

Liposome-Based Drug Delivery for Diabetes: Therapeutic Applications and a Nanomedicine Perspective on Diabetic Complications

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Abstract: Diabetes mellitus (DM) affects approximately 537 million adults worldwide and remains inadequately controlled in a substantial proportion of patients despite the availability of various pharmacological therapies. Conventional antidiabetic treatments are often limited by poor bioavailability, rapid degradation of peptide-based drugs, insufficient tissue targeting, and systemic adverse effects. Liposomes, phospholipid bilayer-based nanocarriers, provide a versatile structural platform capable of simultaneously encapsulating hydrophilic and lipophilic agents, thereby addressing key pharmacokinetic limitations of conventional therapies. Their advantages include enhanced drug stability, improved bioavailability, and controlled release properties, resulting in more favorable pharmacokinetic performance. Surface modifications, such as PEGylation and ligand functionalization, further extend circulation time and enable targeted delivery, enhancing therapeutic efficacy in both type 1 and type 2 diabetes compared with conventional formulations. The evidence synthesized in this review indicates that liposomal systems consistently demonstrate improved pharmacokinetic profiles, enhanced tissue-specific accumulation, and reduced systemic toxicity in preclinical models of diabetes, although high-quality clinical validation remains limited. This review summarizes recent advances in liposome design, fabrication strategies, and therapeutic mechanisms in diabetes and its complications, providing a critical evaluation of their therapeutic benefits and translational barriers. Despite their clear potential, major challenges persist, including gastrointestinal instability, enzymatic degradation of encapsulated peptides, large-scale manufacturing complexity, and regulatory standardization. Addressing these limitations through formulation optimization, advanced targeting strategies, and rigorous clinical validation will be essential for successful clinical translation. Overall, liposomes represent a strategic and evolving nanomedicine platform for precision diabetes therapy.

Keywords: liposomes, nanocarriers system, targeted drug delivery, surface functionalization, diabetes mellitus

Introduction

Diabetes mellitus (DM) is a chronic metabolic condition characterized by sustained hyperglycemia, caused by inadequate insulin production or insulin resistance.¹ Diabetes mellitus (DM) is a significant long-term health concern.² The World Health Organization (WHO) has projected that diabetes will rank as the sixth leading cause of mortality by 2030.³ Globally, approximately 537 million adults are estimated, with projections increasing to 643 million by 2030 and 783 million by 2045.⁴ The problems associated with DM include substantial financial burdens, reduced quality of life, and heightened morbidity and death due to its consequences.⁴ DM includes type 1 and type 2 diabetes, with type 2 diabetes mellitus (T2DM) representing > 90% of the cases.⁵ Chronic hyperglycemia can result in severe complications,

including diabetic retinopathy, which may lead to vision impairment or blindness; nephropathy, potentially advancing to renal failure; and neuropathy, which can induce autonomic dysfunction, such as sexual dysfunction and diabetic foot. Moreover, patients with diabetes are at an elevated risk of developing cardiovascular, peripheral vascular, and cerebrovascular illnesses.^{1,5}

Type 1 diabetes (T1D) is an autoimmune condition in which the immune system gradually destroys pancreatic β -cells responsible for producing insulin. This process is primarily driven by autoreactive CD4⁺ and CD8⁺ T lymphocytes, which mistakenly target and damage these cells. Individuals with T1D require lifelong insulin replacement therapy, which involves daily insulin administration and continuous monitoring of blood glucose levels.⁶ In contrast, type 2 diabetes mellitus is characterized by chronically elevated glucose levels arising from insulin resistance, a condition shaped by complex metabolic disturbances as well as inflammatory and oxidative processes.⁷ Diabetic nephropathy (DN) is a serious complication that accounts for almost 40% of cases of end-stage renal disease cases.⁸ Individuals with diabetes are also approximately five times more likely to develop fungal and bacterial infections. This heightened vulnerability is attributed to multiple factors, notably increased blood glucose levels, which facilitate bacterial proliferation. Moreover, diabetes compromises blood circulation, obstructing the healing of abrasions, open wounds, and other traumas, thereby elevating the risk of infections in diabetic individuals.³ Diabetic retinopathy (DR) is a chronic degenerative effect of diabetes and is considered the most common and distinctive microvascular complication DM. The process is initiated with microaneurysms in the retinal blood vessels, causing retinal damage through abnormal vascular proliferation, edema, and leakage of intravascular fluids, which may result in vision impairment or blindness.² Diabetes mellitus often leads to ocular complications, with diabetic neurotrophic keratopathy being the predominant clinical manifestation affecting the cornea.⁹ Foot ulcers affect approximately 25% of individuals with diabetes and primarily result from peripheral neuropathy and impaired wound healing, which are marked by disrupted angiogenesis, chronic inflammation, and reduced collagen synthesis. Diabetic foot ulcers frequently result in recurrent hospitalizations and, in severe instances, amputations, leading to elevated medical costs and reduced quality of life for those affected.¹⁰

Despite considerable advancements in insulin therapies, the imperative for alternative anti diabetic pharmacotherapies persists, chiefly because a significant proportion of patients with type 1 diabetes (T1D) experience insulin intolerance.¹¹ Prolonged administration of insulin formulations may reduce the sensitivity of pancreatic islets, leading to diminished efficacy and the onset of insulin resistance.¹² Acidic conditions (pH 1.2–2.0) and the presence of digestive enzymes in the gastrointestinal tract lead to the denaturation and degradation of insulin, significantly reducing its bioactivity and therapeutic effectiveness.¹³

Type 2 diabetes mellitus (T2DM) is primarily managed using oral hypoglycemic agents, including biguanides, sulfonylureas, α -glucosidase inhibitors, and thiazolidinedione derivatives. Although these medications operate via distinct mechanisms, they are often associated with significant adverse effects and are generally ineffective in preventing the onset of diabetes or mitigating its complications. Although newer agents including glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucokinase (GK) agonists, protein tyrosine phosphatase 1B (PTP-1B) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors offer improved glycemic control, their clinical utility is limited by suboptimal pharmacokinetics, limited activity, and potential toxicity.¹² Metformin is commonly prescribed as a first-line therapy for T2DM, however, prolonged oral administration has been associated with an elevated risk of lactic acidosis. The clinical efficacy of metformin is limited by its low bioavailability, short biological half-life, and the challenges associated with transmembrane transport. To overcome these limitations, sustained-release formulations have been developed as a potential strategy to enhance bioavailability and reduce adverse effects.⁵ These limitations underscore the necessity of creating sophisticated drug delivery systems (DDS) that enhance drug stability, maximize bioavailability, and facilitate targeted delivery to particular tissues.¹⁴

Advanced therapeutic alternatives have been developed owing to the development of novel therapeutic approaches, aided by notable advancements in nanotechnology. Among these, nanotechnology-based drug delivery systems have become the most widely used strategy for improving therapeutic efficacy.^{10,15} Enhanced intracellular absorption, sustained drug release, increased localization at the target site through targeted mechanisms, and protection against enzymatic or chemical degradation are just a few of the therapeutic benefits of nanocarriers.¹⁰ Drug delivery systems

based on nanotechnology have been used to enhance the pharmacokinetic and pharmacodynamic characteristics of therapeutic drugs. This allows dose reduction and minimizes side effects, which increases the overall therapeutic index.¹⁶

Various of lipid-based delivery systems, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, emulsions, biomimetic nanovesicles, and exosomes have been investigated for the administration of therapeutically challenging drugs. Liposomes have become one of the most popular nanocarriers for diabetes management because they are one of the most widely used nanoparticle-based drug delivery systems. They are especially promising because they can help drugs enter the body more effectively. Additionally, drug delivery systems (DDSs) such as liposomes can greatly improve the pharmacological effects of regular drugs by changing how they move through the body and how they are distributed.^{1,3,17}

Liposomes are small, spherical vesicular systems composed primarily of phospholipids and cholesterol, featuring one or more concentric bilayers enclosing an internal aqueous core (Figure 1). Their structural characteristics such as size, lamellarity, and compartmentalization enable them to encapsulate a wide variety of therapeutic agents. Hydrophobic compounds can be incorporated into the lipid bilayer, whereas hydrophilic molecules are sequestered within the aqueous interior. Owing to their excellent biocompatibility, liposomes not only reduce drug toxicity and enhance stability, but also enable sustained drug release, making them effective carriers for a broad range of pharmaceuticals, including antibiotics, antifungals, and cytotoxic agents.^{16,18} Liposomes have several advantages over traditional drug delivery systems. They are not harmful, break down easily, and are not usually immunogenic. Encapsulating bioactive compounds within liposomes can markedly improve their bioavailability and stability. Owing to their structural similarity to biological membranes, liposomes can transport therapeutic agents into cells by fusing with the cell membrane. Moreover, certain active ingredients added to liposomal systems may act in addition to their role as excipients by enhancing the overall therapeutic effect of the main drug.⁵

Figure 2 illustrated the schematic representation of liposomes application for diabetic disease. Liposome-based drug delivery systems have emerged as a promising strategy for improving diabetes therapy by enhancing drug targeting, pharmacokinetics, bioavailability, and formulation stability. Functionalization of the liposomal surface with specific ligands enables the active targeting of particular tissues or organs, thereby improving delivery precision and therapeutic efficacy while minimizing off-target effects.^{19,20} In addition, encapsulation of therapeutic agents within liposomes protects drugs from rapid enzymatic degradation, premature metabolism, and early systemic clearance, allowing controlled and sustained drug release, which may prolong therapeutic action and reduce dosing frequency.^{21,22} Liposomes further enhance drug absorption and bioavailability by increasing the residence time at biological interfaces and facilitating the transport of poorly water-soluble drugs across lipid membranes, which improves cellular uptake and systemic exposure.^{22–24} Surface modification of liposomes with hydrophilic polymers such as polyethylene glycol (PEG) significantly extends the systemic circulation time by reducing recognition and clearance by the reticuloendothelial system, decreasing particle aggregation, and minimizing immunogenic responses, thereby promoting greater accumulation at pathological sites and potentially mitigating first-pass metabolic effects.^{15,25} Moreover, liposomes enhance formulation stability by protecting encapsulated drugs from dilution in physiological fluids and enzymatic degradation,

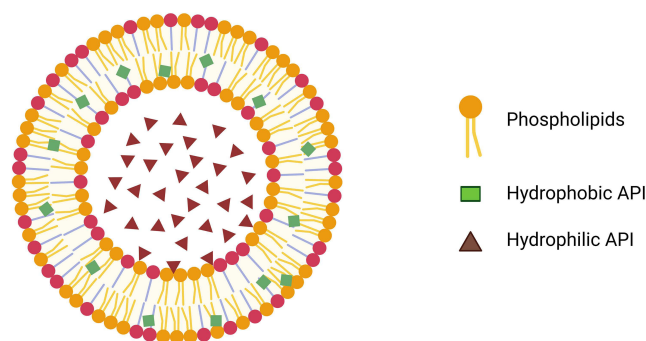


Figure 1 Illustration of the Liposome Structure.

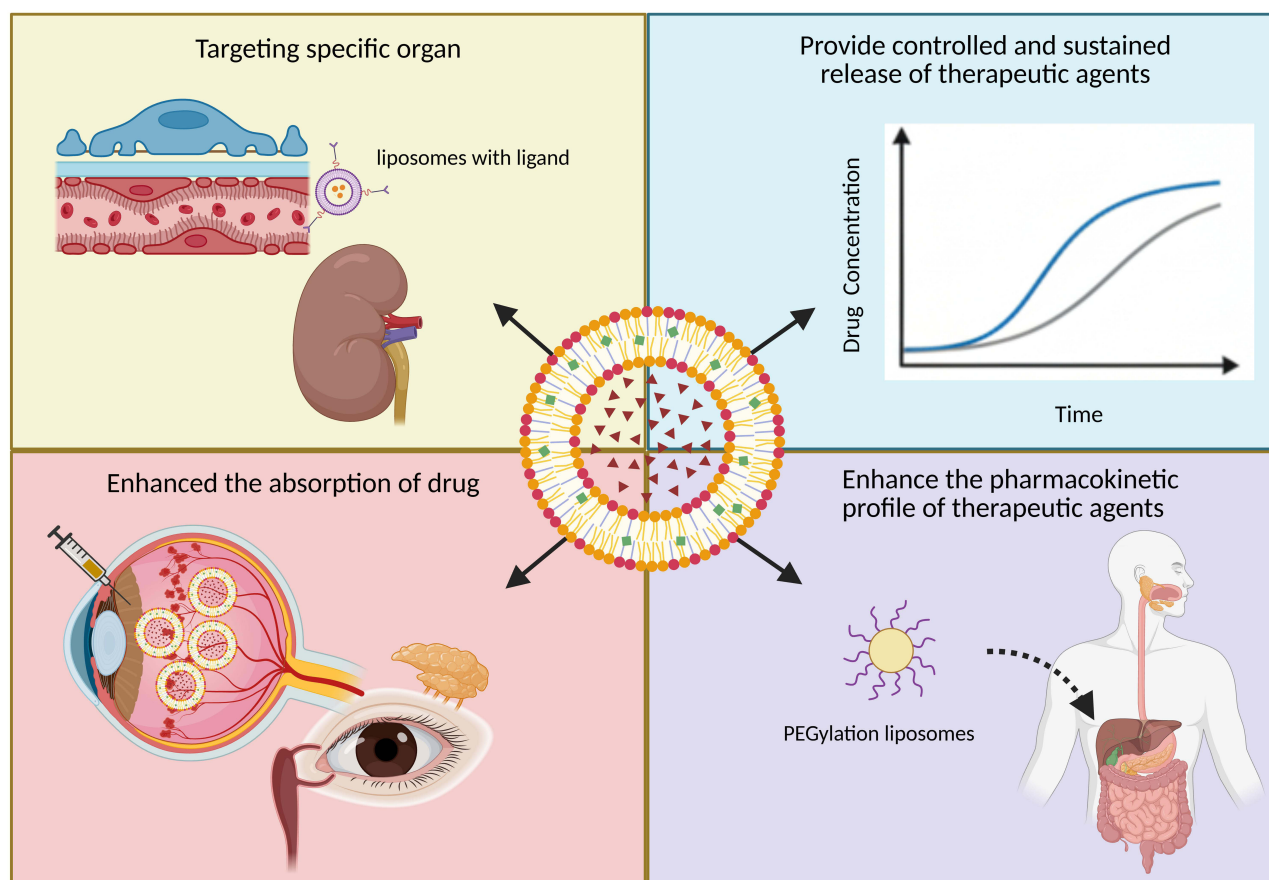


Figure 2 Schematic Representation of Liposomes Application for Diabetic Disease.

