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REVIEW article

Transforming diabetes management: Promising nano-formulation approaches in drug delivery

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Abstract: Diabetes mellitus is a chronic metabolic condition that is marked by hyperglycemia, insulin resistance, and compromised pancreatic beta-cell functionality. Traditional approaches to anti-diabetic treatment are typically limited by insufficient solubility, bioavailability, frequency of administration, and safety, causing poor therapeutic results. Nanotechnology-based drug delivery systems have become a promising approach to conquer these hurdles by enhancing solubility, stability, delivery by targeting, and release of drugs. Various nano-formulations, such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, dendrimers, nano-emulsions, and herbal-based nanoparticles, are identified in this review and have been applied in the delivery of specific anti-diabetic agents, including metformin, insulin, glibenclamide, pioglitazone, sitagliptin, and bioactive herbal compounds, such as curcumin and berberine. The main points of discussion are mechanisms of action, targeting strategies, pharmacokinetics, pharmacodynamics, evaluation parameters, clinical status, regulatory considerations, and prospects, including personalized and glucose-responsive nanomedicine. Combining nanotechnology with smart drug delivery systems can improve therapeutic effect, minimize side effects, enhance patient compliance, and offer precision medicine strategies for diabetes treatment. This overview highlights how nano-formulations can revolutionize traditional diabetes treatment and pave the way for next-generation, patient-centric therapies.

Introduction

Diabetes mellitus (DM) is a long-lasting metabolic condition due to chronic and persistently elevated glucose levels caused by impairments in either the secretion of insulin, the activity of insulin, or both. The state results in disruptions in carbohydrate, fat, and protein metabolism, and eventually damages vital organs, including the eyes, kidneys, nerves, heart, and blood vessels in the long term [1]. DM is already an epidemic in the world. The International Diabetes Federation (IDF) stated that there were about 463 million adults with DM in 2019, comprising about 9.3 percent of the world population, with the number projected to reach 700 million (10.9%) by the year 2045. Likewise, the 10th edition of the IDF Diabetes Atlas (2021) presented global prevalence rates of 10.5, 8.8, and 10.9 as the projected rates in South-East Asia and India, respectively, by 2045. This worrying trend highlights the importance of implementing more effective management programs because DM presents a gigantic social, economic, and public-health burden around the globe [2, 3].

Although several therapeutic agents are available, including insulin, oral hypoglycemic agents like biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors, the

treatment of DM is problematic [4, 5]. The traditional anti-diabetic agents typically do not sustain long-term glycemic regulation and are linked with various disadvantages, such as low bioavailability, low solubility, low biological half-life, and undesirable side effects, such as hypoglycemia and weight gain. Additionally, most orally ingested medications have a high rate of hepatic metabolism and degradation in the gastrointestinal tract, which decreases their treatment efficacy. Multiple daily doses or injections decrease patient compliance and quality of life, and non-specific drug delivery frequently results in systemic side effects [4]. Thus, the optimization of the system of drug delivery to eliminate these constraints has become a significant topic in modern pharmaceutical science. As a solution to these problems, more sophisticated drug-delivery methods have been devised to improve the pharmacodynamics and pharmacokinetics of anti-diabetic agents. These systems are designed to enhance bioavailability, to produce controlled and sustained release of medicine, to hinder the enzyme- and acid-catalyzed degradation of drugs, and to deliver medicines to specific tissues, e.g., pancreatic beta cells or hepatic cells. Intelligent delivery that is sensitive to physiological stimuli such as glucose levels is another advancement of accurate and convenient therapy. Not only do these advanced delivery systems enhance the therapeutic outcome, but they also decrease the frequency of dosing and adverse effects, which results in increased adherence to the treatment in the patient. Amid these new strategies, nanotechnology has presented remarkable potential in changing the management of DM. Polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nano-emulsions, dendrimers, liposomes, and nanocrystals are all nanocarriers that have important advantages over traditional formulations [6]. Their reduced size contributes to drug solubility, stability, intestinal absorption, and cellular absorption, resulting in increased bioavailability [6]. Moreover, nanocarriers can deliver controlled and sustained drug release, prevent degradation of sensitive molecules such as insulin, and be targeted or receptor-mediated to pancreatic beta cells [7]. Glucose-responsive release or co-delivery of other therapeutic agents (antioxidants and hypoglycemics) can be achieved with functionalized nanoparticles [8]. Nano-formulations can also minimize systemic side effects because they avoid high plasma drug peaks and concentrations at the target site. Together, these qualities have rendered nanotechnology-based preparations a valuable approach toward improving the therapeutic effectiveness and safety of the anti-diabetic preparations. The design and preclinical evaluation of nano-based anti-diabetic drug delivery systems have gained significant momentum, but there are still a number of translational challenges to overcome, including mass production, long-term toxicity testing, cost-efficiency, and regulatory approval. But there are still untapped opportunities in the use of nanotechnology combined with pharmaceutical sciences in the design of effective, patient-compliant, and targeted treatments of DM.

