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Review Article

Nanobetes: A Recent Advancement in Pharmaceuticals

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ABSTRACT

The use of nanotechnology in diabetes research is increasing day by day. It is a branch that involves nanomaterial, nanostructure, nanoparticle design and their application in human beings. It also provides accurate information regarding diagnosis of diabetes mellitus. It increases drug delivery to those areas which were unfavorable to macromolecules. The combination of nanotechnology and medicine has created a new field "nanomedicine" to enhance human health care. Some of the application of nanotechnology include artificial pancreas, instead of pancreas transplantation use of artificial beta cells, for oral delivery of insulin, use of microsphere for biodegradable polymer and many others. Diabetes, or medically known as diabetes mellitus, is a metabolic disease that happens when the person has high blood sugar, also known as glucose, either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. The patients will usually experience polyuria, which is a word for frequent urination. They can also experience 'polydipsia', which means the patient will become very thirsty, or 'polyphagia', which means the patient, will experience extreme hunger. All types of diabetes are treatable. Type-1 diabetes lasts a lifetime, there is no known cure, but there is something that makes it less severe. Usually, type-2 diabetes lasts a lifetime; however people have managed, through a lot of exercise, diet and excellent body weight control to get rid of their symptoms without using medications. Diabetes is a sickness that affects the body and does not properly allow food to use as energy. When someone experience diabetes, the body does not make enough insulin or cannot use its own insulin as well as should. This causes sugars to build up in the blood. This is why people sometimes relate diabetes with sugar. The recent trends in nanotechnology in diabetes have developed the novel glucose measurements and insulin delivery modalities, which improves the patient's safety and quality of life. This article reveals about the application of nanotechnology (Nanomedicine) in diabetes, which brings a new outlook and advancement in the treatment and management of diabetes.

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1. Introduction

Nanotechnology is a leading scientific technique, that offers technologies that provide more accurate and timely medical information for diagnosing disease, and miniature devices that can administer treatment automatically if required. Some tests such as diabetes blood sugar levels require patients to administer the test themselves to avoid the risk of their blood glucose falling to dangerous levels. Certain users such as children and the elderly may not be able to perform the test properly, timely or without considerable pain (Veiseh *et al*., 2015). Nanotechnology can now offers new implantable and/or wearable sensing technologies that provide continuous and extremely accurate medical information. The purpose of this review is to throw more light on the recent advances and impact of nanotechnology on biomedical sciences to cure diabetes (Prausnitz & Langer, 2008). The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. The application of nanotechnology to medicine holds many possible advantages, Nanomedicine has also enabled more robust insulin delivery systems that can detect fluctuation in blood glucose levels and automatically modulate the rate of insulin release to maintain normoglycemia (WHO diabetes Care, 2004). It has been seen that diabetes is now a most common diseases of youth and middle age people. The application of nanotechnology in medicinal field called nanomedicine. It has been define as "Research and technology development at the atomic, molecular and macromolecular level in the nano range to provide a fundamental understanding of phenomena and material at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size" (Arya *et al*., 2008).

2. Diabetes

Diabetes, or medically known as diabetes mellitus, is a metabolic disease that happens when the person has high blood sugar, also known as glucose, either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. The patients will usually experience polyuria, which is a word for frequent urination. They can also experience 'polydipsia', which means the patient will become very thirsty, or 'polyphagia', which means a patient, will experience extreme hunger. All types of diabetes are treatable (Kuzuya *et al*., 2002) .Type 1 diabetes lasts a lifetime, there is no known cure, but there is something that makes it less severe. Usually, type two diabetes lasts a lifetime; however people have managed, through a lot of exercise, diet and excellent body weight control to get rid of their symptoms without using medications. Diabetes is a sickness that affects the body and does not properly allow food to use as energy (Arya *et al*., 2008).

2.1. Pre-diabetes

Before a person suffer from type-2 diabetes mellitus, they have pre-diabetes, blood glucose level is higher than the normal level but not high enough to be diagnosed as diabetes, this may be due to the fasting glucose tolerance. Type-1 diabetes is caused by combination of genetic susceptibility and environmental factors. In Type-2 diabetes pancreatic cell becoming resistant to the action of insulin, and pancreas is unable to make enough insulin to overcome this resistance (Anonymous, 2009). Gestational diabetes is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy and other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis- related diabetes, steroid diabetes include by high dose of glucocorticoids and several forms of monogenic diabetes. Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking, alcohol and maintain a healthy body weight. Diabetes contributes to high blood pressure and linked with high cholesterol which significantly increases the risk of heart attacks and cardiovascular disease (Diabetes atlas, 2009).

