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Review Article

Lipid-Based Nanocarriers for Diabetes Management: Mechanisms, Therapeutic Applications, and Future Directions

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder marked by sustained hyperglycaemia and progressive complications affecting multiple organ systems. Current treatment approaches rely heavily on oral hypoglycaemic medications and subcutaneous insulin injections, both of which face substantial limitations including poor oral bioavailability for certain agents, frequent dosing schedules, elevated risk of hypoglycaemia, systemic adverse reactions, and suboptimal patient adherence. These clinical challenges have driven intensive research into advanced drug delivery platforms capable of enhancing therapeutic outcomes while improving patient convenience and safety. Lipid-based nanocarriers encompass diverse colloidal systems such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, niosomes, and lipid–drug conjugates. These platforms offer significant advantages including protection of labile molecules from gastrointestinal degradation, enhancement of intestinal permeability, facilitation of lymphatic transport, modulation of drug release kinetics, and potential for tissue-specific targeting. They are particularly valuable for delivering insulin and other antidiabetic agents via oral, transdermal, pulmonary, and topical routes, thereby reducing dependence on invasive injection-based therapies.This review critically examines the scientific rationale for employing lipid nanocarriers in diabetes management, their structural and functional characteristics, mechanisms underlying enhanced drug absorption, current preclinical and emerging clinical evidence, safety profiles, and translational challenges. While these systems demonstrate considerable promise for revolutionizing diabetes care, obstacles related to large-scale manufacturing, regulatory approval pathways, and long-term safety monitoring must be systematically addressed before widespread clinical implementation becomes feasible.

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INTRODUCTION

Diabetes mellitus comprises a heterogeneous group of metabolic disorders unified by chronic elevation of blood glucose resulting from deficient insulin secretion, impaired insulin action, or both (1). Type 1 diabetes is primarily an autoimmune condition leading to absolute insulin deficiency through progressive destruction of pancreatic β-cells, whereas type 2 diabetes involves a complex interplay of insulin resistance and β-cell dysfunction, strongly influenced by obesity, sedentary lifestyle, genetic susceptibility, and chronic low-grade inflammation (2, 3). Prolonged hyperglycaemia precipitates microvascular complications including retinopathy, nephropathy, and neuropathy, alongside accelerated macrovascular atherosclerosis and impaired wound healing (4). The International Diabetes Federation estimates that hundreds of millions of individuals worldwide currently live with diabetes, with projections indicating steep increases over coming decades, amplifying both healthcare system pressures and economic burden (5).

Despite the availability of multiple therapeutic classes metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and various insulin analogues conventional treatment frequently fails to achieve durable glycaemic targets (6). Key limitations include variable oral bioavailability for certain agents, narrow therapeutic indices, pronounced hypoglycaemia risk with insulin and secretagogues, weight gain or fluid retention with some drugs, gastrointestinal intolerance, and the substantial psychological as well as physical burden of daily injections (7, 8). Progressive β-cell deterioration necessitates stepwise treatment intensification from monotherapy to complex basal–bolus or basal–GLP-1 combinations, further complicating regimens and compromising adherence (9).

Nanotechnology-enabled drug delivery has gained considerable traction as a strategy to circumvent these obstacles by improving drug stability, enabling targeted tissue distribution, and enhancing patient convenience (10). Among various nanosystems including polymeric nanoparticles, dendrimers, and metallic nanoparticles lipid-based carriers hold particular appeal because they closely mimic physiological lipids, exhibit favourable biocompatibility and biodegradability, and can simultaneously incorporate hydrophilic peptides such as insulin and lipophilic small molecules used in type 2 diabetes management (11, 12). This review synthesizes current mechanistic understanding, preclinical and emerging clinical evidence, and translational challenges for lipid nanocarriers in diabetes therapy.

2. LIMITATIONS OF CONVENTIONAL DIABETES THERAPY

2.1 Inability to address root pathophysiology

Current treatment strategies for diabetes predominantly focus on glycaemic control and symptom relief rather than disease modification (1). Existing therapies including insulin, insulin analogues, and non-insulin hypoglycaemic drugs temporarily manage symptoms but cannot permanently cure or reverse autoimmune β-cell destruction in type 1 diabetes, nor fully restore insulin sensitivity and β-cell mass in type 2 diabetes (2, 13). Consequently, most patients require progressive treatment intensification over time to maintain target glycaemia as β-cell function declines (9, 14).