Pathophysiology of DM: DM is a multifactorial and chronic metabolic condition that is associated with unresolved hyperglycemia due to impairment of insulin secretion, insulin activity, or both. The condition causes changes in carbohydrate, lipid, and protein metabolism and contributes to the emergence of microvascular and macrovascular complications, including neuropathy, nephropathy, retinopathy, and cardiovascular disease [9]. According to etiology and clinical features, DM falls into the broad categories of Type 1 DM (T1DM), Type 2 DM (T2DM), and gestational DM (**Figure 1**).

Insulin-dependent DM, known as T1DM, is an autoimmune disorder that causes the selective destruction of the pancreatic beta cells in the islets of Langerhans, leading to an absolute insulin deficiency [10]. Autoimmune-mediated inflammation is mediated by autoantibodies and autoreactive T-cells targeting beta-cell antigens, including insulin, glutamic acid decarboxylase, and islet cell antigen 2. Disease onset has been linked to genetic predisposition, viral infection, and environmental triggers [11]. On the contrary, T2DM, which constitutes about 90.0% - 95.0% of all DM, is mainly related to insulin resistance and dysfunction of the beta cells. In this case, the secretion of insulin at first accelerates to counteract the decreased sensitivity of the peripheral tissues, but the chronic metabolic stress results in beta-cell depletion, apoptosis, and insulin secretion defects [12]. GDM, in contrast, is an issue of pregnancy caused by insulin resistance due to placental hormones and inadequate pancreatic adjustment. Not only does this form raise the risk of perinatal complications, but it also predisposes the mother and the child to developing T2DM in the future [13].

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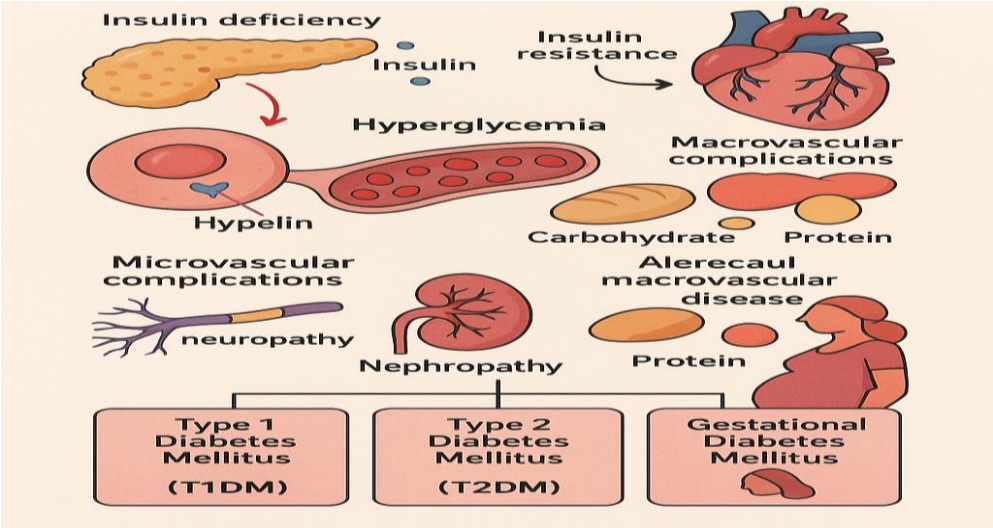


Figure 1: Pathophysiology of diabetes mellitus - overview of insulin dysfunction, metabolic alterations, and associated complications

In physiological conditions, the homeostatic process of glucose is highly regulated by the interaction between insulin and glucagon. After food intake, a high blood glucose level causes pancreatic beta cells to produce insulin, which attaches to insulin receptors on target tissues (liver, skeletal muscle, and adipose tissue) to aid in glucose uptake and storage [14]. During the fasting condition, the glucagon secreted by alpha cells stimulates glycogenolysis and gluconeogenesis in the liver to sustain basal glucose levels. This balance is altered in DM, which causes hyperglycemia and imbalance in metabolism. T2DM is associated with insulin resistance, where the insulin-sensitive tissues do not respond to insulin signaling. Insulin resistance at the molecular level is linked to impaired phosphorylation of insulin receptor substrate (IRS) proteins, decreased phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) activation, and glucose transporter 4 (GLUT4) translocation dysregulation [15]. Insulin resistance is also worsened by chronic inflammation, oxidative stress, mitochondrial dysfunction, and free fatty acid deposition, which disrupts cellular signaling cascades [16].

It is directly based on this knowledge of its molecular pathogenesis that key therapeutic targets in DM can be identified. Strategies revolve around enhancing insulin sensitivity, provoking insulin secretion, decreasing hepatic glucose production, and increasing peripheral Glucose uptake [17]. Therapies that involve incretin receptors like glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors enhance beta-cell activities and inhibit glucagon secretion. Other methods focus on the sodium-glucose co-transporter-2 (SGLT2) present in the renal tubules to stimulate glucose release [18]. Also, the pathways in oxidative stress, inflammation, and B-cell apoptosis, including NF-kB, AMPK, and PPAR-g, have become new molecular targets for drug development [19]. Knowledge of these processes not only helps to make pharmacological interventions but also to design nanotechnology-based delivery systems, which can selectively target anti-diabetic drugs to their target sites and enhance treatment efficacy and reduce systemic side effects.

