



Development of Biodegradable Nanocarriers for Sustained Release of Antidiabetic Drugs

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ABSTRACT: Management of diabetes mellitus relies heavily on antidiabetic agents – insulin, sulfonylureas, biguanides, and incretin-based peptides – whose conventional dosage forms are frequently limited by short plasma half-life, enzymatic degradation, poor membrane permeability, and the need for frequent dosing, all of which compromise sustained glycemic control and patient adherence. Biodegradable nanocarriers constructed from polyesters (poly(lactic-co-glycolic acid), polylactic acid, polycaprolactone) and natural biopolymers (chitosan, alginate, xanthan gum) have emerged as a mechanistically coherent strategy to overcome these limitations by protecting labile antidiabetic actives, prolonging systemic or mucosal residence, and enabling programmable, sustained drug release as the carrier undergoes hydrolytic or enzymatic biodegradation. This review comparatively examines conventional and biodegradable nanocarrier-based delivery of representative antidiabetic drugs – insulin, glibenclamide, gliclazide, glipizide, and metformin – across physicochemical, sustained-release, pharmacodynamic, and safety dimensions. Across the reviewed literature, biodegradable nanocarrier encapsulation consistently improved encapsulation efficiency, prolonged and pH-responsive drug release, and produced more stable glycemic control in preclinical models relative to conventional dosage forms. However, incomplete characterization of polymer biodegradation kinetics, nanotoxicological uncertainty, and the absence of harmonized regulatory pathways continue to constrain clinical translation. We conclude that biodegradable nanocarriers represent an empirically supported route to achieve sustained-release antidiabetic therapy, provided that standardized biodegradation characterization, robust safety evaluation, and harmonized regulatory frameworks are developed in parallel.

KEYWORDS: Biodegradable nanocarriers; antidiabetic drugs; sustained release; PLGA; chitosan; controlled drug delivery

1. Introduction

Diabetes mellitus is a chronic metabolic disorder that requires long-term pharmacological management to maintain glycemic control and reduce the risk of microvascular and macrovascular complications. Current pharmacotherapy encompasses several classes of agents, including insulin and its analogues, sulfonylureas, biguanides such as metformin, and

incretin-based therapeutics. Despite their established clinical efficacy, these agents present distinct physicochemical, pharmacokinetic, and administration-related limitations that can compromise consistent drug exposure and glycemic control [1]. Peptide therapeutics such as insulin are particularly challenging because they are susceptible to gastrointestinal enzymatic degradation and exhibit poor epithelial permeability, thereby necessitating predominantly parenteral administration [1, 2].

Biodegradable drug-delivery systems have emerged as a promising strategy for addressing these limitations. Synthetic biodegradable polyesters, including poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL), can be engineered to provide controlled drug release through predictable hydrolytic degradation [2, 3]. Natural biopolymers such as chitosan, alginate, and xanthan gum provide complementary advantages, including mucoadhesion, biocompatibility, pH-responsive behavior, and enzymatic biodegradability. These characteristics make biodegradable carriers particularly attractive for chronic diseases such as diabetes, in which prolonged therapeutic exposure and reduced dosing frequency could improve treatment convenience and adherence [4].

The conceptual distinction between conventional antidiabetic delivery and biodegradable nanocarrier-based delivery is illustrated in Figure 1. Conventional formulations may be limited by rapid drug elimination, enzymatic degradation, poor solubility or permeability, and frequent dosing. In contrast, incorporation into biodegradable carriers can protect labile drugs, modify dissolution and absorption, and regulate drug release through diffusion and carrier degradation. The potential result is prolonged drug exposure and more sustained glycemic control, although the extent of improvement depends strongly on the drug, carrier material, formulation properties, and administration route.

