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Novel Drug Delivery Systems for Antidiabetic Therapy: Current Status and Future Perspectives

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ABSTRACT:

Diabetes mellitus is a global metabolic disorder requiring long-term management, and conventional antidiabetic therapies frequently encounter difficulties like poor bioavailability, rapid degradation, frequent dosing, and low patient compliance. Novel Drug Delivery Systems (NDDS) have attracted a lot of interest for improving therapeutic outcomes through controlled, targeted, and efficient drug delivery. Nanocarriers including polymeric nanoparticles, nanocapsules, liposomes, and lipid nanoparticles enhance drug stability, prolong circulation, and facilitate better absorption, especially for peptide-based drugs like insulin. Glucose-responsive systems using phenylboronic acid or glucose oxidase further enable self-regulated insulin release, mimicking natural physiological mechanisms. Advances in oral insulin delivery, gene therapy, and stem-cell–assisted nanoplatforms offer promising alternatives to invasive treatments. Although NDDS show excellent potential in enhancing safety and efficacy, challenges remain regarding large-scale manufacturing, toxicity, and regulatory approval. Continued innovation is expected to transform diabetes management into a more precise and patient-friendly therapy.

Keywords: Novel Drug Delivery Systems (NDDS), Diabetes Mellitus, Nanoparticles, Polymeric Nanocapsules, Liposomes, Lipid Nanoparticles, Glucose-Responsive Delivery, Oral Insulin, Gene Therapy

INTRODUCTION

Diabetes mellitus (DM) has become a global epidemic, ranking as the fifth leading cause of mortality in the majority of both developed and developing nations. A common metabolic illness and non-infectious endocrine ailment, DM is linked to hyperglycemia, or elevated blood glucose levels, which are brought on by the body's compromised capacity to metabolize glucose. Around 693 million individuals are predicted to have DM between 2017 and 2045, as the number of DM cases continues to climb globally.[1] The increased prevalence of type 2 diabetes is the primary cause of this circumstance. One of the two primary forms of diabetes is type 2, while the other is type 1. Insulin shortage often results from the death of pancreatic beta cells in type 1 diabetes, an autoimmune illness. Type 2 diabetes is a common metabolic disease caused by several factors, including poor insulin production, insulin-sensitive tissue resistance, aging, and environmental factors including stress and obesity [2].

Weight loss, impaired eyesight, polyuria, and polydipsia are typical signs of diabetes. Growth retardation and susceptibility to some infections are common in people with persistent hyperglycemia. Long-term effects of DM on many bodily systems are seen in Individuals with high blood sugar levels. Blindness, neuropathy, exocrine gland insufficiency, renal failure, and foot amputation are examples of long-term consequences [3]. Additionally, diabetes raises the possibility of hypertension and cardiac failure and other cardiovascular conditions. Hyperglycemia, or persistently elevated blood sugar, is a hallmark of diabetes, a chronic metabolic disease brought on by deficits in either insulin production, insulin action, or both. Long-term issues that impact different organs may result from the compromised glucose metabolism [4]. Diabetes affects millions of individuals worldwide and necessitates continuous blood glucose monitoring, making treatment especially difficult. The primary therapeutic choices for the treatment of diabetes have always been traditional medication delivery techniques like oral tablets and injectable formulations [5].

While the main cause of type 1 diabetes is an absolute lack of insulin, type 2 diabetes is characterized by varying degrees of reduced insulin secretion, elevated insulin resistance, and glucose production [6].

Small endogenous, non-coding RNA molecules known as microRNAs (miRNAs) have the ability to alter the expression of the genes they target. Its biogenesis and pathogenic function have significantly progressed since its discovery, revolutionizing the study of molecular biology. Furthermore, persistent extracellular/circulating miRNAs that are shielded from the activities of endogenous ribonucleases have been discovered in tissues and biological fluids such as blood, according to current research [7]. A major global health concern is type 2 diabetes mellitus (T2DM). The previous ten years have seen a significant increase in incidence. T2DM has been diagnosed

using a variety of assays. However, the creation of biomarkers is crucial for early detection and development [8].

