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A Review of Nanotechnology in Diabetic Drug Delivery

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ABSTRACT
Nanotechnology holds significant promise for transforming the treatment of diabetes and neurological disorders, particularly Alzheimer's disease, Parkinson's disease, brain tumors, and stroke. It has become a key area of focus in diabetes research, where nanoparticles are demonstrating considerable potential for enhancing the management and treatment of the condition. Diabetes mellitus is a major global health crisis of the 21st century, defined by insufficient insulin secretion and action, resulting in elevated blood sugar levels. Despite the existing antidiabetic treatments, 4.2 million individuals lost their lives to diabetes in 2019. The most critical challenges in diabetes management, like monitoring blood glucose and administering insulin injections, are being addressed through advancements in nanomedicine, which provides innovations such as glucose nanosensors, layer-by-layer fabrication, carbon nanotubes, quantum dots, oral insulin formulations, microspheres, artificial pancreases, and nanopumps.

Keywords: Nanotechnology, diabetes, glucose Monitoring.

I. INTRODUCTION

The presence of hyperglycemia due to an absolute or relative deficiency of insulin production or activity characterizes diabetes mellitus, which encompasses a variety of diseases. The sustained hyperglycemia associated with diabetes mellitus is connected to damage, dysfunction, and eventual failure of various organs such as the retina, kidneys, nervous system, heart, and blood vessels [1].

The Centers for Disease Control and Prevention (CDC) in the United States reported that the number of diabetic patients nearly tripled between 1990 and 2010 [2]. Recent data revealed that diabetes mellitus was the third leading cause of death in the US, accounting for 12% of deaths in 2010. Additionally, pre-diabetes as a risk factor increased the overall deaths related to diabetes by 2% [3], indicating the significant underlying danger of diabetes mellitus mortality. The International Diabetes Federation estimated that nearly 415 million adults aged 20–79 years worldwide have diabetes mellitus [4]. This estimate is projected to reach 642 million in the next 20 years [5].

Approximately 8% of children and 26% of young individuals globally are impacted by diabetes mellitus. A comprehensive epidemiological study of type 1 diabetes mellitus (T1D) in human populations presents data on demographic, geographic, biological, cultural, and other factors. The prevalence of T1D has increased by 25% worldwide, with around one in 300 individuals in the United States being affected by the age of 18. Epidemiological research plays a crucial role in comprehending the significance, origins, clinical management, prevention, and treatment of type 1 diabetes in expectant mothers and their offspring before and after delivery [6,7].

Nanotechnology encompasses any technology utilized at the nanoscale with practical applications. It involves managing or reorganizing matter at the atomic and molecular levels within the size range of approximately 1 to 100 nm. It encompasses the science and engineering related to the design, synthesis, characterization, and application of materials and devices with the smallest functional organization in at least one dimension at the nanometer scale. The application of this science to medical issues is termed 'Nanomedicine'. The successful delivery of therapeutic drugs has included placing agents in the microenvironment of the nanocarrier to target the agents appropriately for increased efficacy and safety. The end of the 20th century saw the discovery of new materials, processes, and phenomena at the nanoscale, leading to thedevelopment of new experimental and theoretical study methods and opening up new possibilities for the creation of novel nanosystems and nanomaterials.

II. DIABETES AND ETIOLOGY

Diabetes mellitus, sometimes known as diabetes, is defined by a loss in insulin secretion by pancreatic islet cells, resulting in an increase in blood glucose levels. Diabetes insipidus is characterized by the output of enormous volumes of highly diluted urine, which cannot be removed

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when fluid intake is reduced. This is due to a shortage of antidiuretic hormone (ADH), also known as vasopressin, produced by the pituitary gland. Diabetes mellitus is distinguished by significant weight loss, increased thirst (polydipsia), and an insatiable appetite (polyphagia).

DM has two primary etiopathogenetic categories: T1DM and T2DM (Fig. 1) [11]. Gestational diabetes is also a prevalent form of the condition.

