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REVIEW ON EFFECTIVE AND COMPATIBLE WAY OF DELIVERING THE INSULIN THROUGH NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

Diabetes mellitus is a metabolic disorder arises due to the insufficient insulin present and improper utilisation of fat in the body. Diabetes mellitus is categorised into Insulin dependent diabetes mellitus, Non-Insulin dependent diabetes mellitus and Gestational diabetes mellitus. Type I Diabetes mellitus is treated using Insulin and Type II Diabetes mellitus is treated with oral hypoglycaemic agents. Gestational diabetes mellitus is treated either with Insulin or oral hypoglycaemic agents. Insulin is always administered by parenteral route for treating type I diabetes mellitus which causes pain due to repeated injections, to overcome this problem and to improve the patient compliance, currently various novel drug delivery systems of Insulin are being developed and used. This article is aimed to enlighten on the diverse novel drug delivery systems of Insulin which is primarily used in the case of Type-I Diabetes mellitus.

KEYWORDS: Diabetes, insulin, novel drug delivery system.

INTRODUCTION

Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time. Symptoms of diabetes mellitus often include polyurea, polyphagia and polydipsia. If left untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, damage to the nerves, and damage to the eyes.

Diabetes mellitus occurs due to either the insufficiency of pancreas producing enough insulin, or the cells of the body not responding properly to the insulin produced.[1-4]

Epidemiology

Diabetes mellitus has been reported as 171 million cases as 2.8% over world population in the year 2000 which is increased to be 366 million as 4.4% in the year 2030. Recent studies showed that in the year 2019, approximately 463 million people are affected with Diabetes mellitus.

Types of diabetes mellitus

Type 1 diabetes results from the pancreas's failure to produce enough insulin due to loss of beta cells. This type is referred as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The loss of beta cells is caused by an autoimmune response. The cause of this autoimmune response is unknown.

Type 2 diabetes begins with insulin resistance, a condition in which blood cells fail to respond to insulin properly. As the disease progresses, a lack of insulin may also develop. This form is previously referred as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The most common cause is a combination of excessive body weight and insufficient exercise.

Gestational diabetes is the third main form, and occurs in pregnant women without a previous history of diabetes with high blood sugar levels.[2,5,6]

Signs and symptoms

The classic symptoms of untreated diabetes are unintended weight loss, polyurea (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes. Other symptoms of diabetes include weight loss and tiredness blurred vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can lead to diabetic retinopathy.and diabetic dermatomes.[7-9]

Prevention and treatment

Prevention and treatment involves maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Control of blood pressure, maintaining proper foot care, and eye care are important for people with the disease. Type 1 diabetes must be managed with insulin injections. Type 2 diabetes may be treated with medications with or without insulin. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 diabetes. Gestational diabetes usually resolves after the birth of the baby.[2,10-13]

Anti-diabetic drugs

Drugs used to treat diabetes mellitus by lowering the glucose level in the blood. With the exceptions of insulin, exenatide, liraglutide and pramlintide, all are administered orally and are also called **oral hypoglycemic agents** or **oral anti-hyperglycemic agents**. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors.

Treatment includes (1) agents that increase the amount of insulin secreted by the pancreas, (2) agents that increase the sensitivity of target organs to insulin, and (3) agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Classification of oral hypoglycaemics

- **Sensitizers**
- Biguanides
- Thiazolidinediones
- Lyn kinase activators

- **Secretagogues**
- Sulfonylureas
- Non-sulfonylurea secretagogues

- Alpha-glucosidase inhibitors
- Glycosurics[14]

Sensitizers

Insulin sensitizers address the core problem in type 2 diabetes – insulin resistance.

1. Biguanides

Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle. It can also be used with caution in patients with impaired liver or kidney function, metformin, a biguanide, has become the most commonly used agent for type 2 diabetes in children and teenagers.Eg., Metformin,,Phenformin,Buformin.[15-17]

2. Thiazolidinediones

Thiazolidinediones (TZDs), also known as "glitazones," bind to Peroxisome Proliferator Activated Receptor-Gamma (PPAR-γ), a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on peroxysome proliferator responsive elements (PPRE) which influence insulin-sensitive genes, which enhance production of mRNAs of insulin-dependent enzymes. The final result is better use of glucose by the cells.Eg., Rosiglitazone, Pioglitazone, Troglitazone[18-21]

3. Lyn kinase activators

The LYN kinase activator tolimidone has been reported to potentiate insulin signaling in a manner that is distinct from the glitazones. The compound has demonstrated positive results in a Phase 2a clinical study involving 130 diabetic subjects.[22,23]

- **Secretagogues**

Secretagogues are drugs that increase insulin output from the pancreas.

