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REVIEW

Nano-Based Drug Delivery Systems for Managing Diabetes: Recent Advances and Future Prospects

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Abstract: Diabetes mellitus is a chronic metabolic disorder, which is characterized by high blood glucose levels, and this can lead to serious diabetic complications. According to the World Health Organization, approximately 830 million adults worldwide are living with diabetes in 2024, with its prevalence continuing to rise steadily over the years. To treat this disease, researchers have developed a variety of first-line drugs, such as sulfonylureas and thiazolidinediones. Despite their long clinical use, there are still many drawbacks and limitations. One of the main drawbacks is low bioavailability, this causes the diabetic patients to take the drugs frequently to lower the blood glucose levels continuously. Some patients may have to take multiple drugs to increase the effectiveness of lowering blood glucose levels. To address these limitations, nano-based drug delivery systems have emerged to overcome these problems. It has emerged as a promising approach for diabetes management, which offers controlled and localized release of anti-diabetic drugs, thus enhancing therapeutic efficacy. This review discusses recent advances in the field of nano-based drug delivery systems for diabetes management, safety and toxicity profiles of anti-diabetic drugs, and future perspectives for the development of nanomedicine in diabetic treatment. Literature search was conducted using electronic databases, and only English literatures were used and published between 2014 and 2024. Recent advancements in nanotechnology have facilitated the development of various nanocarriers, such as polymeric carrier nanoparticles, nanoliposomes, nanocrystals, nanosuspension and inorganic nanoparticles, which enhance drug stability, bioavailability, and efficacy. These systems can deliver anti-diabetic drugs and natural compounds more effectively, thereby minimizing side effects and improving patient compliance. As the field continues to evolve, the successful clinical implementation of nanodrugs could revolutionize the management of diabetes and improve the quality of life for millions of diabetic patients worldwide.
Keywords: drug delivery system, diabetes, nanomedicine, anti-diabetic drugs, Nanomedicine

Introduction

Nanotechnology broadly refers to technologies applied at the nanoscale.[1] In recent years, nanotechnology has emerged as a promising field in drug delivery, thus offering innovative solutions to overcome the limitations of traditional pharmaceutical approaches.[2] Although the strict definition of nanoparticles (NPs) is between 1–100 nm, various studies in recent years have extended the upper size range to approximately 1,000 nm in the context of this application. Figure 1 represents the length of the relative size of nanomaterials in comparison to naturally occurring things. At the nanoscale, materials exhibit unique physical, chemical, and biological properties that can be utilized to enhance the efficacy, targeting, and delivery of therapeutic drugs. Similar to cancer therapies, the enhanced permeability and retention (EPR) effect allows NPs to accumulate in tissues with increased vascular permeability, such as inflamed or insulin-resistant tissues. In diabetes, this effect can help to target insulin, or therapeutic agents can be directed to insulin-sensitive tissues, like adipose tissue or muscle, to improve their efficacy.

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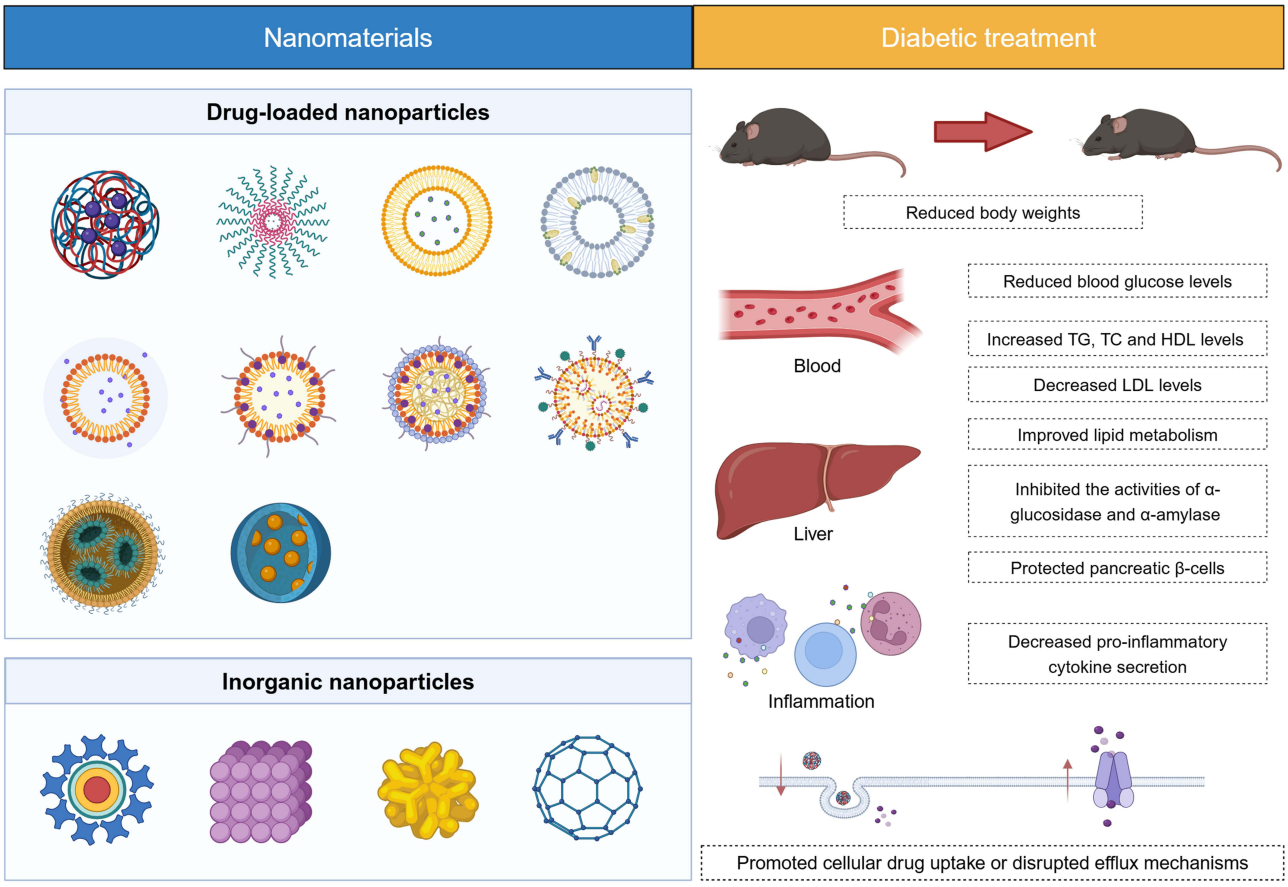
Graphical Abstract



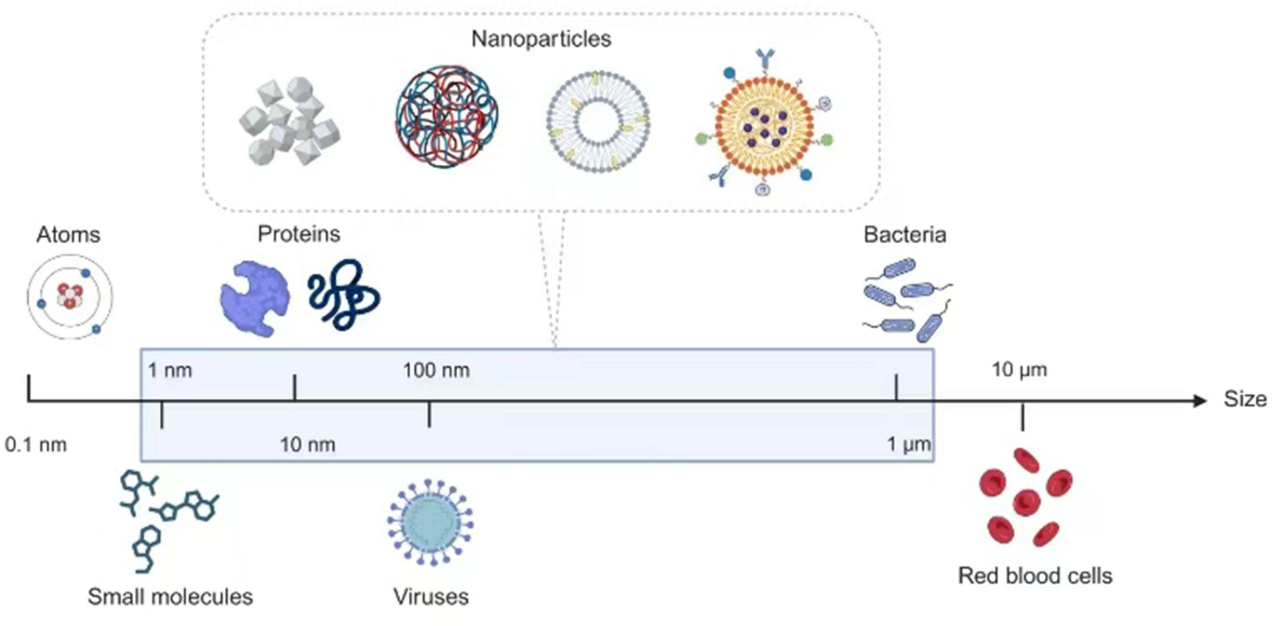


Figure 1 Different types of particles and living things. A nanoparticle is a particle of matter with 1 to 1000 nm in diameter. At the lowest range, metal particles, that are smaller than 1 nm, are usually called atom clusters. Some nanoparticles containing biological materials can be hundreds of nm in diameter.

Nanomaterials can be engineered to interact with cell membranes more effectively through various means, for example, coating NPs with ligands or antibodies that target specific receptors can facilitate endocytosis.[3] Besides, they can also be engineered for controlled drug release through stimuli-responsive systems, releasing drugs in response to specific biological triggers, such as changes in glucose levels.[4] This helps to maintain stable drug levels in the bloodstream, thus reducing the need for frequent dosing and enhancing patient compliance. The development of nano-based drug delivery systems has progressed significantly over the past few decades. The concept of using liposomes as drug carriers was firstly introduced in the 1960s, paving the way for the development of lipid-based NPs.[5] Subsequently, polymeric NPs, such as those made from biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), were explored for drug encapsulation and controlled release.[6] In 2000s, a wide range of NP platforms were developed, including polymeric carriers,[7] dendrimers[8] and inorganic NPs.[9] In addition, targeted drug delivery using NPs functionalized with ligands, antibodies, or other targeting moieties gained prominence in this field of research.[10] The use of NPs for the delivery of biomacromolecules, such as proteins, peptides, and nucleic acids, also becomes an area of active research.[11] Stimuli-responsive NPs that release drugs in specific conditions, such as pH, temperature and enzymes, were also designed.[12] There are many reasons why nanomedicine delivery systems are so popular. One of the primary reasons is the ability to improve the solubility, bioavailability, and stability of drugs.[2] NPs, such as polymeric NPs, liposomes, and micelles, can encapsulate hydrophobic drugs, thus protecting them from degradation and facilitating their transport across biological barriers, such as intestinal epithelium and blood-brain barrier. This helps to overcome a major challenge in traditional drug formulations, where poor solubility and low bioavailability often limit the efficacy of many therapeutic drugs. Besides, the unique size and surface properties of NPs can prolong the circulation time of drugs in the body, thereby leading to enhanced pharmacokinetic profiles.[13] Furthermore, nanocarriers can be engineered to specifically target diseased or desired tissues. This can be achieved through the incorporation of targeting moieties, such as antibodies, peptides or ligands, on the surface of the NPs, which recognize and bind to receptors or markers that are expressed on the target cells or tissues.[14] This targeted delivery approach improves the therapeutic effects by maximizing the drug concentration at the site of action and minimizing systemic exposure and off-target effects.

The superior properties of nanodrugs enable them to have great potential in disease treatment. They are now used to treat cancer,[15] neurodegenerative diseases,[16] cardiovascular diseases,[17] inflammation[18] and diabetes.[19] Among these, the global prevalence of Type 2 diabetes mellitus (T2DM) continues to rise, which poses a significant public health challenge.[20] Conventional therapeutic approaches may fall short in achieving optimal glycemic control and preventing the progression of diabetic complications. Therefore, the emergence of nanodrugs has sparked new hope in revolutionizing the management of diabetes. NP-based insulin formulations can protect the drugs from degradation of insulin, prolong its action, and facilitate more consistent and controlled release, thereby potentially reducing the frequency of insulin injections.[21] In addition, to overcome the challenges of poor absorption and enzymatic degradation in the gastrointestinal tract, NPs can enhance the bioavailability of orally administered insulin, thus improving patient compliance.[13] NPs can also co-deliver insulin and other anti-diabetic drugs, such as metformin or glucagon-like peptide-1 (GLP-1) agonists, that can synergistically improve glycemic control and mitigate diabetic complications. Importantly, common first-line anti-diabetic drugs, such as metformin, GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors, are also being used to design nanomedicine delivery systems. Moreover, many natural compounds with anti-diabetic activities are also expected to be better applied to patients by being prepared into NPs.[22] These advanced drug delivery systems, such as polymeric carriers, lipid carriers, nanocrystal, nanosuspension and inorganic carriers, hold the promise of enhancing therapeutic efficacy, improving patient adherence, and ultimately, transforming the therapeutic approaches for diabetic treatment and prevention of diabetic complications.

In this review, literature search was conducted using electronic databases, including PubMed, Google Scholar and Web of Science. A combination of the following keywords, including "Type 2 diabetes", "nanomedicine", "nanoparticles", "drug delivery systems", "antidiabetic agents" and their related terms, was used for the search of English literatures between 2014 and 2024. This review aims to summarize studies from the past decade on the use of nanomedicine in diabetes treatment, focusing on commonly used anti-diabetic drugs and natural compounds encapsulated in NPs, as well as NPs exhibiting anti-diabetic activities. We focus on the design of different types of NPs and their applications for the improvement of diabetic treatment, as well as their toxicity profiles. Finally, we discuss recent advances and future perspectives for the development of NPs as therapeutic drugs in diabetic treatment.