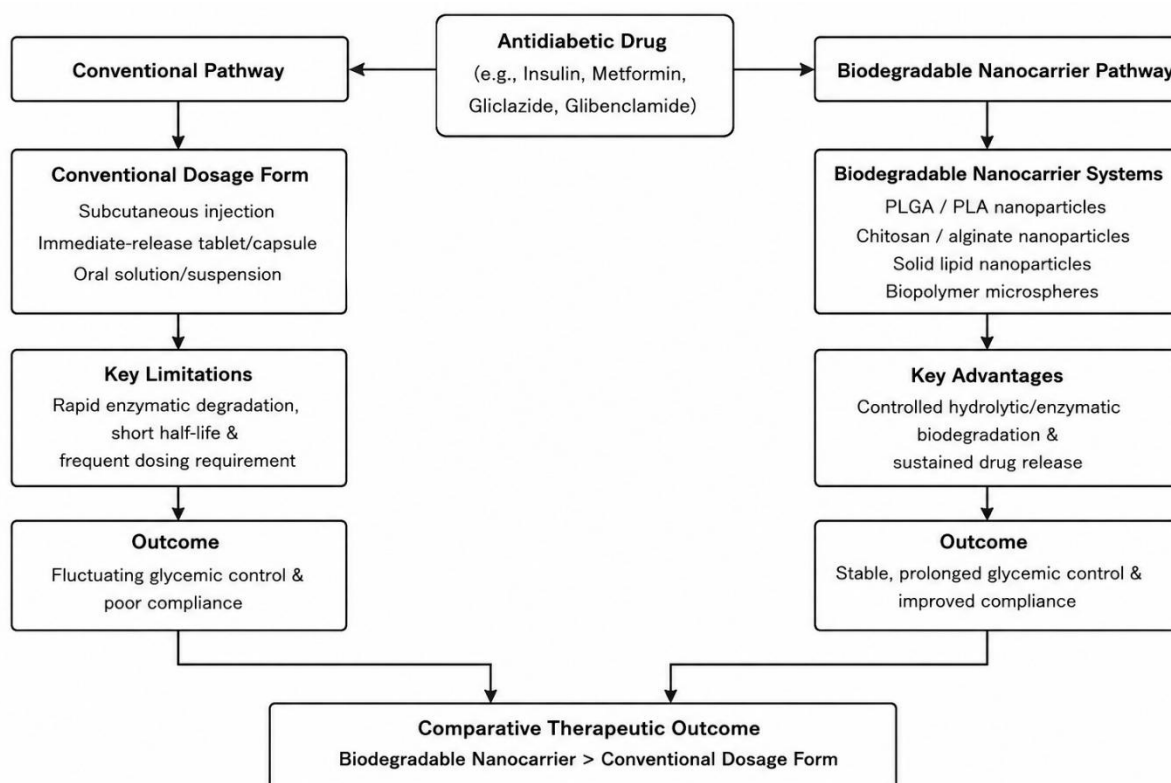


Figure 1. Comparative pathways and therapeutic outcomes of conventional and biodegradable nanocarrier-based antidiabetic drug delivery.

A growing body of preclinical evidence has investigated biodegradable carrier formulations for insulin and small-molecule antidiabetic agents across oral, ocular, and parenteral routes [5–14]. Accordingly, this review critically evaluates biodegradable nanocarrier-based approaches for sustained antidiabetic drug delivery. Particular attention is given to insulin, glibenclamide, gliclazide, glipizide, and metformin as representative therapeutic agents. Specifically, the review aims to: (i) characterize the major physicochemical, pharmacokinetic, and administration-related limitations of conventional antidiabetic formulations; (ii) compare synthetic and natural biodegradable carrier platforms and their drug-release characteristics; (iii) evaluate evidence for improved sustained release, bioavailability, and glycemic efficacy relative to conventional formulations; and (iv) assess biodegradation, nanotoxicological, manufacturing, and regulatory challenges that currently limit clinical translation.

