



Contribution of Nanotechnology and Nanomaterials to the Treatment of Diabetic Patients by Aid of Novel Inventions

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Authors' contributions

This work was carried out in collaboration among all authors. Author SN Invented and designed the study, performed the analysis, wrote the protocol of invention and wrote the first draft of the manuscript. Authors SM and AN managed the analyses of the study as well as the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJOCS/2020/v8i119034

Editor(s):

(1) Dr. Srijita Basumallick, Asutosh College, Calcutta University, India.

Reviewers:

(1) Juliet Sackey, University of South Africa, South Africa.

(2) Yuvraj D. Dange, Shivaji University, Kolhapur, India.

(3) Mircea Tampa, Carol Davila University of Medicine and Pharmacy, Romania.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/57899>

Review Article

Received 02 April 2020

Accepted 08 June 2020

Published 18 July 2020

ABSTRACT

Nanoscience and Nanotechnology are highly growing their significance in diabetic supplies and research nowadays. It is an area that included nanomaterials, nanosensors and nanostructures as well as nanoparticle projects and also their usage in human health research. Particularly, nanotechnology helps to the production of diabetic supplies, materials together with the development of novel glucose and insulin injection devices as well as their measurement sensors by the aid of nanomaterials. These materials mostly could be metal nanoparticles together with carbon nanostructures by nano dimension delivery mechanisms modalities which hold the potential to vividly recover the excellence of life of diabetic patients. Nanoscience and nanotechnology in diabetic research have facilitated and provided more truthful data for identifying diabetes mellitus. It is also worth mentioning that the nanotechnology could highly enhance the impact of drug delivery by addition of nanoscale materials and increase the glucose feeling, temporal response as well as glucose nursing. Furthermore, it is proposing novel nanoscale methods named closed-loop insulin delivery approaches which mechanically release insulin drug in reply to fluctuating blood glucose

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heights. Besides, the mixture of nanotechnology by medication has shaped a novel field of nanomedicine which could enhance human health level. It is worthwhile to mention that some of the applications of nanotechnology for the treatment of diabetic patients can be the production of diabetic supplies by nanotechnology. One of the most important diabetic instruments that could highly relieve the life of patients these days could be nano diabetic shoes which will describe here. In this research, applications of nanoscience and nanotechnology in treating diabetic patients were discussed.

Keywords: Nanospheres; diabetes mellitus; nanomedicine; nanotechnology; diabetic shoes.

1. INTRODUCTION

Diabetes disease (DD), which is a progressively common metabolic illness, makes a significant community health burden. The World Health Organization (WHO) has recognized that the diabetic diseases which also named as non-communicable illness (NCI) are a significant global health hazard and DD is one of the four main NCI which directly affects the global attention [1]. This kind of long-lasting disorder may also one of top 10 reasons of death globally and has attained pandemic proportions worldwide [2]. It is worth mentioning that only at 2015 the diabetes disease killed about 1.6 million persons globally [3]. Also, as stated by the recent Global Burden of Disease Study (GGDS) at 2015, this illness ranked 15th in the worldwide list of foremost reasons of years of life lost [1,4]. Besides, the 3rd highest risk issue of global early mortality is high blood glucose just after high blood pressure and tobacco usage. It is also worthwhile to recall that the Indian Initiative Diabetes Collaborators at December of 2018 did a complete overview of the diabetes load in India and find out some limitations in approximations due to insufficiencies of the data. To this end, the Indian Government launched the State Programmed to prevent and control of diabetes in 2019. Further, the availability of doctors as well as rudimentary drugs similar to metformin leftovers insufficient in many areas, particularly in rural parts of India. It should be also mentioned that due to the feeble implementation of Indian national programmers as well as the inaccessibility of treatment of long-lasting patients, the majority of diabetic people have no other options, caused incurring substantial out-of-pocket spending on treatment global and especially in India as the capital of diabetes and can further aggravated as a result of substantial variation in the prices of drugs in the global as well as Indian pharmaceutical market. Since diabetes is not a notifiable disorder, there are insufficient data obtainable on patients preserved in the private subdivision, then, its actual load

may unknown, for example the load of diabetic patients in India are undervalued [1,2,3,4].