3. Nanotechnology in diabetes (nanobetes)

Nanotechnology possesses rapid advances in the treatment and diagnosis of Diabetes. By diagnosis it can be achieved by following ways by microphysiometer and implant sensor, similarly in treatment by development of microsphere for oral insulin production, artificial a pancreas and Nanopump. Nanobot are nanotechnological device nanomachine, also known as nanite. This is a mechanical device whose dimension is measured in nanometer. Nanobetes can get energy by eating enough molecules in their environments so they can duplicate themselves. They are as little machine, tiny robots that scurry around and do things. They are very small, in a category of microscopic level. 'Nanobots' names come from the word nanometer, the scale that nanobots are made, with the combination of robot. The term nanobots may also be occasionally used to describe a macro-robot that is able to interact at the Nanoscale, using incredibly tiny tools. There are four parts of nanobot. They are the micro-camera, the payload, the capacitor, and the swimming tail. If a person went to the doctor's office to get a treatment for repetitive fever, doctor would not give him a pill or a shot, instead he/she would provide to a particular, special medical team that applies a microscopic robot into his bloodstream. The robot searches for the cause of his fever, travels to the correct system and provides a dose of medication directly to the infected area (Mo *et al.,* 2014). There are three main choices scientists keep their attention on when they are looking at nanobots going through the body. They are navigation, power, and how the nanorobots move through blood vessels. Nanotechnologists (people who study the technology of nanobots) are looking at different selections for each of these choices, while each one has positive and negative aspects. The nanorobots also could emit the radioactive dye, making a pathway behind it as it moves through the body (Nimase *et al*., 2013). Other ways of locating the nanobot include using x-rays, radio waves, microwaves or heat. Right now, technology using these methods on these Nano-sized objects is limited, so it's much more likely that future systems will rely more on other ways Nanobots have especially changed cancer research and other serious diseases. It is thought that once the nanobot has been fully developed, the design may be changed to produce cancer-killing nanobots that swim through the bloodstream, identify a tumor, and remove it cell by cell with some type of laser or similar treatment until the entire cancerous growth has been removed, right down to the last molecule (Anonymous, 2008).

3.1. Microphysiometer (Figure 1)

They are multi walled carbon nanotubes, like flat sheets of carbon atoms stacked into very small tubes. They are used to detect and monitor the response of cell to variety of chemical substances such as ligand specific plasma membrane receptor. In presence of, glucose insulin molecules get oxidized leading to continuous electron transfer and thus microphysiometer (sensor) detects the insulin level. The current in the sensor is directly proportional to the insulin molecules produced by the cells and through this mechanism monitoring of insulin concentration can be done (Gordon *et al*., 2003; Mutharasi *et al*., 2017).

3.2 Implantable sensor (Smart tattoo)

It is used for measuring tissue glucose concentration. The implantable sensor is designed to give diabetes patients an alternative to finger-sticking of short term glucose sensors, as well as limit dangerous glucose level fluctuation known as glucose excursions. The first long term implantable CGM (Continuous glucose monitor) sensor wirelessly sends glucose data to the smart transmitter worn on the upper arm above where the sensor is implanted. In turn the smart transmitter

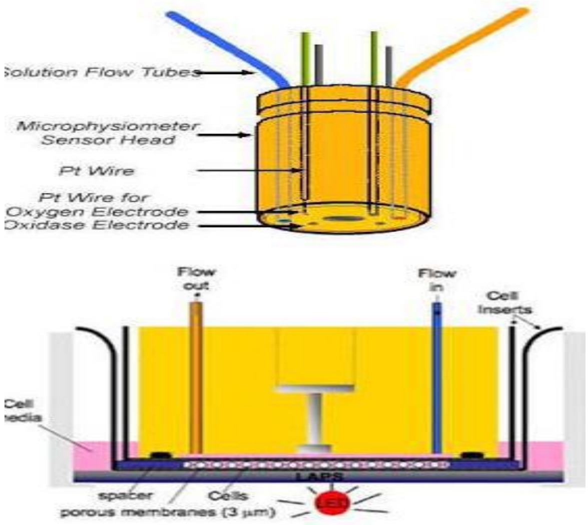

Figure 1. Microphysiometer (Mutharasi *et al*., 2017)