Current Anti-Diabetic Drugs and Their Limitations

Diabetes is one of the largest chronic diseases in the world. According to statistical data, the number of people with diabetes has been more than doubled in the past 20 years.[23,24] Its main characteristics is hyperglycemia, which is accompanied by disturbances in carbohydrate, protein and fat metabolism. There are two types of diabetes commonly seen in clinical practice, Type 1 diabetes mellitus (T1DM) and T2DM.[25] In T1DM, due to an autoimmune response, the body produces antibodies that destroy pancreatic β-cells and cause reduced insulin production.[26] Therefore, insulin injection therapy is an extremely important way to maintain the health of patients with T1DM. T2DM accounts for 85–90% of diabetic patients,[27] and the main causes include genetics, lifestyle and obesity.[28,29] In T2DM, the insulin receptors on the cell membrane of insulin-responsive cells are poorly or even unresponsive to insulin, which is known as insulin resistance, thus the blood glucose levels are increased.[30]

Currently approved drugs for T2DM mainly include biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 analogues.[23] The clinical drugs for T2DM are mainly oral tablets, capsules and suspension. In addition, polyphenols, flavonoids and alkaloids derived from natural plants also have excellent anti-diabetic activities.[31] Many natural product components can play a role in hypoglycemia by protecting pancreatic β-cells, promoting insulin secretion, reducing glucose absorption in the intestine, increasing the number of insulin receptors on target cells, and enhancing insulin sensitivity.[32,33] However, diabetic patients may have suffered from the side effects of anti-diabetic drugs. Common sulfonylureas include glipizide, glibenclamide and gliclazide.[34] They have a certain degree of hypoglycemia, gastrointestinal reactions and may destroy liver and kidney functions. Biguanides are used to treat T2DM by improving the sensitivity of peripheral tissues and liver to insulin, reducing intestinal glucose absorption and enhancing activating anaerobic peripheral tissue glycolysis.[35] The main drug of this class used in the clinic is metformin, but it has adverse effects on liver, kidney and heart functions.[36] On the other hand, α-glucosidase inhibitors reversibly inhibit the activity of α-glucosidase in small intestinal wall cells, thus delaying the degradation of carbohydrates and glucose absorption in the digestive tract. As a result, they effectively delay and reduce the time and process of postprandial glucose rise in diabetic patients, and help to control the development of diabetes.[37] However, it also has gastrointestinal side effects. Most of these anti-diabetic drugs need to be taken for a long time and frequently to achieve the desired effect, which leads to the accumulation of drugs in the body, thereby resulting in various adverse reactions. In recent years, researchers have focused on new targets and new drugs. In addition, for these traditional anti-diabetic drugs, the current focus is to improve their bioavailability and dose reduction, and improve patient medication compliance.[38]

The use of nano-based drug delivery systems has become the first choice for researchers.[39] Wrapping anti-diabetic drugs in nanocarrier system can fully protect drugs from gastrointestinal decomposition and reduce gastrointestinal adverse reactions. In addition, drugs can be released in a gradual and effective manner, thus improving the bioavailability of the drugs, reducing drug accumulation and administration times, and improving patient medication compliance. Over the past few years, many efforts have been made to manufacture suitable materials, systems, and nanostructures for drug delivery and biomedical applications. Several drug delivery systems that have been reported to improve the bioavailability and effective drug delivery for anti-diabetic drugs include polymerized NPs, lipids nanocarrier systems, nanocrystals, nanosuspensions and inorganic nanocarriers.

Nanomedicine for the Management of Diabetes

Nanotechnology has rapidly advanced across many disciplines in recent years.[40,41] Among them, using nanotechnology to deliver the drugs becomes successful and has been used clinically.[42] Nanomedicine can be broadly divided into nanocarrier drugs and nanostructured drugs. Nanocrystals are the most common type of nanostructured drug delivery systems. They have no nanomaterial used as a carrier and are synthesized by breaking the drugs down to the nanoscale.[43] The reduction of particle size greatly improves water solubility, bioavailability and efficacy of the drugs. The other type of nanomedicine is nanocarrier drugs. Nanocarrier drugs utilize carrier materials to bind, adsorb, disperse, or encapsulate genes, proteins and drugs, thus enhancing their transport to the body and bioavailability. Nanocarriers can protect the drugs from degradation, increase their half-life, and improve the solubility of poorly water-soluble drugs. Therefore, they have significant potential in delivering drugs more efficiently for the treatment of diseases, including T2DM. The main types of nanocarrier drugs include natural polymer carrier, synthetic polymer carrier and combination of both.

Polymeric Nanoparticles

Polymeric NPs are composed of polymer materials that have excellent biocompatibility and possess controllable physical and chemical properties.[44] Drugs can interact with polymeric NPs through processes, such as adsorption, encapsulation and covalent binding, thus allowing effective encapsulation within the NPs. Polymeric NPs can encase or physically encase the drugs within the polymer matrix, thereby reducing its interaction with healthy cells and reducing the toxicity of the drugs. The commonly used polymers include natural polymers, such as albumin, dextran, chitosan and hyaluronate, and synthetic polymers, including polyglutamic acid, polyglycolic acid, polyethylene glycol, polycaprolactone and polylactic acid (PLA).

Natural Polymeric Nanoparticles

Natural polymers used for anti-diabetic drug delivery include a wide range of gums, mucilages and polysaccharides.[45] Their primary advantages over synthetic polymers are their non-toxicity and biocompatibility. They can also benefit from lower immune rejection and are biocompatible as all of them are derived from organisms, and their final products are polysaccharides or amino acids, which are easy to absorb and not prone to inflammation.[46] Meanwhile, the problem of degradation can be solved by enzymatic hydrolysis. In addition, natural polymers often have their own biological activities. For example, some natural polymers have anti-bacterial, anti-inflammatory, wound healing effects, which make them to be promising for a wide range of applications in medical and bioengineering fields.[45] They also have the advantages of stable performance, non-toxic, safe application, low cost, so scientists are paying more attention to the development of natural polymers for diabetic treatment. Table 1 summarizes the characteristics and therapeutic effects of natural polymeric NPs for diabetes management.

Chitosan

Chitosan belongs to one kind of natural polymers, which is the product of deacetylation of chitin.[54] It consists of D-glucosamine units that are held together by a β-1,4-glucoside bond.[55] The free active amino group in its structure provides favorable conditions for modification, and is often used to introduce other groups, such as alkyl, carboxylic and aromatic groups.[54,56] Chitosan has the same good biocompatibility and biodegradability as chitin,[57,58] and has unique biological effects, such as bio-adhesion, good safety, anti-bacterial, anti-tumor and anti-diabetic activities.[59–62] It has been widely used to prepare polymeric NPs for diabetic treatment due to its anti-diabetic activity and advantages in drug delivery.

Table 1 Natural Polymeric Nanoparticles for Diabetes Management

Drugs	Nanomaterials	Methods	Particle Sizes	ζ-Potential	Entrapment efficiency	Therapeutic Effects	Ref.
Polydatin	Chitosan, tripolyphosphate	Ionotropic gelation method	144.25 ± 3.37 nm	–	96.74 ± 0.39%	Reduced blood glucose levels and insulin resistance index.	[47]
Glipizide	O-carboxymethyl chitosan	Ionotropic gelation method	216 ± 2.5 nm	−14.2 ± 2.1 mV	80.7 ± 0.8%	Reduced blood glucose levels, insulin resistance index, serum triglyceride and total cholesterol levels, and the levels of TNF-α and IL-6.	[48]
Glycyrrhizin	Chitosan and gum arabic	Ionotropic gelation method	184.1 ± 30.5 nm	+31.4 mV	–	Reversed diabetes-induced body weight loss, lowered blood glucose levels and improved lipid profile.	[49]
Metformin	Carboxymethyl chitosan	Microfluidics technique	77 ± 19 nm	−22 ± 0.12 mV	89 ± 1.70%	Prevented weight loss and lowered blood glucose levels.	[50]
LMW-HA	Hyaluronic acid and chitosan	Self-assembled	221.0 ± 3.1 nm	−25.7 ± 1.3 mV	–	Reduced body weights, food intake and blood glucose levels, adipocyte area, macrophage infiltration, pro-inflammation in the white adipose tissue.	[51]
Exenatide	Hyaluronic acid	Electrostatic adsorption	309.2 nm	–	–	Lowered blood glucose levels and lipid markers, improved glucose tolerance and insulin sensitivity, and prevented pancreatic islet damage.	[52]
Rapeseed-derived peptides	Chitosan and sodium alginate	Ionotropic gelation method	220.2 ± 2.11 nm	−39.75 mV	91.40%	Improved glucose tolerance and increased the GLP-1 levels.	[53]

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Polydain is a polyphenol and resveratrol derivative, and has various pharmacological effects, including anti-inflammatory and antioxidant effects.[63] It is poorly water-soluble and has low bioavailability and high first-pass metabolism, which limits its clinical applications.[64] Abdel-Moneim et al loaded polydain onto chitosan to synthesize polydain-loaded chitosan NPs using a modified ionic gelation method to improve the therapeutic effects of polydain.[47] They added polydain into chitosan solution, and tripolyphosphate aqueous solution was then added to obtain polydatin-loaded chitosan NPs. The particle size of these NPs was 144.25 ± 3.37 nm. These NPs showed excellent in vitro sustained-release ability, which could continuously release polydain when compared with free polydain. Besides, the increased concentration of chitosan in the formulation could result in longer time of release. They suggested that the hydration of chitosan and the dissolution medium formed a gel-like substance, which delayed the release of polydain. Moreover, these NPs were found to prevent body weight loss, lower blood glucose levels and insulin resistance index, and increase plasma insulin levels in diabetic rats, demonstrating better anti-diabetic effects than free polydain. In another study, similar ionic gelation method was used to load glipizide with O-carboxymethyl chitosan (CMC) to synthesize glipizide-CMC-NPs with particle size of 216 ± 2.5 nm.[48] The ζ-potential was −14.2 ± 2.1 mV. O-CMC is a soluble chitosan derivative with both amino and carboxyl groups that enables glipizide to have long-lasting effects on diabetic treatment. Glipizide is a T2DM drug that belongs to the class of sulfonylureas and has several anti-diabetic effects, including enhancing insulin secretion and sensitivity. It has fewer side effects, however, its half-life is short (2–4 h), which requires frequent administration.[65] A more prolonged and superior release profile of these NPs was observed when compared with free glipizide. When the NPs were administered to T2DM mice, it was found that blood glucose levels, insulin resistance index, serum triglyceride and total cholesterol (TC) levels were reduced in the NPs group. Besides, the serum levels of the pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 were also reduced and serum adiponectin levels were increased in the NPs group when compared with the free glipizide group, suggesting that better therapeutic effects were achieved after glipizide was prepared into chitosan NPs.

Glycyrrhizin is a major bioactive component of Licorice, however, its oral bioavailability is very low, and its absorption in the gastrointestinal tract is slow and incomplete.[66] Therefore, glycyrrhizin-loaded NPs were prepared using chitosan and gum arabic as polymers by an ionotropic gelation method.[49] The particle size was 184.1 ± 30.5 nm and ζ-potential was +31.4 mV. The in vitro release of these NPs was slow and sustained. Importantly, glycyrrhizin-loaded NPs only contained about a quarter of the amount that was used in the free glycyrrhizin group. These NPs reversed diabetes-induced body weight loss, lowered blood glucose levels and improved lipid profile in nicotinamide plus streptozotocin (STZ)-induced diabetic rats, demonstrating better therapeutic effects in T2DM.

In addition to the common ionic gelation method, there are other different methods used for the synthesis of NPs, such as emulsion, spray drying and precipitation. The preparation of chitosan-coated NPs by microfluidic method has become more and more popular in recent years. Studies showed that the use of microfluidic method enabled polymeric NPs become smaller and more uniform.[67] Lari et al encapsulated metformin hydrochloride, a commonly used T2DM drug, into novel crosslinked CMC NPs using microfluidics technique.[50] Moreover, CMC has been widely used for the synthesis of NPs due to good safety, water soluble and mucosal adhesion.[68] However, this polymer has some disadvantages, including poor stability and rapid degradation. An ionic crosslinker, such as calcium chloride, can be added to enhance drug loading and control drug release.[69] Metformin-loaded crosslinked CMC NPs were synthesized using calcium chloride as the ionic crosslinker and CMC as the polymer.[50] The blood glucose level reduction of metformin-loaded crosslinked CMC NPs was 15% higher than free metformin in STZ-induced diabetic rats, and these NPs preserved pancreatic islet regeneration, revealing superior therapeutic effects.

