ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2012; 3(2):255-261

REVIEW ARTICLE

Recent Advances & Applications of Nanotechnology in Diabetes

M. S Harsoliya[*1], V. M Patel[2], M. Modasiya[2], J.K.Pathan[3], A. Chauhan[3], M. Parihar[3], M. Ali[4]

[1]*Research Scholar, JJT University, Jaipur, Rajasthan, India*
[2]*Prof. APMC, Himatnagar*
[3]*Swami Vivekananda College of Pharmacy, Indore, M.P, India*
[4]*Jizan University, kingdom of Saudi Arabia, KSA*

Received 04 Jan 2012; Revised 28 Mar 2012; Accepted 06 Apr 2012

ABSTRACT

Nanotechnology is an advanced scientific technique that provides more accurate and timely medical information for diagnosing disease. Diabetes mellitus (DM) is a commonly seen chronic disease, which seriously threatens the health of human beings. Nanotechnology is a focal point in diabetes research, where nanoparticles in particular are showing great promise in improving the treatment and management of the disease. Due to their ability to potentially enhance drug delivery to areas where there are barriers or unfavorable environments for macromolecules, nanoparticles are being explored as vehicles for improved oral insulin formulations. The use of nanotechnology in the development of glucose sensors is also a prominent focus in non-invasive glucose monitoring systems. Nanotechnology can now offers new implantable or wearable sensing technologies that provide continuous and extremely accurate medical information. The purpose of this is to throw more light on the recent advances and impact of nanotechnology on biomedical sciences to cure diabetes. Nanomedicine, the application of nanotechnology to medicine, has already offered some new solutions, and many pharmaceutical companies are trying to develop targeted drug delivery using nanotechnology and already existing drugs. Nanotechnology offers some new solutions in treating diabetes mellitus. Boxes with nonporous that protect transplanted beta cells from the immune system attack, artificial pancreas and artificial beta cell instead of pancreas transplantation, nanospheres as biodegradable polymeric carriers for oral delivery of insulin are just some of them. Use of nanotechnology in diabetes is development of oral insulin, microsphere for oral insulin production. This review concluded that nanotechnology will be effective therapy in diabetes.

Key words: Nanotechnology, diabetes, nanoparticles, nanomedicine, nanospheres.

1. INTRODUCTION

Diabetes mellitus, often simply referred to as 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) and polyphagia (increased hunger)[1].

There are three main types of diabetes:

- Type 1 diabetes: results from the body's failure to produce insulin, and presently requires the person to inject insulin
- Type 2 diabetes: results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency.
- Gestational diabetes: is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

All forms of diabetes have been treatable since insulin became available in 1921, and type 2 diabetes may be controlled with medications. Both

***Corresponding Author:** M. S Harsoliya**, Email:** sharsoliya@gmail.com

type 1 and 2 are chronic conditions that usually cannot be cured. Pancreas transplants have been tried with limited success in type 1 DM; gastric bypass surgery has been successful in many with morbid obesity and type 2 DM [2]. Gestational diabetes usually resolves after delivery. Diabetes without proper treatments can cause many complications. Acute complications include hypoglycemia, diabetic ketoacidosis, or nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, retinal damage. Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight [3].

1.1 Type 1 diabetes

Diabetes mellitus type 1 (Type 1 diabetes, IDDM, or, formerly, juvenile diabetes) is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss.

In the long run, type 1 diabetes is generally fatal unless treated with insulin. Injection is the most common method of administering insulin; insulin pumps and inhaled insulin have been available at various times. Pancreatic transplants and pancreatic islet cell transplantation have been used to treat type 1 diabetes; however, pancreatic islet cell transplantation is still viewed as experimental, although utilization of the procedure is growing.

Most people who develop type 1 are otherwise healthy. Although the cause of type 1 diabetes is still not fully understood it is believed to be of immunological origin.

Type 1 can be distinguished from type 2 diabetes via a C-peptide assay, which measures endogenous insulin production.

