

“NO PAIN, NANO’S THE GAME”

THE USE OF NANOTECHNOLOGY IN THE MANGEMENT AND
TREATMENT OF DIABETES, TYPE 1 AND 2

BY

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Abstract

Diabetes is a very prevalent disease in today's society. There are approximately 2.3 million people suffering with diabetes in the UK alone [1], as well as another half a million ignorant of their condition. Everyday these patients go through painful and crude procedures in order to obtain blood samples to monitor their blood sugar levels. They then need to inject the hormone insulin parenterally in order to regulate the metabolism of fats and carbohydrates in the body. This paper will examine the prospective role which nanotechnology could provide by introducing varied non-invasive glucose monitoring systems and manual administration of insulin, which could relieve the discomfort diabetics suffer everyday and significantly increase their quality of life.

Introduction

In 1959 the physicist Richard Feynman in his lecture "Theres plenty of room at the bottom", first used the concepts found in "nanotechnology" by describing a process by which the ability to manipulate individual atoms and molecules might be developed. Nanotechnology research in recent years has had a tremendous impact on fields such as materials, electronics, and medicine. The first nanoparticle, buckminsterfullerene, was discovered in 1985, and carbon nanotubes some years later. These two particles happened to be the unknown allotropes of carbon that chemists had been seeking for many years. Buckminsterfullerene or the "buckyball" comprised of carbon bonded in 20 hexagons and 12 pentagons, known as C₆₀, forming a spherical shape. Carbon nanotubes comprised of a similar structure, but they were only bonded in hexagons and flat which could then be rolled into tubes, the novel properties of these particles like electrical and thermal conductivity. However, this kind of manipulation at an atomic level is no easy feat and one that can only be achieved with very precise equipment and under strict conditions in a vacuum, at a temperature just a few degrees above zero. Nanotechnology was first developed by IBM in 1989, when engineers undertook the challenge to make the smallest company logo. They succeeded by writing the letters "IBM" out of 35 individual xenon atoms, which could only be identified through a scanning tunnelling microscope, a creation of IBM Zürich 8 years earlier.

Engineering in nanotechnology is working on a scale of about nanometer = 10^{-9} metre. Just to give a sense of how small things are, here are some entities and their average size: atom diameter 0.15 nm, diameter of double strand DNA 2 nm, and cell 1000 nm. The aim of nano-scientists is to virtually imitate nature. [6] By working on such a small scale, they are constructing components out of their most basic matter (atoms), this provides an unprecedented amount of accuracy and control of the final product. Such techniques to replicate nature in science are known as bio-mimicry.

Nanotechnology has boomed in almost all fields of industry in the last year. Governments and corporations worldwide have ploughed over 4 billion USD into nanotechnology [4]. However, despite great investments and hard scientific work, development is still moving slowly. Most Scientists believe that nanotechnology will start seriously influencing our lives around the year 2020 [5].

The application of nanotechnology to medicine is called nanomedicine, it is defined as “Research and technology development at the atomic, molecular and macromolecular levels in the length scale of approximately 1 – 100 nanometer range, to provide a fundamental understanding of phenomena and materials 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.”[19] Nanomedicine subsumes three mutually overlapping and progressively more powerful molecular technologies: nanoscale structured materials and devices; genomics, proteomics and artificial engineered microbes; and medical nanorobots. [7]

Nanoscale structured materials are an area of rapid development. Pharmaceutical companies are trying to develop targeted drug delivery using nanotechnology, so that these drugs are specifically attracted to the target cells in question. They can be used to deliver chemotherapies to tumor cells with greater efficacy with reduced cytotoxicity to peripheral healthy tissues. This could be the next foothold in the fight against diseases like cancer. Nanoparticles, such as buckminsterfullerene, sparked great interest in the medical world, as researchers started to suggest ways in which these new particles could improve areas of medicine like drug delivery. This was first considered when it was discovered that other atoms could be restrained within the spherical molecule. This suggested that various other organic substances like proteins could also be stored within the nanoparticle, while being protected from the conditions of the external environment, however, the problem is the release of the contents. This is where polymeric nanoparticles came into being. The content is encapsulated with a biodegradable polymer which protects the contents and allows release at a particular time or when a target cell is reached, although, there is still much research to be done on timed release. There are two types of polymeric nanoparticles; nanocapsules are vesicular systems where the drug is confined to a cavity surrounded by a polymer membrane, and nanospheres which are matrix systems in which the drug is physically and uniformly dispersed. [8]

