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THE EMERGING TRENDS OF NANOPARTICLES IN THE TREATMENT OF DIABETES

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Abstract:

The review was carried out to discuss in detail about the polymeric nanoparticles for diabetic treatment. The diabetes is the chronic metabolic disorder characterized by the deficiency of insulin production. The various treatments are available for the diabetes and the nanoparticles are having the several advantages. The various types of nanoparticles are available for the anti-diabetic drugs; the polymeric nanoparticles are the one of the most commonly used nanoparticles. The polymeric nanoparticles are commonly 10-1000nm in size. The polymeric nanoparticles are formulated by drug with the polymers. The main advantages of the polymeric nanoparticles are the simplest preparation method, targeted delivery, the minimizing of the dose and high therapeutic efficiency. In this review was mainly can be focused on advantages, disadvantages of polymeric nanoparticles, various polymers, various formulation techniques, diabetes disease profile, insulin production, various anti-diabetic drugs and the polymeric nanoparticle formulation of anti-diabetic drugs.This route of drug administration is attributed to low patient comfort due to the risk of pain, distress, and local inflammation/infections. Nanoparticles have indeed been suggested as insulin carriers to allow the drug to be administered via less invasive routes other than injection, such as orally or nasally.

Keywords: *Diabetes, Nanoparticle, Liposome, Insulin, Polymer.*

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INTRODUCTION:

In recent years, diabetes mellitus (DM) has become a global epidemic and has been identified as the fifth leading cause of death in the majority of developed and developing nations. Its chronic hyperglycaemia will harm the body's tissues and organs and could result in complications. Recently, diabetes mellitus has become a common metabolic disorder. Diabetes has become a serious medical problem that affects people of all ages, genders, cultures, and races, and its prevalence has been rising at a startling rate. The pancreatic beta cells are primarily responsible for diabetes. As a result, the amount of insulin produced declines, and/or the peripheral tissues become more resistant to the effects of insulin. There are various varieties of diabetes, each with its cause[1].

1. Types of diabetes are:

1.1. TYPE 1 DIABETES MELLITUS- Type 1 diabetes is an autoimmune disease in which insulin deficiency usually occurs due to the destruction of pancreatic beta cells. Insulin-dependent diabetic Mellitus (IDDM) is another name for it. Degeneration of beta cells, viral infection, congenital abnormality of beta cells, and autoimmune disorders are all causes of type 1 diabetes mellitus[2].

1.2. TYPE 2 DIABETES MELLITUS- Type 2 DM is characterised by insulin resistance, insulin deficiency, or both. It is a more typical form of diabetes mellitus. Non-insulin-dependent Diabetes Mellitus is referred to as NIDDM. Type 2 diabetes mellitus is caused by a combination of genetic abnormalities, stress, and lifestyle modifications like poor eating patterns and inactivity. Both oral and injectable medications are available to treat patients with type 2 diabetes.

1. 3. GESTATIONAL DM- This condition affects pregnant people who have never had diabetes before. Later, it might cause T2DM. This type of DM affects approximately 2-5% of all pregnancies but may get better after delivery. By way of its complications, the foetus may develop macrosomia, or high birth weight, as well as cardiac and central nervous system abnormalities[3].

2.Global prevalence and Present scenario of Diabetes mellitus

The projection is that by the year 2030, an estimated 366-438 million (i.e., 7.8% of the world population) people will have diabetes, an increase of 54% compared to that predicted in 2010. According to IDF Diabetes Atlas, an estimate of 415 million people in the age group of 20-79 were diabetic, 5 million deaths owed to diabetes and a total of 673 billion US dollars as global health expenditure due to diabetes were observed in 2015. The diabetics of this age group are only going to increase, that to 642 million by 2040 even with the social, financial, and health system implications. The prevalence and economic burden of diabetes are soaring in developed countries, mainly affecting the lives of the urban poor. The estimated WHO report about the diabetic epidemic in India is that 69.2 million people live with diabetes till 2015 and the scenario to be raised to 98 million by 2030[4].

3.USE OF NANOPARTICLES IN ANTI-DIABETIC THERAPY

Recent years have seen a rise in popularity of nanoparticles due to their advantages in terms of decreased dosing frequency, increased bioavailability, prevention from degradation specifically in the harsh gastric environment, site specificity, and decreased side effects. However, conventional dosage forms have a number of drawbacks, including insolubility in water, gastric irritation, diarrhoea, appetite loss, lactic acidosis in people with abnormal kidney or liver function, and they do not adhere to the patients' safety and efficacy. Nanoparticles were created in order to get around these limitations in conventional dosage forms. They used to offer sustained effective concentration for a longer period of time as well as effective optimal concentration at the desired site of action[5].

