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Nanotechnology In Diabetes Management - Advances In Diagnosis Drug Delivery And Therapeutic Management

MS.DIVYA VASANT SURYAWANSHI , MS.ASHWINI BAHIR ,DR.SUNIL S JAYBHAYE

Abstracts:

Diabetes mellitus, a widespread worldwide health issue marked by high blood glucose levels, requires novel treatment strategies for increased effectiveness and better patient compliance. Drug delivery systems could be revolutionized by nanotechnology, which operates at the nanoscale (1–100 nanometers) and offers a revolutionary paradigm in medicine called nanomedicine. The potential of nanotechnology to transform diabetes care is examined in this review, with an emphasis on improving medication delivery for diabetes control. Liposomes, polymeric nanoparticles, and dendrimers are examples of nanoparticles that provide targeted delivery, enhanced bioavailability, and regulated release kinetics. These formulations selectively accumulate therapeutic agents in diabetic tissues by taking advantage of improved permeability and retention. With their sensors and feedback systems, smart nanoparticles react to changes in blood sugar levels to deliver individualized treatment in real time. Nanosensors that identify biomarkers linked to diabetes provide insights into the course of the disease in addition to drug delivery. By customizing treatments to each patient's unique profile, this integrated approach is consistent with personalized medicine. In order to advance diabetes management into a new era of precision medicine for better patient outcomes and fewer treatment-related burdens, this review critically examines current knowledge in the fields of materials science, pharmacology, and bioengineering. The objective is to introduce novel therapeutic approaches while emphasizing how nanotechnology is revolutionizing the treatment of diabetes.[1]

KEYWORDS: Nanotechnology, Diabetes, Drug-Delivery, Liposomes, Nano-Particles

Introduction:

Millions of people worldwide suffer from diabetes mellitus, a chronic metabolic disease marked by high blood glucose levels. Type 2 diabetes (T2D) is the most common type of the disease, making up about 90% of all cases. Innovative therapeutic approaches are necessary to improve treatment efficacy, reduce side effects, and increase patient compliance due to the complex nature of type 2 diabetes. Recent years have seen the emergence of nanotechnology as a revolutionary paradigm in medical science, with previously unheard-of possibilities to transform drug delivery systems and have a major impact on the treatment of chronic illnesses. The manipulation of materials at the nanoscale, usually between 1 and 100 nanometers, is the focus of nanotechnology.

Materials at this scale have distinct physicochemical characteristics that set them apart from their bulk counterparts, offering a plethora of opportunities for targeted drug delivery and enhanced therapeutic results. Nanomedicine—the use of nanotechnology in medicine—has become very popular, especially in the treatment of diabetes, where accuracy and effectiveness are crucial. With an emphasis on improving drug delivery systems for diabetes control, this review aims to investigate the potential of nanotechnology in changing the field of diabetes management. A number of issues with traditional therapeutic approaches, such as poor bioavailability, systemic side effects, and the requirement for frequent dosing, could be resolved by incorporating nanotechnology into diabetes treatment. Achieving sustained and controlled release of anti-diabetic medications to maintain ideal blood glucose levels while reducing side effects is one of the main challenges in managing diabetes. By offering regulated release kinetics, enhanced bioavailability, and targeted delivery to particular tissues, nanoparticles like liposomes, polymeric nanoparticles, and dendrimers provide a flexible platform for drug delivery. Additionally, the nanoscale formulations can selectively accumulate therapeutic agents in diabetic tissues by taking advantage of the enhanced permeability and retention effect frequently associated with pathological tissues. In addition to drug delivery, nanotechnology allows for the creation of smart systems that can respond to the changing nature of diabetes. Smart nanoparticles with sensors and feedback mechanisms can release drugs based on fluctuating glucose levels. This offers a personalized and immediate therapeutic approach. Such precision is vital for preventing hypoglycemia and improving overall treatment effectiveness. The use of nanotechnology goes beyond drug delivery to include diagnostics and monitoring. Nanosensors that detect biomarkers linked to diabetes can provide important information about disease progression and help in the early detection of complications. This approach fits with the idea of personalized medicine, which tailors treatment strategies to each patient for the best results.This review aims to analyze the current knowledge on nanotechnology applications in diabetes treatment. It emphasizes the potential to optimize drug delivery systems for better diabetes control. By integrating information from various scientific fields, such as materials science, pharmacology, and bioengineering, this study hopes to add to the ongoing discussion about the transformative role of nanotechnology in diabetes care and its implications for the future of personalized medicine. Ultimately, the goal is to develop new therapeutic strategies that improve patient outcomes, lessen treatment-related burdens, and move diabetes management into a new era of precision medicine.[1,3,4]

Type 1 Diabetes (T1D):

T1D, often called juvenile diabetes, is an autoimmune disease where the immune system attacks insulin-producing pancreatic β-cells . This results in a total lack of insulin, forcing people to rely on outside sources of insulin for survival . The exact cause of T1D is still unclear, but both genetic factors and environmental triggers, like viral infections, likely contribute. Given that several factors must be present to trigger T1D, the condition is uncommon, but it is not rare. T1D makes up about 5 to 10% of all diabetes cases and usually appears in childhood or adolescence, although it can occur at any age . In 2021, around 8.4 million people

worldwide had T1D, with roughly 510,000 new cases diagnosed that year. Of those estimated cases, 18% were under 20 years old, 64% were between 20 and 59 years old, and the rest were 60 or older. About 35,000 undiagnosed individuals died within a year of showing symptoms. Mortality rates differ significantly between countries based on their economic conditions, as 20% of individuals with T1D lived in low-income and lower-middle-income countries. T1D develops quietly over a few months to years. Once autoimmunity begins, the disease progression has three stages. Stage 1 shows two or more autoantibodies. Stage 2 includes the autoantibodies from stage 1 along with β-cell dysfunction due to the ongoing loss of β-cell mass. Stage 3 is defined by the clinical symptoms of T1D. Individuals diagnosed in stage 1 have a 35-50% chance of advancing to stage 3 within 5-6 years. This risk increases to 75% for those diagnosed in stage 2, with clinical symptoms appearing within 2 years.[7]

Figure 1. Schematic illustration of types of diabetes. Among the three types, type 1, type 2 and gestational diabetes, type 2 is most common and contributes to an estimate of 90–95% of all diabetes cases.