while advances in lipid composition optimization and storage conditions allow contemporary liposomal formulations to maintain particle size, encapsulation efficiency, and structural integrity for extended periods under refrigerated or, in some cases, ambient conditions.^{22,26}

Although liposome-based drug delivery offers numerous advantages, significant knowledge gaps remain in the current literature. While previous reviews have broadly discussed liposomes, none have comprehensively focused on formulations specifically for diabetes therapy and its complications. Critical aspects such as surface modification and functionalization strategies, long-term stability under physiological conditions, and their impact on pharmacokinetic and pharmacodynamic performance have not been thoroughly addressed. Moreover, comparative evaluations of different liposomal platforms in terms of improving bioavailability, achieving targeted tissue delivery, and reducing systemic toxicity remain insufficiently contextualized. To address these gaps, this review provides a comprehensive and critical assessment of recent advances, identifies existing limitations, and proposes directions for future research to facilitate the clinical translation of liposome-based therapies for diabetes.

This narrative review is based on peer-reviewed literature retrieved from Scopus, PubMed, and ScienceDirect published between 2015 and 2025. Studies were selected using keywords such as “liposomes”, “diabetic”, and “nanocarriers”. Articles were included if they focused on liposomal formulation, liposomal drug delivery in diabetes management, reported on formulation strategies, therapeutic mechanisms, or clinical applications, and were published in English. Studies without relevant outcomes or not focused on diabetes were excluded. This review aims to critically evaluate the current advances in liposome-based drug delivery systems for diabetes management, identify existing limitations, and highlight future research directions.

Preparation Methods for Liposomes

Numerous techniques for liposomes preparation have been proposed and refined. Liposome preparation methods based on drug loading are generally categorized into two passive and active approaches. Passive loading consist of the lipid hydration method (Bangham Method), microemulsification, probe sonication method, bath sonication, French pressure cell extrusion, membrane extrusion, dried reconstituted vesicles, freeze-thaw method, solvent dispersion method, ethanol injection method, ether injection (solvent evaporation) method, double emulsification method, reverse phase evaporation method, and detergent removal method (removal of non-encapsulated materials). Active loading techniques involve the formation of liposomes from proliposomes and lyophilization.^{19,20}

In passive loading, the drug is mixed before the liposomes are formed or added as they are assembled. This method is divided into three categories, each with its own set of techniques. Hydrophilic drugs are usually dissolved in the aqueous phase and end up in the inner water-filled core of the liposome, whereas hydrophobic drugs tend to settle in the phospholipid bilayers. For example, water-soluble compounds become trapped in the internal aqueous compartment as liposomes form, whereas lipid-soluble substances blend into the hydrophobic region the bilayer.²⁰ Encapsulating hydrophilic drugs typically does not alter the physicochemical properties of liposomes, as they do not strongly interact with vesicle. In contrast, inserting lipophilic drugs into the bilayer can noticeably change the properties of the liposome, including alterations in the phase transition temperature (T_c), which may influence the membrane's structure and overall behavior.²¹

Active loading techniques are suitable only for certain types of compounds especially those with ionizable groups or amphipathic properties that allow them to cross the liposomal membrane even after vesicles have formed. Because these molecules can interact with both aqueous and lipid environments, they can move into preformed liposomes and become efficiently encapsulated. However, passive loading traps the drug before or during the liposome formation. This means that the compounds are added to the vesicle as they form and cannot enter once the structure is fully formed. As a result, active loading can be applied to a relatively limited group of drugs that possess the necessary physicochemical characteristics.^{20,22}

Figure 3 illustrates that multiple techniques have been utilized to create liposomes for diabetes treatment, including the thin-film hydration (Figure 3A), solvent injection (Figure 3B), reverse phase evaporation methods (Figure 3C), and microfluidic approach (Figure 3D).

Thin-Film Hydration (TFH) Method

The Bangham method, often referred to as the thin film hydration (TFH) technique, is one of the most commonly used methods for producing liposomes. In this approach, lipids are first dissolved in volatile organic solvents, such as chloroform, dichloromethane, or methanol. Once the solvent was removed, a thin layer of lipid formed on the inner wall of the round-bottomed. When this dry film is hydrated with an aqueous solution, liposomes spontaneously form. To further adjust their properties especially to fine tune and reduce particle size researchers typically add extra steps such as sonication, membrane extrusion, or high-pressure homogenization.^{23,24}

This technique is relatively straightforward and offers satisfactory encapsulation efficiency (EE) for both low and high molecular weight drug molecules. Nevertheless, it is associated with several drawbacks, such as the extensive use of organic solvents that are challenging to eliminate, limited control over particle size and fundamental limitations of the TFH method for large-scale production.^{25–27} Although the TFH method is straightforward controlling the particle size and polydispersity index (PDI) is highly dependent on multiple manual parameters, including solvent evaporation rate, lipid composition, and hydration speed. As a result, substantial batch-to-batch variability frequently occurs, limiting the reproducibility of preclinical studies that require robust quantitative data.^{25,26} TFH is a batch-based, laboratory-friendly process; however, it is inherently difficult to scale it up for continuous or industrial production. In contrast, modern approaches such as microfluidics, micro mixing, and continuous manufacturing provide superior control over the particle size and offer more practical and realistic pathways toward good manufacturing practice (GMP) compliant production.²⁸

TFH followed by extrusion remains one of the easiest and most common methods for preparing liposomes in the laboratory. This method produces vesicles of the same size by making thin films, adding water, and then pushing them out.²⁹

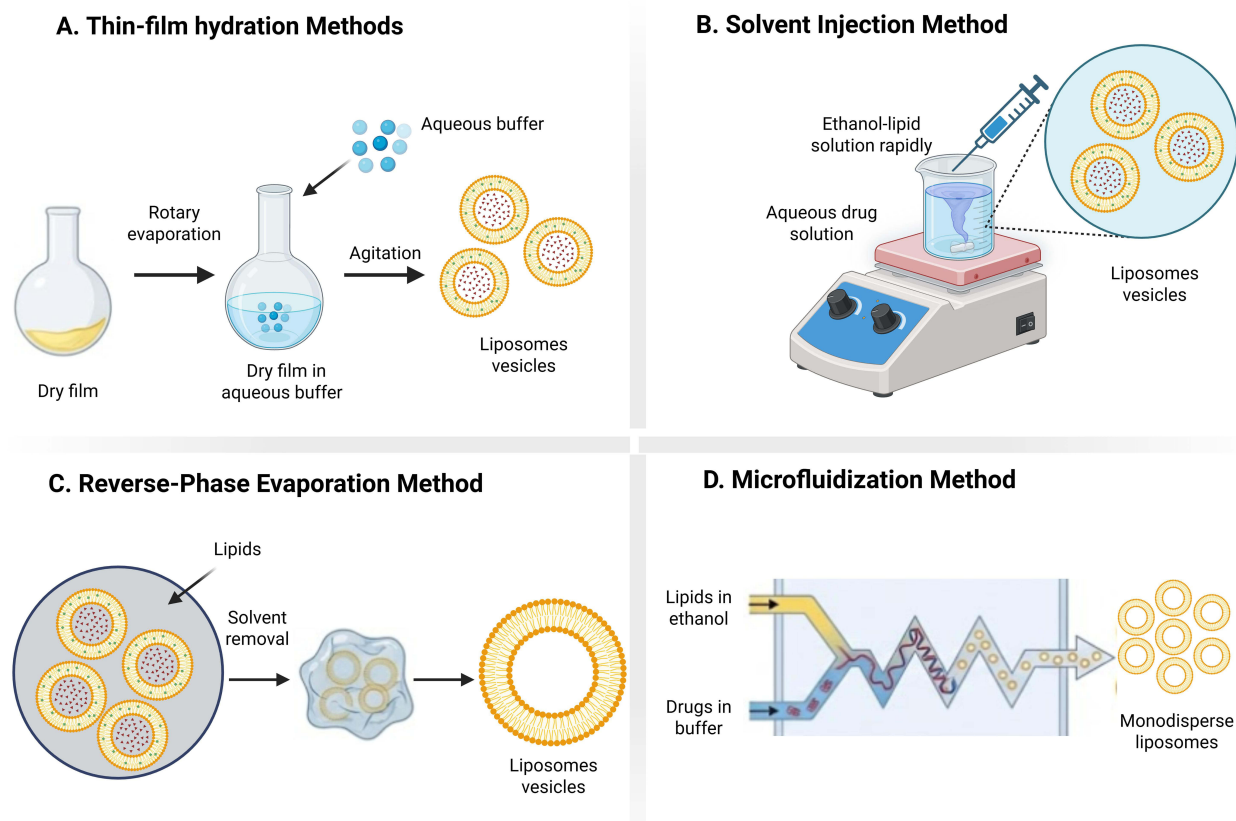


Figure 3 Primary Methods of Liposome Preparation for Diabetes Related Applications. (A) Thin-film hydration Methods; (B) Solvent Injection Method; (C) Reverse-Phase Evaporation Method; (D) Microfluidization Method.

Solvent Injection Method

The solvent injection method involves dissolving lipids in an organic solvent, followed by the controlled injection of this solution into an aqueous phase. Among the solvents commonly used for this approach, ethanol and diethyl ether are the most widely employed in the preparation of liposomal nanoformulations.^{25,26}

Ethanol injection (EI) is the most commonly employed solvent injection technique. This process involves adding a lipid ethanol solution to water maintained at 50–60 °C, which causes immediate formation of liposomal vesicles. The EI method is widely used for preparing liposomes on a large scale because it is simple and can be easily performed on a larger scale. However, this approach is not suitable for biologically active macromolecules or thermosensitive drugs.²³

The ethanol injection method offers several advantages: it is simple to perform, highly reproducible, uses ethanol as a relatively safe solvent, and is well-suited for large-scale production. However, this method has several limitations. These include the challenge of fully eliminating residual ethanol due to its azeotropic interaction with water, and the formation of a highly diluted and heterogeneous liposomal population, generally measuring 30–110 nm in size. Furthermore, even minimal concentrations of ethanol may pose a risk of inactivate biologically active macromolecules.²⁶ This technique is particularly suitable for the preparation of large-volumes liposomal formulations.^{24,30}

Reverse-Phase Evaporation Method

The reverse-phase evaporation (REV) begins with the dispersion of an aqueous phase into a lipid-containing organic phase to form a water-in-oil emulsion. When the organic solvent is removed under reduced pressure, a thick gel-like material appeared, and this intermediate transformed into large unilamellar vesicles upon hydration. This technique is particularly effective for loading hydrophilic drugs, because the internal aqueous phase is initially well preserved, allowing for high encapsulation efficiency. It is also suitable for the incorporation of large macromolecules.^{29,31}

However, the use of considerable amounts of organic solvents, together with the complexity of forming and breaking down the emulsion, makes scaling up and ensuring reproducibility more difficult.³¹

REV is well known for producing liposomes with a large internal aqueous volume and high encapsulation efficiency.^{32,33} Thus, it often performs better than the thin-film hydration method.³⁴ This method usually produces unilamellar or oligolamellar vesicles with an aqueous core approximately 30 times larger than that produced by sonication. These vesicles can trap more than 62% of the particles.³⁵ Another important aspect of the REV method is that it is sensitive to factors, such as the polarity of the solvent and the ratio of lipids to solvents. These factors greatly influence the final characteristics of the liposomes, including size, size distribution, and overall stability.³²

