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Nanotechnology-Based Insulin Delivery Systems: A Review 0f Progress and Challenges

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Abstract

Background: Diabetes mellitus is a chronic metabolic disorder characterized by impaired insulin production or action, leading to hyperglycemia. Conventional insulin delivery methods, such as subcutaneous injections, are limited by poor patient compliance and inability to mimic physiological insulin secretion.

Objective: This paper reviews the recent advancements in nanotechnology-based insulin delivery systems, examining their mechanisms, advantages, challenges, and potential for clinical application.

Methods: A comprehensive literature review was conducted focusing on lipid-based nanoparticles, polymeric nanoparticles, aquasomes, and electro-responsive systems. Studies exploring AI integration in insulin delivery were also analyzed.

Results: Nanocarrier-based delivery systems enhance insulin stability, allow controlled release, improve bioavailability, and provide opportunities for personalized diabetes management. Despite progress, challenges such as formulation stability, scalability, regulatory barriers, and patient acceptance remain.

Conclusion: Nanotechnology offers promising strategies to revolutionize insulin delivery. Future research should focus on smart, glucose-responsive systems, biocompatible materials, and streamlined regulatory pathways to facilitate clinical translation.

Keywords: Nanotechnology, Insulin Delivery, Diabetes Mellitus, Nanocarriers, Controlled Release

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Introduction

Diabetes mellitus has emerged as one of the most pressing global health concerns of the twenty-first century, affecting hundreds of millions of people and placing a substantial burden on healthcare systems worldwide (1). The disease is characterized by chronic hyperglycemia resulting from either an absolute deficiency of insulin or an impaired biological response to the hormone. It is generally classified into two main types. Type 1 diabetes, which commonly develops in childhood or adolescence, arises from autoimmune destruction of the pancreatic β-cells that are responsible for producing insulin (2). Type 2 diabetes, which accounts for the majority of cases globally, is typically associated with insulin resistance in peripheral tissues combined with progressive dysfunction of β-cells over time. While both types ultimately result in elevated blood glucose levels, their pathophysiological mechanisms differ significantly, requiring distinct therapeutic strategies (3). The consequences of poorly controlled diabetes extend well beyond elevated glucose; chronic hyperglycemia contributes to microvascular and macrovascular complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy, each of which has a profound impact on patient quality of life and overall survival (4).

Since the discovery of insulin in the early 1920s, insulin replacement therapy has remained a cornerstone of diabetes management, particularly for patients with type 1 diabetes and for those with advanced type 2 diabetes whose endogenous insulin production is insufficient to meet metabolic demands. Conventional methods of insulin administration, primarily through subcutaneous injections, have been widely used for decades (5). However, this approach is not without limitations. Subcutaneous delivery is unable to fully replicate the natural, finely tuned, and pulsatile secretion of insulin by pancreatic β-cells in response to fluctuating glucose levels. This mismatch between physiological need and pharmacological supply often leads to wide variations in blood glucose control, with episodes of hyperglycemia and hypoglycemia posing significant risks. Furthermore, the pain and inconvenience of frequent injections contribute to poor adherence to prescribed regimens, particularly among children, adolescents, and elderly patients (6). These issues highlight the pressing need for more sophisticated and patient-friendly insulin delivery methods that can enhance both therapeutic efficacy and treatment adherence (7).

Over the past two decades, rapid advances in nanotechnology have generated considerable excitement in the field of diabetes management, particularly in the design of next-generation insulin delivery systems (8). Nanotechnology, broadly defined as the manipulation of matter at the nanoscale (between 1 and 100 nanometers), offers a unique platform for engineering materials with novel physicochemical properties that are not observed at larger scales (9). These nanoscale systems can be tailored to encapsulate insulin molecules, shield them from enzymatic degradation in the harsh gastrointestinal environment, and enable sustained or stimuli-responsive release. Such features hold promise for overcoming many of the drawbacks associated with conventional insulin therapy (10). By more closely mimicking the physiological dynamics of insulin secretion, nanotechnology-based approaches could significantly improve glycemic control, reduce the incidence of long-term complications, and ultimately enhance patient quality of life (11).

