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Control, Management and Treatment of Diabetes Using Modern Drug Delivery Systems and Special Properties of Nanoparticles

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ABSTRACT

One of the important applications of nanotechnology in the medical field is the use of it in drug delivery to target tissue for therapy of disease such as diabetes. Despite the limitations in the use of traditional medicine systems, there are also lack of target specificities, which reduce the effects of compounds due to drug metabolism in the body and the cellular toxicity of some of the drug. The biocompatible nanoparticles with physical, chemical and biological properties can be applied to optimize and overcome these limitations by improving drug solubility, increasing the rate of drug release and developing the penetration and distribution of drugs. Therefore, drug delivery systems provide the routes for drug delivery, which dramatically promote therapeutic drugs. Encapsulation of drugs by nanoparticles prevent decomposition, thus, it is prevented the incidence of side effects used by the opening of capsules of track to reach the target tissues. The data of this review were extracted from scientific sites and then meta-analyzed. The research in this area suggests that: if the materials used in manufacture of capsules contain nanoparticles smaller than 100 nm, the pore size for capsules becomes smaller due to the high surface to volume ratio and the solubility power of capsule will be higher. These advantages can improve the drug penetration and distribution by the capsules significantly. The new generation of drug delivery systems has more advantages than traditional systems. This article is written about the need for nanoparticle drug delivery systems, advantages, limitations and the recent developments in the use of such systems in the treatment of diabetes.

Key words: Nanoparticles, Diabetes, Drug delivery, Encapsulation

1. INTRODUCTION

Over the world, it is estimated that more than 285 million people suffer from chronic and pandemic diabetes which is often refer to the inability of the pancreas to control glycemic conditions (1). Diabetes is a disease of carbohydrate metabolism disorder that results from defects in insulin secretion from pancreatic beta cells and insulin dysfunction or both of them (2, 3). One of the most obvious symptoms of diabetes is increasing blood glucose which is the results of reduction in consumption of glucose by the liver and peripheral tissues and also increased glucose production by the liver (4).Hypoglycemia is the first and most important factor for clinical diabetes development and complications of diabetes (5, 6). Though, some of sequences of the mechanisms of producing diabetes could be cytotoxic free and activate radicals which slowly effect on beta cells and damage these cells with result of producing type 1 diabetes (7). The increased levels of free radicals and decreased antioxidant defensive mechanism causes damage to cellular organelles,enzymes, increased lipid peroxidation and increased insulin resistance (8, 9).The active oxygen affects the normal function of the pancreases. Effective amount of a key enzyme in the sweep of reactive oxygen species (10) in pancreatic tissue is lower than other, therefore increases the chance of injury by oxidative stress in these cells (11, 12). Gene expression and the activity of a number of key enzymes and antioxidant of the pancreas, such as superoxide dismutase and catalase in comparison to tissues such as the liver are low (13). Decreasing the

expression of antioxidant enzymes will be increased vulnerability of beta cells against reactive oxygen species (10) and increased the destruction of free radicals and finally the death of beta cells in type 1 diabetes (14). Type 2 diabetes is caused by insulin resistance or reduction in insulin sensitivity combined with reduction in insulin secretion. Incomplete body tissues response to insulin almost certainly involves the insulin receptor in cell membranes. Gestational diabetes occurs in women without previously diagnosed diabetes that show high blood glucose during pregnancy. No specific cause has been identified but it is believed that the hormones produced during pregnancy might increase blood glucose (15). Glycemic control is recommended through diet, physical activity and oral treatment for diabetes treatment. The past few decades often fails to mimic glucose homeostasis observed in healthy individuals (16). In this pathway insulin is delivered to the peripheral circulation not the portal circulation, which is directly inserted into the liver that is the physiological pathways in normal subjects (17). Therefore, injecting insulin several times a day is referring to poor patient compliance with subcutaneous route treatment. Therefore, many studies are on finding better and safer route for insulin administration. In this case, the application of nanotechnology in medicine could be a solution to overcome this problem. The big problem about control diabetes is the inappropriate administration of insulin by which the medical nanotechnology gained improved to insulin delivery. During the past two decades, researchers that deal with the advancement medical factor found that, drug delivery is a major part of the medical development. With this regards, a wide range of drug delivery systems were identified. All of this systems will improve stability, adsorption and drug therapy concentration in target tissue, in addition to those long-term redistribution and release of drug facilitated at the target site (18). The frequency drug administration is also reduced and improves patient comfort. New systems of drug supply protecte and improve the pharmacokinetic of peptides and biodegradable proteins which have often short half-life in vivo (10). Oxidative stress is one of the diabetes complications which caused a delay in wound healing which is a well-known problem in diabetic patients. It can be treating by the use of some nanoparticles (aluminum oxide, cerium oxide, gold, vanadium, and zinc) that act as an ROS absorbent. Over the past few decades, studies show that nano-medicines used to treat diabetes have been performed. Modern drug delivery systems owe their remarkable success to nanoparticles and nanoparticles have appropriate characteristics as:

1. High capacity for transporting drugs
2. Very large active surface for the reaction
3. Suitable small body to cross the blood levels
4. Ability of accumulation in the target tissue
5. And low toxicity

Nanoparticles for the delivery of insulin

A common nanostructures which are studied for insulin delivery systems represented in Figure 2, includ (19, 20);

1. Bio-degradable nanoparticles including spherical nanoparticles and nano-capsules
2. Ceramic nanoparticles
3. Dendrimer
4. Polymeric micelles
5. Liposomes are

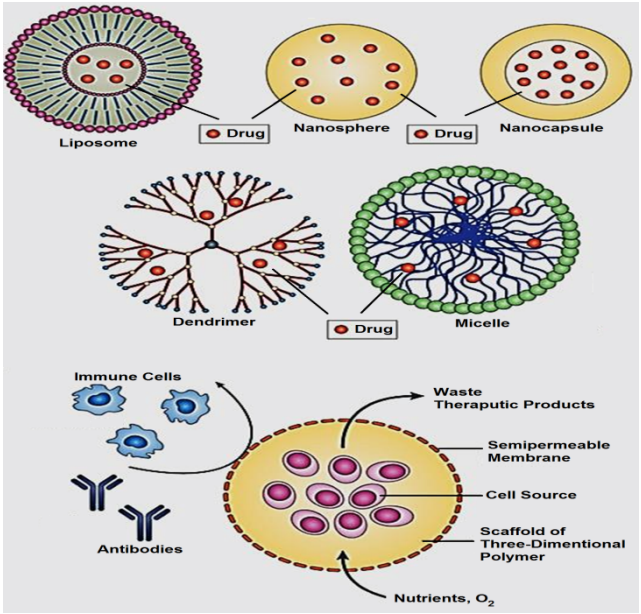

Figure 1. Schematics representation of different nanotechnology-based drug delivery systems

2. Polymeric nanoparticles

Depending on the method of preparation of two types of nanoparticles there are solid colloidal particles in 10-100 nm size that call nanospherical and nanocapsules (21, 22) . The nanostructures which are completely different for release drugs that have been as capsules (Figure 2). The nanosphericales are vesicular systems which the drug within a polymeric membrane is limited and the drug are delivered to the target tissue (23). The polymer is decomposed to lactic acid and glycolic acid finally will restore carbon dioxide and water via the kerbs cycle. Previous studies have been emphasized the use of natural polymers such as collagen, cellulose, etc. as bio-degradable systems (24, 25). Cytotoxicity experiments showed that the drug release from spherical nanospherical reinforced and does not harm the cells (26). Polymeric nanoparticles have made significant material for oral and intravenous forms towards the performance and effectiveness, so polymeric nanoparticles with special management can be used in a particular situation in delivery of high concentrations of pharmacological agents. These nanoparticles could be as ideal candidates for insulin therapy and insulin delivery. Polymeric nanoparticles are used as carriers of insulin (20). These biodegradable polymers with matrix polymer of insulin by a membrane

are covered with nano-holes glucose oxidase coupled.

