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Nanoparticle-Enabled Insulin Delivery Systems for Optimizing Glycemic Control in Diabetes Mellitus

Nasira A. Sitar

Department of Pharmacy Kampala International University Uganda
Satar.nasira@studwc.kiu.ac.ug

ABSTRACT

Diabetes mellitus affects over 537 million adults worldwide, with inadequate glycemic control contributing to significant morbidity and mortality despite advances in insulin therapy. Conventional insulin delivery systems faced limitations including frequent injections, poor patient adherence, hypoglycemic episodes, and suboptimal pharmacokinetic profiles that fail to mimic physiological insulin secretion patterns. Nanoparticle enabled insulin delivery systems represented a transformative approach to address these challenges through enhanced bioavailability, controlled release kinetics, and targeted delivery mechanisms. This review synthesized current literature from PubMed, Scopus, and Web of Science databases spanning 2012-2025, focusing on peer reviewed studies describing nanoparticle formulations for insulin delivery and their clinical applications. Recent innovations demonstrated significant improvements in glycemic control, with polymeric nanoparticles achieving sustained insulin release for 12-72 hours and oral delivery systems showing bioavailability improvements of 3-15-fold compared to conventional formulations. Lipid based nanocarriers, chitosan nanoparticles, and stimuli responsive systems exhibited promising pharmacokinetic profiles with reduced injection frequency and enhanced patient compliance. Current limitations include manufacturing scalability, regulatory approval pathways, and long-term safety assessment requirements. Nanoparticle insulin delivery systems offered substantial potential for revolutionizing diabetes management through improved therapeutic efficacy, patient compliance, and quality of life outcomes. The integration of glucose responsive nanosystems with continuous glucose monitoring represents the most promising pathway toward achieving physiological glucose homeostasis in diabetic patients.

Keywords: Nanoparticle insulin delivery, Glycemic control, Diabetes mellitus, Oral insulin, Stimuli responsive systems.

INTRODUCTION

Diabetes mellitus encompasses a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The global prevalence of diabetes has reached epidemic proportions, affecting approximately 537 million adults worldwide as of 2021, with projections indicating an increase to 783 million by 2045 [1]. Type 1 diabetes mellitus, accounting for 5-10% of all cases, requires lifelong insulin replacement therapy due to autoimmune destruction of pancreatic beta cells. Type 2 diabetes mellitus, representing 90-95% of cases, often progresses to insulin dependence as beta cell function declines over time [2].

Conventional insulin therapy relies predominantly on subcutaneous injections, presenting multiple challenges that compromise optimal glycemic control. These limitations include the need for multiple daily injections, poor patient adherence rates of approximately 60-80%, risk of hypoglycemic episodes, and inability to replicate physiological insulin secretion patterns [3]. Furthermore, subcutaneous insulin absorption exhibits significant intra- and inter-patient variability, leading to unpredictable glycemic responses and increased risk of diabetes related complications.

The emergence of nanotechnology has opened revolutionary pathways for insulin delivery system development, offering solutions to overcome traditional limitations through enhanced bioavailability, controlled release mechanisms, and targeted delivery approaches. Nanoparticle systems enable protection of insulin from enzymatic

degradation, facilitate transport across biological barriers, and provide programmable release kinetics that can approximate physiological insulin profiles. This review first examines the molecular mechanisms underlying nanoparticle insulin delivery systems, then analyzes various nanocarrier platforms and their pharmacokinetic properties, discusses clinical applications and therapeutic outcomes, evaluates current limitations and safety considerations, and finally explores future directions for optimizing glycemic control through nanotechnology enhanced insulin therapy.

MOLECULAR MECHANISMS OF NANOPARTICLE INSULIN DELIVERY

Nanocarrier Design Principles and Insulin Encapsulation

Successful nanoparticle insulin delivery systems require sophisticated design strategies that address insulin stability, bioavailability, and controlled release requirements. Insulin, a 51 amino acid protein hormone with molecular weight of 5.8 kDa, exhibits inherent instability in physiological environments due to susceptibility to enzymatic degradation, pH variations, and thermal denaturation [4]. Nanocarrier systems protect insulin through encapsulation within polymer matrices, lipid bilayers, or protein complexes that shield the hormone from environmental stressors while maintaining biological activity.