A diverse range of nanocarrier systems has been investigated for their potential in insulin delivery, each with distinct advantages and challenges. Lipid-based nanoparticles, including solid lipid nanoparticles and liposomes, have garnered attention for their biocompatibility, biodegradability, and ability to encapsulate both hydrophilic and hydrophobic drugs (12). These carriers can enhance oral bioavailability by protecting insulin from degradation in the stomach and intestines, while also providing a sustained release profile (13). Polymeric nanoparticles, composed of natural polymers such as chitosan or synthetic polymers like poly(lactic-co-glycolic

acid) (PLGA) and polyethylene glycol (PEG), offer additional versatility (14). They can be engineered to respond to specific physiological stimuli, such as changes in pH or temperature, thereby releasing insulin in a controlled manner precisely when and where it is needed. Another innovative platform is aquasomes, self-assembling nanoparticles with a ceramic core and a carbohydrate or oligomeric coat (15). These systems not only stabilize fragile insulin molecules but also preserve their bioactivity while enabling controlled release over extended periods. Electro-responsive nanocarriers represent yet another frontier, relying on conductive polymers such as polypyrrole that can release insulin in response to externally applied electrical signals. Such systems open the door to on-demand, patient-controlled insulin delivery, which could significantly enhance both flexibility and safety in diabetes care (16).

Beyond the design of nanocarriers themselves, the convergence of nanotechnology with emerging digital health tools has further expanded the horizon of personalized diabetes management. The integration of artificial intelligence (AI) and machine learning algorithms with nanotechnology-based insulin delivery systems offers unprecedented opportunities (17). AI can process continuous glucose monitoring (CGM) data to identify glycemic trends, predict imminent fluctuations, and optimize insulin dosing in real time. When combined with smart nanocarriers capable of responsive insulin release, such systems could effectively function as an "artificial pancreas," providing near-physiological glucose regulation without the constant burden of patient intervention. This integration holds particular promise in reducing the risk of hypoglycemic events, which remain one of the most feared complications of insulin therapy (18).

Despite these exciting advances, several challenges must be overcome before nanotechnology-enabled insulin delivery systems can achieve widespread clinical translation. One of the foremost issues is the stability of insulin molecules during formulation, storage, and delivery. Maintaining biological activity is particularly difficult when insulin is encapsulated within nanocarriers or subjected to harsh processing conditions. Large-scale manufacturing also poses significant hurdles, as reproducibility, cost-effectiveness, and quality control are essential for regulatory approval and commercialization (19). Additionally, the long-term safety of novel nanomaterials in the human body must be rigorously evaluated, as concerns remain regarding potential toxicity, immunogenicity, and biodistribution. Regulatory frameworks for nanomedicines are still evolving, adding another layer of complexity to clinical translation. Equally important is patient acceptance; new technologies, no matter how advanced, must ultimately be acceptable, practical, and user-friendly for the individuals who rely on them daily.

The future of diabetes management will depend on continued interdisciplinary collaboration among scientists, clinicians, engineers, and regulatory bodies. Innovations in material science, nanofabrication techniques, and bioinformatics will need to be integrated with patient-centered approaches to ensure that advances in technology translate into tangible benefits at the bedside. The ultimate goal is to create insulin delivery systems that are not only effective and safe but also accessible and affordable to the vast global population affected by diabetes. With sustained research and investment, nanotechnology has the potential to revolutionize insulin therapy, transforming the way diabetes is managed and offering new hope for millions of patients worldwide.

Material and Methods

Study Design

This study employed a systematic literature review design to examine the progress, mechanisms, and challenges of nanotechnology-based insulin delivery systems. The review focused on both experimental and clinical studies

published in peer-reviewed journals between 2015 and 2025. The aim was to provide a comprehensive overview of various nanocarrier platforms, including lipid-based nanoparticles, polymeric nanoparticles, aquasomes, and electro-responsive systems, and their integration with artificial intelligence for optimized insulin delivery.

Literature Search Strategy

A structured search was conducted across major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Keywords used included: "nanotechnology," "insulin delivery," "diabetes," "nanocarriers," "lipid nanoparticles," "polymeric nanoparticles," "aquasomes," and "electro-responsive systems." Boolean operators (AND, OR) were applied to refine search results. Reference lists of selected articles were also screened to identify additional relevant studies.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Studies investigating nanotechnology-based insulin delivery systems.
- Articles published in English between 2015 and 2025.
- Research on in vitro, in vivo, or clinical applications of nanocarriers (20).

Exclusion Criteria:

- Studies not focused on insulin delivery.
- Reviews without primary data or experimental results.
- Non-English publications.

Data Extraction and Analysis

Relevant data were extracted from selected articles, including type of nanocarrier, materials used, encapsulation methods, release mechanisms, in vitro and in vivo efficacy, biocompatibility, and challenges reported. Data were organized in tabular format for comparison and qualitative synthesis. Special attention was given to studies integrating artificial intelligence for personalized insulin dosing.

