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Nanotechnology for Diabetes Management: Transforming Anti-diabetic Drug Delivery Systems

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Keywords

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Abstract

To prevent major complications, people with chronic diabetes mellitus, a metabolic condition characterised by increased blood sugar, require continuous care. Although current pharmacological treatments, such as insulin and oral hypoglycemic agents, are effective, they are often limited by poor bioavailability, short half-life, and systemic side effects. Drug delivery systems based on nanotechnology provide encouraging answers to these problems, allowing for the targeted, precise, and regulated administration of anti-diabetic medications. In order to improve therapeutic efficacy, decrease the frequency of administration, and increase drug bioavailability, nanoparticles, liposomes, nanogels, and microneedles are becoming important technologies. For example, liposomes increase the solubility and durability of hydrophobic medications, whereas nanoparticles can shield medications from deterioration and enable continuous release. In response to hyperglycemia, nanogels that are engineered to react to particular stimuli, such as pH or glucose levels, allow regulated medication release that mimics the body's normal production of insulin. Insulin and other anti-diabetic medications can be delivered painlessly via microneedles, a minimally invasive substitute for conventional injections. Notwithstanding these developments, issues with scalability, cost, regulatory approval, and long-term safety still affect the clinical translation of these technologies. This study looks at the state of diabetic medication delivery systems based on nanotechnology, emphasising how they have the potential to transform treatment approaches and enhance patient outcomes. Future research should focus on overcoming these barriers, conducting clinical trials, and exploring new nanomaterials to maximize the therapeutic potential of these systems.

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1. Introduction

A major worldwide health concern is diabetes mellitus, a chronic metabolic disease marked by persistent hyperglycemia. Diabetes is becoming more common due to a number of variables, including ageing populations, sedentary lifestyles, and rising obesity rates. This highlights the urgent need for novel and efficient treatment approaches. Insulin treatment, medication, and lifestyle changes are the mainstays of current diabetes care strategies [1]. However, these conventional methods often face limitations, including poor bioavailability of oral drugs, invasive administration routes, frequent dosing requirements, and side effects that compromise patient adherence and long-term therapeutic outcomes. Nanotechnology has recently surfaced as a game-changing strategy for

tackling these issues, providing innovative ways to distribute anti-diabetic medications and improve diabetes care [2]. Designing, creating, and using materials at the nanoscale (1–100 nm), where special physicochemical characteristics allow for improved medication delivery and therapeutic efficacy, is known as nanotechnology. The creation of nanocarriers, including nanoparticles, liposomes, micelles, dendrimers, and nanotubes, has been made possible by nanotechnology in the context of diabetes and offers several benefits over conventional drug delivery methods [3]. These benefits include less systemic adverse effects, tailored administration to certain tissues or cells, controlled and prolonged release, increased stability, and better drug solubility. By using these potentialities, nanotechnology-based systems might transform the delivery of anti-diabetic medications, increasing glycaemic control, lowering complications, and improving the quality of life for diabetic patients [4].

A major obstacle in the treatment of diabetes is the low bioavailability of oral anti-diabetic medications, including GLP-1 receptor agonists, sulfonylureas, and metformin. This problem is solved by nanotechnology, which encapsulates these medications in nanocarriers that improve absorption and shield them from gastrointestinal system breakdown. For example, polymeric nanoparticles and solid lipid nanoparticles have been used to encapsulate metformin, improving its solubility and bioavailability [5]. Similarly, liposomes and micelles have been explored for the delivery of GLP-1 receptor agonists, enabling controlled release and prolonged activity, thereby reducing the need for frequent dosing. Another significant contribution of nanotechnology is its potential to overcome the limitations of insulin therapy, a cornerstone of diabetes management [6]. Subcutaneous injections and other traditional insulin administration techniques are linked to discomfort, inconvenience, and low patient compliance. Alternative delivery methods made possible by nanotechnology include less intrusive and more patient-friendly oral, transdermal, and inhalable devices. For example, oral insulin administration using nanoparticles has demonstrated potential in promoting insulin absorption via the intestinal epithelium and shielding it from enzymatic breakdown in the gastrointestinal system [7]. Transdermal insulin delivery systems, such as microneedles and nanogels, enable painless and sustained release of insulin, improving patient adherence. Inhalable insulin, delivered using nanostructured aerosol particles, offers rapid onset of action and convenience, although challenges related to lung deposition and long-term safety need to be addressed [8].