2.2 Risk of hypoglycaemia and treatment burden

Intensive glycaemic control, while reducing long-term complications, increases the incidence of severe hypoglycaemia a common acute complication particularly in individuals treated with insulin, sulfonylureas, or glinides (15). Fear of hypoglycaemia represents a major psychological barrier that impairs patients' ability to achieve optimal glycaemic targets (15). Moreover, insulin therapy typically requires multiple daily subcutaneous injections or continuous infusion, contributing to injection fatigue, lipodystrophy, local tissue reactions, and reduced adherence (7, 16).

2.3 Adverse effects of antidiabetic drug classes

Each drug class carries characteristic adverse-effect profiles that limit tolerability and long-term use. Metformin, the first-line agent for type 2 diabetes, commonly causes gastrointestinal symptoms including diarrhoea and nausea, and is contraindicated in advanced renal or hepatic impairment owing to lactic acidosis risk (9, 17). Sulfonylureas and meglitinides pose high hypoglycaemia risk, cause weight gain, and may be associated with increased cardiovascular mortality (15, 13). Thiazolidinediones can precipitate fluid retention, heart failure exacerbation, bone fractures, and bladder cancer risk with long-term pioglitazone use (9). Incretin-based therapies carry pancreatitis warnings and gastrointestinal side effects, while SGLT2 inhibitors increase rates of genital mycotic infections and rare cases of euglycaemic ketoacidosis (9). These limitations underscore an urgent need for innovative delivery systems capable of enhancing drug stability, reducing dosing frequency, minimizing adverse effects, and offering non-invasive administration routes.

3. OVERVIEW OF LIPID-BASED NANOCARRIERS

Lipid-based nanocarriers are colloidal systems composed predominantly of physiological or synthetic lipids arranged as vesicles, solid or semi-solid matrices, emulsion droplets, or covalent conjugates (18). Their principal advantages in diabetes therapy derive from several key properties: they protect peptides and labile molecules from harsh acidic environments and proteolytic enzymes in the gastrointestinal tract; they enhance intestinal permeability through modulation of tight junctions and uptake via enterocytes or M-cells; they enable lymphatic transport, thereby bypassing hepatic first-pass metabolism; they can be engineered for controlled or stimuli-responsive release kinetics; and their surfaces can be functionalized to achieve tissue-specific targeting (12, 19).

Six major classes of lipid-based nanocarriers are relevant to diabetes management: liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, niosomes, and lipid–drug conjugates. Each offers distinct structural characteristics and performance advantages for delivering insulin, oral antidiabetic drugs, and bioactive phytochemicals.

Table 1: Summary of lipid-based nanocarrier classes and applications in diabetes.

Nanocarrier Type	Key Advantages	Diabetes Applications
Liposomes	Biocompatible, dual loading capacity	Oral/intranasal insulin delivery
Solid lipid nanoparticles	High stability, controlled release	Insulin, glibenclamide formulations
Nanostructured lipid carriers	Higher drug loading, reduced expulsion	Metformin, pioglitazone, phytochemicals
Nanoemulsions	Enhanced solubility, rapid absorption	Quercetin, wound healing agents
Niosomes	Greater stability, lower cost	Curcumin, berberine delivery
Lipid–drug conjugates	Very high loading, lymphatic transport	Long-acting pioglitazone

4. TYPES AND PROPERTIES OF LIPID-BASED NANOCARRIERS

4.1 Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core, typically ranging from 50 to 2,000 nanometers in diameter (18). Phosphatidylcholine serves as the predominant structural lipid, often combined with cholesterol to modulate membrane fluidity, enhance rigidity, and reduce drug leakage (20). The amphiphilic architecture permits simultaneous encapsulation of hydrophilic agents such as insulin in the aqueous core and hydrophobic molecules within the lipid bilayer (12).

Surface modification with polyethylene glycol prolongs systemic circulation by reducing opsonization and clearance by the reticuloendothelial system, a strategy termed "PEGylation" that creates so-called stealth liposomes (21). Conjugation of targeting ligands such as vitamin B12, folic acid, or monoclonal antibodies enables receptor-mediated uptake by specific cell types including enterocytes (22). Vitamin B12–functionalized liposomes exploit intrinsic factor mediated ileal uptake mechanisms, demonstrating approximately 28% reduction in blood glucose within 30 minutes and sustained effects for up to 4 hours in diabetic animal models (22).