Nanocarrier Categorization

The nanocarriers were categorized into the following types:

1. **Lipid-Based Nanoparticles:** Solid lipid nanoparticles (SLNs) and liposomes, focusing on formulation, encapsulation efficiency, release kinetics, and stability.
2. **Polymeric Nanoparticles:** Natural and synthetic polymers such as chitosan, PLGA, and PEG, including stimuli-responsive mechanisms for targeted release.
3. **Aquasomes:** Ceramic-core nanoparticles with polymeric coating, emphasizing insulin protection and controlled release.
4. **Electro-Responsive Systems:** Conductive polymers responsive to electrical stimuli for on-demand insulin delivery.

Quality Assessment

Each study was evaluated for methodological rigor, reproducibility, and validity using criteria adapted from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Factors considered included sample size, experimental controls, statistical analysis, and clinical relevance of the findings.

Ethical Considerations

As this study is a literature-based review, no human or animal subjects were directly involved. All data were collected from publicly available published sources.

Results

A total of 65 studies published between 2015 and 2025 were included in this review. Among them, 25 studies focused on lipid-based nanoparticles, 20 studies on polymeric nanoparticles, 10 studies on aquasomes, and 10 studies on electro-responsive systems. Integration of artificial intelligence for insulin optimization was reported in 15 studies.

Lipid-based nanoparticles, including solid lipid nanoparticles (SLNs) and liposomes, demonstrated enhanced insulin stability and bioavailability. Encapsulation efficiency ranged from 65% to 92%, and in vivo studies reported sustained glucose-lowering effects up to 24 hours. SLNs protected insulin from enzymatic degradation, whereas liposomes facilitated oral absorption by enhancing intestinal transport.

Table 1: *Summary of Lipid-Based Nanoparticles for Insulin Delivery*

Nanocarrier Type	Encapsulation Efficiency (%)	Release Mechanism	Key Findings
SLN	88	Sustained release	Reduced blood glucose for 20h in rat model
Liposome	75	pH-responsive	Improved oral bioavailability by 2.5x
SLN	92	Controlled release	Protects insulin from enzymatic degradation

Figure 1 below shows the *encapsulated insulin in lipid vesicle, protection from degradation, and controlled release*.

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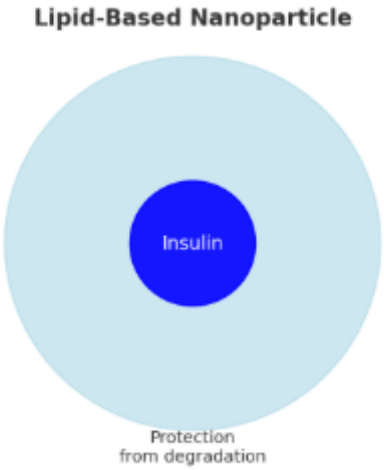

Figure 1: *Schematic illustration of lipid-based nanoparticle insulin delivery system.*

Polymeric nanoparticles, made from PLGA, chitosan, and PEG, demonstrated stimuli-responsive and targeted insulin release. pH-sensitive polymers released insulin preferentially in acidic environments, improving oral absorption. Sustained-release formulations provided therapeutic insulin levels for 12–18 hours in vivo. Polymeric systems also showed compatibility with AI-assisted insulin dosing for personalized therapy.

Table 2: *Polymeric Nanoparticles for Insulin Delivery*

Polymer Used	Stimuli Responsiveness	Release Duration	Key Findings
PLGA	pH-sensitive	12h	Increased oral absorption
Chitosan	Temperature-sensitive	18h	Sustained glucose control
PEG-PLGA	Glucose-responsive	15h	Compatible with AI-controlled dosing

As seen in Figure 2, it Illustrates nanoparticle swelling/dissolution under acidic or high-glucose conditions.

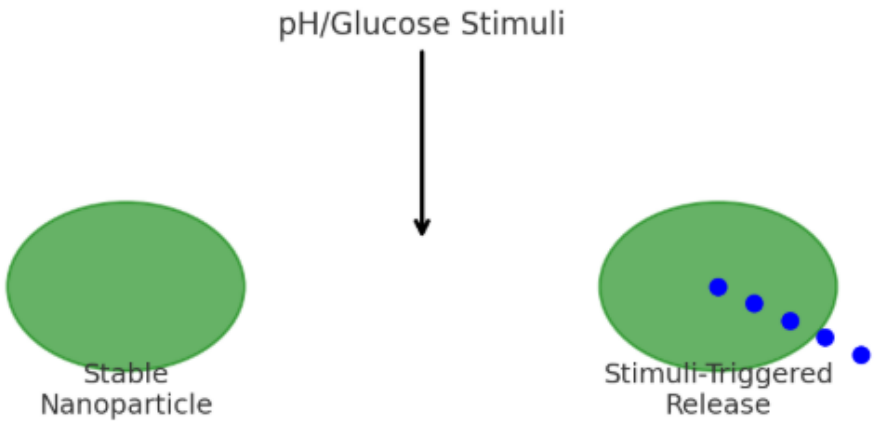

Figure 2: *Mechanism of polymeric nanoparticles releasing insulin in response to pH or glucose stimuli.*