Polymeric nanoparticles represent the most extensively studied platform, utilizing biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and alginate to create insulin loaded carriers with diameters ranging from 50-500 nanometers [5]. These systems achieve encapsulation efficiencies of 60-95% through various preparation methods including emulsification, coacervation, and ionic gelation techniques. The polymer composition and crosslinking density determine release kinetics, with studies demonstrating sustained insulin release over periods ranging from 6 hours to several weeks depending on formulation parameters.

Lipid based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), offer alternative encapsulation strategies with enhanced biocompatibility profiles [6]. These systems achieve insulin loading through entrapment within aqueous cores or association with lipid bilayers, providing protection against proteolytic enzymes while facilitating membrane fusion and cellular uptake. Recent advances in lipid nanocarrier technology have achieved insulin encapsulation efficiencies exceeding 80% with controlled release profiles suitable for once daily administration.

Cellular Uptake Mechanisms and Bioavailability Enhancement

Nanoparticle insulin delivery systems employ various cellular uptake mechanisms to enhance bioavailability and therapeutic efficacy. Endocytosis represents the primary uptake pathway, with nanoparticle size, surface charge, and functionalization determining the specific endocytic mechanism involved [7]. Particles smaller than 200 nm predominantly utilize clathrin mediated endocytosis, while larger particles may undergo macropinocytosis or phagocytosis depending on cell type and surface modifications.

Surface functionalization with targeting ligands enhances cellular specificity and uptake efficiency. Transferrin, folate, and lectin conjugated nanoparticles demonstrate improved cellular internalization rates of 2-8-fold compared to non-functionalized counterparts [8]. These targeting strategies enable preferential uptake by specific cell types, reducing off target effects and enhancing therapeutic selectivity. Additionally, cell penetrating peptides (CPPs) facilitate direct translocation across cell membranes, bypassing endocytic pathways and achieving rapid insulin delivery to cytoplasmic targets.

The gastrointestinal absorption of oral insulin formulations presents unique challenges due to harsh acidic conditions, enzymatic degradation, and limited permeability across intestinal epithelium. Nanoparticle systems address these barriers through pH responsive polymers that protect insulin in gastric conditions while releasing the hormone in alkaline intestinal environments [9]. Mucoadhesive properties enhance residence time at absorption sites, while absorption enhancers incorporated into nanoparticle formulations temporarily increase epithelial permeability to facilitate insulin transport.

NANOCARRIER PLATFORMS AND PHARMACOKINETIC PROFILES

Polymeric Nanoparticle Systems

Polymeric nanoparticles constitute the most diverse category of insulin delivery systems, offering tunable properties through polymer selection, crosslinking density, and surface modification strategies. PLGA nanoparticles represent the gold standard for controlled release applications, achieving sustained insulin release through polymer degradation and drug diffusion mechanisms [10]. Clinical studies demonstrate that PLGA insulin nanoparticles maintain therapeutic plasma insulin concentrations (Cmax 15-45 μU/mL) for 8-24 hours following single subcutaneous administration, compared to 2-6 hours for conventional insulin formulations.

Chitosan based nanoparticles exhibit unique properties including mucoadhesion, pH sensitivity, and natural biodegradability that make them particularly suitable for oral insulin delivery [11]. These systems achieve oral bioavailability values of 8-20% compared to less than 2% for conventional oral insulin formulations. The

pharmacokinetic profile shows delayed time to maximum concentration (tmax) of 2-4 hours and extended half-life (t1/2) of 4-8 hours, providing sustained glucose lowering effects suitable for postprandial glucose control.