Difficulties with traditional anti-diabetic treatment: Although many anti-diabetic drugs are available, standard therapeutic interventions are unable to produce optimal glycemic control in patients with a variety of pharmacokinetic and pharmacodynamic constraints. Among the main issues with traditional anti-diabetic agents are low oral bioavailability and low solubility. Repaglinide, glibenclamide, and pioglitazone, to name a few, are low aqueous solubility drugs and are characterized by erratic plasma profiles and subtherapeutic plasma concentrations following oral ingestion. Drug solubilization and absorption is further affected by the gastrointestinal environment, volatile in pH and activity of enzymes. This results in erratic therapeutic efficacy, especially with poorly dissolving lipophilic drugs that demand novel formulation methods to increase dissolution and systemic accessibility (**Figure 2**).

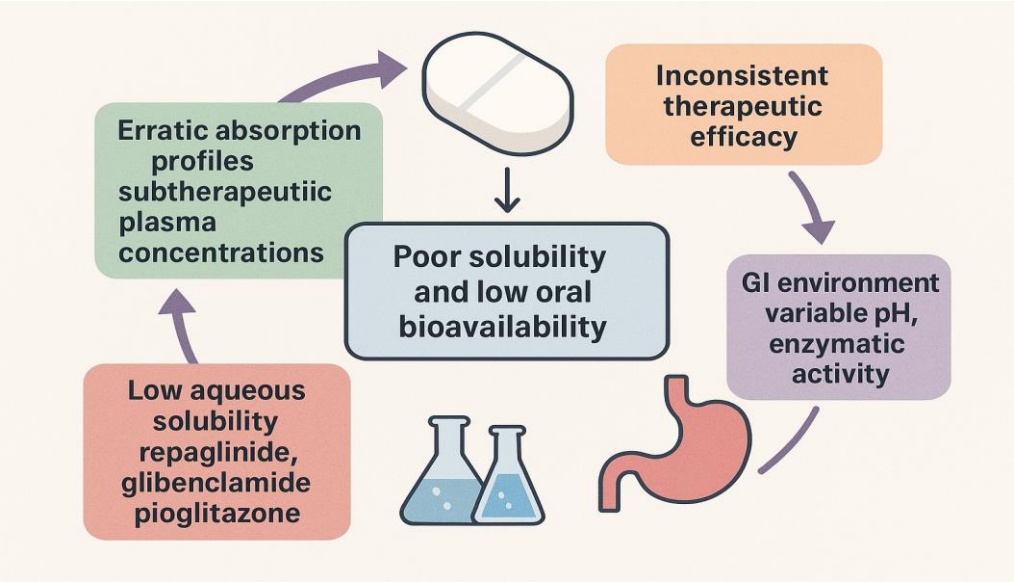


Figure 2: Challenges associated with conventional anti-diabetic drugs - factors affecting solubility, absorption, and therapeutic efficacy

A second significant weakness is that it requires frequent dosing, which directly leads to patient non-compliance. Traditional oral preparations of insulin secretagogues, biguanides, or sulfonylureas require several injections a day to stabilize plasma glucose levels. Nevertheless, the intensive dosing regimens are commonly cumbersome and add to the chances of missed doses, leading to intermittent glycaemic fluctuations and poor glycemic regulation. Additionally, adherence to therapy is further diminished by side effects of some oral anti-diabetic medications, like gastrointestinal discomfort with metformin or hypoglycemia with sulfonylureas. This highlights the need for sustained and modulated drug delivery systems that would be able to maintain therapeutic levels over long periods and reduce the frequency of doses and the side effects.

Further impediments to effective anti-diabetic therapy are gastrointestinal degradation and hepatic first-pass metabolism. The peptide-based drugs, including insulin and analogs of glucagon-like peptide-1 (GLP-1), are highly vulnerable to degradation in the gastrointestinal tract, which makes their administration orally ineffective [20]. Moreover, numerous small-molecule anti-diabetic drugs are metabolized extensively by the hepatic system before entering systemic circulation, dramatically decreasing their bioavailability and pharmacological potential. Not only does this metabolic loss require higher doses to produce efficacy but also it is more prone to cause systemic toxicity and metabolic overload on the liver. Lastly, traditional dosage regimens do not always produce the desired and sustained delivery of drugs, which is essential in long-term DM management. The vast majority of anti-diabetic agents are systemic, not tissue-specific in targeting pancreatic beta cells, hepatic tissues, or insulin-responsive peripheral cells. This random distribution may cause ineffective drug concentration at the site of action and unwanted side effects in non-target organs. Continued administration is also required to ensure a stable plasma glucose level to avoid glycemic variability, which causes secondary diseases like neuropathy and retinopathy. To address these issues, scientists are turning more to the use of nanotechnology-driven drug delivery systems that can improve the solubility, absorption, bypass hepatic metabolism, and targeted delivery of drugs in a controlled way [21]. These nano-formulation approaches have great potential in enhancing therapeutic efficacy and increasing patient compliance in the management of DM.

