IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023

Emergence of Nanoparticles in Revolutionizing Diabetes Treatment

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Abstract: *People have known about diabetic mellitus for 2,000 years. Diabetes is a group of metabolic illnesses characterized by insulin deficiency or resistance. Diabetes prevalence has increased due to age, ethnicity, and lifestyle. One challenge in diabetes management is optimizing drug use to regulate glucose, blood pressure, and cholesterol and minimize side effects. Many researches are focusing on innovative diabetes treatments. Nanomedicine seems to be the most promising option. A brief overview of nanoparticles (NPs) in diabetes treatment is provided in this publication. Better oral insulin administration is needed to reduce daily subcutaneous injections for diabetes. Oral insulin administration may mimic insulin's natural fate in diabetics while reducing injection discomfort and damage. Casein, alginate, calcium pectinate, zinc oxide, chitosan, and other polymer NPs have been utilized to deliver insulin orally. Insulin buccal plus absorption enhancers exhibited 12% maximum pharmacological action. Natural degradability A nanoporous membrane with grafted glucose oxidase surrounds the insulin matrix in polymeric NPs for parenteral insulin delivery. Increased blood glucose alters the nanoporous membrane, causing biodegradation and insulin release. Polymeric nanoparticle-based inhalable medication delivery systems have been studied for TB and cardiovascular disease. This approach can deliver insulin via inhaled nanoparticles. All previous studies indicated that NPs collected in skin and eyes following treatment. These medication delivery techniques are in various stages of development. Nanotechnology offers several medical applications that might heal diabetes and other diseases.*

Keywords: Diabetes Mellitus, Nanoparticles, Nanomedicine, Nanotechnology

I. INTRODUCTION

Humanity has been aware of diabetes mellitus (DM) for about 2,000 years.1 In both developed and developing countries, it is probably going to rank among the most common and significant illnesses in terms of economic impact in the twenty-first century. Diabetes mellitus (DM) is a category of metabolic disorders characterized by total or partial insulin deficiency, or insulin resistance, culminating in hyperglycemia. In many nations, DM has spread like an epidemic. Over the next few years, it is anticipated that the prevalence of type 2 diabetes (T2DM) would rise sharply. By 2025, it's predicted that 35% of the world's population will have diabetes.3. Three factors have contributed to the rise in the prevalence of diabetes: age, ethnicity, and lifestyle. Several attempts have been made to mitigate the effect on morbidity and mortality that follows. The treatment of chronic illnesses is challenging because protracted latency, chronicity, multi-organ involvement, and the requirement for long-term care are characteristics of diabetes mellitus.

Developing and implementing diabetes preventive management strategies for clinical practice is one of the current issues in clinical diabetology. The risk of developing diabetes from impaired glucose tolerance was shown to be lowered by pharmacologic preventive methods, diet, and exercise, as well as by lifestyle intervention, according to recent research.7 Because there are more opportunities for sedentary behavior and overeating in the contemporary society, many people still find it difficult to maintain a healthy lifestyle despite the well-established benefits of lifestyle modification.

The optimization of currently available therapies to ensure adequate glycemic, blood pressure, and lipid control and to reduce complications is one of the five current challenges in diabetes management. Other challenges include educating patients about diabetes self-management, enhancing patient adherence to lifestyle and pharmacologic interventions, lowering barriers to the early use of insulin, and enhancing the way that chronic condition patients receive healthcare.8

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In addition, the use of insulin for the long-term therapy of anaeroxia nervosa, fatty liver, and brain atrophy is restricted by insulin resistance.[9] Materials and structures designed at the molecular level may be used to monitor, repair, create, and regulate human biological systems at the cellular level. This process is known as nanotechnology.10 Using nanotechnology in medicine to improve human health care is known as nanomedicine. Nanomedicine makes use of materials as small as 1/80,000th of a human hair's diameter. Materials and equipment may interact uniquely with cells and biological molecules at the 1 nanometer scale.[11]

Applications of nanomedicine include the delivery of medicinal chemicals to specific tissues, the detection of substances like proteins or DNA, and imaging enhancers.[12] Nanomedicine holds the potential to produce human hormones through engineered microbes, effective drug delivery through nano-formulations, intelligent drugs that only activate when needed, and even autonomous "nanorobots" that could replace or supplement our immune system, red blood cells, and many other biological systems.[13] As a result, the purpose of this study is to provide a quick summary of the uses of NPs in the treatment of diabetes.