Recent innovations include glucose-responsive liposomal systems incorporating pH-sensitive polymers or phenylboronic acid derivatives that trigger insulin release under hyperglycaemic conditions, potentially mimicking physiological β-cell responsiveness and reducing hypoglycaemia risk (23). Such intelligent formulations hold promise for closed-loop oral insulin delivery, though clinical validation remains pending.

4.2 Solid lipid nanoparticles

Solid lipid nanoparticles consist of a solid hydrophobic lipid core stabilized by surfactant shells in aqueous dispersion, typically sized between 10 and 1,000 nanometers (24). Unlike liquid emulsions, the lipid matrix remains solid at both ambient and physiological temperatures, conferring superior physical stability and protection against oxidative degradation (25). Common solid lipids include triglycerides such as tripalmitin and tristearin, partial glycerides like glyceryl monostearate, fatty acids including stearic and palmitic acids, and various waxes, while surface stabilizers comprise phospholipids, lecithins, or poloxamers (26). Active pharmaceutical ingredients are dissolved or dispersed within the lipid matrix, and controlled drug release occurs via matrix erosion, diffusion, or enzymatic lipid degradation (27).

These nanoparticles address the significant challenge of low oral insulin bioavailability by shielding peptides from gastric acidity and proteolytic enzymes including pepsin and trypsin (16). Preclinical investigations report that insulin-loaded solid lipid nanoparticles achieve up to fivefold increases in relative bioavailability compared with free insulin solutions, with measurable glucose-lowering effects sustained for 24 hours in diabetic rodent models (16, 28). Chitosan-coated variants further enhance mucoadhesion and permeation by transiently opening enterocyte tight junctions, augmenting insulin absorption (29). Nebulizer-compatible formulations for pulmonary insulin delivery have also demonstrated effective plasma glucose reduction in animal studies, offering an alternative non-invasive route (5).

4.3 Nanostructured lipid carriers

Nanostructured lipid carriers represent second-generation solid–lipid nanocarriers engineered to overcome limited drug-loading capacity and drug-expulsion phenomena observed with conventional solid lipid nanoparticles (24). These carriers feature a core matrix blending solid lipids such as stearic acid and glyceryl behenate with liquid oils including Miglyol and oleic acid, creating an imperfect, less-ordered crystalline lattice that accommodates higher drug payloads and prevents drug expulsion during storage (30).

The disordered structure provides more molecular space for drug incorporation, yielding entrapment efficiencies often exceeding 70% (31). Drug release from nanostructured lipid carriers can be fine-tuned by adjusting the solid-to-liquid lipid ratio, enabling sustained release profiles that maintain therapeutic concentrations over extended periods (32). Their small size and lipophilic nature facilitate chylomicron-mediated lymphatic uptake, bypassing hepatic first-pass metabolism and improving systemic bioavailability of orally administered drugs (31).

These carriers protect insulin from gastrointestinal proteases and pH extremes more effectively than first-generation solid lipid nanoparticles while achieving higher loading (33). Recent studies have employed nanostructured lipid carriers to deliver natural antidiabetic compounds such as baicalin, demonstrating significantly greater hypoglycaemic activity in diabetic animal models versus free drug (34). Furthermore, metformin-loaded nanostructured lipid carriers have shown enhanced anti-inflammatory and organ-protective effects in experimental diabetic nephropathy, with improved bioavailability and reduced gastrointestinal side effects compared to conventional metformin (35, 36). Surface functionalization with polyethylene glycol or chitosan further enhances mucosal adhesion and intestinal permeability, optimizing oral delivery (21).

4.4 Nanoemulsions

Nanoemulsions are kinetically stable, heterogeneous colloidal systems comprising oil-in-water or water-in-oil droplets stabilized by surfactants, typically ranging from 20 to 500 nanometers (37). Unlike microemulsions, nanoemulsions require energy input such as high-pressure homogenization or ultrasonication for formation and remain kinetically rather than thermodynamically stable (38). Their high surface area per unit volume markedly enhances dissolution rate and absorption of poorly water-soluble drugs (39).

Formulations typically comprise an oil phase including triglycerides or essential oils, an aqueous phase with water or co-solvents, and emulsifiers or co-surfactants such as Tween 80, lecithin, or Span 60 selected to achieve appropriate hydrophile–lipophile balance (40). The small droplet size confers optical transparency and resists gravitational separation, improving shelf stability compared with conventional emulsions (41).