Nanotechnology-based approaches for anti-diabetic therapy: Nanotechnology has emerged as a promising frontier in pharmaceutical sciences, offering innovative solutions to overcome the limitations associated with conventional anti-diabetic drug delivery systems (**Figure 3**). The nanoscale dimension of these carriers, typically ranging from 1 to 100 nm, allows precise control over physicochemical properties such as particle size, surface charge, and morphology, which can significantly influence drug solubility, permeability, and

stability [22]. In anti-diabetic therapy, nanotechnology-based delivery systems including polymeric nanoparticles, solid lipid nanoparticles, nano-micelles, liposomes, nano-emulsions, dendrimers, and metallic nanoparticles have been developed to enhance the pharmacokinetic and pharmacodynamic performance of drugs like insulin, metformin, glibenclamide, and pioglitazone [23]. These systems enable site-specific delivery and controlled release of therapeutic agents, thereby minimizing systemic side effects and improving glycemic control in diabetic patients [24].

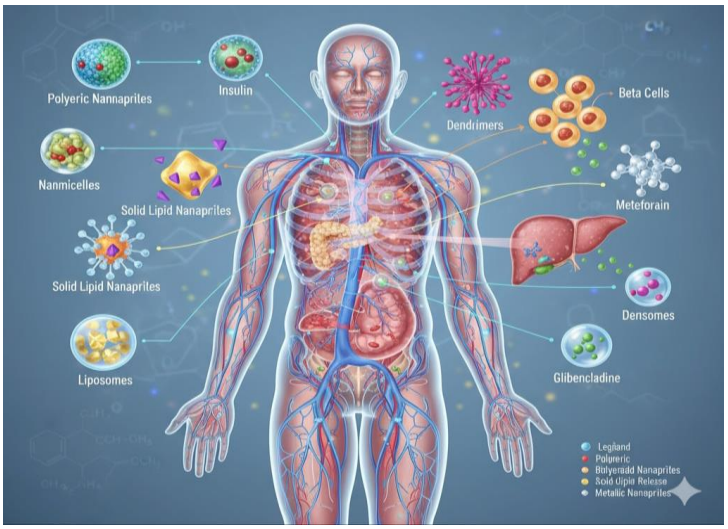


Figure 3: Nanotechnology in anti-diabetic drug delivery: Site-specific and controlled release for improved glycemic control

The advantages of nano-formulations over conventional systems lie primarily in their ability to overcome solubility and permeability barriers while providing sustained and targeted drug release. Unlike traditional oral or parenteral formulations that often exhibit erratic absorption and poor bioavailability, nano-formulations enhance drug dissolution due to their large surface area-to-volume ratio and improved wetting properties [25]. Additionally, the encapsulation of drugs within biodegradable nanocarriers protects them from enzymatic degradation and premature metabolism in the gastrointestinal tract and liver. This protection prolongs systemic circulation time and ensures more consistent plasma concentrations, leading to enhanced therapeutic efficacy. Furthermore, nano-formulations can be engineered for targeted delivery to specific tissues such as pancreatic β-cells, liver, or muscle, through surface functionalization with ligands like antibodies, peptides, or folic acid, thereby increasing site-specific drug accumulation and reducing off-target effects.

The mechanisms underlying the enhanced bioavailability and cellular uptake of nano-formulations are multifactorial. Nanocarriers can cross biological membranes via transcellular and paracellular pathways, often facilitated by endocytosis mechanisms such as clathrin-mediated, caveolae-mediated, or macro-pinocytosis. Their small size and modifiable surface charge enable them to interact effectively with cell membranes, enhancing internalization into target cells. For hydrophobic drugs, the nanoscale encapsulation enhances solubility and improves passive diffusion across lipid membranes, whereas for macromolecular drugs like insulin, nanoparticle-based oral formulations can exploit M-cell-mediated uptake in Peyer's patches to enter systemic circulation [26]. In addition, the surface modification of nanoparticles with mucoadhesive polymers such as chitosan can increase their residence time at absorption sites, facilitating better uptake through mucosal tissues [27-29]. Collectively, these mechanisms contribute to improved pharmacological activity, reduced dosing frequency, and greater patient adherence. Nanotechnology thus represents a transformative platform for anti-diabetic therapy, addressing the key challenges of conventional drug delivery through controlled release, enhanced permeability, and targeted cellular uptake. With continuous advancements in materials science and biocompatible nanocarriers, nano-formulations hold immense potential for next-generation DM management.

Types of nano-formulations used in anti-diabetic drug delivery

Polymeric nanoparticles: Polymeric nanoparticles have gained wide attention for anti-diabetic drug delivery owing to their tunable composition, biocompatibility, and controlled-release characteristics. Biodegradable polymers such as poly (lactic-co-glycolic acid (PLGA), chitosan, and alginate are commonly employed to encapsulate small molecules and peptides like insulin or incretin analogs (**Figure 4**). These nanoparticles protect drugs from enzymatic degradation in the gastrointestinal tract and enhance mucosal absorption through mucoadhesive and transcellular pathways. Surface functionalization with ligands or antibodies enables targeted delivery to pancreatic β-cells or intestinal receptors, improving pharmacokinetic efficiency and glucose-lowering efficacy in preclinical diabetic models [30].