Type 1 treatment must be continued indefinitely in all cases. Treatment is not intended to significantly impair normal activities, and can be done adequately if sufficient patient training, awareness, appropriate care, discipline in testing and dosing of insulin is taken. However, treatment remains quite burdensome for many people. Complications may be associated with both low blood sugar and high blood sugar, both largely due to the non-physiological manner in which insulin is replaced. Low blood sugar may lead to seizures or episodes of unconsciousness and requires emergency treatment. High blood sugar may lead to increased fatigue and can also result in long term damage to organs.

1.2 Type 2 diabetes

Diabetes mellitus type 2 – formerly non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes – is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Diabetes is often initially managed by increasing exercise and dietary modification. If the condition progresses, medications may be needed. Often affecting the obese, diabetes requires patients to routinely check their blood sugar.

Unlike type 1 diabetes, there is very little tendency toward ketoacidosis though it is not unheard of. One effect that can occur is nonketonic hyperglycemia. Long-term complications from high blood sugar can include increased risk of heart attacks, strokes, amputation, and kidney failure. For extreme cases, circulation of limbs is affected, potentially requiring amputation. Loss of hearing, eyesight, and cognitive ability has also been linked to this condition.

1.3 Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life.

Even though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia[4].

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action or

both. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism. It is the most common endocrine disorder and by the year 2012, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the severe diabetic complication such as retinopathy, neuropathy, nephropathy, cardiovascular complication and ulceration. Most complications of diabetes are due to either acute metabolic disturbances or chronic tissue damage. Thus diabetes covers a wide range of heterogeneous disease. Preventative methods for diabetes are as yet poorly developed. More progress has been made with potentially curative surgery. However, at present the vast majority of people with diabetes require long-term management of established disease [5].

2. NANOTECHNOLOGY

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 (Kralj and Pavelic, 2003). When applied to medicine, Nanotechnology is referred to as nanomedicine – a discipline where there are promises of revolutionary opportunities to fight against many diseases (Logothetidis, 2006). Nanotechnology is likely to have a significant impact on society, and is perceived as a human affair designed to serve human purposes (Schiemann, 2005). Nanotechnology is the science of the small; the very small. It is the use and manipulation of matter at a tiny scale. At this size, atoms and molecules work differently, and provide a variety of surprising and interesting uses**.** The prefix of nanotechnology derives from 'nanos' – the Greek word for dwarf.[6] To gain a sense of proportion, 1 nanometer is about 100 000 times smaller than the diameter of a single human hair. At the heart of nanotechnologies promise lies the concept of controlling matter at the atomic and molecular level. The development of nanotechnology is occurring at an unprecedented rate. Although still in its experimental stage, nanomedicine holds the potential to revolutionise the management of diabetes, thereby contextualizing the notion of non-adherence in history. It is useful, therefore, to review the potential that nanomedicine has in the field of nursing and diabetes care [7].

Nanotechnology (sometimes shortened to "nanotech") is the study of manipulating matter on an atomic and molecular scale. Generally, nanotechnology deals with structures sized between 1 to 100 nanometre in at least one dimension, and involves developing materials or devices possessing at least one dimension within that size. Quantum mechanical effects are very important at this scale, which is in the quantum realm.

Nanotechnology is very diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly, from developing new materials with dimensions on the nanoscale to investigating whether we can directly control matter on the atomic scale.

There is much debate on the future implications of nanotechnology. Nanotechnology may be able to create many new materials and devices with a vast range of applications, such as in medicine, electronics, biomaterials and energy production. On the other hand, nanotechnology raises many of the same issues as any new technology, including concerns about the toxicity and environmental impact of nanomaterials, and their potential effects on global economics, as well as speculation about various doomsday scenarios. These concerns have led to a debate among advocacy groups and governments on whether special regulation of nanotechnology is warranted.