Alginate–chitosan multilayer-coated insulin nanoemulsions protect insulin from gastric degradation and enhance intestinal permeability, resulting in significant hypoglycaemic effects in diabetic rats (42). Quercetin-loaded nanoemulsions have demonstrated superior oral bioavailability and therapeutic efficacy in managing glucose levels, body weight, and lipid profiles while protecting pancreatic β-cells and hepatocytes from oxidative stress (43). Topical insulin-loaded nanoemulsions have been explored for treatment of diabetic foot ulcers, promoting faster wound contraction, collagen deposition, and re-epithelialization through localized, sustained drug release (44, 45).

4.5 Niosomes

Niosomes are self-assembled vesicular structures consisting of non-ionic surfactant bilayers combined with cholesterol, structurally analogous to liposomes but offering superior chemical stability and lower raw-material cost (46). Surfactants with hydrophile–lipophile balance values between 4 and 8 typically yield stable unilamellar or multilamellar vesicles (47). Cholesterol incorporation regulates membrane fluidity, prevents drug leakage, and enhances physical stability during storage (48).

Niosomes can simultaneously encapsulate hydrophilic drugs in their aqueous core and lipophilic agents within the bilayer, and they are biodegradable, non-immunogenic, and relatively non-toxic (49). They exhibit controlled-release characteristics, enabling sustained therapeutic effects over 24 hours or longer (50).

Niosomal encapsulation protects insulin from acidic gastric pH and enzymatic proteolysis, and increases oral bioavailability of poorly soluble natural antidiabetic compounds such as curcumin or berberine by three- to fivefold (51). Niosomal formulations using Span 40 or Span 60 have demonstrated blood glucose reductions up to 47% with extended glycaemic control over 24 hours in experimental models (50). Glucose-sensitive niosomes incorporating enzymatic or pH-responsive triggers represent an emerging area for smart insulin delivery that could automate release in response to blood glucose fluctuations (52).

4.6 Lipid–drug conjugates

Lipid–drug conjugates involve covalent attachment of a drug molecule to a lipid moiety such as fatty acids or sterols via ester, amide, ether, or salt linkages (53). This conjugation transforms hydrophilic drugs into lipophilic prodrugs, dramatically enhancing their incorporation into lipid nanocarriers with drug loading reaching 33–47% and promoting chylomicron-mediated lymphatic absorption (54).

These conjugates bypass hepatic first-pass metabolism by mimicking dietary fat absorption pathways, and the covalent bond is cleaved by lipases or esterases to release the active drug in a controlled manner (55). For example, insulin conjugated with stearic acid protects the peptide from gastric proteases and enhances intestinal absorption, while pioglitazone lipid conjugates have been formulated for once-monthly injectable depot therapy, improving patient compliance (53, 56). Poly-glutamic acid–phloridzin conjugates have shown superior inhibition of intestinal glucose transporters compared with free phloridzin, contributing to improved postprandial glucose control (5).

5. MECHANISMS OF ENHANCEMENT

Lipid nanocarriers employ multiple synergistic mechanisms to improve the pharmacokinetic and pharmacodynamic profiles of antidiabetic agents.

5.1 Protection from gastrointestinal degradation

Oral insulin faces rapid enzymatic hydrolysis by pepsin in the acidic stomach and by trypsin, chymotrypsin, and pancreatic peptidases in the intestine, resulting in negligible bioavailability below 1% when administered without protection (16). Encapsulation within lipid matrices or vesicles provides a physical shield that prevents premature enzymatic access, thereby preserving peptide integrity until reaching absorptive sites (19). Studies have demonstrated that insulin-loaded solid lipid nanoparticles retain more than 80% of peptide activity after exposure to simulated gastric and intestinal fluids, whereas unprotected insulin is completely degraded (28).

5.2 Enhancement of intestinal permeability

The intestinal epithelium presents formidable barriers including mucus layers, tight junction proteins such as occludin and claudins, and efflux transporters. Lipid nanocarriers overcome these obstacles via several pathways. Cationic polymers such as chitosan that coat nanocarriers electrostatically interact with negatively charged mucins, prolonging residence time and transiently opening tight junctions by redistributing zonula occludens-1 and occludin proteins, thereby facilitating paracellular transport (29). Small nanoparticles below 200 nanometers are internalized by enterocytes via clathrin or caveolin-mediated endocytosis, while particles in the 200–500 nanometer range are preferentially taken up by M-cells overlying Peyer's patches, providing direct lymphatic access (19).