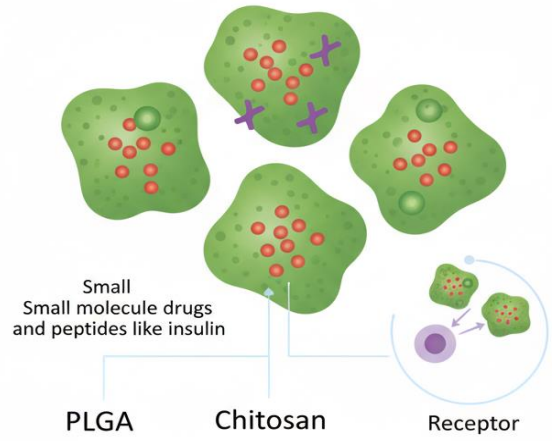


Figure 4: PLGA-chitosan nanoparticle system for targeted delivery of small molecule drugs and insulin

Lipid-Based Nanoparticles (SLNs and NLCs): Lipid-based nanoparticles, comprising Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs), have demonstrated significant potential in improving the solubility and bioavailability of lipophilic anti-diabetic agents. SLNs are formed from solid physiological lipids that offer high biocompatibility and protect the encapsulated drug from acidic and enzymatic degradation. NLCs, developed as a second generation of lipid carriers, incorporate solid and liquid lipids to increase drug-loading capacity and reduce drug expulsion during storage. These carriers exhibit sustained release, improved permeability, and enhanced oral absorption of drugs such as metformin and glibenclamide, providing better glycemic control in vivo [31].

Nano-emulsions and SNEDDS: Nano-emulsions and self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oils, surfactants, and co-solvents that spontaneously form nanosized emulsions upon dilution with gastrointestinal fluids. They are particularly useful for poorly water-soluble anti-diabetic drugs, as the nanoscale droplets increase the dissolution rate and promote efficient absorption through intestinal lymphatic transport. These systems can also be designed with mucoadhesive coatings to prolong intestinal residence time, thereby improving drug uptake and bioavailability. Several preclinical studies have demonstrated enhanced plasma drug concentration and improved glycemic response with SNEDDS formulations compared to conventional oral dosage forms [32].

Nano-micelles: Nano-micelles are self-assembled structures composed of amphiphilic molecules that form a hydrophobic core surrounded by a hydrophilic shell. This architecture allows the solubilization of hydrophobic anti-diabetic agents and facilitates their diffusion through mucosal barriers. In addition, surface functionalization with targeting ligands can enable receptor-mediated uptake at specific tissues, such as pancreatic or hepatic sites. Nano-micellar systems have shown enhanced dissolution rates and extended hypoglycemic effects in diabetic animal models, making them a promising option for oral and parenteral delivery of antidiabetic therapeutics [33].

Dendrimers: Dendrimers are highly branched, monodisperse macromolecules characterized by a well-defined core-shell structure and abundant surface functional groups. Their interior cavities can encapsulate drugs, while surface moieties can be conjugated with ligands or polymers to improve solubility, stability, and targeted delivery. In anti-diabetic applications, dendrimers such as poly(amidoamine) (PAMAM) have been employed to enhance the solubility of poorly soluble drugs and to deliver bioactive peptides or genes for β-cell regeneration. These systems exhibit controlled release profiles and improved therapeutic efficacy, though cytotoxicity and high-production costs remain challenges to overcome [34].

Nanocrystals: Nanocrystals consist solely of drug particles reduced to nanometer size, eliminating the need for polymeric or lipidic carriers. This approach enhances the dissolution rate and saturation solubility of poorly soluble anti-diabetic drugs through a large surface-area effect. Nanocrystal formulations of compounds like glimepiride and plant-derived polyphenols have demonstrated improved oral absorption and rapid onset of hypoglycemic action. The simplicity of production, stability, and scalability make nanocrystals an attractive alternative for formulating insoluble anti-diabetic drugs [35, 36].

Gold and silver nanoparticles: Metallic nanoparticles, particularly gold and silver, have attracted attention for their multifunctional role in DM management. Gold nanoparticles (GNPs) can serve as insulin carriers or act as insulin-mimetic agents, facilitating trans-mucosal and trans-dermal transport of therapeutic peptides. When conjugated with insulin or specific ligands, they enhance bioavailability and stability while exhibiting minimal immunogenicity. Silver nanoparticles have also been investigated for their inherent antioxidant and anti-inflammatory properties, showing beneficial effects in diabetic wound healing and oxidative stress regulation. However, their potential long-term toxicity necessitates cautious optimization of particle size, coating, and dose [37].