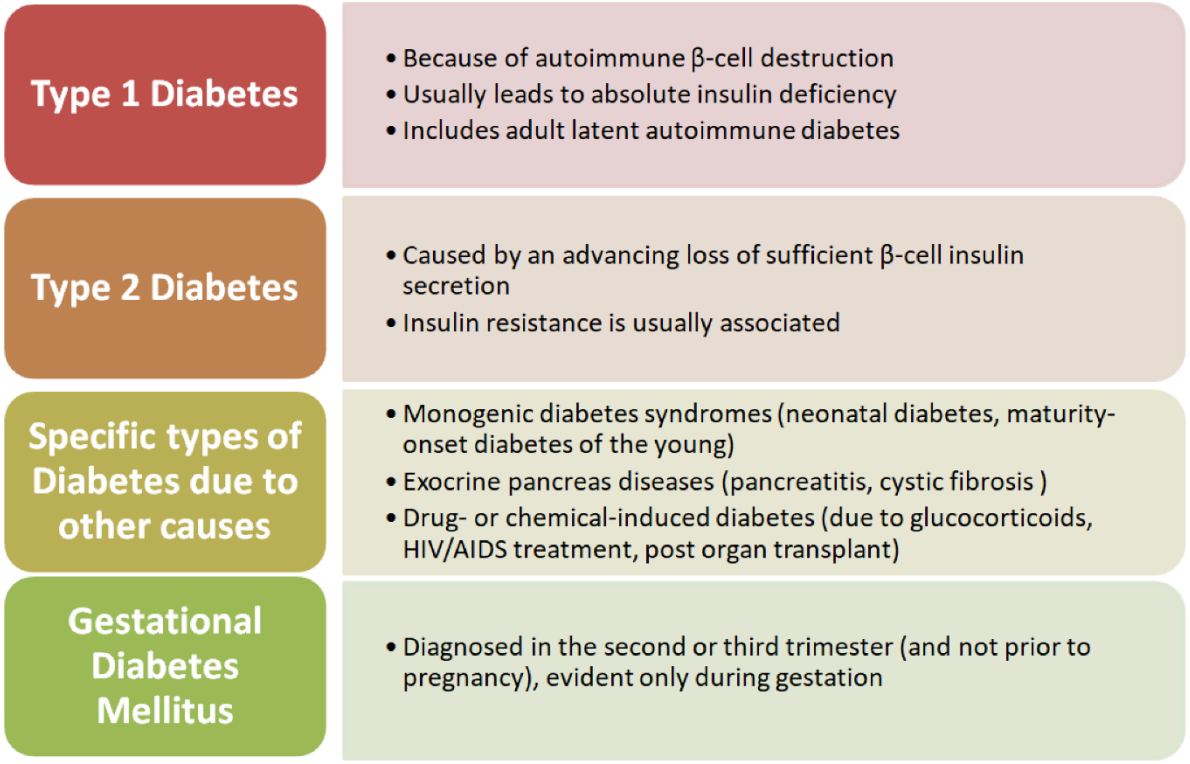

Fig 1: Types of Diabetes Mellitus

TYPES 1 DIABETES MELLITUS

T1DM can be identified long in advance of the onset of aberrant insulin production, with a consistent decrease beginning at least two years prior to diagnosis. Simultaneously, β-cell sensitivity to glucose decreases. The final insulin response increases as the initial insulin response falls, which may be a sign of a compensatory mechanism. The reduction in insulin sensitivity continues to accelerate in the early post-diagnosis phase [9]. Insulin secretion has been shown to fall biphasically in the initial years after diagnosis, with the first year being more difficult than the second. After a diagnosis is obtained, insulin secretion may continue to decline for years until little to no insulin is produced [10]. Even in the normal range, elevated glucose levels are indicative of type 1 diabetes. Significant glucose fluctuations occur when T1D manifests. Metabolic indicators, such as dysglycemia, may help predict the onset of diabetes in at-risk individuals more precisely. To further enhance prediction, risk Ratings can consider changes in glucose and C-peptide levels [11].