2. Pharmacological and Pharmacokinetic Limitations of Conventional Antidiabetic Drug Delivery

2.1. Physicochemical and Pharmacokinetic Challenges of Antidiabetic Agents.

Conventional antidiabetic drugs exhibit substantially different physicochemical limitations, making formulation requirements highly drug-specific. Glibenclamide and gliclazide are poorly water-soluble compounds whose oral absorption and onset of pharmacological action depend strongly on dissolution behavior and formulation characteristics [9, 10]. Insufficient dissolution may result in variable gastrointestinal absorption and consequently inconsistent systemic exposure. Metformin presents a contrasting formulation challenge. Although highly water-soluble, it has a relatively short elimination half-life and conventional formulations may require repeated daily administration to maintain therapeutic exposure [12, 13]. Gastrointestinal intolerance can further reduce treatment acceptability in some patients. Thus, both poorly soluble and highly soluble antidiabetic compounds may benefit from controlled-release strategies, although the mechanisms through which nanocarriers provide improvement differ substantially.

2.2. Limitations of Peptide-Based Antidiabetic Therapeutics.

Peptide-based therapeutics face more complex delivery barriers than most small-molecule antidiabetic agents. Unprotected insulin administered orally is readily degraded by gastric and intestinal proteolytic enzymes and exhibits extremely limited transepithelial permeability, resulting in very low oral bioavailability [6, 7]. Consequently, insulin treatment remains largely dependent on subcutaneous administration. Although injection provides reliable systemic delivery, repeated administration can cause discomfort, local tissue reactions, and treatment burden, particularly among patients requiring multiple daily injections [5]. Successful non-invasive insulin delivery therefore requires a carrier capable of simultaneously protecting insulin against enzymatic degradation, facilitating interaction with biological membranes, and controlling release at the intended absorption site.

2.3. Patient Compliance and Dosing-Frequency Challenges.

The physicochemical and pharmacokinetic limitations described above ultimately translate into practical treatment challenges. Frequent injections or repeated oral dosing can increase treatment burden and may contribute to inconsistent adherence during long-term diabetes management. Inadequate adherence can, in turn, contribute to greater variability in drug exposure and glycemic response. These limitations demonstrate that the rationale for biodegradable drug delivery extends beyond improving formulation characteristics alone. An effective carrier should ideally reduce dosing frequency, prolong therapeutically relevant drug concentrations, and maintain predictable release without introducing additional toxicity. The major limitations of selected conventional antidiabetic agents and the reported improvements following biodegradable carrier formulation are compared in Table 1.

Table 1. Physicochemical/pharmacokinetic comparison of conventional vs. nanocarrier-based antidiabetic drugs.

Antidiabetic Drug	Conventional-Form Limitation	Nanocarrier Type	Reported Improvement (vs. Conventional)	Ref.
Insulin	Enzymatic degradation and rapid clearance; short duration of action after injection	PLGA nanoparticles embedded in PVA hydrogel	Sustained blood-glucose suppression over 24 h from a single intraperitoneal dose	[5]
Insulin	Poor mucosal penetration and proteolysis limiting non-injectable delivery	pH-sensitive chitosan/alginate core-shell nanoparticles	~85% encapsulation efficiency; pH-responsive gastric protection and sustained intestinal release	[6]
Insulin	Susceptibility to enzymatic degradation across mucosal epithelia	Amino-acid-conjugated & trimethyl chitosan nanoparticles	Improved mucoadhesion, epithelial permeability, and in vivo hypoglycemic efficacy	[7]
Glibenclamide	Very poor aqueous solubility (BCS class II) limiting oral absorption	Solid lipid nanoparticles (Precirol/Compritol)	Improved storage stability and prolonged, near-complete in vitro release profile	[9]
Gliclazide	Poor aqueous solubility and variable oral bioavailability	Compritol-based solid lipid nanoparticles	Prolonged plasma exposure and sustained antidiabetic action with acceptable subacute safety	[10]
Metformin	Short half-life necessitating multiple daily dosing; GI intolerance	Xanthan gum biopolymer microspheres	93% encapsulation efficiency; pH-dependent sustained intestinal release (~90% at 6 h)	[13]