Artificial engineered microbes are already being used to produce human hormones, for example. Human DNA is incorporated in the genome of the bacteria, which then start to produce human hormones, used to cure endocrine diseases. [9] This research has also lead into the development of Nanorobots. This area of science is still very much in the development and research phase, but presents an incredible prospective for medicine. Rice University has made a single molecule car which uses the buckminsterfullerene molecule as wheels, however, it can only be actuated by the tip of a scanning tunnelling microscope. Robert A Freitas has made a design for an artificial red blood cell called a respirocyte, a spherical shaped nanorobot the same size as a bacterium cell. It would comprise of 18 billion atoms exactly and organised in a crystalline structure to form a

pressure tank, then when these are injected in the bloodstream, sensors on the surface detect the levels of oxygen and carbon dioxide and signal when to load oxygen and unload carbon dioxide, however, this is still theory.

Other applications of nanomedicine include targeted molecular imaging in vivo (e.g. tissue complications) using quantum dots (QDs) or gold nanoparticles, and in therapy techniques where buckyballs are used to trap free radicals produced by allergic reactions and reduce inflammation. Diabetes is a disease that could benefit from almost all these areas of nanotechnology, but before these are examined in more detail, it is important to know the pathophysiology of diabetes itself.

Pathophysiology

Insulin is the hormone that regulates the uptake of glucose from the blood into most bodily cells (primarily muscle and fat cells), by making the liver cells store glucose as a compact polysaccharide called glycogen. When the glucose level is too high, the glycogen then breaks back down into glucose when blood sugar levels fall. Diabetes is a disease where the patient cannot produce a sufficient amount of insulin, or none at all, or perhaps the cells do not respond to the insulin as they would normally, resulting in high sugar content in the blood.

Insulin is released into the blood by beta cells (β -cells) of the islets of Langerhans, located inside the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by the cells in the body to absorb glucose which is needed for respiration to produce ATP (adenosine triphosphate) which is the fuel these cells need in order to carry out normal activity.(fig 1)

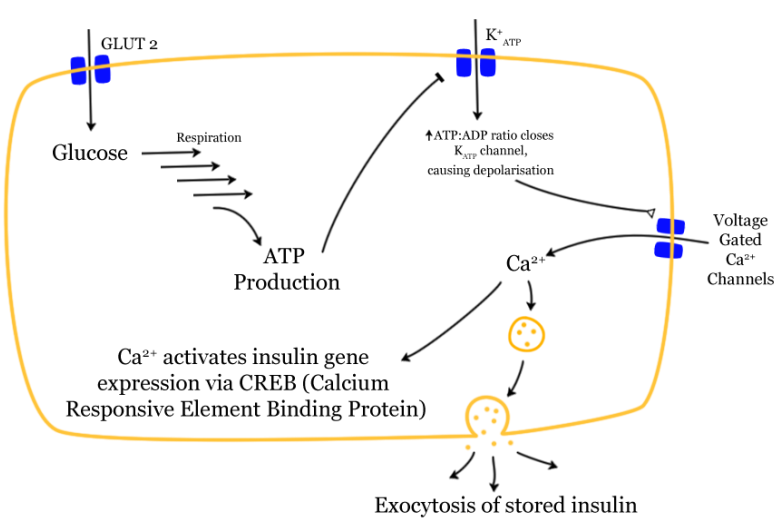


Fig 1: Illustrating the mechanism of insulin release in a normal pancreas

If the amount of insulin available is insufficient, and the cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not have its usual effect and will not be absorbed properly. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis (increased acidity of blood). Prolonged high glucose absorption can have many symptoms including weight loss,

vomiting, skin rashes and even cause the shape of the lenses in the eye to change shape resulting in impaired and blurred vision.