Idiopathic T1D

"Idiopathic diabetes," a rare form of T1D that is less severe than autoimmune T1D and is not brought on by autoimmunity, has been documented. Both insulin insufficiency and episodic

ketoacidosis can occur in people with idiopathic diabetes. People with Asian or African ancestry are more likely to have this variation [12].

Fulminant T1D

Serum C-peptide levels, a measure of the endogenous production of insulin, are undetectable while blood glucose levels are high (288 mg/dL), and keto-acidosis happens soon after hyperglycemia begins. This disorder, which has been mostly described in East Asian countries, affects about 20% of Japanese individuals with acute-onset T1D (5000–7000 cases). It results in essentially no remaining insulin production due to the extremely rapid and nearly total death of β-cells. Hereditary and environmental factors are the primary causes of this illness. An antiviral immune response may result in the death of pancreatic β-cells through an enhanced immune response without observable autoantibody production against these cells. Reports of this kind of diabetes during pregnancy have also been made [13].

Type 2 Diabetes Mellitus

To maintain appropriate glucose levels, insulin production fluctuates greatly in relation to insulin sensitivity. The curvilinear link between insulin secretion and sensitivity is measured by the disposition index. Additionally, people with type 2 diabetes have a low disposition index, which makes it difficult for them to effectively increase their insulin production in order to fight insulin resistance [14].Given the degree of their insulin resistance, even when insulin-resistant obese T2D patients have greater absolute insulin levels than insulin-sensitive lean control individuals, the levels are still too low. Glucose stimulation causes the initial phase of insulin production to be drastically decreased or abolished. Over time, hyperglycemia often gets worse and is harder to treat. Another characteristic of T2D development is the ongoing reduction in β-cell function [15].

Gestational Diabetes Mellitus

Hyperglycaemia during pregnancy raises the possibility of negative effects for the mother, foetus, and baby. Whether the hyperglycaemia takes on the T2D form that was identified prior to or during pregnancy, there is still a risk. Adult diabetes is more likely to develop in newborns whose moms had gestational diabetes. Hyperglycaemia during pregnancy, which results in bigger neonates, is the main cause of the increased prevalence of pregnancy-related problems, including preterm birth, large-for-gestational-age births, macrosomia (birth weight > 4.5 kg), caesarean delivery, and preeclampsia [16]. Evaluation of fasting blood sugar levels, blood sugar levels following a 75-gram oral glucose load, and other pertinent indicators are among the criteria used to identify gestational diabetes [17].

NOVEL DRUG DELIVERY SYSTEM (NDDS)

Novel Drug Delivery Systems (NDDS) are methods, formulations, technologies, and systems for safely delivering a pharmaceutical chemical to the body in order to provide the intended therapeutic effects. In contrast to traditional drug delivery methods, NDDS is a drug delivery system. It combines cutting-edge methods with novel dosage forms that are superior to traditional dosage forms. Novel drug delivery systems provide several benefits, including optimal dosage at the ideal time and place, effective use of costly medications, lower manufacturing costs, patient benefit, and enhanced comfort and quality of life [18].

Novel drug delivery systems are a new area of pharmacy research and innovation that has been sparked by the pharmaceutical industry's growing need for improved therapeutic efficacy and fewer side effects. These methods are intended to overcome the drawbacks of traditional drug delivery, including short half-lives, poor targeting, limited solubility, and bioavailability. The development of effective and secure drug delivery methods, especially biopharmaceutical formulations, has attracted considerable attention both locally and worldwide as the fields of pharmacy, materials science, and biomedicine continue to progress and merge [19].

NANOMATERIAL USED IN THE MANAGEMENT OF DIABETES

Polymeric Nanoparticle

The normal size of polymeric nanoparticles (PNP), which are composed of polymers, ranges from 1 to 1,000 nanometers. There are two types of these tiny particles: solid nanospheres and liquid or solid nano-capsules with a polymeric outer shell [20].

PNPs have unique properties, including the ability to encapsulate different medicinal compounds, tuneable size, and a very high surface area to volume ratio. PNPs are appropriate for drug administration, medical imaging, and other biological applications because of their characteristics [21].