3. Biodegradable Nanocarrier Platforms for Antidiabetic Drug Delivery

3.1. Polyester-Based Nanocarriers.

Among synthetic biodegradable polymers, PLGA is one of the most extensively investigated materials for controlled drug delivery because its degradation and release characteristics can be adjusted through polymer composition, molecular weight, particle characteristics, and formulation conditions [2–4]. Hydrolysis of the polyester backbone enables gradual carrier degradation and can support prolonged drug release. For antidiabetic applications, PLGA-based systems have been investigated for peptide and small-molecule therapeutics. Insulin-loaded PLGA nanoparticles incorporated into PVA hydrogels, for example, produced prolonged glucose-lowering effects in streptozotocin-induced diabetic mice [5]. PLGA-based micro- and nanosystems have also been investigated for insulin, GLP-1-related therapeutics, and metformin, demonstrating the flexibility of polyester carriers for molecules with markedly different physicochemical characteristics [4]. PLA and PCL provide additional biodegradable

polyester alternatives. Differences in crystallinity, hydrophobicity, molecular weight, and degradation rate allow these materials to be selected according to the desired duration of drug release. Carrier selection should therefore be guided not merely by biodegradability but by matching degradation kinetics with the pharmacological requirements of the encapsulated drug.

3.2. *Natural Biopolymer-Based Nanocarriers.*

Natural biopolymers provide different functional advantages. Chitosan is particularly attractive for mucosal drug delivery because of its mucoadhesive characteristics and ability to interact with epithelial surfaces. In chitosan/alginate core-shell systems, alginate can protect encapsulated insulin under acidic conditions, whereas the surrounding chitosan layer contributes to structural stability and mucosal interaction [6]. Chemical modification can further improve carrier performance. Amino-acid-conjugated and trimethylated chitosan derivatives have been investigated to enhance mucoadhesion and epithelial permeability for oral insulin delivery [7]. Chitosan nanoparticles have also been employed for other antidiabetic bioactives, illustrating that natural-polymer systems are not restricted to peptide delivery [8]. At the microscale, xanthan gum and related polysaccharides can provide pH-responsive swelling and sustained release. Xanthan-gum microspheres containing metformin, for example, have demonstrated high drug entrapment together with delayed and sustained intestinal release [12, 13]. These systems illustrate the importance of considering biodegradable delivery platforms beyond nanoparticles alone when sustained release is the principal therapeutic objective.

3.3. *Solid Lipid Nanoparticles and Lipid-Based Biodegradable Carriers.*

Biodegradable lipid carriers are particularly attractive for poorly water-soluble antidiabetic compounds. Solid lipid nanoparticles (SLNs) can incorporate hydrophobic drugs within a lipid matrix, thereby modifying dissolution, protecting the active compound, and extending release. Glibenclamide-loaded SLNs have demonstrated improved formulation stability and prolonged *in vitro* release [9]. Similarly, Compritol-based gliclazide SLNs have produced prolonged drug exposure and sustained pharmacological effects compared with immediate-release formulations while maintaining acceptable preclinical safety [10]. Nanomicellar approaches have also been investigated for glipizide, further illustrating the versatility of nanoscale delivery strategies for poorly soluble sulfonylureas [11]. The major biodegradable carrier platforms, their representative compositions, size ranges, and antidiabetic applications are summarized in Table 2. The comparison demonstrates that carrier selection should be based on the intended therapeutic function: polyester systems are particularly useful for degradation-controlled release, chitosan/alginate systems for mucosal and pH-responsive delivery, lipid nanoparticles for poorly soluble compounds, and polysaccharide microspheres for prolonged gastrointestinal release.

Table 2. Overview of major biodegradable nanocarrier platforms applied to antidiabetic drug delivery.

Nanocarrier Type	Representative Composition	Typical Particle Size	Principal Antidiabetic Application	Ref.
PLGA nanoparticles	Poly(lactic-co-glycolic acid), various lactide:glycolide ratios	150–600 nm	Sustained/controlled release of insulin and GLP-1 analogues	[2,5]
PLA / PCL-based carriers	Poly(lactic acid), polycaprolactone (biodegradable polyesters)	100–500 nm	FDA/EMA-approved biodegradable matrices for peptide and small-molecule sustained release	[3]
Chitosan/alginate nanoparticles	Natural cationic (chitosan) / anionic (alginate) polysaccharide complexes	100–400 nm	Mucoadhesive oral and ocular insulin delivery with pH-responsive release	[6,14]
Modified chitosan nanoparticles	Amino-acid-conjugated or quaternized (trimethyl) chitosan derivatives	150–350 nm	Enhanced epithelial permeation for oral peptide (insulin) delivery	[7]
Solid lipid nanoparticles	Glyceryl behenate, Precirol, or related biodegradable lipid matrices	100–300 nm	Oral bioavailability enhancement of poorly soluble sulfonylureas	[9,10]
Natural biopolymer microspheres	Xanthan gum and related polysaccharide matrices	100–250 μ m	Sustained oral release of small-molecule antidiabetics (e.g., metformin)	[12,13]

