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Nanoliposome-based drug delivery systems for the treatment of diabetes mellitus: a review

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Diabetes mellitus (DM) is one of the leading world health complications, with chronic hyperglycemia that is due to a lack of insulin production or insulin action. Although many pharmacological agents are available, the current treatment modality is hampered by low bioavailability, rapid drug clearance, frequent dosing, and adverse effects. Such difficulties have been especially pronounced in the treatment of type 1 and type 2 diabetes, where long-term glycemic control that does not undermine patient compliance has been hard to reach. Nanotechnology has become one of the most revolutionary tools in drug delivery to achieve targeted, sustained, and more effective therapeutic outcomes in the past few years. Nanoliposomes are nanoscale vesicles formed from lipid bilayers and have exhibited remarkable potential due to their biocompatibility, ability to host both hydrophilic and lipophilic drugs, and controlled release. Nanoliposomes have the potential of improving solubility of drugs, protect therapeutic agents against enzyme activities, and produce a controlled drug release, which offers a new possibility in the treatment of diabetes. In addition to glucose-lowering, targeted liposomal treatment approaches combat major complications, such as cardiomyopathy, nephropathy, and retinopathy, through increased myocardial protection, renal resilience, and ocular drug exposure. This review provides a thorough overview of the progress, formulation methods, and therapeutic value of nanoliposomal-based delivery systems targeting antidiabetic drugs. It also focuses on the recent trend in research, the challenges of clinical translation, and the future of nanoliposomes as a paradigm-altering platform in the treatment of diabetes mellitus.

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1. Introduction

Millions of individuals worldwide suffer from diabetes mellitus, a chronic and crippling metabolic disorder that is brought on by the incapacity of the body to make or use insulin.[1] An estimated 3.4 million people died from diabetes in 2024 alone, making it a major global public health concern. It is projected that by the year 2030, DM will overtake all other causes of death, and by the year 2045, according to the International Diabetes Federation (IDF), approximately one in eight adults, or 783 million people, will have diabetes.[2] More than 20% of those affected people experience complications, including poor wound healing, cardiac diseases and cancer diseases, which will increase the potential risk of morbidity and mortality.[3]

Maintaining stable blood glucose levels is vital to keep glucose levels within the healthy range, typically between 70 and 140 mg dL^{-1}, which is known as euglycemia.[4] Primarily, traditional strategies such as the use of phytochemicals from different natural sources were commonly exercised.[5–7] However, many other possibilities always remained in investigation to achieve best results.[8–10] Currently, metformin along with other drugs are commonly prescribed to treat high glucose level.[11] The most effective drug for regulating blood glucose levels, particularly in treating severe diabetes, remains insulin. The subcutaneous insulin injections are currently the primary mode of treatment for treatment of DM.[12] Numerous problems, such as fat buildup at injection sites, skin thickening, insulin resistance, and hard lumps beneath the skin, can result from frequent injections. These problems may lead to pain, discomfort and needle phobia for the patient and less effective treatment.[13,14] On the other hand, oral intake of insulin is preferable option to get over the limitations associated with insulin injections. But it also associated with a set of drawbacks. Being a polar and water-soluble protein, insulin is extremely susceptible to denaturation and degradation. The acidity of the

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stomach and digestive enzymes can break down insulin, making it almost ineffective in its main biological functions.[15,16]

With the last several years, nanotechnology has emerged one of the most promising methods of making the diabetes treatment process more effective and safe. Specifically, delivery systems based on nanoparticles have shown great potential towards enhancing the curative value of antidiabetic drugs and mitigating their drug side effects. These are valuable methods of overcoming the limitations of conventional diabetes therapy because they administer insulin and other insulin-resistant drugs *via* an exacted discharge, focus, and amplified bioavailability. One of the nano-carriers that have drawn massive focus is nanoliposomes due to its versatility, biocompatibility, and potentially to enclose hydrophobic as well as hydrophilic drugs. This review aims at providing an in-depth discussion of the status of drug delivery systems using nanoliposome in the treatment of diabetes with focus in its formulation, design and application. Although considerable advances have been made regarding the treatment of diabetes, most past studies have either dealt with the traditional therapeutic methods,[17] or with single nanocarrier systems without a detailed up to date analysis of the nanoliposomes in the specific case of antidiabetic drug delivery.[18] There is also no apparent comparison of formulation strategies, and therapeutic outcomes in different liposomal systems compared in the existing literature. To fill the existing gaps, the current review describes the recent progress in the development of nanoliposomes-based-drug delivery in diabetes, their benefits over the traditional methods and their potential in enhancing bioavailability, target delivery and long-term glycemic regulation.