Since a complete lack of insulin secretion is a hallmark of type 1 diabetes, patients with this condition are insulin dependent. A few diseases of the pancreatic islet β-cells that typically result in an absolute insulin shortage are included in T1DM. Insulin-mediated diabetes mellitus (T1DM) is mostly caused by autoimmune destruction of pancreatic β-cells. Since pancreatic β-cells exhibit an autoimmune pathologic process, which is the initial pathologic alteration in T1DM patients' pancreas, individuals with a high risk of the disease can typically be diagnosed by serological evidence of this process as well as by genetic marker analysis [11]. Anti-islet antibodies are found in the blood at the time of diagnosis in 80–85% of T1DM patients [12]. Certain patients with type 1 diabetes who did not have β-cell autoimmunity were shown to have underlying problems in insulin production, which are typically brought on by genetic impairments in the sensitivity of the pancreatic β-cell to glucose [13]. Most cases of T1DM in younger persons occur before the age of thirty. Polydipsia, polyuria, polyphagia, and weight loss are signs of type 1 diabetes (T1DM), which typically affects lean people and often manifests as ketoacidosis. T1DM differs genetically from other types of diabetes mellitus, and in addition to autoimmune β-cell death, it may also result from viral or toxic β-cell destruction [12]. T1DM is closely related to human leukocyte antigen (HLA) antigen.

About 85 to 90% of cases of diabetes mellitus are classified as type 2 diabetes (T2DM), which is insulin-independent. The complicated illness known as type 2 diabetes (T2DM) is linked to the metabolism and endocrine system. It is caused by a combination of environmental and hereditary factors. A combination of pancreatic β-cell malfunction, insufficient compensatory insulin production, and different degrees of resistance to insulin action is responsible for the development of type 2 diabetes [11]. Obesity and excess weight are known to be important risk factors for the development of type 2 diabetes and insulin resistance. T2DM is often not associated with ketoacidosis, and while insulin therapy is occasionally required to control fasting blood glucose levels, it is not usually necessary to maintain life [12]. Compared to T1DM, T2DM has a distinct genetic foundation. Although there is a high familial history in T2DM patients, there are no HLA antigen correlations, and circulating anti-islet antibodies are typically absent [12]. Although there is room for improvement, the majority of the pancreatic islets of β-cells are present in sufficient numbers. There is a reduction in some insulin receptors on the plasma membrane in patients with type 2 diabetes who have normal fasting plasma glucose but postprandial hyperglycemia. This results in impaired insulin action. On the other hand, aberrant post-receptor insulin activity is the main cause of hyperglycemia and reduced insulin action in individuals who are fasting [12].

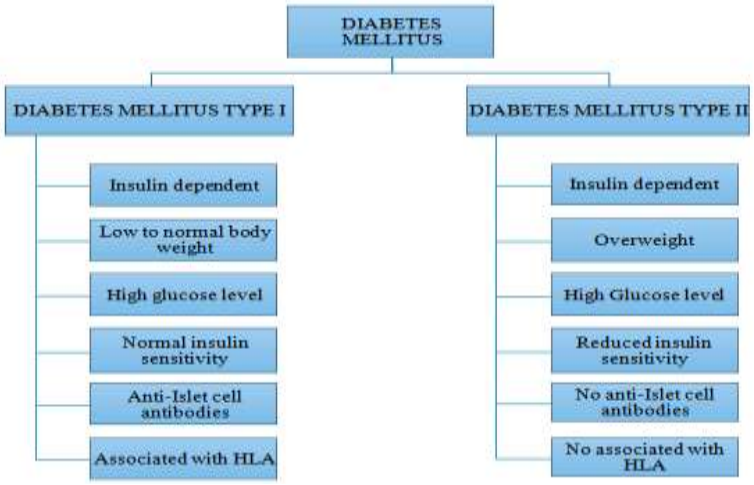

Fig 1: Characteristics of Diabetes mellitus type 1 and type 2

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III. DRAWBACKS IN CONVENTIONAL DELIVERY OF ANTIDIABETIC DRUGS

The majority of oral hypoglycemic medications come in tablet or capsule form. However, these traditional forms have drawbacks such as short duration of action due to their short half-lives, frequent dosing, risk of hypoglycemia, low bioavailability, high protein binding, gastric irritation, diarrhea, insolubility in water, and lack of adherence to patient safety and efficacy [14]. Subcutaneous insulin administration also has limitations, including multiple injections, self-injection, difficulties with the vial and syringe technique, local tissue necrosis, infection, nerve damage, high cost, potential dosing errors, and fear of painful injections, all of which can hinder patient compliance. These limitations highlight the restricted accessibility of traditional dosage forms at the intended site of action, increased systemic toxicity, a narrow therapeutic window, complex dosing schedules for long-term treatment, and contribute to poor patient compliance [15]. Numerous research studies are exploring the use of nanotechnology and nano-sized particles to address these limitations in the delivery of anti-diabetic drugs. Various types of nanotechnology-based drug delivery systems are being developed, including polymer-drug conjugates, micellar formulations, liposomes, nano-sized drug particles, and protein-bound drugs [16].