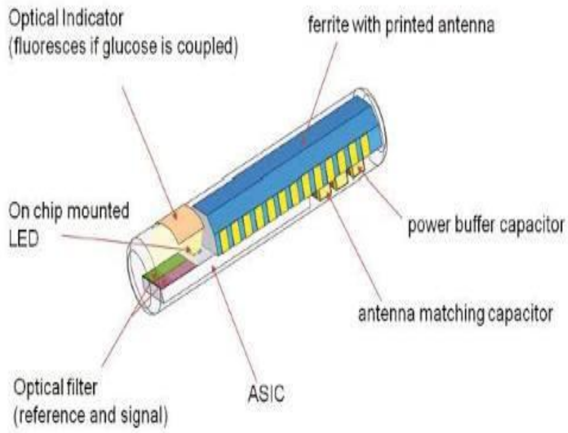

Figure 2. Implantable sensor (Mutharasi *et al*., 2017)

calculates the current glucose value along with the direction it's headed, how fast, and whether glucose values are expected to exceeds pre-set low and high targets (Figure 2) (Harsoliya *et al.,* 2012; Mutharasi *et al*., 2017).

3.3. Microsphere for oral insulin

It helps in protecting the gastric enzyme and proteolytic degradation in stomach and upper part of GI tract. It acts as encapsulating membrane against degradation within its matrix and permeation enhancer.

3.4. Nanopump

Nanopump are used to inject the insulin to the patient's body in a constant rate, balancing the amount of sugar and also the pump can administer small drug dosages over long period of time. The nanopump relies on microfluidic micro-electro-mechanical system *(or MEMS)* technology and can be mounted on a disposable skin patch to provide a continuous insulin infusion throughout the day (Hanazaki *et al.,* 2001). This insulin pump therapy also known as continuous subcutaneous insulin infusion *(or CSII)* injects the insulin into the tissue directly under the skin where it is then distributed throughout the body. Besides the lack of needles the other advantage to this continuous delivery of insulin is that it better mimics the pancreas natural secretion (Woldu *et al.,* 2014; Anonymous, 2008b)

3.5. Nanopore immunoisolation devices

The pore in nanopores allow oxygen, glucose and insulin to pass through but are sufficiently but are sufficiently small to impede the passage of larger molecules that trigger an immune response, thus rendering the device rejection free animal models.

4. Artificial Pancreas

The artificial pancreas (Figure 3) device system is a system of devices that closely mimics the glucose regulating function of a healthy pancreas. Most artificial pancreas device systems consist of three types of devices already familiar to many people with diabetes: a continuous glucose monitoring system (CGM) and an insulin infusion pump. A blood glucose device (such as glucose meter) is used to calibrate the CGM (Arya *et al.,* 2008). A computer controlled algorithm connects the CGM and insulin infusion pump to allow continuous communication between the two devices. Sometimes an artificial pancreas device system is referred to as "closed loop" system, or an "autonomous system for glycemic control." An artificial pancreas device system will not only monitors glucose levels in the body but also automatically adjusts the delivery of insulin to reduce high blood glucose levels and minimize the incidence of low blood glucose with little or no input for from the patient (Anonymous, 2008).

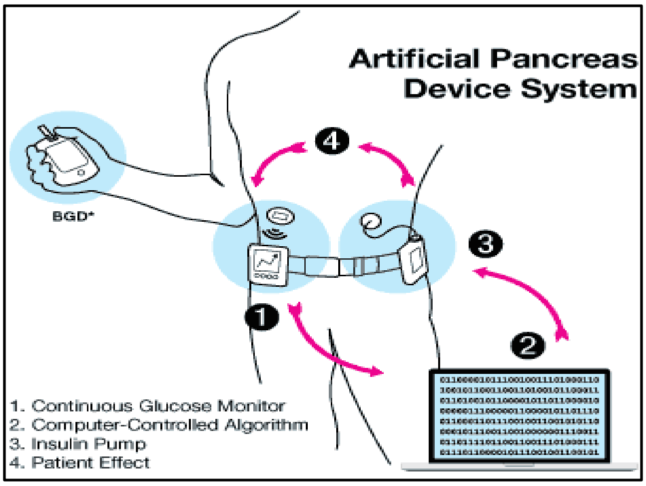

Figure 3. Artificial Pancreas

(Available at: http://www.fda.gov/medical devices/products and medical procedure/artificial pancreas