4. Comparative Sustained-Release Performance and Therapeutic Efficacy

4.1. Sustained-Release Kinetics and Encapsulation Efficiency.

The value of a biodegradable carrier should ultimately be assessed according to whether its formulation characteristics translate into improved drug-release behavior and pharmacological performance. Across the reviewed systems, encapsulation generally transformed rapid drug release into a more prolonged profile governed by diffusion, swelling, erosion, or carrier biodegradation. For example, pH-sensitive chitosan/alginate insulin nanoparticles achieved approximately 85% encapsulation efficiency while limiting premature release under simulated gastric conditions and enabling sustained release under intestinal conditions [6]. Xanthan-gum microspheres achieved approximately 93% encapsulation efficiency for metformin, with relatively limited gastric release followed by substantially greater release under intestinal conditions [13]. Such findings demonstrate that release kinetics can be engineered according to the physiological environment in which drug liberation is desired. However, high encapsulation efficiency alone should not be interpreted as evidence of therapeutic superiority. Particle stability, initial burst release, degradation kinetics, bioavailability, and maintenance of drug biological activity must also be considered when evaluating formulation performance.

4.2. Glycemic Control and Pharmacodynamic Outcomes.

More clinically relevant evidence is provided by comparative pharmacodynamic studies. Insulin-loaded PLGA nanoparticles incorporated into PVA hydrogels sustained glucose reduction for approximately 24 h following a single administration in diabetic mice [5]. This finding suggests that carrier-mediated sustained release can extend the pharmacological effect of insulin beyond that expected from rapidly available free drug. Gliclazide-loaded SLNs similarly provided prolonged plasma exposure and sustained antidiabetic activity relative to an immediate-release formulation [10]. In another example, polydatin-loaded chitosan nanoparticles improved glycemic and metabolic parameters compared with free polydatin in a

type 2 diabetic rat model [8]. These observations support the potential of biodegradable carriers to translate modified release behavior into improved pharmacodynamic outcomes, although direct comparison remains complicated by differences in formulation composition, dose, administration route, and experimental model.

4.3. Route-Specific Delivery Outcomes.

An important advantage of biodegradable carriers is their adaptability to different administration routes. For oral peptide delivery, modified chitosan systems can provide protection against gastrointestinal degradation while promoting interaction with the intestinal epithelium [7]. For ocular administration, insulin-loaded chitosan nanoparticles demonstrated sustained release, enhanced ocular retention, and measurable glucose-lowering activity in experimental models [14]. Parenteral PLGA nanoparticle-hydrogel systems, meanwhile, can function as local drug depots that progressively release insulin as the carrier undergoes diffusion and degradation [5]. These findings demonstrate that the therapeutic advantage of a biodegradable carrier cannot be evaluated independently of the administration route. Carrier composition, surface properties, degradation behavior, and release kinetics must be designed according to the biological barriers encountered at the intended delivery site. The principal comparative outcomes reported for conventional and biodegradable carrier-based antidiabetic formulations are summarized in Table 3. Across the reviewed preclinical models, carrier-based delivery generally provided prolonged release or glucose-lowering activity relative to conventional or free-drug administration. Nevertheless, the evidence remains predominantly preclinical, and superiority in experimental models should not be interpreted automatically as equivalent clinical benefit.