Nanotechnology is a focal point in diabetes research, where nanoparticles in particular are showing great promise in improving the treatment and management of the disease. Due to their ability to potentially enhance drug delivery to areas where there are barriers or unfavourable environments for macromolecules, nanoparticles are being explored as vehicles for improved oral insulin formulations. The use of nanotechnology in the development of glucose sensors is also a prominent focus in non-invasive glucose monitoring systems [8]. There are a few limitations in the use of conventionally available drug delivery systems as pharmacological agents in disease treatment. Lack of target specificity, altered effects and diminished potency due to drug metabolism in the body [9].

3.RECENT ADVANCES 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 ways-

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. It can be used to detect and monitor the response of cells to a variety of chemical substances, especially ligands for specific plasma membrane receptors [10]. 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.

By implantable sensor:

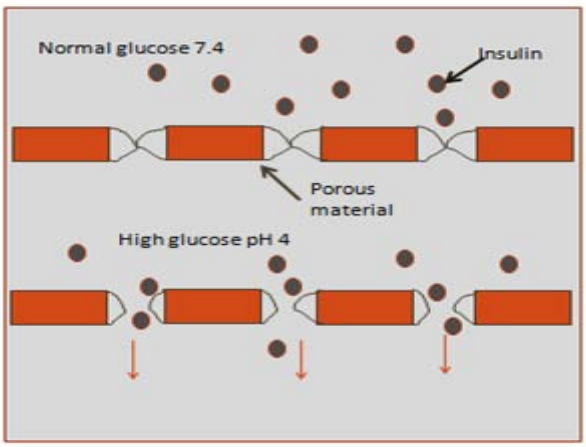
An implantable sensor capable of long-term monitoring of tissue glucose concentrations by wireless telemetry has been developed for eventual application in people with diabetes [11]. The implantable sensor is designed to give diabetes patients an alternative to finger-sticking or short-term glucose sensors, as well as limit dangerous glucose level fluctuations known as "glucose excursions.[12] 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 [13].

4. RECENT ADVANCES OF NANOPARTICLES IN THE TREATMENT OF DIABETES

4.1 Polymeric Nanoparticles

Polymeric nanoparticles have been used as carriers of insulin. The use of biodegradable polymeric nanoparticles for controlled drug delivery has shown significant therapeutic potential [14]. These are biodegradable polymers, with the polymer–insulin matrix surrounded 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 subsequent insulin delivery. The glucose/glucose oxidase reaction causes a lowering of the pH in the delivery system's microenvironment. This can cause an increase in the swelling of the polymer system, leading to an increased release of insulin. The polymer systems investigated for such applications include copolymers such as *N*, *N*-dimethylaminoethyl methacrylate and polyacrylamide. This "molecular gate" system is composed of an insulin reservoir and a delivery rate–controlling membrane made of poly [methacrylic acid-g-poly (ethylene glycol)] copolymer. The polymer swells in size at normal body pH (pH = 7.4) and closes the gates. It shrinks at low pH (pH = 4) when the blood glucose level increases, thus opening the gates and releasing the insulin from the nanoparticles (**Fig 1**). These systems release insulin by swelling caused due to changes in blood pH. The control of the insulin delivery depends on the size of the gates, the concentration of insulin, and the rate of gates' opening or closing (response rate). These self-contained polymeric delivery systems are still under research, whereas the delivery of oral insulin with polymeric nanoparticles has progressed to a greater extent in the recent years [15].

Fig 1: Schematic of polymeric nanoparticles with pH-sensitive molecular gates for controlled insulin release triggered by the presence of glucose in blood



4.2 Oral Insulin Administration by Using Polysaccharides and Polymeric Nanoparticles

Polysaccharides are natural biodegradable hydrophilic polymers, which exhibit enzymatic degradation behavior and good biocompatibility [16]. 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. 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 for a longer period, resulting in slower absorption and longer availability in the bloodstream.

4.3 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. 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-co-glycolide) nanospheres demonstrated a significant reduction in blood glucose level with a prolonged effect over 48 hours when compared with insulin solution. 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. The major factors limiting the bioavailability of nasally administered insulin include poor permeability across the mucosal membrane and rapid mucociliary clearance mechanism that removes the non mucoadhesive formulations from the absorption site. To overcome these limitations, mucoadhesive nanoparticles made of chitosan/tripolyphosphate and starches have been evaluated. These nanoparticles showed good insulin-loading capacity, providing the release of 75% to 80% insulin within 15 minutes after administration [17].