Solvent evaporation, coacervation, and self-assembly procedures are some of the synthesis processes that have a substantial impact on the structure of PNPs. Amphiphilic block copolymers may self-assemble into structures known as micelles or vesicles, which are important for medication administration [22].

Stimuli-responsive compounds, which are activated by environmental changes like temperature or pH variations, can be included into PNPs for controlled drug release. This flexibility minimizes adverse effects while increasing their efficacy in targeting particular organs. PNPs can be surface modified using a variety of chemical techniques to enhance their targeting and biocompatibility. Because of their distinctive structural characteristics and capacity to be tailored for various uses,

these nanoparticles are unique. New therapeutic approaches to the treatment of diabetes and other disorders may be made possible by developments in the use of PNPs [23].

Polymeric Nanocapsule

Polymeric nanocapsules are nanostructures with a core-shell structure, in which a polymeric shell encloses a liquid or solid core. They differ from polymeric nanospheres, which are made of a solid polymeric matrix without a core, due to their special structure. While the shell of polymeric nanocapsules is often formed of biocompatible polymers like poly(lactic-co-glycolic acid) and poly(alkylcyanoacrylate), the core can be made of a variety of materials, such as oils, medications, or other active chemicals. The selection of materials for the shell and core is essential since it affects the stability of the nanocapsule, the release kinetics, and the overall functioning in many applications [24].

There are several ways to create nanocapsules, such as layer-by-layer assembly, interfacial polymerization, and Mini emulsion polymerization. For biomedical applications, the creation of nanocapsules with regulated sizes typically less than 100 nm is made possible by miniemulsion polymerization. The polymeric shell can serve as a diffusion barrier for the release of the encapsulated core material in controlled drug delivery systems, which is very advantageous. Different polymer mixes can be used to chemically modify nanocapsules in order to improve their performance. Polymeric nanocapsules' structural features are essential to their operation because they offer a safe environment for the contents they contain. In response to particular stimuli, such pH or temperature changes, this may allow the responsive systems to release their contents. Because therapeutic chemicals may be released in accordance with the physiological state of the target areas, this responsiveness is very useful in targeted medication delivery. Additionally, their characteristics can be changed to enhance their targeting and biocompatibility for greater therapeutic effectiveness [25].

Liposomes

Liposomes are spherical vesicles made of lipid bilayers that are used in biomedical applications such as drug delivery. Lipid content determines the structure of these nanoparticles and affects their size, charge, fluidity, stability, and other physicochemical characteristics. Phospholipids, which are frequently altered with different components to improve their function, normally make up the lipid bilayer. According to a recent study, adding cholesterol to liposomes has a major impact on membrane fluidity and permeability, which affects medication release rates [26]. Lipids are arranged into bilayers in an aqueous environment during the self-assembly process that creates liposomes. Numerous variables, including temperature, the concentration of lipids, and the presence of other chemicals, might have an impact on this process. Recent research has demonstrated that some

methods, including micromixing in acoustic fluids, may precisely manipulate the sizes and forms of liposomes, enabling them to be specially designed for targeted drug administration [27].

Designing liposomes also depends on how they interact with biological systems. Liposomes change their biodistribution when biological fluids penetrate them and create a protein corona. The liposomes' hydrophobicity, surface charge, and surrounding proteins all affect the corona. Depending on the particular interactions with the target cells, cationic liposomes can either facilitate or prevent cellular absorption by attracting negatively charged proteins [28].

These nanoparticles are added to liposomal structures in research, which has been shown to improve their functioning. They can be included into the liposomal bilayer, which offers further characteristics like photothermal or magnetic responsiveness. For instance, magneto-liposomes, whose magnetic characteristics allow for regulated liposome movement, have been developed to target medication delivery and imaging applications. Liposome nanoparticles have a complicated structure, and their size, surface, and lipid content all affect how well they carry drugs [29].

Lipid Nanoparticle

Lipid nanoparticles (LNP) are recognized as versatile drug delivery vehicles, particularly for genetic material and medicinal chemicals. Although LNPs and liposomes have a similar shape, LNPs differ from liposomes in that they have a single phospholipid layer as opposed to liposomes' several layers [30].