Applications of Nanotechnology forDiabetes Management

Buccal insulin

The buccal insulin delivery device uses an anaerosol spray to deliver the medicine into the mouth, unlike inhalers. The back of the mouth and cheeks absorb insulin instead of the lungs.[14] Insulin buccal plus absorption enhancers exhibited 12% maximum pharmacological action. The effectiveness of bioadhesive formulation for insulin buccal mucosal administration has been studied, as have nanoparticles.[15] Generex Biotechnology Corporation is developing buccal insulin using RapidMistTM. Oral-lynTM is a spray-propelled liquid human regular insulin for prandial insulin administration. The aerosol produced by the combination contains micelles larger than 10 μm, making them too large to enter the lungs. Each puff should give 10 units of insulin. Since 10% of insulin is absorbed in puff form, 1 U is delivered each 10 U puff; 10 puffs supply 10 U for a meal.[16]

Oral insulin

Novel insulin carriers are closely connected to new oral insulin delivery methods.17 If accessible, oral is the most convenient and recommended way.18 Developing better oral insulin delivery is crucial for treating DM without daily subcutaneous injections. Oral insulin is degraded by gastrointestinal enzymes.19 In vivo and in vitro bioassays show nanoencapsulated insulin is bioactive.20

Oral insulin may imitate insulin's physiological destiny and reduce injection discomfort and trauma in diabetics.[9,21] Pro-drugs (insulin-polymer conjugation), micelles, liposomes, solid lipid nanoparticles (NPs), and biodegradable polymer NPs may be used to administer oral insulin.[9,22]

Chitosan, a natural polymer derived from chitin, is a popular choice for oral insulin administration due to its chemical modification and excellent biological features.18 Chitosan shields insulin from gastric juices and improves bloodstream absorption.[13,18] Chitosan-coated NPs had a greater transport capability than free drug and unmodified particles. In recent years, oral insulin administration using polymeric NPs has improved. Therefore, nano-sized polymeric particles seem potential for oral insulin administration.Calcium pectinate-insulin NPs at pH 3 released 12.6% ± 3.2% and 21.7% ± 8.7% insulin after 8 and 24 hours, respectively, because to the sustained-release effect of pectin-insulin interaction (23-25).26 Oral zinc oxide NPs treatment [Figure 1] showed significant antidiabetic benefits, including enhanced glucose tolerance, increased serum insulin (70%), decreased blood glucose (29%), reduced non-esterified fatty acids (40%), and reduced triglycerides (48%).[27]

Insulin should be protected from gastrointestinal enzymes by a matrix. Encapsulating insulin molecules in PNPs does this. One trial employed insulin-loaded PNP pellets for oral administration.

The blood sugar level significantly decreased after receiving insulin via buccal route, according to the data. It has been shown that temperature-sensitive nanospheres composed of poly(N-isopropylacrylamide) and poly(ethylene glycol) dimethacrylate shield loaded insulin from extreme heat and shear stress; this kind of polymeric system may prove to be an efficient insulin carrier.[23]

Copolymer poly (N-isopropylacrylamide [NIPAM]-acrylamide [AAm]- 2-aminomethyl-5-fluorophenylboronic acid [FPBA]) loaded with insulin also demonstrated excellent smart-release behavior across a range of pH values and functioned as a pH stimulant in the stomach and intestine.[28]

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In acidic medium, alginate-dextran particles inhibited insulin release, but in nearly neutral conditions, they encouraged a sustained release.20 Because of this, Alginate NPs' chemical makeup makes them suitable for use as a glucose binder or oral insulin carrier in the treatment of diabetes.[29]

In a different research, casein a milk protein—was mixed with the calcium phosphate, poly(ethylene glycol), and insulin combination. Evaluation of pH-sensitive oral insulin-loaded with poly (lactic-co-glycolicacid) NPs (PINPs) was given orally to rats induced with diabetes mellitus (DM), and the response of blood glucose and insulin levels was evaluated. The casein coating shields the insulin from this process. It was discovered that the rate of insulin release was slower at acidic pH values; at pH 1.0, 90% of the insulin was released in 11 days. In an alkaline environment, the release happened more quickly; at pH 7.8, 90% of the release was seen in 3 days. These studies showed that oral PINPs may efficiently administer insulin and lower blood sugar levels in animals; this suggests that oral PINPs may be a viable insulin delivery method for the management of diabetes.[30]