5.APPLICATIONS OF NANOTECHNOLOGY IN DIABETES

Diabetes is considered to be one of the major afflictions of modern western society. To date, diabetic patients control their blood-sugar levels via insulin introduced directly into the blood stream using injections. This unpleasant method is required since stomach acid destroys protein-based substances such as Insulin, making oral insulin consumption useless. The new system is based on inhaling the insulin (instead of injecting it) and on a controlled release of insulin into the bloodstream (instead of manually controlling the amount of insulin injected). The treatment of diabetes includes the proper delivery of insulin in the blood stream which can be achieved by nanotechnology in the following ways:

5.1 Development of Oral Insulin:

Inhalable, polymeric nanoparticle-based drug delivery systems have been developed 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 being exhaled [18]. Production of pharmaceutically active peptides, proteins [19], such as insulin, in large quantities has become feasible. The oral route is considered to be the most convenient and comfortable means for administration of insulin for less invasive and painless diabetes management, leading to a higher patient compliance. Nevertheless, the intestinal epithelium is a major barrier to the absorption of hydrophilic drugs, as they cannot diffuse across epithelial cells through lipid bilayer cell membranes to the bloodstream. Therefore, attention has been given to improving the paracellular transport of hydrophilic drugs. A variety of intestinal permeation enhancers including chitosan have been used for the assistance of the absorption of hydrophilic macromolecules. Therefore, a carrier system is needed to protect protein drugs from the harsh environment in the stomach and small intestine, if given orally. Additionally, chitosan nanoparticles enhanced the intestinal absorption of protein molecules to a greater extent than aqueous solutions of chitosan in vivo. The insulin loaded nanoparticles coated with mucoadhesive chitosan

may prolong their residence in the small intestine, infiltrate into the mucus layer and subsequently mediate transiently opening the tight junctions between epithelial cells while becoming unstable and broken apart due to their pH sensitivity and/or degradability. The insulin released from the broken-apart nanoparticles could then permeate through the paracellular pathway to the bloodstream, its ultimate destination.

5.2 Microsphere for Oral Insulin Production:

The most promising strategy to achieve oral insulin is the use of a microsphere system which is inherently a combination strategy. The oral drug delivery device for insulin and to protect the sensitive drug from digestive enzymes and proteolytic degradation in stomach and upper part of gastro intestinal tract [20]. Microspheres act both as protease inhibitors by protecting the encapsulated insulin from enzymatic degradation within its matrix and as permeation enhancers by effectively crossing the epithelial layer after oral administration.

5.3 Artificial Pancreas:

An artificial pancreas system is an automated, closed-loop system that combines a continuous glucose monitor, an insulin infusion pump, and a glucose meter for calibrating the monitor. The devices are designed to work together, monitoring the body's glucose levels and automatically pumping appropriate doses of insulin as determined by a computer algorithm [21]. Development of artificial pancreas could be the permanent solution for diabetic patients. 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. This could temporarily restore the body's delicate glucose control feedback loop without the need of powerful immunosuppressant that can leave the patient at a serious risk of infection. Scientists are also trying to create a nano robot which would have insulin departed in inner chambers, and glucose level sensors on the surface. When blood glucose levels increase, the sensors on the surface would record it and insulin would be released [22]. Yet, this kind of nano-artificial pancreas is still only a theory. The biosensors are also useful in the artificial pancreas [23].

5.4 The 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, 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. The pump can also administer small drug doses over a long period of time.

6. SUMMARY AND CONCLUSION:

Diabetes mellitus, often simply referred to as 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) and polyphagia (increased hunger). It is the most common endocrine disorder and by the year 2012, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the severe diabetic complication such as retinopathy, neuropathy, nephropathy, cardiovascular complication and ulceration.