Type 2 Diabetes (T2D):

T2D is a complex, multi-factor genetic disease primarily driven by pre-obesity and obesity. It is marked by insulin resistance, where insulin-sensitive tissues do not respond well to insulin, along with a gradual decrease in pancreatic insulin production. As a result, individuals with the condition show high levels of blood glucose, or hyperglycemia. T2D mainly affects adults, but it is increasingly diagnosed in younger populations due to rising obesity rates, an aging population, and sedentary lifestyles. The International Diabetes Federation (IDF) reports that around 537 million adults aged 20 to 79 years are living with diabetes worldwide. If current trends continue, this number could reach 783 million by 2045. T2D makes up about 90 to 95% of these cases. In 2021, high body mass index (BMI) was found to contribute to over 50% of global T2D disabilityadjusted life years (DALY). Several reports indicate a link between T2D and differences in gender, with males showing a higher prevalence than females. Age is another key risk factor for T2D, particularly with a 24.4% increase in diabetes among those aged 75 to 79 years; however, there was also a greater than 1% increase in the under 20 age group. Other factors influencing the prevalence of T2D include poor dietary choices, tobacco use, alcohol consumption, environmental factors, and physical inactivity. Additionally, genetics plays a small but important role in diabetes, with heritability estimated between 30% and 70%, depending on the age of diabetes onset and the glycemic status of those with diabetes. Globally, diabetes accounts for 12% of all health spending, totaling over $966 billion USD each year. This includes costs for medication, hospitalizations, and managing complications. Beyond financial costs, diabetes significantly impacts quality of life due to its

chronic nature and related complications. Efforts to reduce the disease burden are varied, focusing on early detection, lifestyle changes, and improved treatments; however, healthcare disparities and challenges in diabetes management remain significant concerns. [7]

figure 2. Conventional treatment strategies for diabetes mellitus

Nanotechnology in Medicine:

Nanomedicine is the area of nanotechnology focused on using nanoscale technologies to diagnose and treat various diseases. It has seen significant progress, particularly in cancer diagnosis and treatment. The goal is to improve how drugs are absorbed and released in a controlled way while ensuring they are safe. When it comes to T1DM and T2DM, we discuss antidiabetic treatment options along with future advancements that could be added to diabetes care. The basis of nanomedicine in diabetes therapy is the need to enhance the absorption and distribution of antidiabetic treatments to overcome several challenges. These challenges include physical barriers like the pH levels in the GI tract, gut microbiota, temperature, and the difficulties of getting drugs into cells. This task can be quite challenging since the human body is constantly changing to maintain balance. However, using nanotechnology in diabetes treatment could prove to be very valuable. In fact, nanoparticles (NPs), which are particles ranging from 1 to 100 nm in size, can carry a drug and improve its distribution throughout the body and its entry into cells.NPs used in diabetes treatment are spherical systems that fall into four main categories based on their physical and biological characteristics: polymeric NPs or nanospheres, polymeric nano-capsules, liposomes, and lipid NPs. Polymeric NPs are made from natural polymers like polysaccharides (chitosan, hyaluronic acid, and sodium alginate) and proteins (gelatin, albumin), or synthetic polymers like polylactic acid (PLA) or poly lactic-co-glycolic acid (PLGA). They contain a polymer matrix where the drug is evenly spread, which protects it from physical barriers and allows for controlled release. These polymeric NPs, known as nanospheres, can release both water-soluble and fatsoluble drugs in a controlled way. Polymeric nanocapsules are different because they have a solid polymer surface surrounding an oily core where the drug is mainly dissolved. They can also carry both hydrophilic and lipophilic drugs, protect them from the body's environment, and enhance their bioavailability.The third type consists of liposomes. Liposomes are spherical structures made of one or more layers of phospholipids that encase an aqueous phase. Their structure resembles the cell membrane, which helps deliver the drug directly to specific lesions in the body. These vehicles can enable the use of higher doses with fewer side effects. The last group of NPs is lipid NPs, which have only one phospholipid layer around a core that contains inverted micelles. Lipid NPs can be surrounded by surfactants and can encapsulate small molecules, nucleic acids, and even monoclonal antibodies.Other classifications of NPs also exist. They can be categorized as liposomes, nanospheres, polymeric micelles, solid lipids, metallic NPs, niosomes, and porous silicon NPs. Niosomes are similar to liposomes but contain a non-ionic surfactant arranged in layers and stabilized by cholesterol. Because they are non-ionic, niosomes have low toxicity and increased bioavailability. Metallic

NPs are made from metals like gold, silver, zinc, or iron oxide. Their main advantage is their ability to accurately target specific areas. As nanomedicine continues to grow rapidly, more types of NPs are likely to be discovered and utilized soon, leading to an evolving classification of NPs.[6]

Main Types of Nanoparticles Used in the Management of Diabetes:

Small on the nanometric scale, generally in the range of 100 to 300 nm, nanoparticles can be administered orally or through injections. They are biocompatible and biodegradable spherical systems that act as drug carriers. They protect drugs, including conventional drugs and biological ones like peptides and oligonucleotides, from environmental conditions at the site of administration. These particles transport the drug to specific body compartments and release it in response to environmental signals at the target site.