Another type of nanodrug delivery system being investigated for the delivery of insulin is nanoparticles. Researchers have created insulin-loaded nanoparticles using a variety of polymers, including dextran, polylactide-co-glycolic acid, and chitosan. Insulin delivery through solid lipid nanoparticles has also been developed. The lymphatic system in the small intestine, which has a mucus layer covering the enterocytes, is known to absorb other types of nanoparticles, mucus penetrating nanoparticles. These nanoparticles are specifically made to pass through this thick mucus layer before reaching the blood stream. Without using invasive methods, nanoparticles enable the controlled release of the medication into intraocular tissues. The amount of drug being absorbed and its bioavailability both rise as the retention time is extended. Site-specific targeting with nanoparticles can reduce the possibility of negative side effects[6].

4.Nanoparticles

Definition:

Nanoparticles are defined as a small tiny particle having a size range of 1-100nm. Nanoparticles are broad class of materials which comprises of specific substances, that have dimension less than 100 nm.

Depending on shape the nanoparticles may be zero dimensional, one dimensional, two dimensional, three dimensional. Nanoparticles are complex molecules itself and thus consist of three layers.
1) the surface layer 2) the shell layer 3) the core.

5.Classification of Nanoparticles:

Nanoparticles are mainly classified in to three classes.

5.1.One dimension nanoparticles

For decades One dimensional system had been used. Monolayer / Thin films (1–100 nm) is now common place in the arena of solar cells recommending, different technological applications, for instance biological and chemical sensors, magneto-optic and optical device, information storage systems, fiber-optic systems[7].

5.2.Two dimension nanoparticles

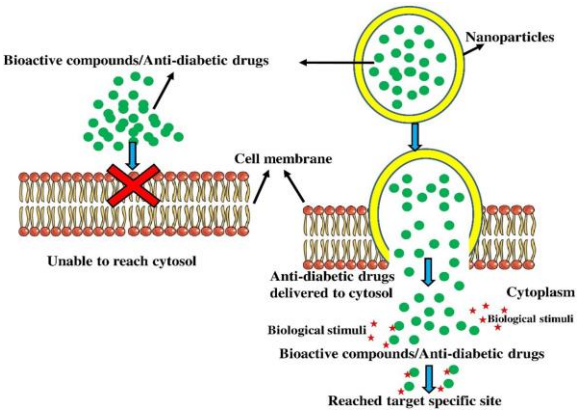
Carbon nanotubes

5.3.Three dimension nanoparticles

Dendrimers, Fullerenes (Carbon 60), Quantum Dots

Another classification based on physical and chemical characteristics;

Carbon-based NPs, Metal NPs, Ceramics NPs,, Semiconductor NPs, Polymeric NPs, Lipid-based NPs, Alloy NPs, Magnetic NPs[8].



6.NANOTECHNOLOGY IN MEDICATIONS

The phrase "Nanotech" refers to manipulating molecular, atomic, and supramolecular levels at which distinctive quantum theory effects occur .Hence, lowering at least one dimension just at nano-sized (1-100 nm) particles entails the configuration, fabrication, characterization, and application of different nano-sized components in different potential areas, resulting in innovative technological progress. Nanoparticles have such several superior properties compared to parent structures because nano-materials seem to be more completely reliant on shape, size, and interactions that are easily accessible. The application of nanomaterials and nanodevices in health and pharmaceutics has paved the way for developing unique nanoscience and nanomedicine areas. Nanotechnology progressions in treatments can be categorized as follows[9].

7.Current types of treatment for Diabetes:

Diabetes management: The management of diabetes is very necessary. The diabetes impact your full body. The following steps are needed to maintain your risk factors under limit and in normal range

- By taking given prescribed medicines , enhancing your activity level and taking a diet plan, maintain your blood glucose levels nearby to normal.
- As possible as maintain your HDL and LDL levels i.e blood cholesterol and triglyceride levels to normal values.
- Keep your blood pressure under control. It should be not more than 140/90 mmHg Diabetes treatment : Treatments for diabetes based on type of diabetes.
- Type 1 diabetes: patient should take insulin every day, if having this type of diabetes. pancreas no longer produces insulin.
- Type 2 diabetes: treatments can comprise medications, insulin and lifestyle changes like as weight losing, producing healthy food selections and being extra physically active[10].

