benefits

- 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.
- It can provide more flexibility with meal planning.
- It can help protect against the serious long-term complications of diabetes, including heart disease, kidney disease, stroke and nerve and eye damage.

Insulin Pen

Pen devices are novel in that they combine the insulin container and the syringe into a single modular unit. Insulin pens eliminate the inconvenience of carrying insulin and syringes. The first insulin pen (NovoPen®) was introduced by Novo Nordisk in 1987. Many pens are available since then in a variety of types and shapes. There are two main types of pens, one that is reusable and the other a prefilled device. In the former case, the patient must load an insulin cartridge prior to use. Regardless of the type, both pens hold cartridges containing from 1.5 ml to 3 ml of U100/ml insulin. The number of steps required to change an insulin cartridge with reusable pens varies between the different pen device manufacturers. Prefilled devices are well accepted in a bedtime insulin regimen for type 2 patients.

Reusable insulin pens offer a wide range of advantages such as their durability, eliminating the need of cartridge refrigeration and flexibility in carrying three to five day supply. The pens also offer discreetness by resembling fountain pen. The refilled insulin pens are smaller in size and lighter in weight. They cause minimal pain due to the finest and shortest disposable insulin needles. In addition, they are quick and easy to use as they resemble the fountain pen; they are considered to be discreet.

The devices can add lifestyle flexibility and may result in better glycemic control. The precision of insulin doses varies between different pens but remains better than that obtained in studies where traditional syringes were used. Many newer generation pens are able to deliver 60 U at a time for type 2 patients. Insulin pens have become very popular in some countries such as France where over 50 percent of insulin-treated patients are using insulin pens. Some studies indicated wider acceptability in elderly and adolescent patients with respect to easier and faster injection and greater comfort. While pens offer convenience, comfort, accuracy, discretion, durability and ease of storage, patient education is essential in order to avoid operational errors, particularly when changing the cartridge in reusable pens. The proper use of insulin pens has been shown to enhance patient compliance during multiple insulin regimens.

Alternative devices

Insulin pens provide a convenient, easy-to-use way of injecting insulin and may be less painful than a standard needle and syringe. An insulin pen looks like a pen with a cartridge. Some of these devices use replaceable cartridges of insulin. Other pens are prefilled with insulin and are totally disposable after the insulin is injected. Insulin pen users screw a short, fine, disposable needle on the tip of the pen before an injection. Then users turn a dial to select the desired dose of insulin, inject the needle, and press a plunger on the end to deliver the insulin just under the skin. Insulin pens are less widely used in the United States than in many other countries. Insulin pens are a convenient alternative to a needle and syringe for insulin injections [7].

External insulin pumps

External insulin pumps are typically about the size of a deck of cards or cell phone, weigh about 3 ounces, and can be worn on a belt or carried in a pocket. Most pumps use a disposable plastic cartridge as an insulin reservoir. A needle and plunger are temporarily attached to the cartridge to allow the user to fill the cartridge with insulin from a vial. The user then removes the needle and plunger and loads the filled cartridge into the pump. Insulin pumps contain enough insulin for several days. An infusion set carries insulin from the pump to the body through flexible plastic tubing and a soft tube or needle inserted under the skin.

Disposable infusion sets are used with insulin pumps to deliver insulin to an infusion site on the body, such as the abdomen. Infusion sets include a cannula-a needle or a small, soft tube-that the user inserts into the tissue beneath the skin. Devices are available to help insert the cannula. Narrow, flexible plastic tubing carries insulin from the pump to the infusion site. On the skin's surface, an adhesive patch or dressing holds the infusion set in place until the user replaces it after a few days. Users set the pumps to give a steady trickle or "basal" amount of insulin continuously throughout the day. Pumps can also give "bolus" doses-one-time larger doses-of insulin at meals and at times when blood glucose is too high based on the programming set by the user. Frequent blood glucose monitoring is essential to determine insulin dosages and to ensure that insulin is delivered [8].

Injection ports

Injection port provide an alternative to daily injections. Injection ports look like infusion sets without the long tubing. Like infusion sets, injection ports have a cannula that is inserted into the tissue beneath the skin. On

the skin's surface, an adhesive patch or dressing holds the port in place. The user injects insulin through the port with a needle and syringe or an insulin pen. The port remains in place for several days and is then replaced. Use of an injection port allows a person to reduce the number of skin punctures to one every few days to apply a new port.