Hyaluronic Acid (HA)

HA is a high molecular weight polymer and a linear polysaccharide that is composed of D-glucuronic acid and n-acetylglucosamine.[70] Its molecular weight can reach as much as 25 kDa.[71] As a natural polymer, HA is biocompatible, biodegradable and non-toxic. In addition, due to its structural particularity, it can be subjected to different chemical modifications to achieve different physical and chemical properties, such as conjugation, nanotubes, dendritic macromolecules, liposomes and self-assembled NPs.[72] In recent years, HA has been widely studied for targeted and long-acting drug delivery in the biomedical research. It is worth noting that HA can bind and interact with CD44, which allows HA

to exert therapeutic effects for the treatment of many diseases, such as diabetes, inflammatory diseases and cancer.[51,73,74] HA has a negative charge under physiological pH conditions, so as a nanocarrier, it can enrich the negative charge and escape the capture of serum proteins.[75] In addition, HA is hydrophilic, which can avoid the effects of opsonization. Meanwhile, hydrophilicity allows HA to introduce bound water, thus establishing its barrier and extending its circulation time in the body. Due to its rich functional groups and binding sites, the chemical modification of HA can also be varied.[71] As a common nanocarrier material, drugs loaded with HA exhibit a longer biological half-life, which significantly enhanced cellular uptake. In the study of Bhujbal et al, extremely stable NPs were formed by loading HA with the common T2DM drug metformin, and their strong permeability was verified in Caco-2 intestinal epithelial cells.[76] Besides, the NPs loaded with HA as the carrier also showed good therapeutic effects on diabetes in vivo (Figure 2A and B).[51,52,77]

Due to the ability of HA in recognizing and binding to CD44, a study synthesized self-assembled amphiphilic HA-conjugated NPs with particle size of 221.0 ± 3.1 nm particle size and ζ-potential of −25.7 ± 1.3 mV.[51] These NPs could aggregate in the adipose tissue and inhibit the binding of free low molecular weight (LMW) HA to CD44, thereby inhibiting the pro-inflammatory effects of LMW HA in mouse bone marrow-derived macrophages (BMDMs). IL-1β and TNF-α levels were significantly decreased in the HA NPs group of CD44 +/+ BMDMs, but not in CD44 -/- BMDMs, suggesting that the effects were through CD44. HA NPs successfully reduced body weight, food intake and blood glucose levels in high-fat diet (HFD)-induced obese mice, and also significantly reduced adipocyte area, macrophage infiltration and pro-inflammation in the white adipose tissue. Therefore, HA alone, without drug loading, showed

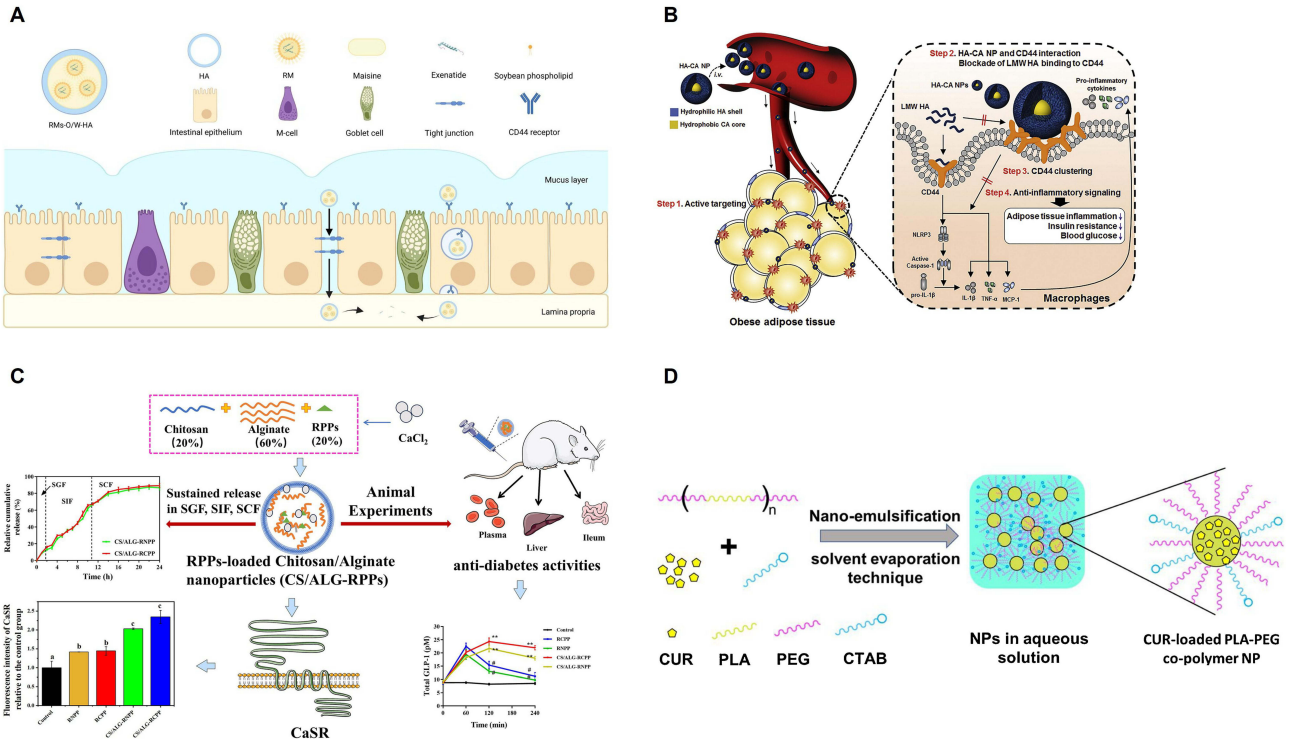

Figure 2 Polymeric nanoparticles (NPs) as drug delivery systems for the management of diabetes. (**A**) Schematic illustration of RMs-O/W-HA mucus penetration and CD44-mediated endocytosis to facilitate the uptake of Exenatide. Adapted from *Eur J Pharm Biopharm*, volume 191, Lu Y, Wu L, Lin M, et al. Double layer spherical nanoparticles with hyaluronic acid coating to enhance oral delivery of exenatide in T2DM rats. 205–218, Copyright 2023, with permission from Elsevier.[52] (**B**) Schematic illustration of the therapeutic effects of self-assembled HA-NPs on adipose tissue inflammation and insulin resistance. Adapted from *J Control Release*, volume 279, Rho JG, Han HS, Han JH, et al. Self-assembled hyaluronic acid nanoparticles: implications as a nanomedicine for treatment of type 2 diabetes. 89–98, Copyright 2018, with permission from Elsevier.[51] (**C**) Schematic illustration of chitosan-sodium alginate nanocarrier system for controlling the release of rapeseed-derived peptides and enhancing anti-diabetic efficacy. Adapted from *Int J Biol Macromol*, volume 265, Wang Q, Dong X, Castañeda-Reyes ED, et al. Chitosan and sodium alginate nanocarrier system: controlling the release of rapeseed-derived peptides and improving their therapeutic efficiency of anti-diabetes. 130713, copyright 2024, with permission from Elsevier.[53] (**D**) Schematic diagram showing curcumin-loaded PLA-PEG copolymer NPs for the treatment of liver inflammation in streptozotocin-induced diabetic rats. Adapted from *Colloids Surf B*, volume 177, El-Naggar ME, Al-Joufi F, Anwar M, Attia MF, El-Bana MA. Curcumin-loaded PLA-PEG copolymer nanoparticles for treatment of liver inflammation in streptozotocin-induced diabetic rats. 389–398, copyright 2019, with permission from Elsevier.[78]

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significant therapeutic effects on diabetes. Moreover, HA is more widely used as an external coating of NPs with drug loading to achieve better therapeutic effects. In the study of Lu et al, a positively-charged reverse micelle self-emulsifying polypeptide drug delivery system encapsulated with exenatide, a T2DM drug, was firstly developed, and then HA was wrapped around the micelles by electrostatic adsorption to synthesize exenatide NPs.[52] The particle size was 309.2 nm. HA coating improved the adhesion of NPs and enhanced CD44-mediated endocytosis to increase cellular uptake in Caco-2 intestinal epithelial cells. Besides, it also enhanced NP accumulation in the gastrointestinal tract of HFD + STZ-induced diabetic rats. Exenatide NPs coated with HA also showed better therapeutic effects than uncoated NPs in diabetic rats, including lowered blood glucose levels and lipid markers, improvement in glucose tolerance and insulin sensitivity, and prevention from pancreatic islet damage.

Sodium Alginate

Sodium alginate is a kind of natural hydrophilic polysaccharide extracted from brown algae. It is a polymer composed of d-mannuronic and l-guluronic acids.[79,80] Sodium alginate, as the main component of the cell wall and extracellular matrix of brown algae, has certain mechanical strength and flexibility, which allows it to have the natural advantage for drug delivery.[81] Due to its low extraction and separation cost and good biocompatibility, sodium alginate has been increasingly used in nanomedical drug delivery systems.[82] Besides, Shilpa et al has shown that sodium alginate has the highest mucosal adhesion strength when compared with other polymers, such as CMC, polystyrene, PLA and chitosan.[83]

For the treatment of diabetes, natural peptides have been shown to exhibit excellent efficacy with fewer side effects.[84] However, due to the action of gastrointestinal digestive enzymes and rapid metabolism in the body, the delivery of natural peptides has become a thorny problem. To solve this problem, Wang et al used chitosan and sodium alginate to deliver rapeseed-derived peptides.[53] Sodium alginate was crosslinked with calcium to form a gel, and stable NPs were formed by electrostatic adsorption with chitosan under ultrasonic conditions, which could protect the polypeptides and achieve continuous drug release in the intestine (Figure 2C). The particle size was 220.2 ± 2.11 nm and ζ-potential was −39.75 mV. In Sprague Dawley rats, these NPs improved glucose tolerance, and GLP-1 levels were increased and peaked at 120 mins after administration. They also suggested that calcium-sensing receptor played an important role in regulating glucose homeostasis by these NPs.

Synthetic Polymeric Nanoparticles

Comparing to the inartificial polymers, synthetic polymers are easier to synthesize in large quantities, and there are no significant differences between batches. Synthetic polymers can also be modified according to the desired properties.[85] These nanomaterials are stable in the blood, non-toxic, non-thrombotic, non-immunogenic, non-inflammatory, non-activating neutrophils, biodegradable.[86] They can avoid the reticuloendothelial system and are suitable for encapsulating various molecules, such as drugs, proteins, peptides and nucleic acids. It is worth noting that we need to consider many factors for synthetic polymers, such as their structures, degree of deacetylation, molecular weights and solubility. The physical and chemical properties of polymers determine their absorption, distribution and metabolism in the body. The surface modified NPs have anti-adhesion properties due to the extended configuration of the particle surface, which acts as a spatial barrier, thereby reducing the clearance of circulating macrophages in the liver and increasing the possibility of enhanced osmotic processes. Besides, the release mechanism can be regulated by the molecular weight of the polymers. The higher the molecular weight of the polymers, the slower the release of the drugs.[87] Biodegradable polymers, such as PLA and their co-polymers, poly-p-dioxanone, poly(L-lactide-co-ε-caprolactone) (PLCL) and co-polymers of trimethylene carbonate and glycolide, have been used in a number of clinical applications.[88,89] Table 2 summarizes the characteristics and therapeutic effects of synthetic polymeric NPs for diabetes management.

Polylactic Acid

PLA polymer is a biocompatible and biodegradable material that breaks down into lactic acid monomer units in the body. PLA NPs are mainly prepared by solvent evaporation, solvent displacement, salting out and solvent diffusion.[94] Stevioside is an US Food and Drug Administration (FDA)-approved non-toxic, natural, non-caloric sweetener, which has been shown to display anti-diabetic activity. It regulates blood glucose levels by enhancing insulin secretion and reducing

Table 2 Synthetic Polymeric Nanoparticles for Diabetes Management

Drugs	Materials	Methods	Particle Sizes	ζ-Potential	Entrapment Efficiency	Therapeutic Effects	Ref.
Stevioside	PLA, acetone and pluronic	Precipitation method	140 ± 10 nm	–	64.40%	–	[90]
Extracts of *Tinospora cordifolia*	PLA, PVA and DCM	Double solvent evaporation	134.4 to 236.8 nm	−28 mV	–	Reduced plasma TC and TG levels, and increased HDL levels.	[91]
Curcumin	PLA-PEG and EtOAc	Emulsion-diffusion evaporation technique	117 nm	+35 mV	98.30%	Reduced blood glucose levels and improved insulin resistance.	[78]
GLP-1 and DPP-4 inhibitor	PLGA and chitosan	Water-in-oil-in-water (w/o/w) double emulsion technique	286.7 ± 5.5 nm	+34.7 ± 2.8 mV	–	Reduced blood glucose levels and improved insulin resistance.	[92]
Gliclazide	PLCL	Solvent evaporation - high pressure homogenization method	120 nm	–	60–81.37%	–	[93]

phosphoenolpyruvate carboxykinase levels.[95] However, due to its low bioavailability, poor intestinal absorption and rapid metabolism, its therapeutic effect was not obvious. Barwal et al successfully encapsulated stevioside in Pluronic-F-68-PLA NPs by the precipitation method.[90] The particle sizes were between 134.4 and 236.8 nm and ζ-potential was −28 mV. The structure of stevioside was successfully preserved without heating and ultrasonic damage during the preparation process. This study is helpful for further research on the application of stevioside for the treatment of diabetes. Similarly, PLA NPs loaded with stem extracts of *Tinospora cordifolia* was synthesized by double solvent evaporation using PLA polymer.[91] The decreased blood glucose levels in NPs-treated diabetic rats was almost similar to that in positive control (glibenclamide)-treated rats. In addition, *Tinospora cordifolia*-loaded PLA NPs also significantly reduced plasma insulin, total cholesterol and triglyceride (TG) levels, and increased high-density lipoprotein (HDL) levels when compared with diabetic group, and exerted anti-oxidant activities.

Polyethylene Glycol (PEG)

In recent years, PLA is often combined with PEG for drug delivery.[96] As we know, PEG, which is widely used due to its biodegradability and the possibility of multiple molar masses. The FDA has approved PEG for use in food, cosmetics and pharmaceuticals.[97] The use of PEG prevents NPs from being quickly recognized and cleared by the immune system, thereby prolonging the circulation time of drugs in the body. As the molecular weight of PEG increases, its blood circulation time is prolonged and PEG attachment to tissues is enhanced, which reduces renal filtration.[98] In addition, PEG with different molecular weights have been used to form additional coatings during the preparation and packaging of PLA NPs, thus the stability of the nanomaterials can be greatly improved. As PEG can form a hydration layer on the surface of the NPs, which increases its stability, reduces the direct contact between the drug and the blood, and decreases the rate of drug degradation. Besides, these coatings provide a protective barrier against widespread uptake of human monocytes.

El-Naggar et al designed and developed curcumin-loaded PLA-PEG NPs using nano-emulsification technique (Figure 2D).[78] The particle size was 117 nm and ζ-potential was +35 mV. Curcumin-loaded PLA-PEG NPs were administered orally to STZ-induced diabetic rats, it significantly reduced hyperglycemia, increased plasma insulin levels when compared with free curcumin group. It also protected the liver by reducing liver inflammation. This was through inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, down-regulating hepatic cyclooxygenase-2 (COX-2) and transforming growth factor-β (TGF-β) levels and up-regulating peroxisome proliferator-activated receptor-γ (PPAR-γ) expression.