8.DIABETIC TREATMENT WITH NANO-DRUG DELIVERY SYSTEM

Because of their distinctive in-vivo properties, such as good design flexibility, nanoparticle-based drug delivery systems emerged as a potential framework for improving the oral bio- availability of organic drugs. The organicdrugs can be loaded with nanoparticles to improve their con- sistency in the gastrointestinal tract. Furthermore, nanopar- ticles can help organic drugs cross the mucosal barrier and epithelial cell layer, increasing their oral bioavailability in the bloodstream. Numer- ous endeavors have been undertaken to develop oral peptide drugs NPs for diabetes mellitus[11]

9.Use Of Nanoparticles In Treatment Of Diabetes:

Buccal insulin

Oral insulin

Poymeric NanoParticles for parenteral insulin administration

Insulin delivery through inhalable nanoparticles

Intranasal insulin delivery

Transdermal insulin[12]

Biological micro electro mechanical systems for insulin Delivery

Glucose nanosensors

Nanoparticle-based ocular drug delivery systems

Implantable nanomedical device, which comprises pancreatic beta cells from animals[13].

10.USE OF NANOTECHNOLOGY IN THE DETECTION OF INSULIN AND BLOOD SUGAR

A new method that uses nanotechnology to rapidly measure minute amounts of insulin and blood sugar level is a major step toward developing the ability to assess the health of the body's insulin-producing cells. It can be achieved by following way

BY MICROPHYSIOMETER:

The microphysiometer is built from multiwalled carbon nanotubes, which are like several flat sheets of carbon atoms stacked and rolled into very small tubes. The nanotubes are electrically conductive and the concentration of insulin in the chamber can be directly related to the current at the electrode and the nanotubes operate reliably at pH levels characteristic of living cells. Current detection methods measure insulin production at intervals by periodically collecting small samples and measuring their insulin levels. The new sensor detects insulin levels continuously by measuring the transfer of electrons produced when insulin molecules oxidize in the presence of glucose. When the cells produce more insulin molecules, the current in the sensor increases and vice versa, allowing monitoring insulin concentrations in real time[14].

BY IMPLANTABLE SENSOR :

Use of polyethylene glycol beads coated with fluorescent molecules to monitor diabetes blood sugar levels is very effective in this method the beads are injected under the skin and stay in the interstitial fluid. When glucose in the interstitial fluid drops to dangerous levels, glucose displaces the fluorescent molecules and creates a glow. This glow is seen on a tattoo placed on the arm. Sensor microchips are also being developed to continuously monitor key body parameters including pulse, temperature and blood glucose. A chip would be implanted under the skin and transmit a signal that could be monitored continuously[15].

11.RECENT ADVANCEMENT OF NANOPARTICLES IN ANTI-DIABETIC THERAPY

Inadequate insulin administration is a major challenge in controlling diabetes, and nanotechnology in medicine has made insulin delivery more effective. Drug delivery has been a key component of medical advancement for the past 20 years, according to researchers who study the improvement of the medical factor. In this regard, a wide variety of drug delivery methods were acknowledged. In addition to long-term redistribution and drug-assisted release at the target site, these systems will enhance stability and drug therapy concentration in objective tissue. Drug administration occurs less frequently, which improves patient comfort[16].

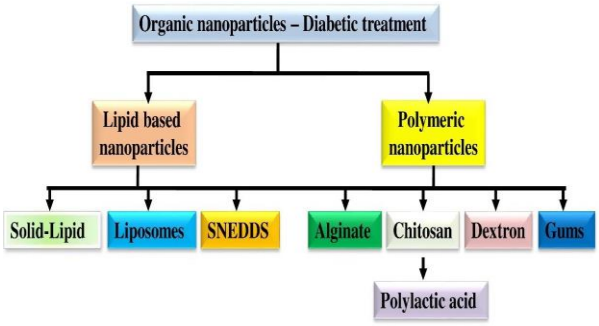


Fig.2

Advantages of polymeric nanoparticles

- Preparation method is easy
- Targeted drug delivery method
- Because of their lesser size Nanoparticles enter small capillary and are taken up through the cell which allows for well-organized drug buildup at the target sites in the body.
- Good control of over size and size distribution.
- Good protection of the compressed drug.
- Retaining of the drug at active site.
- clearance time is longer
- High therapeutic efficacy.
- High bioavailability.
- Dose proportionality.
- Faster dissolution of active agents
- Faster dissolution generally equates with greater bioavailability.
- Lesser drug doses.
- Less toxicity[17].