Targeted drug delivery is another area where nanotechnology has demonstrated significant potential in diabetes management. Diabetic complications such diabetic retinopathy, nephropathy, and neuropathy are frequently linked to diabetes and must be treated precisely and locally to reduce systemic adverse effects [9]. Ligands that selectively target receptors or biomarkers expressed in impacted tissues can be used to functionalise nanocarriers. For example, nanoparticles conjugated with folate or transferrin ligands have been used to deliver drugs selectively to pancreatic β-cells or diabetic wound sites, enhancing therapeutic efficacy while minimizing off-target effects. Anti-VEGF medications have been delivered to the retina by nanocarriers in the treatment of diabetic retinopathy, eliminating the need for repeated intravitreal injections [10]. Controlled and sustained drug release is another critical aspect of diabetes management that nanotechnology addresses effectively. Traditional drug delivery methods often result in fluctuations in blood glucose levels due to rapid drug clearance or inconsistent absorption. Drugs can be released from nanocarriers in a regulated way over a long length of time, preserving steady therapeutic levels and enhancing glycaemic control. For instance, polymer-based nanoparticles and hydrogels have been designed to release insulin in response to changes in blood glucose levels, mimicking the physiological secretion of insulin by pancreatic β-cells [11]. By attaining accurate and dynamic glycaemic management, these glucose-responsive devices have the potential to lower the incidence of hypoglycemia and associated consequences. Nanotechnology not only enhances medication delivery but also presents intriguing opportunities for non-invasive glucose monitoring and diagnosis. Nanostructured sensors have been designed to detect glucose in biological fluids including tears, perspiration, and saliva. These sensors are based on materials like graphene, carbon nanotubes, and gold nanoparticles [12]. These sensors provide real-time and accurate glucose measurements, eliminating the need for finger-prick blood tests and enhancing patient comfort. Furthermore, nanotechnology-based biosensors can be integrated with wearable devices, enabling continuous glucose monitoring and personalized diabetes management [13].

Despite its transformative potential, the application of nanotechnology in diabetes management is not without challenges. Issues such as the scalability of nanocarrier production, potential toxicity, regulatory hurdles, and cost constraints need to be addressed before these technologies can achieve widespread clinical adoption. Thorough clinical trials and long-term safety investigations are necessary to prove the effectiveness and biocompatibility of systems based on nanotechnology [14]. Additionally, collaboration among researchers, clinicians, regulatory agencies, and industry stakeholders will be critical for translating nanotechnology innovations from the laboratory to the clinic. With its novel approaches to the administration of anti-diabetic medications and the management of problems associated with diabetes, nanotechnology is a paradigm change in the field of diabetes care [15]. Nanotechnology-based solutions have the potential to greatly improve treatment results and patient quality of life by tackling important issues such inadequate bioavailability, invasive delivery methods, and the requirement for precise glycaemic control. It is anticipated that nanotechnology will become more significant in the creation of next-generation diabetes treatments as this field of study develops, opening the door to more efficient, individualised, and patient-centered methods of diabetes treatment [16].

Table 1: Nanotechnology for Diabetes Management

S. No.	Nanotechnology System	Description	Examples	Advantages
1.	**Nanoparticles**	Nanoscale particles (usually 1-100 nm) that can encapsulate anti-diabetic drugs, providing protection from degradation and enabling controlled and sustained release.	Polymeric nanoparticles, liposomes, chitosan-based nanoparticles	1. Enhanced drug bioavailability 2. Controlled drug release 3. Improved stability of drugs in circulation
2.	**Liposomes**	Vesicles made of lipids that contain both hydrophilic and hydrophobic medications. Liposomes are utilised for oral and parenteral medication administration, and they improve the stability and solubility of drugs.	Insulin-loaded liposomes, liposomal formulations for oral insulin	1. Improved solubility for hydrophobic drugs 2. Enhanced drug absorption 3. Reduced systemic toxicity
3.	**Nanogels**	Cross-linked networks of hydrophilic polymers that expand and release medications in reaction to environmental factors including temperature, pH, or glucose levels. They imitate the release of insulin naturally.	Glucose-responsive nanogels, insulin-loaded nanogels	1. Stimulus-responsive drug release 2. Mimics physiological insulin secretion 3. High biocompatibility
4.	**Microneedles**	Small, minimally invasive needles (ranging from microns to millimeters) that penetrate the skin without causing significant pain. Used for painless, transdermal drug delivery.	Insulin microneedles, dissolving microneedles	1. Painless and minimally invasive 2. No need for syringes 3. Enhanced patient compliance
5.	**Multifunctional Nanoplatforms**	Nanoplatforms that integrate both therapeutic and diagnostic functions, enabling real-time	Quantum dots for glucose sensing, mesoporous silica	1. Dual functions (diagnostic + therapeutic) 2. Real-time