LNPs have inverted micelles inside their core, which is made of a lipid center surrounded by a lipid bilayer. To improve the stability, encapsulation effectiveness, and bioavailability of enclosed medications, this structure can be altered. These nanoparticles' ability to interact with biological systems and deliver drugs effectively depends on their core-shell structure [31].

Phospholipids in water spontaneously form bilayer vesicles known as lipid nanoparticles (LNPs). Based on their internal liquid composition, LNPs are classified as either lipid core liposomes (LLNP) or aqueous core liposomes (ALNP). And based on their internal characteristics, LLNP are further divided into solid lipid nanoparticles (SLNs), liquid lipid core (lipid nanoemulsion (LNE), lipid nanoencapsulation (LNC)), and nanostructured lipid nanocarriers (NLCs)[32].

Additionally, studies show that the elasticity of nanoparticle cores may be changed by varying the hydrogel core's crosslinking density, which can then draw proteins from the biological environment. The circulation lifespan of LNPs and their interactions with biological barriers are significantly influenced by their physical properties, including their dimensions and flexibility [33].

Glucose sensitive drug delivery

The management of diabetes has significantly improved because to glucose-sensitive medication delivery systems, especially for the delivery of insulin. These devices can imitate the pancreas'

natural production of insulin by reacting dynamically to variations in blood glucose levels. Changes in the hydrophilicity of the drug delivery vehicle are made possible by the introduction of phenylboronic acid (PBA), a glucose-sensitive component that forms reversible covalent bonds with glucose. When blood glucose levels rise, the delivery system swells or disassembles, making it easier for medications to be released. PBA-based micelles, for example, have shown improved glucose response at physiological pH, which qualifies them for insulin administration [34]. PBA's incorporation into polymeric structures has also shown promise in developing self-regulating systems that effectively control insulin release with little patient intervention. It has also shown promise to include glucose oxidase into medication delivery systems. The oxidation of glucose is catalyzed by glucose oxidase, which also generates hydrogen peroxide. Drugs may be released by pH-sensitive carriers as a result of the local pH being lowered. This glucose-triggered insulin release mechanism is dual-responsive, which can improve the treatment's therapeutic effectiveness. Combining glucose oxidase with other substances, such PBA, also showed a multifunctional system that can successfully combine medication release and glucose sensing activities [35].

The development of glucose-sensitive medication delivery systems has been greatly aided by the use of nanotechnology. Higher drug loading and improved release under typical physiological settings have been made possible by the creation of nanocarriers, such as hybrid nanogels and supramolecular vesicles. A recent research showed significant potential for the practical application of glucose-responsive supramolecular vesicles in the treatment of diabetes by engineering them to release insulin in a regulated manner. These devices may be made to respond to particular bodily cues, increasing their efficacy and lowering the frequency of injections [36].

DRUG DELIVERY USING NANOPARTICLES IN ORAL ADMINISTRATION

Insulin is typically difficult to administer orally because of low absorption and gastrointestinal tract instability. Recent developments in nanotechnology have demonstrated interesting solutions, employing different nanoparticles to improve pharmacokinetics, preserve insulin, and increase absorption. These developments are intended to improve the bioavailability of insulin taken orally. Oral insulin delivery methods based on chitosan nanoparticles—a naturally occurring polysaccharide that is hydrophilic, biocompatible, and biodegradable—have been extensively studied. In diabetic research, these nanoparticles have demonstrated potential in regulating blood sugar. According to research, after administering 100 IU/kg of insulin, chitosan-pentasodium tripolyphosphate nanoparticles may maintain stable blood glucose levels for up to 11 hours [37].

To improve the stability and absorption of insulin, researchers have also looked at the use of other natural polymers, such as alginate and hyaluronic acid. For example, hyaluronic acid-coated

chitosan nanoparticles have shown improved transcellular insulin delivery, which can successfully get beyond the intestinal mucosa's barriers [38].