Disadvantages of polymeric nanoparticles

- Wide use of polyvinyl alcohol as a detergent – subjects with toxicity.
- Limited targeting capabilities.
- Termination of therapy is not possible.
- Cytotoxicity.
- Pulmonary inflammation and pulmonary carcinogenicity.
- The trouble of autonomic inequity by nanoparticles consuming straight result on heart and vascular function[18].

12.ORGANIC NANOPARTICLES

Natural organic polymers-based nanoparticles are low in the production process and cost and abundant in nature. The key benefits of natural organic polymers over inorganic polymers are non-toxicity and biocompatibility. Naturally available polymers such as chitosan, gum rosin, sodium alginate, dextran, and gum arabica have been established to deliver anti-diabetic drugs[19]

A. Chitosan Based Nanoparticles

Chitosan is one of many intestinal permeation boosters that have been used to aid in the absorption of hydrophilic macromolecules. Therefore, if protein drugs are administered orally, a carrier system is required to shield them from the hostile environment in the stomach and small intestine[20]. Furthermore, chitosan nanoparticles (NPs) improved intestinal protein absorption more than chitosan aqueous solutions did in vivo. Due to their pH sensitivity or degradability, the insulin-loaded nanoparticles coated with mucoadhesive Chitosan may prolong their stay in the small intestine, infiltrate into the mucus layer, and subsequently mediate transiently opening the tight junctions between epithelial cells[21].

B. ALGINATE MEDIATED NANOPARTICLES

Alginate is also another natural organic polymer desired after chitosan. Alginate seems to be a water-soluble anion exchange copolymer widely distributed in brown algae cell walls. Alginate's broad pharmaceutical suitability stems from its distinctive tendency to construct hydrogel in the liquid phase or at minimal pH in the occurrence of Ca2+ ions. Electrostatic attraction among oppositely charged groups allows alginate and chitosan to establish polyelectrolyte structures. The low pH dissolution rate of the alginate channel reduces the high pH solubilization of chitosan, which is far poor dissolvable at elevated pH and stabilizes the alginate. The alginate and chitosan blend helps protect the encapsulated drug and is efficiently and slowly released compared to chitosan and alginate alone. For example, the in vitro study revealed that the chitosan and alginate blend considerably increased the releasing period[22].

C. DEXTRAN MEDIATED NANOPARTICLES

Dextran is a polysaccharide with a negative charge easily soluble in water. It is mostly made up of linear - 1,6-linked glu - copyranose residues with 1.3-branching. Dextran is derived mainly from Lactobacillus and Streptococcus cultures grown in a sucrose-enriched environment[23]. Drug encapsulation appears to be difficult due to the poor affinity among water-soluble polymeric (matrix) and lipophilic bioactive compounds. Berberine-loaded O-hexadecyl-dextran nanoparticles were effective as berberine to avoid raised glucose-stimulated cell damage, mitochondrial damage, and reduction of apoptosis in in vitro experiments on hepatocyte. Despite being extremely degradable, the constraint of organic polymers is related to batch-to-batch significant variation since they are typically retrieved from dis - tinct species, provinces, and climates, making them less ap - pealing than synthetic polymers, which are more adaptable and efficacious[24].

13. Metallic Based Nanoparticle

Metallic nanoparticles have made significant strides in the biomedical sciences and can inhibit antibacterial, anti-diabetic, and anticancer effects. Since it has produced impressive results, a decade of research on entrapping plant extracts in metallic nanoparticles has attracted the attention of numerous scientists[25]. Metallic nanoparticles have special qualities that make them advantageous for biotechnology, targeted drug delivery, and potential in vivo imaging, such as large surface areas, specialised functional groups, effective quantum self-assembly, and the capacity to conjugate with the drug of interest. Metallic nanoparticles have also demonstrated a number of benefits, including ease of manufacturing, repeatability, economy, stability, environmental friendliness, and high entrapment efficiency, which makes them a good candidate for a variety of applications. Gold, silver, copper, and titanium-cerium-zinc oxide are among the metals and metal oxides most commonly used in the synthesis and production of metallic nanoparticles[25].