The main types of nanoparticles used in diabetes treatment include polymeric nanoparticles, polymeric nanocapsules, liposomes, and lipid nanoparticles as follows.[5,6]

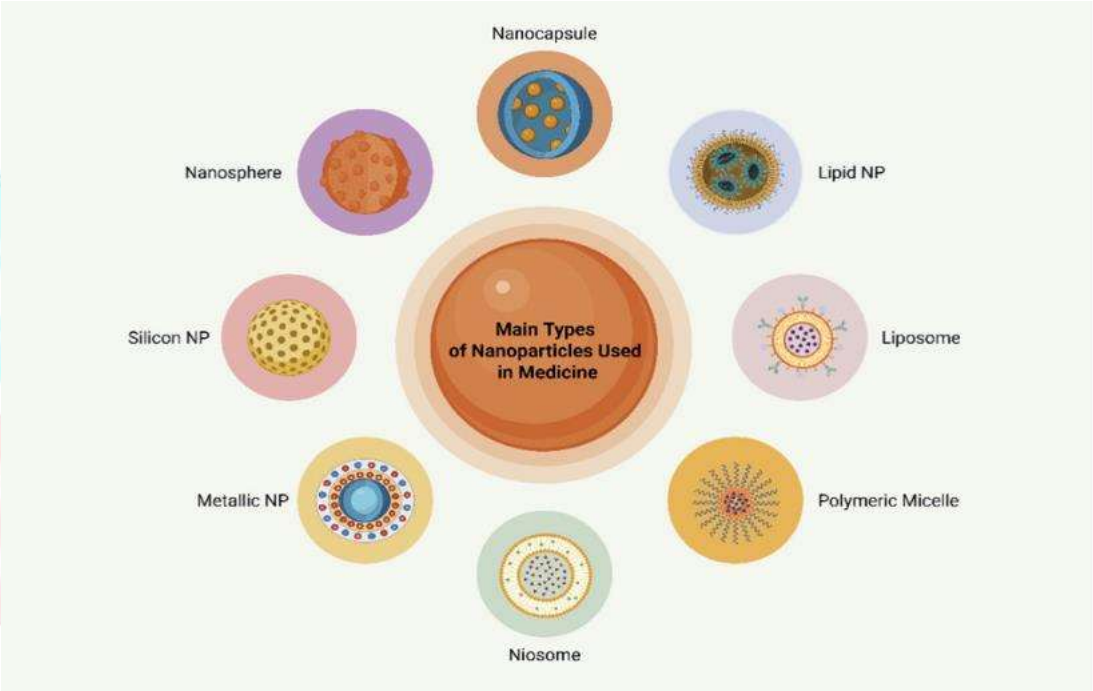

Figure 3. Main types of nanoparticles used in experimental medicine.

Polymeric Nanoparticles:

Polymeric nanoparticles are made of solid polymer matrices that hold drugs evenly throughout. The polymers can be natural, like polysaccharides (chitosan, sodium alginate, hyaluronic acid) and proteins (serum albumin, gelatin, keratin), or synthetic, like polylactic acid (PLA), poly lactic-coglycolic acid (PLGA), and polyethyleneimine. Drug release happens when these matrices break down in the body's fluids. Hydrophilic matrices based on polysaccharides and proteins break down quickly as water penetrates and causes them to swell. They are good for releasing hydrophilic molecules like insulin and other biological drugs. Hydrophobic matrices made from PLA or PLGA break down over time through biodegradation as water slowly penetrates. These matrices can deliver both hydrophilic and lipophilic drugs when a prolonged release is needed.

Polymeric Nanocapsules:

Polymeric nanocapsules have solid polymer shells that surround internal liquid phases. The polymer shell can include proteins like serum albumin, which needs to be cross-linked to prevent it from dissolving in the body's fluids during administration. Albumin nanocapsules hold hydrophobic liquids, such as vegetable oils, that are good for enclosing lipophilic drugs. When the polymer shell is made of PLA or PLGA, the liquid inside the nanocapsules is water-based. This makes them suitable for encapsulating hydrophilic drugs like insulin and other biologics.

Liposomes:

Liposomes are small vesicles made of phospholipid bilayers that contain a water phase. They work well for hydrophilic drugs, which dissolve in water, and for hydrophobic medicines, which dissolve in the lipid bilayer. Choosing the right types of phospholipids and mixing them with other lipids can change the physical and chemical properties of the liposome surface. This, in turn, affects how drugs are released at various administration sites and throughout different parts of the body.

Lipid Nanoparticles:

Lipid nanoparticles are structures similar to liposomes. They are commonly used to deliver proteins and oligonucleotides. Unlike liposomes, lipid nanoparticles have a single layer of phospholipids and contain inverted micellar structures in their core. These inverted micelles can trap water-soluble drugs inside the nanoparticles. This offers a protective system for substances like proteins or oligonucleotides, which can break down quickly in bodily fluids. You can change the shape of lipid nanoparticles and how much drug they carry by adjusting the physical and formulation factors.

Nanocarrier Systems Used	Antidiabetic Drugs/Entity	Administration's Route	Nanostructure Particularity
Solid Lipid Nanoparticles (SLNs)	Insulin	Oral route	Bioavailability enhanced fivefold compared to the pure insulin solution.
	Glibenclamide (GLB)	Oral route	Enhanced bioavailability through controlled and sustained release.
	Insulin	Pulmonary route	Developing an alternative method for insulin delivery with improved effectiveness.
Liposomes	Insulin (camel milk-derived liposomes)	Oral route	Effective reductionin blood glucose level.
	Metformin Hcl (hyodeoxycholic acid-modified liposomes)	Oral route	Improved blood sugar-lowering effect of metformin.
	Insulin (liposomal hydrogel)	Oral route	Enhanced insulin retention duration and intestinal absorption.
	Insulin	Oral route	Substantially reduced elevated glucose levels and enhanced the drug's bioavailability.
Niosomes	Insulin	Vaginal route	Prolonged release of insulin with a significant hypoglycemic effect.
	Glipizide and metformin hydrochloride	Oral route	Establishing combination therapy and sustain as well as control release pattern.
	Pioglitazone (Niosomal gel)	Transdermal route	Increased bioavailability compared to marketed pioglitazone tablet.
Polymeric Nanoparticles	Insulin (PLGA-coated NPs)	Oral route	Enhanced bioavailability with sustained hypoglycemic effects.
	Insulin (PLGA nanospheres)	Pulmonary route	Reduced blood glucose levels with prolonged duration of action.
	Glipizide (chitosan coated)	Transdermal route	Higher drug concentration achieved without causing skin irritation.
	Metformin Hcl (polymeric microneedles)	Dermally inserted	Bioavailability was found to be 95.8 ± 2.7% compared to subcutaneous injection of metformin.
Dendrimer-Derived Nanostructures	Incretin-based gene therapy	Intravenous route	Increased insulin production.
	Insulin (PAMAM dendrimers)	Pulmonary route	Improved pulmonary absorption of insulin with the G3 generation.
	Insulin	Intraperitoneal, intragastric, or subcutaneous routes	Subcutaneous route was identified as the most balanced approach, offering moderate toxicity while lowering hyperglycemia markers.