Despite all the advantages of PEG, there are several issues that still need to be addressed. As the molar mass of the polymers increases, PEG tends to accumulate within certain organs, which must be overcome.[99,100] The second concern is the possibility of

immune responses due to complement C activation, which can lead to hypersensitivity reactions that result in anaphylactic shock. To solve these problems, the researchers made different modifications to the PEG. In the study of Moghimi et al, liposomes with a nonionic 1-O-phospholipid-mPEG conjugate were designed. They demonstrated that methylated PEG did not activate the complement in human and rat serum. This might be because methylation could prevent phosphate oxygen from binding to complement, or interfere with the complement to prevent PEG from binding to the complement.[101]

Poly(Lactic-Co-Glycolic Acid)

PLGA is a synthetic, biodegradable block copolymer obtained from lactic acid and glycolic acid, which has been approved by the FDA for human and nanomedicine use. The surface modification of PLGA, the encapsulation method and particle size of the drugs, the additive added during the preparation process, the molecular weight of the drugs, and the ratio of lactide to glycolactone have great influence on the release and effective reaction of the prepared nanomedical drugs. Due to its modified versatility, PLGA is one of the most useful synthetic, biodegradable copolymers for the design and development of controlled and targeted drug delivery systems.[102]

Silybin is a polyphenolic flavonoid isolated from Silybum marianum and Cynara scolymus with poor water solubility and bioavailability. It was formulated into chitosan-stabilized PLGA NPs.[103] These NPs were shown to reduce blood glucose levels, improve glucose tolerance, increase plasma insulin levels, improve lipid profile and liver function in STZ-induced diabetic rats when compared with free silybin. In addition to being used to deliver insoluble natural compounds, PLGA is also used to deliver peptides and proteins. A novel multifunctional composite system has been designed for the dual delivery of GLP-1 and DPP-4 inhibitor.[92] First, they prepared PLGA NPs loaded with GLP-1, and then modified PLGA NPs with chitosan and cell-penetrating peptides. Finally, it was encapsulated in a pH-sensitive polymer loaded with DPP-4 inhibitor, thus resulting in a dual-delivery composite system. The final particle size of this system was 286.7 ± 5.5 nm and ζ-potential was +34.7 ± 2.8 mV. This system demonstrated increased hypoglycemic effects and improved glucose tolerance when compared with free GLP-1-DPP-4 inhibitor solution in STZ and nicotinamide-induced diabetic rats. Blood glucose levels were reduced by 44% at 4 hours after glucose administration, and plasma insulin levels were increased at 6 hours after oral administration of this system.

Poly(L-Lactide-Co-Caprolactone)

Drugs are generally encapsulated inside polymer NPs or bound to the surface of NPs. Some studies have found that biodegradable polymer nanomaterials have a constant and slow degradation rate under fixed experimental conditions,[87] which provides a new way to solve the problem that diabetic patients who take drugs frequently to achieve good therapeutic effects. A complex of a polymer with a drug or other active agents is taken up into the cells or tissues or blood, and then the drug is released from the nanomaterial in a controlled manner under pre-designed response condition.[104] Naik et al designed a novel delivery system using PLCL as a carrier to maintain peak plasma levels of gliclazide.[93] Gliclazide was encapsulated in the PLCL NP system rather than coupling to the surface. The release of gliclazide from NPs was divided into two stages, the early rapid release occurring within 2–5 hours (up to 75–80%) and the PLCL begins to degrade at the same time. The remaining drug was released slowly over the next 26 hours.

Inorganic Nanoparticles

Metals are essential components in the body and play important roles in physiological processes, such as glucose metabolism.[105] Inorganic nanocarriers refer to the use of metals as nanocarriers in the drug delivery systems. The existing drugs have side effects and low bioavailability, and nanotechnology has emerged as a new strategy to be developed for enhancing target delivery and the bioavailability of drugs, and there are increasing interests in developing bioactive metallic NPs for the treatment of diseases. Metallic NPs can be used to deliver the drugs to target sides and reduce off-target effects, and release drugs in a low and sustained manner.[106] These metallic NPs can be synthesized by biological sources, such as bacteria, fungi, yeast and medicinal plants, and their synthesis only requires environmental-friendly solvents, good reducing and stabilizing agents, so this is regarded as green synthesis. They also have the characteristics of small size with large surface area, which help to bind to targeting agents effectively on their surface for tissue-targeting delivery. Besides, they can also penetrate into the skin, cell membrane and nucleus to deliver and release the drugs to target sites and exert biological activities, thus increasing bioavailability and reducing side effects. Table 3 summarizes the characteristics and therapeutic effects of inorganic nanocarriers for diabetes management.

Table 3 Inorganic Nanocarriers for Diabetes Management

Drugs	Materials	Particle Sizes	ζ-Potential	Therapeutic Effects	Ref.
Zinc oxide NPs and silver NPs	–	–	–	Reduced blood glucose levels and increased insulin levels, glucokinase activity and the gene expressions of insulin, insulin receptor, GLUT-2 and glucokinase.	[107]
Zinc oxide NPs	*Hibiscus sabdariffa* leaf extract	12–46 nm	–	Reduced TNF-α, IL-1β and IL-6 levels and increased IL-4 and IL-10 levels.	[108]
Zinc oxide NPs-Red sandalwood extract conjugate	Red sandalwood extract	20 nm	–	Inhibited α-amylase and pancreatic glucosidase activities.	[109]
Zinc oxide NPs	*Nigella sativa* aqueous extract, chitosan	130.2 nm	−12.6 mV	Inhibited α-amylase and α-glucosidase and exerted free radical scavenging effects.	[110]
Zinc-iron NPs	–	–	–	Reduced body weights, blood glucose levels, plasma insulin levels, adipocyte diameters, liver weights, plasma and insulin-sensitive tissue pro-inflammatory cytokine levels, and improved lipid profile and glucose tolerance.	[111]
Zinc oxide NPs, Cerium oxide NPs and silver NPs	*Momordica charantia* extract	24–55 nm	–	Decreased blood glucose levels, increased plasma insulin levels, and restored the damage of pancreatic β-cells.	[112]
Silver NPs-MECP	*Costus pictus* leaf methanolic extract (MECP)	–	–	Inhibited α-amylase and pancreatic glucosidase activities.	[113]
Silver NPs	*Rumex hymenosepalus* extract	9 nm	–	Decreased blood glucose levels and improved glucose tolerance.	[114]
Silver NPs	*Clausena anisata* extract	–	–	Inhibited α-amylase activity, glucose uptake by yeast cells and glucose diffusion, enhanced glucose adsorption capacity and free radical scavenging activity.	[115]
Silver NPs	*Phyllanthus niruri* leaf extract	55 nm	–	Improved body weights, glucose tolerance and lipid profile, and protected against the damage of pancreatic islet cells.	[116]
Silver nanorods	Berberine	672 nm	–	Reduced blood glucose levels and improved lipid profile.	[117]
Silver/gold nano-cinnamon particles	Cinnamon extract	45.34 nm	–	Reduced blood glucose levels.	[118]
Gold NPs	*Gymnema sylvestre* leaf extract	50 nm	−17.5 mV	Reduced blood glucose levels, lipid profile and serum TNF-α, IL-6 and C-reactive protein levels, and slightly restored the damage of pancreatic islet cells.	[119]
Gold NPs	Fenugreek-derived vicenin-2	90.87 nm	−6.53 mV	Enhanced glucose uptake in 3T3-L1 adipocytes.	[120]
Gold NPs	*Sargassum swartzii* extract	37 nm	–	Decreased blood glucose levels, improved lipid profile, and increased plasma insulin levels.	[121]
Gold nano-extract	*Bauhinia variegata* leaf extract	–	–	Decreased blood glucose levels along with increased insulin levels, improved lipid profile, kidney and liver functions.	[122]
Chitosan-gold NPs	Chitosan NPs	15.51 nm	–	Inhibited activities of α-glucosidase and α-amylase.	[123]
Iron III oxide/gold NPs	*Calendula persica* extract	15–25 nm	–	Decreased blood glucose levels.	[124]
Copper NPs	*Dioscorea bulbifera* tuber extract	12–16 nm	–	Inhibited α-amylase and α-glucosidase and exerted free radical scavenging activity.	[125]
Manganese dioxide NPs	Anise extract	–	–	Decreased blood glucose levels and reduced oxidative stress.	[126]
Platinum-silicon dioxide NPs	DNPME, DMF, ethanol, DSPE-PEG and cholesterol	200 nm	–	Decreased mitochondrial membrane potential and ROS levels, lowered blood glucose and TG levels, improved glucose tolerance and insulin resistance, and increased SOD activity.	[127]

Several metallic NPs were developed for the treatment of diabetes, including zinc, silver, copper and gold NPs. Zinc oxide NPs and silver NPs were used for the study of their anti-diabetic effects in STZ-induced diabetic rats.[107] Zinc is an essential metal in the body, and plays a vital role in glucose metabolism and insulin synthesis and action,[128] while silver is not involved in any physiological processes, but it displays potent anti-bacterial effects.[129] They demonstrated that both zinc oxide NPs and silver NPs could reduce blood glucose levels and increase insulin levels in diabetic rats, and zinc oxide NPs were more potent than silver NPs.[107] In the study of Bala et al, zinc oxide NPs were also synthesized using *Hibiscus sabdariffa* leaf extract, and exhibited anti-bacterial and anti-

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diabetic effects.[108] The average particle sizes were between 12 and 46 nm. They decreased blood glucose levels over the period of the study in STZ-induced diabetic mice. As T1DM is associated with pancreatic inflammation, they also showed that zinc oxide NPs significantly reduced TNF-α, IL-1β and IL-6 levels and increased IL-4 and IL-10 levels in the pancreas of diabetic mice, suggesting that they exerted protective effects against T1DM. Interestingly, zinc oxide NPs were also synthesized and conjugated with red sandalwood (RSW) extract.[109] RSW was shown to possess anti-diabetic, anti-inflammatory and antioxidant activities.[130] The average size of this zinc oxide NPs-RSW conjugate was 20 nm, and the conjugation was through the carboxylic group of the components of RSW.[109] Zinc oxide NPs showed higher inhibition of α-amylase activity than zinc oxide NPs-RSW conjugate, in contrast, this conjugate highly inhibited murine pancreatic glucosidase when compared with zinc oxide NPs, and both of them exhibited similar inhibition on murine intestinal glucosidase. These enzymes are responsible for breaking down polysaccharides into glucose, so this conjugate exhibited anti-diabetic effects. In addition, chitosan was used to coat on the surface of zinc oxide NPs for the enhancement of therapeutic efficacy.[110] Chitosan is a natural polymer that is commonly used in the drug delivery system due to its biocompatibility and bioadhesive properties, and its coating on the surface of metallic NPs could make them become more biocompatible.[131] This study used *Nigella sativa* aqueous extract to synthesize zinc oxide NPs, and then chitosan was coated on the surface of zinc oxide NPs to form NS-CS/ZnONPs.[110] The final particle size was 130.2 nm and ζ-potential was −12.6 mV. They exerted potent inhibition on α-amylase and α-glucosidase and free radical scavenging effects, demonstrating significant anti-diabetic effects. Furthermore, zinc-iron NPs were synthesized for the controlled release of hydrogen molecules (H_2) in the stomach and enhanced therapy in T2DM.[111] H_2 was shown to be an anti-inflammatory agent for inflammatory diseases such as metabolic diseases,[132] and H_2-rich water could improve glucose metabolism in T2DM patients,[133] however, there are many issues for the efficient delivery of H_2. The amount of H_2 delivered to the body by water administration is relatively low. This study firstly synthesized zinc microparticles, and then iron was added to form zinc-iron NPs (Figure 3A).[111] Oral administration of these NPs in

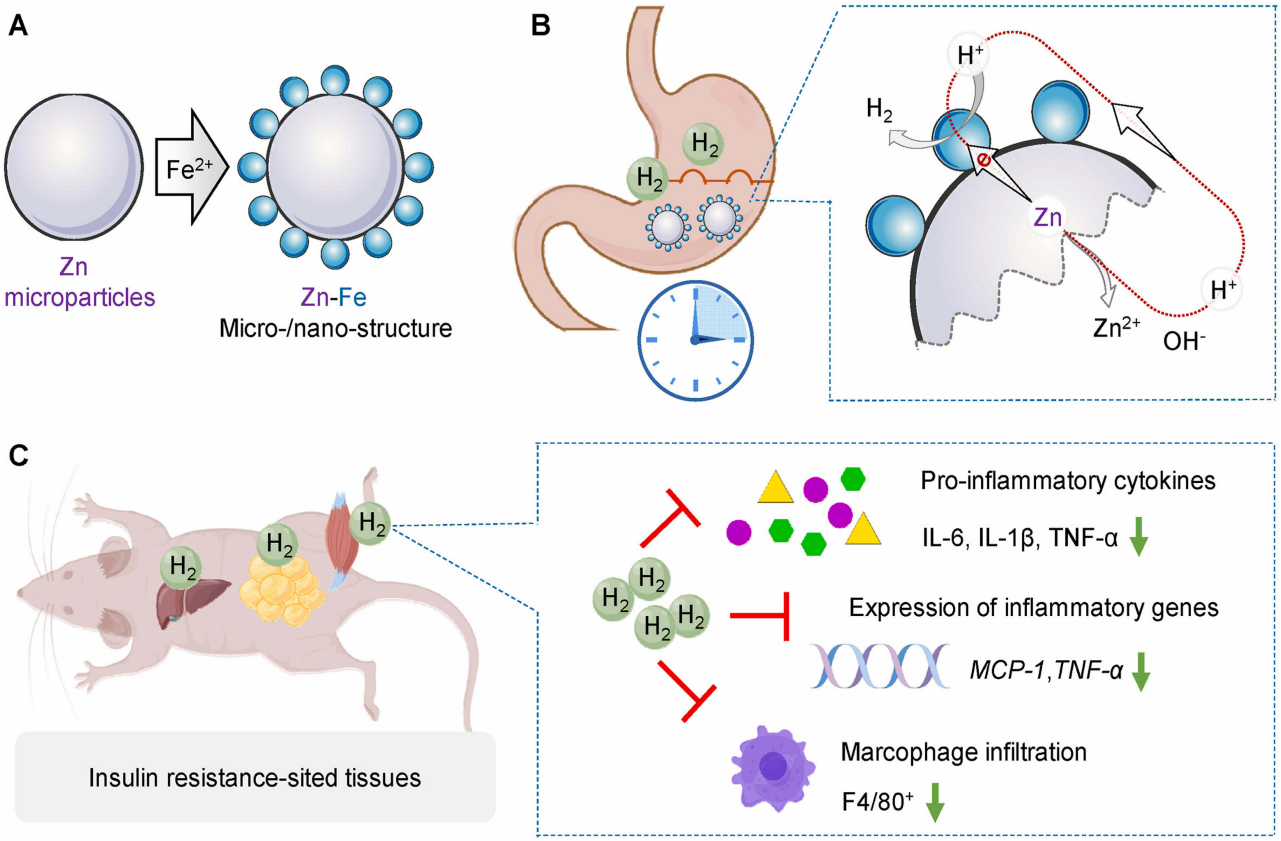

Figure 3 Inorganic nanoparticles (NPs) as drug delivery system for diabetes management. (**A**) Schematic illustration for the design of zinc (Zn)-iron (Fe) primary-battery micro-/nano-structure. (**B**) A new strategy of controlled hydrogen molecules (H_2) release to match the time window of gastric emptying for maximizing the bioavailability and therapeutic outcome of H_2. This enhanced the hydrolysis rate of Zn by constructing a Zn-Fe primary-battery micro-/nano-structure. (**C**) Schematic diagram showing the therapeutic effects of Zn-Fe micro-/nano-structure in *ob/ob* mice. Reprinted from Liu B, Lv P, Zhang X, et al. Zn-Fe primary battery-enabled controlled hydrogen release in stomach for improving insulin resistance in obesity-associated type 2 diabetes. *Bioact Mater.* 2024;33:242–250. Creative Commons[111].