PNPs for parenteral insulin administration

Polymers have been employed in pharmaceutical and biotechnology applications for almost 40 years.[31] Solid colloidal particles comprised of macromolecules between 10 and 1000 nm are called PNPs.32 NPs may be nanospheres or nanocapsules depending on preparation.[33]

Biomaterials or technologies that release drugs at preset or customizable rates in response to triggers and external stimuli are called "controlled release systems". Due to its simplicity of physico-chemical, synthetic, biocompatible, and degrading modification using tried-and-true procedures, polymeric materials are popular controlled release systems.[31]

Synthetic and natural PNPs are insulin delivery matrices. Natural polymers are intriguing because they are nontoxic, biocompatible, biodegradable, and hydrophilic.18 Today, the most common polymers for controlled drug release include PLGA, PLA, PGA, PCL, HPMA, and poly(amino acids). PLGA, PGA, and PLA are employed in many controlled release products because of their biocompatibility and biodegradability.[31, 34]

Biodegradable PNPs with grafted glucose oxidase nanoporous membranes produce insulin. Increased blood glucose alters the nanoporous membrane, causing biodegradation and insulin release. The glucose/glucose oxidase reaction lowers delivery system microenvironment pH. This may boost insulin release by increasing the polymer system.[23] The first smart cell medicine delivery study was reported in 2003.[35, 36] Research on insulin-loaded poly(epsilon-caprolactone) nanoparticles (NPs) created utilizing the water-in-oil-in-water emulsion process showed safe, effective, biocompatible, and controlled insulin release.[37]

Copolymers like polyacrylamide and N,N-dimethylaminoethyl methacrylate are also being studied for these applications. A poly [methacrylic acid-g-poly(ethylene glycol)] copolymer distribution rate-controlling membrane and an insulin reservoir make up this "molecular gate" system. Polymers expand and close gates at 7.4 pH, the average human body pH. Higher blood glucose contracts at low pH (pH=4), opening gates and releasing insulin from NPs. These mechanisms cause swelling via blood pH changes and insulin release. The amount of insulin supplied depends on gate size, insulin concentration, and response rate.[23]

Zinc oxide poly(NIPAM–AAm–FPBA) hybrid nanogels may detect glucose in highly reproducible fluorescent signals with good sensitivity and selectivity in the clinically relevant glucose concentration range of 18–540 mg/dl, according to another At a normal glucose level of 108.0 mg/dl, nanogels release insulin slowly (~5% in 76 hours), but accelerates when glucose levels climb.[38]

Insulin delivery through inhalable nanoparticles

Nanotechnology has revived interest in using the lungs to deliver systemic and local drugs. Lungs' high alveolar surface area, weak epithelial barrier, and considerable vascularization may improve medication transport and absorption.39 Mass median aerodynamic diameter is used to describe inhalation treatment particle sizes.40 Inhaled insulin formulations work better when made in the right size range.[41]

Different inhaler methods provide dry powder and solution inhaled medications. Thus, insulin molecules may be encapsulated in NPs and inhaled as dry powder [Figure 4]. Exubera® powdered rapid-acting insulin was investigated in type 1 and T2DM patients.14 Phase III clinical studies using Exubera's dry-powder inhaler device show that pre-meal insulin inhalation is equally effective as mealtime insulin injections.[16]

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Previous TB and cardiovascular disease treatments used inhalable PNP-based drug delivery devices. Such techniques may administer insulin via inhalable NPs. The NPs should be tiny enough to minimize lung congestion but big enough to avoid exhalation. This approach delivers insulin molecules directly to the circulation without breakdown.[23,42] Insulin-loaded polybutylcyanoacrylate (PBCA) NPs were examined and showing that pulmonary injection might considerably extend insulin's hypoglycemic impact.43 When compared to pulmonary injection of insulin solution, insulin-loaded PBCA NPs were shown to prolong the duration of the hypoglycemic impact over a 20-hour period when administered to the lungs of rats.44 When compared to insulin solution, preclinical investigations using insulin-loaded poly(lactide-co-glycolide) nanospheres in guinea pig lungs showed a considerable drop in blood glucose level with a persistent impact over 48 hours.