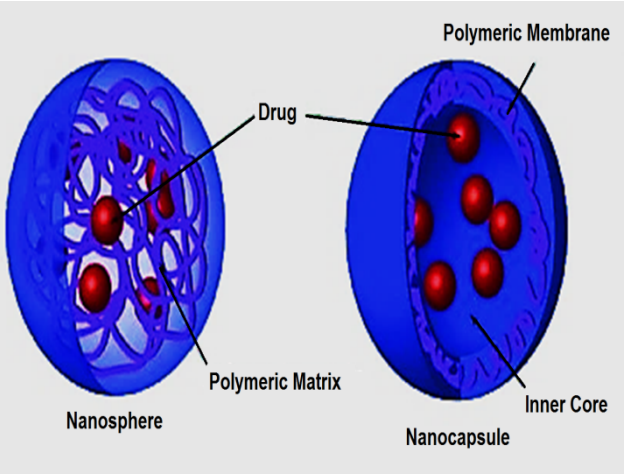

Figure 2. Schematics representation of Polymeric nanoparticles: Nano spheres and Nano capsules

3. Ceramic nanoparticles

Ceramic nanoparticles are made of calcium phosphate, silica, alumina or titanium. The ceramic nanoparticles have the certain advantages such as easy preparation, high bio-compatibility, extra small size (less than 50 nm) and high stability of the fourth dimension (27). These particles can effectively protect drug molecules against denaturation occurs by changing the external PH and temperature. Optical syntheses of water–insoluble anticancer drugs loaded in the ceramic nanoparticles are drug delivery systems for photodynamic therapy for cancer treatment (28). However, their surfaces can be easily modified with different functional groups to dispatch with different ligands or monoclonal antibodies to bind to a specific position (29). These nanoparticles can be developed on the size, shape and quantity of the desired porosity. Ceramic nanoparticles by environmental changes not affected inflation or changes in pore. Core of calcium phosphate nanoparticles are used as carriers of insulin. Recent studies have shown that calcium phosphate nanoparticles can be used for oral insulin delivery (30).

4. Nanoparticles and oral insulin delivery

Oral insulin in diabetic patients can not only be helpful to reduce pain and damage caused by the injection, it can also mimic the fate of physiologic insulin (16, 31). However, oral administration of protein drugs such as insulin faces by the problem of low PH and digestive enzyme of the stomach. Intestinal epithelium as well as a major barrier to the absorption of hydrophilic macromolecules (such as proteins, polysaccharides and nucleic acids) before it reaches it to target cell for a particular operation (32). Therefore, improving the delivery of hydrophilic molecules in cell parameters by using nanotechnology has been considered in diabetes research (33). Nano medicine technology may be used for oral delivery of insulin include Pre- drugs (conjugated insulin-polymer), micelles and liposomes, solid lipid nanoparticles and biodegradable polymer nanoparticles. Pre-drug technology are used for the formulation of the drug is often made of polyethylene glycol (PEGylation) ; for example , drug conjugated with polyethylene glycol (PEG) to increase the solubility, stability and permeability. Insulin–PEG pre-drug have shown the many advantages of oral delivery (34). Scott Moncrieff et al (35) created biliary salt and fatty acid mixed micelles system and found that the micelles which are contain sodium glycols 30mm and linoleic acid 40mm significantly improves insulin intestinal absorption. Unfortunately, the micelles to delivery hydrophobic drugs appear to be not ideal. Instead, liposomes can have a better performance for the delivery of insulin. The liposomal delivery system containing glycol recently been developed as an inhibitor for oral delivery of insulin and enhanced ion permeate which has been shown as the best insulin ionic protection against enzymatic degraded by pepsin, trypsin and chymotrypsin (36). Biodegradable polymers such as (poly lactic glycolic acid, PLGA) and polycaprolactone, were studied as well as for the oral delivery of insulin. However, these nanoparticles may not be ideal for the delivery of hydrophobic drugs. However, how the oral delivery of hydrophobic drugs such as insulin is still a significant challenge. Thus improving the transfer of parcel of hydrophilic drugs was considered (37, 38). Various types of intestinal penetration and carrier such a chitosan (cs) have been used to aid the absorption of hydrophilic molecules (39). So if it is administered orally, carrier system is required for protection of protein drugs in the harsh environment of the stomach and small intestine (40). In addition, the Cs nanoparticles increases intestinal absorption protein molecules more than that of aqueous CS solutions within the body (41). Insulin- loaded nanoparticles which coated with sticky CS mucus may be longer period of time their residues can stay in the small intestine, penetrate into the mucous layer and then temporarily open the tight junction between epithelial cells that is mediated, while the mode becomes unstable due to their senility to PH or degradation which broken apart. Insulin is released from the particles break apart then can penetrate from cells and go through to the blood flow for its final destination. The most promising strategy for achieving oral insulin is using micro spherical system, which essentially is a combination of strategies. Micro-spherical as protease inhibitors by protecting the encapsulated insulin from enzymatic degradation in the matrix as well as penetration enhancers effectively pass through the epithelial layer of intestine (17). Dextran nanoparticle composition vitamin B12 was studied to overcome the intestinal digestion of vitamin B12 bound to peptide/protein (42). These nanoparticles prevent from entrapment of insulin in the intestinal proteases. Dextran – vitamin B12 nanoparticle composition show a suitable release profile for oral insulin delivery systems. In addition, gold nanoparticles have also been tasted for carrying insulin, gold nanoparticles synthesized in the presence of chitosan as a regenerative and have been studied in order to carry insulin (43).