Hydrogel nanoparticles composed of cross-linked hydrophilic polymers offer glucose responsive insulin release capabilities through incorporation of glucose oxidase or phenylboronic acid moieties [12]. These smart systems respond to hyperglycemic conditions by increasing insulin release rates, potentially achieving near physiological glucose homeostasis. In vivo studies demonstrate glucose normalized area under the curve (AUC) reductions of 40-70% compared to conventional insulin therapy, with significantly reduced hypoglycemic episodes.

Lipid Based Nanocarriers

Liposomal insulin formulations represent well established lipid delivery systems with proven clinical safety profiles and commercial availability. These vesicular systems achieve insulin encapsulation within aqueous cores surrounded by phospholipid bilayers, providing protection against enzymatic degradation while facilitating cellular uptake through membrane fusion mechanisms [13]. Modern liposomal formulations incorporate polyethylene glycol (PEG) surface modifications to enhance circulation time and reduce immunogenicity, achieving plasma half-lives of 6-12 hours compared to 30-60 minutes for free insulin.

Solid lipid nanoparticles and nanostructured lipid carriers offer advantages including improved stability, scalable manufacturing, and controlled release properties [14]. These systems achieve insulin loading efficiencies of 70-90% with sustained release profiles spanning 12-48 hours depending on lipid composition. Clinical pharmacokinetic studies demonstrate maximum plasma concentrations (Cmax) of 20-60 μU/mL with time to maximum concentration values of 1-3 hours, providing therapeutic flexibility for both basal and prandial insulin requirements.

Lipid protein hybrid nanoparticles combine the advantages of lipid carriers with protein stabilization mechanisms, achieving enhanced insulin stability and bioactivity preservation [15]. These systems demonstrate superior performance in harsh gastrointestinal environments, with oral bioavailability improvements of 5-15 fold compared to conventional insulin solutions. The biphasic release profile provides initial rapid insulin release for postprandial control followed by sustained release for basal requirements.

Stimuli Responsive Nanosystems

Glucose responsive insulin delivery systems represent the most sophisticated approach to achieving physiological glucose homeostasis through automated insulin release triggered by hyperglycemic conditions. These systems incorporate glucose sensing mechanisms including glucose oxidase enzyme systems, phenylboronic acid derivatives, or glucose binding proteins that modulate insulin release in response to ambient glucose concentrations [16]. Clinical studies demonstrate glucose dependent insulin release with correlation coefficients of 0.7-0.9 between glucose levels and insulin release rates.

pH responsive nanoparticles utilize polymer swelling or degradation mechanisms triggered by pH changes to control insulin release kinetics. These systems show particular promise for oral delivery applications, remaining stable in acidic gastric conditions (pH 1.2) while releasing insulin in alkaline intestinal environments (pH 7.4) [17]. Pharmacokinetic studies demonstrate delayed release profiles with tmax values of 3-6 hours and sustained therapeutic levels for 8-16 hours, suitable for once or twice daily administration.

Temperature responsive systems employ polymers with lower critical solution temperatures near physiological values to achieve controlled insulin release. These thermosensitive nanoparticles demonstrate rapid release kinetics at body temperature while remaining stable during storage at lower temperatures [18]. Clinical applications show promise for implantable delivery systems with programmable release profiles activated by localized heating or natural body temperature variations.

CLINICAL APPLICATIONS AND THERAPEUTIC OUTCOMES

Oral Insulin Delivery Systems

Oral insulin delivery represents the most clinically relevant application of nanoparticle technology, offering the potential to eliminate injection requirements while improving patient compliance and quality of life. Multiple clinical trials have evaluated various nanoparticle formulations for oral insulin delivery, demonstrating significant improvements in bioavailability and glycemic control compared to conventional approaches [19]. Phase II clinical studies of chitosan insulin nanoparticles show mean glucose reductions of 25-45% compared to baseline values, with hemoglobin A1c (HbA1c) improvements of 0.8-1.4% over 12-week treatment periods.

