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EFFECTIVE UTILIZATION OF NANOTECHNOLOGY IN DIABETES MELLITUS

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ABSTRACT

In the last decade Nanotechnology has proven it applications in effective treatment of diabetes mellitus. This review includes various applications of nanotechnology in diagnosis, treatment, mitigation and prevention of diabetes. This article also reviews the Need, advantages, challenges, limitations, various formulation technologies (conventional and patented), and marketed products of nanotechnology which are essentially useful in diabetes.

INTRODUCTION

About 150 million people suffer from diabetes in the world and it has been predicted that this number will be doubled within years. Type 2 diabetes accounts for about 85% of all cases with diabetes. Type 2 diabetes accounts for about 85% of all cases with diabetes. Type 2 diabetes is considered a paradigm for a multifactoria polygenic disease where common variations in several genes interact to cause the disease polygenic disease where common variations in several genes interact to cause the disease when exposed to the affluent environment of too much food and too little exercise. Recently many scientists focused their research on nanomedicine and nanodiagnostics for many diseases, like diabetes, cancer, spinalcord injury etc. For the scientists to synthesize the nanomedicine (hypoglycemic drugs) for diabetics is on the top priority to reduce the cost and pain of the patients. This article is an attempt to illustrate the diabetes and the use of nanotechnology for benefit of diagnosis and treatment of diabetic patients.[1]

Diabetes mellitus:

Diabetes is a disorder of metabolism— the way the body uses digested food for growth and energy. Most of the food people eat is broken down into glucose, the form of sugar in the blood. Glucose is the main source of fuel for the body. After digestion, glucose passes into the bloodstream, where it is used by cells for growth and energy. For glucose to get into cells, insulin must be present. Insulin is a hormone produced by the pancreas, a large gland behind the stomach. When people eat, the pancreas automatically produces the right amount of insulin to move glucose from blood into the cells. In people with diabetes, however, the pancreas either produces little or no insulin, or the cells do not respond appropriately to the insulin that is produced. Glucose builds up in the blood, overflows into the urine, and passes out of the body in the urine. Thus, the body loses its main source of fuel even though the blood contains large amounts of glucose.[3]

Diabetes mellitus, or simply diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst). The cause of diabetes depends on the type.[4]

Diabetes mellitus often referred to simply as diabetes, a lifelong progressive disease is a chronic metabolic disorder due to the relative deficiency of insulin secretion and varying degrees of insulin resistance and is characterized by high circulating glucose. Currently it has reached epidemic proportion among the challenging unresolved health problems of the 21st century. Worldwide around 230 million people have been affected by diabetes and the number are expected to reach around 366 million by 2030. Imbalance in body normal oxidative metabolism due to excessive levels of either molecular oxygen or Reactive Oxygen Species (ROS) leads to high glucose levels in blood (hyperglycemia) results in metabolic disturbances (oxidative stress) and chronic complications in diabetes. The management of diabetic conditions by insulin therapy has several drawbacks like insulin resistance and in chronic treatment causes anaeroxia nervosa, brain atrophy and fatty liver. Currently several research studies are goingon with the aid of nano size particles to overcome such limitations in Diabetes mamngement.[10]

Types of diabetes mellitus

There are four major classification of diabetes mellitus, namely

Type I:

This is known as IDDM.(Insulin Dependant Diabetes Mellitus) About 5-10% of patients have type I diabetes mellitus. The pancreas produces inadedequate Amount of insulin, resulting in the need for insulin injections to control the blood glucose. It is characterized by a sudden onset, usually Before the age of 30 years. According to Lewis, Collier and Heitkemper in type I diabetes,also called IDDM, auto-immune B-cell destruction is attributed To a genetic predisposition coupled with viral agent and possibly chemical agents. Individuals susceptible to type I diabetes are linked to HLA (Human Leucocytes Antigen) DR3 and DR4 loci (DR3 and DR4 are just numbers used to identify the antigens).[8]

Type II:

This is also known as the NIDDM.(Non Insulin Dependant Diabetes Mellitus). It results from a decrease in the sensitivity of the cell to insulin and decrease in the amount of Insulin produced. About 90-95% of patients have type II diabetes. This type II diabetes is treated with diet and exercise, and if elevated glucose levels persist, diet is supplemented with oral hypoglycaemic agents. During period of illness or surgery, individuals who usually control their Type II diabetes with diet, exercise and oral agents, many require insulin injections. In some individuals oral agents fail to control hyperglycaemia and insulin injection is required.[8] Whittemore, Chase, Mandle and Roy indicate that type II diabetes accounts for 80-90% of all cases and is the significant cause of morbidity in the United States. The complications of type

II result in disruption of lifestyle, psychosocial adjustment and health care expenses. It is often treated with diet, exercise, self-monitoring of blood glucose and hypoglycaemic agents/insulin.[8]

Lewis indicates that there are two subtypes obese and non obese. Type II has a strong genetic influence but there is no correlation with HLA (Human Leucocytes Antigen) type. Individuals with type II diabetes have a 50% chance of transmitting the disease to their children.[8]

Gestational diabetes:

Gestational diabetes (GDM) is defined as carbohydrate intolerance that normally develops during the 24th through the 32nd week of Pregnancy. This condition after 2 to 5% of all pregnant women and is the most common disease affecting pregnancy.[9]

Other types (type III):

This is where diabetes mellitus is associated with other conditions, for example, pancreatic disease, hormonal disorders and drug such as glucocorticoids and oestrogen-containing preparations. Depending on the ability of pancreas to produce insulin, the patient may require oral agents or insulin.[8]

CAUSES:

Type 1 diabetes is partly inherited, and then triggered by certain infections, with some evidence pointing at Coxsackie B4 virus. A genetic element in individual susceptibility to some of these triggers has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, type 1 DM seems to require an environmental trigger. The onset of type 1 diabetes is unrelated to lifestyle. Type 2 diabetes is due primarily to lifestyle factors, genetics and polyphagia (increased hunger).[5]

SIGNS AND SYMPTOMS

The classic symptoms of untreated diabetes are loss of weight, polyuria (frequent 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.Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change, whereas with type 2 change is generally more gradual, but should still be suspected A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes.[7]

NANOTECHNOLOGY:

The term nanotechnology was first used in 1974 by the late Norio Taniguchi(University Of Tokyo) to refer to the ability to engineer material precisely at the scale of nanometers. This is infacts its current meaning;' engineer materials' is usually taken to comprise the design, characterization production and application of materials, and the scope has nowadays been winded to include device and systems with control at nanometer dimensions.[14]

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization and application of materials and device whose smallest functional organization. in at least one dimension is on the nanometer scale(one-billion of a meter).[11]

Nanomedicine is defined as the application of nanotechnology to health. It exploits the improved and novel physical, chemical and biological properties of material at the nanometric scale. Nanomedicine has potential impact on the prevention, early and reliable diagnosis and treatment of disease. The objective of drug delivery system is to target selected cell or receptors within the body. This techhanique is driven by the need on one hand to more effectively target drugs to the site of disease, to increase patient acceptability and reduce healthcare costs; and on the other hand to deliver new class of pharmaceuticals that can not be effectively delivered by conventional means.[13]

Nanoparticles are defined as particulate dispersion or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nonospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanosphere is a matrix system in which the drug is physically and uniformly dispersed.[15]

Nanotechnology has achieved the status as one of the critical research endeavors of the early 21st century, as scientist harness the unique properties of atomic and molecular assemblages built at the nanometer scale. Our ability to manipulate the physical, chemical, and biological properties of these particles affords researchers the capability to rationally design and use nanoparticles for drug delivery, as image contrast agents, and for diagnosis purposes.[16]

The application of nanomaterials in management of diabetes has been primarily confined to the following areas:

1. Sterile needles, including lancets, are required in clinical and medical settings, and their use in self- monitoring of blood glucose (SMBG) is increasing due to the rise in diabetes. In the development of needles, both low piercing resistance and low-cost, safe sterilizing methods are required. In a conventional method to reduce piercing resistance, a silicone compound was applied to a metal surface in the form of an adhesive coating material comprising a siloxane unit with an amino group and an organosiloxane unit.[16]

2. The oral route is the preferred route of drug administration for patients on chronic therapy. However, the oral delivery of many therapeutic peptides and proteins remain an unresolved challenge mainly because of large size, hydrophilicity, and instability of these macromolecules. Zengshuan propose to use chitosan nanoparticles as a carrier for the oral delivery of insulin. As chitosan is a mucoadhesive polycationic polymer that can facilitate drug absorption by localizing drug concentration around absorptive cells and prolonging drug residence in the gut. It is also an effective permeability enhancer because of its depolymerising action on cellular F-actin and the tight junction protein ZO-1.Co-administered chitosan has been shown to enhance the transport of 14 C- mannitol, buserelin, vasopressin and insulin across the Caco-2 monolayers .chitosan in the form of glutamate solution and nanoparticles,is also reported to promote the transport of insulin through the nasal epithelium of sheep and rabbits repectively.[16]

3. Despite the attractive features of nanoparticles in enhancing insulin delivery, the usual mechanism of sustained release is independent of physiological blood sugar concentration. The best way to treat diabetes, however,is to provide exogenous insulin proportion to the varying blood glucose level in the patients. Nanoparticles constructed from such glucose responsive materials might then not only improve the means of insulin delivery as outlined above but also provide a more desirable release profile.[16]

Nanotechnology Used in Diagnosis of Diabetes Mellitus

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. Continuous glucose monitoring provides information about the direction, magnitude, duration, frequency, and causes of fluctuations.[17]

Approaches for diagnosis of diabetes by using continuous glucose monitoring:

- Non invasive methods.
- Implanted sensors in the vascular system or subcutaneous tissue.
- Minimally invasive sensors (self insertion by patients in the subcutaneous tissue).
- Delivery of interstitial liquid from the tissue to the glucose sensor by using of the micro-dialysis technique.

Non-invasive methods for glucose monitoring require the nanotechnology. For example is the glucose detection possible by using nanotube-based optical sensors. Whose optical properties of commonly used organic and nanoparticle fluorescent probes are depending of quantum yield, human tissue penetration, and photo bleaching stability. Single walled carbon nanotubes are cylindrical molecules based on grapheme where the nanometer scale radius serves to quantum confine electrons, imparting the material with new and unique properties. A select number of carbon nanotubes fluoresce in the near infrared where human tissue penetration is maximum and biological autofluorescence is minimal. They are also infinitely photo-stable and are therefore one of very few fluorphores that are viable as long term optical biosensors.

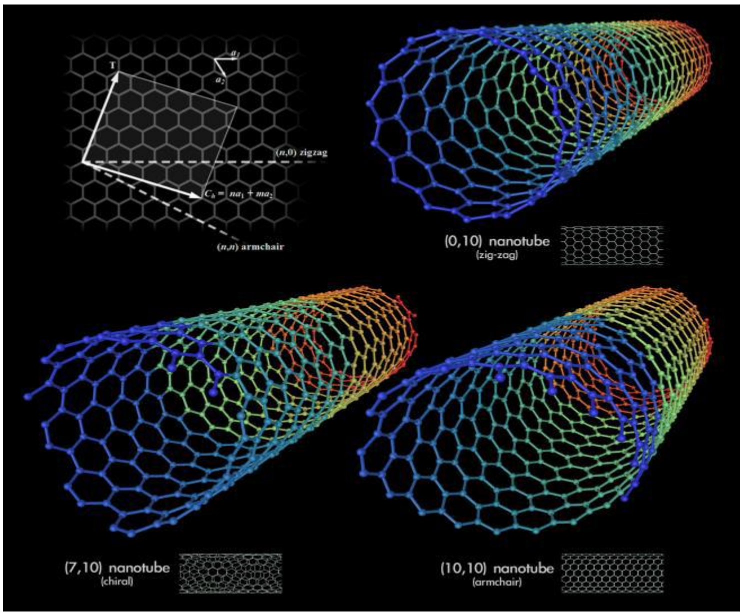

Figure 1: Optical sensors for measurement of the glucose level in patients with diabetes have a nano-tube structure like that shown in the image.