A. Zinc Oxide

ZnO NPs are frequently used for a variety of biomedical purposes, such as anti-inflammatory, anti-cancer, anti-cancer, antifungal, anti-diabetic, and antibacterial activities. In addition to being essential for insulin biosynthesis, secretion, and storage, zinc is also responsible for maintaining insulin structure. Numerous zinc transporters, including zinc transporter8, have been found to be essential for the pancreatic beta cell to secrete insulin, according to research. Zinc may also improve insulin signaling through a number of different pathways, such as elevated phosphoinositide 3-kinase activity, decreased glycogen synthase kinase-3 activity, and increased insulin receptor phosphorylation. Additionally, ZnO NPs can reverse changes in pancreatic tissue brought on by diabetes[26]. According to structural and ultrastructural changes as well as mean biochemical stability around blood sugar and serum insulin, ZnO

NPs reversed pancreatic damage brought on by diabetes. ZnO nanoparticles, alone or in combination with thiamine, have shown to be more effective in the treatment of diabetes. ZnO NPs were discovered in the study to be a promising antidiabetic agent. Also in 2020, a study used a sonochemical technique to create ZnO nanoparticles[27].

B. Cerium oxide Nanoparticles

Calcium phosphate, silica, alumina, or titanium is the materials used to make ceramic nanoparticles. These ceramic nanoparticles are advantageous due to their low size (less than 50 nm), high biocompatibility, and simple preparation methods. They also have good dimensional stability. The insulin was carried by calcium phosphate nanoparticles, which were characterised and studied in vivo. Comparing the effectiveness of this drug delivery systems in vivo performance to that of conventional porcine insulin solution yielded better results. Tricalcium phosphate nanoparticles can be used to deliver insulin orally, according to a recent study[28].

C. Copper Nanoparticles

One of the most significant transitional elements in many biochemical pathways is copper. Cu NPs have superior antioxidant properties, inhibit alpha-amylase and alpha-glycosidase, and are effective trace metal NPs for the treatment of Type 2 diabetes in animals. Cu NPs demonstrated a significant reduction in diabetic cardiovascular defects. These NPs may lessen oxidative stress and improve the vascular endothelium's bioavailability of nitric oxide. A number of earlier studies have demonstrated the value of using copper nanoparticles in the diagnosis of diabetic wounds in mice, not only in controlling the disease but also in promoting faster wound healing. In conclusion, there may be a connection between diabetes patients and Cu NPs[29].

14. Lipid Based Nanoparticles

Biocompatible/biodegradable lipid ingredients are used in lipid-based nano delivery systems, which are generally regarded as safe. Lipids can increase the oral bioavailability of medications that are poorly water soluble, making them absorption enhancers. Drugs that are both hydrophilic and hydrophobic can be successfully encapsulated by lipid NPs, which are lipid-based delivery systems. A lot of research has been done on liposome as drug delivery systems because of how well they can load drugs and are biocompatible.Drugs are wrapped or embedded in a lipid core in lipid-based NPs, which are made up of an inner solid lipid phase and an outer aqueous phase. According to the internal structure of lipid materials, it can be broadly divided into solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Both SLNs and NLCs demonstrated the following benefits: improved solubility, particularly for hydrophobic drugs; avoidance of organic solvents; easily scaled-up synthesis processes; and decreased toxicity through the use of biocompatible and physiologically tolerated lipids components[30].

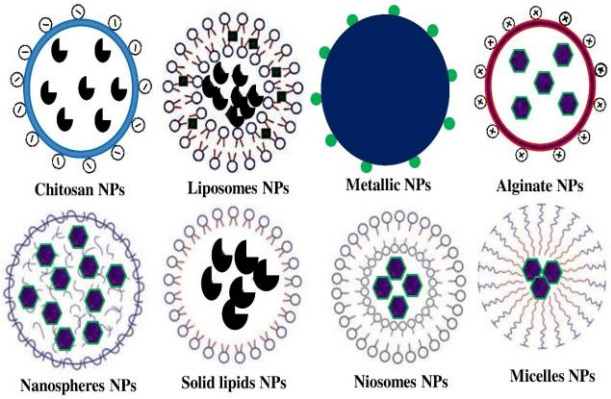
A. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) were created for drug delivery nanoparticulate systems as an alternative to polymeric nanoparticles. Drug bioavailability and solubility can be increased by using solid lipid nanoparticles (SLNs), which are nano size (50-1000 nm) colloidal carriers made of solid lipids (high melting fat matrix). Solid lipid matrices with single layers of phospholipids make up solid lipid nanoparticles (SLNs). When combined with different surfactants, a variety of solid lipids, including triglycerides, fatty acids, and steroids, can produce steric stabilisation in the creation of SLN[31].