Table 3. Comparative sustained-release/glycemic efficacy outcomes: conventional vs. nanocarrier-based antidiabetic drugs

Disease / Biological Model	Conventional Treatment Outcome	Nanocarrier-Based Treatment Outcome	Ref.
Streptozotocin-induced diabetic mice (insulin)	Rapid, short-lived glucose reduction after free insulin injection	Sustained blood-glucose suppression over 24 h with PLGA-PVA hydrogel-embedded insulin nanoparticles	[5]
Oral insulin delivery model (rat)	Negligible oral hypoglycemic effect of unprotected free insulin	Significant, sustained hypoglycemic response with improved relative bioavailability using chitosan/alginate nanoparticles	[6]
Oral insulin permeability model (mucosal epithelium)	Limited epithelial permeation and rapid proteolytic degradation	Enhanced mucoadhesion, epithelial uptake, and in vivo glucose-lowering effect with modified chitosan nanoparticles	[7]
Type 2 diabetic rat model (polydatin)	Limited efficacy of free polydatin due to poor bioavailability	Improved glycemic and metabolic parameters with polydatin-loaded chitosan nanoparticles	[8]
Diabetic rat PK/PD model (gliclazide)	Immediate-release tablet with fluctuating plasma levels	Prolonged plasma exposure and sustained antidiabetic action with acceptable subacute toxicity	[10]
Ocular insulin delivery model (rodent)	Poor ocular bioavailability of free insulin solution	~77% sustained release over 12 h, enhanced retention, and marked blood-glucose reduction	[14]

5. Biodegradation, Safety, and Regulatory Considerations

5.1. Biodegradation Mechanisms and Carrier Clearance.

Biodegradation represents both the principal functional advantage and an important safety consideration of biodegradable drug-delivery systems. PLGA undergoes hydrolytic cleavage of its ester backbone, generating lactic and glycolic acids that subsequently enter endogenous metabolic pathways [2, 3]. The degradation rate can be modified by polymer molecular weight, lactide-to-glycolide ratio, particle dimensions, and environmental conditions, allowing drug-release duration to be adjusted. Natural biopolymers exhibit different degradation mechanisms. Chitosan and alginate are affected by enzymatic degradation, ionic interactions, swelling, and environmental pH, whereas xanthan-gum matrices rely substantially on hydration, swelling, and erosion to control drug liberation [12, 13]. These differences emphasize that “biodegradable” should not be treated as a single material property; rather, degradation mechanism and rate must be characterized for each carrier and linked quantitatively to drug-release kinetics.

5.2. Nanotoxicological and Biocompatibility Considerations.

Biodegradability does not automatically establish biocompatibility. Nanoscale dimensions, high surface area, surface charge, and enhanced cellular interaction may produce biological effects that differ from those of the bulk carrier material. Nanoparticles may induce oxidative stress, membrane disruption, or inflammatory responses depending on their composition, dose, size, surface characteristics, and exposure duration [15]. This consideration is particularly important for diabetes because nanocarrier formulations may be administered repeatedly over prolonged periods. Safety assessment should therefore extend beyond acute cytotoxicity to include repeated-dose toxicity, inflammatory responses, organ distribution, degradation-product clearance, and potential accumulation. Carrier-only controls are also important for distinguishing nanocarrier-associated toxicity from adverse effects caused by the encapsulated drug.

5.3. Manufacturing Standardization and Regulatory Translation.

Clinical translation additionally depends on the ability to manufacture biodegradable carriers reproducibly at scale. Laboratory formulations can exhibit substantial sensitivity to polymer molecular weight, drug-to-polymer ratio, surfactant concentration, processing conditions, and storage. These factors can alter particle size, surface charge, encapsulation efficiency, initial burst release, and long-term release kinetics [4, 12]. Regulatory evaluation is further complicated because conventional pharmaceutical frameworks do not always capture nanoscale-specific attributes adequately. Critical quality attributes should therefore include particle-size distribution, morphology, surface characteristics, drug loading, encapsulation efficiency, degradation kinetics, release profile, stability, sterility where applicable, and reproducibility between manufacturing batches [15]. The relationship among biodegradation, toxicity, manufacturing consistency, and regulatory assessment is summarized in Table 4. Importantly, these factors are interdependent: changes in particle size or polymer composition can simultaneously affect degradation, release kinetics, biodistribution, efficacy, and toxicity.