1. Sulfonylureas

Sulfonylureas were the first widely used oral anti-hyperglycemic medications. They are insulin secretagogues, triggering insulin release by inhibiting the K_{ATP} channel of the pancreatic beta cells.

- First-generation agents; Tolbutamide, Acetohexamide, Tolazamide, Chlorpropamide
- Second-generation agents; Glipizide, Glyburide Or Glibenclamide,Glimepiride, Gliclazide, Glyclopyramide, Gliquidone

2. Non-sulfonylurea secretagogues

Meglitinides

Meglitinides help the pancreas produce insulin and are often called "short-acting secretagogues." They act on the same potassium channels as sulfonylureas, but at a different binding site. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, thereby enhancing insulin secretion.Eg., Repaglinide, Nateglinide.[24-26]

- **Alpha Glucosidase Inhibitors**

Alpha-glucosidase inhibitors are "diabetes pills" act by slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity. These agents are effective by themselves only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in type 2 diabetes. Eg.,Miglitol, Acarbose, Voglibose.

- **Glycosurics**

SGLT-2 inhibitors block the re-uptake of glucose in the renal tubules, promoting loss of glucose in the urine. This causes both mild weight loss, and a mild reduction in blood sugar levels with little risk of hypoglycemia. Eg., Dapagliflozin,Canagliflozin, Empagliflozin The side effects of SGLT-2 inhibitors are derived directly from their mechanism of action; these include an increased

risk of ketoacidosis, urinary tract infections, candidal vulvovaginitis, and hypoglycemia.[27,28]

Insulin

Insulin was discovered in 1921 by Banting and Best who demonstrated the hypoglycaemic action of an extract of pancreas prepared after degeneration of the exocrine part due to ligation of pancreatic duct. It was first obtained in pure crystalline form in 1926 and the chemical structure was fully worked out in 1956 by Sanger.

Insulin is a two chain polypeptide having 51 amino acids and molecular weight of about 6000. The A-chain has 21 amino acids while B-chain has 30 amino acids.

Table 1: Minor differences between human, pork and beef insulin.

Species	A-chain		B-chain
	8th AA	10thAA	30th AA
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

Thus, pork insulin is more homologous to human insulin than in beef insulin. The A and B chains are held together by two disulfide bonds.

Insulin is synthesized in the β cells of pancreatic islets as a single chain peptide Preproinsulin (110 AA) from which 24 AAs are first removed to produce Proinsulin. The connecting or 'C' peptide is split off by proteolysis in Golgi apparatus; both insulin and C peptide are stored in granules within the cell. The C peptide is secreted in the blood along with insulin.[29]

Insulin is usually given subcutaneously, either by injections or by an insulin pump. Research of other routes of administration is underway. In acute-care settings, insulin may also be given intravenously. Insulins are typically characterized by the rate at which they are metabolized by the body, yielding different peak times and durations of action. Faster-acting insulins peak quickly and are subsequently metabolized, while longer-acting insulins tend to have extended peak times and remain active in the body for more significant periods.

- Rapid acting insulins (peak time at ~1 hour)
- Short acting insulins (peak time between 2-4 hours)
- Intermediate acting insulins (peak time between 4-10 hours)
- Long acting insulins (duration ~24 hours, often with no peak)
- Ultra long acting insulins (duration ~42 hours)

Most anti-diabetic agents are contraindicated in pregnancy, in which insulin is preferred.