water enhanced zinc hydrolysis and H_2 generation in the stomach, and then H_2 accumulation in insulin-sensitive tissues, including liver, adipose tissue and skeletal muscle (Figure 3B and C). The ratio of iron to zinc in zinc-iron NPs was 1:100, and H_2 concentrations were increased rapidly in the insulin-sensitive tissues, peaked within 20 mins and remained detectable even after 6 h of treatment. Zinc-iron NPs significantly reduced body weights, blood glucose levels, plasma insulin levels, adipocyte diameters, liver weights, plasma and insulin-sensitive tissue pro-inflammatory cytokine levels, and improved lipid profile and glucose tolerance in *ob/ob* mice. Besides, these NPs exerted no toxicity in the stomach, small intestine, liver, kidney, spleen and heart of *ob/ob* mice. They suggested that oral administration of zinc-iron NPs could be a potential strategy for the clinical use with T2DM patients. Furthermore, zinc oxide NPs, cerium oxide NPs, and silver NPs were also synthesized using the simple green synthesis method.[112] In STZ-induced diabetic rats, zinc oxide NPs, silver NPs and cerium oxide NPs reduced blood glucose levels and increased plasma insulin levels. Zinc oxide NPs and silver NPs demonstrated better anti-hyperglycemic effects than cerium oxide NPs. In addition, silver NPs also showed a better effect of restoring the damage of pancreatic β-cells.

In addition to zinc oxide NPs, silver NPs were also synthesized using the methanolic extract of *Costus pictus* leaves (MECP) for enhancing the dissolution rates and bioavailability of MECP.[113] These silver NPs of MECP (MECPAgNPs) were shown to possess better anti-diabetic activities than MECP, including α-glucosidase and α-amylase inhibition. MECPAgNPs also enhanced the inhibition of glucose uptake in yeast cells when compared with MECP. Similarly, silver NPs with small particle size of 9 nm were synthesized using *Rumex hymenosepalus* extracts as reducing agents and exhibited decreased blood glucose levels in STZ-induced diabetic rats.[114] They also improved glucose tolerance in diabetic rats, demonstrating anti-hyperglycemic effects. Moreover, silver NPs were also synthesized using the ethanolic root extract of *Clausena anisata*.[115] They exerted a dose-dependent inhibition on α-amylase activity, glucose uptake by yeast cells and glucose diffusion, enhancement in glucose adsorption capacity, and free radical scavenging activity, suggesting that it could be a therapeutic agent for diabetes. In addition, silver NPs with particle size of 55 nm were also synthesized using the ethanolic extract of *Phyllanthus niruri* leaves.[116] Their anti-diabetic effects were examined in STZ-induced diabetic rats. These silver NPs significantly decreased blood glucose levels, improved body weights, glucose tolerance and lipid profile, and protected against the damage of pancreatic islet cells in diabetic rats, suggesting that they have potent anti-diabetic effects. Furthermore, a study used a natural compound instead of plant extract to synthesize NPs. Berberine was used as a capping and reducing agent to synthesize silver nanorods.[117] Berberine is a major component that can be found in Chinese medicine and has high reducing ability with anti-diabetic effects.[134] These silver nanorods reduced blood glucose levels and improved lipid profile in STZ-induced diabetic rats, demonstrating a therapeutic agent for diabetic treatment[117].

Gold is not an essential metal in the body, but it is non-toxic and plays an important role in health function. It has been used in medicine with various forms, such as gold NPs, for enhancing the therapeutic effects of drugs. A study used the aqueous extract of *Gymnema sylvestre* leaves to synthesize gold NPs with particle size of 50 nm, demonstrating high colloidal stability.[119] These gold NPs reduced blood glucose levels, lipid profile and serum TNF-α, IL-6 and C-reactive protein (CRP) levels in alloxan-induced diabetic rats, and slightly restored the damage of pancreatic islet cells, so they exerted anti-diabetic and anti-inflammatory effects in diabetic rats. Another study used fenugreek-derived vicenin-2, an apigenin-6,8-di-C-glycoside,5,7,4'-trihydroxyfiavone-6,8'-di-C-glucoside, to synthesize gold NPs.[120] Vicenin-2 can be found in various plants, such as fenugreek. Vicenin-2-gold NPs exhibited no toxicity at concentrations of 30 μM or below and enhanced glucose uptake in 3T3-L1 adipocytes. They also examined the molecular drug targets by molecular docking analysis and found protein tyrosine phosphatase 1B (PTP1B) and AMP-activated protein kinase (AMPK) as potential targets for vicenin-2. Both of these targets are involved in insulin signaling pathway, so they proposed that vicenin-2 could act as a negative regulator of PTP1B or positive regulator of AMPK for insulin signaling. Moreover, gold NPs with particle size of 37 nm were synthesized using *Sargassum swartzii* extract.[121] They decreased blood glucose levels and lipid profile and increased plasma insulin levels in alloxan-induced diabetic rats. The plasma pro-inflammatory marker levels, TNF-α, IL-6 and CRP, were significantly alleviated, and the hepatic enzyme levels were elevated. Meanwhile, they also protected against pancreatic, liver and kidney damage caused by alloxan, demonstrating potent anti-diabetic effects. In addition, silver/gold nano-cinnamon particles were synthesized using cinnamon extract for the study of STZ-induced diabetes.[118] These NPs consisted of 97.32% silver and 2.68% gold in weights. There was no significant difference in body weights of diabetic rats between cinnamon extract and silver/gold nano-cinnamon particles, however, blood glucose levels were significantly lowered in the nano-cinnamon particles-treated group when compared with cinnamon extract-treated group, suggesting that these NPs were more potential

than the cinnamon extract in the management of hyperglycemia. Interestingly, Abdel-Halim et al used *Bauhinia variegata* leaf extract to synthesize gold NPs and then used these gold NPs to encapsulate this extract to form gold nano-extract.[122] *Bauhinia variegata* was shown to possess several pharmacological effects, such as anti-inflammatory and anti-diabetic effects.[129] The gold nano-extract decreased blood glucose levels along with increased insulin levels, improved lipid profile, kidney and liver functions, and exhibited antioxidant activity in STZ-induced diabetic rats when compared with *Bauhinia variegata* leaf extract treatment, suggesting that the gold nano-extract has enhanced the therapeutic efficacy of *Bauhinia variegata* leaf extract.[122] Moreover, nano-chitosan capped gold NPs were synthesized using chitosan NPs as a reducing agent, and chitosan NPs were coated on the surface of gold NPs to form CS-AuNPs with particle size of 15.51 nm.[123] The composition of CS-AuNPs was 78.02% gold and 21.98% chitosan. The CS-AuNPs exhibited higher free radical scavenging activities and inhibition on α-glucosidase and α-amylase activities than chitosan NPs, thus revealing its potential role in anti-diabetic effects. Furthermore, iron III oxide/gold magnetic NPs were also developed.[124] Iron III oxide NPs were firstly synthesized using *Calendula persica* extract, which made a polar environment surrounding iron III oxide, and then gold was added on the surface of iron III oxide to form iron III oxide/gold NPs with particle sizes between 15 and 25 nm. These NPs reduced blood glucose levels, liver weights and its parameters, including alanine transaminase (ALT) and aspartate aminotransferase (AST), in STZ-induced gestational diabetic rats, suggesting that they could protect against gestational diabetes.

Copper is an essential element in the body and plays crucial roles in many physiological processes, including energy metabolism and tissue synthesis.[135] Ghosh et al demonstrated that copper NPs were rapidly synthesized using the aqueous extract of *Dioscorea bulbifera* tubers.[125] The particle sizes were in the range of 12 to 16 nm. They were shown to inhibit α-amylase and α-glucosidase activities and exert free radical scavenging effects, including 2.2-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide and superoxide, suggesting that they have anti-diabetic and antioxidant activities. In contrast, selenium NPs did not decrease blood glucose levels in STZ-induced diabetic nephropathy rats, but they possessed antioxidant activities and protected against diabetic nephropathy.[136] In addition, manganese is also an essential metal in the body, as it plays a vital role in human growth and development and regulates glucose and lipid metabolism.[137] Farhan & Mohammed synthesized manganese dioxide NPs using anise extract for the study for antioxidant and anti-diabetic activities.[126] These NPs exerted potent inhibitory activity on free radicals and reduced blood glucose levels in alloxan-induced diabetic rats, so they exhibited antioxidant and anti-hyperglycemic effects.

People with T2DM have elevated levels of reactive oxygen species (ROS), which result in insulin resistance and affect cellular glucose metabolism. Zhang et al designed liver-targeted NPs, which restored liver function by reducing oxidative stress to improve liver insulin resistance.[127] Platinum (Pt) nanozymes possess high catalytic stability in scavenging ROS. However, due to the small size of Pt nanozymes, it is not easy to enrich in the liver, so they used silicon dioxide (SiO_2) as a nanocarrier to load Pt nanozymes and obtain Pt-SiO_2 for the purpose of liver-targeted therapy. Besides, they also loaded mitochondrial uncoupling agent 2.4-dinitrophenol-methyl ether (DNPME) to reduce mitochondrial membrane potential, thus reducing ROS production. To prevent DNPME from leaking out as it circulates throughout the body, these NPs are also coated with lipids to form D@Pt-SiO2@L with particle size of 200 nm. These NPs showed good ROS clearance and reversed hyperglycemia-induced insulin resistance in HepG2 cells. In HFD + STZ-induced diabetic mice, D@Pt-SiO2@L treatment showed better liver targeting, improved glucose tolerance and insulin sensitivity, increased the phosphorylation of AMPK and SOD activity, and reduced blood glucose levels and TG levels.

Lipid-Based Nanosystems

Lipids are an extremely important class of components in the body. Besides from storing energy and participating in metabolism, lipids are also an essential component of the cell membrane.[138] They have a special amphiphilic structure, including two hydrophobic fatty acid tails and a hydrophilic phosphate group. The amphiphilicity of lipids makes it useful for delivering both hydrophilic and insoluble lipophilic drugs. In addition, they also have good biocompatibility, low toxicity and modifiability.[139] These characteristics make lipids to be one of the most popular carriers in nano-based drug delivery systems. In fact, several lipid NPs have been successfully developed over the past two decades,[138] including nanoemulsion, liposomes, solid lipid NPs (SLNs) and nanostructured lipid carriers (NLCs). Table 4 summarizes the characteristics and therapeutic effects of lipid-based nanosystems for diabetes management.

Table 4 Lipid-Based Nanosystems for the Management of Diabetes

Drugs	Materials	Methods	Particle Sizes	ζ-Potential	Entrapment Efficiency	Therapeutic Effects	Ref.
Resveratrol	Cholesterol, DPPC and DC-CHOL	Film water method	240 ± 30 nm 110 ± 10 nm	−10 ± 3 mV +56 ± 8 mV	–	–	[140]
Resveratrol	DPPC, cholesterol	Film water method	215 ± 4 nm	−45.3 ± 2.1 mV	45.3 ± 2.1%	Protected pancreatic β-cells and improved oxidative stress.	[141]
Resveratrol and curcumin	Precirol ATO 5, palmitic acid, TMC, Gelucire 50/13 and Tween 80	Emulsification and ultrasonication method	100.05 ± 13.74 nm258.28 ± 18.74 nm	−19.06 ± 0.41 mV 20.79 ± 0.63 mV	95.45 ± 2.18% 95.45 ± 2.18%	Improved the bioavailability of the drug.	[142]
Betanin	Lecithin and ethanol	Film water method	40.06 ± 6.21 nm	−17.04 ± 2.03 mV	80.35 ± 1%	Released drug in a slow manner in vitro, reduced blood glucose levels, improved hyperlipidemia and decreased oxidative stress.	[143]
sgRNA	Lecithin, cholesterol, DOGS-NTA-Ni and chloroform	Film water method	220.2 nm	−14.6 mV	95%	Decreased DPP-4 enzyme activity, reduced blood glucose levels and liver and kidney damage, and improved insulin resistance.	[144]
Repaglinide	Oleic acid, isopropyl myristate, glycerol triacetate, caproyl 90, propylene glycol monocaprylic ester, propylene glycol laurate, and labrafac	Titration method	76.23 nm	–	–	Reduced blood glucose levels.	[145]
Fenugreek oil	Fenugreek oil, Tween 80 and water	Emulsion phase inversion and emulsion titration method	–	–	–	Reduced blood glucose levels and decreased LDL levels.	[146]
Quercetin	Castor oil, Capryol 90, oleic acid, Labrafil M 1944 CS, Labrafac PG, Tween 20, Tween 80, Labrasol, and Span 80, Transcutol HP, Cremophor EL, PEG 400, and Plurol Oleique CC	Titration method	19.3 ± 0.17 nm	+0.34 ± 0.13 mV	–	Increased intestinal absorption and oral bioavailability, improved pharmacokinetics, reduced body weights, adipose tissue weights, exhibited no hepatotoxicity and prevented the development of fatty liver.	[147]
Berberine	Sodium caprate, linoleic acid, isopropyl myristate, Brij-98, Poloxamer 407 and ethanol	Stirring method	30.56 ± 0.35 nm	−0.01 ± 0.02 mV	–	Reduced the efflux of P-glycoprotein and blood glucose levels, and improved bioavailability.	[148]
Extract of the *Talinum portulacifolium* leaves	Ethanol and Tween 80	Ultrasonic homogenization	260 nm	−27.7 mV	–	Reduced blood glucose levels, serum insulin, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lipid peroxidase, catalase and glutathione levels.	[149]
Gliclazide	Poloxamer 188, trehalose di-hydrate and Glyceryl behenate	Emulsification and ultrasonication method	245.9 ± 26.2 nm	–	72–82%	Reduced blood glucose levels.	[150]

(*Continued*)

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Table 4 (Continued).