Microfluidization Method

Microfluidization is a widely studied and frequently used technique for producing liposomes. In this method, fluids are driven through precisely engineered microchannels under high pressure. Cavitation, shear forces, and particle impact synergistically enhance emulsification efficacy. These effects synergistically provide numerous advantages, including consistent and highly reproducible processing, scalability for large-volume production, precise control over liposome size, and elevated encapsulation efficiencies that frequently exceed 75%. Additionally, bioactive chemicals remain unexposed to organic solvents or detergents, which can compromise their stability.³⁶ Microfluidization is advantageous for scaling up as it eliminates the need for organic solvents and the many processes associated with conventional technologies, such as the Bangham technique, detergent depletion, reverse-phase evaporation, or injection-based systems. The flow rate of the microfluidizer can be modified to regulate vesicle size, thereby enhancing liposome stability.³⁷ Microfluidic or high-pressure microfluidic homogenization generally yields liposomes with remarkably high encapsulation efficiency, frequently exceeding 90% for lipophilic compounds.³⁸

Microfluidic techniques allow for precise control of liposome size by regulating flow conditions and pressure, leading to the formation of more uniform and monodisperse vesicles than those obtained using conventional methods. This level of control substantially enhances batch-to-batch reproducibility, which is a critical requirement for clinical applications.²⁹ Liposomes prepared using high-pressure microfluidic homogenization can achieve exceptionally high encapsulation efficiencies (>96%), particularly for hydrophobic compounds, without requiring additional sonication or extrusion steps, which are typically necessary in conventional preparation methods.³⁸ Microfluidizer systems and microfluidic chips are often costly and technically complex, and can present significant barriers for laboratories with limited resources. In addition, the optimization of operating conditions, such as flow-rate ratios, pressure, and temperature typically requires extensive trial-and-error experimentation.^{39,40} Depending on the physicochemical properties of the lipids and encapsulated drugs, this method still requires careful adjustment of the processing parameters to prevent lipid or drug loss during purification. For instance, residual ethanol can adversely affect the encapsulation efficiency if it is not adequately managed.²⁸

Collectively, liposome preparation techniques differ substantially in terms of scalability, reproducibility, and translational suitability. While TFH and REV remain valuable for exploratory and preclinical investigations due to their formulation flexibility and relatively high encapsulation efficiency, their inherent batch variability, solvent dependency, and scale-up limitations restrict industrial applicability. Solvent injection allows rapid vesicle formation and improved scalability, though it may compromise thermolabile drugs. In contrast, microfluidic-based technologies offer precise, reproducible, and large-scale production with high encapsulation efficiency, albeit requiring specialized equipment. Nevertheless, their higher operational cost and technical complexity may limit accessibility in early-stage research settings. Accordingly, method selection should consider not only drug characteristics and vesicle properties, but also translational feasibility and regulatory compliance. Well-designed comparative studies evaluating encapsulation efficiency, stability, and scalability remain essential to support the reliable development of liposome-based therapies for diabetes.

Factors Affecting the Stability and Efficacy of Liposomes

The structural stability of liposomes plays a pivotal role in regulating the controlled release of active compounds in both the bloodstream and the intestinal mucosa, depending on whether the drug is administered orally.⁴¹ This stability is governed by storage temperature, light exposure, drug loading, lipid peroxidation and pH fluctuations (Figure 4).

Storage Temperature

The stability of the liposomal compositions is greatly affected by the storage temperature. Previous research indicates that liposomes containing diverse bioactive compounds frequently exhibit reduced stability at elevated temperatures. The storage conditions recorded in these studies varied from -150 to 50 °C, with durations ranging from 24 hours to 90 d. The thermal stability of liposome depends on the properties of the encapsulated molecule and the specific composition of their lipid membranes. Notably, the thermal instability of peptide-loaded liposomes restricts their application to thermally processed products.⁴¹ Studies on curcumin loaded liposomes have shown that curcumin retention is markedly enhanced when stored at 4 °C rather than at 25 °C, primarily because lower temperatures minimize lipid oxidation and vesicle leakage.⁴² Ultra-low-temperature storage (eg, -80 °C), when combined with appropriate cryoprotectants such as a DMSO–sucrose mixture, is capable of preserving liposome stability for several months, achieving a performance comparable to that obtained at -150 °C.⁴³

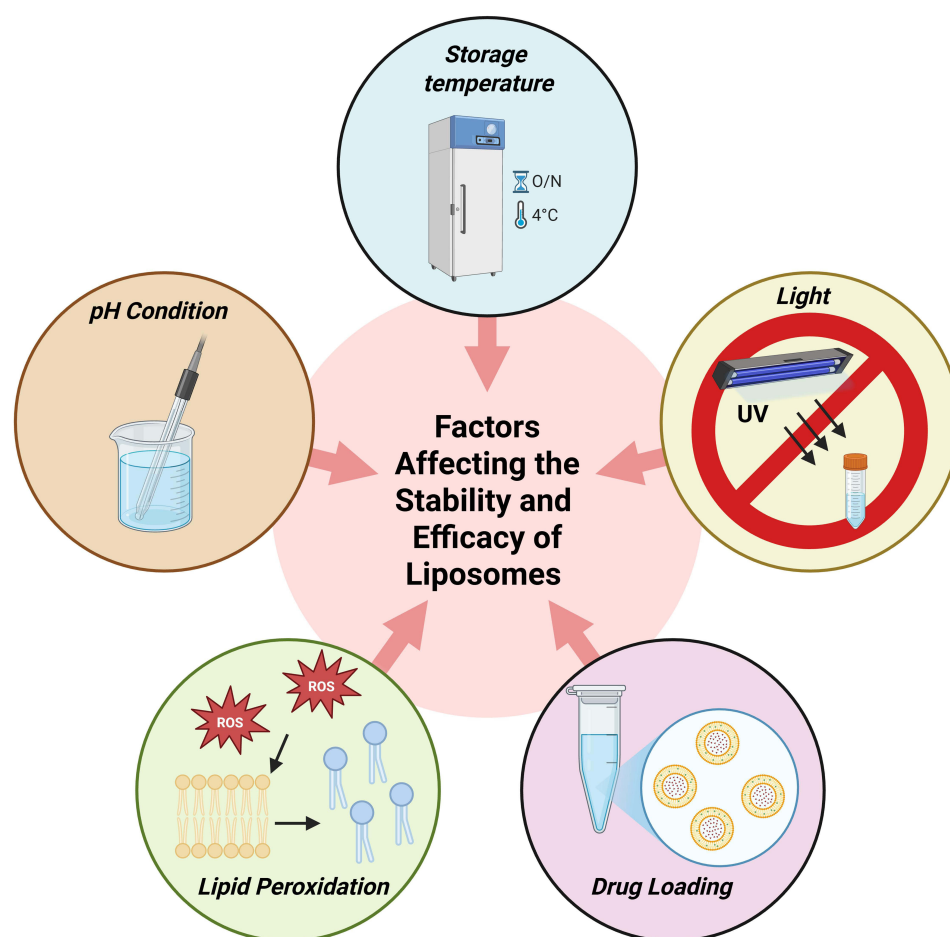


Figure 4 Factors Affecting the Stability and Efficacy of Liposomes.

Light

The photostability of liposomes has been widely investigated by exposing them to different types of light, including ultraviolet A (UV-A), ultraviolet B (UV-B), ultraviolet C (UV-C), and other forms of radiation. Among these, sunlight exposure under varying conditions was the most commonly used, with test durations ranging from a few hours to several months. Liposomes are particularly vulnerable to light-induced degradation, because sunlight, fluorescent light, or UV radiation can trigger lipid oxidation and break down other membrane components. This process disrupts the delicate balance between hydrophobic and hydrophilic interactions, causing structural changes that can negatively affect liposomal stability, permeability, and overall physicochemical properties.⁴¹ In particular, UV light can compromise the bilayer structure and increase membrane fluidity and permeability. Consequently, liposomes may undergo aggregation or fusion, resulting in leakage of their encapsulated contents.⁴⁴ Coating liposomes with polysaccharides or polymers enhances their resistance to light-induced damage, indicating that such protective coatings are advantageous for formulations that are susceptible to light exposure.⁴⁵ Liposomes encapsulating silibinin are particularly susceptible to photodegradation upon exposure to ultraviolet radiation, which promotes phospholipid peroxidation and compromises bilayer integrity. These effects may result in alterations in particle size, decreased drug encapsulation efficiency, and reduced biological activity, emphasizing the inherent sensitivity of the compound to light.⁴⁶

Drug Loading

Liposomes stability is significantly affected by drug loading, as the incorporation of pharmaceuticals can cause conformational changes in lipid membranes. At reduced drug concentrations, the molecules preferentially localize within the outer bilayer adjacent to the aqueous interface. However, as drug loading increases, the compounds infiltrate deeper into the bilayers, inducing structural alterations in the membrane that could result in liposomes aggregation. Consequently, drug–lipid interactions are critical factors influencing liposomal stability. Lipid saturation further influences these interactions, consequently affecting the stability outcomes. Lipids with unsaturated acyl chains typically facilitate higher drug loading because of the increased flexibility of their hydrocarbon chains, whereas saturated fatty acids tend to negatively impact the loading efficacy, likely owing to the rigidity of their carbon chains.⁴⁷ In paclitaxel (PTX)-loaded liposome formulations, vesicles composed of saturated phospholipids frequently encounter difficulties in maintaining elevated drug loading levels. Their inflexible bilayer configuration restricts the integration of PTX, leading to frequent membrane permeability or drug precipitation when attempting to achieve higher loading levels.⁴⁸ Characterization studies of glibenclamide-loaded liposomes have shown that lipid chain length, degree of saturation, and cholesterol content substantially influence key physicochemical properties, such as particle size, loading efficiency, zeta potential, polydispersity index, and drug-release profile. These findings underscore that drug lipid interactions go beyond merely increasing drug content; attaining optimal stability and performance necessitates meticulous optimization of membrane architecture, incorporation methods, and overall lipid composition.⁴⁹

Lipid Peroxidation

The chemical stability of liposomes is strongly affected by the oxidation of their phospholipids, a process referred to as lipid peroxidation. This can occur during lipid purification, sterilization, and the storage process. Lipid peroxidation involves the breakdown of lipids through oxidation, producing free radicals along the fatty acid chains, such as cyclic and hydroperoxides. Unsaturated fatty acids are particularly susceptible to this type of damage compared to saturated fatty acids. The oxidation process can be triggered at different stages of liposome preparation, depending on the technique used. Methods that employ organic solvents such as ethanol, methanol, chloroform, ether, and methylene chloride facilitate efficient lipid dispersion and encapsulation. However, removing residual solvents at high temperatures during the final stages can destabilize lipids and promote oxidative reactions.⁴¹

Coating liposomes with polymer can prevent lipid oxidation in vesicular systems, thus improving their chemical stability. A study was conducted to assess the effects of polymers on liposomes oxidation. The polymer coating of liposomes protects lipids against oxidative degradation, thereby improving their chemical stability. This method has been examined in studies exploring the effects of polymers on liposomal oxidation.⁴⁷ Transition metals, especially iron, can catalyze the oxidative degradation of lipids by facilitating accelerated oxygen consumption and forming lipid peroxides.

Therefore, rigorous regulation of heavy-metal impurities and trace contaminants is essential for liposome purification, formulation, and storage.⁵⁰

pH

Liposomes stability under varying pH conditions is a critical for the delivery of pH-sensitive compounds. Typically, liposomes are prepared in a neutral buffer to ensure that the incorporated active compounds remain in a neutral environment. Experimental studies have evaluated liposomal stability across a pH range of 2.5–10.5, with storage times ranging from 30 min to 30 days, to identify the optimal pH conditions for maintaining long-term stability.⁴¹ Liposomes encapsulating pH-responsive molecules, including curcumin, indicates that acidifying the intravesicular environment (for example, to pH 2.5) improves their chemical stability and slows the release kinetics over the storage period.⁵¹ Liposomal formulations containing an acidic intravesicular environment exhibit superior retention of particle size, zeta potential, and overall structural integrity throughout the stability period relative to those formulated with a neutral internal pH.⁵² Certain liposomal systems are intentionally formulated to maintain structural stability at neutral or physiological pH, however, they undergo enhanced membrane permeability upon exposure to acidic environments. For instance, liposomes incorporating tailored phospholipid compositions or additional design modifications demonstrate accelerated release profiles under low-pH conditions.⁵³ Incorporating stabilizing components such as cholesterol or applying polymer/polysaccharide surface modifications can help maintain bilayer integrity despite pH fluctuations, thereby supporting both physical and chemical stabilities. These strategies are particularly valuable for liposomal systems intended for environments with variable pH such as oral drug delivery, the gastrointestinal tract, or tissues with distinct local acidities.⁵⁴

Liposome stability is influenced by factors such as temperature, light exposure, drug charge, lipid peroxidation, and pH; however, previous studies have reported inconsistent results due to variations in lipid composition, drug properties, and preparation methods. Elevated temperatures and UV exposure can induce oxidation and leakage, whereas polymer coatings may mitigate these effects for some compounds but not others. High drug loading can disrupt membrane stability, with unsaturated lipids generally accommodating higher drug content than saturated lipids. pH variations also affect vesicle integrity and drug release kinetics. These discrepancies highlight the need for comparative studies and integrated formulation strategies to ensure reproducible performance and clinically relevant outcomes across different liposomal systems.