Nanocarrier Systems Used	Antidiabetic Drugs/Entity	Administration's Route	Nanostructure Particularity
Silver Nanoparticles (AgNps)	*Allium sativum* plant extract	Oral route	Enhanced glucose utilization and inhibited starch-digesting enzyme activity without triggering insulin release.
	Azadirachta indica seeds	Oral route	Potential decrease in blood sugar levels and significant dose-dependent activity.
Gold Nanoparticles (AuNps)	*Helichrysum foetidum* Plant extract (chalcone-capped AuNps)	Oral route	Enhanced glucose uptake in mammalian kidney cells.
	non-enzymatic colorimetric glucose estimation device	Dermally inserted	Improved sensitivity and faster response time of the biosensor.
Antisense Oligonucleotide-Coupled Nanocarriers	Gene therapy	Intravenous route	Regulating the expression of genes associated with diabetes mellitus at both the RNA and protein levels, incorporating enhanced potencyand precision-targeted drug delivery mechanisms.

figure 4- Table of Nanocarrier incorporated drug delivery systems for treatment and management of diabetes

Current Anti-Diabetic Drugs and Their Limitations:

Diabetes is one of the most widespread chronic diseases globally. Recent data shows that the number of people with diabetes has more than doubled over the past 20 years. The main feature of diabetes is high blood sugar, along with issues in carbohydrate, protein, and fat metabolism.

In clinical practice, there are two common types of diabetes: Type 1 diabetes mellitus (T1DM)
Currently,common medications for T2DM include biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 analogues. These drugs usually come as oral tablets, capsules, or suspensions.

Natural compounds like polyphenols, flavonoids, and alkaloids also demonstrate strong antidiabetic properties. Many of these natural substances help lower blood sugar by protecting pancreatic β-cells, boosting insulin secretion, decreasing glucose absorption in the intestines, increasing insulin receptors on target cells, and improving insulin sensitivity

However, people with diabetes often experience side effects from the medications. Common sulfonylureas such as glipizide, glibenclamide, and gliclazide can lead to low blood sugar, gastrointestinal issues, and may affect liver and kidney function. Biguanides help manage T2DM by enhancing insulin sensitivity in peripheral tissues and the liver, reducing glucose absorption in the intestines, and promoting anaerobic glycolysis. The main drug in this category is metformin, which can have negative effects on liver, kidney, and heart functions. α-Glucosidase inhibitors work by temporarily blocking α-glucosidase activity in the small intestine, which slows down carbohydrate breakdown and glucose absorption, thereby helping control post-meal blood sugar spikes. However, they can also cause gastrointestinal side effects. Most anti-diabetic medications require long-term use to achieve desired results, leading to drug buildup in the body and a higher risk of adverse reactions. Recently, researchers have been exploring new targets and drugs. For traditional medications, the focus has shifted to improving absorption, lowering dosages, and enhancing patient adherence.

Nano-based drug delivery systems have emerged as a promising research focus. By encapsulating anti-diabetic medications in nanocarriers, these systems safe guard the drugs from breaking down in the gastrointestinal tract and minimize GI side effects. They enable controlled and effective drug release, improve absorption, reduce drug accumulation, lower the frequency of dosing, and enhance patient adherence.

Some reported nano-drug delivery systems that enhance the absorption and effective delivery of anti-diabetic medications include polymerized nanoparticles, lipid nanocarrier systems, nanocrystals, nanosuspensions, and inorganic nanocarriers.

Insulin therapy:

Nanotechnology in diabetes management has mainly focused on how to deliver insulin effectively. Currently, the subcutaneous route of insulin administration, which is the primary treatment for type 1 diabetes (T1DM), has several downsides. Patients often face discomfort from repeated daily injections, leading to poor compliance and hesitation in following treatment. Moreover, insulin injections can cause localized side effects, including skin necrosis, fat deposits at injection sites, and infections. It's important to note that injected insulin acts differently from the insulin produced by the body. Endogenous insulin is released by the pancreas and travels through the portal vein to the liver. Here, the liver contains about 80% of the endogenous insulin, while the rest moves into general circulation. This creates a portal systemic gradient of insulin that regulates insulin levels in peripheral tissues, like muscles, fat, and kidneys.

In contrast, parenteral exogenous insulin does not get trapped by the liver, leading to increased insulin levels in the periphery. To address this issue, researchers are developing other methods to administer insulin, such as orally. When taken orally, insulin is absorbed in the gastrointestinal (GI) tract and enters the portal vein, similar to endogenous insulin. This method avoids the problem of peripheral hyperinsulinemia and is also more convenient for patients.

However, oral insulin encounters challenges due to degradation in the acidic environment of the stomach, breakdown by enzymes, and reduced uptake by intestinal cells because of mucus and tight junctions. These barriers can be addressed using various nano-formulations. Specifically, nanoparticles (NPs) are designed to withstand the acidic gastric pH and enhance intestinal permeability. The mucus layer and tight junctions between intestinal cells create a tough barrier for orally administered insulin to enter these cells.