Examples of rapid acting insulins include

- Regular insulin (Humulin R, Novolin R)
- Insulin lispro (Humalog)
- Insulin aspart (Novolog)
- Insulin glulisine (Apidra)
- Prompt insulin zinc (Semilente, Slightly slower acting)

Examples of intermediate acting insulins include

- Isophane insulin, neutral protamine Hagedorn (NPH) (Humulin N, Novolin N)
- Insulin zinc (Lente)

Examples of long acting insulins include

- Extended insulin zinc insulin (Ultralente)
- Insulin glargine (Lantus)
- Insulin detemir (Levemir)
- Insulin degludec (Tresiba)[30-32]

Novel insulin drug delivery system: (needle free technology)

Earlier and now-a-days, insulin is administered through parenteral route for Type-1 Diabetes mellitus which should be administered regularly. Parenteral route of administration leads to pain in the patients. Hence to combat patient compliance, a newer method of delivering the insulin through is identified.

Needle free insulin injection provides following advantages:

i. Improve concordance with insulin regiment.

ii. Improve the patient health/well-being.

iii. Eliminates the need for sharp disposal and avoids needle stick injuries.

iv. Emotional benefits of using a needle free devices.

v. Fast injection, insulin is delivered in less than 0.3 seconds, regardless of dose.

vi. No additional pressure required to deliver large doses.

Additional benefits: Very fast injection compared with conventional needle and no needle disposal issue. Organizations such as W.H.O. and C.D.C. (Center for Disease Control) support the development of needle free insulin drug delivery.[33-35]

Devices used in painless insulin drug delivery system.

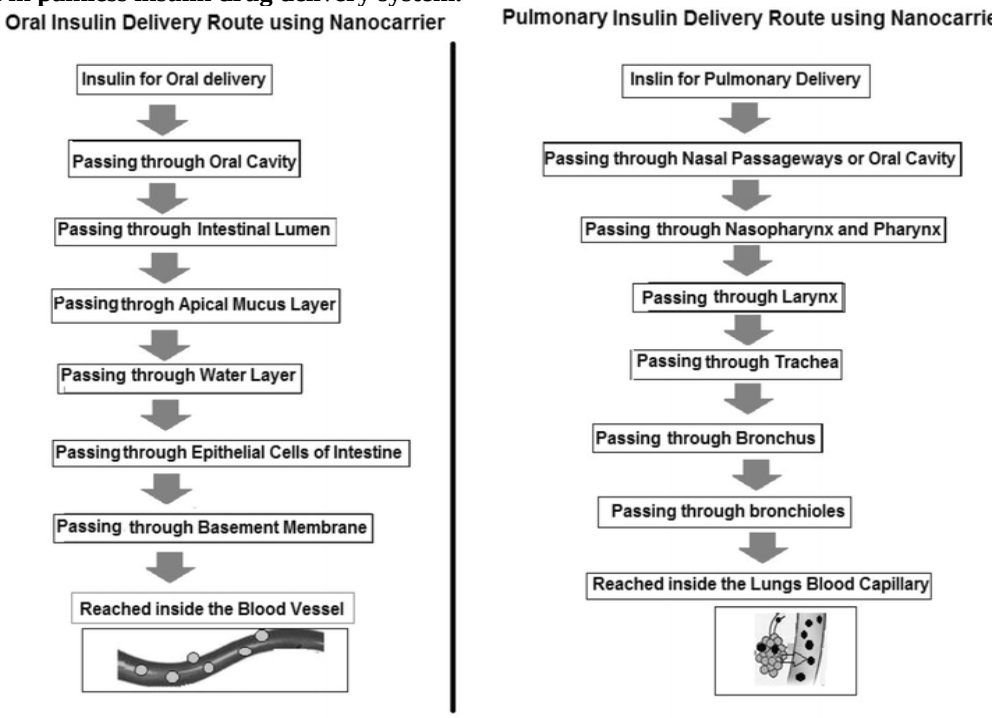

Fig. 1 Major two routes of nanocarrier based insulin delivery.

Due to the drawbacks of conventional injectable insulin, drugs have been modified through nano-carriers with targeting ligands for their selective and targeted delivery meant for oral and pulmonary delivery.

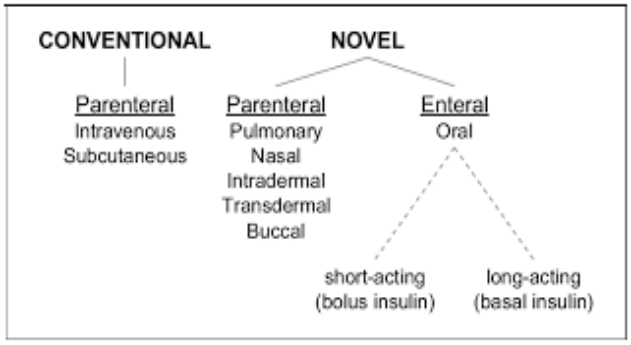

Fig. 2: Different types of insulin loaded nanoparticle based delivery system.