5. The use of antioxidant properties of nanoparticles in the treatment of diabetes

Diabetes increases the level of free radicals and reduces the antioxidant defensive mechanism could cause damage to cellular organelles, enzymes, increase in lipid peroxidation and increase insulin resistance (8, 9). Previous studies demonstrated that some of the nanoparticles can be used as a target drug according to their character which reduces the complications of diabetes and may help improve diabetes and increased insulin secretion. Some of essential elements are exceptional and contain antioxidant properties. Their impacts have been considered in improving diabetes. Since the nanoparticles due to the small size and high ratio of surface/volume have a high reactivity. The use of elements at the nano scale and specific targets could be effective treatment of diseases such as diabetes; for example the nano particles of vanadium, zinc, aluminum, cerium and gold. Vanadium is a special example of elements in the periodic table of transition elements with the -3 to +5 oxidation/reduction capacity. There are many reports on the role of vanadium compounds in treatment of diabetes in experimental models. Vanadium effects on type one and type two diabetes through the reducing plasma concentration of glucose, the normalization of plasma lipid levels, enhancing sensitivity to insulin and insulin-mimicking effects. The vanadium element in streptozotocin-induced diabetic rats has shown the ant diabetic effects (44-48). One of its mechanisms is likely the inhibition of tyrosine phosphatase 1B (PTPB1) which is an important enzyme in the pathway of the insulin receptor. Insulin by stimulating its receptor causes to activate auto phosphorylation, the phosphorylation of various molecules such as insulin receptor substrates. Tyrosine phosphatase inhibits tyrosine kinase activity of insulin receptor. It has been proved that nanoparticles of mono ammonium vanadate has more anti – diabetic effects and less toxic effects than ammonium vanadate. This could be due to physical and biochemical changes of nanoparticles that may be had an effect on the properties of bioavailable, insulin- like insulin tropic ammonium vanadate (49). Cerium oxide (CeO2) plays a major role in the inhibition of free radicals due to its strong potential (50). Oxidation of cerium atoms in both +4 and +3 are known. This dual oxidation state means that the nanoparticles have oxygen holes (51). The loss of oxygen and the reduction of Ce4+ to Ce3+ is with an oxygen vacancy. These features of ceo2 nanoparticles improve its therapeutic properties and consequently will be inhibition of free radicals. Zinc plays an important role in the normal metabolism of insulin in the body. This includes the ability of zinc to adjust the insulin receptor and the intracellular events that will determine the glucose tolerance and is able to support normal pancreatic response to glucose (52). A study in the streptozotocin diabetic rats showed that oral zinc nanoparticles improve glucose tolerance, increasing of serum insulin and decrease of blood glucose (53). The oral use of the gold nanoparticles as the factors of antioxidant exert their function by the inhibition of formation of free radicals (10), clearing free radicals. These kinds of nanoparticles employ strict control on the anti-oxidant enzymes such as GSH, SOD, GPX and catalase, causing the inhibition of lipid peroxidation and also inhibit the production of free radicals in hyperglycemia. Therefore they could be effective in treating diabetes (54).