IV. BLOOD GLUCOSE MONITORING

The finger-prick method is currently the most widely used approach for monitoring glucose levels in people. It involves pricking the fingers with a sharp needle to collect blood into a capillary tube to self-monitor blood glucose. However, this method can lead to several issues, prompting scientists and researchers to focus on creating new smart, miniaturized diagnostic devices for managing diabetes that are more cost-effective, accurate, and easy to use while producing consistent results. Various nanotechnology-based methods have been developed to pursue these goals, such as smart tattoos, the layer-by-layer (LBL) technique, carbon nanotubes, and quantum dots (QDs).

4.1. SMART TATTOOS

In vivo, glucose monitoring can be improved using smart tattoos, which employ fluorescence-based nanosensors that respond to glucose. These nanosensors are embedded in the skin, with the monitoring device extending externally from the body, allowing for non-invasive monitoring [17]. By utilizing fluorescence, the sensors can detect changes in analyte concentrations, offering several advantages over conventional electrochemical electrode implantation and avoiding interference from electroactive tissues, which could affect sensor stability [18].Various synthetic biological glucose receptors, such as enzymes (hexokinase), boronic acid derivatives, and bacterial binding proteins (GBPs), can be modified into nanosensors capable of converting glucose molecules into fluorescence changes [19].

Fig 2:A tattoo-like sticker for monitoring blood sugar.

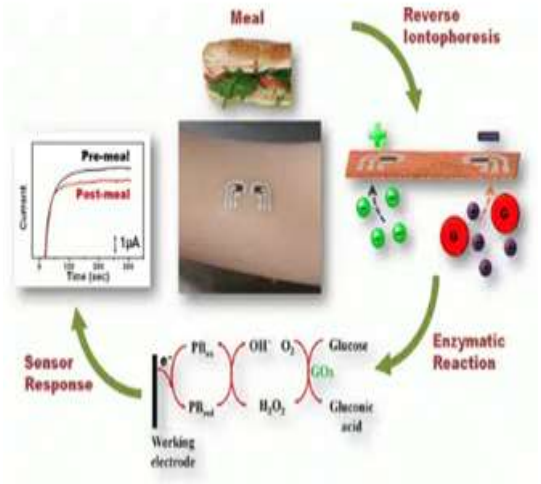

Fig 3: The operation method of the tattoo sticker for measuring blood sugar.

4.2. THE LAYER-BY-LAYER TECHNIQUE

Using the LBL process, random layers of positively and negatively charged polymer are electrostatically assembled. These polymers are produced as small, flexible sheets with regulated holes that are also biocompatible. The typical

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thickness for six bilayers is about 10 nm [20]. These bilayers have the potential to become firmly embedded in the subcutaneous layer over time. Semipermeable capsules permit the entry of glucose from the interstitial fluid while enclosing and shielding the sensor components [21]. The LBL approach is used to create microvesicles by sequentially assimilating polyelectrolytes around the crystals of a glucose-sensing enzyme, such as glucose oxidase or a GBP, onto a sacrificial template. Next, step-by-step additions of charged polypeptides are made, such as poly-l-lysine and poly-l-glutamate.

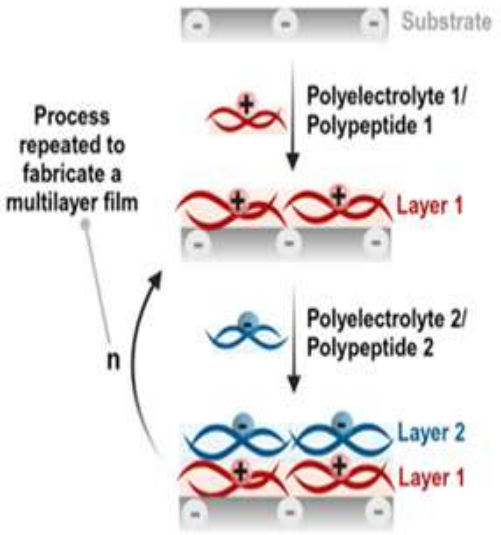

Fig 4: Schematic representation of layer-by-layer (LbL) mechanism based on the alternation of oppositely-charged polyelectrolytes on a generic substrate.