		glucose monitoring and on-demand drug release.	nanoparticles	glucose monitoring 3. On-demand drug release
6.	**Nanocrystals**	Crystals of pharmaceuticals smaller than a micron that increase the solubility and bioavailability of medications that are not very soluble in water.	Insulin nanocrystals	1. Enhanced drug solubility 2. Increased bioavailability 3. Improved pharmacokinetic profile
7.	**Polymeric Nanocarriers**	Polymers with controlled medication delivery and release capabilities. These nanocarriers may be designed for selective distribution and are biocompatible and biodegradable.	Poly(lactic-co-glycolic acid) (PLGA) nanoparticles	1. Biodegradable and biocompatible 2. Controlled drug release 3. Can be modified for targeted delivery
8.	**Solid-Lipid Nanoparticles (SLNs)**	Lipid-based nanoparticles that offer sustained release and better stability for lipophilic drugs. SLNs are less toxic and more biocompatible compared to traditional lipid carriers.	Insulin-loaded SLNs	1. Sustained drug release 2. Improved stability and bioavailability 3. Enhanced safety and biocompatibility
9.	**Nano-structured Lipid Carriers (NLCs)**	A combination of solid lipid nanoparticles and liquid lipids, NLCs improve the loading capacity and stability of drugs. They enhance bioavailability and drug release profiles.	Insulin-loaded NLCs	1. Enhanced drug loading capacity 2. Better stability of the drug 3. Improved bioavailability and controlled release
10.	**Dendrimers**	Highly branched, nanoscale polymers with functional groups that allow precise drug encapsulation. Dendrimers provide targeted drug delivery and can improve solubility.	Dendrimer-based drug carriers	1. Targeted delivery to specific sites 2. High drug-loading capacity 3. Control over drug release kinetics

2. Pathophysiology and Current Therapeutic Challenges

Chronic hyperglycemia brought on by either inadequate insulin production, poor insulin action, or both is a hallmark of diabetes mellitus. The two main categories of the disease are Type 1 diabetes (T1D), an autoimmune disease that causes the pancreatic beta cells that produce insulin to be destroyed, and Type 2 diabetes (T2D), which is linked to insulin resistance and relative insulin insufficiency [46]. Gestational diabetes, a less prevalent kind, raises the chance of acquiring type 2 diabetes in later life and develops during pregnancy. T1D is characterised by a complete lack of insulin due to the autoimmune-mediated death of pancreatic beta cells. As a result, cells become unable to use glucose as fuel, which can result in hyperglycemia, ketoacidosis, and long-term issues like neuropathy, retinopathy, and nephropathy [47]. On the other hand, T2D is typified by both defective beta cells and peripheral tissue insulin resistance. Obesity, a sedentary lifestyle, genetic susceptibility, and ageing are risk factors for type 2 diabetes. Cardiovascular disease, a major cause of death for diabetic patients, is one of the microvascular and macrovascular consequences that are exacerbated by chronic hyperglycemia in type 2 diabetes. Insulin therapy, oral hypoglycemic medications (such as metformin, sulfonylureas, and DPP-4 inhibitors), GLP-1 receptor

agonists, and SGLT2 inhibitors are examples of current therapeutic approaches for the treatment of diabetes [48]. Despite their effectiveness in controlling blood glucose levels, many treatments have drawbacks. Multiple daily injections are frequently necessary for insulin therapy, which can be uncomfortable and unpleasant and result in poor adherence. Oral medications may have low bioavailability and systemic side effects such as gastrointestinal discomfort or increased risk of hypoglycemia. Furthermore, current therapies do not address the underlying pathophysiological mechanisms comprehensively, focusing primarily on symptom control rather than disease modification [49].

Patient adherence is another critical challenge. The need for frequent blood glucose monitoring, complex dosing regimens, and potential side effects can discourage consistent treatment adherence, impacting overall disease management. Additionally, individual variability in response to therapies necessitates personalized treatment approaches, which are not always feasible with existing modalities [50]. The emergence of drug resistance, especially in T2D, further complicates long-term management. As beta-cell function progressively declines, patients often require combination therapies or transition to insulin, which may not always be well-tolerated. These drawbacks emphasise how urgently novel drug delivery methods are needed to increase therapeutic efficacy, lessen side effects, and boost patient adherence to diabetic treatment [51].

2.1. Overview of Diabetes Mellitus

Persistent hyperglycemia brought on by impaired insulin production, action, or both is a hallmark of diabetes mellitus, a chronic metabolic disease. This disorder results from complicated interplay between lifestyle, environmental, and genetic variables that disturb glucose homeostasis. Type 2 diabetes (T2D) and type 1 diabetes (T1D) are the two main categories of diabetes, each having unique clinical manifestations and pathophysiological processes [52].