5.3 lymphatic transport and bypass of first-pass metabolism

Lipophilic drugs or lipid-conjugated prodrugs are incorporated into chylomicrons during triglyceride absorption in enterocytes, entering the lymphatic system and bypassing hepatic first-pass metabolism an effect especially pronounced for compounds with log P greater than 5 (19, 54). This mechanism substantially increases systemic bioavailability for drugs that otherwise undergo extensive hepatic extraction.

5.4 controlled and glucose-responsive release

Lipid matrices enable tunable drug-release kinetics ranging from immediate to sustained release over days or weeks, depending on lipid composition, particle size, and surface coatings (26). Nanostructured lipid carriers with higher liquid-lipid content exhibit faster release, whereas solid lipid nanoparticles with highly crystalline matrices provide slower, prolonged release (32).

Glucose-responsive systems represent an advanced approach wherein nanocarriers incorporate enzymatic or chemical sensors that trigger insulin release specifically under hyperglycaemic conditions (23, 57). Glucose oxidase catalyses glucose oxidation to gluconic acid, lowering local pH and destabilizing pH-sensitive polymers such as chitosan or Eudragit, thereby opening release gates (57). Hypoxia-sensitive nanocarriers containing 2-nitroimidazole–L-cysteine–alginate respond to oxygen depletion caused by glucose oxidation, maintaining normoglycaemia for up to 14 hours following a single oral dose in diabetic mice (23). These systems mimic physiological β-cell responsiveness and could reduce hypoglycaemia incidence compared with conventional insulin regimens.

6. RECENT ADVANCES AND CLINICAL APPLICATIONS

6.1 Oral insulin delivery

Oral insulin delivery remains a major focus of diabetes research due to its potential to improve adherence and mimic the physiological portal-vein insulin gradient (16). Recent systematic reviews and meta-analyses indicate that optimal oral insulin formulations employ particle sizes of 200–400 nanometers, achieve encapsulation efficiencies at or above 90%, and deliver insulin doses around 30 international units to produce clinically meaningful glucose reductions (28).

Chitosan-based nanoparticles have emerged as particularly promising owing to their mucoadhesive properties and capacity to transiently open tight junctions, thereby facilitating paracellular insulin transport (29). PEGylated liposomes modified with vitamin B12 demonstrated improved gastrointestinal stability and achieved rapid onset of glucose lowering with effects lasting several hours in rodent models (22). Similarly, alginate–chitosan-coated insulin nanoemulsions produced significant hypoglycaemic effects and improved oral bioavailability compared with free insulin solutions (42).

Charge-reversible lipid nanoparticles incorporating pH-sensitive lipids represent a novel strategy to protect insulin in the acidic stomach while promoting absorption in the neutral-to-alkaline intestine, yielding favourable pharmacodynamic profiles in streptozotocin-induced diabetic mice (58). These formulations exploit the pH gradient along the gastrointestinal tract to dynamically modulate surface charge and enhance site-specific absorption.

6.2 Enhanced delivery of oral hypoglycaemic agents

Beyond insulin, lipid nanocarriers have been employed to improve the oral bioavailability and therapeutic indices of poorly soluble antidiabetic drugs. Glibenclamide-loaded solid lipid nanoparticles demonstrate enhanced dissolution and absorption, reducing peak dose requirements and gastrointestinal side effects (5). Metformin-loaded nanostructured lipid carriers not only increase metformin bioavailability but also exhibit synergistic anti-inflammatory and organ-protective effects in diabetic nephropathy models, mitigating oxidative stress and fibrosis beyond glucose lowering alone (35, 36).

Pioglitazone-loaded nanostructured lipid carriers prepared via solvent evaporation and emulsification techniques show improved insulin sensitivity and glucose tolerance in high-fat diet-induced diabetic rats, with reduced hepatic steatosis and inflammation compared to free drug (59). These findings suggest that lipid nanocarriers may confer disease-modifying benefits beyond simple enhancement of drug bioavailability.