Parameters Evaluated Reflecting Characteristics of Liposomes

From an application perspective, a thorough characterization of the prepared liposomes is essential. Monitoring both physical and chemical parameters ensures the reproducibility of the formulation and confirms that liposomes perform their intended functions. The key characteristics to be evaluated include the following: (1) average size, size distribution, morphology, and lamellarities; (2) surface charge; (3) drug encapsulation efficiency; (4) drug release; and (5) stability.⁵⁵

Size, Morphologies and Lamellarities

Electron microscopy (EM) provides high-resolution imaging of liposomes under diverse conditions, enabling detailed visualization of their size, morphology, and lamellarity, as well as those of other nanoparticles.²⁶ Specialized variants of transmission electron microscopy (TEM) are frequently employed for liposomal characterization. In the TEM images, the liposomes generally appeared as dark spherical nanoparticles against a light background. Furthermore, TEM aids in differentiating between individual vesicles and aggregates and offers valuable insights into lipid phase transitions, thus allowing a thorough assessment of liposomal structural characteristics.²⁶

In scanning electron microscopy (SEM), a dried sample is examined point by point using an electron beam, and the emitted secondary electrons are detected to produce an image. This approach provides detailed three-dimensional views of surface nanostructures and offers valuable information on liposomal characteristics, including size, shape, and layered (concentric) organization.²⁶

Atomic force microscopy (AFM) is another important technique for assessing liposomal size and morphology is. As a type of scanning probe microscopy (SPM), AFM delivers sub-nanometer resolution and allows three-dimensional profiling of liposomal structures in their native solution environment, without the need for vacuum conditions.²⁶ TEM

and AFM studies have revealed that liposomes can form unilamellar or multilamellar vesicles. The number of lamellae directly affects key properties such as drug encapsulation capacity, release profile, and overall physical stability of the formulation.⁵⁶

Particle size and the polydispersity index (PDI) are two of the most essential parameters in liposome characterization. Smaller liposomes typically exhibit longer circulation time than larger liposomes, and are cleared more swiftly from the bloodstream. Liposomes with a size range of 50–200 nm are considered optimal for drug delivery applications. PDI, which varies between 0 and 1, indicates the extent of size distribution within a liposomal population. A PDI value of ≤ 0.3 indicates a uniform and homogeneous distribution, appropriate for pharmaceutical applications, whereas larger values imply greater size heterogeneity or the existence of multiple liposomal populations. PDI calculations are derived from parameters such as particle size, solvent refractive index, measurement angle, and distribution variance.¹⁹ If the liposome formulation exhibits a broad size distribution such as vesicles ranging from 50 to 2000 nm as documented in a study employing NTA/MANTA the biological activity, stability, and pharmacokinetic properties may vary significantly between the smaller and larger vesicles.⁵⁷

Surface Charge

The surface charge of liposomes in suspension is characterized by their zeta potential, which can be defined as the net electrical charge acquired by the vesicles within a given medium.⁵⁵ Zeta (ζ) potential measurement is a valuable technique for evaluating electrostatic effects in charged nanocarriers. This is determined by the surface charge characteristics of the liposomes, which depend on the lipid composition and headgroup polarity. The zeta potential is a critical factor in governing the colloidal stability, biodistribution, pharmacokinetics, cellular interactions, and drug internalization of liposomes. The ζ potential of a colloidal nanoparticle is generally determined from its electrophoretic mobility (μE), which is evaluated using phase analysis light scattering (PALS). Combining light-scattering methods with zeta potential analysis enables a more comprehensive assessment of electrostatic interactions in charged liposomes and provides valuable insights into the mechanisms governing the interactions between liposomal nanocarriers and target cells or tissues.²⁶ Liposome suspensions are generally regarded as stable when their zeta potential exceeds +30 mV or falls below −30 mV.⁵⁵ In formulation optimization studies, liposomes exhibiting a zeta potential of $+30.1 \pm 1.2$ mV or -36.7 ± 3.3 mV were able to maintain colloidal stability characterized by particle sizes below 150 nm and PDI values under 0.3 in aqueous media for at least two weeks.⁵⁸

Drug Encapsulation Efficiency

Encapsulation efficacy (EE) indicates the number of liposomes in the formulation process that successfully encapsulated a drug. To determine it, the total amount of drug administered the amount of free, unencapsulated drug is subtracted. Then, we divided the result by the amount of drug administered at the start. To determine EE, scientists examine the physicochemical properties of the compound. Common methods include spectrophotometry, fluorometry, and radiometry.³⁰ The process of determining EE usually begins with separating the unbound drug from the liposomal suspension. Mini-column centrifugation is one such method used to achieve this. It takes advantage of the size differences between liposomes and drug molecules, which are not bound to anything else.⁵⁵ Studies comparing different separation methods have shown that the measured EE values can vary significantly depending on the method used. Methods such as size-exclusion chromatography (SEC), solid-phase extraction (SPE), centrifugal ultrafiltration (CF UF), and hollow fiber centrifugal ultrafiltration (HF CF UF) yield very different results.⁵⁹ Nanoparticle Exclusion Chromatography (nPEC) has been evaluated as a rapid and accurate method for separating free drug from liposomes and is applicable to both hydrophilic and lipophilic drugs.⁶⁰

Drug Release

Drug release characterization is typically performed in vitro using dialysis methods. In this method, liposomes are contained within pre-wetted dialysis bags possessing a specific molecular weight cutoff that retains the vesicles while allowing the substance to diffuse through the membrane. The concentration of the released substance was measured at different time intervals to assess the release kinetics of the liposomal formulations. However, in vivo drug release may be

affected by other factors such as dilution within the circulation, pH fluctuations, interactions with plasma proteins and cells, and turbulent flow conditions.³⁰

In situ detection techniques (eg, spectroscopy or chromatography such as HPLC/LC MS, and solid-phase extraction) can be applied by measuring the drug released directly in the medium (or following extraction) without separating the particles. This approach is particularly suitable when the particles are difficult to isolate or are fragile. Although it can reduce separation-induced artifacts, it requires analytical methods that are sensitive and selective.⁶¹

Stability

Liposomal stability is a key factor in determining its effectiveness and suitability for clinical applications. Stability is typically assessed through physical characterization over time ranging from days to months, focusing on parameters such as drug leakage and particle size. Over time, liposomes may undergo undesirable changes, including particle aggregation and deterioration of the lipid membrane structure. Fourier-transform infrared spectroscopy (FTIR) is often used to analyze lipid composition and confirm the absence of degradation. Lyophilization is commonly employed to extend the shelf life and reduce lipid oxidation. These techniques are conducted at specified intervals during storage, with substantial deviations from baseline measurements indicating liposomal instability.³⁰ Liposomal stability involves not only particle size and distribution but also membrane integrity (physical stability) and the chemical preservation of both the lipids and the encapsulated drug.⁴⁷

Liposome size, lamellarity, and morphology, typically evaluated using TEM, SEM, or AFM, directly influence encapsulation efficiency and drug release kinetics. However, vesicle uniformity and reported polydispersity index (PDI) values vary considerably depending on preparation and measurement methods. Surface charge (zeta potential) governs colloidal stability and cellular interactions, yet optimal thresholds differ across studies. Encapsulation and release profiles are method-dependent, with separation and analytical techniques often producing inconsistent results. Stability assessments including physical aggregation, lipid peroxidation, and membrane integrity also vary according to storage conditions, formulation, and analytical approaches. Collectively, these variations underscore the need for standardized comparative evaluations to ensure that liposomal formulations for diabetes therapy achieve consistent, predictable, and clinically relevant performance.

The Therapeutic Application of Liposomes For Diabetes Mellitus

Liposomes have been extensively investigated as a therapeutic strategy for diabetes mellitus, including both type 1 and type 2 diabetes,^{5,62} as well as for the management of various associated complications, such as nephropathy,¹⁸ wounds and infection,⁶³ retinopathy,² and neuropathy⁶⁴ (Figure 5).

Therapeutic Applications of Liposomal Drug Delivery Systems in Type I Diabetes Mellitus (T1DM)

Thin layer hydration is the most widely used method for liposome production in the treatment of type 1 diabetes (Table 1), with reported reductions in diabetic incidence reaching approximately 20–30% compared to 60–80% in untreated controls in NOD models, and prevention of T1D onset up to 60–70% relative to control groups. This method is one of the simplest techniques for liposome synthesis in laboratory environments, typically resulting in heterogeneous multilamellar vesicles (MLVs). Notably, they continue to be significant in modern applications, including large-scale manufacturing procedures. This methodology also demonstrates considerable promise for precise delivery of biologically active therapeutic agents.⁶⁵

Conventional liposomes, generally formulated from phospholipids and cholesterol, are constrained by their instability in the gastrointestinal environment and limited permeability through the intestinal epithelium. Nanoliposome modifications can improve stability within the gastrointestinal environment while simultaneously enhancing absorption by enterocytes. For oral applications, nanoliposomes must exhibit high stability and the ability to penetrate the gastrointestinal epithelium to access the bloodstream and release their payload. For example, PEGylated liposomes measuring

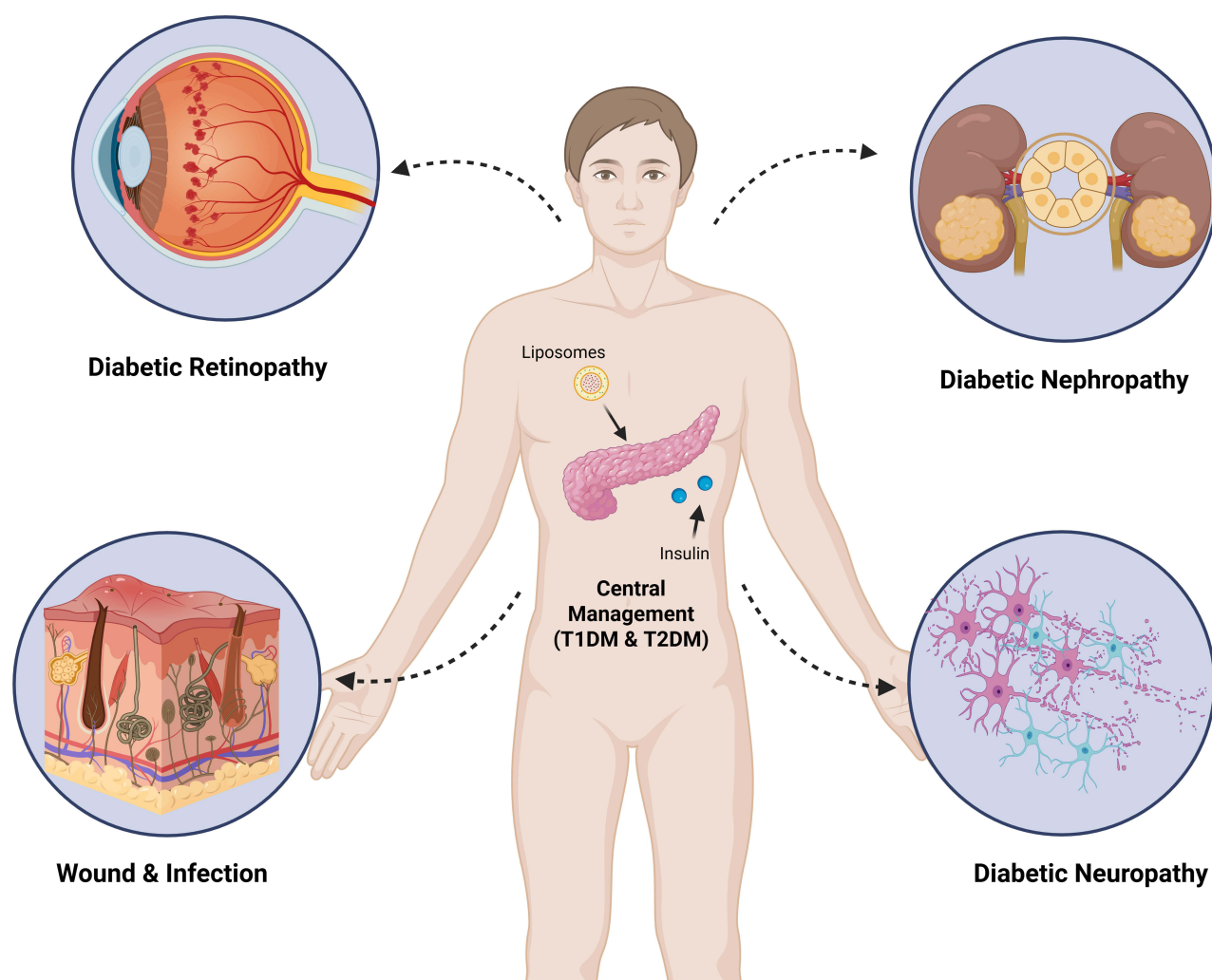


Figure 5 The Therapeutic Role of Liposomes in the Treatment of Diabetes Mellitus and its Associated Complications.