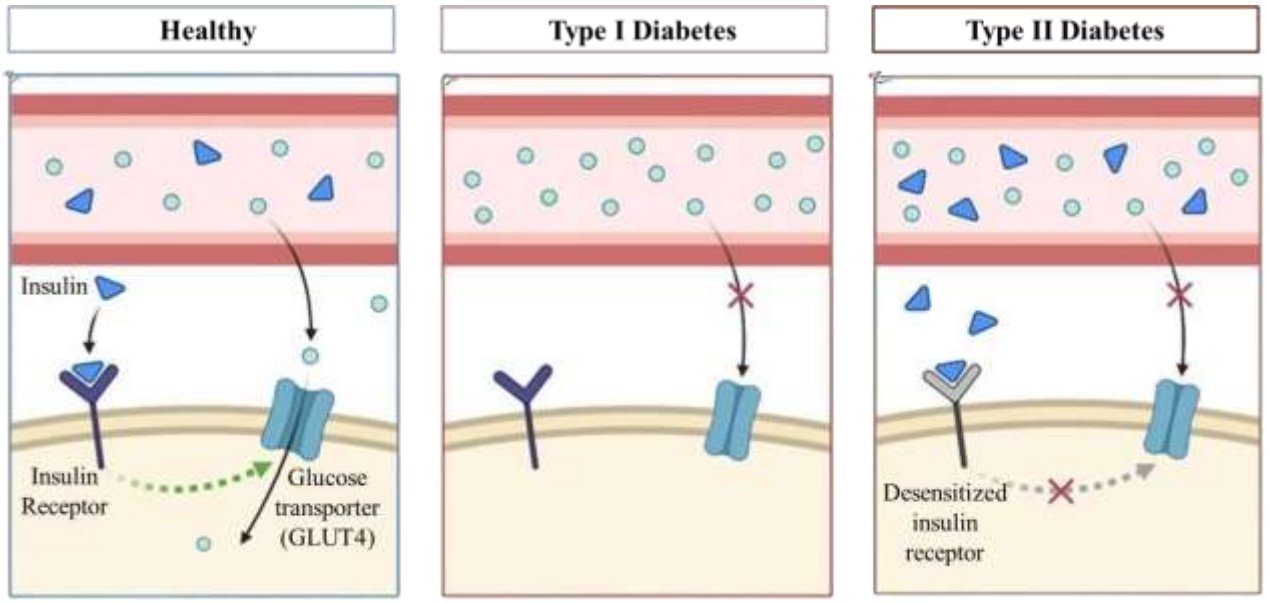

Figure 1: Type I vs. Type II Diabetes

T1D is an autoimmune disease where the immune system mistakenly attacks and kills the pancreatic β-cells that produce insulin. An absolute insulin insufficiency results from this breakdown, requiring lifetime insulin treatment to maintain glycaemic control. Although it can happen at any age, T1D usually manifests in childhood or adolescent. About 5–10% of cases of diabetes are caused by it, and symptoms including polyuria, polydipsia, polyphagia, and inadvertent weight loss are frequently linked to it. Genetic predisposition and environmental triggers like viral infections or dietary variables are examples of risk factors [53]. T2D is a complex illness that is mostly linked to relative insulin insufficiency and insulin resistance. The pancreas must create more insulin to maintain glucose balance in type 2 diabetes because tissues including muscle, liver, and adipose become less receptive to the hormone. Over time,

pancreatic β-cells may become dysfunctional, further exacerbating hyperglycemia [54]. T2D is strongly linked to obesity, sedentary lifestyles, and aging, and it accounts for 90–95% of diabetes cases globally. Symptoms may develop gradually and include fatigue, blurred vision, and increased thirst. Both types of diabetes are associated with complications affecting multiple organ systems, including cardiovascular disease, nephropathy, retinopathy, and neuropathy. To avoid problems and enhance quality of life, effective therapy includes pharmaceutical therapies, lifestyle changes, and routine blood glucose monitoring [55].

2.2. Limitations of Conventional Therapies

Conventional treatments for diabetes mellitus include insulin injections, oral hypoglycemic medications, and lifestyle modifications. While these approaches have significantly improved patient outcomes, they are associated with several limitations that hinder optimal disease management and patient adherence [56].

A key component of treating type 1 diabetes and severe Type 2 diabetes, insulin therapy frequently calls for several daily injections or the use of insulin pumps. This invasive approach can lead to discomfort, inconvenience, and needle-related anxiety, all of which negatively affect patient adherence. Additionally, insulin therapy is associated with a high risk of hypoglycemia, especially in cases of improper dosing or missed meals [57]. Blood glucose levels must be closely monitored since severe hypoglycemia might cause disorientation, unconsciousness, or even potentially fatal consequences. For Type 2 diabetes, oral hypoglycemic medications such DPP-4 inhibitors, sulfonylureas, and metformin are frequently prescribed. Although these drugs effectively lower blood glucose levels, they present challenges such as frequent dosing schedules, potential drug interactions, and side effects [58]. Metformin, for example, can cause gastrointestinal discomfort, including nausea, diarrhea, and abdominal bloating, leading some patients to discontinue its use. Sulfonylureas, while effective in stimulating insulin secretion, carry a significant risk of hypoglycemia and weight gain. Diabetes management greatly benefits from lifestyle changes, such as food adjustments and increased exercise [59]. However, maintaining these interventions long-term is often difficult for patients due to various factors such as lack of motivation, time constraints, or limited access to resources like dietitians or exercise facilities. The inability of conventional therapies to provide precise glycemic control or address underlying pathophysiological mechanisms often results in suboptimal outcomes. These therapies primarily focus on managing symptoms rather than reversing disease progression or preventing complications. For instance, none of these approaches target β-cell regeneration or directly address insulin resistance at the cellular level [60].