Another innovative approach to oral insulin administration is provided by pH-responsive nanoparticles. Researchers have produced poly(ester amide) microspheres, which have been shown to interact with intestinal epithelium due to their hydrophobic nature and biodegradability. This interaction can enhance the absorption of insulin and extend its presence in the stomach [39].

Drug delivery methods using oral nanoparticles have demonstrated significant potential in increasing bioavailability and effectiveness. The improved efficacy of nanoparticles in insulin administration is demonstrated by research on these nano-formulations, which shows that nano-encapsulated insulin has a much greater oral bioavailability than free insulin. Research has demonstrated that insulin-loaded nanoparticles may decrease blood sugar levels in diabetic animal models for an extended period of time, indicating their potential for human application [40].

DIABETES THERAPY USE IN FOLLOWING DRUG

Metformin

The French doctor Jean Sterne initially documented the use of metformin to treat diabetes in 1957 after seeing its capacity to reduce blood glucose. Despite clear pharmacological distinctions, metformin's image was damaged by its affiliation with other biguanides (buformin, phenformin), which were linked to severe lactic acidosis episodes and, as a result, were withdrawn in the majority of nations in the late 1970s. Metformin is an oral antidiabetic drug and the first-line medication used in the management of Type 2 Diabetes Mellitus (T2DM)**.** It belongs to the class of biguanides and helps to control blood glucose levels, primarily by improving the body's sensitivity to insulin [41].

Sulfonyl urea

In the late 1950s, SUs became the first pharmacological class of oral antidiabetic medications to be commercialized. They are linked to an increased risk of hypoglycemia because they function as insulin-secreting agents regardless of plasma glucose levels. They were discovered in France by Auguste Loubatières and his colleagues. SUs have long played a crucial part in the treatment of type 2 diabetes as a substitute for or addition to metformin. Sulfonylureas are oral antidiabetic drugs used mainly in the treatment of Type 2 Diabetes Mellitus (T2DM)**.** They help to lower blood glucose by stimulating insulin secretion from the pancreas.

These drugs are effective only if β-cells (insulin-producing cells) in the pancreas are still functional. Sulfonylureas are effective, affordable oral agents for controlling blood glucose in Type 2 diabetes. They act by stimulating insulin release from the pancreas but carry risks like hypoglycemia and weight gain**,** so they must be used carefully, especially in elderly patients [42].

Thiazolidine

PPAR-gamma agonists known as thiazolidinediones (TZDs, "glitazones") function as insulin sensitizers. The introduction of TZDs (rosiglitazone, pioglitazone) in the 1990s sparked a lot of interest since insulin resistance is a major component of the pathogenesis of type 2 diabetes and is also regarded as a CV risk marker (factor?), with the goal of improving the CV prognosis of T2DM patients. However, a number of side effects, including weight gain and fluid retention, quickly prompted concerns about TZDs' safety profile [43].

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs: acarbose, miglitol, and voglibose) are oral anti-diabetic medications that lower blood sugar levels by inhibiting the breakdown of carbohydrates (like starch), which reduces the quantity of monosaccharides that the intestines can absorb. Without an increased risk of hypoglycemia, the effects of AGI medication on glycaemic management and bodyweight loss were demonstrated to be superior to placebo; nonetheless, there was an increased incidence of gastrointestinal problems [44].

DPP-4 inhibitors

When DPP-4is (gliptins) were introduced shortly after 2000, they were seen as a significant advancement in the treatment of type 2 diabetes. These substances block the DPP-4 enzyme, which renders GLP-1 inactive. Oral antidiabetic medications are referred to as "incretin potentiators" because GLP-1 raises insulin (and decreases glucagon) release in a glucose-dependent way. They are not linked to an increased risk of hypoglycemia or weight gain when compared to SUs the first reduction in blood sugar levels [45].

GENE THERAPY USING NANOSCALE MATERIAL

The use of nanoparticles in gene therapy for the treatment of diabetes has been investigated, and in several studies, they have proven to be a crucial technique. The goal of gene therapy is to either repair damaged genes or replace them with healthy ones so that the body can fend off illness. It shows promise in treating a variety of illnesses, including diabetes. Enhanced transport efficiency, less toxicity, and the capacity to target certain tissues or cells are just a few benefits of using nanoparticles in gene therapy. Because of their special therapeutic potential, researchers have used a variety of nanoparticles in antidiabetic gene treatments.