There are two main types of diabetes, type 1 and type 2. Type 1 diabetes is where the patient loses insulin producing beta cells in the islets of Langerhans within the pancreas. This part of the pancreas contains endocrine cells which secrete hormones into the blood, therefore, the patient suffers from insulin deficiency. It is further categorized into two groups, immune-mediated or idiopathic. The majority of type 1 cases are immune-mediated, where the beta cells are lost due to an autoimmune attack by lymphocytes which do not recognize the cells as constituent parts of the body. Idiopathic type 1 diabetes is unexplained and usually predicted to be a cause of genetic inheritance or as recent research suggests from the Coxsackie B4 virus, which can trigger this autoimmune reaction. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe and presently can only be maintained by intravenous or subcutaneous injections of insulin. [3]

Type 2 diabetes is characterised by insulin resistance. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor, however, the defect itself is currently unknown. The onset of type 2 diabetes shows a strongly correlated relationship with unhealthy living, genetic inheritance is also considered to be one of the causes. Type 2 diabetes can be maintained by injecting insulin or regular exercise combined with a low sugar diet. A routine dose of aspirin and other diabetic drugs have also shown improved outcomes in some cases.

Discussion

Nanotechnology has many prospects in the treatment of diabetes, it can help to monitor blood glucose levels and offers alternatives to subcutaneous or intravenous administration of insulin but also provides means of treating the disease itself.

Sensors

The microphysiometer (fig 2) was developed by a team of Vanderbilt researchers headed by Associate Professor of Chemistry David Cliffel. It is built from multiwalled carbon nanotubes, which comprise of several flat sheets of carbon atoms stacked and rolled into very small tubes. [2] The Nanotubes are electrically conductive so the concentration of insulin in the chamber can be controlled directly by varying the current at the electrode end of the tube. The microphysiometer has a great advantage against present monitoring equipment, as it can monitor insulin levels in real time, by continuously measuring the transfer of electrons when the insulin oxidises in the presence of glucose, so when

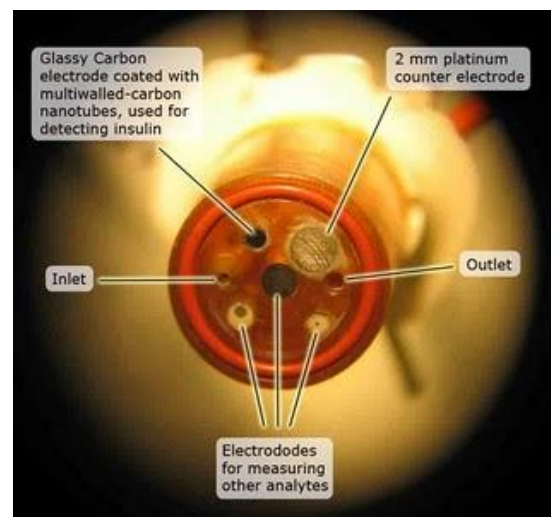


Fig 2: an image showing the microphysiometer

there is less insulin in the blood the current measured in the nanotubes will be lower and vice versa.

The future prospect for the microphysiometer is to measure insulin, oxygen, lactate and possibly other chemicals in the blood simultaneously. This could have great benefit for future researchers, who could study how the islet cells in the pancreas react to new diabetic drugs, and therefore, judge their effectiveness, like aspirin, which has claimed to show improved outcomes for many type 2 diabetics. It could also help to verify the health of islet cells which could be used for transplantation and help test immunosuppressive drugs to find the best way of dealing with rejection. This sensor could also possibly be used to control an insulin pump. Insulin pumps presently supply a small, constant supply of insulin into the patient's bloodstream, however, the microphysiometer could be used as part of a feedback system to dynamically control insulin levels even in patients who don't have islet cell transplants.

Another type of sensor which has been developed by researchers, is implanted in the body of the patient, usually in the wrist. It uses polyethylene glycol beads coated with florescent molecules which are injected under the skin and remain in the interstitial fluid which are displaced by glucose and glow, informing the patient that insulin is needed. The device can transmit up to 10 – 14 feet to a device worn like a watch which shows the patient their blood glucose level. The device is also being altered to continuously monitor other body parameters like temperature and pulse. The device has been previously tested on a pig lasting a year without any difficulties and 10 months in another.

This device could also have signalling potential by calling particular numbers when the patient's blood sugar reaches dangerous levels, this could be particularly effective by waking someone nearby during the night to stop the patient in question from going into nocturnal hypoglycemia. However, if the device were to be able to contact mobile phones, it would involve the use of microwaves, this creates a possible risk, as it is understood that microwaves are absorbed by water, fats and other molecules which are found in the body, increasing the temperature of bodily cells and possibly damaging them.