Liposomes and niosomes: Vesicular nanocarriers such as liposomes and niosomes are well-established delivery systems for hydrophilic and lipophilic antidiabetic drugs. Liposomes are composed of phospholipid bilayers that encapsulate the drug within aqueous or lipid compartments, providing biocompatibility and controlled release. Niosomes, formed from nonionic surfactants, offer improved stability, lower production cost, and enhanced entrapment efficiency. Carriers protect drugs like insulin and metformin from enzymatic degradation and can be surface-modified for targeted delivery to intestinal or hepatic tissues. Their applications extend to oral, parenteral, and topical routes, particularly for sustained release and improved therapeutic efficacy in diabetic management [38].

Mechanisms of action and targeting strategies (Table 1)

Controlled and sustained drug release: Nanoparticle-based drug delivery systems provide controlled and sustained release of anti-diabetic agents, enhancing therapeutic efficacy and patient compliance. Polymeric nanoparticles, lipid-based carriers, and dendrimers can be engineered to degrade or release their payloads in response to physiological stimuli, such as pH changes or glucose concentrations, mimicking natural insulin secretion patterns [39]. Therefore, this controlled release reduces fluctuations in plasma drug levels, minimizes dosing frequency, and lowers the risk of hypoglycemia associated with conventional formulations. Furthermore, surface modifications can tailor release profiles, allowing for site-specific and prolonged therapeutic effects (**Figure 5**).

Improved intestinal permeability and absorption: Oral bioavailability of many anti-diabetic drugs is limited due to poor intestinal permeability. Nanocarriers enhance drug solubility and stability, protecting labile molecules like insulin from enzymatic degradation and promoting better absorption [40]. Surface modifications with mucoadhesive polymers (e.g., chitosan) or PEGylation increase adhesion to intestinal mucosa and prolong residence time, enhancing transcellular and paracellular transport. Furthermore, some nanoparticles exploit lymphatic pathways, bypassing first-pass hepatic metabolism, thereby improving systemic bioavailability.

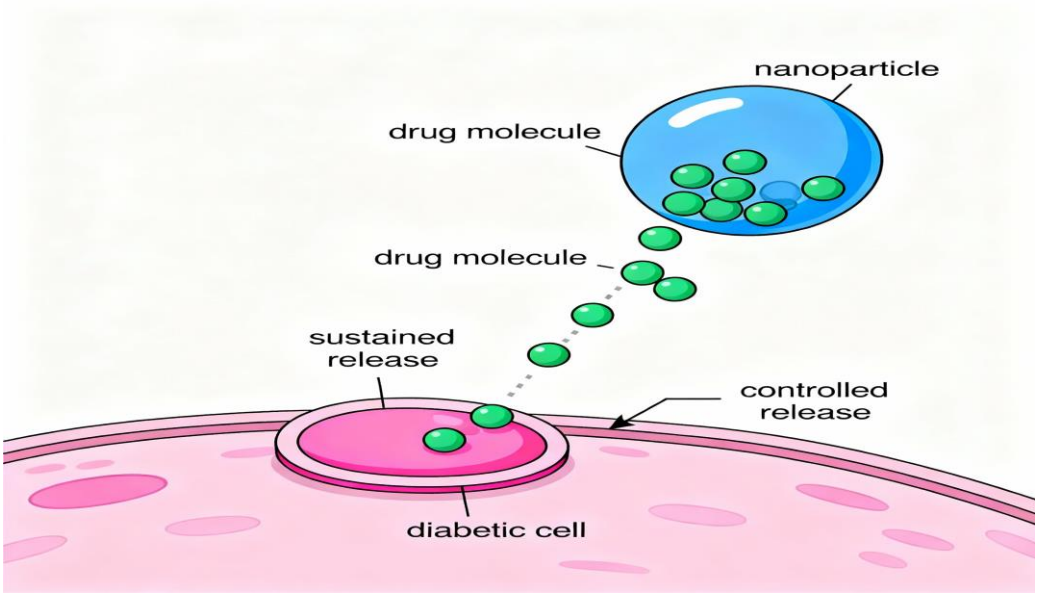


Figure 5: Mechanism of controlled and sustained drug release from nanoparticle-based delivery systems targeting pancreatic β-cells

Targeted delivery to pancreatic β-cells: Targeting pancreatic β-cells is a key strategy for improving therapeutic efficacy while minimizing off-target effects. Nanoparticles functionalized with specific ligands, peptides, or antibodies can selectively bind to β-cell receptors, facilitating precise delivery of anti-diabetic drugs [8]. For example, GLP-1 receptor-targeted nanoparticles have been shown to improve insulin secretion and β-cell function effectively [41]. This targeted approach ensures the therapeutic payload accumulates preferentially at the site of action, enhancing efficacy while reducing systemic toxicity.

Receptor-mediated endocytosis and site-specific action: At the cellular level, many nano-formulations are internalized via receptor-mediated endocytosis, including clathrin-mediated, caveolae-mediated, or macro-pinocytosis pathways. Once internalized, nanoparticles release their payloads intracellularly, allowing for site-specific action and improved therapeutic efficiency. This mechanism is particularly important for peptide-based drugs and macromolecules that require intracellular delivery for activity. The combination of passive targeting via particle size and active targeting through ligand-receptor interactions enhances drug bioavailability and therapeutic precision [38].