One benefit of utilizing nanoparticles for gene delivery is that they may encapsulate genetic material, such as plasmid DNA and short interfering RNA, which can change the expression of certain genes associated with diabetes. Tumor necrosis factor α, a protein important in the healing of diabetic wounds, may be suppressed by lipid nanoparticles [46].

Patients with diabetes may benefit from our altered nanoparticles' improved targeting and biocompatibility. Additionally, studies demonstrate that therapeutic genes supplied by nanoparticles

can efficiently control glucose metabolism. Oral administration of insulin plasmid-loaded nanoparticles to diabetic mice maintained therapeutic gene expression and markedly decreased hyperglycaemia [47].

The encapsulating properties of lipid-based nanocarriers were also studied, and they were used in gene therapy to counteract inflammatory cytokines during the chronic wound healing process in diabetic patients. The use of polyplex nanoparticles containing certain genes to functionalize gene-activated collagen scaffolds has also demonstrated promise in improving the regeneration ability of human adipose-derived stem cells in diabetic patients. Silver nanoparticles' therapeutic promise in the treatment of diabetes has also been acknowledged in a recent research [48].

Nanoparticle in stem cell therapy

A potential area of diabetes treatment is cell therapy. The main goals of stem cell treatment are to promote wound healing, lower complications, and repair and enhance the function of β-cells, which produce insulin. Stem cell treatment can be used to regenerate these β-cells that produce insulin. Research has demonstrated that mesenchymal stem cells may successfully differentiate into cells that secrete insulin. These mesenchymal stem cells have the potential to treat diabetes since they are generated from organs like bone marrow and adipose tissue [49].

CURRENT STATUS OF ANTI-DIABETIC DRUG

Oral insulin: big progress in preclinical and early clinical work, but *no widely approved oral insulin yet*. Multiple technologies (nanoparticles, enteric coatings, permeation enhancers, carrier-mediated systems) show promising injection-comparable bioavailability in animals; several oral insulin candidates are in Phase 1–2 trials or advanced preclinical development. The field is maturing but still faces reproducibility, safety and manufacturing scale-up hurdles [50].

Long-acting/extended-release GLP-1 and depot biologics clinical success: long-acting depot and microsphere formulations for GLP-1 receptor agonists (weekly/monthly dosing) are an established success story (examples include PLGA microsphere depots). Newer depot platforms and sustained-release technologies are actively being developed for broader indications (diabetes + obesity) [51].

Weekly insulin (injectable) very active clinical pipeline but regulatory caution**:** companies (e.g., Novo Nordisk, Eli Lilly) have weekly long-acting insulins in late-stage development. Regulators and advisory panels have flagged hypoglycaemia risk and require careful dosing/monitoring data before approvals — so timing to market depends on safety data and advisory outcomes [52].

Nanocarriers / nanoparticles for small molecules and peptides (metformin, insulin, GLP-1): intense preclinical work shows improved bioavailability, targeting, and reduced side effects. Examples include metformin-loaded nanoparticles and engineered nanoplatforms for GLP-1R targeting —

most are at preclinical to early clinical stages. Safety (toxicity, immunogenicity) and consistent manufacturing remain the main barriers [53].

Sustained-release microspheres, implants, and combination drug-device systems: these platforms (biodegradable microspheres, implants, long-acting injectables) are moving from concept to clinic for incretins and insulin analogs; some are already commercially used (exenatide long-acting formulations), while newer platforms aim at monthly or multi-month dosing [54].