Regulatory assessment should therefore consider the nanocarrier as an integrated drug-delivery system rather than evaluating individual formulation characteristics in isolation.

Table 4. Biodegradation, safety, and regulatory considerations for biodegradable antidiabetic nanocarriers.

Aspect	Key Safety / Regulatory Concern	Common Assessment Approach	Ref.
Polymer biodegradation	Hydrolytic/enzymatic breakdown kinetics of PLGA and related polyesters affecting release duration and burst release	In vitro degradation and drug-release kinetic studies	[2,3]
Cellular / molecular toxicity	Oxidative stress, membrane disruption, and inflammatory responses induced by nanoparticle physicochemical properties	In vitro cytotoxicity assays and molecular toxicity screening	[15]
Manufacturing standardization	Batch-to-batch variability in particle size, encapsulation efficiency, and burst-release behaviour	Standardized physicochemical characterization (size, zeta potential, entrapment efficiency)	[4,12]
Regulatory framework	Absence of harmonized, nanoparticle-specific regulatory guidelines for biodegradable antidiabetic nanocarriers	Comparative regulatory gap analysis across national/regional authorities	[15]

6. Future Research Directions

Despite encouraging preclinical findings, several evidence gaps must be addressed before biodegradable nanocarrier-based antidiabetic therapies can achieve broader clinical translation. First, future investigations should adopt standardized methods for reporting particle characteristics, drug loading, encapsulation efficiency, degradation kinetics, burst release, and sustained-release behavior. This would improve comparability across carrier platforms and facilitate identification of formulation characteristics associated with optimal pharmacological performance. Second, greater emphasis should be placed on long-term safety under repeated administration, rather than relying primarily on short-duration cytotoxicity and acute animal studies. Chronic biodistribution, carrier degradation, renal and hepatic clearance, immunological responses, and potential tissue accumulation are particularly relevant for diabetes because treatment may continue for years. Third, future studies should employ rigorous head-to-head comparisons between nanocarrier-based and conventional formulations using equivalent doses and standardized pharmacokinetic and pharmacodynamic endpoints. Translation should ultimately focus on clinically meaningful outcomes such as reduced dosing frequency, improved bioavailability, reduced glycemic variability, lower hypoglycemia risk, improved tolerability, and better adherence rather than formulation performance alone. Finally, scalable manufacturing and regulatory requirements should be incorporated earlier in formulation development. Collaboration among pharmaceutical scientists, clinicians, toxicologists, manufacturers, and regulatory agencies will be essential for translating promising biodegradable carriers from experimental systems into reproducible therapeutic products.

7. Conclusions

Biodegradable nanocarriers offer a versatile strategy for addressing several limitations of conventional antidiabetic drug delivery, including poor solubility, enzymatic degradation, limited mucosal permeability, rapid elimination, and frequent dosing. Synthetic polyesters, natural biopolymers, and biodegradable lipid systems can be engineered to protect antidiabetic agents and regulate their release according to drug properties and administration route. Preclinical evidence indicates that these systems can prolong drug release, improve

bioavailability, and extend glucose-lowering effects for selected antidiabetic agents. However, the evidence remains dominated by *in vitro* and animal studies, and clinical superiority over established formulations has not yet been demonstrated consistently. Future translation therefore depends on standardized characterization, long-term safety evaluation, reproducible scale-up, and appropriately designed clinical comparisons. Addressing these challenges will determine whether the promising sustained-release characteristics of biodegradable nanocarriers can translate into safer, more convenient, and more consistent diabetes therapy.

Author Contributions

Both authors contributed equally to the conceptualization, literature review, writing, and revision of this manuscript. F.N.A. led the analysis of pharmacokinetic and physicochemical evidence and drafted the introduction and Sections 1–2; C.W.L. led the analysis of comparative efficacy and safety/regulatory evidence and drafted Sections 3–4. Both authors jointly designed the tables and figure, and both authors read, critically revised, and approved the final manuscript.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review.

Data Availability Statement

No new experimental data were generated or analysed in this review.

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