Non-invasive administration of insulin

Pharmaceutical development has been trying to take advantage of the unique properties of nanoparticles as drugs or constituents of drugs or are designed for new strategies to controlled release.[2] Oral insulin is considered to be the most comfortable and convenient way of administering insulin, and is likely to have the best patient compliance. Polymeric nanoparticles have been used to contain the insulin within a matrix enclosed by a nanoporous membrane. Insulin cannot be taken alone as it is a protein and would undergo degradation in the stomach due to gastric contents like enzymes and low Ph. These polymers will allow for a greater concentration of the insulin to reach the small intestine for a prolonged period, resulting in sustained absorption and longer bioavailability. In a study, insulin-loaded polymeric

nanoparticles were used in the form of pellets for oral delivery of insulin in diabetic rats. The results showed a drastic decrease in blood sugar level following the administration of insulin through the buccal cavity. [13] There are already some branded products like Bioral® which was developed in collaboration with the University of Albany and the University of New Jersey Medical and Dental School, that uses the same principles of encapsulation to deliver an antifungal drug, amphotericin B, without chemically bonding with the drug. [22] Nevertheless, the intestinal epithelium is a major barrier for the absorption of hydrophilic drugs, as they cannot diffuse across epithelial cells through lipid-bilayer. [2] The most promising strategy in oral insulin is the use of a microsphere system which is inherently a combination strategy. Microspheres act both as protease inhibitors by protecting the encapsulated insulin from

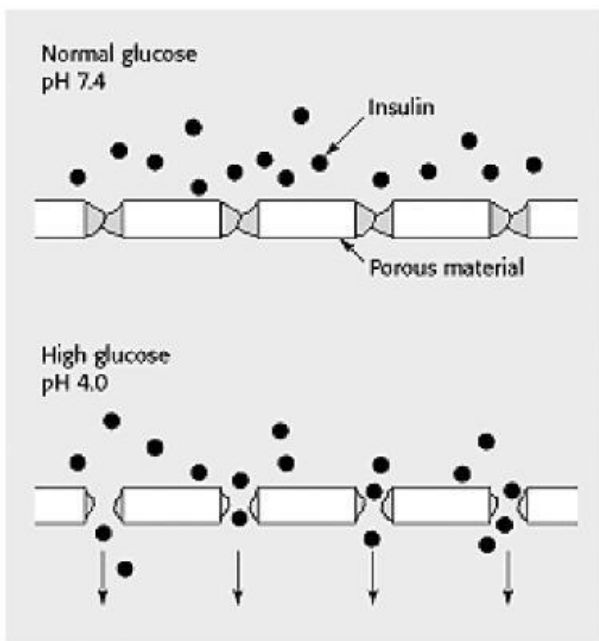


Fig 3: a schematic showing the molecular gat system

enzymatic degradation within its matrix and as permeation enhancers by effectively crossing the epithelial layer after oral administration.

Because this paracellular absorption is quite difficult, the effects of the insulin are not felt until a few hours later, however, it is known that polymers like N, N-dimethylaminoethyl methacrylate and polyacrylamide have a kind of “molecular gate” system (fig 3) where the nanoparticle swells or contracts due to changes in pH. They swell at normal body pH (pH≈7.4) and close their gates (i.e. the nanoporous membrane closes). It shrinks at low pH (pH ≈ 4) when the blood glucose level increases, thus opening the gates and releasing the insulin from the nanoparticle. The regulation of the insulin delivery depends on the size of the gates, the

concentration of the insulin, and the response rate of the gates opening and closing. These are more effective as an oral substitute or better yet if injected into the bloodstream as a form of long lasting insulin.