In description of diabetic disease, it could be mention that the diabetes known as a kind of metabolic illness which happens when the level of Blood Glucose (BGIs) raises which caused occurring an inability of balancing the BGIs [5,6,7]. It may also be interesting to know that diabetes has 2 types. Persons who have type 1 diabetes may have a problem in insulin production due to the autoimmune obliteration of the insulin creating cells of their pancreas, which identified as beta cells [7,8]. On the other hand, the Type 2 diabetes is considered by insulin resistance, or a deficiency in cellular response to insulin production in the bloodstream [6,8,9,10]. It is important to mention that, at both diabetes of 1 and 2, the damage of homeostasis-regulation appliances can cause recurrently high or low blood glucose points identified as hyperglycemia or hypoglycemia, respectively [7,11,12,13]. It is worthwhile to point that, the hyperglycemia illness can cause a diversity of symptoms with cardiovascular besides neurological problems [14,15,16], however hypoglycemia can cause absence of energy, oblivion or death [8,17].

Scientific methods are help in sensing the skills or tiny procedures to analyze the diseases precisely and also in time. The wide variety of offers of nanotechnology in the arena of medicine and drug delivery and furthermore for simplifying the oral usage of proteins and peptides nanocarriers as well as their adaptation with human's body [10,15,18]. Also, nanoparticles are utilized to bring RNA and also proteins for identifying the disease as well as screening their development.

It is worth mentioning that diabetes has grown up to become one of main public health tasks worldwide, implicated near to twenty five million person in the United States in addition of about forty million universal and the mentioned number is expected to grow to near fifty million until 2035

[8,9,19,20,21] and also it is predicted to become the seventh main reason of death globally through 2030 [14,22].

It also should be noted that, insulin injections or glucose test are both painful and time consuming for all the diabetic patients. For overcoming the disadvantages of injection treatment, numerous skills have been established such as continuous glucose screens or insulin pumps to recover patient needed dosages as well as dermally of liquids [11,23]. Although these methods can sometimes balance the blood glucose level up to certain degree, nevertheless still they are powerless for attaining to factual health as injection of insulin could and they are very time consuming phenomenon. That means, they may cause several risks and problems for patients due to damages of sensors or also their need to frequent spare and maintenance which can charge the patients a lot, too. Consequently, there is critical need for assuming novel, safer and more cost-effective treatments. To this end, at the last years, a number of methods have been planned for non-invasive observing level of blood glucose and this only could be made promising by aid of nanotechnology.

In summary, the application of nanoscience and nanotechnology for humans heals have many conceivable advantages, like as entree to minor and clinically pertinent parts of cells as well as ability of analysis the most of small size materials [24,25,26,27]. Furthermore, it is very interesting to know that, the appearance of quantum properties which leads to motivating and valuable physical properties, such as, polymeric biodegradable nanoparticles or polymeric micelles and ceramic nanoparticles as well as liposomes, contemporary known as highly standards of care [28,29,30,31]. The other example of nanomaterials also could be nanoscale carbon which although, using in medicine and drugs but very stronger than steel with high malleable properties as well as fluorescent which could shows electrical conductivity and utilizes at engineering instruments as well [10,32]. For instance, the better glucose sensor skill has an important influence on the health of diabetic's patients, due to highly improving their blood sensation which caused to more precise insulin dosing as well as diabetes organization. Also, some other diabetic's instruments such as diabetic shoes with aid of modern technologies such as nanotechnology for helping the patients for better life were recently invented as well as many

progressive advances in nanomedicine which have already eased new sensors which are more frequent and convenient for patient's living [9, 11,16,32,33]. Nanomedicine science also has the ability of detecting variations in diabetic disease and then automatically balanced the rate of needed medicines [9,17,34]. To sum, numerous kinds of nanoparticles are now studied for drug delivery in diabetes treatment and their clinical applications will let diabetic's patients to manage their illness more effectively and recover their health as well as their life quality.