approximately 150–210 nm with a negative surface charge demonstrated enhanced cellular uptake and improved in vivo hypoglycemic effects compared to conventional liposomes.⁶⁹

Receptor-mediated endocytosis is an important approach for improving the oral bioavailability of drugs. To ensure optimal absorption, ligands that bind to receptors on intestinal cells are utilized. The principal mechanism of targeted nanoparticle transfer is clathrin-mediated endocytosis, although some nanoparticles may also be transported across cells through transcytosis. Previous studies have investigated the role of vitamins as mediators of intestinal liposome absorption. For example, folic acid, the synthetic variant of vitamin B9, is a vital nutrient with receptors present on intestinal cells, allowing folic acid conjugates to be efficiently taken up by folate receptors.⁶⁹

PEGylation is a modification method in which proteins, peptides, or non-peptide compounds are conjugated to one or more polyethylene glycol (PEG) chains. PEG is non-toxic, non-immunogenic, highly water-soluble, and has been approved by the Food and Drug Administration (FDA) for use as a polymer. PEGylation is a crucial factor in drug delivery systems, as it can improve the stability and therapeutic effectiveness of peptide- and protein-based treatments.⁶⁷ Folic acid-conjugated PEGylated liposomes can augment the stability of liposomes within the gastrointestinal tract and enhance the systemic absorption of orally administered insulin relative to conventional liposomes. Liposomes measuring approximately 150–210 nm in size, possessing a negative charge, and featuring PEGylation along with a folic acid ligand, exhibited enhanced cellular uptake and more significant in vivo hypoglycemic effects compared with conventional liposomes, although complete prevention of diabetes progression was not consistently achieved across models.⁶⁹

Table 1 Examples of Liposomal Formulations of Type 1 Diabetes Mellitus (T1DM) Drugs with Their Preparation Methods and Categories

Preparation Method	Formulation	Categories of Liposomes	Drug	Pharmacological Uses	Result	Ref
Thin-film hydration	DOPC, DOPG, and Chol (50: 20: 30)	Liposome modified with ligand	Insulin B peptide	Type 1 diabetes mellitus (T1DM)	Prevents T1D onset and strengthens regulatory cell protection against diabetogenic cells in an antigen-specific manner up to 60–70% relative to the control	[66]
Thin-film hydration	DOPE, cholesterol	PEGylated liposome	Insulin	Type 1 diabetes mellitus (T1DM)	Liposomes may serve as an alternative to conventional insulin formulations for diabetes treatment	[67]
Thin-film hydration	Phosphatidylethanolamine and cholesterol (3:1, mol/mol)	Conventional liposomes	Insulin	Type 1 diabetes mellitus (T1DM)	A promising platform to protect insulin during digestion, enhance intestinal absorption	[13]
Thin-film hydration	DOPS, DLPC, Cholesterol	Conventional liposomes	Peptide	Type 1 diabetes mellitus (T1DM)	Insulin peptide-loaded liposomes reduced T1D incidence in the NOD mouse model, PS-liposome + antigen: ~20–30% diabetic incidence vs control: ~60–80% ($p < 0.05$)	[68]
Thin-film hydration with extrusion	HSPC/CHOI (60/40)	PEGylated liposomes	Insulin	Type 1 diabetes mellitus (T1DM)	Enhances oral delivery efficiency of liposomes, warranting further investigation	[69]
Solvent injection	1,2-dimyristoylsn-glycero-3-phosphocholine and cholesterol	Conventional liposomes	Phosphatidylserine	Type 1 diabetes mellitus (T1DM)	PS-liposomes can target macrophages ~64% uptake by human macrophages in vitro at 100 μ M and provide insights into the mechanism of antigen-specific autoimmunity arrest in preclinical immunotherapy	[62]

Abbreviations: DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; DOPG, 1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol); DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; DOPS, 1,2-dioleoyl-sn-glycero-3-phospho-L-serine; DLPC: 1,2-dilauroyl-sn-glycero-3-phosphocholine; HSPC, Hydrogenated Soy Phosphatidylcholine.

Furthermore, PEGylated liposomal or lipid nanocarriers with supplementary modifications can improve stability within the gastrointestinal tract, safeguard insulin from degradation, and facilitate drug release in the intestine rather than in the stomach, which is an aspect essential for therapeutic effectiveness.⁷⁰ Nevertheless, despite modifications such as PEGylation and ligand conjugation, substantial challenges persist, including degradation within the stomach, exposure to proteolytic enzymes, and limited permeability across the intestinal epithelium.⁷¹

However, this approach has several limitations. Despite various formulation modifications, liposomes remain vulnerable to degradation within the gastrointestinal tract, particularly under acidic gastric conditions and in the presence of proteolytic enzymes. This observation is consistent with the broader consensus that PEGylation alone is insufficient to

overcome the physiological barriers associated with oral delivery of peptide. Furthermore, although receptor-mediated endocytosis such as targeting folate receptors may enhance cellular uptake, the expression levels and accessibility of these receptors on intestinal epithelial cells can vary substantially among patients and across animal models, thereby limiting the general applicability of such targeting strategies.⁷²

Liposomal delivery of peptide-based therapies, particularly insulin, shows promise in improving stability, protecting against enzymatic degradation, and enhancing cellular uptake. Although PEGylation and folic acid conjugation strategies have been shown to significantly enhance the stability and intestinal uptake of liposomal insulin, comparative studies indicate that these modifications alone are insufficient to fully overcome gastrointestinal barriers. Variability in receptor expression, intestinal pH, and enzymatic activity among patients and experimental models contributes to inconsistent therapeutic outcomes highlighting the need for optimized formulations and mechanistic studies to facilitate clinical translation.

Therapeutic Applications of Liposomal Drug Delivery Systems in Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM), also known as non-insulin dependent or adult-onset diabetes, is primarily characterized by insulin resistance and β -cell dysfunction.⁷³ Therapeutic strategies include insulin therapy, oral pharmacological agents (including sulfonylureas and thiazolidinediones), and non-pharmacological measures such as dietary management and physical exercise. However, these treatments frequently fail to sustain optimal glucose homeostasis, especially insulin and sulfonylureas, which are commonly linked to adverse effects such as hypoglycemia and weight gain.⁷⁴ The pathogenesis of insulin resistance is affected by various factors, including inflammatory reactions and oxidative stress.⁷

Liposomes serve as a particularly significant delivery system for natural compounds and peptides in the treatment of T2DM as they can overcome inherent challenges such as limited solubility and reduced bioavailability associated with agents including curcumin, berberine, silybin, ginsenoside Rg3, and quercetin (Table 2).^{7,16,75–77} Notably, HuGLP-1-loaded liposomes (≈ 80 – 150 nm; encapsulation efficiency 65–85%) reduced blood glucose levels by approximately 30–45% and prolonged hypoglycemic effects for up to 8–12 hours in diabetic models.⁷⁴ Similarly, taxifolin-loaded

Table 2 Examples of Liposomal Formulations of Type 2 Diabetes Mellitus (T2DM) Drugs with Their Preparation Methods and Categories

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Ethanol injection	HSPC, CHOL, and DSPE-PEG2000 (molar ratio=7:122:65:11)	Conventional liposomes	Curcumin	Type 2 diabetes mellitus (T2DM)	Reversed HFD/STZ-induced weight loss and improved glucose regulation and insulin sensitivity in mice	[7]
Ethanol injection	HSPC (304 mg) and cholesterol (30.4 mg)	Conventional liposomes	Berberine	Type 2 diabetes mellitus (T2DM)	Enhance insulin biosynthesis and ameliorate diabetic liver injury in T2DM rats by promoting AMPK/mTOR-mediated autophagy and reducing ER stress	[75]
Ethanol injection	Phospholipids and cholesterol (20:2)	Conventional liposomes	Silybin	Type 2 diabetes mellitus (T2DM)	Improves hepatic glucose and lipid metabolism in T2DM-NAFLD by activating the AMPK/TGF- β 1/Smad pathway, offering a potential therapeutic strategy	[76]

(Continued)

Table 2 (Continued).

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Ethanol injection	PC (1 mg) and cholesterol (5 mg)	PEGylated liposomes	Ginsenoside Rg3	Type 2 diabetes mellitus (T2DM)	Prevents T2DM progression by suppressing adipogenesis, enhancing glucose and lipid metabolism, and alleviating obesity and hepatic steatosis in diabetic mice	[77]
Ethanol injection	Soybean phosphatidylcholine and cholesterol	Conventional liposomes	Human glucagon-like peptide-1 (HuGLP-1)	Type 2 diabetes mellitus (T2DM)	Effectively lowered blood glucose levels and exhibited (≈ 80 – 150 nm; EE 65–85%) reduced blood glucose by ~ 30 – 45% , prolonged hypoglycemic effects up to 8–12 h	[74]
Thin-film hydration	Lecithin:cholesterol (3:1;4:1;5:1)	Conventional liposomes	Taxifolin	Type 2 diabetes mellitus (T2DM)	Controlled drug release, improved oral bioavailability (~ 2 – $3\times$), and enhanced hypoglycemic efficacy (~ 35 – 50% glucose reduction)	[17]
Thin-film hydration	Lecithin and HDCA	Conventional liposomes	Metformin	Type 2 diabetes mellitus (T2DM)	Lowered fasting blood glucose, improved glucose tolerance, and regulated glucose metabolism markers	[5]
Thin-film hydration	Phosphatidylcholine (60 mg) and cholesterol (15,22 mg)	Conventional liposomes	Exenatide-4 and Coenzyme Q10	Type 2 diabetes mellitus (T2DM)	Reduced oxidative stress, restored pancreatic β -cell function, and alleviated diabetes	[78]
Thin-film hydration with extrusion	Soybean L- α -phosphatidylcholine, cholesterol, and DSPE-mPEG2000	Conventional liposomes	Quercetin	Type 2 diabetes mellitus (T2DM)	Significantly elevated the p-Akt/Akt ratio, suggesting reduced insulin resistance	[16]
Thin-film hydration	Soy lecithin, cholesterol	Conventional liposomes	Oleanolic acid	Type 2 diabetes mellitus (T2DM)	Exhibited improved gastrointestinal stability, permeability and oral bioavailability	[79]
–	DSPE-PEG200, cholesterol, lecithin	Long circulating liposomes (PLLs)	Polydatin	Type 2 diabetes mellitus (T2DM)	Prolonged polydatin release, enhanced blood concentration and bioavailability, and improved anti-diabetic effects in HFD-induced hyperglycemic mice	[12]
–	Phospholipon 90G	Conventional liposomes	Silibinin	Type 2 diabetes mellitus (T2DM)	Phospholipid liposomes achieved high silibinin encapsulation, sustained stability, and enhanced therapeutic utility in diabetes treatment	[14]

Abbreviations: HSPC, Hydrogenated Soy Phosphatidylcholine; Chol, Cholesterol; DSPE-PEG2000, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000; PC, Phosphatidylcholine; HDCA, Hydoxycholeic Acid.

liposomes improved oral bioavailability by approximately 2–3-fold and achieved glucose reductions of about 35–50% compared with free drug formulations.¹⁷

Among liposomal formulations, liposomes loaded with berberine and Rg3 have demonstrated significant potential in preclinical models of T2DM. Liposomal berberine (Lip-BBR) has been reported to mitigate hepatic injury and steatosis, while enhancing activation of the AMPK/mTOR signaling pathway, inducing autophagy, and decreasing endoplasmic

reticulum stress. Simultaneously, PEGylated liposomal Rg3 (PEG-L-Rg3) has been shown to enhance fasting insulin concentrations and insulin sensitivity in T2DM mouse models, accompanied by favorable pharmacokinetic properties marked by extended circulation duration without inducing accelerated blood clearance.^{75,77}

Conventional liposomes are subject to regulation via the adsorption of plasma proteins, which are subsequently recognized and cleared by the reticuloendothelial system (RES), thereby restricting their capacity to produce pharmacological effects.⁸⁰ The surface properties of liposomes are crucial determinants of their clearance rate within the systemic circulation. Phospholipid modification with polyethylene glycol (PEG), such as N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE-PEG2000), facilitates the formation of long-circulating liposomes that markedly extend the duration of drug circulation in the bloodstream and improve in vivo bioavailability. For example, polydatin-loaded long-circulating liposomes demonstrated prolonged systemic exposure and enhanced anti-diabetic efficacy in HFD-induced hyperglycemic mice compared with non-modified formulations.¹² For compounds exhibiting low solubility or intricate pharmacological characteristics, although liposomes can improve bioavailability, key parameters such as encapsulation efficiency, in vivo stability, controlled release profiles, toxicity, and clearance by the reticuloendothelial system (RES) continue to present significant challenges. For example, conventional liposomes tend to undergo plasma protein adsorption and are rapidly cleared. Consequently, surface modifications such as PEGylation (eg, with DSPE PEG2000), are essential for imparting prolonged circulation properties.⁸¹

PEGylation, which is widely employed to prolong liposomal circulation time, can induce undesirable immune responses, particularly the formation of anti-PEG antibodies (IgM/IgG), leading to accelerated blood clearance (ABC) of liposomes. This response results in more rapid elimination of liposomes from circulation upon repeated administration, which may ultimately reduce therapeutic efficacy in chronic treatments such as type 2 diabetes mellitus.⁸² Beyond the ABC phenomenon, liposomes are also susceptible to opsonization and protein corona formation, which can alter their biodistribution and promote preferential uptake by the reticuloendothelial system (RES), particularly in the liver and spleen.⁸³

In T2D, liposomes have been used to enhance the delivery of small-molecule antidiabetic agents and natural compounds, such as berberine, Rg3, and quercetin. Across preclinical studies, liposomal formulations generally demonstrated glucose reductions ranging from approximately 30–50% and improved oral bioavailability up to 2–3-fold compared with free drug counterparts, highlighting their pharmacokinetic advantage. Although surface modifications such as PEGylation have enhanced systemic circulation and bioavailability of liposomal therapies in type 2 diabetes, these strategies do not fully overcome challenges such as immune-mediated accelerated clearance, protein corona formation, and variability in uptake by the reticuloendothelial system (RES). Notably, most studies have relied on short-term animal models, which may not accurately capture the long-term immunological consequences of repeated administration. Comparative studies of different liposomal platforms and long-term preclinical evaluation are still limited, impeding translation to clinical settings.