Currently available CGM sensors measure the glucose level minimal invasiveness through continuous measurement of interstitial fluid. The handling for bringing a sensor into contact with ISF include inserting an indwelling sensor subcutaneously (into the abdominal wall or arm) to measure ISF in situ or harvesting this fluid by various mechanisms that compromise the skin barrier and delivering the fluid to an external sensor. After a warm-up period of up to 2 h and a device –specific calibration process, each device's sensor will provide a glucose reading every 5 min for up to 72 h. The data's are transferred to a small monitor.[17]

Figure 2: Guardian REAL-Time (Medtronic) for continuous glucose monitoring.

The small sensor measures the glucose in the interstitial tissue (enzymatic reaction by using glucose oxidase). The data's transferred with a transmitter to the monitor (radio transmission).

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.[20]

Nanorobots:

There are certain cases, such as diabetes, where regular tests by patients themselves are required to measure and control the sugar level in the body. Children and elderly patients may not be able to perform this test properly. Another similar example is regular tests of persons exposed to hazardous radiations or chemicals. The objective is the detection of the disease in its early stage so that appropriate action for higher chances of success can be taken. Implantable sensors and nanorobots can be useful in health assessment. CNT-based nanosensors have the advantages that they are a thousand times smaller than even microelectromechanical systems (MEMS) sensors and consume less power. Therefore, because of their small size and less power consumption, they are highly suitable as implantable sensors.[21]

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 detlects 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 .[21]

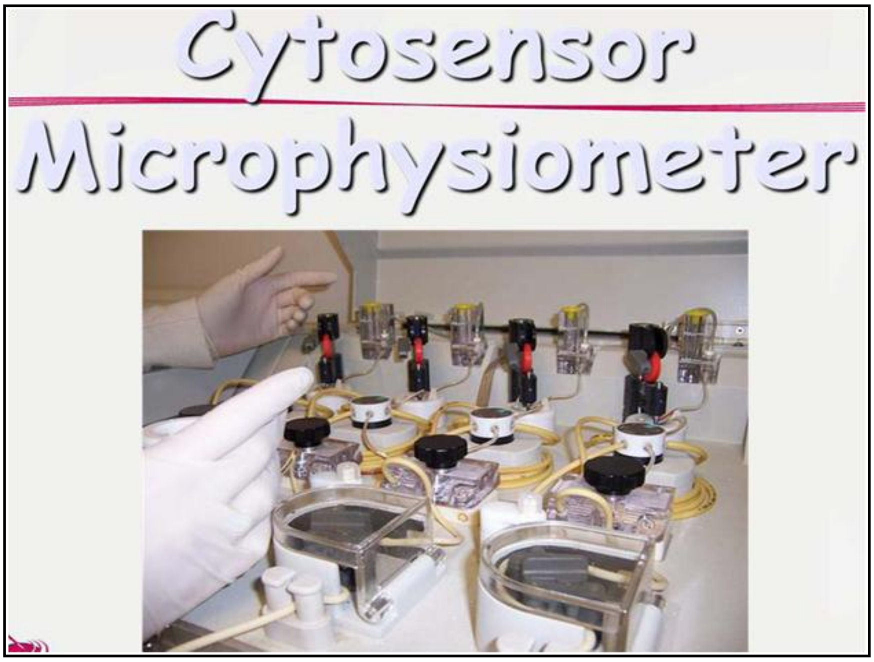

Figure 3: Cytosensor Microphysiometer

NANOTECHNOLOGY USED IN THE TREATMENT OF DIABETES MELLITUS

Insulin nanopump:

The nanopump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by Debiotech for 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. The pump can also administer small drug doses over a long period of time.[32]

The insulin pump will deliver a steady basal rate of insulin 24 hours a day. Most modern pumps can be adjusted for different basal insulin rates during the day and night. Extra insulin is given with meals by pushing a button on the pump (bolus dose). The insulin is pumped through a thin tubing (catheter) that is connected to a metal needle or indwelling catheter placed subcutaneously. With an insulin pump the insulin will be deposited in the same site for several days and the absorption will be more even. The total insulin requirement per 24 hours usually decreases 15 - 20 % after starting with insulin pump treatment. The glycemic control often improves, which results in lowering the Hb (Himoglobin). Some patients (especially teen age girls) will gain weight when they start using an insulin pump if they don't decrease their food intake as their glycemic control improves. But the advantage of insulin pump is that with the help of this device we can achieve continuous insulin supply possible.[30]

Insulin pumps have been in circulation around 20 years; they allow tighter control of blood glucose levels, so as to increase the patients quality of life in comparison with injections and medication, mainly due to the relative freedom from the structured meals and exercise regimes previously needed to control the disease. Pumps also offer greater convenience and discretion and in some cases where neuropathy has complicated treatment there have been report of alleviation or total disappearance of pain. However pumps are much more expensive than injection and have the added risk of breakage and long term damage.[31]

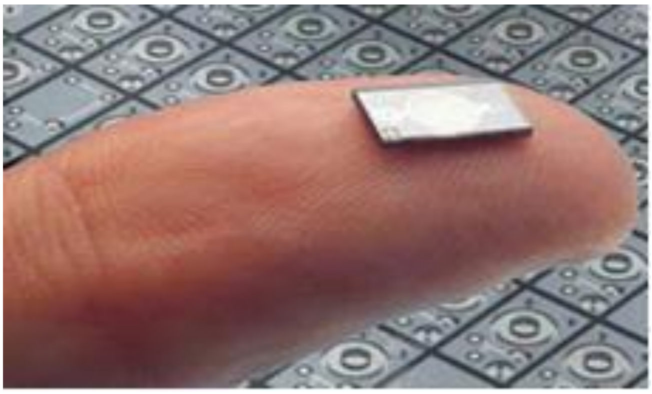

Figure 4: Insulin nanopump.

A lightweight device about the size of a cell phone holds insulin that flows through a tube and needle inserted into the patient's abdomen. The patient wears this device day and night, occasionally removing it for activities such as athletics or showering. Insulin pumps continuously deliver basal doses of insulin to control glucose (blood sugar). The pump also allows the patient to release bolus doses of insulin as needed. Patients who use insulin pumps have to take an active role in managing their care. They must commit to glucose monitoring several times a day and keeping a close watch on carbohydrate consumption. A recent innovation is a small pod-like device with an adhesive bottom that adheres to the skin. It delivers the insulin through a short, thin tube (cannula) and is replaced after a few days. The wireless unit is remotely controlled with a handheld gadget, similar to a personal digital assistant (PDA) that incorporates a glucose monitor. Insulin pump deliver the medication in three ways: Basal rate: This is a continuous trickle of insulin that keeps blood glucose levels stable overnight and between meals. Many pumps allow patients to set different basal rates throughout the day. Thus a patient can program basal rates appropriate to levels of activity such as sleep or exercise. Bolus dose: This is a surge of insulin that occurs shortly before a person eats and prepares the body to break down the glucose in the food about to be ingested. Patients who use rapid-acting insulin can make their pump provide a burst of insulin around mealtime. Those who use regular insulin may be instructed to take a bolus dose about half an hour before eating. Corrective or supplemental doses: Patients who use insulin pumps must make a serious commitment to the treatment. Training may take a day or longer. Patients are required to perform glucose monitoring on the schedule recommended by their physician (generally every three or four hours), and to keep a close watch on consumption of carbohydrates. When pumps quit delivering insulin for whatever reason, dangerously elevated glucose levels can quickly result. This hyperglycemia requires immediate attention. Pumps come with built-in warning systems that alert patients when insulin flow has been halted, batteries are low or other conditions have arises that require the patient's attention. Patients who use insulin pumps may discover hyperglycemia during periodic testing.[33]

Advantages with insulin pump

1: The basal rate will give you sufficient amounts of insulin in the early morning to avoid a high blood glucose level when you wake up.