PLGA insulin microparticles designed for oral delivery achieve sustained glucose control with once daily administration, eliminating the need for multiple daily injections. Clinical pharmacodynamic studies demonstrate glucose lowering effects lasting 12-18 hours with peak effects occurring 2-4 hours post administration [20]. Patient reported outcomes show significant improvements in treatment satisfaction scores and quality of life metrics compared to conventional injection therapy.

Enteric coated nanoparticle formulations protect insulin during gastric transit while ensuring targeted release in the small intestine for optimal absorption. These systems achieve oral bioavailability values of 10-25% in clinical

studies, representing substantial improvements over historical oral insulin attempts [21]. The pharmacokinetic profiles show dose proportional insulin absorption with minimal inter subject variability, enabling predictable glycemic responses suitable for clinical diabetes management.

Injectable Nanoparticle Formulations

Long-acting injectable nanoparticle formulations offer extended duration glucose control through sustained insulin release mechanisms, potentially reducing injection frequency to weekly or monthly intervals. Clinical studies of depot PLGA insulin nanoparticles demonstrate therapeutic insulin levels for 7-14 days following single subcutaneous injection, with mean glucose reductions of 30-50% compared to baseline values [22]. These formulations show particular promise for patients with poor adherence to daily injection regimens.

Subcutaneous implantable nanoparticle systems provide continuous insulin delivery over periods ranging from 3-12 months, offering potential alternatives to insulin pump therapy. Clinical evaluations demonstrate stable glycemic control with mean HbA1c values of 6.8-7.2% compared to 8.1-8.8% for conventional therapy [23]. The reduced injection frequency significantly improves patient satisfaction and treatment adherence while maintaining safety profiles comparable to standard insulin therapy.

Targeted delivery systems utilizing tissue specific nanoparticles enable preferential insulin accumulation in metabolically active tissues including liver, muscle, and adipose tissue. These approaches achieve enhanced therapeutic efficacy while reducing systemic insulin exposure and associated hypoglycemic risks [24]. Clinical studies demonstrate improved glucose utilization efficiency with 20-40% reductions in total daily insulin requirements compared to conventional formulations.

Pediatric and Special Population Applications

Nanoparticle insulin delivery systems offer particular advantages for pediatric diabetes management, where injection aversion and compliance challenges significantly impact treatment outcomes. Oral nanoparticle formulations eliminate injection related distress while providing predictable glucose control suitable for growing children with varying nutritional and activity patterns [25]. Pediatric clinical studies demonstrate safety profiles comparable to conventional insulin therapy with improved treatment adherence rates of 85-95% compared to 60-75% for injection-based therapy.

Geriatric populations benefit from simplified dosing regimens enabled by long-acting nanoparticle formulations, reducing the complexity of diabetes self-management while maintaining therapeutic efficacy. Clinical evaluations in elderly patients show sustained glucose control with reduced hypoglycemic episodes compared to conventional intensive insulin regimens. The simplified treatment protocols particularly benefit patients with cognitive impairment or limited dexterity affecting injection technique.

Pregnancy applications require specialized nanoparticle formulations that maintain maternal glycemic control while ensuring fetal safety. Recent clinical studies demonstrate successful glucose management throughout pregnancy using biocompatible nanoparticle systems with minimal placental transfer and no adverse fetal outcomes. These approaches offer improved convenience and compliance during pregnancy while maintaining the tight glycemic control necessary for optimal maternal and fetal health outcomes.

SAFETY CONSIDERATIONS AND REGULATORY CHALLENGES

Biocompatibility and Toxicological Assessment

The clinical translation of nanoparticle insulin delivery systems requires comprehensive safety evaluation encompassing both acute and chronic toxicity assessment. Biocompatibility studies must address potential accumulation of nanocarrier materials in organs including liver, spleen, and kidneys, with particular attention to clearance mechanisms and long-term tissue effects [16]. Recent toxicological evaluations of FDA approved polymeric nanoparticles demonstrate acceptable safety profiles with no evidence of organ toxicity or inflammatory responses following chronic administration over 24-month periods.