Drugs	Materials	Methods	Particle Sizes	ζ-Potential	Entrapment Efficiency	Therapeutic Effects	Ref.
Pioglitazone	Fatty acids, oil, Tween 20 and Span 40	Solvent emulsification evaporation method	152 nm	−16.6 to −27.15 mV		Increased permeability and release time in vivo.	[151]
Baicalin	Chloroform, ethanol and pluronic	High pressure homogenization	92 ± 3.1 nm	−31.35 ± 3.08 mV	85.29 ± 3.42%	Reduced blood glucose, TG and TC levels.	[152]
Silymarin	Cetyl palmitate, Lauroroglycol 90 and Brij S20	Emulsion/ evaporation/ curing method	265.9 ± 13.4 nm	−34.5 ± 8.1 mV	93.2 ± 4.6%	Reduced blood glucose and TG levels, protected liver structure and function.	[153]

Liposomes

Liposomes are usually composed of a phospholipid bilayer and an internal hydrophobic region. Typically, hydrophobic drugs are encapsulated in a lipophilic double layer of the shell, while hydrophilic drugs are embedded in the water phase of the nucleus.[154] Many methods have been developed to prepare liposomes, including injection, microfluidic-based, and film water methods.[155]

As common T2DM drugs, metformin and glimepiride have poor absorption and bioavailability.[156,157] In the study of Nomani & Govindasamy, the membrane material of phospholipid and cholesterol liposome was prepared by ethanol injection method, and this allowed both drugs to be captured in the liposomes.[158] These liposomes were shown to be released slowly at relatively low doses over a longer duration. In contrast to these synthetic drugs, anti-diabetic drugs isolated from natural plants are more difficult to use in clinical treatment.[159] Resveratrol, a potent antioxidant found in grapes and berries, has anti-diabetic effects by reducing oxidative stress, lowering blood glucose levels, and protecting the pancreatic β-cells.[160,161] As a natural product, resveratrol has the disadvantages of poor water solubility, short half-life and fast metabolism.[162] Bonechi et al prepared resveratrol-loaded liposomes by using saturated phosphatidyl-choline and cholesterol.[140] They used both mouse fibroblast tumor NIH3T3 cells and human U373-MG astrocytes to verify that resveratrol-loaded liposomes did not affect the cell viability. In the study of Yücel et al, multilayer anionic liposomes loaded with resveratrol were prepared by thin film water method and were able to maintain structural stability within three weeks.[141] The particle size was 215 ± 4 nm and ζ-potential was −45.3 ± 2.1 mV. These liposomes were able to prolong the release of resveratrol in pancreatic β TC cells. After treatment with liposomes, the glucose levels were significantly reduced and insulin levels were significantly increased in β TC cells of glucose- and STZ-induced diabetic groups. These results were well explained by the changes in the activity of antioxidant enzymes, glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), indicating that they reduced oxidative stress by enhancing the activity of antioxidant enzymes, thereby protecting β-cells and exerting anti-diabetic effects. In addition, betanin has poor oral absorption and extremely low bioavailability, so it was prepared into nanoliposomes by thin film water method.[143] Betanin-loaded nanoliposomes with particle size of 40.06 ± 6.21 nm and ζ-potential of −17.4 ± 2.03 mV were developed, and displayed a prolonged release profile.[143] The blood glucose levels were significantly reduced and insulin levels were increased in the nanoliposome group of STZ-induced diabetic rats. It is worth mentioning that the insulin levels of free betanin group did not differ significantly from that of the model group. The lipid and liver profiles were also improved in the nanoliposome group. This suggested that liposomal encapsulation improved the therapeutic effects of oral betanin, which was possibly due to reduced betanin degradation in the stomach and enhanced its intestinal absorption.

To treat diabetes effectively, researchers have explored various approaches. Among these, gene editing therapy, an advanced technology, has been extensively investigated.[163] However, due to its instability and limited efficacy, its practical use remains constrained. GLP-1, a crucial hormone stimulating insulin secretion, plays a key role in diabetic management.[164] One therapeutic strategy employed involved the inhibition of the activity of DPP-4, an enzyme responsible for GLP-1 degradation. Cho et al proposed using liposomes loaded with CRISPR associated protein 9 (Cas9) complexes for gene editing.[144] These liposomes encapsulated Cas9 and single-stranded guide RNA (sgRNA) targeting DPP-4 (Figure 4A). By electrostatic interactions between positively charged cationic lipids and negatively

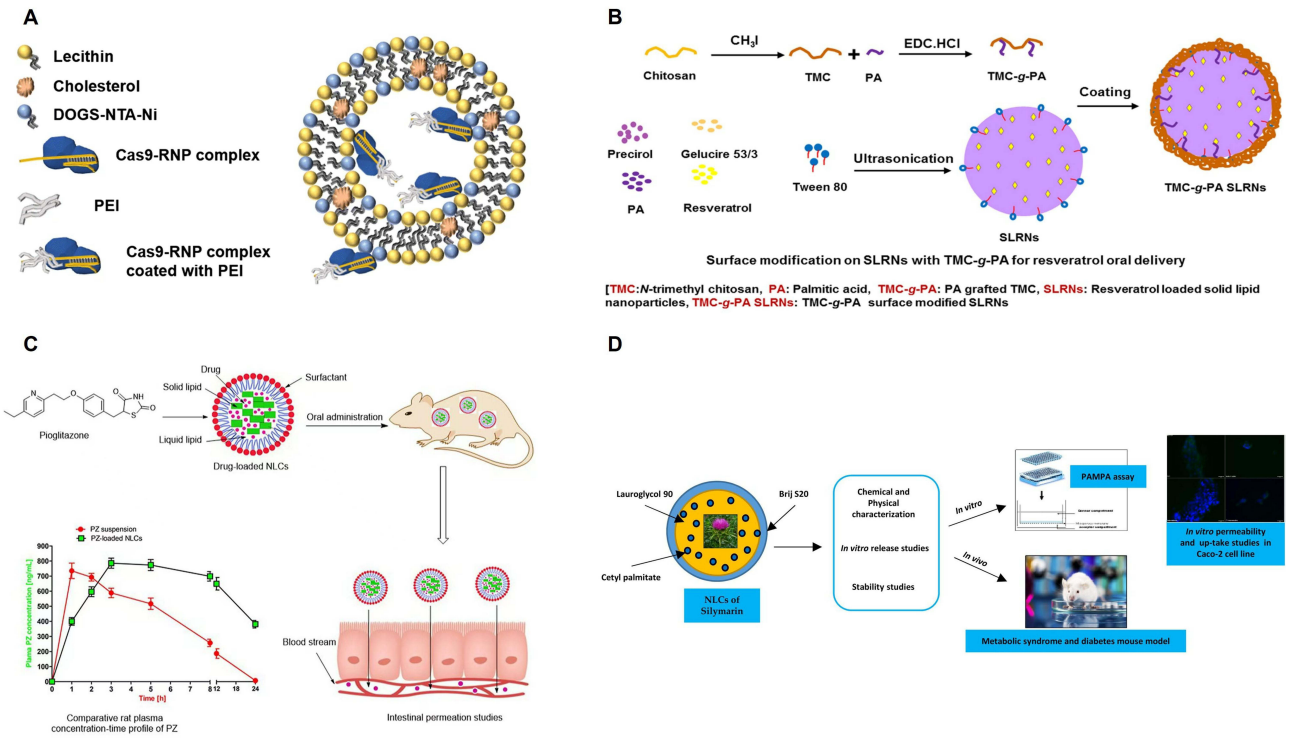

Figure 4 Lipid-based nanosystems for the management of diabetes. (**A**) Schematic diagram showing nanocarrier primarily consisting of lecithin that could efficiently target liver disease and encapsulated complexes of Cas9 with single-stranded guide RNA (sgRNA) ribonucleoprotein (Cas9-RNP) through polymer fusion self-assembly. Adapted from Cho EY, Ryu J-Y, Lee HAR, et al. Lecithin nano-liposomal particle as a CRISPR/Cas9 complex delivery system for treating type 2 diabetes. *J Nanobiotechnol*. 2019;17:1–12. Creative Commons.[144] (**B**) Schematic illustration of the design of resveratrol-loaded N-trimethyl chitosan-g-palmitic acid surface-modified solid lipid nanoparticles. Adapted from *Colloids Surf B*, volume 139, Ramalingam P, Ko YT. Improved oral delivery of resveratrol from N-trimethyl chitosan-g-palmitic acid surface-modified solid lipid nanoparticles. 52–61. Copyright 2016, with permission from Elsevier.[142] (**C**) Schematic diagram showing the design of pioglitazone-loaded nanostructured lipid carriers in improving the bioavailability of pioglitazone. Adapted from *J Drug Delivery Sci Technol*, volume 79, Faiz S, Arshad S, Kamal Y, et al. Pioglitazone-loaded nanostructured lipid carriers: in-vitro and in-vivo evaluation for improved bioavailability. 104041, copyright 2023, with permission from Elsevier.[151] (**D**) Schematic diagram showing the delivery of silymarin via a nanostructured lipid carrier (NLC) and its therapeutic effects in diabetic mice. Adapted from *Int J Pharm*, volume 572, Piazzini V, Micheli L, Luceri C, et al. Nanostructured lipid carriers for oral delivery of silymarin: improving its absorption and in vivo efficacy in type 2 diabetes and metabolic syndrome model. 118838, copyright 2019, with permission from Elsevier.[153]

charged complexes, they achieved successfully through polymer fusion self-assembly. The final particle size was 220.2 nm and ζ-potential was −14.6 mV. These liposomes were injected directly into *db/db* mice to disrupt the DPP-4 gene expression. They successfully induced gene deletion of 18 base pairs at the DPP-4 locus. In human hepatoma SNU398 cells, the uptake of the liposomes did not cause any cellular toxicity and stresses. The DPP-4 protein and mRNA levels were significantly reduced in the liver of liposome-treated *db/db* mice when compared with untreated *db/db* mice, while the blood GLP-1 levels were significantly increased. These results were accompanied by the improvement in glucose tolerance, insulin sensitivity, and reduced kidney and liver damage in *db/db* mice, suggesting superior diabetic treatment using gene-editing capable liposomes.

Nanoemulsion

Nanoemulsion is a kind of NP preparation that is composed of two immiscible liquids under the stable action of a small amount of surfactant. Common nanoemulsions include oil in water, water in oil, and multiple nanoemulsions.[165] As a class of nano-formulations, nanoemulsions can coat the drugs and effectively protect them from hydrolytic enzymes, or harsh pH and other environmental conditions, thus providing many opportunities to improve the oral bioavailability of strong lipophilic drugs.

Repaglinide is an effective second-generation oral hypoglycemic drug that is widely used to treat diabetes.[166] It works by stimulating the release of insulin from pancreatic β-cells. Due to its extremely short half-life and poor bioavailability, patients need to take it frequently. Akhtar et al developed nanoemulsion loaded with repaglinide, which was prepared by

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titration using lipids, water and Tween 80 as raw materials.[145] The particle size was 76.23 nm. The therapeutic effects were verified in STZ-induced diabetic rats, and the nanoemulsion showed hypoglycemic effects.

Fenugreek oil is a volatile oil component extracted from fenugreek, which has a variety of pharmacological functions. It has been reported to treat diabetes by restoring blood glucose levels, glucose intolerance, and insulin sensitivity.[167] Hassan & Mujtaba prepared nanoemulsion with fenugreek oil, water and Tween 80.[146] Oral fenugreek oil nanoemulsion treatment showed stronger ability to lower blood glucose and low-density lipoprotein (LDL) cholesterol levels, and increase HDL levels in STZ-induced diabetic rats. In addition, an effective quercetin-loaded oral delivery system was designed to improve its solubility and bioavailability, thereby enhancing its anti-obesity effect.[147] Oil-in-water nanoemulsion loaded with quercetin was prepared by aqueous phase titration. Quercetin-loaded nanoemulsion significantly enhanced in vitro artificial intestinal membrane permeability and Caco-2 cell monolayer permeability. It also effectively reduced the body weight and white adipose tissue weights of HFD-fed mice, and prevented from the development of fatty liver. Furthermore, berberine is a common natural product used to treat diabetes. Several studies loaded berberine into NPs to improve its low permeability and reduce its massive elimination in the gut, thereby increasing bioavailability. Berberine was prepared as nanoemulsion to improve its hypoglycemic effects.[148] Berberine nanoemulsion prevented the degradation of berberine by intestinal enzymes and increased intestinal permeability and oral bioavailability. After four weeks of oral administration, it was found that the blood glucose levels were reduced by 3 times in the nanoemulsion-treated group when compared with the free berberine group of HFD and STZ-induced diabetic mice, and their liver functions were also improved.

Solid Liposome Nanoparticles (SLNs)

SLNs are gradually developing as a more advanced technique on nanoliposome preparation.[168] Unlike the lipid bilayer ring of the nanoliposomes, SLNs may not have a continuous bilayer structure, and are solid particles at room temperature. They also have excellent biocompatibility, targeting and slower release properties. In addition, SLNs have better physical and chemical stability than nanoliposomes. High shear homogenization, high pressure homogenization and solvent emulsification technology are commonly used for SLN preparation.