Insulin port

Using an injection port reduces the number of skin punctures to one every few days to apply a new port. The user injects insulin through the port.

Injection aids

Injection aids are devices that help users give injections with needles and syringes through the use of spring-loaded syringe holders or stabilizing guides. Many injection aids have a button the user pushes to inject the insulin.

Stemcell Technology

A better treatment for type I diabetes is just one of the hopes for stem cell therapy.Stem cells are a type of cell that can be transformed into virtually any of the 200 kinds of cell in the human body. This means that in theory at least, they can be 'grown to order' to help people suffering from degenerative diseases. In practical terms, there are two big challenges: persuading the stem cells to develop into exactly the kind of cell you want, and persuading the body to accept them. It's not easy, but progress has been rapid since the first human stem cell line was created just three years ago. The first big problem with stem cells is where to get them. Everyone has stem cells — they exist in the bone marrow, for example, where new blood cells are constantly regenerating — but in adults and children, these are already partly specialised. Many researchers doubt that they are truly capable of developing into any kind of cell [9].

Insulin nano pump

Advantages of Insulin Nano Pump

Patients with insulin pump report better quality of life compared to using other devices for administering insulin. The improvement in Quality of life is reported in type 1 and insulin-requiring type 2 diabetes subjects on pumps. The use of rapid-acting insulin for basal needs offers relative freedom from a structured meal and exercise regimen previously needed to control blood sugar with slow-acting insulin. The alternative basal insulin, such as the long lasting insulin injected once a day, often release their insulin at a very unpredictable rate. Insulin pumps make it possible to deliver more precise amounts of insulin than can be injected using a syringe. This supports tighter control over blood sugar and Hemoglobin A1c levels, reducing the chance of long-term complications associated with diabetes. This is predicted to result in a long-term cost savings relative to multiple daily injections. Many modern "smart" pumps have a "bolus wizard" that calculates how much bolus insulin you need taking into account your expected carbohydrate intake, blood sugar level, and still-active insulin. Insulin pumps can provide an accurate record of insulin usage through their history menus. On many insulin pumps, this history can be uploaded to a computer and graphed for trend analysis. Neuropathy is a troublesome complication of diabetes resistant to usual treatment. There are reports of alleviation or even total disappearance of resistant neuropathic pain with the use of insulin pumps. Recent studies of use of insulin pumps in Type 2 diabetes have shown profound improvements in HbA1c, sexual performance, and neuropathy pain.

Disadvantages

Insulin pumps, cartridges, and infusion sets are far more expensive than syringes used for insulin injection. Since the insulin pump needs to be worn most of the time, pump users need strategies to participate in activities that may damage the pump, such as rough sports and activities in the water. Some users may find that wearing the pump all the time is uncomfortable or unwieldy. An episode of diabetic ketoacidosis may occur if the pump user does not receive sufficient fast acting insulin for many hours. This can happen if the pump battery is discharged, if the insulin reservoir runs empty, the tubing becomes loose and insulin leaks rather than being injected, or if the cannula becomes bent or kinked in the body, preventing delivery. Therefore pump users typically monitor their blood sugars more frequently to evaluate the effectiveness of insulin delivery. Possibility of insulin pump malfunctioning, and having to resort back to multiple daily injections until a replacement becomes available [8,9].

Insulin Capsule

Insulin capsule chemists have developed polymeric capsules to protect insulin from destructive effect of digestive juices. Stable and remain intact in acid medium and they gradually insulin in a neutral medium.

Future Scope

Painless technology not only plays important role in delivering insulin but also it is used in delivering drugs in flu, hepatitis-B vaccine, growth hormone, female hormones and some antibiotics which are not suitable for oral delivery. A review says “1 million people every year suffer from injury or infection from hypodermic needles, requiring treatment from a health care professional [7,9].

Table 1: Types of Insulin

Type	Onset (hr)	Peak (hr)	Duration	Can be mixed
Rapid acting: Insulin lispro Insulin aspart Insulin glulisine	0.2-0.4 0.2-0.4 0.3-0.5	1-2 1-1.5 1-2	3-5 3-5 2-4	Regular, NPH Regular, NPH Regular, NPH
Short acting: Regular (soluble) insulin	0.5-1	2-4	6-8	All preparations (except glargine)
Intermediate acting: Insulin zinc suspension or Lente Neutral protamine hagedorn(NPH) or isophane insulin	 1-2 1-2	 8-10 8-10	 20-24 20-24	 Regular Regular
Long acting: Protamine zinc insulin(PZI) Insulin glargine.	4-6 2-4	14-20 5-12	24-36 24	Regular None

Table 2. Insulin analog formulation (insulin analog formulations available in pen and doser devices.)