Inhalable insulin was available from September 2006 to October 2007, however, it was withdrawn mainly due to cost. Inhalable, polymeric based drug delivery systems, were first deployed for tuberculosis, then research was directed towards insulin delivery and a dry powder formulation of insulin encapsulated within nanoparticles was made. The nanoparticles were small enough to avoid clogging up the lungs, but large enough to avoid being exhaled, this allowed direct delivery to the bloodstream without degradation. Aerogen in Galway Ireland, and Dance Pharmaceuticals in San Francisco, California, have announced a drug-delivery

partnership, and will produce inhaled insulin to the patients friendly with low cost. [14] This is still not very long lasting and an injection is still needed later, but perhaps with the addition of polymers like N, N-dimethylaminoethyl methacrylate and polyacrylamide with the “molecular gate” system may solve this problem.

Todd Zion from Nanostructure Materials Research Laboratory has developed technology for diabetes treatment called SmartCell the author says about his technology: "When glucose rises in the bloodstream, it will eat away Smart Cell's structure. As the SmartCell protein matrix breaks down, insulin is released. The more glucose is present, the faster matrix will erode." [20] This smart cell technology means that the patient will only need one injection, and experiments with lab rats have shown very positive results. Therefore, if the insulin compound normally used for inhalation was replaced with Smartcell, only one dose would need to be inhaled without the need to inject.

Artificial pancreas

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. [18]

Another permanent solution to diabetes is the artificial pancreas. 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. [17] The artificial pancreas is probably the most effective treatment yet.

Ethics of nanotechnology-a few of many

This paper has only provided a small insight into the prospects of nanotechnology in medicine and more specifically how it could revolutionise the way we treat diabetes, but is there a step too far? For years, man has sought a way to end suffering caused by disease and injury. Researchers today believe that nanotechnology is the gateway to such a goal.

Nanomedicine and nanotechnology is generally an area with little experimental data on possible adverse side effects and risks. For example, nanoparticles in the long term might somehow affect the biochemical pathways and processes with which we function. The main concern is toxicity and exposure of these pathways. The concerns are over the nanowaste from things like polymeric nanoparticles in the body and also the possible environmental contamination from the manufacture of nanomedical tools. "Although this is not altogether different from the long-term

risks associated with exposure to chemotherapeutic or radiologic agents, it is an important risk factor that must be disclosed to patients taking nanomedicine or any kind of intervention involving nanoparticles or nanomaterials." [21] Only time will be able to tell the long term effects, but perhaps such a long term test could be carried out on higher primates, but this again sparks another whole issue of animal welfare.

It is also thought that in the future nanotechnology will conflict greatly with privacy and confidentiality, for example, implanted or swallowed diagnostic tools will make the collection of an enormous amount of individual cellular information possible, which can then be transmitted to a medical database server to be analysed. It is feared that this could be exploited if in the wrong hands. Once diagnostic technologies have reached this stage it will require reconceptualising understanding of disease. In some cases, more information might just be too much information. Nevertheless, the balance of information processed and disseminated versus benefit to society and individual health is a significant consideration for the ethics of nanotechnology-based diagnostic technologies. [21]

One controversial topic in the future treatment of diabetes is the artificial beta cell. There have been many attempts to develop such a cell. The main approach has been to change molecules on the beta cell surface that are targets for lymphocytes during autoimmune attack. The beta cells can also be genetically altered so that they respond to the rise and fall of glucose in the blood as the cells in a healthy patient would. Nanomedicine enhancement is also concerned with the creation or improvements of bodily parts that have been previously damaged or perhaps even missing from birth, but many people view this approach as unethical. It could be used to develop artificial limbs physically far superior to that of normal humans which immediately gives rise to concern over possible unscrupulous exploitation by third parties. Many religions are also opposed to such treatment, as it is defying the natural state of the patient and essentially "playing God". Would this be acceptable if in turn, it improves the well-being of the patient, by helping them improve their quality of life? Do they not have the right to live without their impairment if the technology is available to cure them, but others do not deem it ethical? These are but few of the views causing controversy.

Professor Freitas puts the topic into an interesting light, "on a long term perspective nanotechnology envisages not only the creation of autonomous nanomachines to be used inside the human body but the enhancement and even transformation of the human body and human identity particularly in case they were used to modify the human brain." [21] This is the point where the technology should be reviewed in great detail before venturing further, as the brain is the most vital organ of the body and is what defines us as a species.

Conclusion

This paper concludes that in the foreseeable future the likelihood is that the artificial pancreas will be the most important clinical application of nanotechnology, as the pharmacological

approach has been disappointing thus far. As diabetes care advances so does the demand for management systems capable of continuous monitoring of blood sugar levels with the seamless administration of insulin. [16] Many patients will be less compliant to treat themselves everyday knowing that the technology is available to cure them.