4.3. CARBON NANOTUBES

Carbon nanotubes are buckyball-shaped structures that resemble graphite sheets coiled into container lids at one or both ends. These carbon nanotubes fall into one of two types: single- or multi-walled. Multi-walled carbon nanotubes, or several flat sheets of carbon atoms stacked and coiled into tiny tubes, are the building blocks of a microphysiometer. By confirming the transfer of electrons generated when insulin molecules are oxidized in the presence of glucose, the sensor within the tubes continuously measures insulin levels [22]. Real-time insulin level monitoring is made possible by the sensor's ability to detect increases in current when cells release more insulin and vice versa [23].

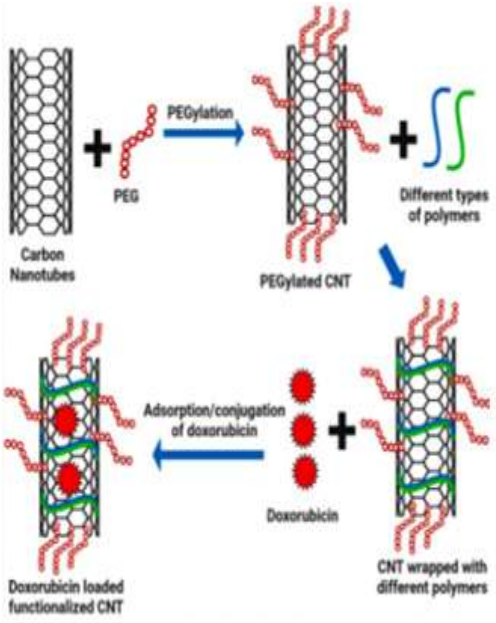

Fig 5: Schematic representation of carbon nanotubes mechanism

4.4. QUANTUM DOTS

Nanocrystals known as quantum dots typically have a size of 2–10 nm. These materials are made of cadmium selenide and have a cap (silica) to increase their solubility and a shell (zinc sulfide) to improve their optical qualities [24]. Because QDs are special structures made for targeted imaging by tagging molecules with a fluorescent probe, they can be used as a diagnostic or therapeutic tool in a variety of biological domains [25]. QDs have only favorable properties as probes due to their ability to produce quantum effects, such as high and consistent quantum yield fluorescence that is resistant to photobleaching [26].

V. NANO-BASED DRUG DELIVERY SYSTEM

Over the course of the last several decades, a number of nano-based drug delivery systems have been developed to either selectively administer therapeutic medications to specific areas under strict control, serve as medical diagnostic tools, or combine the two functions a process known as "theranostics" to treat and diagnose simultaneously [27]. Numerous advantages have been shown by nano-based drug delivery systems, such as the possibility of a more convenient administration route, the capacity to reduce the total drug dose with regulated delivery, a decrease in toxicity and side effects, an increase in active

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concentration, and enhanced safety and efficacy [28]. Thus, one of the primary objectives of pharmaceutical research is to create novel nano-based drug delivery systems with as few side effects as possible and as many therapeutic benefits as possible. It has become evident, therefore, that precisely directing drugs to the right locations is difficult. The administration location of a medicine is usually placed far from its intended site of action. Finding safe and effective "vehicles" that can deliver a bioactive molecule to the intended site of action (drug targeting) and ensure that a desired concentration is maintained at the target for the necessary duration (controlled release) remains a challenge. After safe and efficient therapeutic effects, any leftover drug particles in the body should also be eliminated.

A certain cell type needs to be catered for in the nano-based drug delivery system in order to maximize the efficacy of the targeted medication. Using biological interactions, one or more conjugated targeting moieties on the surface of the nano-based drug delivery devices precisely connect with target cell antigens or receptors to carry out active targeting. It has been possible to use ligands like as proteins, peptides, nucleic acids, or polysaccharides for diverse activation targeting [29].