Therapeutic Applications of Liposomal Drug Delivery Systems in Nephropathy

Diabetes and obesity both induce heightened oxidative stress in renal tissues, ultimately leading to renal impairment and metabolic disturbances.⁸⁰ Diabetic nephropathy constitutes a spectrum of renal injuries, spanning from subtle oxidative modifications to severe and irreversible fibrosis, accompanied by different levels of inflammation and oxidative stress-induced damage.^{84,85} The initial progression of this condition is complex and encompasses extracellular matrix accumulation, glomerular enlargement, basement membrane thickening, and podocyte loss, which may occur concurrently or sequentially.⁸⁶ Microalbuminuria (UMA) is frequently used as an early diagnostic indicator. Although the precise mechanisms remain incompletely understood, existing evidence emphasizes that oxidative stress and inflammation as primary factors driving disease progression.⁸⁷ Further complicating management, numerous oral antidiabetic agents may induce adverse effects or impose additional stress on the kidneys, thereby complicating the treatment of diabetes-associated renal injuries.⁸⁸

Liposomal formulations are generally administered via local or systemic injection to treat nephropathy.⁸⁷ Local drug administration may accelerate recovery at the injection site; however, its limitation lies in the insufficient distribution

throughout the renal tissue, thereby failing to restore kidney function optimally.⁸⁹ Particles with diameters <5–7 nm can traverse the glomerular filtration barrier and undergo tubular reabsorption. In contrast, conventional liposomes are typically larger and require tailored approaches to ensure their retention within the glomerulus for targeted delivery.⁹⁰ Most liposomal formulations developed for diabetic nephropathy are prepared using thin-film hydration, commonly employing phospholipid-to-cholesterol ratios of approximately 9:1, which have been associated with improved structural stability and renal drug retention in preclinical studies (Table 3).⁸⁸

To enhance the safety and efficacy of therapy, various drug delivery systems have been developed to enable specific and targeted drug distribution to the kidneys (Table 3). Surface modification of liposomes with saccharide ligands enables active targeted drug delivery and has the potential to enhance their therapeutic effects. Liposome modification with sugar ligands not only enhances targeting efficiency and reduce the adverse effects of drugs. Mannose ligands can be distributed to the kidneys of diabetic rats, thereby offering the potential for targeted drug delivery to this organ.⁹¹ Surface modification with saccharide ligands, such as mannose or glucose, has been proposed to enhance uptake by renal

Table 3 Examples of Liposomal Formulations of Nephropathy Drugs with Their Preparation Methods and Categories

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Thin-film hydration	Egg yolk lecithin (225 mg), cholesterol (25 mg)	Conventional liposomes	Coenzyme Q10 (CoQ10)	Diabetic nephropathy	Supports vascular repair, preserves podocytes, and inhibits apoptosis to prevent diabetic nephropathy	[89]
Thin-film hydration	Lecithin:cholesterol: polyethylene glycol 4000 (13:4:1)	PEGylated liposomes	Quercetin	Diabetic nephropathy	The formulation conferred renal protection by reducing oxidative stress, suppressing AGE expression, and slowing DN progression	[18]
Thin-film hydration	Yolk lecithin (3 mL) and cholesterol (1.5 mL)	Liposome modified with ligand	Mannose	Diabetic nephropathy	Effectively targets diabetic nephropathy by enhancing drug solubility and utilizing renal GLUT overexpression for targeted delivery	[91]
Thin-film hydration	Yolk lecithin (95) and cholesterol (20) in molar ration	Conventional liposomes	Glutathione	Diabetic nephropathy	Enhances glutathione bioavailability and antioxidant capacity while inhibiting AR activity and sorbitol accumulation in the polyol pathway to treat diabetic nephropathy	[92]
Thin-film hydration	Phospholipid (225 mg) and cholesterol (25 mg) (9:1, w/w)	Conventional liposomes	Coenzyme Q10	Diabetic nephropathy	A promising approach for renal drug delivery, with potential to reverse early-stage diabetic nephropathy progression	[93]
Thin-film hydration	DSPC and BC at a molar ratio of 4:3	Conventional liposomes	Hirudin	Diabetic nephropathy	Exhibits strong renal targeting, alleviating DN by suppressing renal VEGF and TGF- β 1 expression	[94]

(Continued)

Table 3 (Continued).

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Thin-film hydration	Dioleoylphosphatidylglycerol and lipid	Conventional liposomes	Glycyrrhetic acid	Diabetic nephropathy	CY-loaded GA liposomes enhance renal function, attenuate fibrosis, and suppress hRIF proliferation via TGFBR1/Smad2/3 pathway inhibition	[8]
Thin-film hydration	Lecithin (100 mg), cholesterol (10 mg)	Conventional liposomes	Taxifolin	Diabetic nephropathy	Improved oral bioavailability of taxifolin and ameliorated renal function markers in diabetic kidney injury mice	[95]
Reverse-phase evaporation	Lipids and cholesterol (9:1)	Conventional liposomes	Basic fibroblast growth factor (bFGF)	Diabetic nephropathy	Delays diabetic nephropathy progression by suppressing NF- κ B activation and reducing TGF- β 1, MCP-1, IL-6, and IL-1 β expression	[96]

Abbreviations: DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; BC, bile components.

cells, including glomerular mesangial cells that overexpress specific transporters (eg, GLUT1). Although ligand-mediated targeting can improve localization, its overall efficacy is strongly influenced by the variability in receptor expression under different disease conditions and by competition with endogenous circulating ligands.⁹⁰

Most evidence supporting liposomal therapies for DN is derived from preclinical animal models, that may not fully capture the complexity of human renal disease. Variations in glomerular architecture, transporter expression, immune responses, and nephropathy progression contribute to significant translational uncertainty. Furthermore, the long-term safety, immunogenicity, and pharmacokinetic profiles of liposomal formulations in patients with chronic not been sufficiently investigated.⁹⁷

Saccharide-modified liposomes demonstrate promise for targeted delivery in preclinical models of diabetic nephropathy (DN); however, variability in receptor expression and competition with endogenous ligands may limit the reproducibility of clinical outcomes. In addition, interspecies differences in renal physiology underscore the need for further investigations into long-term safety, pharmacokinetics, and immunogenicity.

Therapeutic Applications of Liposomal Drug Delivery Systems in Wound and Infection

One of the most common clinical complications of diabetes mellitus is delayed wound healing, which may ultimately lead to impaired or incomplete recovery in patients. At advanced stages, this condition is triggered by a combination of factors, including insulin resistance, impaired tissue regeneration, vasculopathy, neuropathy, and inflammatory responses.⁹⁸ Hyperglycemic condition in diabetic wounds induces oxidative stress and endoplasmic reticulum (ER) stress, ultimately leading to chronic inflammation and delayed healing. In addition, hyperglycemia increases the susceptibility of wounds to infections.⁹⁹ Bacterial colonization can further exacerbate oxidative stress and the inflammatory response, thereby triggering cell apoptosis and further impairing the healing process.¹⁰⁰

Liposomes represent a promising delivery platform for the treatment of diabetic wounds, owing to their several significant advantages (Table 4). They improve the stability of labile bioactive agents, including antioxidants and anti-inflammatory compounds, thereby maintaining their therapeutic efficacy when applied to incisions. Furthermore, liposomal formulations facilitate controlled release, permitting sustained delivery of active compounds from the bilayer and extending local therapeutic effects, thereby reducing the frequency of application.¹⁰¹ The ability of liposomes to

Table 4 Examples of Liposomal Formulations of Wound and Infection Drugs with Their Preparation Methods and Categories

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Thin-film hydration	–	Conventional liposomes	Cinnamon ethanolic extract	Diabetic wound	Liposomes exhibited greater stability, controlled aggregation, and enhanced wound-healing efficacy in diabetic rats	[103]
Thin-film hydration	Soy lecithin and cholesterol (95:5)	Conventional liposomes	Resveratrol	Diabetic foot ulcer	Enhanced skin penetration, lowered blood glucose, and increased GAGs, promoting ulcer healing and wound closure	[98]
Thin-film hydration	Lecithin (120 mg), cholesterol (20 mg)	Conventional liposomes	Taxifolin	Diabetic wound	Promoted wound healing in diabetic mice by regulating inflammatory factors and upregulating autophagy-related proteins	[104]
Thin-film hydration	Phosphatidylcholine (100 mg)	Conventional liposomes	Curcumin	Diabetic wound	Effectively promoted re-epithelialization and angiogenesis	[105]
Thin-film hydration	Soybean lecithin choline (60 mg), and cholesterol (10 mg)	Conventional liposomes	Phlorizin	Diabetic wound	Accelerates diabetic wound healing via controlled drug release, antimicrobial activity, and high biocompatibility	[106]
Thin-film hydration	Phospholipids, and cholesterol	Conventional liposomes	Glabridin	Diabetic wound	Exhibits strong mechanical properties, cell and blood compatibility, and enhances wound healing by accelerating closure, promoting remodeling and collagen deposition, and reducing inflammation	[107]
Thin-film hydration	Soybean lecithin (120 mg), cholesterol (10 mg)	Conventional liposomes	Taxifolin	Diabetic wound	Accelerated diabetic wound healing by inhibiting the I κ B α /NF- κ B pathway and modulating pro-inflammatory factors	[108]
Thin-film hydration	Phosphatidylcholine: cholesterol: tween 80:stearylamine (7:3:1:0.5)	Conventional liposomes	Bacteriophages (Phage cocktail MR-5 C MR-10, 1:1)	Diabetic wound infection	Enhanced phage therapy efficacy by improving stability, delaying clearance, and enabling controlled release at infection sites for faster healing	[3]
Thin-film hydration	SPC (166.5 mg) and DSPE-MPEG2000 (13.5 mg)	Conventional liposomes	Curcumin	Diabetic wound	Efficiently delivered curcumin into macrophages, induced M0-to-M2 polarization, and significantly promoted wound healing in diabetic mice	[101]
Thin-film hydration	Lipid (100 mg), Chitosan (0.3%), and 5 mg of cholesterol	Polymer coated liposomes	Citicoline	Diabetic wound	Displayed sustained release, high stability, and enhanced wound healing in diabetic rats.	[10]

(Continued)

Table 4 (Continued).