2. DIABETIC EQUIPMENT

2.1 Diabetic Shoes

A kind of shoes which named diabetic shoes or sometimes also called as extra depth shoes, therapeutic or sugar shoes are one of the best equipment for controlling the painful foot ulcers. These type of shoes have special and different design, such as different wearing section, various materials, and different comfortability or even they have completely new design like the invented shoes by the authors of this article, which are totally smart, alarming and controlling shoes for preventing of foot ulcers. It is also expected from them to highly reduce the risk of skin breakdown as well as painful ulcers in diabetic persons or even any persons who have pre-existing foot illness.

It is notable that, unfortunately, persons with diabetic neuropathy in their feet, mostly have an untrue and insufficient information about their safety such as the real risk which menace their feet [1,34,35]. It is worth mentioning that, foot ulcers can just grow in a couple of hours. To this end, the first goal of therapeutic shoes is to stop start of the ulcers, or even amputations of diabetic patients due to poor blood circulation [36,37,38,39]. Also it should be mentioned that the neuropathy is very important which can sometimes even change the shape of a person's feet then highly limits the variety of shoes that can be safely utilized [3,40,41,42,43]. As well as meeting strict guidelines, diabetic shoes should be approved by the physicians and approved by a certified global health committee, similar to an orthotics. These kind of shoes could not find in the shoe shops, consequently, the invented diabetic shoes should be custom-molded and produce by producer's effort as a defensive system to aid diabetics avoid ugly foot ulcers and improve mobility. Here we are going to more describe the diabetic shoes invention:

2.2 Technical Problems and Description of the Goals of the Invention

It should be again recalled that, nowadays, diabetic diseases have affected most of developed and also developing societies. After the beginning of the disease, if the patients left unchecked, it can highly destroy many parts of their body, especially the feet which are more at risk. The feet are one of the most vital parts of the body with a small volume of the whole body, but should carry almost the entire weight of whole body which means should withstand very high pressures [44,45]. Because the foot ulcers of diabetic patients lead to long-term hospitalizations and finally may amputation, they can place a heavy psychological and economic burden on the individuals as well as their family and also the community's health system [46].

It should be emphasized that, Ischemia, neuropathy, and infection are three important pathological factors that lead to complications of diabetic foot. Although not all diabetic wounds and diabetic feet ulcers can be prevented, but they can be greatly reduced. In this regard, the patient's awareness is in the first place and very important and then the treating physicians, clinical examinations, appropriate treatment of small lesions, teaching the basics and finally covering method of feet may help to prevent most of the wounds [47,48,49,50].

It should be highlighted that the basic principles in the control and treatment of diabetic foot ulcers are: a) ability of estimating its production time and proximity of the ulcer and thus controlling of prevention of infection, b) controlling and establishing proper arterial blood flow and c) Remove the pressure from the foot [51,52,53,54].

Although various advances have been made in the treatment of foot ulcers, but, most of the treatments have been relatively effective and complementary, and to treat this complication, prevention of problems and ulcers could be the most important and effective pillars in the life of diabetic patients [55,56]. That means, by continuously monitoring the amount of blood volume in the feet of diabetic patients with using highly sensitive sensors, with aid of novel technologies such as nanotechnology, the invented shoe could determine the exact time of the possibility of foot ulcers. On the other words, this kind of invented shoes prevents sores and

painful discomfort in the foot before they will be formed and simply inform the patients [57,58,59].

2.3 Description of the Invention

2.3.1 Title of the invention

Smart, Alarming and Controlling Shoes to Prevent Formation of Diabetic Foot Ulcers with related to technical background of Biomedical Engineering.