B. Niosomes

Niosomes are bilayered nanostructures that self-assemble and are made of cholesterol and non-ionic surfactants. A hydrophilic head that faces the aqueous solvent and a hydrophobic tail make up the bilayered framework (oriented far from the solvent). Their distinctive structure aids in trapping hydrophilic and hydrophobic drugs in the aqueous core and lipid bilayer, respectively. Niosomes have been used as a system to increase the bioavailability of medications with extremely low aqueous solubility and to extend the time that the active medication is available for action at the desired site[32].

C. Liposomes Liposomes are vesicular systems that have been synthesised and are primarily made of a lipid bilayer. An aqueous core and lipid bilayer structure make up liposomes. A liposome is created by the aqueous core and lipid bilayer, and it can carry both hydrophobic and hydrophilic drugs into the body.



Drug solubility is improved by liposomes, which also prevent biological and chemical deterioration when the drugs are stored.The physicochemical characteristics, onset time, and toxicity of the incorporated compounds can all be enhanced[33] .

15 .Polymeric nanoparticles

Depending on the method of preparation of two types of nanoparticles there are solid colloidal particles in 10-100 nm size that call nanospherical and nanocapsules . The nanostructures which are completely different for release drugs that have been as capsules. The nanospherícales are vesicular systems which the drug within a polymeric membrane is limited and the drug are delivered to the target tissue. The polymer is decomposed to lactic acid and glycolic acid finally will restore carbon dioxide and water via the kerbs cycle. Previous studies have been emphasized the use of natural polymers such as collagen, cellulose, etc. as biodegradable systems. Cytotoxicity experiments showed that the drug release from spherical nanospherícals reinforced and does not harm the cells[34].

16. Nanoparticles and oral insulin delivery:

Oral insulin in diabetic patients can not only be helpful to reduce pain and damage caused by the injection, it can also mimic the fate of physiologic insulin. However, oral administration of protein drugs such as insulin faces by the problem of low PH and digestive enzyme of the stomach. Intestinal epithelium as well as a major barrier to the absorption of hydrophilic macromolecules (such as proteins, polysaccharides, and nucleic acids) before it reaches it to target cell for a particular operation. Therefore, improving the delivery of hydrophilic molecules in cell parameters by using nanotechnology has been considered in diabetes research Nano medicine technology may be used for oral delivery of insulin include Pre- drugs (conjugated insulin-polymer), micelles and liposomes, solid lipid nanoparticles and biodegradable polymer nanoparticles. Pre-drug technology are used for the formulation of the drug is often made of polyethylene glycol (PEGylation)[35]

17. USE OF NANOTECHNOLOGY IN THE TREATMENT OF DIABETES

17.1 ARTIFICIAL PANCREAS:

Development of artificial pancreas could be the permanent solution for diabetic patients. The original idea was first described in 1974. The concept of its work is simple: a sensor electrode repeatedly measures the level of blood glucose; this information feeds into a small computer that energizes an infusion pump, and the needed units of insulin enter the bloodstream from a small reservoir. Another way to restore body glucose is the use of a tiny silicon box that contains pancreatic beta cells taken from animals. The box is surrounded by a material with a very specific nanopore size (about 20 nanometers in diameter). These pores are big enough to allow for glucose and insulin to pass through them, but small enough to impede the passage of much larger immune system molecules. These boxes can be implanted under the skin of diabetes patients.

17.2 THE NANOPUMP:

The Nano pump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by DE biotech, is Insulin delivery. The pump injects Insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood.

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Disclosure of conflict of interest

The authors have no conflict of interest to declare.

CONCLUSION:

The DM is an tremendous burden not only for patient's diabetes, but also for their families. All forms of diabetes should be identified as soon as possible, and treated properly to avoid its development and complications. The main reason diabetes treatment fails is non-compliance, primarily due to the unwanted side effects of traditional medicines. The latest discovery shows the potential for using nanoparticles as a treatment for diabetes, it has used ZnO NPs, Cu NPs, Se NPs, CeO2 NPs, and MgO NPs that may have antidiabetic activity. Despite the reality that only a few extreme side effects have been noted during therapies, prolonged human toxicity testing investigation has still been underwhelming. The FDA recently released guidelines to aid in nanoparticle-based clinical products' secure progression. Too much clinical study is necessary. Above all, nanoparticle-based drug delivery methods for T2D treatment are quite a viable anti-diabetic drug delivery strategy. One such review could provide scientists with exciting anti-diabetic organic-based drug delivery methods to investigate further pharmacotherapy opportunities.

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