FUTURE PROSPECTIVE OF ANTIDIABETIC DRUG

The landscape of antidiabetic therapy is shifting from simply lowering blood glucose toward safer, more convenient, and disease-modifying strategies. Several converging trends are likely to shape the next decade:

1. **Oral and non-invasive peptide delivery:** Overcoming the gastrointestinal and enzymatic barriers that have historically restricted peptide drugs will remain a priority. Advances in engineered carriers, permeation enhancers, and protective coatings aim to make oral insulin and other peptide therapies (GLP-1 analogues, dual agonists) feasible without injections. Parallel work on inhaled, nasal, and transdermal routes seeks to offer patient-friendly alternatives that preserve efficacy while reducing treatment burden [55].
2. **Long-acting and depot formulations:** Sustained-release platforms including biodegradable microspheres, implants, and novel depot chemistries will expand the interval between doses (weekly, monthly, or longer). These formulations can improve adherence, smooth pharmacokinetic fluctuations that cause hypoglycaemia, and enable combination delivery (for example, insulin plus an incretin) from a single device or injection [56].
3. **Precision delivery and targeting:** Nanocarriers and ligand-directed systems will increasingly be used to direct drugs to specific tissues (pancreas, liver, adipose) or cell types (β-cells, hepatocytes). Targeted delivery promises to enhance potency, lower systemic exposure and side effects, and open opportunities for lower-dose or combination regimens tailored to patient phenotypes [57].
4. **Combination biologics and multi-agonists:** Drugs that engage multiple metabolic pathways simultaneously (e.g., GLP-1/GIP/ glucagon multi-agonists) show potential to produce greater weight loss and glycemic control than single-target agents. Future delivery systems will focus on stabilizing and co-delivering these complex biologics while maintaining favorable safety profiles [58].
5. **Smart and responsive systems:** Closed-loop and glucose-responsive formulations that release drug in response to blood glucose or other biomarkers are an active direction. Integrating

sensing technologies with drug reservoirs chemically (glucose-sensitive polymers) or electronically (sensor-controlled pumps) could sharply reduce hypoglycaemia risk and improve glycaemic time-in-range.

6. **Personalized and phenotype-driven therapies:** As genetic, metabolic and behavioural profiling become cheaper and more common, choice of agent and delivery format will be increasingly personalized. For example, therapies may be matched to residual β-cell function, insulin resistance phenotype, or comorbidity profile (cardiovascular, renal), and dosing schedules adapted to lifestyle and adherence patterns [59].

7. **Manufacturing, safety and regulatory innovation:** Widespread adoption of novel delivery technologies depends on scalable manufacturing, predictable long-term safety, and regulatory frameworks that can evaluate complex platforms. Expect more emphasis on reproducible production methods, standardized toxicity testing for nanomaterials, and adaptive clinical trial designs that measure meaningful patient-centered outcomes.

8. **Broader public-health integration:** Beyond individual drugs, delivery innovations will be linked with digital health (telemedicine, adherence apps), supply-chain improvements, and cost-reduction strategies to make advanced therapies accessible in diverse healthcare settings [60].

CONCLUSION

The development of novel drug delivery systems has opened a new era in the management of diabetes mellitus. Conventional antidiabetic therapies often face limitations such as poor bioavailability, frequent dosing, and patient non-compliance. NDDS approaches—such as nanoparticles, liposomes, microspheres, transdermal patches, oral and nasal systems—offer improved therapeutic outcomes by enhancing drug stability, prolonging release, and providing targeted delivery. These systems not only improve glycaemic control but also reduce adverse effects and dosing frequency, thereby enhancing patient adherence.

Recent advances in nanotechnology, biodegradable polymers, and smart drug carriers have made it possible to design controlled and site-specific formulations for insulin and other antidiabetic agents. Although challenges like large-scale production, long-term safety, and regulatory approval still remain, continuous research and innovation promise a future where diabetes management becomes more effective, convenient, and personalized. Thus, NDDS holds great potential to revolutionize antidiabetic therapy and significantly improve the quality of life for diabetic patients.

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DECLARATION OF CONSENT:

We, the authors of the manuscript titled Insights into the **Novel Drug Delivery Systems for Antidiabetic Therapy: Current Status and Future Perspectives** declare that the work is original, has not been published or submitted elsewhere, and that all authors have read and approved the final version of the paper. All authors consent to the publication of this manuscript in the journal and accept responsibility for its content.

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