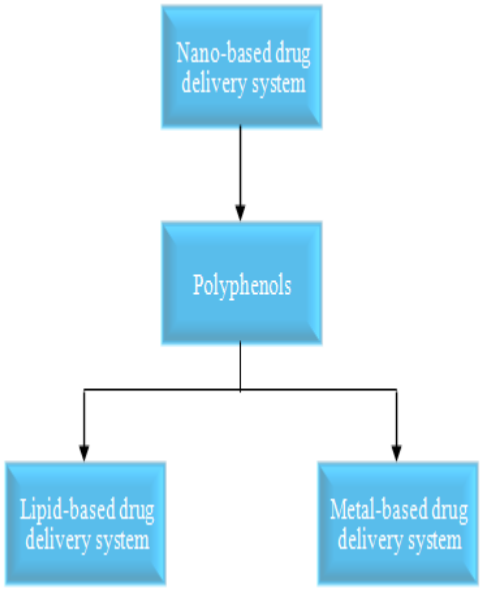

Fig 6: Classification of nano-based drug delivery system

POLYPHENOLS

Natural components are a major source for the pharmaceutical industry's drug development process. Currently, the Food and Drug Administration (FDA) has authorized drugs that contain about 40% natural sources. Natural commodities can originate from many different sources, including bacteria, plants, and animals, but one of the most noteworthy sources is plants [30].

5.1. LIPID-BASED DELIVERY

Lipid-based delivery techniques are divided into several subgroups. The following sections will discuss these systems as liposomes, solid lipid NPs (SLNs), and nanostructured lipid carriers (NLCs) have all been studied as possible polyphenol carriers in diabetes mellitus.

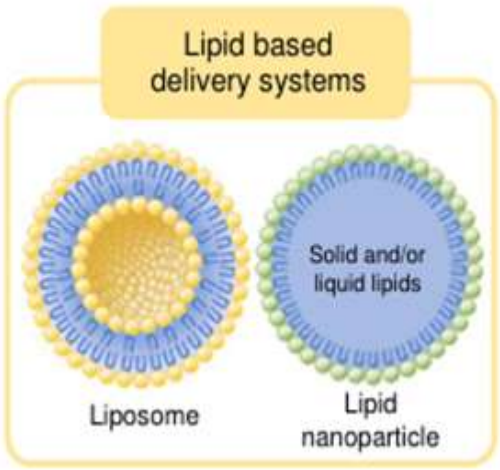

Fig 7: Lipid-based delivery system

5.1.1. LIPOSOMES

The liposome is the most widely used and well-studied nano-delivery technique for targeted drug delivery [31]. Numerous health advantages are purportedly offered by these nano-based drug delivery methods, such as stabilizing therapeutic substances, resolving issues with tissue and cellular absorption, and improving the biodistribution of molecules to the proper target locations. Liposomes can bind to a broad range of chemicals because of their unique ability to escape both hydrophobic and hydrophilic medications [32]. Hydrophobic molecules are incorporated into the phospholipid bilayer membrane, whereas hydrophilic molecules can only be contained in the aqueous phase.

Two flavonoids delphinidin chloride and cyanidin chloride in both free and liposomal forms

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have been shown to suppress the albumin glycation process in vitro and in vivo [33]. Preventing protein glycation is considered a practical strategy to lessen the difficulties associated with diabetes. The mean particle size of the liposomes containing the flavonoids employed in this study was 94 nm. Liposomes were made with phosphatidylcholines and cholesterol. The scientists found that a variety of factors affected the liposome's capacity to encapsulate molecules, including the kind (physicochemical properties) of loaded chemicals and the interactions between those compounds and the lipid bilayer. Due to the additional hydroxy group in the delphinidin backbone, it was observed that liposomal delphinidin chloride demonstrated a higher encapsulation efficiency of around 90% compared to liposomal cyanidin chloride. The study found that both forms of liposomes were more effective at inhibiting albumin glycation compared to free flavonoids, with consistent significance for both types of liposomal formulations.

5.1.2.SOLID NANOPARTICLES (SLNS) AND NANOSTRUCTURED LIPID CARRIERS (NLCs)

Lipid nanoparticles (NPs) have been used for medication delivery by an increasing number of research teams since their discovery in the 1990s. Lipid NPs, which are also called SLN and NLCs, are composed of either solid lipids or a mixture of liquid and solid lipids stabilized by surfactants, which are also called emulsifiers or surface-active agents. Solid lipids comprise SLN at room temperature and body temperature. These include triglycerides, high purity fatty acids, and waxes.To further stabilize these NPs, phospholipids, bile salts, and non-ionic surfactants such as polysorbates and poloxamers may be used. 50 to 1000 nm is the SLN range [34,35].