3. Nanotechnology-Based Drug Delivery Systems

3.1. Nanoparticles

Anti-diabetic medications can be encapsulated by nanoparticles, such as metallic and polymeric nanoparticles, which prevent degradation and allow for prolonged release. For example, chitosan-based nanoparticles have demonstrated improved glucose regulation and bioavailability of encapsulated drugs. In the treatment of diabetes, nanoparticles have shown great promise as a technology, providing notable improvements over traditional drug delivery techniques [61]. These nanoscale particles, typically ranging from 1 to 100 nanometers, provide a versatile platform for encapsulating anti-diabetic drugs, enhancing their therapeutic efficacy and bioavailability. Nanoparticles are primarily classified into polymeric nanoparticles and metallic nanoparticles, both of which exhibit unique properties that make them suitable for addressing the challenges of diabetes treatment [62].

Because of their capacity to encapsulate both hydrophilic and hydrophobic medications, polymeric nanoparticles—such as those made of biodegradable substances like chitosan, poly (lactic-co-glycolic acid) (PLGA), and alginate—have attracted interest. These carriers prolong the stability of encapsulated medications and allow for regulated release by shielding them from gastrointestinal tract enzymatic breakdown [63]. For example, it has been shown that chitosan-based nanoparticles improve the bioavailability of encapsulated medications like insulin and GLP-1 receptor agonists. Their mucoadhesive qualities allow them to stay in the stomach for a longer period of time, which improves glucose management and facilitates effective absorption. Metallic nanoparticles, such as gold and silver nanoparticles, have also demonstrated promise in the treatment of diabetes because of their capacity to modify surfaces, change their size, and undergo biofunctionalization [64]. These nanoparticles can be conjugated with anti-diabetic drugs or ligands to achieve targeted delivery to specific tissues, such as pancreatic β-cells or insulin-resistant muscles. Gold nanoparticles, for example, have been explored for delivering insulin orally, providing a non-invasive

alternative to subcutaneous injections. In addition to drug encapsulation and sustained release, nanoparticles enable responsive drug delivery, a critical feature for achieving precise glycemic control [65]. Drugs can be released by nanoparticles that include glucose-sensitive components in response to variations in blood glucose levels. For example, pH-sensitive or glucose-responsive polymeric nanoparticles release insulin only when hyperglycemia is detected, mimicking the physiological secretion of insulin by pancreatic β-cells [66]. Despite their advantages, challenges such as potential toxicity, large-scale production, and regulatory hurdles remain to be addressed for the clinical translation of nanoparticle-based systems. Nonetheless, the versatility and efficacy of nanoparticles in protecting drugs, enabling sustained release, and facilitating targeted delivery make them a promising tool for transforming diabetes management and improving patient outcomes [67].

3.2. Liposomes

Liposomes are lipid-based vesicles that enhance the solubility and bioavailability of hydrophobic drugs. Insulin-loaded liposomes have been shown to improve glucose control with reduced injection frequency. Liposomes, which are spherical vesicles with an aqueous core surrounded by lipid bilayers, have become well-known as a flexible drug delivery method for the treatment of diabetes [68]. These nanocarriers are particularly effective in enhancing the solubility, stability, and bioavailability of hydrophobic drugs, making them ideal for encapsulating various anti-diabetic agents, including insulin. Liposomes' special structural characteristics allow them to transport hydrophilic and hydrophobic medications, providing regulated and prolonged release for better therapeutic results [69].