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Thin-film hydration	DPPC and cholesterol	Conventional liposomes	–	Diabetic systemic infection of <i>Candida albicans</i>	Cleared infections and reduced diabetes-related complications in diabetic mice	[109]
Thin-film hydration	Soy lecithin and cholesterol	Liposomes responsive pH	Astilbin and diclofenac sodium	Diabetic wound	It plays a significant role in suppressing inflammation, stimulating angiogenesis, and accelerating fibrotic tissue repair during wound healing	[110]
Microfluidization	HPC (78.4 mg), cholesterol 23 (20 mg), DOTAP (7.5 mg)	Conventional liposomes	LMWP-fused 3 EGF	Diabetic wound	Enhanced chronic wound healing with both rapid and sustained effects and improved permeation	[63]
Ethanol injection	Cholesterol and lecithin	Conventional liposomes	<i>Astragalus membranaceus</i>	Diabetic wound	Effectively accelerates diabetic wound healing and demonstrates promising potential for applications in diabetic wound dressings and tissue engineering.	[111]
–	Dipalmitoyl-phosphatidylcholine	Conventional liposomes	Lycopene and tobramycin	Diabetic wound	Accelerated healing of infected diabetic wounds in rats	[100]
–	–	Conventional liposomes	Hemoglobin	Diabetic wound	Enhanced tissue perfusion, suppressed inflammatory cytokines, and accelerated skin wound healing	[112]

Abbreviations: DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; DSPA, 1,2-distearoyl-sn-glycero-3-phosphatidic acid; SPC, Soy Phosphatidylcholine; DSPE-MPEG2000, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; HPC, Hydrogenated Phosphatidylcholine; DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane.

enable sustained drug release can enhance the effectiveness of drug delivery to specific layers of the epidermis. Their structure and characteristics, which are analogous to biological membranes, enable penetration through the epidermal barrier, thereby establishing liposomes as a viable delivery system for the treatment of skin infections.⁹⁸ Liposome particle sizes of approximately 150–250 nm are generally considered to be optimal for effective skin penetration.¹⁰²

Liposomes accelerate re-epithelialization, collagen deposition, and angiogenesis more effectively than single-agent formulations, indicating that liposomes act not only as carriers but also as platforms for multi mechanistic therapy in diabetic wounds.¹¹³ For instance, curcumin-loaded liposomes promoted re-epithelialization and angiogenesis, while taxifolin-loaded systems regulated inflammatory mediators and inhibited the IκBα/NF-κB pathway, demonstrating anti-inflammatory and pro-regenerative mechanisms.^{105,107,108} For example, hydrogel liposome composites or bFGF-loaded liposomal scaffolds have been shown to promote increased vascularization.¹¹⁴

While most liposome fabrication techniques rely on thin film hydration, certain tailored modifications such as pH responsive liposomes encapsulating astilbin and diclofenac illustrate sophisticated strategies for controlled drug release in response to the local wound microenvironment. A pH responsive delivery system incorporating liposomal astilbin and diclofenac within an oxidized sodium alginate and carboxymethyl chitosan hydrogel facilitates controlled dual-drug release tailored to the wound microenvironment. Diclofenac is quickly released during the initial phase within acidic inflammatory exudate, whereas astilbin liposomes offer a sustained release of antioxidants, collectively reducing inflammation and enhancing angiogenesis as well as effective tissue repair in diabetic ulcers.¹¹⁰ Studies using

protopanaxadiol-loaded liposomal hydrogel have demonstrated an increased expression of CD31 and α -SMA in wound tissues, indicating enhanced angiogenesis.¹¹⁵ Additionally, the application of chitosan coating on liposomes provides multiple benefits, such as increased stability, prevention of drug leakage, extended-release duration, and enhanced cellular absorption. Furthermore, chitosan demonstrated antibacterial efficacy against both gram-negative and gram-positive bacteria, thereby significantly contributing to the wound-healing process.¹⁰

Despite these promising findings, several critical challenges remain. Many studies have been limited in scope, often lacking standardized wound models or long-term evaluation of therapeutic outcomes. The complex interactions among liposome composition, particle size, surface modifications (eg, chitosan coating), and the local microenvironment are not yet fully understood, which may affect reproducibility and hinder clinical translation. Furthermore, potential immunogenicity, inter-patient variability in skin penetration, and stability under physiological conditions warrant further investigation.

Therapeutic Applications of Liposomal Drug Delivery Systems in Retinopathy

Diabetic retinopathy (DR) is characterized by increased oxidative stress resulting from biochemical alterations induced by hyperglycemia, which subsequently triggers inflammation, excitotoxicity, and a reduction in neurotrophin levels. These mechanisms ultimately lead to neurodegenerative phenomena, representing an early hallmark of disease progression, potentially preceding the onset of vascular abnormalities.¹¹⁶ The administration of high protein concentrations in the eye is limited by the tendency for precipitation, which may trigger adverse reactions. In addition, protein-based ocular therapies face multiple challenges, including susceptibility to enzymatic degradation, short vitreous half-life, ion permeability, immunogenicity, post-translational modifications, aggregation, and denaturation.¹¹⁷ The delivery of corticosteroids to the posterior segment of the eye remains a challenge, as systemic administration often causes undesirable side effects, whereas eye drop formulations exhibit limited penetration.¹¹⁶ Although oral and topical administration of corticosteroids is considered safer than intravitreal injection, their effectiveness against vitreoretinal disorders remains limited. This restriction is mainly attributable to the blood retinal barrier, which limits drug entry into the posterior segments of the eye. To reduce ocular risks associated with intravitreal injections, several topical approaches have been devised to enhance drug delivery into the vitreous cavity.¹¹⁸ To address these obstacles and improve patient adherence, drugs can be encapsulated within liposomes to extend intraocular release, consequently decreasing the frequency of administration, the risk of infection, and treatment expenses.¹¹⁷

Multiple topical liposomal formulations have been devised for the delivery of drugs to the posterior segment of the eye for the managing diabetic macular edema (Table 5). Most formulations are prepared using thin-film hydration with defined lipid ratios, such as EPC:cholesterol (5:1) for ellagic acid delivery and DPPC:Chol:PEG (56:40:4) for endothelial cell protein C receptor–targeted systems. Liposomes are a promising alternative in ocular drug delivery systems because

Table 5 Examples of Liposomal Formulations of Retinopathy Drugs with Their Preparation Methods and Categories

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Thin-film hydration	EPC and cholesterol 5:1	Conventional liposomes	Ellagic acid	Diabetic Retinopathy	Restoring vascular homeostasis and preserving retinal structure	[120]
Thin-film hydration	Soybean lecithin, cholesterol	Conventional liposomes	Naringenin	Diabetic Cataract	Markedly reversed HFD/STZ-induced weight loss and improved glucose tolerance and insulin sensitivity in mice	[121]
Thin-film hydration	Phospholipids, lecithin, cholesterol	Conventional liposomes	Curcumin	Diabetic Retinopathy	Improved curcumin bioavailability and therapeutic efficacy in ocular treatment, particularly for diabetic retinopathy	[122]

(Continued)

Table 5 (Continued).

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Thin-film hydration	DPPC:Chol: PEG (56:40:4)	Conventional liposomes	Endothelial cell protein C receptor	Diabetic Retinopathy	Enhanced uptake improved anti-inflammatory efficacy by reducing IL-8 and IL-6 secretion and suppressing tube formation	[123]
Thin-film hydration with extrusion	DPPC:DOPE: DPPG: Cholesterol	Conventional liposomes	Bevacizumab	Diabetic Retinopathy	Demonstrated liposomal efficacy through sustained release and preserved anti-VEGF antibody activity.	[117]
–	Soy lecithin and Eudragit® L100	Polymer coated liposomes	Lisosan G	Diabetic Retinopathy	Liposomal encapsulation of Lisosan G markedly improved prevention of diabetic retinopathy in diabetic models.	[116]
–	–	Conventional liposomes	Triamcinolone acetonide	Diabetic Macular Edema (DME)	Topically safe, well tolerated, and therapeutically effective in humans	[118]

Abbreviations: EPC, Egg Phosphatidylcholine; Chol, Cholesterol; PEG, polyethyleneglycol; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; DPPG, 1,2-dipalmitoyl-sn-glycero-3-phospho-(1'-rac-glycerol).

of their multiple advantages, including extended drug residence time for absorption, protection of encapsulated molecules from environmental degradation, prolonged vitreous half-life with minimal toxicity, enhanced efficacy, therapeutic index, and penetration into ocular tissues.¹¹⁸ Current research has focused on the development of liposomal formulations aimed at targeting multiple pathophysiological mechanisms involved in diabetic retinopathy (DR), including anti-angiogenic strategies (such as anti-VEGF agents), anti-inflammatory effects, and antioxidant properties, thereby promoting a more comprehensive therapeutic approach.¹¹⁹

Encapsulation of the nutraceutical Lisosan G (LG) into liposomes (LipoLG) has been shown to enhance bioavailability and confer protective effects on the retina against diabetes-induced alterations in animal models of diabetes. In streptozotocin-induced diabetic mice, both doses of LipoLG significantly prevented retinal damage, as assessed by electrophysiological and molecular markers including VEGF expression, apoptosis, and maintenance of Blood-Retinal Barrier (BRB) integrity more effectively than non-encapsulated LG.¹¹⁶ The concentration of therapeutic drugs reaching the retina is generally low because of the presence of the blood-eye barrier. Owing to their easily modifiable surface, ligand-conjugated liposomes have been developed as targeted delivery systems for lesions. Liposomes modified with $\alpha v \beta 3$ ligands, such as RGD or isoDGR peptides, show potential as carriers for the targeted treatment of diabetic retinopathy. These functional liposomes have been shown to improve the hypoxic microenvironment in diabetic retinopathy and regulate retinal vascular tissues by inhibiting the VEGF-p-VEGFR2 signaling pathway.¹²⁰ Liposomes engineered to recognize the Endothelial Protein C Receptor (EPCR) on human retinal endothelial cells demonstrated markedly improved cellular uptake compared to non-targeted formulations. Through surface functionalization with an EPCR-binding ligand, researchers have achieved substantially enhanced drug delivery to retinal endothelial cells, which is central to the development and progression of diabetic retinopathy.¹²³

For optimal ocular delivery, particle sizes of approximately 80–200 nm are often recommended, and a slightly negative or neutral surface charge can improve vitreous diffusion. PEGylation can prolong circulation or residence time and minimize undesirable protein adsorption, although it may also hinder cellular penetration necessitating careful design compromises. In addition, assessments of local toxicity assessments (including irritation, intraocular pressure, and inflammation) are essential and must be reported.¹²⁴

Therapeutic Applications of Liposomal Drug Delivery Systems in Neuropathy

Therapeutic strategies for diabetic neuropathy typically encompass a combination of mechanism based and symptomatic treatments, such as neurotrophic agents, antioxidants, aldose reductase inhibitors, and microcirculation enhancers.¹²⁵ Despite the existence of these options, no pharmaceutical agent to date has exhibited exceptional clinical specificity and an ideal safety profile, highlighting the necessity for the development of more efficacious and safer therapeutic approaches.⁶⁴

Liposomes enhance the pharmacokinetic profile of medications and facilitate the achievement of optimal drug concentrations for therapeutic efficacy (Table 6). The half-life of liposomes in the bloodstream can be extended from a few minutes to several hours through surface coating with hydrophilic polymers such as PEG. In addition to inhibiting internalization and opsonization by the reticuloendothelial system, PEG enhances the solubility, reduces aggregation, and decreases the immunogenicity of liposomes. Consequently, PEG plays a crucial role in prolonging circulation time, and increasing liposomal accumulation in damaged tissues also in the context of diabetic nephropathy (DN), which can be achieved through the regulation of endoplasmic reticulum (ER) stress and the modulation of autophagy processes.¹⁵

Long-circulating liposomes extend their residence time in the bloodstream by attaching polyethylene glycol (PEG) molecules to their surface, forming a hydration layer. This layer enhances the hydrophilicity and flexibility of the liposomes while minimizing their interactions with plasma proteins. In addition, PEG inhibits phagocytosis by the mononuclear phagocyte system (MPS), thereby allowing liposomes to exert optimal effects on tissues or organs beyond the liver and spleen.⁶⁴

Quercetin-loaded liposomes significantly enhanced peripheral nerve function in diabetic neuropathy models by improving nerve conduction velocity and attenuating oxidative stress through the upregulation of mitochondrial activity.¹²⁷ Conversely, chrysin encapsulated in PEGylated liposomes demonstrated substantial molecular modulation by alleviating endoplasmic reticulum (ER) stress and stimulating autophagy in sciatic nerve cells, thereby preventing neurodegeneration. Chrysin encapsulated in PEGylated liposomes (Chr-PLs) exhibited pronounced neuroprotective effects in alloxan-induced diabetic rats. Treatment with Chr-PLs reduced endoplasmic reticulum (ER) stress markers including ATF-6, CHOP, XBP-1, and BiP—by approximately 32–44%, while simultaneously upregulating autophagy-

Table 6 Examples of Liposomal Formulations of Neuropathy Drugs with Their Preparation Methods and Categories

Preparation Method	Liposome Composition	Categories of Liposomes	Active Substance	Pharmacological Uses	Result	Ref
Solvent injection	Phosphatidylcholine from soybean, cholesterol, and PEG4000 (13:03:01)	PEGylated liposomes	Chrysin	Diabetic neuropathy	Prevented sciatic nerve degeneration and protected against DN by regulating ER stress markers (GRP78 and CHOP by ~35–50%) and autophagy	[15]
Thin-film hydration	Phospholipid to cholesterol (12:1; 10:1; 8:1)	Long circulating liposomes (PLLs)	Quercetin	Diabetic peripheral neuropathy	Lowered blood glucose and improved nerve conduction velocity, demonstrating efficacy against diabetic peripheral neuropathy	[64]
Thin-film hydration with extrusion	DSPC (2 mg) DSPE-PEG 2000 (3,5 mg), cholesterol (1,75 mg), DOPE (12,8)	Conventional liposomes	Alpha-tocopherol	Diabetic peripheral neuropathy	Decreased ROS production in a hyperglycemia-induced neuropathy model	[126]
–	–	Conventional liposomes	Clodronate	Diabetic neurotrophic keratopathy	Ameliorated nerve degeneration in mice with diabetic neurotrophic keratopathy, restored nerve fiber length to ~75% of normal levels	[9]

Abbreviations: PEG4000, polyethyleneglycol-4000; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; DSPE-PEG2000, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino (polyethyleneglycol)-2000]; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine.

related markers such as AMPK, ULK1, Beclin-1, and LC3-II by 78–181% in sciatic nerve tissue, compared to untreated controls. These findings highlight that Chr-PLs exert molecular-level modulation of the ER stress and autophagy pathways, extending beyond observable phenotypic improvements.¹⁵

In addition, alpha tocopherol loaded liposomes act as strong scavengers of reactive oxygen species (ROS) in high-glucose-exposed Schwann cells, diminishing ROS levels and limiting oxidative injury, with further improvement in dermal delivery when combined with ultrasound. Regarding ocular manifestations, clodronate liposomes induce macrophage depletion within the cornea of diabetic mice, reducing inflammatory cell infiltration and facilitating corneal nerve repair via IL-1 β and IL-34 associated pathways.^{9,15,126}

Although preclinical studies show encouraging outcomes, translating these liposomal strategies into clinical practice remains challenging. Most investigations have been conducted in animal models that do not fully capture the complexity of the human retinal microenvironment, including variability in blood–retinal barrier integrity, immune responses, and disease progression. Systematic studies on liposome design parameters are required to ensure consistent retinal drug delivery.