❖ **Jet injector**

A jet injector is a type of medical injecting syringe device used for a method of drug delivery known as jet injection, in which a narrow, high-pressure stream of liquid penetrates without needle the outermost layer of the skin (stratum corneum) to deliver medication to targeted underlying tissues of the epidermis or dermis ("cutaneous" injection, also known as classical "intradermal" injection), fat ("subcutaneous" injection), or muscle ("intramuscular" injection). Jet injectors are used for mass vaccination, and as an alternative to needle syringes for diabetics to inject insulin. Similar devices are used in other industries to inject grease or other fluid.[36-38]

❖ **Jet injector gun**

The Jet Injector Gun 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.

Fig. 3: Jet Injector Gun.

Device 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. For highly needle-phobic patients, such as small children, the biojector has optional "Elephant Ears", which can help reduce anxiety.

Fig. 4 "Elephant Ear" model of Biojector.

Hypodermal jet injectors without needle "JET 2000"
This injector offers the users a valuable alternative to the traditional syringe and it is a painless means for the administration of medicines. Also the cutaneous absorption is faster than the one given by a traditional syringe to a major depth of injection and to a larger cutaneous area concerned. In this way, it is possible to avoid any kind of trauma and the liquid substance is rapidly absorbed by the sub-cutaneous vascular system.

Biojector 2000
The Biojector 2000 is an innovative, versatile needle-free injection system that works by the principle of forcing liquid medication through a tiny orifice that is held against the skin. This creates a very fine, high-pressure stream of medication that penetrates the skin, depositing medication in the tissue beneath. The system has three components, a durable injection device, a disposable needle-free syringe, and a CO_2 cartridge.[39-41]

❖ **Inhalable insulin**
Inhalable insulin is a powdered form of insulin, delivered with an inhaler into the lungs where it is absorbed. In general inhaled insulins have been more rapidly absorbed than subcutaneous injected insulin, with faster peak concentration in serum and more rapid metabolism.[42,43]

Fig. 5 Inhalable Insulin.

❖ **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.

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.[39,41,44]

Fig. 6 Insulin Spray.

❖ **Insulin pen**
Insulin pen is composed of an insulin cartridge (integrated or bought separately) and a dial to measure the dose, and is used with disposable pen needles to deliver the dose. Insulin pens offer several significant advantages over insulin syringes, ease of handling, accuracy, and they are more discreet to use and easier to transport.[45,46]

Fig. 7 Insulin Pen.

❖ **Insulin micropump**
Flamel micro pumps technologies, a controlled release system which permits delayed and extended delivery of small molecule drugs. It is suitable in particularly narrow window of absorption from the upper part of the small intestine.

Description
Flamel micro pump technology consists of a multiple per capsule or tablet containing micro particles per capsule or tablet. The 200-500 mm diameter size microform in the stomach and pass into the small intestine, where each micro particle, operation delivery system release the drug by osmotic pump at a adjustable rate (micro pump first

or delayed for micro pump second) and over and extended period of transit time.[39,41,47]

Fig. 8 Insulin Micropump.

❖ **Insulin port**

An insulin port functions as a medication delivery channel directly into the subcutaneous tissue (the tissue layer located just beneath the skin). When applying the injection port, an insertion needle guides a soft cannula (a small, flexible tube) under the skin. Once applied, the insertion needle is removed and only the soft cannula remains below the skin, acting as the gateway into the subcutaneous tissue. To inject through insulin port the needle of a syringe or insulin pen is used. It is usually used to deliver insulin through the use of an insulin pump.[48]

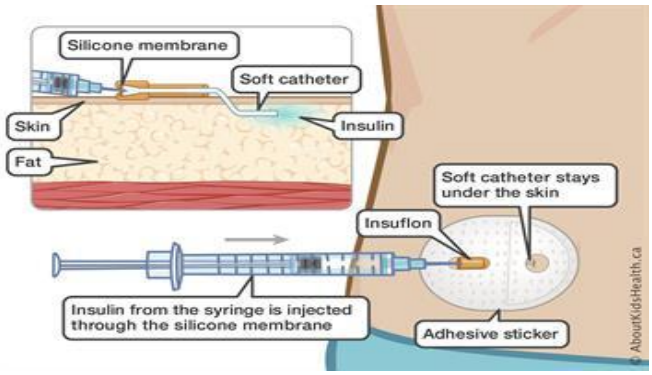

Fig. 9 Insulin Port.