2.3.2 Technical problem and articulation of the goals of the invention

Although various advances have been made in the treatment of diabetic foot ulcers, but, most of them have had relative and complementary effects. To this end, several of scientists agreed with prevention of problems as the best and most effective and high important supporting way in patients' lives [60,61]. Due to high sensitivity of foot in diabetic patients as well as high cost of treatment, together with prevention of annoyance of the patients after injuring and their long treatment period, this group has designed a very efficient and effective shoes which could smartly alarm and inform the patients before prevention of painful ulcers by smart sensors [62,63,54].

In addition, to having a flexible structure which completely be in harmony with physique of the patients' feet, this group provide extraordinary features for their invented shoes such as monitoring the blood supply to the arteries of the feet, warning of the possibility of injury as well as warning time of removing the shoes for rest at each of the designed models. It is worthwhile mentioning that, such facilities are not available in any of the produced diabetic shoes till now as shown in Fig. 1 [64,65,66,67,68].

2.4 Objectives of the Invention

The purpose of the current invention is to prevention of the painful feet ulcers of diabetic patients, together with controlling the rate of blood flow of the arteries of their feet, which could be the main cause of diabetic feet ulcers, and to prevent further post-traumatic strokes.

2.4.1 Description of status of prior knowledge and history of advances in relation to the alleged invention

According to extensive research, no similar case has been found with the specific capabilities of this claimed invention and all the previous cases have focused only on the materials, type of

shoes or ultimately the radiation to eliminate germs [69,70,71]. In the former researches none of the high important Internal factors which can cause wounds or even continuous examinations of arterial for knowing blood flow for avoiding from creation of painful lesions and physical and mental suffering of patients did not investigated. To this end the inventors have provided a sufficient and integrated descriptions and solution for the mentioned technical problems by this invention. These shoes can precisely determine the time of injury by closely monitoring the feet of diabetic patients with using special skin sensors which embedded in 9 susceptible points of diabetic wounds in the sole of the person's foot. It should be noted that this system is much cheaper and less sensitive to body movements compared to ultrasonic systems [72,73,74].

2.5 Some Other Supports of Nano Technology for the Diabetics

2.5.1 Injectable nanogel

Nanogels define as colloidal hydrogel nanoparticles which have three-dimensional networks throat physical or chemical crosslinking [75], where they could store and hold a great quantity of water without dissolving into the aqueous medium [76].

It is very interesting to know that, nowadays scientists use injectable nanogels for screening the level of blood sugar of diabetic patients for increasing the insulin level secretly when required.

It is also worth mentioning that the project of Injectable nanoparticles has been invented for the first time at Massachusetts Institute of Technology (MIT) due to eliminating the need of insulin for diabetics Type 1 patients. In the other word, the scientist invent a way for continually monitoring the diabetic patients' blood sugar level for injection of needed dosage of insulin [5,75,76,77].

The nanoparticles were smartly found the intended glucose level in the patients' blood then acting by releasing of the appropriate dosage of insulin, like as pancreatic islet cells, which were demolished in diabetes Type 1 patients [78,79,80]. Eventually, this kind of scheme could safeguard of blood sugar levels and continue balancing and recover the quality of these

patients' life, due to the researcher's findings [81,82].

It should be recall that, the insulin actually works, but the main problem is the patients who are couldn't always get the correct needed dosage of their medicine. At this time, by this invented system of extended release, the quantity of secreted medicine is relative to the requirements of the potions body [83,84,85].

At present, people who have Type 1 diabetes usually hole their fingers many times in a day for drawing blood to test their level of blood sugar. Once the level of sugar are high, they should inject insulin to themselves, which could reduce the sugar level of their blood [86,87].

Nowadays, several investigators have required to develop a proper systems for insulin delivery which may act like an "artificial pancreas," mechanically sensing the glucose levels of blood and secreting the needed insulin. One novel method is utilizing the hydrogels for knowing the amount of glucose levels, but this system is slow for responding because letting the insulin to leak out due to the lack of mechanical strength. So, to this end, the MIT scientists set out to make a novel sturdy, biocompatible scheme which could reply extra quickly to changes the glucose levels of patients' blood as well as be simple to manage [88,89].