2: Certain individuals need a higher level of insulin between meals, insulin pump can provide.

3: The continuous supply of basal insulin will make you less dependent of the mandatory interval of not more than 5 hours between meals in multiple injection treatment.

4: You always have your insulin with you and it is easier to take a bolus dose with the pump than to take an injection with a pen or syringe, especially if you don't feel like injecting when out with a group of people.

5: If the pump can be programmed for different basal levels you will have the advantage of adjusting the pump for the differing needs of basal insulin during the day and night.

6: The pump uses only short-acting insulin which ensures a more predictable insulin effect compared to intermediate- and long-acting insulin.

7: Possibility of adjusting the premeal doses in 1/10th unit increments.

8: The risk of severe hypoglycemia is usually reduced when using an insulin pump.

9: An insulin depot will decrease risk for unpredictable release of insulin during physical exercise.

10: During exercise a temporary basal rate can be used.[30]

Disadvantages with insulin pump

1: A small insulin depot will make you very sensitive to an interruption in the insulin supply, risking the rapid development of ketoacidosis.

2: You must take more tests when using an insulin pump.

3: The insulin pump will be connected to you 24 hours a day. Some feel that this makes them more tied up to their diabetes.

4: The pump will be very obvious, for example when going to a public bath. Your diabetes will no longer be a secret disease. Often you will get curious questions about the pump, something that a person who has not fully accepted his/her diabetes fully might experience as uncomfortable.

5: The pump's alarm will trigger every now and then and you might need to stop your activities to change the needle or tubing at an inconvenient time.[30].

Insulin pen:

These devices resemble fountain pens and use a cartridge of insulin and its size is 10 nm to 1000 nm. Patients turn a dial to set the dosage and press a plunger to deliver the medicine, usually in the abdomen, upper arms, thighs or buttocks. It is important that patients using insulin pens ensure that they properly mix the insulin before injecting the medication. Recent research indicates that many patients are not properly mixing their dosages, which results in insulin that is absorbed too quickly. This increases the chance of episodes of low glucose (hypoglycemia).[40] a common problem with pen injectors and syringes is that the insulin will not always give quite the same effect even if the dose is exactly the same.[30]

CONCLUSION

Nanoparticles have larger surface area when compared to their volume their function as a drug delivery system. Due to their minute size these drug carrier can be cleared away from the body by body's excreatory pathways. Diabetes is a rapidly growing global problem, which require management at patient level, via blood glucose control to prevent worsening effects of the disease. Given the limited diagnostic tool, there is a need for better method to measurethe blood glucoselevel. Nanotechnology has proven beneficial in this case by not only increasing the available surface area of sensor-receptor complex but also by improving the catalytic properties of electrodes and providing nanoscale sensors. other nanotechnologies include layer by layer-by-layer films, which nano-capsulate sensor and could revolutionize insulin delivery through enhanced islet encapsulation and oral formulations. Through looking at research into cure for diabetes we conclude that a sensitive sensor that can measure concentrations of different chemicals in the breaths of humans will be most useful in the future. We believe that a whole host of disease could be diagnosed in this way, and could become the norm for every family to have such a device, and use it regularly to ensure that they are healthy. In the foreseeable future, the most important clinical application of nanotechnology will probably be in pharmaceutical development for controlled drug release, drug targeting and salvage of drugs with low bioavailability. Hopefully, the new kind of treatment may help in making the everyday lives of millions of diabetes patients more tolerable.

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