❖ **Transdermal patches**

The Altea Therapeutics Passport System was the first product in developed by US FDA to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the skin. The 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 an effective, economical and patient-friendly 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 hypoglycemia associated with an inadvertent overdose of insulin, the insulin transdermal patch can be simply removed, thus immediately ending the influx of insulin.[49-51]

Fig. 10 Transdermal patches.

❖ **Insulin nanopump**

Based on the Nanopump technology, the Insulin Nanopump offers unmet improvement in diabetes therapy. It is extremely small in size and weight allows wearing it completely hidden under the clothes, its ultra-precision permits an accurate delivery of insulin even at very low delivery rates and independently of external conditions, its built-in functional monitoring guarantees perfect safety during its use and its general conception makes it more affordable for patients.[52]

Fig. 11 Insulin Nanopump.

❖ **Insulin pills**

Earlier, Azopolymer coated pellets were used to deliver insulin to the colon region. The azopolymer protects the entrapped therapeutic agent till the pellets reach the colon. As only the bacteria inhabiting the colon secrete enzymes that can breakdown the azopolymer, insulin release will be initiated once the pellets reach the large intestine. Microencapsulation of insulin in polymeric microspheres coated with pH responsive polymers such as alginate is also known.

Alginate coating protects the spheres in the acidic pH of the stomach but dissolves in the intestine where the pH increases to above 7 and liberates the entrapped insulin. Recently several biotech companies have been conducting pilot trials in the effort to develop an insulin pill as a potential alternative to injected or pumped insulin. The attempt requires the development of novel delivery technology.

For example, Nobex Corporation has developed hexyl-insulin monoconjugate 2 (HIM- 2) in which single amphiphilic oligimer is covalently linked to the free amino group on the Lys-β 29 residues of recombinant human insulin via an amide bond. This alters the physical-chemical characteristics, leading to an enhanced stability and resistance to intestinal degradation of ingested insulin.

Also Depomed, Inc. is developing oral medications using its Gastric Retention (GR) system, an advanced polymer-based, oral drug delivery formulation. Initially small enough to be easily swallowed by the patients, the pill swells following its ingestion. Simultaneously, the system begins a period of extended drug release.

This sustained delivery lead to an insulin pill that provides steady release into the bloodstream, minimizing the number of doses required per day. In trials in Type I diabetic patients, the insulin pill helped control glucose levels as well or better as taking injections of short-acting insulin before meals.[53]

Fig. 12 Insulin Pills.

❖ **Insulin capsule**

Chemists have developed polymeric capsules to protect insulin from destructive effect of digestive juices. Researchers of the Chemical Faculty, Lomonosov Moscow State University have found the way to protect insulin from the destructive effects of the digestive juices and to preserve the ability to perform its function.

These polymeric capsules are stable and remain intact in acid medium and they gradually excrete insulin in a neutral medium. The two polymers used are positive protamin and negative dextransulphate. They form layers in series one upon the other and make a multi-layer covering around the insulin filling, which makes up to 85% of the entire microparticle.

Insulin covered by protective capsule is stable in acidic medium of pH from 1.7 to 5. When pH increases to a level above 5, insulin gets released. Further pH increase of up to 8 results in accelerated protein release rate. Such behavior of particles occurs due to the fact that at pH higher than 5.5 of insulin acquires negative charge and its bond with the negatively charged polymer of the first layer dextransulphate gets destroyed. Such pH-dependence of protective polymeric capsules provides fundamental capability to create insulin in pills.

Fig. 13 Insulin Capsule.