6.3 Delivery of phytochemical antidiabetics

Natural antidiabetic compounds including quercetin, curcumin, berberine, and baicalin possess potent antioxidant, anti-inflammatory, and insulin-sensitizing properties but suffer from poor aqueous solubility and extensive first-pass metabolism (60). Quercetin-loaded nanoemulsions achieve superior oral bioavailability and demonstrate significant improvements in glycaemic control, body weight, lipid profiles, and pancreatic β-cell morphology in diabetic rodent models (43). Baicalin-loaded nanostructured lipid carriers exhibit markedly enhanced hypoglycaemic activity compared with free baicalin suspension, attributed to improved intestinal absorption and sustained plasma levels (34). Curcumin- and berberine-loaded niosomes similarly increase oral bioavailability by three- to fivefold and provide sustained glucose-lowering effects over 24 hours (51).

6.4 Targeted therapy for diabetic complications

Recent applications have expanded beyond systemic glucose control to address tissue-specific complications.

Diabetic retinopathy: Lipid nanoparticles are being investigated as non-viral vectors for mRNA and gene therapy targeting retinal neovascularization and inflammation (61). These systems provide sustained ocular drug exposure and efficient transfection while avoiding the immunogenicity and insertional mutagenesis risks of viral vectors (61).

Diabetic nephropathy and cardiomyopathy: PEGylated liposomes delivering fibroblast growth factor 1 or antioxidants such as betanin have demonstrated enhanced myocardial protection and renal structural preservation in diabetic animal models (22). Metformin loaded nanostructured lipid carriers attenuate renal oxidative stress, inflammation, and fibrosis in streptozotocin-induced diabetic rats, yielding renoprotective effects superior to free metformin at equivalent doses (35).

Diabetic wound healing: Chronic non-healing ulcers represent a major cause of morbidity and lower-limb amputations in diabetes. Topical nanoemulsions delivering antimicrobials such as levofloxacin, insulin, or growth factors promote faster wound closure by ensuring sustained local drug concentrations, disrupting biofilms, enhancing collagen synthesis, and stimulating re-epithelialization (44, 45). Gold nanoparticles combined with epigallocatechin gallate accelerate diabetic wound healing through antioxidant, anti-inflammatory, and angiogenic mechanisms (62). Polymeric and lipid nanomedicines loading growth factors, exosomes, or nitric oxide donors represent emerging strategies for multifunctional diabetic wound management (63).

6.5 Glucose-responsive intelligent systems

A major technological advance involves engineering nanocarriers that autonomously release insulin in response to elevated blood glucose, effectively mimicking pancreatic β-cell function. Glucose oxidase-based systems catalyse glucose oxidation to gluconic acid, creating localized acidification that triggers pH-sensitive polymer disassembly or hypoxia-sensitive nanoparticle degradation (23,57). Hypoxia-responsive nanoparticles incorporating 2-nitroimidazole derivatives can maintain near-normoglycaemia for up to 14 hours following a single oral dose in diabetic mice without inducing hypoglycaemia (23).

Phenylboronic acid derivatives reversibly bind 1,2 or 1,3-diols on glucose molecules, undergoing structural changes that destabilize nanoparticle architecture and release insulin proportionally to ambient glucose concentration (64). These closed-loop systems hold promise for reducing hypoglycaemia risk and improving patient quality of life by minimizing the need for frequent blood glucose monitoring and dose adjustments, though clinical translation remains in early stages.

7. SAFETY PROFILE AND REGULATORY CONSIDERATIONS

7.1 Biocompatibility and toxicological data

Lipid-based nanocarriers are generally composed of natural, biocompatible, and biodegradable lipids including phosphatidylcholine, cholesterol, triglycerides, and fatty acids that are metabolized via physiological pathways (22). Preclinical toxicity studies in rodents and rabbits typically show minimal systemic toxicity at therapeutic doses, with no significant alterations in liver enzymes, renal function, or histopathological organ changes (5, 16).

However, certain formulations have raised safety concerns. High doses of cationic lipids or surfactants can induce localized irritation, inflammation, or hypersensitivity reactions (4). Long-term accumulation of non-biodegradable components including some PEGylated lipids in reticuloendothelial organs requires further evaluation (16). Additionally, rapid insulin release from nanocarriers in the intestine, if uncontrolled, may precipitate hypoglycaemia; glucose-responsive systems aim to mitigate this risk but require careful pharmacodynamic validation (28).