These lipid nanoparticles can be produced affordably, without the need for organic solvents, and with sustained release, non-toxicity, and scale-up viability. However, few results suggest a relationship between low loading capacity and SLN. The NLCs, or other lipid NPs, were developed to solve specific problems with SLN. NLCs are made up of a mixture of liquid and solid lipids. By mixing different types of lipids, the lipid matrix becomes less ordered, which increases the drug loading capacity and prevents early drug ejection, improving the effectiveness of drug entrapment. NLC research in humans is still in the preclinical phases, with no clinical uses planned [35]. Only two trials have employed SLNs and NLCs to provide polyphenols for the management of diabetic mellitus.

5.2. METAL-BASED DRUG DELIVERY SYSTEM

Metal-based drug delivery devices have been studied as means of delivering drugs due to their optical, catalytic, and magnetic properties, as well as their simple surface modification and large surface area. Researchers have explored AuNPs and magnetic NPs as two types of metal-based drug delivery systems for delivering polyphenols in the treatment of diabetes mellitus [36].

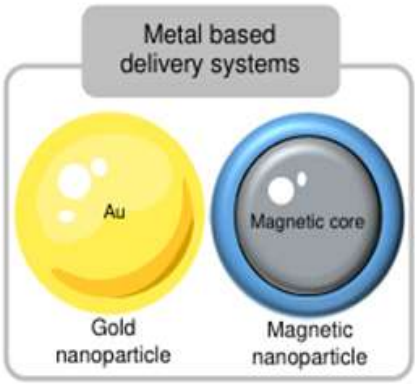

Fig 8: Metal-based delivery system

5.2.1. GOLD NANOPARTICLE

Colloidal gold particles are used to create AuNPs, which are drug-delivery devices with a size of up to 100 nm [37]. Resveratrol-containing AuNPs were produced using a green synthesis method by Dong et al. The spherical resveratrol AuNPs, without polymers, had a median size of 20 nm [38]. In a study, male Wistar rats were orally administered 200 or 300 mg/kg of resveratrol AuNPs once a day for three months to evaluate their effectiveness in treating streptozotocin-induced DM. The results were compared with the positive control, calcium dobesilate, a commercial pharmaceutical drug used to treat diabetic retinopathy by reducing capillary permeability (dose of 500 mg/kg/day). This study did not evaluate the presence of free resveratrol in a diabetic rat model. The results indicated that the group treated with resveratrol AuNPs experienced a decrease in blood glucose levels, unlike the positive control group. Additionally, neither the resveratrol AuNPs-treated group nor the positive control group exhibited any noticeable reduction in body weight. The study also examined the impact on diabetic retinopathy, and generally, the resveratrol AuNPs

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tested demonstrated advantages in diabetic retinopathy. The study assessed retinal vascular permeability in diabetic rats exposed to either 200 or 300 mg/kg of resveratrol AuNPs for three months and 500 mg/kg of calcium dobesilate, which served as the positive control. The 300 mg/kg dose of resveratrol AuNPs yielded superior outcomes compared to calcium dobesilate. The authors did not evaluate the activity of free resveratrol, so it is not possible to correlate the results obtained with resveratrol AuNPs and the free compound.

5.2.2.MAGNETIC NANOPARTICLE

Magnetic nanoparticles (NPs) are inorganic nanoparticles (NPs) composed of oxides of iron (Fe), manganese (Mn), cobalt (Co), nickel (Ni), and other magnetic elements. The most often used are iron oxides, also known as iron oxide-based magnetic nanoparticles (NPs) [39]. These include magnetite (Fe3O4), hematite (-Fe2O3), and maghemite (-Fe2O3). Iron-based NPs became the subject of special investigation because iron has been demonstrated to be a biocompatible material.[38] Fe3O4 is an essential in vivo magnetic nanoparticle (IONP) for in vivo clinical applications because of its superparamagnetic properties. Superparamagnetic iron oxide nanoparticles (SPIONs) have drawn a lot of interest for their potential applications in drug delivery [38]. The ability of these NPs to interact with an external magnetic field allows them to be transported to the targeted locations because tissues are permeable to the magnetic field. These particles have lost all of their magnetic.

