



Polymeric Nanoparticles versus Conventional Oral Solid Dosage Forms in Diabetes Management: A Comparative Review of Efficacy, Pharmacokinetics, and Clinical Prospects

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ABSTRACT :

Diabetes mellitus represents one of the most challenging chronic metabolic disorders of the twenty-first century, affecting hundreds of millions worldwide. Conventional oral solid dosage forms, including tablets and capsules, remain the mainstay of pharmacological intervention for type 2 diabetes, while injectable insulin continues to dominate type 1 diabetes management. However, these conventional formulations are often limited by poor bioavailability, extensive first-pass metabolism, gastrointestinal degradation, and suboptimal patient compliance. Polymeric nanoparticle-based drug delivery systems have emerged as a transformative approach to overcome these limitations. This review provides a comprehensive comparative analysis of polymeric nanoparticles versus conventional oral solid dosage forms in diabetes management, focusing on pharmacokinetic enhancement, therapeutic efficacy in both type 1 and type 2 diabetes, safety profiles, and clinical translation challenges. A meta-analytical perspective is incorporated to quantitatively validate the superiority of nanoparticulate systems in enhancing oral drug bioavailability. The evidence presented suggests that polymeric nanoparticles offer significant advantages over conventional formulations, including enhanced bioavailability, sustained drug release, improved glycemic control, and reduced dosing frequency, positioning them as a promising platform for next-generation diabetes therapeutics.

Keywords: *polymeric nanoparticles, diabetes mellitus, oral drug delivery, PLGA, chitosan, bioavailability, insulin, metformin, controlled release.*

1. Introduction

Diabetes mellitus constitutes a global public health crisis of unprecedented magnitude, with the International Diabetes Federation estimating that over 537 million adults were living with diabetes in 2021, a figure projected to exceed 783 million by 2045.^{1,2} The disease encompasses two primary forms: type 1 diabetes mellitus (T1DM), characterized by autoimmune destruction of pancreatic beta cells and absolute insulin deficiency, and type 2 diabetes mellitus (T2DM), which involves progressive insulin resistance coupled with relative insulin insufficiency. Both forms necessitate lifelong pharmacological intervention to maintain euglycemia and prevent debilitating microvascular and macrovascular complications.

Current therapeutic strategies rely heavily on conventional oral solid dosage forms, such as immediate-release and modified-release tablets and capsules, for T2DM management, alongside subcutaneous insulin injections for T1DM and advanced T2DM. While these formulations have served patients for decades, they are fraught with inherent limitations including poor aqueous solubility of many anti-diabetic agents, extensive presystemic metabolism, fluctuating plasma drug concentrations, and poor patient adherence due to frequent dosing requirements and gastrointestinal adverse effects. The oral bioavailability of protein therapeutics such as insulin remains negligible without protective delivery systems, necessitating invasive parenteral administration.

In this context, nanotechnology-based drug delivery systems, particularly polymeric nanoparticles, have garnered substantial research interest as a paradigm-shifting approach to diabetes pharmacotherapy.³ Polymeric nanoparticles, typically ranging from 1 to 1000 nanometers in size, can encapsulate, protect, and modulate the release of anti-diabetic drugs, thereby overcoming many of the physiological and pharmaceutical barriers that limit conventional formulations. This review critically examines the comparative performance of polymeric nanoparticles against conventional oral solid dosage forms in diabetes management, synthesizing evidence from preclinical and clinical studies to evaluate their pharmacokinetic profiles, therapeutic outcomes, safety considerations, and translational potential.

2. Limitations of Conventional Oral Solid Dosage Forms.

Conventional oral solid dosage forms, despite their widespread use and manufacturing convenience, present several formidable challenges when employed for diabetes management. The foremost limitation concerns the bioavailability of orally administered anti-diabetic drugs. Many agents, including the first-line drug metformin, exhibit oral bioavailability ranging from only 50% to 60%, primarily due to their limited intestinal absorption and rapid renal clearance. The biguanide structure of metformin renders it highly hydrophilic, resulting in poor membrane permeability and necessitating

high daily doses of up to 2550 mg to achieve therapeutic efficacy. Similarly, sulfonylureas such as glibenclamide suffer from poor aqueous solubility, which significantly limits their dissolution rate and subsequent absorption from the gastrointestinal tract.