Insulin-loaded liposomes have demonstrated exceptional promise in the treatment of diabetes by overcoming the drawbacks of traditional insulin delivery techniques. Insulin is protected from enzymatic breakdown in the gastrointestinal system by being encapsulated in liposomes, which makes non-invasive administration methods like oral or inhalation possible. Studies have demonstrated that liposomal formulations improve the pharmacokinetics of insulin, leading to enhanced glucose regulation with reduced dosing frequency compared to traditional insulin injections [64]. This reduction in injection frequency significantly improves patient adherence and quality of life. Liposomes can be engineered for targeted delivery, ensuring that encapsulated drugs are selectively released at the desired site of action [70]. For example, liposomes functionalized with ligands targeting glucose transporters or insulin receptors can preferentially accumulate in insulin-sensitive tissues, such as skeletal muscles or the liver, enhancing therapeutic efficacy while minimizing systemic side effects [71]. Additionally, pH-sensitive or glucose-responsive liposomes have been developed to release insulin in response to hyperglycemia, mimicking the body‘s physiological insulin secretion. Liposomes also offer the advantage of biocompatibility and low immunogenicity due to their composition, which is similar to biological membranes. These characteristics make them a safer alternative for drug delivery, reducing the risk of adverse reactions [72]. Despite these benefits, challenges such as limited stability during storage, high production costs, and potential leakage of encapsulated drugs must be addressed to facilitate their clinical translation. A noteworthy development in anti-diabetic medication delivery methods is liposomes. They have the potential to completely transform diabetes care by providing patients with more practical and efficient treatment alternatives through their capacity to encapsulate insulin and other therapeutic agents, enhance medication stability, and enable controlled release [73].

3.3. Nanogels

Hydrophilic networks of polymers, known as nanogels, may react to environmental stimuli like pH and glucose levels. Glucose-responsive nanogels loaded with insulin release the drug in response to elevated glucose levels, mimicking physiological insulin secretion. Nanogels are very adaptable, hydrophilic networks of polymers that have drawn a lot of interest in the treatment of diabetes because of their special qualities and sensitivity to outside stimuli [74]. These nanoscale structures are designed to encapsulate therapeutic agents, such as insulin, within a soft, hydrated matrix, offering controlled drug release and high biocompatibility. Nanogels are especially well-suited for targeted and on-demand medication administration because of their sensitivity to environmental variables including pH, temperature, and glucose levels [75].

A highly promising use of nanogels in diabetes treatment is the creation of glucose-responsive nanogels. These systems closely resemble the normal secretion patterns of pancreatic β-cells, releasing insulin in response to high blood glucose levels. The mechanism relies on glucose-sensitive components,

such as phenylboronic acid or glucose oxidase, integrated into the nanogel structure [76]. When blood glucose levels rise, the interaction between glucose and these components triggers structural changes in the nanogel, leading to the release of encapsulated insulin. This responsive behavior allows for precise glycemic control, reducing the risk of both hyperglycemia and hypoglycemia. Nanogels also offer the advantage of non-invasive delivery options, such as subcutaneous, oral, or transdermal administration [77]. Their high water content and soft, deformable nature enable them to penetrate biological barriers efficiently and provide prolonged drug release. The therapeutic effectiveness of nanogels can also be increased by modifying them with ligands to transport them specifically to insulin-sensitive organs. The potential of nanogels to increase insulin's stability and bioavailability is another important advantage [78]. Nanogels prolong the half-life of insulin by shielding it from enzymatic breakdown and early clearance, which lowers the frequency of injection needed. Notwithstanding their benefits, issues including long-term stability, large-scale manufacture, and regulatory approval need to be resolved before they can be widely used in clinical settings. Nonetheless, glucose-responsive nanogels' ability to offer a more physiological and patient-friendly method of managing diabetes underscores its potential as a game-changing invention in the sector. By combining responsiveness, biocompatibility, and efficient delivery, nanogels offer a powerful tool for advancing insulin therapy and improving the quality of life for diabetic patients [79].

3.4. Microneedle Arrays

For the transdermal administration of insulin and other anti-diabetic medications, microneedles offer a minimally invasive method. These technologies improve patient compliance by facilitating painless medication delivery. An inventive and least invasive method for the transdermal administration of insulin and other anti-diabetic medications is microneedle arrays. [80]. Arrays of tiny needles, usually composed of biocompatible materials like silicon, metal, or polymers, make up these devices. They are intended to pierce the stratum corneum, the outermost layer of the skin, without getting to the pain-sensitive nerve endings. This special quality makes it possible to administer medications painlessly, which solves a major drawback of traditional insulin injections and increases patient compliance [81].

The microneedle approach offers several advantages in diabetes management. By bypassing the gastrointestinal tract, microneedles prevent enzymatic degradation of insulin, making them suitable for delivering biologics that are otherwise challenging to administer orally. Additionally, these devices ensure stable blood glucose levels and less frequent administration by delivering a regulated and sustained release of medications [82]. Microneedles can also be engineered for rapid drug release, allowing for immediate glucose regulation in cases of hyperglycemia. Solid, coated, dissolving, and hydrogel-forming microneedles are among the several types of microneedle arrays. Insulin is applied topically after solid microneedles form microchannels in the skin. Coated microneedles are pre-coated with drugs that dissolve upon insertion. Dissolving microneedles are made from drug-loaded, biodegradable materials that dissolve completely after delivery, leaving no residual waste [83]. Hydrogel-forming microneedles swell upon skin insertion, enabling sustained release of encapsulated drugs. In addition to insulin, microneedle arrays are being explored for delivering GLP-1 receptor agonists and other anti-diabetic agents. Advanced designs, such as glucose-responsive microneedles, release insulin only when elevated glucose levels are detected, mimicking physiological insulin secretion and reducing the risk of hypoglycemia [84]. Despite their potential, challenges remain in the large-scale manufacturing and commercialization of microneedles. Ensuring consistent drug loading, sterility, and long-term stability are critical for their clinical application. Moreover, patient education on proper usage and handling is essential for maximizing the benefits of this technology. Microneedle arrays offer a transformative approach to diabetes management, combining efficacy, patient comfort, and convenience. Their ability to provide painless, controlled, and efficient drug delivery positions them as a promising alternative to traditional methods, with the potential to enhance therapeutic outcomes and patient satisfaction [85].