The preparation of 44 inhalable glycol chitosan-coated polylactic acid nanoparticles (PLGA NPs) containing chitosan-modified exendin-4 (chitosan-Ex4) and palmitic acid-modified exendin-4 (Pal-Ex4) NPs revealed that the chitosan Pal-Ex4 PLGA NPs have a great deal of potential as a long-acting inhalation delivery system for the management of type 2 diabetes.[45]

Additionally, it was observed that when insulin nanoparticles (NPs) were given to normal rats via the pulmonary route, their bioavailability was significantly better than that of the solution; but, when NPs were provided subcutaneously, their bioavailability was considerably lower than that of the solution administered in the same manner.[43]

Limitations of inhaled NPs: regional deposition, retention, solubility, redistribution, translocation into the circulation, metabolism, accumulation in specific organs, and the excretion pathways via urine and faeces are just a few of the mechanisms that must be understood in order to estimate the dose of inhaled particles. The geometry of the respiratory tract, the properties of the particles themselves, and certain ventilational elements like breathing technique all influence or govern particle deposition.46

Intranasal insulin delivery

According to a study, administering gold nanoparticles (GNPs) loaded with insulin and decreased with chitosan via the nasal route enhanced the pharmacodynamic activity of insulin.[47] The primary variables that restrict the amount of insulin that can be absorbed via the nose are the mucosal membrane's low permeability and the mucociliary clearance mechanism's quick removal of non-mucoadhesive formulations from the absorption site. Mucoadhesive NPs composed of starch and chitosan/tripolyphosphate48 have been tested as a way around these restrictions. The release of 75% to 80% insulin after 15 minutes of treatment demonstrated the strong insulin-loading potential of these NPs.[23]

Transdermal insulin

Transdermal insulin administration eliminates the need for needles and all of the drawbacks of other delivery methods, such the pulmonary and nasal routes. The main obstacle to insulin penetration reaching usable levels is the stratum corneum, the skin's outermost layer. It has also been reported that microneedles work well as transdermal insulin delivery methods. Compounds can only permeate tiny, lipophilic molecules. A number of physical and chemical enhancement methods, including iontophoresis, sonophoresis, electroporation, microneedles, laser ablation, and chemical enhancers, have been investigated as ways to get through the stratum corneum barrier and boost insulin permeability in the skin.[16, 49, 50]

Fluorescent micro/nanoscale devices for glucose sensing may be created. Utilizing micro/NPs in the dermis may enable transdermal glucose variations in interstitial fluid to be monitored.[51]

Biological micro electro mechanical systems for insulindelivery

Implantable biological micro electro mechanical systems, or BioMEMS, may control insulin delivery as blood glucose levels rise. BioMEMS is growing in popularity for drug delivery, immunoisolation capsules, pacemakers, and biosensors.52 Insulin molecules are housed in BioMEMS' medication reservoir. Biosensors and nonporous membranes with 6-nm pores detect blood glucose and insulin release on the outside. MEMS' compact size allows responsive hydrogels to be used in sensing and valving applications. Hydrogels that expand in response to osmotic pressure, pH, temperature, or analyte concentration may be useful for in vivo sensing.[53]

A biocapsule comprised of two micro-machined membranes joined together to encapsulate cells and seal with nanopore membranes was previously described. Microfabricated membranes with 18 nm pores can pass insulin, glucose, and

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oxygen. The nanopores allowed larger cytotoxic cells, macrophages, complement, and antibodies but blocked glucose, insulin, and other metabolically active products with their microscopic size.[23,54] BioMEMS devices may treat diabetes and deliver insulin using these biocapsules.