DEVICES	INSULIN	MANUFACTURE
Disposable (Prefilled) Pens: Flexpen Lilly pen soloSTAR	Levemir, novolog mix 70/30 Prefilled Humalog Mix 70/30, Humalog Mix 75/25, Humalog Mix 50/50, humalin N	Novo nor disk ELI LILLY SANOFI-AVANTIS
Durable (cartridge) pens: Novopen 3 Novopen Junior Humanpen LUXURA HUMAPEN memoir DosersInnolet	Levemir, novolg, novolg mix 70/30. Levemir, novolog, novolog 70/30. Humalog, humulin. Humalog. Novolin N, NovolinR, Novolin 70/30.	Novo nor disk Novo nor disk Eli lilly Eli lilly Novo nordisk

Table 3. Sample regimen using insulin NPH and regular insulin

	before breakfast	before lunch	before dinner	at bedtime
NPH dose	12 units		6 units	
regular insulin dose if fingerstick glucose is (mg/dl) [mmol/L]:				
70-100 [3.9-5.5]	4 units		4 units	
101-150 [5.6-8.3]	5 units		5 units	
151-200 [8.4-11.1]	6 units		6 units	
201-250 [11.2-13.9]	7 units		7 units	
251-300 [14.0-16.7]	8 units	1 unit	8 units	1 unit
>300 [>16.7]	9 units	2 units	9 units	2 units

Sample regimen using insulin glargine and insulin lispro

insulin glargine 20 units at bedtime

insulin lispro to be given as follows:

if fingerstick glucose is (mg/dl) [mmol/L]:	before breakfast	before lunch	before dinner	at bedtime
70-100 [3.9-5.5]	5 units	5 units	5 units	
101-150 [5.6-8.3]	6 units	6 units	6 units	
151-200 [8.4-11.1]	7 units	7 units	7 units	
201-250 [11.2-13.9]	8 units	8 units	8 units	1 unit
251-300 [14.0-16.7]	9 units	9 units	9 units	2 units
>300 [>16.7]	10 units	10 units	10 units	3 units