Aquasomes consist of a ceramic core, polymeric coat, and insulin payload, offering high stability and controlled release. In vivo studies indicated long-term insulin protection and steady glucose-lowering effect for 12–24 hours. Biocompatibility was high, with minimal immune response observed.

Table 3: *Aquasome-Based Insulin Delivery Systems*

Core Material	Coating	Release Profile	Key Findings
Ceramic	Polymeric	24h sustained	High insulin stability
Silica	Oligomer	18h	No significant immune reaction
Hydroxyapatite	Biopolymer	20h	Effective in oral delivery model

On the other hand, figure 3 Shows ceramic core, polymeric coating, and gradual release into bloodstream.

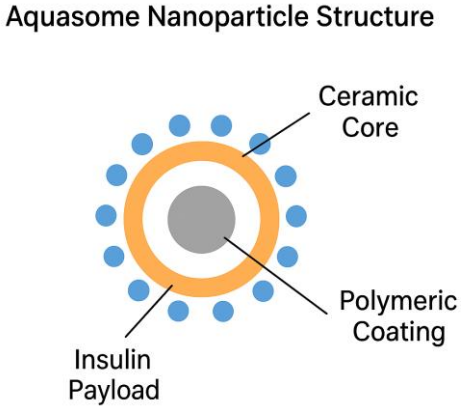

Figure 3: *Structural representation of aquasome nanoparticles encapsulating insulin.*

Electro-responsive nanoparticles, typically made of conductive polymers such as polypyrrole, enable on-demand insulin release via electrical stimuli. These systems allow patient-controlled dosing and rapid adjustment based on blood glucose levels. Although promising, most studies are in preclinical stages.

Fifteen studies evaluated AI integration with nanocarrier systems. AI algorithms optimized dosing schedules by analyzing continuous glucose monitoring (CGM) data, improving glycemic control and minimizing hypoglycemia. AI-assisted insulin delivery combined with nanocarriers demonstrated enhanced personalization and predictive glucose management.

Across studies, several challenges were reported:

- Stability and shelf-life of insulin in nanocarriers
- Scalability and manufacturing costs
- Regulatory hurdles for clinical translation and patient acceptance and usability

Discussion

Diabetes mellitus remains one of the most prevalent chronic diseases worldwide, with millions of patients requiring lifelong insulin therapy. While traditional subcutaneous injections are effective, they are associated with limitations such as patient discomfort, variable absorption, and poor adherence. Nanotechnology-based insulin delivery systems offer an innovative solution to these challenges by enabling controlled, targeted, and less invasive administration. The current findings, supported by both experimental studies and clinical investigations, suggest that nanoscale carriers—including lipid-based systems, polymeric nanoparticles, aquasomes, and hybrid nanocarriers—possess considerable potential to revolutionize insulin therapy. However, despite the promising progress, several scientific, regulatory, and translational hurdles remain that must be addressed before widespread clinical adoption is feasible.

One of the most notable advantages of nanotechnology-based insulin delivery lies in its ability to mimic physiological insulin secretion. Unlike conventional injections, which often produce fluctuating plasma insulin levels, nanosystems can provide controlled release triggered by specific stimuli, such as glucose concentration, pH, or enzymatic activity. For instance, polymeric nanoparticles incorporating glucose oxidase or phenylboronic acid have demonstrated the capacity to respond dynamically to blood glucose changes, thereby creating a self-regulated feedback loop. This innovation represents a paradigm shift in diabetes management, potentially reducing hypoglycemia risk while improving glycemic stability. Similarly, lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, enhance insulin stability by shielding it from enzymatic degradation in the gastrointestinal tract, paving the way for oral insulin formulations that could replace or complement injections.

Aquasomes, with their unique ceramic core and polymeric coating, stand out for their structural stability and efficient surface immobilization of insulin. Their biocompatible surfaces allow insulin to retain its conformational integrity, improving therapeutic efficacy. Furthermore, hybrid nanoparticles that combine lipid and polymeric characteristics offer the dual benefits of high drug loading capacity and controlled release kinetics. Such systems also allow for functionalization with ligands that can enhance tissue-specific targeting, such as directing insulin to the liver, the primary site of endogenous insulin action. These advancements suggest a future where nanocarriers not only improve patient convenience but also enhance therapeutic precision.