Their invented organization contains of an injectable gel like system with a surface similar to toothpaste. The gel comprises a combination of oppositely charged nanoparticles which highly attract each other, then, keeping the mentioned gel intact and stopping the particles from leaking away from the body after going inside [90,91,92]. To this end, the researchers designed a kind of gel which is sensitive to acidity by aid of a modified polysaccharide which identified as dextran. So, each of nanoparticle includes of spheres of dextran full of an enzyme which converts the glucose inside the gluconic acid [93,94,95]. Then, the glucose could diffuse easily inside the gel, so if sugar levels of blood are raised, the mentioned enzyme produces great amounts of the gluconic acid, causing the local environment become additionally acidic. This acidic situation will causes to the disintegration of dextran spheres and then releasing the insulin. After releasing, Insulin performs its usual function, changing the glucose in the bloodstream into glycogen, which is engrossed into the liver for storing.

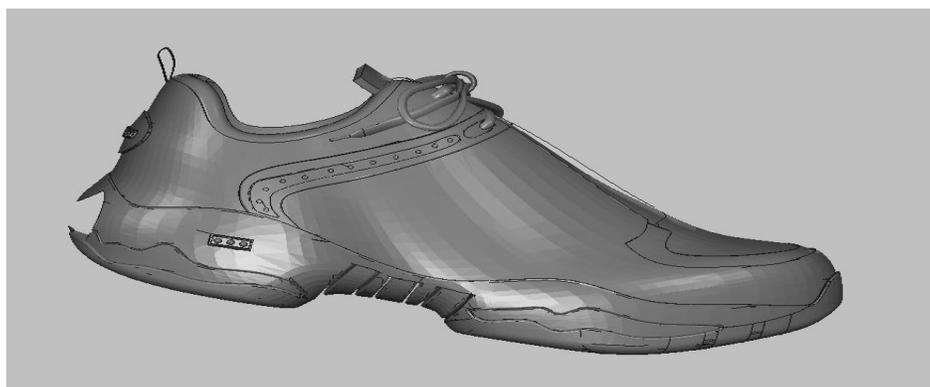


Fig. 1. Schematic of invented diabetic shoes

2.5.2 Long-term control

In the primary part of tests which done on animals with diabetes type 1, the scientists found that a single injection of the mentioned gel could maintained the normal blood sugar stages for about of ten days. Due to the biocompatibility of particles which mostly comprised of polysaccharides, they are finally absorb to the body.

The scientists are currently trying to adapt the particles for faster responding to the variations of glucose levels, same of the speed of pancreas islet smart cells as these cells can very quickly release insulin as soon as feeling high sugar levels.

It is worth mentioning that, before trying this nano particles in the diabetic patients, the researchers' strategy will be to additional develop the organization's delivery properties and to work harder on balance the dosage which will be wanted for use in patients [96,97,98].

2.5.3 The technology of closed-loop insulin delivery by aid of nanotechnology

It is very interesting to introduce the closed-loop schemes as an alternative of traditional insulin injection method which can endlessly monitor the level of blood sugar and release insulin as soon as needing. The several benefits of this system over the traditional methods can be nominated as: 1) better control of BGLs, which caused in the reduction of the problems of the diabetic patients [39,40,99,100] and also 2) this system could lead to reduction of the dosage of consumed insulin, as well as 3) reduction of the amount of hypoglycemic and hyperglycemic proceedings. These compensations have led to substantial

attention in developing the mentioned close-loop schemes. Finally 4) it should be noted that, the stated systems have shown promising results in relation of receptiveness and biocompatibility [7,41,101,102].

2.5.4 Others researches attempts

Numerous scientists have attempted to make platforms which show a stepwise reply to glucose concentration as well as ability of delivering multiple drugs. For example, Zhao and his co-authors have worked on porous Silica nanoparticles as a stage of glucose receptive release for the insulin as well as cyclic adenosine monophosphate [69,103,104,105]. Then, the silica nanoparticles were encumbered with aforementioned cyclic adenosine monophosphate and covered and bound to gluconic acid adapted insulin.