Fig: 1. Structure of insulin

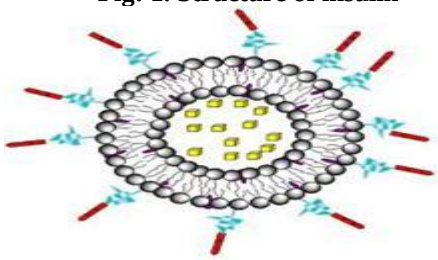


Fig: 2. Human insulin structure

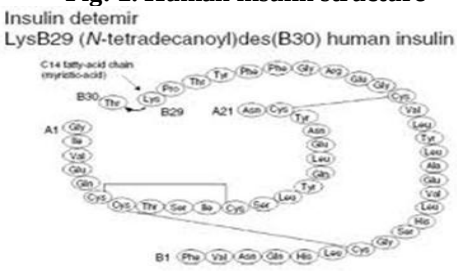


Fig: 3. Rapid acting insulin

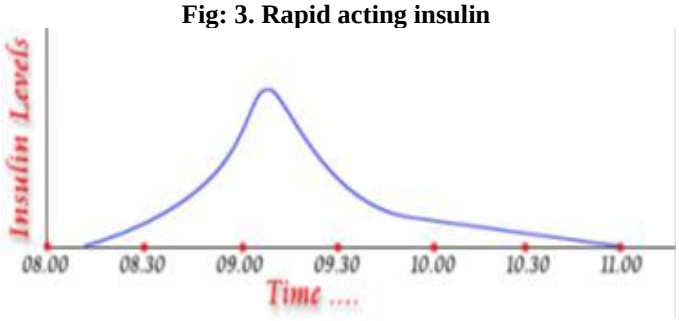


Fig: 4. Short acting insulin

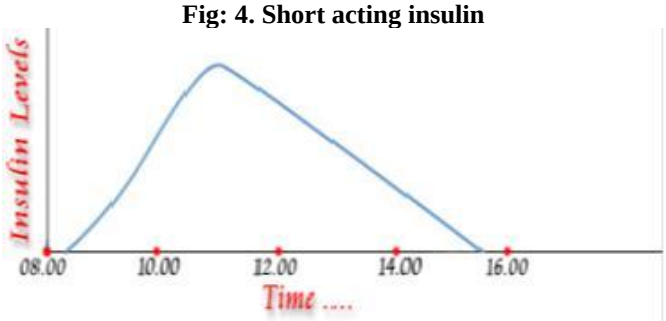


Fig: 5. Intermediate acting insulin

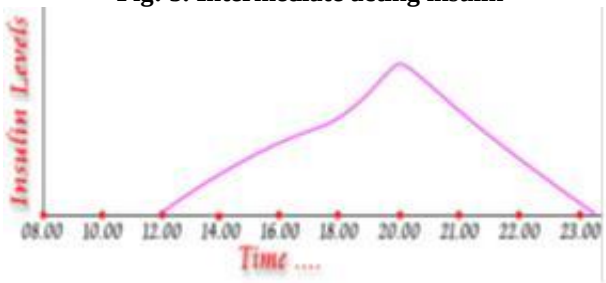


Fig: 6. Long acting insulin

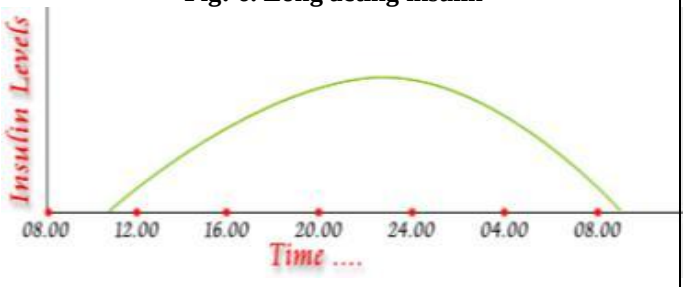


Fig. 7. Jet injector gun

Fig. 8. Jet injector gun

Fig. 9. Needle free insulin for children

Fig 10. Infusion pump

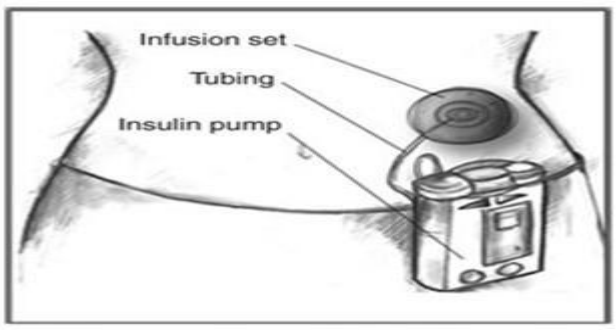


Fig 11. Insulin Inhalers

Fig 12. Insulin Spray

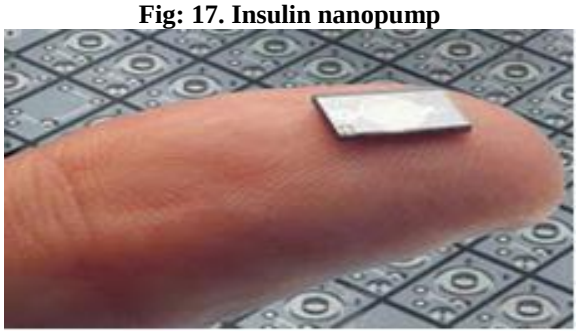
Fig 13. Insulin Spray

Fig 14. Insulin pill

Fig 15. Implantable Insulin Pump

Fig 16. Islet cell transplant

Fig: 17. Insulin nanopump



CONCLUSION

The advanced methods of insulin delivery systems would gradually progress toward physiological insulin replacement and reduce the long-term complications of diabetes mellitus. Thus, a feasible alternative route for insulin delivery is likely to emerge in the future. This new millennium promises a revolutionary change in the delivery of insulin, which is not too far off for billions of sufferers who are reliant on subcutaneous administration. The approaches that seem to hold potential must be consolidated and converted to a working protocol. Among the various alternative delivery systems, each have their own set of favourable and unfavourable properties. Some unfavourable aspects have to be circumvented to make this alternative insulin delivery system a reality and make them to reach the market.

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