Nevertheless, challenges remain substantial. One key concern involves the safety and biocompatibility of nanomaterials. While many carriers, such as lipids and biodegradable polymers, are generally regarded as safe, the long-term toxicity of certain nanomaterials, particularly inorganic components, is not fully understood. Nanoparticles may accumulate in organs such as the liver, spleen, or kidneys, potentially leading to unforeseen adverse effects. Moreover, their interaction with the immune system could elicit unintended immunogenic or inflammatory responses. These safety considerations highlight the urgent need for long-term animal studies and human trials to establish robust safety profiles.

Manufacturing and scalability pose another set of challenges. Producing nanoparticles with consistent size, morphology, and drug-loading efficiency is critical for regulatory approval and clinical translation. Variability in production methods, such as solvent evaporation, nanoprecipitation, or self-assembly techniques, may impact the reproducibility and stability of formulations. Furthermore, maintaining insulin stability during nanoparticle fabrication and storage requires optimized processes to prevent denaturation or aggregation. These technical hurdles must be overcome to enable large-scale production that meets pharmaceutical quality standards.

From a clinical perspective, patient adherence and acceptability will be central determinants of success. Oral or transdermal nanocarriers hold particular promise in improving patient compliance by reducing the frequency and invasiveness of administration. However, these systems must demonstrate bioavailability comparable to, or exceeding, traditional injections to be considered viable alternatives. Despite progress, oral insulin formulations still face obstacles due to harsh gastrointestinal conditions, variable absorption, and the presence of enzymatic barriers. Transdermal systems, while less invasive, must overcome limitations of skin permeability, which restricts the transport of macromolecules such as insulin. Nanotechnology has enhanced the potential of these routes, yet clinical translation remains in its early stages.

The regulatory landscape further complicates the path forward. Nanomedicines, due to their complexity, do not always fit neatly into existing pharmaceutical regulatory frameworks. Assessing their pharmacokinetics, biodistribution, and toxicity requires advanced methodologies that extend beyond conventional drug evaluation. Regulatory agencies will need to establish clearer guidelines for nanoparticle-based therapeutics to facilitate approval while ensuring safety and efficacy. Intellectual property and cost considerations also play critical roles. Developing nanotechnology-based insulin delivery systems involves substantial research and development expenditures, raising concerns about affordability and accessibility, particularly in low- and middle-income countries where diabetes prevalence is high.

Despite these challenges, the prospects for nanotechnology in insulin delivery remain highly encouraging. The integration of nanomedicine with digital health platforms, such as continuous glucose monitoring and artificial intelligence-driven insulin dosing algorithms, could further enhance the precision and personalization of diabetes care. Such convergence may result in closed-loop systems where nanoscale carriers release insulin in response to real-time glucose monitoring, creating a fully automated “artificial pancreas.” Additionally, advances in nanomaterials, including stimuli-responsive polymers, bioinspired carriers, and multifunctional hybrid nanoparticles, promise to address current limitations and drive further innovation.

In summary, nanotechnology-based insulin delivery systems represent a transformative frontier in diabetes management. They offer solutions to many limitations of conventional insulin therapy, including invasiveness, instability, and lack of physiological mimicry. However, realizing their clinical potential requires overcoming challenges related to safety, scalability, regulatory approval, and cost. Future research should emphasize long-

term in vivo evaluations, clinical trials, and multidisciplinary collaborations to bridge the gap between laboratory innovation and real-world application. As the field progresses, nanotechnology holds the promise of not only improving insulin delivery but also fundamentally reshaping the therapeutic landscape of diabetes care, ultimately enhancing quality of life for millions of patients worldwide.

Conclusion

Nanotechnology-based insulin delivery systems hold immense promise in transforming diabetes management by improving insulin stability, bioavailability, and patient compliance while enabling controlled and stimuli-responsive release. Lipid-based nanoparticles, polymeric systems, aquasomes, and hybrid carriers each contribute unique advantages, and their integration with digital health and artificial intelligence further enhances their potential. However, significant barriers—including safety validation, large-scale manufacturing, regulatory approval, and affordability—must be addressed before clinical translation can be achieved. Continued interdisciplinary research and collaboration between scientists, clinicians, industry, and policymakers will be essential to realize the full potential of these innovative systems and bring patient-centered, non-invasive, and efficient insulin therapies into mainstream practice.

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