4. Applications in Diabetes Management

4.1. Glucose-Responsive Systems

Glucose-responsive nanoparticles and hydrogels offer precise control of blood glucose by releasing drugs only when hyperglycemia is detected. This approach reduces the risk of hypoglycemia. Glucose-responsive systems represent a cutting-edge innovation in diabetes management, offering precise and autonomous control of blood glucose levels. These systems replicate the natural insulin production of pancreatic β-cells by only releasing therapeutic drugs, like insulin, in response to hyperglycemia, or

increased glucose levels [86]. Glucose-responsive devices reduce the risk of hypoglycemia, a frequent and possibly harmful side effect of traditional insulin therapy, by offering on-demand medication delivery. Among the most advanced glucose-responsive technologies are glucose-responsive nanoparticles and hydrogels. These systems are engineered with components that detect changes in glucose concentration and respond by altering their structure or properties to release the encapsulated drug [87]. For instance, nanoparticles incorporating glucose oxidase respond to hyperglycemia by generating acidic by-products, triggering the release of insulin. Similarly, phenylboronic acid-based nanoparticles bind to glucose, inducing structural changes that allow the drug to be delivered. Glucose-responsive hydrogels are another promising approach. A regulated release of insulin can result from the swelling or degradation of these hydrophilic polymer networks in response to glucose. They provide localised, prolonged medication delivery, which lowers the frequency of administration and increases patient compliance [88].

4.2. Oral Insulin Delivery

Oral insulin delivery has long been a sought-after alternative to traditional subcutaneous injections for diabetes management. Insulin's limited permeability across the gastrointestinal (GI) epithelium and vulnerability to enzymatic breakdown provide the main obstacles. However, advancements in nanotechnology, particularly the development of protective nanocarriers, have significantly advanced the potential for effective oral insulin formulations [89]. Insulin must be protected from the hostile enzymatic environment of the GI tract by nanocarriers such liposomes, polymeric nanoparticles, and solid lipid nanoparticles. These systems encapsulate insulin within protective matrices, ensuring its stability during transit through the stomach and small intestine. Moreover, these carriers can be engineered with bioadhesive properties to enhance their interaction with the intestinal mucosa, promoting drug absorption [90]. For the administration of insulin orally, pH-sensitive nanoparticles have shown great promise. These nanoparticles are designed to stay stable in the stomach's acidic environment and only release their payload when the small intestine's pH is neutral or slightly alkaline. For instance, polymeric carriers made of materials like chitosan or poly(lactic-co-glycolic acid) (PLGA) exhibit pH-dependent behavior that protects insulin during gastric transit and promotes its release at the site of absorption. In preclinical studies, oral insulin formulations utilizing nanocarriers have demonstrated improved bioavailability and glycemic control compared to conventional oral methods [91]. Some formulations have even achieved blood glucose-lowering effects comparable to subcutaneous injections, highlighting their potential as a non-invasive alternative. While challenges such as scalability, cost, and regulatory approval remain, oral insulin delivery systems represent a significant leap forward in diabetes management. By improving patient adherence and comfort, they could revolutionize treatment paradigms, enhancing outcomes and quality of life for individuals with diabetes [92].

4.3. Multifunctional Nanoplatforms

Multifunctional nanoplatforms represent an advanced frontier in diabetes management by integrating therapeutic and diagnostic capabilities into a single system. These nanostructures are designed to perform dual roles: real-time glucose monitoring and controlled drug delivery, streamlining diabetes care and improving patient outcomes. By combining these functions, they offer a significant advantage over traditional approaches that treat monitoring and therapy as separate processes. One notable example of multifunctional nanoplatforms is the use of quantum dots (QDs) [93]. These nanoscale semiconductor particles exhibit unique optical properties, enabling highly sensitive glucose sensing. Functionalized with glucose-binding molecules, QDs can detect glucose concentration changes in real-time through fluorescence signals. Simultaneously, these platforms can be loaded with insulin or other anti-diabetic drugs, releasing them in a controlled manner in response to glucose levels. This dual functionality mimics the natural feedback mechanism of the pancreas, offering precise glycemic control while minimizing risks like hypoglycemia [94]. Beyond quantum dots, other nanoplatforms, such as gold nanoparticles and mesoporous silica nanoparticles, are being explored for similar multifunctional applications. These systems can be engineered to respond to stimuli such as pH or glucose, ensuring targeted and timely drug delivery. Additionally, their surfaces can be modified for improved biocompatibility and reduced systemic toxicity [95].