7.2 Clinical translation status

Despite promising preclinical data, clinical evidence for lipid-based nanocarrier formulations in diabetes remains limited. Few formulations have progressed beyond Phase I or Phase II trials, and none have yet achieved regulatory approval for routine clinical use in diabetes management (16). Major barriers include manufacturing complexity and scalability, regulatory pathway uncertainties, interspecies extrapolation challenges given substantial differences in gastrointestinal physiology between rodents and humans, and cost considerations related to development and quality control (28, 65).

Addressing these hurdles will require collaborative efforts among academic researchers, pharmaceutical industry, and regulatory bodies to establish standardized manufacturing protocols, predictive in vitro–in vivo correlation models, and streamlined regulatory frameworks specifically for nanomedicines (16, 65).

8. FUTURE DIRECTIONS

8.1 Personalized nanomedicine approaches

Integration of nanotechnology with precision medicine principles may enable design of lipid nanocarriers tailored to individual patient characteristics including genetic polymorphisms affecting drug metabolism, disease stage, and comorbidities for optimized therapeutic outcomes (14). Co-encapsulation of multiple antidiabetic agents with complementary mechanisms within a single nanocarrier could simplify regimens and enhance synergistic efficacy (11).

8.2 Alternative non-invasive delivery routes

Beyond oral delivery, lipid nanocarriers are being explored for transdermal delivery using microneedle patches, intranasal administration, pulmonary inhalation, and buccal absorption, each offering distinct advantages in terms of absorption kinetics, patient convenience, and avoidance of gastrointestinal degradation (5, 16). Microneedle-based transdermal insulin delivery using lipid nanoparticles embedded in dissolvable arrays provides painless administration with rapid onset and bypasses both gastrointestinal and hepatic barriers (45).

8.3 Gene and regenerative therapies

Lipid nanoparticles are increasingly employed as non-viral vectors for delivering plasmid DNA, mRNA or siRNA targeting insulin production, glucose metabolism, or β-cell regeneration pathways (66). Compared with viral vectors, lipid nanoparticles offer advantages including lower immunogenicity, absence of insertional mutagenesis risk, and scalable manufacturing (61). Encapsulation of pancreatic islet cells or stem-cell-derived β-like cells within immunoisolatory lipid-based microcapsules may enable allogenic or xenogeneic transplantation without chronic immunosuppression, representing a potential curative approach for type 1 diabetes (66).

8.4 Clinical trial priorities

Key priorities for moving lipid-based nanocarrier formulations from bench to bedside include development of Good Manufacturing Practice-compliant production methods ensuring batch to batch reproducibility, establishment of robust in vitro models that predict in vivo performance, conduct of dose-ranging and safety studies in larger animals with gastrointestinal physiology more similar to humans, design of adequately powered randomized controlled trials with clinically relevant endpoints including glycated haemoglobin, time in range, hypoglycaemia rates, and patient reported outcomes, and post-marketing surveillance for long-term safety signals (16, 28).

9. CONCLUSION

Lipid-based nanocarriers represent a versatile and scientifically robust platform for improving the delivery of insulin and other antidiabetic agents, addressing multiple limitations of conventional diabetes therapy. Liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, niosomes, and lipid–drug conjugates each offer unique structural and functional advantages including protection from enzymatic degradation, enhancement of intestinal permeability and lymphatic uptake, controlled or glucose-responsive release, and potential for targeted delivery to pancreatic, hepatic, renal, ocular, and wound tissues.

Preclinical evidence strongly supports the capacity of these systems to increase oral insulin bioavailability, prolong hypoglycaemic effects, reduce adverse effects, and improve patient adherence through non-invasive administration routes. Recent innovations in glucose-responsive and targeted nanocarrier systems further advance the vision of autonomous, closed-loop diabetes management that mimics physiological insulin secretion.

Despite these advances, clinical translation has been hindered by manufacturing complexity, regulatory uncertainties, limited human trial data, and cost considerations. Overcoming these barriers will necessitate multidisciplinary collaboration, standardized production protocols, predictive preclinical models, and rigorous clinical evaluation. With sustained research effort and technological refinement, lipid-based nanocarriers hold substantial promise to transform diabetes care in the coming decade, providing safer, more effective, and more patient-friendly therapeutic options that may significantly improve glycaemic control and reduce the burden of diabetic complications.

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