Research has proven that an injectable insulin-encapsulated nano-network and a focused ultrasonic system (FUS) can remotely regulate insulin release in vitro and in vivo. A single subcutaneous nano-network injection and sporadic FUS administration lowered type 1 diabetic mice's blood glucose levels for 10 days.[55]

Glucose nanosensors

Continuous glucose readings may be possible using fluorescence glucose sensors inserted inside capillary tubes, capsules, microcapsules, microbeads, nano-optodes, or detachable wire-shaped subcutaneous or intravenous catheters.56 In mutants with altered sugar transport, metabolism, and signaling, plants harboring nanosensors are able to assess glucose flow, invertase-mediated sucrose hydrolysis, root absorption, and glucose consumption.[57]

Other nanoparticulate systems for insulin delivery anddiabetes management

Diabetes is a major source of systemic problems. Diabetes-related retinopathy (eye disease), diabetic neuropathy (nervous system illness), heart disease, kidney disease, delayed wound healing, and several other disorders are connected with the condition. In the last ten years, ocular medication delivery methods based on nanoparticles have already been reported. The use of NPs composed of chitosan, polylactide, and polyacrylic acid for ocular medication delivery has advanced in recent years.[23] Insulin-loaded chitosan-reduced GNPs show promise in reducing postprandial hyperglycemia.[58]

The scientific community is attempting to cure diabetes-related issues by using medication delivery systems based on nanoparticles. In addition to PNPs and ceramic, GNPs have also been investigated as insulin transporters. The pharmacodynamic action of insulin was enhanced by the oral and nasal delivery of chitosan-reduced, insulin-loaded GNPs. Because of their improved penetration and retention effects, insulin-conjugated GNPs had a greater pharmacological influence than even straight conventional insulin solution.The use of animal-derived pancreatic beta cells in implantable nanomedical devices has shown promise. The goal of this device is to temporarily restore the body's intricate feedback loop for controlling glucose without the need of potent immunosuppressants.[11]

Limitations of Nanoparticles

The majority of the science and information that the scientific community now has about nanotechnology and its many, possible uses comes from laboratory research.[60,61] Consequently, the scientific community still lacks a full understanding of how these NPs and nanosystems, which are serving as medication transporters, will affect the human body. Therefore, the purpose of these research projects is to get an understanding of the behavior of matter at the nanoscale.61 Nanosystems are not actually subject to the same circumstances and factors that regulate the behavior of macrosystems.

It is important to discuss the main restrictions and technical challenges that nanotechnology and its uses in the field of medication delivery must overcome.The surface area of 60 NPs is greater than their volume. It is unavoidable for the NPs to interact and cluster together into a bigger structure, which might impair their ability to transport drugs. These drug carriers are so small that the body's excretory pathways may remove them from the body. Larger NPs have the potential to build up in important organs and cause toxicity that ends in organ failure if they are not eliminated. A recent mouse research found that the distribution of GNPs in tissue is size dependant, with the smallest NPs being 15–50 nm in size.

One disadvantage of liposomes is that they might be ensnared by the body's defense mechanism. Researchers are currently testing liposomes' ability to carry drugs, and the results are not yet clear. Every prior study found that the NPs accumulated in the skin and eyes after treatment. GNPs often build up in organs and bone joints. In order to stop NPs from having negative effects on humans, once they are injected into the body, they need be under external control. Different phases of research and development are being conducted on these drug delivery methods. Within the next five to ten years, it is anticipated that these obstacles will be solved and the findings will be put to use.

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Reactive oxygen species production and the ensuing oxidative stress in cells and organs are thought to be one of the NPs' damaging mechanisms. It is advisable to include testing for NPs' interactions with different kinds of cells and proteins in the toxicological assessment. Depending on the properties of the nanoparticle under study, the body may absorb and translocate nanoparticles via oral exposure (ingestion), cutaneous exposure (neuronal absorption, translocation across lung epithelium, and inhalation exposure), and inhalation exposure. There is currently little knowledge on the biological destiny of NPs, including their distribution, accumulation, metabolism, and organ-specific toxicity, with the exception of airborne particles that are inhaled and end up in the lungs.[46]

II. CONCLUSION

Every day that goes by, the influence of nanotechnology on medicine increases. Despite being a relatively new field of study, nanomedicine has great promise for the treatment of diabetes. In particular, oral insulin may show promise since research on nanotechnology has advanced the treatment and made it possible for various forms of encapsulations to avoid the acidic environment of the stomach. Nanotechnology has a plethora of medicinal uses that might revolutionize medicine and cure diabetes, among other conditions.

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