1.1. Methodology of literature selection

To provide a detailed and organized review, we collected the reported literature from major scientific databases, such as Scopus, Web of Science, PubMed, ScienceDirect, and Google Scholar, to manage the review systematically.[19] The keyword used in literature collection mainly were nanoliposomes, liposomal drug delivery, diabetes mellitus, oral insulin, phytochemical-loaded liposomes, and nanocarrier-based therapeutics. In this review, 10% of the chosen articles were published prior to 2010, 50% were published between 2010 and 2020, and the remaining 40% were published in 2021–2025, which also means that most of the evidence belongs to the studies carried out within the past ten years. The inclusion criteria included peer-reviewed articles, original research, reviews, and clinical or preclinical studies pertinent to nanoliposome-based delivery in diabetes and published in English language. The exclusion criteria were non-English papers, abstracts of conferences without full texts, non-liposomal nanocarriers, and papers that were not related to therapeutic or mechanistic considerations. This methodology (Fig. 1) allowed to select high-quality, more recent literature based on the scope of the given review.

2. Diabetes mellitus: pathophysiology and therapeutic challenges

According to World Health Organization (WHO), DM is a chronic metabolic disease characterized by the excessive level of glucose in the blood that eventually harm heart, kidney, blood vessels and nerves. This, consequently, will impose the serious threat to the healthcare systems and the economy. It can be categorized mainly into three forms including type 1, type 2, and gestational diabetes (Fig. 2).

Type 1 DM (T1DM) is the deficiency of production of insulin (Fig. 2) and is usually recognized at the earlier stages of childhood and youth. It comprises ~5–10% of the total diabetes cases.[20] This form of diabetes was initially identified as beginning in childhood and requiring insulin therapy from an early stage. Its development is primarily driven by an autoimmune response that targets and destroys the insulin-producing beta cells in the pancreatic islets. T1DM diabetes is classified into two distinct types: the autoimmune type 1 diabetes, also known

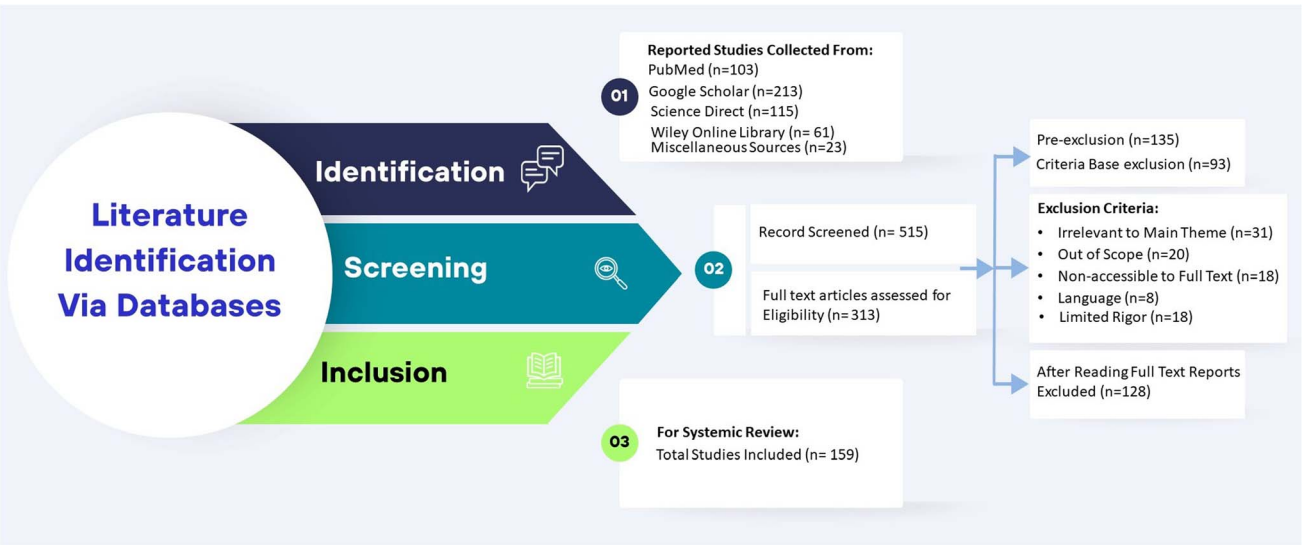

Fig. 1 The inclusion and exclusion criteria of literature collected from major scientific data base.