Medical imaging is currently seeing an increase in the use of magnetic nanoparticles. Clinically approved magnetic nanoparticles (NPs) for liver and spleen imaging include Feridex I.V. ® and Endorem ®, and for bowel imaging, Lumiren ® and Gastromark ® [40]. But most magnetic nanoparticles (NPs) approved by the FDA have been demonstrated to work well as iron replacement therapies. Examples of these medications are Feraheme®, Venofer®, Ferrlecit®, INFed®, and Dexferrum®, which are used to treat anemia resulting from chronic renal illness [41].

5.3. OTHER NANO-BASED DRUG DELIVERY SYSTEM

In a related study, Zhang and colleagues developed a nanotechnology-based method for delivering insulin and gallic acid, two phenolic acid medications. They used hydroxyapatite nanoparticles as the core and coated them with PEG. Gallic acid was linked with glucagon and then combined with PEG. Hydroxyapatite nanoparticles have a history of being used for medical delivery and as materials for bone tissue engineering in insulin apparatus. The porous nature of hydroxyapatite makes it an ideal medium for delivering drugs. The resulting insulin-gallic acid nanoparticles were 400 nm in size. It was found that Caco-2 cells absorbed the insulin-gallic acid nanoparticles into their cytoplasm, according to the researchers. Insulin alone and insulin-gallic acid NPs similarly increased the expression of PI3K, PKB, or AKT and GLUT4 in HepG2 cells compared to untreated cells. In a rat model of type 1 diabetes, the authors evaluated the antidiabetic effects (the specific rat strain was not specified). The treatment group was administered subcutaneous insulin injections at a dosage of 50 IU/kg, while the control group was given a saline solution. The rats in the treatment group received insulin-gallic acid NPs via intragastric gavage.

After the insulin-gallic acid NPs were administered, the fasting blood glucose level significantly decreased, which had a long-lasting hypoglycemic effect. Research conducted in vivo utilizing fluorescent insulin on insulin absorption suggests that the rat small intestine may absorb insulin-gallic acid NPs. The results also showed that treated animals gained weight and that, after two weeks, the groups receiving insulin-gallic acid NPs had significantly higher glycogen stores in the liver and kidney. The delivery of insulin and insulin-gallic acid NPs resulted in the normal anatomical structures of the pancreas, liver, heart, spleen, and renal tissues. Even though they did not evaluate the effects of free gallic acid in this experiment, the scientists concluded that the insulin-gallic acid NPs demonstrated promising outcomes for oral insulin and gallic acid delivery [42].

Fig 9: Other nano-based delivery system

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VI. APPLICATIONS OF NANOTECHNOLOGY IN HEALTH CARE AND DISEASE

The rapidly expanding industry of nanotechnology, which involves the development of engineered nanomaterials, holds significant potential and finds applications in various fields, including nanomedicine. Nanomaterials (NMs) exhibit distinct properties and are used in drug delivery and imaging, offering the potential to enhance diagnostics and treatment of numerous human conditions, such as neurodegenerative disorders, by their ability to cross the Blood-Brain Barrier (BBB). Nanoparticles (NPs), due to their nano size and large surface area, display heightened reactivity and even an inert bulk material like gold can trigger a response in humans when utilized as nanomaterials. However, there are concerns that the unique properties that make NMs so valuable could also lead to unintended effects on human health. Therefore, to identify and stop major adverse effects on humans, it is critical to gather knowledge regarding the possible toxicity of nanomaterials. Realizing the enormous potential and advantages of nanomaterials while lowering the risk associated with their use must be the aim.

Nanomedicine is a rapidly developing science that has brought new applications to many aspects of healthcare. The development of life quality with benefits to the economy and society is the fundamental driving force. The following are a few of the most promising fields [43,44].

- Nanodiagnostics (biosensors, molecular diagnostics, imaging using NP-based contrast agents)
- Nanopharmaceuticals, which include nanotechnology-based medications, targeted drug delivery, implanted nanopumps, and nanocoated stents.
- Reconstructive surgery (placement of artificial tissues and organs resistant to rejection, tissue engineering)
- Nanorobotics (cancer detection and annihilation, vascular surgery)
- Nanosurgery (implanted nanosensors in catheters, nanolasers)
- Regenerative medicine (repair of tissues)
- Sequencing DNA extremely quickly.

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