4.1. Continuous glucose monitor (CGM)

A CGM provides a steady stream of information that reflects the patient's blood glucose levels. A sensor placed under the patient's skin (subcutaneously) measures the glucose in the fluid around the cells (interstitial fluid) which is associated with blood glucose levels. A small transmitter sends information to a receiver. A CGM continuously displays both an estimate of blood glucose levels and their direction and rate of change of these estimates reduce. Studies have shown that CGM systems may help to reduce person hypoglycemia. CGM provides real-time, dynamic glucose information every five minutes- up to 288 readings in a 24 hour period. CGM system usually consists of a glucose sensor, a transmitter, and a small external monitor to view the glucose levels (Subramani et al., 2012). A blood glucose meter only provides a brief snapshot of person glucose levels at a single moment in time. CGM provides:

- Direction of person glucose levels are going
- Early notification of oncoming lows and highs
- Alerts for lows or highs while person are sleeping or anytime.
- Insights into how food, physical activity, medication, and illness impact of person diabetes.

4.2. Blood glucose device (BGD)

Currently, to get the most accurate estimates of blood glucose possible from a CGM, the patient needs to periodically calibrate the CGM using a blood glucose measurement from a BGD; therefore, the BGD still plays a critical role in the proper management of patients with an APDS. However, over time, we anticipate that improved CGM performance may do away with the need for periodic blood glucose checks with a BGD.

4.3. Control algorithm

A control algorithm is software embedded in an external processor (controller) that receives information from the CGM and performs a series of mathematical calculations. Based on these calculations, the controller sends dosing instructions to the infusion pump (Krauland *et al*., 2004). The control algorithm can be run on any number of devices including an insulin pump, computer or cellular phone. The FDA does not require the control algorithm to reside on the insulin pump.

4.4. Insulin pump

Based on the instructions sent by the controller, an infusion pump adjusts the insulin delivery to the tissue under the skin.

4.5. The patient

The patient is an important part of Artificial Pancreas Delivery System. The concentration of glucose circulating in the patient's blood is constantly changing. It is affected by the patient's diet, activity level, and how his or her body metabolizes insulin and other substances (Smyth *et al.,* 2006).

5. Polymeric nanoparticles

Polymeric nanoparticles have been used as carriers of insulin. These are biodegradable polymers, with the polymer insulin matrix enclosed by the nanoporous membrane containing grafted glucose oxidase. A rise in blood glucose level triggers a change in the surrounding nanoporous membrane, resulting in biodegradation and subsequently releases insulin (Ramadas *et al.,* 2000). The glucose/glucose oxidase reaction causes a reducing the pH in the delivery system's. This can cause an increase in the swelling of the polymer system, leading to an increased release of insulin. The polymer systems examined for such applications include copolymers such as N, N-dimethylaminoethyl methacrylate and polyacrylamide

6. Oral insulin by using polysaccharides and polymeric nanoparticles

Polysaccharides are natural biodegradable hydrophilic polymers, which exhibit enzymatic degradation behavior and good biocompatibility. The development of improved oral insulin administration is very essential for the treatment of diabetes mellitus to overcome the problem of daily subcutaneous injections. Insulin, when administered orally, undergoes degradation in the stomach due to gastric enzymes. Therefore, insulin should be enveloped in a matrix like system to protect it from gastric enzymes. This can be achieved by encapsulating the insulin molecules in polymeric nanoparticles (Robert *et al*., 2005). In one such study, calcium phosphate–poly (ethylene glycol)–insulin combination was combined with casein (a milk protein). The casein coating protects the insulin from the gastric enzymes. Due to casein's mucoadhesive property, the formulation remained concentrated in the small intestine.