It is interesting to know that Wu and his co-authors had also invented a multifunctional hybrid nanogel system for serving as an insulin delivery expedient as well as glucose sensor [9,62,106,107]. This polymer is also accomplished of crosslinking to procedure a nanogel which experiences a phase change in reply of glucose concentration. It is worthwhile mentioning that this group which comprised of silver nanoparticles at the essential of the nanogel, had endows them with robust fluorescence.

Finally it should be noted that, the nanogels able to release 56–91% of the stored insulin at high glucose stages, and also could rapidly modulate among high and low insulin release taxes in reply of altering glucose concentrations and released insulin at lower levels which could be continued for more than 2 days.

3. CONCLUSIONS

The above paper evaluates numerous advances of nanotechnology and nanomaterials with the aim of improve the quality of life of many diabetic patients who suffering a lot from painful ulcers, and have many deep and extensive health problems during overall status of their life. This problem currently is the most widespread public health problem world while.

The authors are placing emphasis on some of these devices, as a shoe developed to alleviate the suffering and diminish the risk of complications from diabetic ulcers and necrosis caused by diabetic neuropathy, which can lead, on a larger timeframe, to amputation.

As it can be concluded from this research, very important advances in diabetic shoes, glucose sensors as well as self-regulated insulin delivery schemes have been eased by nanoscience and nanotechnology. The diabetic shoes as explained in this study, is a novel invention which aids patients to better life. Also in this shoes the nanotechnology and nanomaterials were employed to produce a new antibacterial diabetic shoes. It should be highlighted that the basic principles in the control and treatment of diabetic foot ulcers are: a) ability of estimating their production time and proximity of them, then, controlling of prevention of infection, b) controlling and establishing proper arterial blood flow and c) Remove the pressure from the foot, which all could control by this kind of invented shoes which described before. The utilization of novel invented diabetic shoes which prevent painful foot ulcers is highly desirable, as replacements which could avoid amputation or even tissue damage [5,108,109].

Moreover, the amperometric sensors with aid of nanotechnology currently ease fast, precise as well as highly sensitive glucose capacities in blood level together with other clinically relevant liquids, including even tears or urine. Furthermore, the clinical understanding of a continuous glucose device may lead to closed-loop schemes which help to utilize current insulin pumps [6,110,111]. This method may dismiss the patients from the painful injure of continuously measuring their blood sugar level, and also obviously recover their long term health consequences and well-being. Regarding the current developments of nanotechnology in nanoscale glucose detecting, great improvement at clinical applications of diabetic diseases in the near future will be expectable [7,112]. Current

closed-loop schemes are able to releasing great quantities of insulin; but, clinical realization needs close-fitting control of drug release to decrease the danger of insulin overdose.

Shoes systems that proposed can act as remote control for the preventing the release of insulin and really a promising development in dynamic insulin delivery. Stanley and his co-authors invented some nanoparticles which coated with antibodies and capable of binding to calcium channels on genetically engineered cells [113-115]. They also showed that, the application of radio frequency signal causes contained heating of the station by heating of the nanoparticles, then this heating may reasons of subsequent road of calcium into the cell, activating the manufacturing of insulin in the cells [75,112] and caused to release the insulin into the bloodstream [75]. Moreover, Di, et al. established the drug release with the full of nanocapsules by absorbed ultrasound [76].

Finally, it should be mentioned that a nano-network [48] comprised of various nanoparticles which contain of insulin were used to form an insulin reservoir, then, could be selectively degraded by the application of focused ultrasound to lead to releasing the needed dosage of insulin [76]. These remotely triggered strategies may lead to novel insulin delivery modalities which could reduce the pain associated with repeatedly injecting insulin and increase patient compliance [5], and may serve as an element of closed-loop glucose therapies as well. Also, it can be concluded that, the best way of tackling the challenges ahead is by taking a multidisciplinary approach and joining information of material science, physical chemistry, as well as pharmacology to grow more organizations which may dynamic and steady.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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