Table 1: Nanoformulation of anti-diabetic agents, mechanisms of action, and targeting strategies

Nanoformulation	Description/mechanism	Key findings/advantages	Ref.
Nanoformulated Metformin	Metformin-loaded nanoparticles (polymeric nanoparticles, SLNs, PEGylated carriers) improve solubility, protect from degradation, and enhance absorption.	Reduced plasma glucose, improved oxidative stress and endothelial function, better pharmacokinetics, reduced dosing frequency; co-encapsulation with antioxidants further enhances glycemic control.	[42]
Nano-insulin Formulations	Polymeric nanoparticles, nanogels, glucose-responsive nanoparticles; oral and nasal insulin formulations for non-invasive delivery.	Controlled and sustained release mimicking physiological insulin secretion; glucose-responsive release reduces hypoglycemia; oral/nasal delivery improves adherence and bioavailability.	[43]
Nanoformulated Glibenclamide, Pioglitazone, Sitagliptin	Self-nanoemulsifying drug delivery systems (SNEDDS), polymeric and lipid nanoparticles enhance solubility and release profiles.	Glibenclamide-loaded SNEDDS improve solubility and control release; Sitagliptin nanoparticles provide sustained release; Pioglitazone nanoparticles improve insulin sensitivity and anti-inflammatory activity; all improve compliance and therapeutic outcomes.	[44]
Herbal-Based Nanoformulations	Curcumin, berberine, and Gymnema sylvestre loaded into nanoparticles, liposomes, or SLNs.	Improved stability and absorption; curcumin enhances insulin sensitivity and antioxidant activity; berberine improves glucose and lipid profiles; Gymnema sylvestre stimulates insulin secretion and β-cell regeneration; offers complementary therapy.	[45]

Evaluation and characterization parameters

Particle size, Polydispersity Index (PDI), and zeta potential: The physicochemical properties of nanoparticles, such as particle size, PDI, and zeta potential, are critical determinants of their stability, cellular uptake, and biodistribution. Nanoparticles with sizes in the range of 100 - 200 nm typically show enhanced cellular uptake and prolonged circulation time, which is ideal for drug delivery applications [46]. The PDI indicates the uniformity of particle size distribution; values closer to 0 suggest a more uniform population, essential for consistent drug delivery [47]. Zeta potential reflects the surface charge of nanoparticles, influencing their stability and interaction with biological membranes. A zeta potential above ± 30 mV generally indicates good colloidal stability and reduced aggregation [48].

Entrapment efficiency and drug loading: Entrapment efficiency (EE) and drug loading (DL) are crucial parameters to evaluate the effectiveness of nanoparticle drug delivery systems. High EE ensures that a significant proportion of the drug is encapsulated, protecting it from degradation and premature release, while DL determines the drug content relative to the total nanoparticle weight, affecting the therapeutic dose and frequency. For example, solid lipid nanoparticles (SLNs) often show high EE and DL for hydrophilic and hydrophobic drugs, thereby enhancing therapeutic outcomes.

In vitro release profile and stability studies: In vitro release studies provide insight into how nanoparticles release drugs under controlled conditions, allowing prediction of their behavior in vivo. These studies help determine the release mechanism, which may follow zero-order, first-order, or Higuchi kinetics, and inform dosage regimen design [49]. Stability studies assess the physical and chemical integrity of nanoparticles over time under various environmental conditions such as temperature, humidity, and light exposure. Stable formulations maintain drug efficacy and safety throughout the product's shelf life.

In vivo pharmacokinetic (PK) and pharmacodynamic (PD) evaluations: In vivo PK and PD evaluations are essential to assess how nanoparticles behave inside the body and their therapeutic effects. PK studies focus on absorption, distribution, metabolism, and excretion (ADME), providing data on bioavailability and half-life. PD studies examine the relationship between drug concentration and therapeutic effect, helping to establish optimal dosing regimens [45]. Advanced analytical techniques, such as imaging, bioassays, and computational modeling, are used to comprehensively evaluate nanoparticle performance *in vivo* [46, 48].

Clinical trials of nano-formulated anti-diabetic drugs

Recent advancements in nanotechnology have enabled the development of nano-formulated anti-diabetic drugs, which have shown promising outcomes in clinical trials. Several studies have demonstrated that nano-based drug delivery systems can improve therapeutic efficacy, reduce side effects, and enhance patient adherence [50]. For example, nano-formulated insulin and metformin systems have been tested for oral and controlled-release applications, showing better glycemic control compared to conventional therapies [50]. Plant-derived nano-formulations, including curcumin and berberine nanoparticles, are also being evaluated in early-phase clinical studies for their potential to enhance bioavailability and anti-diabetic activity. These trials highlight the translation of nanotechnology from preclinical studies to clinical applications, underscoring the potential of nano-formulations to address the limitations of conventional anti-diabetic therapies.