The gastrointestinal environment poses additional barriers to drug stability and absorption. Gastric acid, digestive enzymes, and bile salts can degrade sensitive therapeutic agents before they reach systemic circulation. For protein-based drugs such as insulin, oral administration without protective encapsulation results in near-complete enzymatic degradation by pepsin in the stomach and trypsin/chymotrypsin in the intestine, yielding negligible bioavailability. Furthermore, the extensive first-pass hepatic metabolism of many anti-diabetic compounds substantially reduces the fraction of unchanged drug that reaches systemic circulation. Conventional formulations also produce sharp peaks and troughs in plasma drug concentrations, which fail to mimic the physiological patterns of endogenous insulin secretion and contribute to postprandial hyperglycemia and interdose hypoglycemia.

Patient compliance represents another critical limitation of conventional oral solid dosage forms. The need for multiple daily doses, combined with adverse gastrointestinal effects such as nausea, diarrhoea, and abdominal discomfort, leads to suboptimal adherence rates among diabetic patients. These challenges collectively underscore the urgent need for advanced drug delivery platforms capable of enhancing bioavailability, providing sustained release, and improving the overall therapeutic experience for diabetic patients.

3. Polymeric Nanoparticles as Advanced Drug Delivery Systems.

3.1 Composition and Classification

Polymeric nanoparticles represent a versatile class of nanoscale drug carriers formulated from biodegradable and biocompatible polymers that have demonstrated exceptional promise for diabetes management. These systems are broadly classified into nanospheres, in which the drug is uniformly dispersed within the polymeric matrix, and nanocapsules, in which the drug is confined to a liquid or solid core surrounded by a polymeric shell. The polymers employed in their fabrication can be categorized as synthetic or natural, each offering distinct physicochemical and biological properties.

Among synthetic polymers, poly (lactic-co-glycolic acid) (PLGA) stands as the most extensively investigated and clinically validated material for drug delivery applications. PLGA is a biodegradable copolymer approved by the United States Food and Drug Administration and the European Medicines Agency for human use.^{4,5} Its degradation products, lactic acid and glycolic acid, are metabolized through the Krebs cycle into carbon dioxide and water, rendering the material exceptionally safe for in vivo applications.⁴ The degradation kinetics of PLGA can be precisely tuned by varying the lactide-to-glycolide ratio and molecular weight, enabling controlled drug release profiles ranging from days to several months.⁴ Other synthetic polymers, including poly-epsilon-caprolactone (PCL), polyvinyl alcohol (PVA), and Eudragit derivatives, have also been employed for diabetes drug delivery with favorable outcomes.

Natural polymers, particularly chitosan and its derivatives, have emerged as particularly attractive candidates for oral anti-diabetic drug delivery. Chitosan is a cationic polysaccharide derived from the deacetylation of chitin, composed of D-glucosamine and N-acetyl-D-glucosamine units linked by beta-(1-4) glycosidic bonds. Its unique mucoadhesive properties, attributed to electrostatic interactions with negatively charged mucin glycoproteins, prolong gastrointestinal residence time and enhance drug absorption. Chitosan nanoparticles exhibit excellent biocompatibility, biodegradability, and the capacity to transiently open intestinal tight junctions, thereby facilitating paracellular drug transport. Other natural polymers, including alginate, dextran, gelatin, and pectin, have similarly demonstrated utility in nanoparticle-based diabetes drug delivery systems.

3.2 Formulation Methods

The formulation of polymeric nanoparticles for diabetes drug delivery employs a variety of well-established techniques, each offering distinct advantages regarding particle size control, drug encapsulation efficiency, and scalability. The double-emulsion solvent evaporation method represents the most widely employed technique for encapsulating hydrophilic drugs such as insulin and metformin within PLGA nanoparticles. This method involves the formation of a water-in-oil-in-water emulsion, followed by organic solvent removal to yield nanoparticles with diameters typically between 150 and 400 nm. Alternative methods, including nanoprecipitation, ionic gelation, electrospraying, and microfluidic-assisted synthesis, offer additional control over particle morphology, surface charge, and drug loading capacity.

4. Pharmacokinetic and Pharmacodynamic Comparisons

4.1 Enhanced Bioavailability

The pharmacokinetic superiority of polymeric nanoparticles over conventional oral solid dosage forms has been demonstrated across numerous preclinical studies and validated through quantitative meta-analysis. Hathout⁶ conducted a comprehensive meta-analysis of published studies investigating the bioavailability of orally administered drugs loaded in polymeric nanoparticles compared to conventional formulations. The analysis, utilizing the area under the plasma concentration-time curve as the primary pharmacokinetic endpoint, revealed a statistically significant increase in systemic drug exposure, with a pooled standardized mean difference of 4.048 and a p-value of less than 0.001.⁶ This meta-analysis definitively established that polymeric nanoparticles substantially augment the oral bioavailability of encapsulated drugs, irrespective of whether synthetic or natural polymers were employed as carrier materials.⁶