The leaves of *Talinum portulacifolium* are mainly located in the regions of South Africa and America and have anti-diabetic effects.[169] In the study of Bindu et al, ethanol extracts obtained from fresh plants were prepared into SLNs with particle size of 260 nm and ζ-potential of −27.7 mV by ultrasonic homogenization.[149] These SLNs were found to be safe when administered orally in the rats. After SLN administration, the hypoglycemic effect was significantly enhanced and even close to that of the positive drug group, and the lipid profile was also improved. It is worth mentioning that the poor stability and sudden release behavior of SLNs under acidic pH conditions lead to increased aggregation of NPs in the gastrointestinal environment, thus limiting drug delivery. To solve these problems, the researchers tried to modify the structure of SLNs. In Ramalingam & Ko study, N-trimethyl chitosan grafted with palmitic acid was used to add a coating to the surface of resveratrol-loaded SLNs (Figure 4B).[142] These SLNs enabled sustained drug release, protect their structure from being destroyed by stomach acid and increase their absorption time in the gastrointestinal tract, thus enhancing their bioavailability. Oral administration of these resveratrol-loaded SLNs resulted in a 3.8-fold increase in the oral bioavailability of resveratrol.

Nazief et al designed SLNs that were loaded with gliclazide.[150] SLNs were prepared by ultra-sonication technique and used glyceryl behenate as the lipid portion. To protect the structure of the SLNs, they also adopted trehalose dihydrate as a cryo-protectant to freeze dry SLNs. The average particle size of these SLNs was 245.9 ± 26.2 nm. Gliclazide-loaded SLNs exhibited prolonged drug release when compared with the gliclazide commercial immediate release tablets (Diamicron®). Besides, gliclazide-loaded SLNs increased 5 times in bioavailability than gliclazide powder. In HFD and STZ-induced diabetic rats, SLNs decreased blood glucose levels when compared with gliclazide powder, thus demonstrating better hypoglycemic effects.

Nanostructured Lipid Carriers (NLCs)

The development of SLNs is used to overcome the limitations of other colloidal carriers, and SLNs have the advantages of better release curves and excellent physical stability. However, SLNs have low drug loading efficiency and limitations. Therefore, NLCs, the second generation of SLNs, were developed. NLCs are modified SLNs that improve the stability and loading capacity.[170] In contrast to SLNs, NLCs are characterized by the lipid phase that contains both solid and liquid

lipids at room temperature. It presents as a mixture of solid and liquid phases (oil) to form an amorphous matrix, which improves the stability and loading capacity.

In the study of Faiz et al, pioglitazone nanostructured lipid carrier was prepared by solvent emulsion evaporation method.[151] The average particle size of pioglitazone-loaded NLCs was 152 nm and polydispersity index (PDI) was 0.19. Drug entrapment efficiency and loading capacity were shown to be 83% and 5.8%, respectively. Osmosis studies showed enhanced permeability of pioglitazone, and in vivo studies confirmed its enhancement in bioavailability. In the study of Shi et al, baicalin was prepared into NLCs by high pressure homogenization and administered orally in HFD and STZ-induced diabetic rats (Figure 4C).[152] This NLC was composed of Precirol as the solid lipid, Miglyol as the liquid lipid, and Pluronic as the surfactant. The particle size of was 92 ± 3.1 nm and ζ-potential was −31.35 ± 3.08 mV. Baicalin was shown to be released from NLC in a sustained manner. Besides, the levels of blood glucose, TG and TC in NLC-treated group were much lower than that of free baicalin and diabetic groups. Moreover, Piazzini et al prepared silymarin-loaded NLCs by emulsion/evaporation/solidifying method to improve the bioavailability of silymarin (Figure 4D).[153] The particle size was 265.9 ± 13.4 nm and ζ-potential was −34.5 ± 8.1 mV. This NLC was composed of cetyl palmitate as the solid lipid, Lauroroglycol 90 as the liquid lipid, and Brij S20 as the surfactant. They also used freeze-drying method to prolong the stability of these NLCs. The uptake of silymarin-loaded NLCs by Caco-2 cells was shown to be mainly through caveolae-dependent endocytosis pathway. In addition, the levels of blood glucose, triglyceride and TC were reduced in silymarin-loaded NLCs group of HFD and STZ-induced diabetic mice, indicating better anti-diabetic effects. This treatment also protected against the development of fatty liver in diabetic mice.

Nanosuspensions

Drug nanosuspensions are a common form of drug delivery systems that is used to improve drug solubility and bioavailability. Nanosuspensions refer to the colloidal dispersion of nano-drug particles stabilized by surfactants and can also be defined as a two-phase system where non-soluble drugs are dispersed in aqueous solutions, and the particle size of the drug-suspended NPs is within 1 μm.[171] The preparation method of nanosuspensions is simple, which is suitable for drugs that are difficult to dissolve in water thus improving their stability and bioavailability. It is often prepared by wet grinding method, high pressure homogenization method, emulsifying solvent evaporation and super-critical fluid.[171,172] Nanosuspensions have been widely used for treatment of diabetes. Studies have prepared different nanosuspensions, including glibenzide nanosuspensions,[173] repaglinide suspensions,[174,175] curcumin suspensions,[176–178] trans-resveratrol suspensions,[179] and naringenin suspensions.[180] Table 5 summarizes the characteristics and therapeutic effects of nanosuspensions for diabetes management.

Table 5 Nanosuspensions for the Management of Diabetes

Drugs	Materials	Methods	Particle Sizes	ζ-Potential	Therapeutic Effects	Ref.
Repaglinide	Methanol, poloxame and Tween 80	Solvent evaporation method	–	–	Reduced blood glucose levels, facilitated the continuous release of the drug.	[174]
Curcumin	Acetone, PVP-K30 and SDS	Antisolvent precipitation method	105.3 ± 4.67 nm	−32.7 ± 2.45mV	Enhanced drug uptake in HepG2 cells and improved bioavailability.	[176]
Curcumin	Chloroform, and Tween 80	Solvent evaporation method	333 ± 6 nm	−26.1 mV	Reduced blood glucose levels, improved glucose tolerance and lipid profile, and increased pancreatic SOD and GSH activities.	[177]
Curcumin	Sodium bicarbonate buffer	Ultrasonic assisted ball grinding method	–	–	Reduced serum triacylglycerol, CK-MB, LDH and AST levels.	[178]
Gliclazide	Acetone, lecithin and SDS	Solvent-antisolvent precipitation method	96.49 ± 15 nm	−22 ± 5.6 mV	Improved drug dissolution, enhanced effective intestinal permeability in vitro, and reduced blood glucose levels.	[181]
Glibenclamide	Chloroform, PVP and Tween 80	Nanoprecipitation technique	216 nm	+9 to 26 mV	Reduced blood glucose levels.	[182]

(*Continued*)

Table 5 (Continued).

Drugs	Materials	Methods	Particle Sizes	ζ-Potential	Therapeutic Effects	Ref.
Berberine	D-α-tocopheryl polyethylene glycol 1000 succinate and hypromellose	High pressure homogenization technology	72.4 nm	+6.95 mV	Reduced body weights, blood glucose and TC levels.	[183]
Ursolic acid	Ethanol, acetone and PVA	Nanoprecipitation method	246.4 ± 4.21 nm	−31.2 ± 5.17 mV	Lowered blood glucose levels and serum TG and TC levels, improved liver and kidney pathology.	[184]
Betulin	Ethanol and Tween 80	Solvent-anti-solvent precipitation method	110 nm	–	Improved dissolution and bioavailability, reduced blood glucose levels.	[185]
Araucaria angustifolia pinhão seed coat	–	Microfluidic method	–	–	Lowered weight gain, blood glucose levels, and serum TG and TC levels.	[186]
Terminalia arjuna bark extract	Ethanol and polysorbate	Nanoprecipitation approach	90.53 nm	−15.7 mV	Improved the dissolution rate and bioavailability.	[187]

Drug nanosuspensions were shown to have better therapeutic effects for the treatment of diabetes. In the study of Hemalatha et al, repaglinide nanosuspension was developed to enhance the oral bioavailability of repaglinide, a T2DM drug.[174] Repaglinide was dissolved in aqueous solvent for the preparation of repaglinide nanosuspension. This nanosuspension significantly reduced blood glucose levels when compared with repaglinide in alloxan-induced diabetic rats, suggesting that it enhanced therapeutic effects. Similarly, repaglinide nanosuspension was prepared in aqueous solutions with stabilizer and surfactants using microfluidics technology and was found to increase water solubility.[175] This nanosuspension also reduced blood glucose levels, increased body weights and improved lipid profile in STZ-induced diabetic rats. At 28 days of treatment, plasma insulin levels and antioxidant enzyme levels were increased, liver biomarkers were decreased, suggesting that this preparation could enhance therapeutic efficacy. In addition, gliclazide is an anti-diabetic drug with high first-pass metabolism and low water solubility. In order to resolve these issues, gliclazide nanosuspension was prepared using the solvent-antisolvent precipitation method.[181] This nanosuspension showed better hypoglycemic effects than free gliclazide and commercial formulation. Another T2DM drug, glibenclamide, is poorly water-soluble, exhibits poor bioavailability following oral administration and is classified as BSC class II drug.[188] As it has high first-pass metabolism, Hashem et al designed a glibenclamide nanosuspension for inhaler administration.[182] The glibenclamide nanosuspension inhaler was shown to reduce blood glucose levels by 60% in STZ-induced diabetic rats when compared with oral glibenclamide, demonstrating better therapeutic effects.

Polyphenols have relatively low bioavailability as they could interact with the food matrix and metabolize by the liver.[189] Curcumin is a polyphenol that can be isolated from the rhizomes of *Curcuma longa*. It has various pharmacological effects, including anti-diabetic effects. It has a good safety profile, but its clinical use is limited due to poor water solubility and bioavailability.[190] Li et al developed curcumin nanosuspension to enhance its solubility, bioavailability and anti-diabetic effects.[176] Curcumin was dissolved in acetone solution to form an organic phase, and then this organic phase was added to distilled water to form curcumin nanosuspension with particle size of 105.3 ± 4.67 nm and ζ-potential of −32.7 ± 2.45mV. This nanosuspension enhanced drug uptake in HepG2 cells and increased bioavailability. Similarly, curcumin-loaded pluronic nanomicelles were also synthesized with particle size of 333 ± 6 nm and ζ-potential of −26.1 mV.[177] They reduced blood glucose levels, improved glucose tolerance and lipid profile, and increased pancreatic antioxidant enzymes SOD and glutathione (GSH) activities in STZ-induced diabetic rats. However, it did not increase serum insulin levels, but slightly up-regulated insulin gene expression. They also found that the anti-diabetic effects of curcumin nanosuspension were suggested to be through the up-regulation of pancreatic duodenal homeobox-1 (Pdx-1) and NK6 homeobox 1 (Nkx6.1). Another curcumin nanosuspension was also developed for the study of anti-diabetic effects.[178] This nanosuspension did not alter body

weights, blood glucose levels and serum insulin and cholesterol levels in STZ-induced diabetic rats. However, it reduced serum triacylglycerol, creatine kinase-myocardial band (CK-MB), lactate dehydrogenase (LDH) and AST levels when compared with diabetic rats, suggesting that this nanosuspension exhibited only limited therapeutic effects. In the study of Wang et al, berberine was prepared into nanosuspension using high pressure homogenization technology.[183] The particle size of the berberine nanosuspension was 72.4 nm and ζ-potential was +6.95 mV. Mice treated with berberine nanosuspension showed lower fasting blood glucose levels in STZ-induced diabetic mice when compared with free berberine administration, demonstrating enhanced therapeutic effects. In addition, ursolic acid, another polyphenol, is found in cranberries and other fruits. It is hydrophobic, which is water insoluble.[191] Singh et al prepared its nanosuspension using nanoprecipitation method, and the concentrations of ursolic acid used in nanosuspension were only 25% and 50% of the concentration of free ursolic acid.[184] Surprisingly, these nanosuspensions could effectively lower blood glucose levels and serum TG and TC levels in STZ-induced diabetic rats, suggesting that its anti-diabetic effect was superior to free ursolic acid. Furthermore, betulin is a pentacyclic lupane-type terpenoid, which has low water solubility and high intestinal permeability. Betulin nanosuspension was prepared by the solvent-anti-solvent precipitation method.[185] Ethanol was used as the solvent, while deionized water was used as the anti-solvent. The particle size was 246.4 nm ± 4.21 nm and ζ-potential was −31.2 ± 5.17 mV. It was proved that the structure of the particles in the nanosuspension was consistent with that of betulin. The in vitro dissolution rate, maximum solubility and bioavailability were 3.12, 1.54 and 2.21 times more than the original drug, respectively. Besides, the blood glucose levels of Sprague–Dawley rats were lower than the control group and the free betulin group, and the oral bioavailability was enhanced, demonstrating better diabetic treatment.

Araucaria angustifolia seeds pinhão seed coat was also used to prepare nanosuspension.[186] The pinhão seed coat was found to exert anti-diabetic activity in Wistar rats previously.[192] It was homogenized in water and then compressed into nano-size using microfluidizer to become nanosuspension.[186] This nanosuspension that was given to rats was found to lower weight gain, blood glucose levels, and serum TC and triglyceride levels when compared with the control group, and displayed no toxicity, suggesting its therapeutic role in diabetes. Moreover, Terminalia arjuna is a Pakistan traditional medicinal plant, in which its major component has low water solubility and poor bioavailability that limit its clinical applications.[193] Nanosuspension was prepared from *Terminalia arjuna* bark extract using the nanoprecipitation approach.[187] The particle size of was 90.53 nm, and it was found to improve its dissolution rate and bioavailability in Wistar rats.

Nanocrystals

Nanocrystals refer to crystalline or amorphous drugs with particle size of less than 1 μm, no carrier and stable existence.[194] When nanocrystalline drugs exist in liquid forms, they are called nanocrystalline suspensions, which include nanocrystalline, stabilizer and liquid dispersion medium. In contrast to polymerized nanoparticles, drug nanocrystals are 100% composed of drugs without any carrier material. The preparation of drugs into nanocrystals can increase the dissolution rate of drugs and improve their bioavailability. When the drugs form nanocrystals, their size decreases, and their specific surface area increases. According to the Noyes and Whitney equations, the dissolution rate increases, the saturation solubility becomes higher.[195] The increase in saturation solubility and dissolution rate results in a higher drug concentration gradient between the gastrointestinal tract and blood vessels, which helps to improve the absorption and increase the bioavailability of drugs.[43] There are three common preparation methods of nanocrystalline drugs, which are top-down, bottom-up and combined.[196] "Top-down" methods include milling, high pressure homogenization, and ultrasound methods. "Bottom-up" technology refers to the methods that take the drug solutions as the starting materials, precipitate the drugs, and generate them into nanocrystals with the final particle sizes within the nanometer range. One representative of bottom-up method is antisolvent precipitation. Table 6 summarizes the characteristics and therapeutic effects of nanocrystals for diabetes management.