❖ **Insulin tablets**

Physiologist John Raymond Murlin et al (University of Rochester) formulated a compound of insulin and hexylresorcinol which may be swallowed as a tablet. It is effective because the hexylresorcinol neutralizes pepsin and acid, and emulsifies fat. Thus there remains nothing to impede insulin's absorption by the diabetic's sugar-laden body.[54,55]

Fig. 14 Insulin Tablets.

❖ **Islet cell transplantation**

Islet transplantation is the transplantation of isolated islets from a donor pancreas into another person. Once transplanted, the islets begin to produce insulin, actively regulating the level of glucose in the blood. Islets are usually infused into the person's liver. If the cells are not from a genetically identical donor the person's body will recognize them as foreign and the immune system will begin to attack them as with any transplant rejection. To prevent this immunosuppressant drugs are used.[56-58]

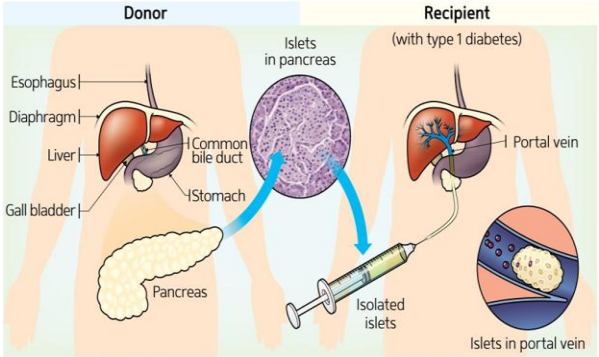

Fig. 15 Islet Cell Transplantation.

❖ **Insulin analogue**

An insulin analog is an altered form of insulin, and available to the human body for performing the same action as human insulin in terms of glycemic control. Through genetic engineering of the underlying DNA, the amino acid sequence of insulin can be changed to alter its ADME (absorption, distribution, metabolism, and excretion) characteristics. Officially, the U.S. Food and Drug Administration (FDA) refers these as "insulin receptor ligands", although they are more commonly referred to as insulin analogs.

There are two types of insulin analogs: those that are more readily absorbed from the injection site and therefore act faster than natural insulin injected subcutaneously, intended to supply the bolus level of insulin needed at mealtime (prandial insulin); and those that are released slowly over a period of between 8 and 24 hours, intended to supply the basal level of insulin during the day and particularly at nighttime (basal insulin). Long acting and Fast acting[59]

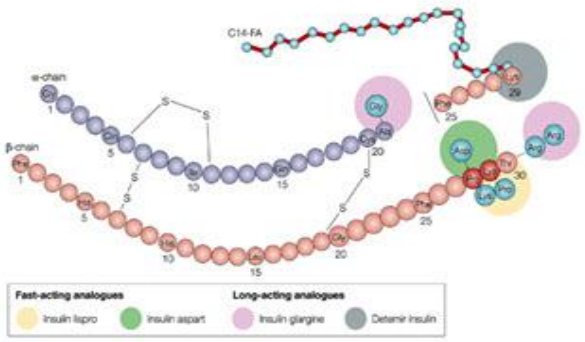

Fig. 16 Insulin Analogue.

❖ **Stem cell technology**

A better treatment for type I diabetes is stem cell therapy. Most of the stem cells now being used in research were originally sourced either from leftover IVF embryos or from aborted foetuses.[60]

❖ **Capsule that delivers the insulin**

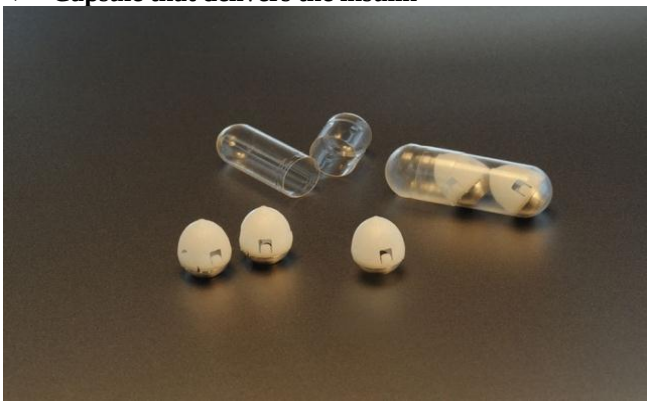

Fig. 17 Capsule that delivers Insulin.