In the context of diabetes management, nanoparticle-based glibenclamide formulations exhibited a 1.5- to 2-fold increase in maximum plasma concentration and over a 2-fold increase in area under the curve compared to conventional tablet formulations.⁷ Similarly, metformin-loaded nanoparticles

demonstrated a 2.6-fold enhancement in oral bioavailability relative to standard metformin tablets in pharmacokinetic studies.⁸ For oral insulin delivery, chitosan-coated PLGA nanoparticles achieved a relative pharmacological bioavailability of 30.43%, a value previously considered unattainable for oral insulin administration. These improvements are attributed to several mechanistic advantages: protection of the encapsulated drug from gastrointestinal degradation, enhanced mucosal adhesion and penetration, bypass of efflux transporters such as P-glycoprotein, and improved lymphatic uptake.

4.2 Sustained Release Kinetics

A distinguishing feature of polymeric nanoparticle formulations is their capacity to provide sustained and controlled drug release, maintaining therapeutic plasma concentrations over extended periods and thereby reducing dosing frequency. PLGA nanoparticles degrade through hydrolysis of their ester linkages, releasing the encapsulated drug in a controlled manner that can be modulated from several days to months by adjusting polymer molecular weight and composition.⁴ Chitosan-coated PLGA nanoparticles loaded with insulin demonstrated glucose-lowering effects persisting for up to 24 hours following a single oral administration in diabetic rat models, compared to the rapid onset and short duration of action observed with subcutaneous insulin injections.⁹ Metformin-loaded chitosan nanoparticles provided sustained release exceeding 12 hours in vitro, in stark contrast to conventional tablets that release nearly all drug within one hour under intestinal conditions.

4.3 Comparative Pharmacokinetic Parameters

The following table summarizes key pharmacokinetic parameters from comparative studies evaluating nanoparticle formulations against conventional oral solid dosage forms for representative anti-diabetic drugs:

Parameter	Drug	Conventional	Nanoparticle	Improvement
C _{max} (µg/mL)	Glibenclamide	120	190	1.58x
T _{max} (h)	Glibenclamide	2.0	1.0	50% faster
t _{1/2} (h)	Glibenclamide	4.1	7.8	1.9x longer
AUC (µg.h/mL)	Metformin (SLN)	3100	4570	1.47x
Bioavailability (%)	Insulin (CS-PLGA)	<1	30.43	30x
Glucose reduction (%)	Insulin (Ternary NPs)	25	54	2.16x

Table 1: Comparative pharmacokinetic parameters of conventional versus nanoparticle-based anti-diabetic formulations.^{6,7,8,9,10,11}

5. Applications in Type 1 and Type 2 Diabetes

5.1 Type 1 Diabetes: Oral Insulin Delivery

The delivery of insulin via the oral route represents one of the most transformative potential applications of polymeric nanoparticle technology in diabetes management. Despite nearly a century of insulin therapy, subcutaneous injection remains the sole clinically viable administration route, causing significant patient discomfort, poor adherence, and non-physiological peripheral hyperinsulinemia. Polymeric nanoparticles offer a multifaceted solution to the formidable barriers that have historically prevented oral insulin bioavailability.

Sheng and colleagues¹⁰ developed N-trimethyl chitosan chloride-coated PLGA nanoparticles that simultaneously overcome multiple barriers to oral insulin absorption. These nanoparticles, with a mean diameter of 247.6 nm and zeta potential of 45.2 mV, demonstrated enhanced mucus penetration in HT29-MTX cells, improved cellular uptake via clathrin-mediated endocytosis in Caco-2 cells, and increased paracellular permeability through transient tight junction opening.¹⁰ Pharmacological studies in diabetic rats revealed that orally administered insulin-loaded TMC-PLGA nanoparticles produced a hypoglycemic effect with approximately 2-fold higher relative pharmacological availability compared to unmodified PLGA nanoparticles.¹¹ Similarly, zwitterionic micelles developed by Han and colleagues achieved an oral insulin bioavailability of 42.6% in diabetic rats, representing a nearly 5-fold improvement over conventional polysorbate 80 formulations.¹²

5.2 Type 2 Diabetes: Small-Molecule Drug Delivery

For T2DM management, polymeric nanoparticles have demonstrated remarkable efficacy in enhancing the delivery of small-molecule anti-diabetic agents, including metformin, glibenclamide, gliclazide, and repaglinide. Metformin-loaded chitosan PLGA nanoparticles, prepared via nanoprecipitation, exhibited controlled release over six days with cumulative release exceeding 90%, alongside enhanced in vitro bioavailability.⁸ In intestinal adhesion studies, mucosal nanoparticle adhesion reached 67.27% compared to merely 10.52% for free metformin, indicating substantially prolonged gastrointestinal residence.⁹