For these reasons, chitosan-based NPs have been widely studied. Chitosan NPs can form electrostatic bonds with the anionic components of mucin because of their positive charge. They also have the ability to interact with tight junctions, potentially increasing their permeability. Their interactions with junctional adhesion molecule-1 (JAM-1), claudin-4, and zona-occludens-1 may improve intestinal permeability. Consequently, chitosan-based NPs may allow for better entry into intestinal cells compared to other formulations. These NPs display good adhesive qualities, cell penetration, biocompatibility, and low toxicity. However, the enhanced permeability achieved by interfering with tight junctions could also allow unwanted pathogens to enter the gut microbiota through the intestinal barrier. Thus, while chitosan-based NPs can increase intestinal permeability, they may also contribute to “leaky gut” and dysbiosis. "Leaky gut" refers to a compromised intestinal barrier that lets harmful bacteria from the gut enter the bloodstream, potentially leading to endotoxemia. Increased intestinal permeability might allow not just NPs to penetrate cells, but also bacteria and their lipopolysaccharides (LPS) into general circulation, with unknown consequences.

Additionally, chitosan-based NPs are more soluble at low gastric pH, which leads to faster insulin release in the stomach. This can limit the effective delivery of insulin to the intestines, impacting their therapeutic success unless further modifications are made. One approach to control insulin release is the ionic gelation

method. For example, dextran sulfate (DS), a negatively charged polymer, has been combined with cationic chitosan-based NPs. Pecheckin et al. developed a chitosan–dextran sulfate (CS-DS) nanoformulation for oral insulin delivery. More recently, Fathy et al. introduced silica-coated CS-DS NPs and compared their performance to uncoated CS-DS NPs. Their study showed that the silica-coated NPs had better insulin release characteristics across different pH levels. They concluded that silica-coated CS-DS NPs deserve more research, as their controlled release under varying pH conditions shows promise for improving oral protein delivery systems. Other formulations like sodium alginate, hyaluronic acid, and synthetic polymers such as PLA and PLGA are also under investigation. Polysaccharide-based NPs have shown improved biocompatibility, and their ability to be modified makes them good candidates for oral insulin delivery systems. Still, the limited absorption of these NPs remains an issue.

In comparison to polysaccharide-based NPs, solid lipid NPs protect proteins from enzymes in the GI tract, which include proteases, trypsin, chymotrypsin, and pepsin, while also being less toxic. Several solid lipid NP formulations are currently being researched. These NPs often use fatty acids, like palmitic acid and stearic acid, as well as glycerides such as glyceryl palmitostearate and glyceryl monostearate, and triglycerides. Their lipid composition contributes to their potential as a nano-formulation for oral insulin. However, they also have drawbacks, such as a short circulation time and limited encapsulation ability. The same limitations apply to liposomes, which are popular for their high biocompatibility and safety but also show low encapsulation efficacy. Notably, Eudragit, an NP made of methacrylic acid ester polymers, is promising because it enhances insulin absorption by Peyer's patches in the intestines. When Eudragit RS (a polymer made from methyl methacrylate, ethyl acrylate, and methacrylic acid ester with ammonium groups) is combined with poly-ε-caprolactone (PCL), it improves how insulin is absorbed by the M cells of Peyer's patches in the ileum. Other promising methods involve combining organic and inorganic materials into nanocapsules for oral insulin delivery. Inorganic compounds tend to be more stable and provide better protection for drugs compared to organic materials. On the flip side, organic materials can enhance the functionality of the nano-formulation. Common organic/inorganic nano-formulations include mesoporous silica NPs and hydroxyapatite NPs. Mesoporous silica NPs offer a modifiable pore size and outer membrane, along with excellent biocompatibility. Zhang et al. added a membrane-penetrating peptide to the surface of a mesoporous silica NP, mimicking viruses. These NPs successfully mimicked viral processes in endocytosis by enterocytes, reducing glucose levels and creating an effective system for oral insulin delivery. However, the combination of organic and inorganic materials remains complex and requires more research, given its significant potential.

Nanoparticles for the Oral Administration of Insulin: formulations could offer valuable treatment options for diabetes. However, the oral uptake of insulin, like many biological drugs, faces several physiological challenges. These include breakdown in the acidic environment of the stomach, degradation by digestive enzymes, and difficulty Oral administration is clearly the best way to deliver drugs because it is simple, practical, and patients usually comply with it. In the case of insulin, oral delivery is particularly advantageous for treating diabetes since it mimics the way the body naturally produces insulin. The pancreas releases endogenous insulin, which travels to the liver through the portal vein before entering the overall circulation. Of the insulin that reaches the liver, up to 80% is captured due to first-pass metabolism. This results in a much higher concentration of insulin in the portal vein compared to the systemic circulation. The remaining insulin then moves into the bloodstream and goes to various parts of the body. This portal-peripheral gradient, where insulin concentrations are much higher in the liver than in other organs, manages how insulin is extracted from the liver and helps maintain the right levels of insulin in the rest of the body.

When taken orally, insulin is absorbed through the intestinal wall and sent to the liver via the portal vein. This creates a portal-peripheral insulin gradient similar to how the body usually secretes insulin. On the other hand, injected insulin first enters the peripheral circulation before it reaches the liver, which can lead to higher levels of insulin in the bloodstream. Thus, developing oral insulin absorbing through the intestinal lining. Using enteric-coated formulations, enzyme inhibitors, and absorption enhancers to open tight junctions in the intestinal cells only slightly improves insulin's oral bioavailability. Recently, nanomedicine has emerged as a promising avenue for enhancing the oral absorption of biological drugs, including insulin. Formulating drugs in nano-sized particles can protect them from degradation in the digestive system.

Moreover, nanoformulations can improve drug absorption through the mouth because they can cross the intestinal lining. This occurs through paracellular diffusion between the cells and endocytosis in specialized cells of the intestinal lining. Different properties of nanoparticles can be adjusted to enhance transport across the epithelial barrier. Modifying surfaces by attaching ligands to specialized receptors on the cells can boost receptor-mediated endocytosis. Positively charged groups can help nanoparticles enter cells through interactions with the negatively charged membranes. Making particles smaller and coating them with hydrophilic materials can aid in diffusion through the intestinal space.