Safety, toxicity, and biocompatibility issues: Safety, biocompatibility, and toxicity remain critical considerations for nano-formulated anti-diabetic drugs. Functionalized nanoparticles such as mesoporous silica and lipid-based systems are effectively internalized by cells without inducing significant cytotoxicity or inflammatory responses. Studies on antioxidant nanoparticles, such as cerium oxide-based carriers, indicate minimal toxicity while providing additional protective effects against oxidative stress. Despite these promising findings, long-term safety evaluations are necessary, as nanoparticle accumulation, degradation, and immunogenicity may vary depending on particle size, surface chemistry, and route of administration [51]. Comprehensive preclinical and clinical assessments are crucial to ensure safe therapeutic use in DM patients.

Regulatory guidelines for nano-based drug delivery: The regulatory framework for nanomedicines is evolving to address the unique characteristics of nano-based drug delivery systems. Agencies such as the FDA and EMA guide quality, safety, and efficacy assessment, including specifications for particle size, surface characteristics, drug release profiles, and toxicity evaluation. Regulatory considerations also include stringent requirements for manufacturing processes, reproducibility, and stability studies, ensuring that nano-formulations meet consistent quality standards. Adherence to these guidelines is essential for the successful translation of nano-formulated anti-diabetic drugs into clinical practice. Furthermore, regulatory authorities are increasingly emphasizing the need for pharmacokinetic, pharmacodynamic, and immunogenicity studies to fully assess the safety and performance of nanomedicines. As research progresses, harmonization of international guidelines will be important to facilitate global approval and commercialization of safe and effective nano-formulated therapies.

Prospects and challenges

Translational barriers and large-scale production: Despite significant progress in nano-formulated anti-diabetic drugs, translating laboratory-scale formulations into commercially viable products remains challenging. The complexity of nanoparticle synthesis, variability in raw materials, and the requirement for stringent quality control make large-scale production difficult. Additionally, reproducibility issues and batch-to-batch variations can impact drug efficacy and safety, posing hurdles for clinical translation. Developing cost-effective, scalable, and standardized manufacturing protocols is crucial to overcome these barriers and facilitate the widespread adoption of nanomedicines. Continuous innovation in green synthesis methods and modular manufacturing platforms may further support efficient large-scale production.

Long-term safety and biodegradability: Long-term safety and biodegradability are critical concerns for nano-formulations. While many nanoparticles exhibit short-term biocompatibility, chronic exposure may lead to accumulation in tissues or unintended immunogenic responses. Biodegradable materials such as PLGA, chitosan, and lipid-based carriers are preferred to ensure safe degradation and elimination from the body [52]. Moreover, the degradation products must be non-toxic and metabolizable, preventing interference with physiological functions. Systematic preclinical and clinical studies are essential to evaluate potential chronic toxicity, organ accumulation, and immune responses over prolonged use.

Personalized nanomedicine for DM management: Personalized nanomedicine represents a promising frontier in DM management, enabling drug delivery systems tailored to individual patient profiles [53]. Nano-formulations can be designed to respond to patient-specific biomarkers, such as insulin sensitivity or glucose levels, thereby optimizing therapeutic outcomes. Incorporating genetic, metabolic, and lifestyle information into the design of nanocarriers may further enhance precision treatment, reduce side effects, and improve adherence. The integration of AI and machine learning with nanomedicine design can accelerate the development of patient-specific therapies [54].

Integration with smart drug delivery systems: Smart drug delivery systems, such as glucose-responsive nanoparticles, are emerging as advanced tools for DM management [55]. These systems release insulin or anti-diabetic drugs in response to fluctuating blood glucose levels, closely mimicking natural pancreatic function. Further integration with wearable sensors, continuous glucose monitors, and feedback-controlled insulin pumps can create fully automated, closed-loop systems [56]. Such technologies promise improved glycemic control, reduced risk of hypoglycemia, and enhanced quality of life for patients. Continued research into biocompatible, responsive materials and device integration will be key for clinical success.

Conclusion: Nanotechnology has emerged as a transformative strategy in the management of diabetes mellitus, addressing the inherent limitations of conventional therapies. Several nano-formulations, including polymeric nanoparticles, solid lipid nanoparticles, liposomes, dendrimers, nano-emulsions, and herbal-based nano-

particles, have demonstrated significant improvements in drug delivery, targeted action, and controlled release. Specific anti-diabetic agents have been successfully incorporated into nanocarriers, enhancing therapeutic efficacy, patient compliance, and safety profiles. Despite these promising outcomes, several challenges remain, including long-term safety, biodegradability, scalability of production, regulatory compliance, and clinical translation. The integration of personalized nanomedicine and smart, stimuli-responsive systems such as glucose-responsive nanoparticles holds immense potential to revolutionize DM management by providing precise, patient-tailored therapy with minimized adverse effects. Thus, nano-formulations offer a promising and versatile approach to achieving more effective, safer, and patient-friendly diabetes mellitus treatment, paving the way for next-generation therapeutics in conventional and complementary medicine.

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