Pills containing miniature hypodermics that can painlessly inject drug into the lining of the stomach have shown promise in initial tests in pigs.Each pill capsule contains a number of tiny injectors. Inside each injector is a needle with a tip mostly made of a dried drug, such as insulin. The shape of these injectors – rounded with a flat bottom – is inspired by the leopard tortoise, and means they self-right within around a tenth of a second after landing of the floor of the stomach, ensuring the needle points downwards.

At the base of the needle is a compressed spring held in place by sugar. When the sugar dissolves in the stomach, the needle is fired down and the tip goes a millimetre or so deep into the stomach lining, where the drug is released and enters the bloodstream.

The stomach wall is 4 to 6 millimeters thick, so the needles should never penetrate all the way through. The stomach lining has no receptors for sharp pain and heals very quickly.

The test results indicated that the pills only work when the stomach is empty, so the pills probably cannot be taken after eating. First thing in the morning would probably be best.[61]

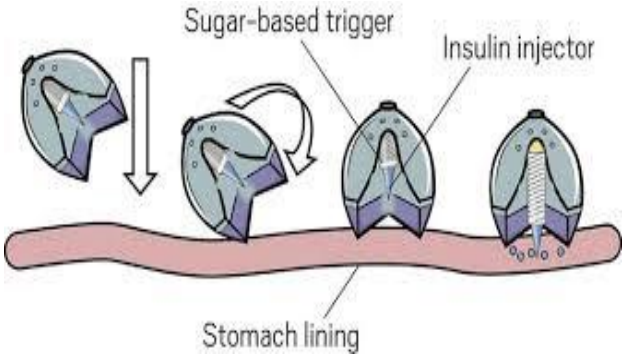

Fig. 18 Orientation of Capsule.

About the size of a blueberry, the capsule contains a single and small needle made of compressed insulin, which is injected after the capsule reaches the stomach. The tip of the needle is made of nearly 100 % compressed, freeze-dried insulin.

The findings, published in the journal Science, showed that the researchers could successfully. More recently, they have been able to deliver from 300 micrograms of insulin to dose of 5 milligrams, which is comparable to the amount that a patient with Type-2 diabetes would need to get injected. Furthermore, no adverse effects from the capsule is found, which is made from biodegradable polymer and stainless steel components.[62]

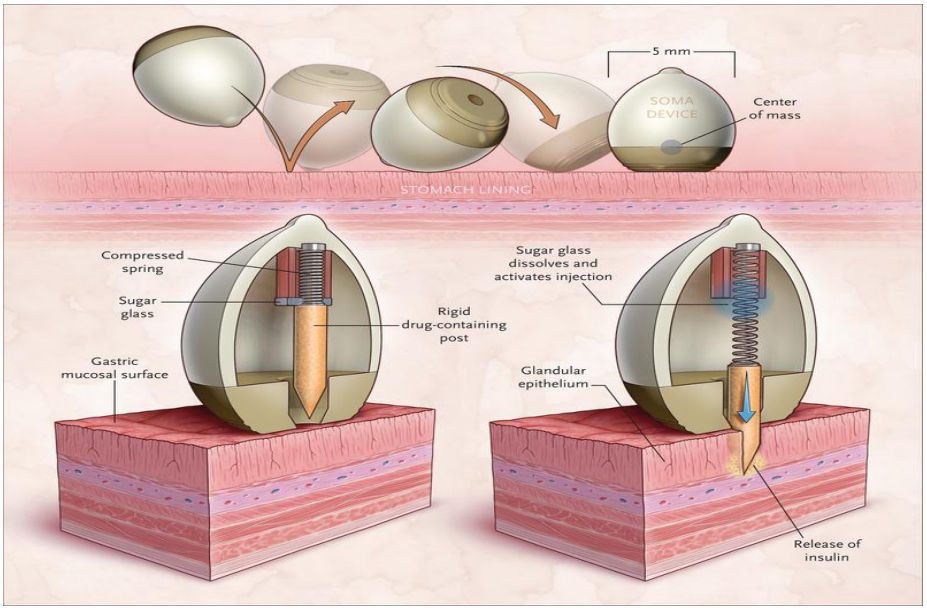

Fig. 19 Orientation and Release of drug from capsule.

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