The use of oral insulin nanoparticles might mainly replace long-acting insulin injections. However, replacing rapid-acting insulin will require more predictable absorption. Oral insulin delivery systems must show fast, consistent, and reliable uptake to control glucose levels during meals. Yet, factors like varying gastric emptying times, changes in pH, enzyme breakdown, and inconsistent absorption in the intestines make it hard for current oral nano-formulations to match the fast action of rapid-acting insulin injections. So, even though oral insulin nanoparticles have potential for long-acting insulin alternatives, we still need significant research progress before they can effectively replace rapid-acting insulin for managing glucose levels during meals.

Further research is crucial to efficiently improve the absorption of nanoparticles through the intestinal cells. This will help ensure that enough nanoparticles accumulate in the liver to store and release insulin based on the body's needs. Achieving these goals would make oral administration a practical solution for the challenges of daily injections, benefiting diabetic patients. Additionally, nanoformulations can help ensure effective drug absorption via the mouth by crossing the intestinal lining, while also protecting insulin from being broken down in the digestive tract.

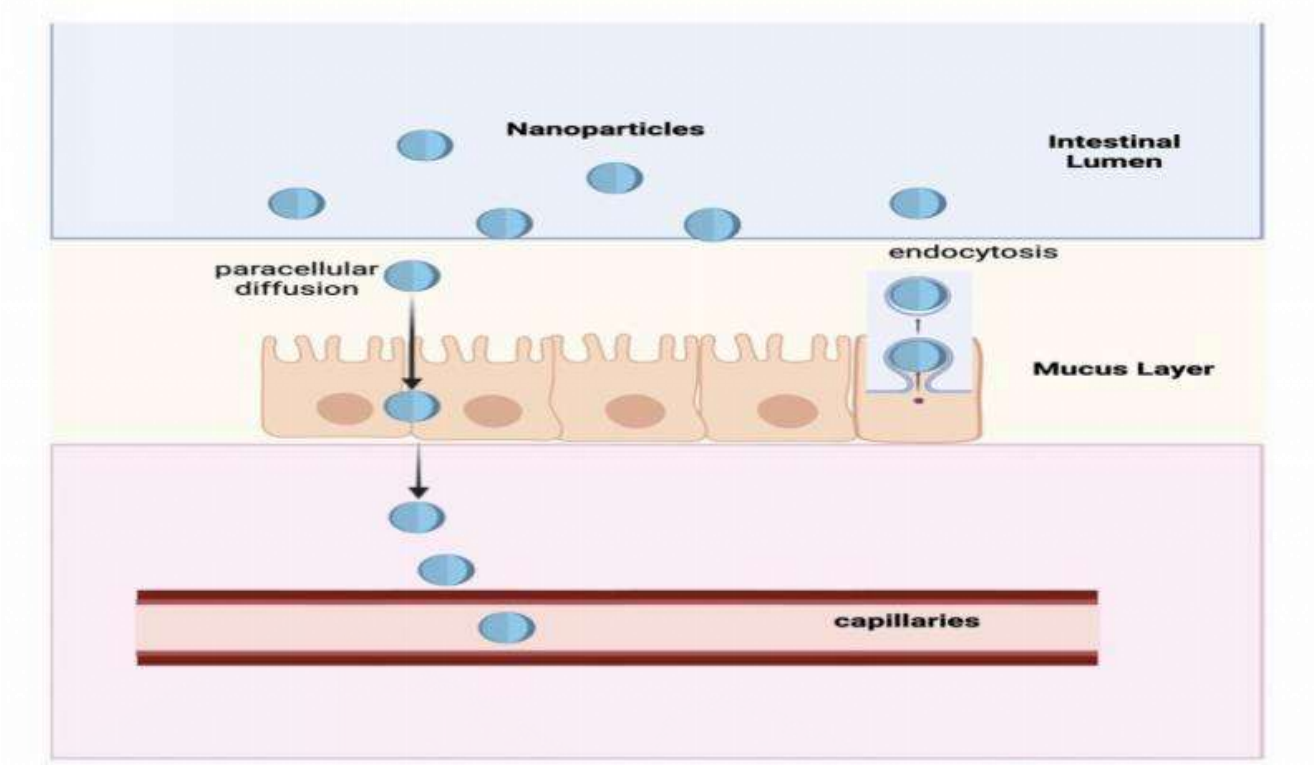

figure 5. Schematic representation of the main mechanisms of nanoparticle absorption through the intestinal mucosa: Paracellular diffusion occurs between endothelial cells and endocytosis in Mcells (or microfold cells), whose name derives from their particular composition. M-cells are specialized intestinal cells and are part of GALT lymphoid follicles such as Peyer's patches. Their function is to transport antigens from the luminal side to the sub-epithelium (transcytosis). This is possible due to an exclusive cellular structure, including many basolateral membrane invaginations that enable macrophages and other immune cells to begin an immune response. Transcytosis is also being explored as an intestinal drug and vaccine delivery opportunity.(5)

Phytomedicines with Antidiabetic Properties and Nanotechnology:

Phytochemicals (PHYs) are active compounds derived from plants. It is well known that some PHYs have strong antidiabetic effects. However, their effectiveness is limited because they are poorly absorbed in the body; most are not soluble in water. Additionally, most PHYs are broken down by enzymes and gut bacteria before they can work in the body. Their quick elimination also reduces their potential benefits. Using nanotechnology with PHYs could help address these issues.

Well-known PHYs like curcumin, resveratrol, berberine, silymarin, and anthocyanins show antidiabetic properties. outlines major PHYs currently being studied as potential antidiabetic agents using nanoformulation-based drug delivery systems. The lack of clinical research indicates that PHYs in the context of nanotechnology are still in a very early stage.[6]

Table 1:

• Main natural compounds with antidiabetic features explored with nanoformulation-based drug delivery systems.