Initially, studies formulated traditional diabetic drugs into nanocrystal suspensions with the aim of enhancing their solubility. For example, repaglinide, an anti-diabetic drug, was prepared into 187 nm nanocrystalline suspension using the high pressure homogenization method, and the drug release reached 80.58% in vitro, and could be stably stored for three months.[197] Wang et al also demonstrated that glibenclamide nanocrystal could allow glibenclamide to retain in the body for a longer period of time, thus slowing its elimination.[198] This nanocrystal also improved the pharmacokinetic parameters, which could favor to improve the therapeutic effects of glibenclamide in diabetes.

Table 6 Nanocrystals for the Management of Diabetes

Drugs	Materials	Methods	Particle Sizes	ζ-Potential	Therapeutic Effects	Ref.
Repaglinide	Acetone and PEG_{4000}	High pressure homogenization method	187 ± 5.09 nm	−29.4 ± 1 mV	–	[197]
Glibenclamide	Polyvinylpyrrolidone K30	Jet milling	237.6 nm	–	Improved drug solubility and dissolution rate *in* vitro, slowed down drug elimination and sustained the drug in the body for a longer time.	[198]
Gliclazide	PLGA, Poloxamer-188, PEG_{4000} and HPMC E15	Emulsion diffusion, High pressure homogenization and solvent evaporation method	106.3 ± 2.69 nm	−18.2 ± 1.30 mV	Improved pharmacokinetics, increased bioavailability, prolonged the effect of lowering blood glucose levels.	[199]

Nanocrystals have strong mucosal adhesion and stay in the body for a long time. The nanocrystals that contain only drugs and a small amount of stabilizer without any carriers are known as the first generation of nanocrystals. To further enhance the therapeutic effects of drug nanocrystals, further processing or surface modification can be conducted, and other high molecular polymer materials can also be added as carriers to produce a slow releasing effect, and this is regarded as the second generation of nanocrystals (SGNCs).[200] SGNCs are designed to exhibit more stable and bioavailable effects at lower therapeutic doses. In the study of Panda et al, a PLGA-based nanocrystalline composite system was designed to deliver a BSC Class II and T2DM drug gliclazide.[199] PLGA-gliclazide was prepared using the combination of emulsion diffusion, high pressure homogenization and solvent evaporation method. Its dissolution rate and bioavailability were enhanced when compared with free gliclazide. Interestingly, this nanocrystal could be released quickly at the beginning, and then changed to delayed release with higher bioavailability, thereby providing more efficient drug delivery of gliclazide for T2DM treatment.

Safety and Toxicity of Nanoparticles

The use of NPs for the treatment of diabetes is an area of active research, but it also raises some potential toxicity concerns that need to be carefully considered.[201] Depending on the size, materials, surface chemistry and route of administration, some NPs may accumulate in certain organs or tissues, potentially leading to localized toxicity effects. Besides, the ability of NPs to cross biological barriers, such as the blood-brain barrier, can result in unintended distribution and potential toxic effects. However, it is possible to adjust particle size, shape, and surface chemistry to improve the biocompatibility and targeting of NPs, while reducing whole-body exposure. In addition, NPs may interact with the immune system to trigger inflammatory responses or alter immune function.[202] This can be concerning for individuals with T2DM, who often have underlying immune dysregulation.[203,204] Common methods to reduce the immunotoxicity of NPs include imbionic encapsulation of cell membranes in the outer layer of NPs and immune escape by grafting biomaterials. In addition, some NPs may induce the generation of reactive oxygen species, thus leading to oxidative stress and potential cellular damage.[205,206] This can be particularly problematic in the context of T2DM, which is associated with increased oxidative stress.[207] To mitigate this concern, several strategies have been developed, such as coating NPs with antioxidants and polymeric coating of NPs. It is also important to note that the specific toxicity profile of NPs can be varied depending on their physicochemical properties, route of administration, and target diseases or conditions.[202] Rigorous safety evaluations, including in vitro and in vivo studies, are crucial before the clinical application of NP-based therapies for diabetes.

Gliclazide is an oral hypoglycemic drug that is used to treat non-insulin-dependent diabetes. Nazief et al conducted a 14-day sub-acute toxicity study on gliclazide-loaded SLNs in Wistar rats.[150] Sub-acute toxicity tests evaluate whether the NPs induce any hematological, biochemical and physiological changes to the organs and tissues of the body. Gliclazide-loaded SLNs were given to the rats by oral gavage for 14 consecutive days. There were no death or adverse reactions in the rats. Gliclazide-loaded SLN group did not cause any significant changes in food and water consumption and body weights when compared with the control group. In addition, there were no significant changes in the structure of the organs of rats, including stomach, intestine, liver and kidneys, and organs weights relative to the body weights. Moreover, liver and kidney functions were similar between the control, and treated groups. Therefore, repeated administration of blank and gliclazide-loaded SLNs for 14 consecutive days

did not cause any sub-acute toxicity to the rats. In addition, the toxicities of different inorganic NPs, such as zinc oxide NPs, cerium oxide NPs and silver NPs, were evaluated in Swiss albino mice.[112] These NPs were given to the mice daily by oral gavage for 28 consecutive days. After 28 days of oral administration, mouse organs, including pancreas, kidney, spleen, heart and liver, were evaluated, and there were no significant changes to their structures when compared with the control group. Therefore, these NPs did not induce any signs of death and sub-acute toxicity after repeated administration of 28 days.

Although some toxicity studies of NPs for the treatment of diabetes have shown that NPs have low toxicity and good safety in the cells and organisms, the vast majority of NPs require verification through in vitro and in vivo safety assessments to understand their toxicity profiles. Investigating the underlying mechanisms of NP-induced toxicity, such as cellular uptake, intracellular trafficking, and specific molecular pathways, can help to solve the problems effectively. Therefore, ongoing research is aimed to address these toxicity concerns through the development of biocompatible, targeted, and controlled-release NP systems that can minimize adverse effects while maximizing their therapeutic effects for diabetic management.

Clinical Studies of Diabetic Nanomedicine

At present, there are no FDA-approved nanodrugs for the treatment of diabetes, and most of the ongoing research are pre-clinical studies. Although oral or subcutaneous insulin is commonly used in diabetic patients, they present several significant challenges that are difficult to overcome.[208] Due to its large size and hydrophobic nature, insulin has poor bioavailability. It is inactivated by proteolytic enzymes in the stomach and intestinal membranes through hydrolysis, thus leading to low permeability and bioavailability. To overcome these problems, a hepato-directed vesicular (HDV) insulin was developed.[209] HDV insulin is an innovative oral insulin delivery system that was designed to target the liver by incorporating biotin-phosphatidylethanolamine into its phospholipid matrix. The phospholipid bilayer of the vesicles incorporated a proprietary hepatocellular targeting molecule (HTM), biotin-phosphatidylethanolamine (biotin-PE). Following administration, HDV insulin protected the insulin from degradation by proteolytic enzymes in the upper gastrointestinal tract, thereby enhancing its absorption. This design allowed HTM to selectively deliver insulin to hepatocytes, thus mimicking the physiological delivery of insulin under normal conditions. The particle size was within 150 nm. This approach mimicked portal vein insulin delivery, allowing a more natural biological distribution of insulin. Interestingly, this HDV insulin has entered Phase II clinical trials.[210] This is a 6-month study evaluating a liver-targeted rapid-acting insulin formulation in patients with T1DM. HDV-insulin lispro (HDV-L) group was shown to enhance insulin effects and reduce TC levels, with no severe adverse events and no differences in liver functions between groups. Therefore, HDV insulin, combined with hepatocyte targeting through pharmaceutical treatments to address diseases affecting whole-body metabolism, demonstrates significant potential for nanomedicine delivery systems in the treatment of diabetes.

Conclusion and Future Perspectives

In recent years, diabetes has become one of the world's largest chronic diseases, with the number of patients increasing dramatically year by year.[211] According to the World Health Organization, approximately 830 million adults worldwide are living with diabetes in 2024, with its prevalence continuing to rise steadily over the years. Diabetes does not only affect the health of the diabetic patients but also causes many life-threatening complications.[212] It also imposes a heavy burden on patient's family, economy, and public health system.[211] The conventional pharmacological treatment of diabetes often involves oral tablets or capsules, which can be accompanied by adverse side effects.[213] The development of such side effects during treatment underscores the limited effectiveness of current drug therapies, particularly their inability to sustain long-term and controlled drug release.[38] As a result, patients with diabetes may be prescribed with multiple drugs to increase the effectiveness of lowering blood glucose levels. The application of nanotechnology for the management of diabetes holds great promise.[19,214] Nanomedicine offers several advantages over conventional therapeutic approaches, including improved drug delivery, enhanced targeting, and the ability to improve the pharmacokinetics and biodistribution of drugs, thereby leading to better glycemic control and reduced side effects.[215] Various studies have demonstrated that NPs can effectively deliver both conventional drugs and natural compounds, such as flavonoids and curcumin, to enhance their therapeutic effects and minimize diabetic complications.[216] One of the important therapeutic approaches is that nano-based anti-diabetic drugs should aim to reduce blood glucose levels as close to normal blood glucose levels as possible over a long period of time.[217] Therefore, one of the main research focuses is to study the

release and dissolution of nanomedicine in vitro, in addition to the study of their therapeutic effects. In addition, the site of action and the method of administration should be considered when designing and preparing anti-diabetic drugs into nano-preparations. For example, when preparing the drugs into liposomes or with polymer carrier coating, the drugs are released slowly in a controlled manner and are not degraded by the gastrointestinal tract.[218]

In addition to the design of nanodrugs, the successful translation of nanodrugs for diabetic treatment requires careful consideration of their safety and toxicity profiles.[219,220] Nanodrugs have already been tested in rodents and human volunteers and demonstrated their safety with low toxicity and improved efficacy.[112,150,221] Besides, rigorous in vitro and in vivo assessments are necessary to optimize the physicochemical properties of NPs and minimize potential adverse effects. Although anti-diabetic nanomedicine has shown excellent efficacy in both cellular and animal models, their relevant pharmacological mechanisms are still not entirely clear. Many questions remain unanswered, including the distribution of NPs within the body, their mechanism of action and their metabolism.[13] As multiple anti-diabetic drugs are prescribed to diabetic patients to increase the effectiveness of lowering blood glucose levels. Future directions might be focused on the development of nano-based drug delivery systems to encapsulate two or more anti-diabetic drugs to enhance their therapeutic efficacy. Besides, glucose-sensitive or insulin-sensing drug delivery systems loaded with anti-diabetic drugs could also be developed to offer a more precise and responsive approach to manage the blood glucose levels of diabetic patients. Several strategies have been developed to achieve glucose-sensitive drug delivery systems, including glucose oxidase-based, phenylboronic acid (PBA)-based, and concanavalin A (Con A)-based systems.[222–224] They show great promise for the treatment of diabetes, however, several challenges need to be addressed, including safety, manufacturing scalability and regulatory hurdles.

Although nanomedicine holds significant promise for the treatment of diabetes, several challenges need to be addressed for its successful implementation. Some NPs may induce unwanted toxicity in tissues, particularly if their sizes, surface properties or material composition can interact with biological tissues. Long-term exposure to some NPs may lead to organ toxicity and activation of immune responses. Besides, some NPs may accumulate in certain organs, such as liver, spleen and kidney, which can disrupt their normal function and cause adverse effects. Moreover, the production of NPs are complex and costly. The synthesis of NPs involves intricate processes that may be challenging for large-scale production, and the high cost of raw materials further complicates their commercialization. On the other hand, the field of nanomedicine is relatively new, the regulatory departments are still developing guidelines for their approval as drugs. Different countries have varying guidelines, creating challenging situations for manufacturers.

In conclusion, the integration of nanotechnology with diabetes research holds great promise for the development of more effective, safe, and personalized treatment strategies. As the field continues to evolve, the successful clinical implementation of nanodrugs could revolutionize the management of diabetes and improve the quality of life for millions of diabetic patients worldwide.

Abbreviations

ALT, alanine transaminase; AMPK, AMP-activated protein kinase; AST, aspartate aminotransferase; biotin-PE, biotin-phosphatidylethanolamine (biotin-PE); BMDMs, bone marrow-derived macrophages; Cas9, CRISPR associated protein 9; CK-MB, creatine kinase-myocardial band; CMC, carboxymethyl chitosan; Con A, concanavalin A; COX-2, cyclooxygenase-2; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; DPPH, 2.2-diphenyl-1-picrylhydrazyl; EPR, enhanced permeability and retention; FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide 1; GSH, glutathione; GSH-Px, glutathione peroxidase; H_2, hydrogen molecules; HA, hyaluronic acid; HDL, high-density lipoprotein; HDV, hepato-directed vesicular; HDV-L, HDV-insulin lispro; HFD, high-fat diet; HTM, hepatocellular targeting molecule; IL, interleukin; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LMW, low molecular weight; MECP, methanolic extract of *Costus pictus* leaves; MECPAgNPs, silver NPs of MECP; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nkx6.1, NK6 homeobox 1; NLCs, nanostructured lipid carriers; NPs, nanoparticles; PBA, phenylboronic acid; PDI, polydispersity index; Pdx-1, pancreatic duodenal homeobox-1; PEG, polyethylene glycol; PLA, polylactic acid; PLCL, poly(L-lactide-co-ε-caprolactone); PLGA, poly(lactic-co-glycolic acid); PPAR-γ, peroxisome proliferator-activated receptor-γ; PTP1B, protein tyrosine phosphatase 1B; RSW, red sandalwood; SGLT2, sodium-glucose cotransporter-2; SGNCs, second generation of nanocrystals; SLNs, solid lipid NPs; SOD,

superoxide dismutase; SgRNA, single-stranded guide RNA; STZ, streptozotocin; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; TNF, tumor necrosis factor.

Data Sharing Statement

No datasets were generated or analysed during the current study.

Ethical Approval and Consent to Participate

This study does not contain any animal and human experiments.

Consent for Publication

All authors agreed to publish this manuscript.

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Disclosure

The authors declare no competing interests in this work.

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