5. Challenges and Future Perspectives

Despite significant progress in developing innovative drug delivery systems for diabetes management, several challenges must be addressed before these technologies can be widely implemented in clinical practice. Key hurdles include scalability, cost,

regulatory approval, long-term safety, and the complexities of translating preclinical success into real-world applications. One of the primary challenges is the scalability of manufacturing advanced delivery systems. Technologies like nanoparticles, microneedles, and glucose-responsive hydrogels often involve intricate fabrication processes, making large-scale production both time-consuming and expensive [96]. Ensuring batch-to-batch consistency and maintaining the functional properties of these systems at a commercial scale remains a significant technical barrier. Addressing this issue will require innovations in manufacturing techniques and the adoption of cost-effective materials that maintain efficacy and stability. Cost is another critical consideration. Many advanced delivery systems rely on high-cost materials and sophisticated processes, potentially limiting their accessibility, particularly in low-resource settings. Developing affordable alternatives without compromising performance is essential for widespread adoption. Regulatory approval poses its own set of challenges. Regulatory bodies require robust evidence of safety, efficacy, and quality, often demanding extensive preclinical and clinical data [97]. For technologies like multifunctional nanoplatforms or glucose-responsive systems, demonstrating biocompatibility, stability, and precise control of drug release under physiological conditions is particularly complex. Establishing clear guidelines and collaborating with regulatory agencies early in the development process could streamline approval pathways. The long-term safety of these technologies remains a significant concern [98]. For example, nanoparticles may accumulate in tissues, posing potential risks of toxicity, while microneedle devices need to ensure no residual materials are left in the skin. Addressing these issues requires long-term studies to assess biocompatibility and potential adverse effects. Looking forward, future research should prioritize resolving these challenges through interdisciplinary collaboration. Advances in materials science, such as developing biodegradable polymers or smart materials, can address scalability and safety issues. Similarly, machine learning and computational modeling could optimize drug release profiles and predict long-term behavior, accelerating design and testing phases. Another critical area is the development of patient-centric systems [99]. Devices and formulations must not only be effective but also convenient and user-friendly to ensure high compliance. For instance, integrating glucose-responsive delivery systems with wearable technology could allow real-time monitoring and automated insulin administration, significantly improving quality of life for patients. Finally, conducting extensive clinical trials is crucial to bridge the gap between laboratory research and practical application. Trials should include diverse patient populations to assess efficacy and safety across different demographics and disease severities. Partnerships between academia, industry, and regulatory bodies will be essential to ensure these technologies reach patients promptly and effectively [100].

Conclusion

Nanotechnology is poised to revolutionize the management of diabetes by offering novel and highly effective solutions for controlled and targeted drug delivery. The ability to encapsulate anti-diabetic agents such as insulin in nanocarriers allows for more efficient drug release, improved bioavailability, and sustained therapeutic effects. By overcoming the limitations of conventional insulin therapies—such as poor bioavailability, frequent injections, and the risk of hypoglycemia—nanotechnology provides an opportunity to significantly enhance the treatment experience for diabetic patients. The development of advanced nanocarriers, such as nanoparticles, liposomes, microneedles, and glucose-responsive systems, offers a more precise, patient-friendly approach to diabetes management. These systems not only improve the efficacy of existing treatments but also enable the creation of novel delivery methods, such as oral insulin formulations and multifunctional platforms that combine both therapeutic and diagnostic functions. These innovations are paving the way for more personalized and dynamic treatment options, which could transform the way diabetes is managed in the future. However, despite the promising advancements, several challenges remain, including scalability, cost, regulatory approval, and long-term safety concerns. To overcome these obstacles, interdisciplinary research and collaboration between academia, industry, and regulatory bodies are crucial. Such partnerships will help accelerate the translation of these breakthroughs into clinical practice, ensuring that they are both effective and accessible to a wide range of patients. Nanotechnology holds immense potential to improve the quality of life for individuals with diabetes. By addressing current treatment limitations and offering more precise, less invasive solutions, it offers a pathway toward more efficient and personalized diabetes care. With continued research and development, the future of diabetes management looks increasingly promising.

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Author Contributions

S.A. conceptualized the review, drafted the manuscript, and supervised the overall research. **S.G.** conducted the literature review and contributed to manuscript writing. **S.A.A.** assisted in data collection and analysis. **M.K.** reviewed and edited the manuscript for intellectual content and provided technical expertise.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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