7. Insulin delivery through inhalable nanoparticles

Inhalable, polymeric nanoparticle-based drug delivery systems have been tried earlier for the treatment of tuberculosis. Such approaches can be directed toward insulin delivery through inhalable nanoparticles. Insulin molecules can be encapsulated within the nanoparticles and can be administered into the lungs by inhaling the dry powder formulation of insulin. The nanoparticles should be small enough to avoid clogging up the lungs but large enough to avoid 414 being exhaled. Such a method of administration allows the direct delivery of insulin molecules to the bloodstream without undergoing degradation (Figure 4) (Smyth *et al*., 2006; Di *et al*., 2014).

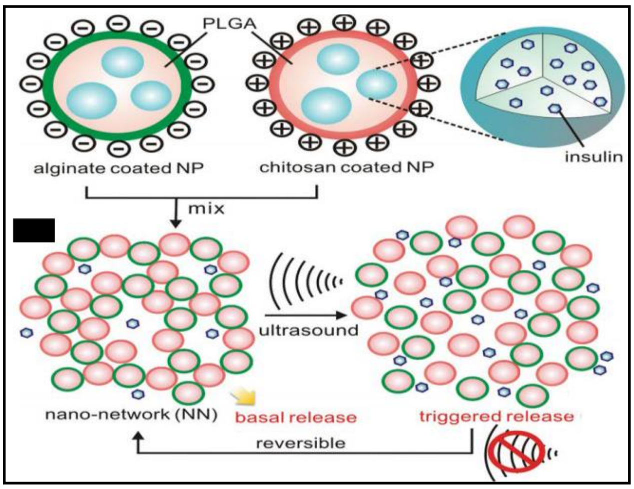

Figure 4. Insulin delivery system (Di *et al*., 2014)

A few studies have been done to test the potential use of ceramic nanoparticles (calcium phosphate) as drug delivery agents. Porous hydroxyapatite nanoparticles have also been tested for the intestinal delivery of insulin. Preclinical studies in guinea pig lungs with insulin-loaded poly (lactide-coglycolide) nanospheres demonstrated a significant reduction in blood glucose level with a prolonged effect over 48 hours when compared with insulin solution (Ramadas *et al.*, 2000). Insulin-loaded poly (butyl cyanoacrylate) nanoparticles when delivered to the lungs of rats were shown to extend the duration of hypoglycemic effect over 20 hours when compared with pulmonary administration of insulin solution (Robert et al., 2005)

Conclusion

The use of nanotechnology on medicine is increasing day by day. It is useful in detection of insulin and blood sugar which are also useful in treatment of diabetes. Oral insulin seems to allow several types of encapsulations by by-passing the gastric acidic environment and thus dealing with the problem of daily subcutaneous injections. Nanotechnology has proven beneficial in treating diabetes mellitus by not only improving the catalytic properties of electrodes but also by increasing the available surface area of the sensor-receptor complex. This can revolutionize insulin delivery through enhanced oral formulations and islet encapsulation. Polyethylcyanoacrylate nanospheres have proven to be successful for insulin delivery in streptozotocin-induced (STZ) diabetic rat model. Hopefully, next generation nanoparticle mediated insulin will improve everyday lives of diabetic patients in the foreseeable future. Nanotechnology can be defined as the monitoring, repairing, construction and control of human biological systems at the cellular level by using materials and structures engineered at the molecular level. It is useful in detection of insulin and blood sugar by the help of microphysiometer and implantable sensors. By using nanotechnology the nanoparticles were formed and these nanoparticles are also useful in treatment of diabetes. In which (a) a polymeric nanoparticle these polymeric nanoparticles have been used as carriers of insulin for giving targeted site of action; (b) oral insulin administration by using polysaccharides and polymeric nanoparticles the development of improved oral insulin administration is very essential for the treatment of diabetes mellitus to overcome the problem of daily subcutaneous injections; (c) insulin delivery through inhalable nanoparticles in this insulin molecules can be encapsulated within the nanoparticles and can be administered into the lungs by inhaling the dry powder formulation of insulin, this will be an effective in treatment of diabetes. And its applications in developments of oral insulin, microsphere for oral insulin production, development of artificial pancreas, nanopumps the pump injects Insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time. These are all about the disease diabetes in which the nanotechnology helps in the treatment of diabetes and its recent advances used for diabetes treatment.

Conflict of interest

Authors report no conflict of interest.

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