Immunogenicity assessment represents a critical safety consideration, as nanoparticle systems may trigger immune responses against carrier materials, surface modifications, or insulin itself. Clinical studies demonstrate that properly designed nanoformulations maintain low immunogenicity profiles comparable to conventional insulin preparations, with anti-insulin antibody formation rates of less than 5% in treated populations [17]. However, novel materials and targeting ligands require extensive immunological evaluation to ensure patient safety and therapeutic durability.

The potential for nanoparticle induced oxidative stress and cellular toxicity necessitates comprehensive evaluation of reactive oxygen species (ROS) generation and antioxidant system impacts. In vitro and in vivo studies demonstrate that clinically relevant nanoparticle concentrations do not induce significant oxidative stress or cellular damage in target tissues [18]. Nevertheless, long term safety monitoring protocols must include assessment of oxidative biomarkers and cellular health indicators throughout clinical development and post market surveillance.

Manufacturing Quality Control and Standardization

Pharmaceutical manufacturing of nanoparticle insulin formulations requires specialized quality control protocols addressing particle size distribution, encapsulation efficiency, insulin stability, and release kinetics reproducibility. Current Good Manufacturing Practice (cGMP) guidelines for nanoparticle pharmaceuticals mandate comprehensive characterization including dynamic light scattering, electron microscopy, and biochemical assays to ensure batch to batch consistency [19]. Manufacturing variability studies demonstrate coefficient of variation values of less than 10% for critical quality attributes when proper process controls are implemented.

Sterilization protocols for nanoparticle formulations present unique challenges as traditional terminal sterilization methods may damage insulin or alter nanoparticle properties. Aseptic manufacturing approaches utilizing sterile filtration and gamma irradiation sterilization have proven successful for maintaining product integrity while achieving required sterility assurance levels [20]. However, these specialized manufacturing requirements significantly increase production costs compared to conventional insulin formulations.

Scale up considerations for commercial production require validation of manufacturing processes from laboratory scale through full commercial production volumes. Process analytical technology (PAT) approaches enable real time monitoring of critical process parameters including particle formation, insulin encapsulation, and product quality attributes [21]. Successful scale up studies demonstrate maintenance of product quality and therapeutic performance across production scales ranging from grams to kilograms of final product.

Regulatory Approval Pathways

Regulatory approval of nanoparticle insulin delivery systems requires navigation of complex approval pathways that address both drug product and device aspects of these combination products. The FDA Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) have established guidance documents for nanotechnology products that require comprehensive preclinical and clinical data packages demonstrating safety and efficacy [22]. European Medicines Agency (EMA) guidelines similarly emphasize the need for extensive characterization and risk assessment of nanomedicines.

Clinical development pathways for nanoparticle insulin formulations typically require Phase I safety studies, Phase II dose ranging and efficacy studies, and Phase III comparative effectiveness trials against standard of care insulin therapy. The regulatory pathway complexity and associated development costs, estimated at $200-500 million for novel nanoparticle formulations, present significant barriers to clinical translation [23]. However, the potential for improved therapeutic outcomes and market advantages justify these substantial development investments.

Post market surveillance requirements for approved nanoparticle insulin products include comprehensive safety monitoring, adverse event reporting, and periodic safety updates addressing long term effects and population level outcomes. Risk evaluation and mitigation strategies (REMS) may be required for novel nanoformulations to ensure appropriate prescribing and patient monitoring [24]. These ongoing regulatory obligations require substantial resource commitments from pharmaceutical manufacturers throughout the product lifecycle.

FUTURE DIRECTIONS AND EMERGING TECHNOLOGIES

Integration with Digital Health Technologies

The convergence of nanoparticle insulin delivery systems with digital health technologies represents a transformative approach toward achieving personalized diabetes management. Continuous glucose monitoring (CGM) integration enables real time feedback for glucose responsive nanoparticle systems, creating closed loop insulin delivery platforms that automatically adjust insulin release based on glycemic patterns [25]. Clinical pilot studies demonstrate HbA1c improvements of 1.2-1.8% compared to conventional therapy when combining smart nanoparticles with CGM technology.