6. Discussion

Polymeric nanoparticles are used as a carrier of insulin (20). These bio-degradable polymers with the matrix of polymeric insulin are covered by a membrane coupled with nano holes with glucose oxidize. Usually oxaloacetate which is starter of Krebs cycle composed of pyruvate, last product of glycolysis, and produce by an enzyme named pyruvate carboxylase. Then in the Krebs cycle combine with a unit of acetyl coenzyme A provided by degradation of fatty acids, to give oxidized acetyl coenzyme A units, called fat burn on absences of sugars. In long-term fasting, low-sugar or high-fat diet, fasting and type one diabetes oxaloacetate which is the Krebs cycle starter will be used in gluconeogenesis pathway and is not available for condensation with acetyl coenzyme A to make tetra carboxylic acid. Under these conditions the accumulation of acetyl coenzyme A in the mitochondrial matrix leads to make Beta hydroxy butyric acid, Acetic acid and Acetone known as ketone bodies. Ketone bodies can be considered Trans able and soluble shape units of acetyl in circulation that are important as sources of energy. Heart muscle and renal cortical sections prefer acetoacetic acid on glucose in long-term starvation. 75% of fuel in the brain is provided by ketone bodies. But some conditions can lead to the risk of death due to blood levels of ketone bodies. The most common conditions are diabetic ketosis in type1 diabetes patient. In the absence of insulin, the liver is unable to uptake glucose for producing oxaloacetate to bond acetylcoenzyme a units to start the krebs cycle. Therefor the liver produces plenty of ketone bodies, which are relatively strong acids. This is the result of acidosis. The reducing PH causes damage of active tissues especially the central nervous system and inhibits the important enzyme of glycolytic pathway such as phosphofructokinase-1which. This condition is dangerous for cells. Polymer systems have been used from changing the PH of blood that occurs due to increasing of blood glucose levels. These bio-degradable polymers are covered with an insulin polymer matrix by a membrane will nano-hole pores with glucose oxidase (55). Therefore, the increase in blood glucose levels causes the changes in nano-pores in the membrane that leads to insulin delivery and biodegradable of polymer. Glucose oxidase reaction is reduces PH in the delivery system of micro-environment that is leads to inflation in the delivery system of micro-environment and thus leads to an increasing release of insulin. Polymeric systems

investigated for such applications included; copolymer N-dimethylaminoethyl methacrylate (56) and polyacrylamide (57). This system (Molecular valves) consists of an insulin receptors with a delivery rate controlling membrane. In normal conditions the body PH (PH=7.4) polymers swell and valves are closed, in low PH (PH=4) when the blood glucose level rises polymers get smaller, the valves open and insulin is released from the nanoparticles. These systems release insulin by the inflation caused by changes in blood PH. Control of insulin delivery, depends on the size of valves, insulin concentrate and the amount, of opening or closing valves. Of polymeric systems that have been studied, co-polymeric vesicles (PLA-P85-PLA) can be named as a new carriers which developed for oral delivery of insulin and has been proved that have an excellent biocompatibility (58). In another study the co-polymer coated with (Nps: FA-PEG-PLGANPS) or iron nanoparticles with PLGA nanoparticles were studied and demonstrated that these polymeric nanoparticles increases the bioavailability of oral insulin by twofold (59). According to the main problem describe of insulin, the use of nanotechnology can be promising directions for treatment and improving this epidemic disease. Despite all the purpose studies which have shown that increase the surface area of nanoparticles will increase the rate of chemical reaction and nanoparticle accesses to the cell and effects on protein and DNA synthesis steps could have irreversible effects on growth, reproduction and cell metabolism (60). Therefore, studies need to be done on the use and application of nanoparticle in this subject.

7. CONCLUSION

This study was a review research to discuss advantages, limitation and recent advances in the use of nanoparticles drug delivery systems in the treatment of diabetes. The data of this review were extracted from scientific sites and then meta-analyzed. The main sources of the data are PubMed, Google scholar, science direct and other databases. The nanoparticles used in drug delivery systems or as drug targets should be thoroughly investigated in terms of the toxicity, the dosage, the particle size, and the short term and long-term effects on cells to prevent of side effects consequences.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration between all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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