Banting and Best discovered insulin 85 years ago, ever since millions of lives have been saved and now diabetic patients can live long and fulfilled lives regardless of their condition. However, we must consider that 285 million suffers worldwide need daily treatment and if this can be improved and associated costs reduced, then the benefits would be twofold to society. The patients' quality of life would be improved because they would only endure one medical procedure (implantation of artificial pancreas). Initially patients would require subsequent medical intervention, however, in the future this would be eliminated. As the number of diabetic cases in the western world increases, so does the demand of costly artificially engineered insulin. These funds could potentially be saved or diverted to other areas of medical research.

Nanotechnology is not in the distant future, it is happening today, but in parallel with its development caution must be taken at every stage to avoid potential exploitation. Organisations and institutions worldwide are starting to recognize the applications of nanotechnology and identifying it as viable and independent science.

References

Gerardo P. Carino, Edith Mathiowitz. Oral insulin delivery; *Advanced Drug Delivery Reviews* 35,249–257(1999). [15]

Neil Gordon , Uri Sagman . Nanomedicine Taxonomy; *Canadian NanoBusiness Alliance* 1-28(2003) [19]

Web based

<http://www.netdoctor.co.uk/diseases/facts/diabetes.htm> [1]

<http://www.chalcogen.infim.ro/Kumar-Arya.pdf> [2]

http://en.wikipedia.org/wiki/Diabetes_mellitus [3]

<http://www.zyvex.com/nanotech/nanotechAndMedicine.html> [4]

<http://www.zyvex.com/nanotech/howlong.html> [5]

<http://www.idb.hr/diabetologia/05no4-1.pdf> [6]

<http://medicinar.mef.hr/tekstovi.php?id=39> [7]

http://www.nanopharmaceuticals.org/Polymeric_nanoparticles.html [8]

<http://www.tweetlebeetle.ca/wp-content/uploads/2010/10/Nanotechnology-and-Diabetes.pdf> [9]

<http://www.netdoctor.co.uk/diseases/facts/diabetes.htm> [10]

<http://nextbigfuture.com/2008/04/microphysiometer-using-multiwall-carbon.html> [11]

http://www.google.co.uk/imgres?imgurl=http://www.saudigazette.com.sa/myfiles/Images/2010/07/31/bm02-big.jpg&imgrefurl=http://www.saudigazette.com.sa/index.cfm%3Fmethod%3Dhome.con%26contentid%3D2010073179634&usq=_4TzI8mbQ8C6DM-fC7x3foXArIj8=&h=200&w=220&sz=9&hl=en&start=10&zoom=1&um=1&itbs=1&tbnid=qTWWCD3K4G_jmM:&tbnh=97&tbnw=107&prev=/images%3Fq%3Dimplantable%2Bsensor%2Bfor%2Bdiabetes%26um%3D1%26hl%3Den%26safe%3Doff%26sa%3DN%26rlz%3D1W1ADSA_en%26tbs%3Disch:1&ei=oZp7TZreJdCHhQezj9nzBg [12]

<http://www.pharmainfo.net/satheeshbabu/blog/nanoparticles-treatment-diabetes> [13]

http://en.wikipedia.org/wiki/Inhalable_insulin [14]

<http://www.pepex.com/implantable-sensor-device.html> [16]

http://www.sciencedirect.com/science?_ob=Article [17]

<http://www.nanomedicine.com/Papers/NMRevMar05.pdf> [18]

<http://eng-2k-web.engineering.cornell.edu/> [20]

<http://www.nanowerk.com/spotlight/spotid=3938.php> [21]

<http://www.biodeliverysciences.com/Bioral.php> [22]

Fig 1

<http://upload.wikimedia.org/wikipedia/commons/2/21/Glucose-insulin-release.png>

Fig 2

http://2.bp.blogspot.com/_VyTCyizqrHs/SAk7U5hLbxI/AAAAAAAAAdY/6cZS8cS0yZU/s1600-h/realtimeinsulinmonitor.jpg

Fig 3

http://www.pharmainfo.net/files/u3747/Untitled-1_copy.jpg