Across all major diabetic complications, liposomal drug delivery has demonstrated promising preclinical outcomes, including enhanced drug stability, tissue-specific accumulation, and therapeutic efficacy. However, clinical translation in humans remains limited due to incomplete understanding of organ- and tissue-specific delivery, variable pharmacokinetics, immunogenicity, and long-term safety. The effects of liposome size, surface modifications, ligand functionalization, and PEGylation have not been systematically compared, resulting in inconsistent findings across studies. These gaps underscore the need for mechanistic investigations, standardized comparative evaluations, and optimized formulation strategies, which collectively could facilitate reliable clinical testing of liposome-based therapies for diabetes.

Clinical Trials and Clinical Application

Several liposomal formulations have been approved by the U.S. Food and Drug Administration (FDA) for various indications, such as Doxil[®] for ovarian cancer and AmBisome[®] for systemic fungal infections.¹²⁸ However, the application of liposomal technology in diabetes therapy remains in the preclinical or early clinical stage, and to date, no formulation has progressed to advanced clinical trials or obtained regulatory approval. Most liposome-related studies in the context of diabetes have focused on in vitro and in vivo investigations, primarily aimed at enhancing the bioavailability of antidiabetic drugs, prolonging their duration of action, and accelerating the healing of diabetic wounds.^{63,122}

Several preclinical studies have reported that liposome-based delivery systems can enhance the stability, bioavailability, and efficacy of various antidiabetic drugs, including insulin, glibenclamide, and metformin.⁵ In diabetic mouse models, liposomal formulations have been shown to lower blood glucose levels more rapidly and sustain the hypoglycemic effect for a longer duration than conventional formulations.^{5,7}

Numerous liposomal formulations have been clinically evaluated as non-diabetic topical treatments, including insulin-liposome gels for managing aphthous ulcers and liposomes encapsulating antimicrobial peptides to facilitate wound healing.¹²⁹ The favorable results of these studies demonstrate that liposomes have an excellent safety profile and significant therapeutic potential, positioning them as prospective candidates for further advancement in the treatment of diabetic foot ulcers.

Ultimately, while liposomes provide a versatile nanotechnological platform for delivering insulin and other antidiabetic agents, their clinical application in systemic glycemic management has not yet been achieved. Therefore, enhanced collaboration among formulation scientists, clinical researchers, and regulatory authorities is crucial for expediting the progress of liposome-based diabetes therapies from preclinical studies to clinical implementation from the laboratory to the bedside. A clinical investigation involving three months of oral liposomal glutathione (L GSH) supplementation in individuals with T2DM demonstrated a reduction in oxidative stress, stabilization of blood glutathione (GSH) levels, and modulation of cytokine profiles (enhanced IFN, TNF α , IL 2; reduced IL 6, IL 10). This method is not a standard liposomal treatment for diabetes (hypoglycemia), but it demonstrates how an immuno-antioxidant adjuvant strategy can work. These results highlight the potential of liposomes as delivery mechanisms for non-pharmacological small molecules, including antioxidants, to influence oxidative stress and immune function in individuals with T2DM.¹³⁰

Although encouraging safety profiles have been reported in non-diabetic clinical applications and adjunctive interventions, no advanced-stage clinical trials have specifically targeted diabetes mellitus and its associated complications. This highlights a clear gap between preclinical efficacy and robust clinical validation. While liposomal systems have

consistently demonstrated improved pharmacokinetic performance and enhanced therapeutic outcomes in experimental models, these advantages have not yet translated into regulatory approval for diabetes management.

This discrepancy suggests that formulation success under controlled laboratory conditions does not inherently guarantee clinical effectiveness, regulatory acceptance, or long-term safety in heterogeneous patient populations. Therefore, standardized clinical trial designs, comprehensive long-term outcome evaluations, and harmonized regulatory pathways are essential to bridge this gap and facilitate meaningful clinical translation.

Challenges and Limitations

Although liposomes show considerable potential for oral drug delivery, the bioavailability of insulin delivered via this route is low. Digestive enzyme mediated degradation and limited permeability of the intestinal epithelium are major obstacles, leading to poor overall effectiveness of oral insulin in liposomes. Once administered orally, insulin is exposed to extensive enzymatic breakdown in gastrointestinal tract first by gastric pepsin, followed by trypsin and chymotrypsin in the small intestine which severely restricts the absorption of this peptide-based molecule.^{72,131} Another notable challenge is the initial hepatic metabolism during the first pass. Even when a portion of insulin traverses the intestinal mucosa, it enters the portal circulation and is transported directly to the liver, where a significant portion is rapidly metabolized prior to reaching the systemic circulation.¹³² Ongoing research aims to enhance the stability of liposomes and improve the intestinal absorption of insulin, with the overarching objective of attaining greater oral bioavailability.⁷²

Liposomes designed for oral drug delivery encounter considerable stability challenges, because their lipid bilayers are susceptible to oxidation, hydrolysis, and structural modifications throughout manufacturing and storage. These conditions hinder the preservation of entrapment efficiency, induce instability in particle size, and increase the risk of drug leakage from the vesicles. At increased production scales, methods such as homogenization or dehydration may further compromise bilayer integrity, complicating efforts to maintain formulation consistency. Therefore, the adaptation of liposomes for oral delivery necessitates the utilization of more stable lipids, antioxidants, and suitable stabilization strategies to maintain the entrapment efficiency and particle size.⁷²

Overall, these limitations indicate that the major barriers to the clinical translation of oral liposomal insulin extend beyond gastrointestinal biological instability. Rather, they reflect the complex integration required between formulation optimization, scalable manufacturing, and regulatory compliance. Overcoming enzymatic degradation alone will not ensure clinical success without reproducible large-scale production, sustained physicochemical stability, and clearly defined quality control frameworks aligned with approval pathways.

Regulatory Considerations

From a regulatory standpoint, the assessment of nanomedicine-based pharmaceuticals poses distinct challenges owing to their intrinsic complexity. Conventional pharmacokinetic and chemical models are frequently inadequate, and standardized testing protocols are still being developed, which may result in delayed approval. Regulatory agencies such as the FDA and EMA are revising their guidelines to underscore the importance of exhaustive physicochemical characterization, extensive preclinical safety evaluations including long term toxicity and immunogenicity potential and rigorous manufacturing quality assurance.¹³³

From a regulatory standpoint, nanomedicine-based interventions including liposomal systems present significant complexities that surpass those associated with conventional small-molecule or biological therapeutics. As non-biological complex drugs (NBCDs), liposomes demonstrate intrinsic variability in parameters such as particle size, lamellarity, lipid composition, and surface properties, which complicates quality assessment and impedes the development of a universal regulatory framework for generic equivalence.¹³⁴

As non-biological complex drugs (NBCDs), liposomal formulations exhibit intrinsic variability in critical parameters such as particle size, lamellarity, lipid composition, and surface characteristics. This structural complexity complicates quality assessment and poses substantial challenges to the development of universal regulatory frameworks, particularly with respect to establishing generic equivalence. The regulatory intricacies surrounding liposomal products underscore the urgent need for globally harmonized characterization standards. In the absence of standardized evaluation criteria for

particle size distribution, lamellarity, and surface functionality, cross-study comparisons and the determination of bioequivalent generic formulations will remain highly challenging and potentially inconsistent.

International collaboration is essential for harmonizing global standards and the accelerating the development of nanomedicine-based therapies. Enhancing regulatory frameworks, advancing safety research, and establishing comprehensive risk management strategies are equally vital to ensure that nanocarrier systems such as liposomes are safe, effective, and readily available for the treatment of diabetes. These initiatives are also essential for advancing the future of personalized nanomedicine and its incorporation with emergent wearable technologies.¹³³

A recent patent application for layer-by-layer coated nanoliposomes designed for oral insulin delivery (US2023285296A1) further demonstrates increasing interest in multilayer liposomal architectures as a means of improving insulin stability and absorption through oral administration.

Future Perspectives and Research Directions

In the coming years, liposomal insulin delivery systems may be integrated with advanced biosensors and continuous glucose monitoring (CGM) technologies. Such integration would enable feedback-controlled insulin release, where real-time biosensor data regulates the delivery of liposomal insulin an essential component of the artificial pancreas system. In addition, the use of artificial intelligence (AI) in formulation design could allow lipid composition and insulin dosing to be customized to an individual's metabolic profile, offering a more precise and adaptable therapeutic approach.⁶ Future strategies for autoimmune diabetes may also benefit from combining regenerative agents such as liraglutide with liposome-based immunotherapies, including PSAB-liposomes. Liposomes provide a versatile and targeted delivery platform capable of finely tuning immune responses while supporting the preservation or regeneration of β -cells.¹³⁵

Although liposomal technology has progressed considerably in the pharmaceutical industry, its implementation in clinical diabetes treatment remains in its preliminary stages. A novel method for glucose-responsive insulin delivery was devised using multivesicular liposomes (MVLs) that respond to variations in pH and hydrogen peroxide (H_2O_2). This biocompatible MVL system provides an advanced insulin delivery platform capable of adaptively responding to variations in glucose levels, representing a promising approach for more effective and physiologically appropriate management of diabetes. Furthermore, this system has considerable potential as a basis for creating closed-loop insulin therapies capable of autonomously adjusting insulin secretion in response to the body's metabolic requirements.¹³⁶

Future research is anticipated to progressively emphasize noninvasive insulin delivery methods, including oral, transdermal, and intranasal systems, to address the limitations inherent to injectable insulin. Liposomal formulations encapsulated within alginate or chitosan-based hydrogels can safeguard insulin from gastric degradation while improving its absorption in the intestinal tract. This oral delivery strategy provides a promising platform for maintaining insulin stability during digestion, facilitating its transport and absorption within the gastrointestinal tract, and ultimately enhancing its oral bioavailability.¹³

Without parallel consideration of scalable production and regulatory alignment, these advanced platforms may remain confined to experimental settings rather than achieving clinical implementation.

Conclusion

Liposomes represent a highly versatile nanocarrier platform for targeted diabetes therapy, with preclinical studies consistently showing improved pharmacokinetics, hypoglycemic efficacy, and therapeutic outcomes for insulin, glibenclamide, metformin, and antioxidants. However, substantial variability exists in formulation methods, encapsulation efficiency, vesicle size, lamellarity, and surface charge, highlighting that lipid composition, drug-lipid interactions, and preparation techniques critically influence stability, bioactivity, and pharmacokinetic performance. Despite promising *in vivo* findings, clinical translation remains limited, with few studies reporting favorable outcomes in oral liposomal glutathione or topical insulin-liposome gels, while systemic glycemic management has yet to achieve regulatory approval. Challenges such as low oral bioavailability, enzymatic degradation, first-pass metabolism, lipid oxidation, storage instability, and regulatory complexity underscore the need for optimized formulations and protective strategies. Future efforts should focus on glucose-responsive multivesicular liposomes, noninvasive delivery, integration with continuous glucose monitoring or artificial pancreas systems, and AI-assisted individualized formulation, complemented

by standardized characterization protocols, harmonized regulatory frameworks, and rigorous clinical trials. Collectively, these strategies can enable liposome-based nanomedicine to transition from preclinical promise to safe, effective, and patient-centered interventions for diabetes and its complications.

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