PHYs.	Antidiabetic Properties/Action
Naringenin	Under investigation for improvement in early DR due to its antioxidant properties. Amelioration in DKD due to inhibition of ferroptosis via the SIRT1/FOXO3a pathway [73–75].
Quercetin	It may be useful in DR, DKD and DN due to its antioxidant, anti-fibrotic, anti-inflammatory potential and by affecting pyroptosis. As a hydrogel, it is postulated to improve wound healing due to its antioxidant properties
Rosmarinic Acid	It has been suggested to ameliorate cardiac dysfunction (cardiomyopathy) in DM due to its antioxidant properties. Instillation on the eyes has been proposed to improve DR due to its antioxidant capacity. Also, it is undergoing evaluation as a gel for diabetic wounds. In addition, it has been suggested to interfere with the deposition of β-amyloid in the brain
Thymoquinone (from *Nigella sativa*)	It is suggested to possess nephroprotective potential via the Nrf2/NOX2 pathway. It has been suggested to be useful in diabetic wounds due to its antioxidant, anti-inflammatory and antimicrobial properties as well as its angiogenesis amelioration
Ferulic Acid	It has been implicated in ameliorating DKD by means of improving autophagy. It has been suggested as a nanogel to be involved in healing diabetic wounds due to its antioxidant and antimicrobial potential
Seagrass *Halodule uninervis*	Very recently, it has been suggested to exhibit antioxidant and anti-inflammatory properties
Arbutus unedo	It has been proposed to exert antidiabetic, antioxidant, anti-inflammatory as well as antimicrobial potential
Epigallocatechin-3 gallate	This polyphenolic compound of tea has been suggested to inhibit angiogenesis in the eye by targeting integrins; as such, it may be further exploited in DR [92].
PHYs.	**Antidiabetic Properties/Action**
Curcumin	↓ FPG; ↓ IR Also used in diabetic wounds in a nanoformula hydrogel as it has healing properties due to its inhibition of MMP-9
Resveratrol	↓ FPG; ↓ IR It is undergoing evaluation on the treatment of DR due to its inhibition of VEGF-1,ICAM-1, MCP-1 and ERK1/2
Berberine	↓ FPG; ↓ IR
Silymarin	↓ FPG; ↓ IR

Figure6. \:reduction. Abbreviations: DN: diabetic neuropathy; DKD: diabetic kidney disease; DR: diabetic retinopathy;ERK1/2: extracellular signal-regulated kinase 1/2; FPG: fasting plasma glucose; ICAM-1: intercellular adhesiol molecule-1; IR: insulin resistance; MCP-1: monocyte chemotactic proteins-1; MMP-9: matrix metallo-proteinase-9;VEGF-1: vascular endothelial growth factor-1.

Table 2:

Figure7- Pros and cons of nanotechnology in diabetes mellitus management.

Pros of NPs	Cons of NPs
Improved absorption	Unknown safety in the long term
More controllable release allowing for plausible better compliance	Lack of clinical trials
Resistance to various pH values as well as to enzymatic degradation throughout the GIT	High costs
Improved entry into the targeted cells	Research is in its very early stages

Diabetes Screening and Diagnosis:

Diabetes is a chronic condition marked by high blood sugar levels. It requires early and accurate diagnosis for timely treatment, effective management, and the prevention of complications. The methods used for screening and diagnosis vary between Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D) because of their different biological processes and clinical signs. For both types, biomarkers are crucial for early detection and assessing risk. According to the National Institutes of Health (NIH), biomarkers are measurable signs of biological processes, diseases, or responses to treatments. They include molecular, cellular, and physiological features. Biomarkers can be used in various areas such as diagnosis, predicting outcomes, monitoring progress, assessing responses, and ensuring safety. This review focuses on traditional and new diagnostic and predictive biomarkers.[9]

Nano biosensors in Diabetes:

The integration of sensor technology with nanotechnology has been vital in developing improved detection systems. These biosensors use various nanomaterials, including metal-based materials, metal oxides, quantum dots (QDs), carbon-based structures, and metal-organic frameworks (MOFs). They achieve high sensitivity, specificity, and versatile detection abilities.

Nanomaterials are substances with at least one dimension between 1 and 100 nm. They can be categorized by their shape, size, composition, or dimensions. Their nanoscale size gives them unique properties, such as optical, electrical, thermal, and mechanical characteristics, which bulk materials usually lack. The high surface area-to-volume ratio, adjustable shape and size, and ease of surface modification provide nanobiosensors with significant advantages over traditional biosensors.

Safety and Toxicity of Nanoparticles:

The use of nanoparticles (NPs) for treating diabetes is an active area of research, but it raises concerns about potential toxicity that need careful attention. Depending on their size, materials, surface chemistry, and method of administration, some NPs may accumulate in specific organs or tissues. This can lead to localized toxicity.

NPs can cross biological barriers like the blood-brain barrier, which may cause unintended distribution and possible toxic effects. However, we can adjust particle size, shape, and surface chemistry to improve how compatible NPs are with the body and enhance their targeting while minimizing overall exposure.

NPs might interact with the immune system, triggering inflammatory responses or changing immune function. This is particularly concerning for individuals with type 2 diabetes mellitus (T2DM), as they often have underlying issues with immune regulation.

Common methods to reduce the immunotoxicity of nanoparticles (NPs) include:

- Biomimetic encapsulation using cell membranes on the NP surface.
- Immune-escape strategies through biomaterial grafting.

Some NPs can generate reactive oxygen species (ROS), which lead to oxidative stress and cellular damage. This is especially concerning in Type 2 diabetes mellitus (T2DM), already linked to higher oxidative stress. To reduce ROS-related toxicity, strategies include:

- Coating NPs with antioxidants.
- Applying polymeric protective coatings on NPs.

The toxicity profile of NPs varies. It depends on their physicochemical properties, route of administration, and the targeted disease. Thorough safety evaluations, including both in vitro and in vivo studies, are crucial before NP-based therapies can proceed to clinical use.