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.

REFERENCES

1. Wild S, Roglic G, *et al*. "Global prevalence of diabetes: estimates for 2000 and projections for 2030". Diabetes Care 27 (5): 2004; 1047–53.
2. Agabegi D Elizabeth; Agabegi, Steven S. Step-Up to Medicine (Step-Up Series). Hagerstwon, MD: Lippincott Williams & Wilkins. ISBN 2008; 0-7817-7153-6.
3. Lambert P. "What is Type 1 Diabetes?". Medicine 30: 2002; 1–5.
4. Rother KI. "Diabetes treatment—bridging the divide". The New England Journal of Medicine 356 (15): 2007; 1499–501.
5. Lawrence JM, Contreras R, *et al*. "Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005". Diabetes Care 31 (5): 2008; 899–904.
6. Rathod B Kinjal *et al*. "Glimpses of current advances of nanotechnology in therapeutics". International Journal of Pharmacy and Pharmaceutical Sciences. Vol 3, Issue 1, 2011. Pg No. 8-12
7. Meeto Danny, Mike Lappin. "Nanotechnology and the future of diabetes management". Journal of Diabetes Nursing Vol 13; 2009; 8.
8. Samuel Dannis, Bharali Dhruba. "The role of nanotechnology in diabetes treatment: current and future perspectives. International Journal of Nanotechnology 2011 - Vol. 8, No.1/2 pp. 53 - 65.
9. Subramani Karthikeyan. " Applications of nanotechnology in drug delivery systems for the treatment of cancer and diabetes. International Journal of Nanotechnology - Vol. 3, No.4 2006 pp. 557 - 580.
10. Connell Mc HM *et al*. "The cytosensor microphysiometer: biological applications of silicon technology". Science live journal. Vol. 257 no. 5078. 1992.pp. 1906-1912.
11. Gough A. David et al. "Bioengineering and Diabetes Function of an Implanted Tissue Glucose Sensor for More than 1 Year in Animals". Science translational medicine journal. Vol. 2, Issue 42,2010, p. 42ra53.
12. Monda Erin. "Implantable glucose sensors". Health tech zone medical featured article. Vol 2, 2010, pp-2-6.
13. Kumar Arya* *et al*. "Applications of nanotechnology in diabetes". Digest Journal of Nanomaterials and Biostructures. Vol. 3, No.4, December 2008, p. 221 – 225.
14. JM Chan et al. "Polymeric nanoparticles for drug delivery. Pubmed; 624: 2010: 163-75.
15. Sona P.S. "Nanoparticulate drug delivery systems for the treatment of diabetes**".** Digest Journal of Nanomaterials and Biostructures Vol. 5, No 2, April-June 2010, p. 411 – 418.
16. Sarmento Bruno *et al*."Oral Bioavailability of Insulin Contained in Polysaccharide Nanoparticles". Biomacromolecules, Vol. 8, No. 10, 2007 pp-3054-3060
17. Moghimi S. Moein. "Nanomedicine current status and future aspects". FASEB journal vol 19 march 2005; 8-12.
18. Babu Satheesh. "Nanoparticles in the treatment of diabetes". Pharma info pharmaceutical articles. Vol 5. 2011.
19. J Still Gordon. "Development of oral insulin progress and currents status" Diabetes Metab Res Rev. 18 Suppl 1: 2002: S29-37.
20. Jindal Kumar Santosh. "Formulation and evaluation of insulin enteric microspheres for oral drug delivery. Acta Pharmaceutica Sciencia. Vol 51: 121-127 (2009).
21. Crane Mark. " FDA issues graft guidance for artificial pancreas". Medscape Today. Vol 1. 2011.
22. Libert M. A." Bioartificial pancreas: Materials, Devices, Function and Limitations". Diabetes technology and therapeutics. Vol 3 2001; 3.
23. Prow T. W. *et al*. "Nanoparticle-delivered biosensor for reactive oxygen species in diabetes". Science directs Vision Research 48 (2008) 478–485.