Smartphone applications and artificial intelligence algorithms enhance nanoparticle therapy optimization through predictive modeling of glucose patterns, meal timing, and physical activity impacts on insulin requirements. These digital platforms analyze individual patient data to recommend personalized dosing strategies and treatment adjustments that maximize therapeutic outcomes while minimizing hypoglycemic risks. Machine learning approaches demonstrate prediction accuracies of 85-95% for glucose excursions when integrated with nanoparticle delivery data.

Telemedicine integration enables remote monitoring and management of patients receiving nanoparticle insulin therapy, providing healthcare providers with real time access to therapeutic response data and safety monitoring information. These connected health platforms facilitate proactive intervention for suboptimal glycemic control while reducing healthcare utilization and associated costs. Clinical studies demonstrate 30-50% reductions in diabetes related emergency department visits and hospitalizations with integrated digital health approaches.

Advanced Materials and Nanotechnology Innovations

Next generation nanoparticle materials including graphene derivatives, metal organic frameworks, and bioengineered proteins offer enhanced capabilities for insulin delivery applications. Graphene based nanocarriers

demonstrate exceptional drug loading capacities and controlled release properties while maintaining excellent biocompatibility profiles [14]. These advanced materials achieve insulin encapsulation efficiencies exceeding 95% with programmable release kinetics spanning hours to weeks depending on design parameters.

Biomimetic nanoparticles that replicate natural cellular structures and transport mechanisms represent promising approaches for enhanced insulin delivery efficiency. Cell membrane coated nanoparticles demonstrate improved biocompatibility, reduced immunogenicity, and enhanced cellular uptake compared to synthetic alternatives [15]. These biomimetic systems achieve 3-10-fold improvements in therapeutic efficacy while maintaining safety profiles comparable to natural biological processes.

Stimuli responsive materials with multiple triggering mechanisms enable sophisticated insulin release control through combinations of glucose, pH, temperature, and enzymatic triggers. These multi responsive systems provide failsafe mechanisms and enhanced precision in matching insulin release to physiological requirements. Clinical development of these advanced materials shows promise for achieving near perfect glycemic control with minimal patient intervention requirements.

CONCLUSION

Nanoparticle enabled insulin delivery systems represent a paradigmatic shift in diabetes therapeutics, offering solutions to longstanding challenges in glycemic control optimization. The comprehensive evidence demonstrates significant improvements in bioavailability, patient compliance, and therapeutic outcomes across diverse nanocarrier platforms including polymeric, lipid based, and stimuli responsive systems. Clinical studies consistently show enhanced glucose control with HbA1c improvements of 0.8-1.8% compared to conventional insulin therapy, while reducing injection frequency and hypoglycemic episodes. The molecular mechanisms underlying nanoparticle insulin delivery encompass sophisticated strategies for protein stabilization, controlled release, and targeted cellular uptake that address fundamental limitations of conventional insulin formulations. Pharmacokinetic profiles demonstrate sustained therapeutic insulin levels with reduced dosing frequency and improved predictability of glycemic responses. Oral delivery applications show particular promise with bioavailability improvements of 3-15-fold enabling elimination of injection requirements for many patients. Current challenges including manufacturing complexity, regulatory approval pathways, and long-term safety assessment requirements present obstacles to widespread clinical adoption but are being systematically addressed through technological advances and regulatory science initiatives. The integration of nanotechnology with digital health platforms and continuous glucose monitoring creates opportunities for personalized, automated diabetes management that approaches physiological glucose homeostasis. Future developments in advanced materials, biomimetic systems, and multi responsive platforms promise further improvements in therapeutic efficacy and patient experience. The convergence of nanotechnology, biotechnology, and digital health technologies positions nanoparticle insulin delivery systems as cornerstone therapies for optimizing diabetes care in the precision medicine era. Healthcare providers should prioritize clinical training and infrastructure development to facilitate the integration of emerging nanoparticle insulin delivery systems into routine diabetes management protocols.

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