Example: Gliclazide-Loaded Solid Lipid Nanoparticles (Safety Study)

Gliclazide is an oral medication for non-insulin-dependent diabetes. Nazief et al. conducted a 14day sub-acute toxicity study with gliclazide-loaded solid lipid nanoparticles (SLNs) in Wistar rats. These studies check if NPs cause changes in blood, biochemistry, or the function of organs and tissues. In this research, gliclazide-loaded SLNs were given orally for 14 consecutive days.

Findings:

- No deaths or adverse reactions were noted.
- Food intake, water consumption, and body weight showed no significant changes.
- No structural changes were observed in major organs (stomach, intestine, liver, kidneys).
- Organ-to-body-weight ratios stayed normal.
- Tests for liver and kidney function were similar between control and treated groups.

Thus, giving blank SLNs and gliclazide-loaded SLNs repeatedly over 14 days did not harm the rats. The toxicities of various inorganic NPs, like zinc oxide, cerium oxide, and silver NPs, were also measured in Swiss albino mice. These NPs were administered daily by oral gavage for 28 consecutive days. After this period, the mouse organs, including the pancreas, kidneys, spleen, heart, and liver, showed no significant structural changes compared to the control group. Therefore, these NPs did not cause any signs of death or sub-acute toxicity after repeated administration for 28 days.

While some toxicity studies suggest that NPs have low toxicity and are safe in cells and organisms, most NPs still require validation through in vitro and in vivo safety assessments to better understand their toxicity profiles. Studying the underlying mechanisms of NP-induced toxicity, such as how cells take them in, their movement inside cells, and specific molecular pathways can help solve these issues. Ongoing research focuses on addressing these toxicity concerns by developing biocompatible, targeted, and controlled-release NP systems that aim to minimize adverse effects while maximizing therapeutic benefits for managing diabetes.

Clinical Studies of Diabetic Nanomedicine:

Currently, there are no FDA-approved nanodrugs for diabetes treatment, and most research is still in the pre-clinical stage. While oral and subcutaneous insulin are widely used, both forms have significant challenges. Because of its large molecular size and hydrophobic nature, insulin has poor bioavailability. It gets quickly inactivated by proteolytic enzymes in the stomach and intestinal membrane, which leads to low permeability and reduced absorption. To tackle these issues, a hepato-directed vesicular (HDV) insulin formulation was created. HDV insulin is a new oral insulin delivery system that aims to target the liver specifically. This system uses biotin– phosphatidylethanolamine (biotin-PE) within the phospholipid matrix. The phospholipid bilayer includes a proprietary hepatocellular targeting molecule (HTM) that enables liver-specific insulin delivery. After oral administration, HDV insulin protects insulin from being broken down by enzymes in the upper gastrointestinal tract. This improves its absorption and allows selective delivery to liver cells, closely mimicking the natural flow of insulin in the portal vein. The vesicle size is about 150 nm, which is ideal for better transport and stability. HDV insulin has moved on to Phase II clinical trials. This six-month trial tests a liver-targeted rapid-acting insulin formulation in patients with Type 1 diabetes mellitus (T1DM).

The HDV-insulin lispro (HDV-L) group showed:

- improved insulin action
- reduced total cholesterol (TC) levels
- no severe adverse events
- no differences in liver-function parameters between the treatment and control groups.

Thus, HDV insulin, which combines nanocarrier technology with liver-specific targeting, has strong potential as a promising nanomedicine for managing diabetes and treating metabolic diseases.

Traditional approaches to diabetes management:

Including insulin therapy, oral medications, and lifestyle changes has played a significant role in improving disease control. However, these approaches are still not enough to tackle the complex nature of diabetes and its related complications. Several key issues limit their overall effectiveness.

1. Compliance issues: Insulin injections can be uncomfortable, and the need for frequent glucose monitoring can be a hassle. These factors often lead to poor adherence to treatment plans.

2. Side effects of medications: Drugs like metformin and sulfonylureas are often linked to side effects, such as stomach problems and low blood sugar. These issues discourage many patients from sticking with their medications and complicate long-term management.

3. Inadequate blood sugar control: Traditional treatments cannot mimic the body's natural insulin release accurately. This leads to fluctuations between high and low blood sugar, increasing the risk of chronic complications like heart disease and nerve damage.

4. Delayed diagnosis and monitoring: Common glucose monitoring methods, like finger-prick tests, are inconvenient and only provide sporadic readings. This limits our understanding of blood sugar changes and delays the detection of worsening control.

5. Economic constraints: The high costs of insulin, oral medications, and monitoring devices pose a significant challenge, especially in low- and middle-income countries with limited healthcare resources. This financial strain often prevents patients from receiving consistent and effective diabetes care. These challenges point to a pressing need for new strategies that improve treatment results, reduce side effects, and enhance overall quality of life. Importantly, these solutions must be affordable and adaptable for use in settings with limited resources. Nanotechnology has emerged as a promising field, offering innovative solutions to many of these challenges. Advances in nanoscale drug delivery, biosensors, and diagnostic tools are paving the way for more precise, efficient, and patient-friendly diabetes management.

Conclusions:

Therapeutic nanoparticles provide a new way to tackle the inflammation and oxidative stress linked to diabetes. They help reduce complications and improve patients' quality of life. The connections between oxidative stress, inflammation, and diabetes highlight the need for new treatment methods. High levels of reactive oxygen species (ROS) and the resulting cellular damage play a significant role in developing diabetic complications, while ongoing inflammation makes the situation worse.

Nanoparticles that target inflammation and have antioxidant properties offer a hopeful solution to these issues. By improving the absorption of natural antioxidants and using combination therapies, nanoparticles can create combined benefits in managing diabetes. Progress in nanotechnology also boosts the effectiveness of targeted treatments and helps fight oxidative stress and inflammation, representing a significant step forward in diabetes care.

However, despite their promise, nanoparticles face hurdles such as toxicity, stability, immune reactions, scalability, targeting accuracy, and regulatory approval. Future efforts should focus on improving compatibility with the body, fine-tuning delivery methods, and developing reliable ways to produce them on a large scale to fully realize their therapeutic potential.

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