Glibenclamide-loaded PLGA nanoparticles demonstrated a 40-60% greater reduction in fasting blood glucose compared to conventional tablets over a 4-week treatment period in diabetic rat models.⁷ Moreover, glycated hemoglobin levels, the gold standard indicator of long-term glycemic control, exhibited a more substantial decline in the nanoparticle-treated groups, indicating improved disease management.⁷ Glucose tolerance tests revealed that animals receiving nanoparticle-encapsulated metformin displayed superior insulin responsiveness and more rapid glucose clearance compared to those receiving conventional formulations. Histopathological examinations of pancreatic tissue further corroborated these findings, demonstrating reduced islet cell

damage and evidence of regenerative changes in nanoparticle-treated animals.

6. Safety, Biocompatibility, and Clinical Translation

6.1 Biocompatibility and Toxicity Profiles

The safety profile of polymeric nanoparticles intended for diabetes management is governed by the inherent properties of the constituent polymers. PLGA, as an FDA and EMA-approved biomaterial, exhibits an excellent safety record spanning several decades of clinical use in surgical sutures, implants, and drug delivery systems. Its hydrolytic degradation into biocompatible byproducts that are eliminated through normal metabolic pathways ensures minimal systemic toxicity.^{4,5} Preclinical studies have consistently demonstrated that PLGA and chitosan nanoparticles, at therapeutic doses, do not induce significant histopathological changes in major organs, including the liver, kidneys, heart, and pancreas.⁴ Furthermore, chitosan-based nanoparticles reduced total cholesterol, triglycerides, and hepatic enzyme levels in diabetic rat models compared to untreated controls, suggesting a protective effect against diabetes-associated metabolic disturbances.¹³

6.2 Clinical Translation Challenges

Despite the compelling preclinical evidence supporting polymeric nanoparticles for diabetes management, clinical translation remains limited, with most candidates stalling in early-phase trials. Fontana and colleagues have identified several critical barriers to clinical translation, including the inadequacy of conventional animal models to predict human responses to nanomedicines, the complexity of evaluating pharmacokinetic profiles for both the nanocarrier and its drug payload, and the absence of harmonized regulatory frameworks across major agencies.¹⁴ The United States Food and Drug Administration and the European Medicines Agency currently hold divergent views on bioequivalence assessment for nanoparticle-based formulations, creating significant regulatory uncertainty.¹⁴ Additionally, the challenge of scaling up nanoparticle production while maintaining batch-to-batch consistency in particle size, drug loading, and surface properties represents a formidable manufacturing hurdle that must be addressed before widespread clinical adoption can be realized.¹⁴

7. Conclusion

Polymeric nanoparticle-based drug delivery systems represent a paradigm shift in diabetes pharmacotherapy, offering substantial advantages over conventional oral solid dosage forms in terms of enhanced bioavailability, sustained drug release, improved glycemic control, and reduced dosing frequency. The evidence synthesized in this review demonstrates that polymeric nanoparticles, particularly those fabricated from PLGA, chitosan, and their derivatives, can overcome the formidable physiological barriers that have historically limited the efficacy of oral anti-diabetic therapy. For type 1 diabetes, nanoparticle-based oral insulin delivery systems have achieved bioavailability levels previously considered unattainable, while for type 2 diabetes, nanoparticle-encapsulated metformin and sulfonylureas have demonstrated superior pharmacokinetic profiles and therapeutic outcomes compared to conventional tablets.

The meta-analytical evidence confirms a statistically significant enhancement in oral drug bioavailability when polymeric nanoparticles are employed as delivery vehicles, with no significant difference observed between synthetic and natural polymer-based systems. Nevertheless, several challenges must be surmounted before these promising platforms can transition from bench to bedside. The development of more rigorous preclinical models, harmonization of regulatory standards, and advancement of scalable manufacturing processes will be essential for realizing the full clinical potential of polymeric nanoparticles in diabetes management.¹⁵ Future research should focus on large-scale randomized controlled trials to establish the long-term safety and efficacy of nanoparticle-based anti-diabetic formulations, as well as the development of intelligent, glucose-responsive nanoparticle systems capable of mimicking the physiological feedback control of endogenous insulin secretion. The convergence of nanotechnology, materials science, and diabetes medicine holds immense promise for transforming the therapeutic landscape of this pervasive metabolic disorder.

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