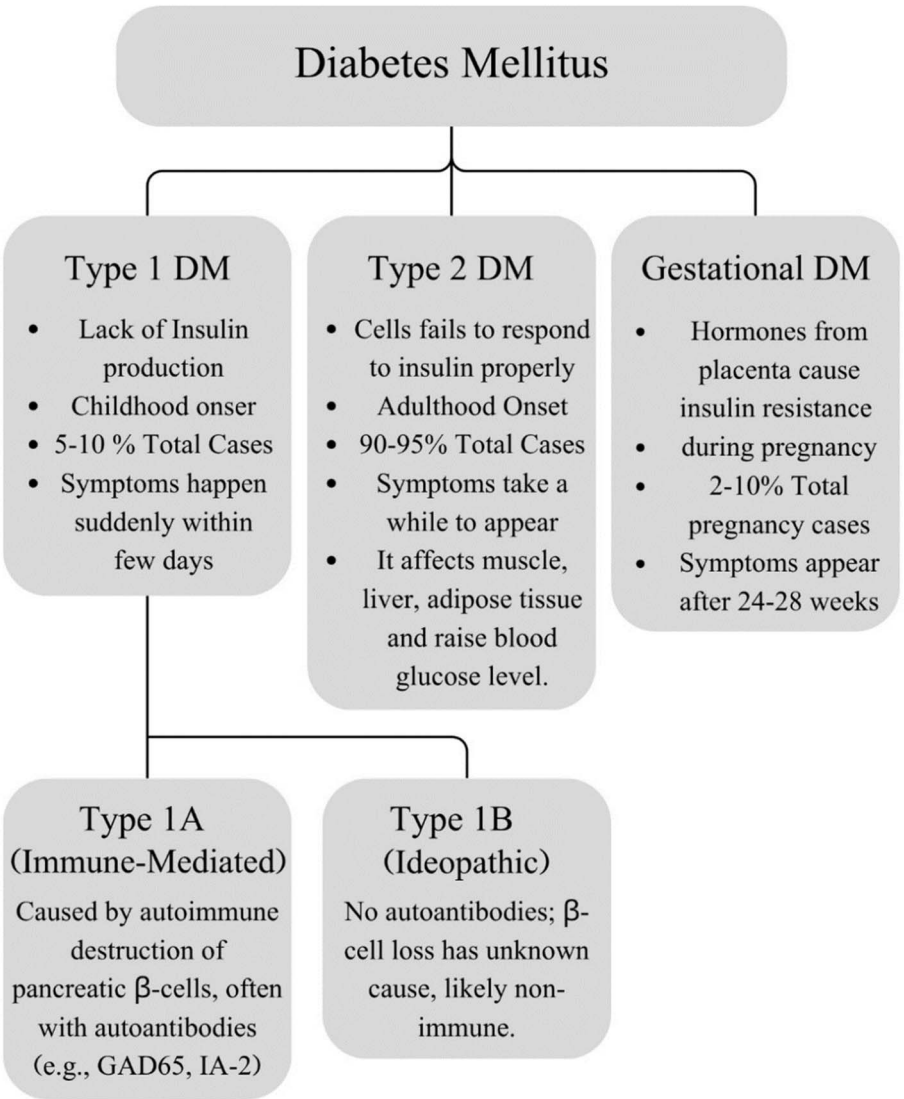

Fig. 2 Classification of diabetes as type 1 DM, type 2 DM, and gestational diabetes.

as type 1A DM, and the idiopathic type 1, also known as type 1B diabetes. A subset of patients diagnosed with idiopathic type 1 diabetes shows no evidence of autoimmune activity, and the underlying cause of their pancreatic beta cell destruction remains unclear. Seventy to ninety percent of patients with type 1 diabetes have autoimmune type 1 diabetes, which is a chronic autoimmune illness with the deficiency of insulin brought on by the death of β cells, resulting in a high blood glucose level.[21]

Type 2 DM (T2DM) is more prevalent (between 90 and 95%) and is marked by decreased insulin or insulin resistance. It is formally known as non-insulin-dependent or adult-onset diabetes. It mostly affects muscle, liver, and adipose tissue and raises blood glucose levels inappropriately.[22] The two main factors are the malfunctioning of pancreatic β-cells in secreting insulin and the insulin-sensitive tissues being unable to respond effectively to insulin (see Fig. 3), which results in hyperglycemia.[23] As glucose homeostasis depends on insulin release and activity, the molecular mechanisms behind insulin production, release, and detection are strictly regulated. The majority of patients with T2DM are obese or have a higher percentage of body fat, primarily in the abdominal area. Adipose tissue in this case leads to insulin resistance (IR) by a number of inflammatory processes, such as elevated production of free fatty acids (FFA) and dysregulation of adipokines.

Due to hyperglycemia and certain elements of insulin resistance, people with T2DM are at increased risk for microvascular consequences, such as retinopathy, nephropathy, and neuropathy, as well as macrovascular problems like cardiovascular comorbidities. In addition to population ageing and genetic factors, environmental factors such as global increase in obesity, sedentary lifestyles, smoking, unhealthy high-calorie meals, and physical inactivity are the main causes of T2DM. They are among the several pathophysiological abnormalities that lead to poor glucose homeostasis.

According to American Diabetes Association, gestational diabetes is the third kind of diabetes mellitus. On the global

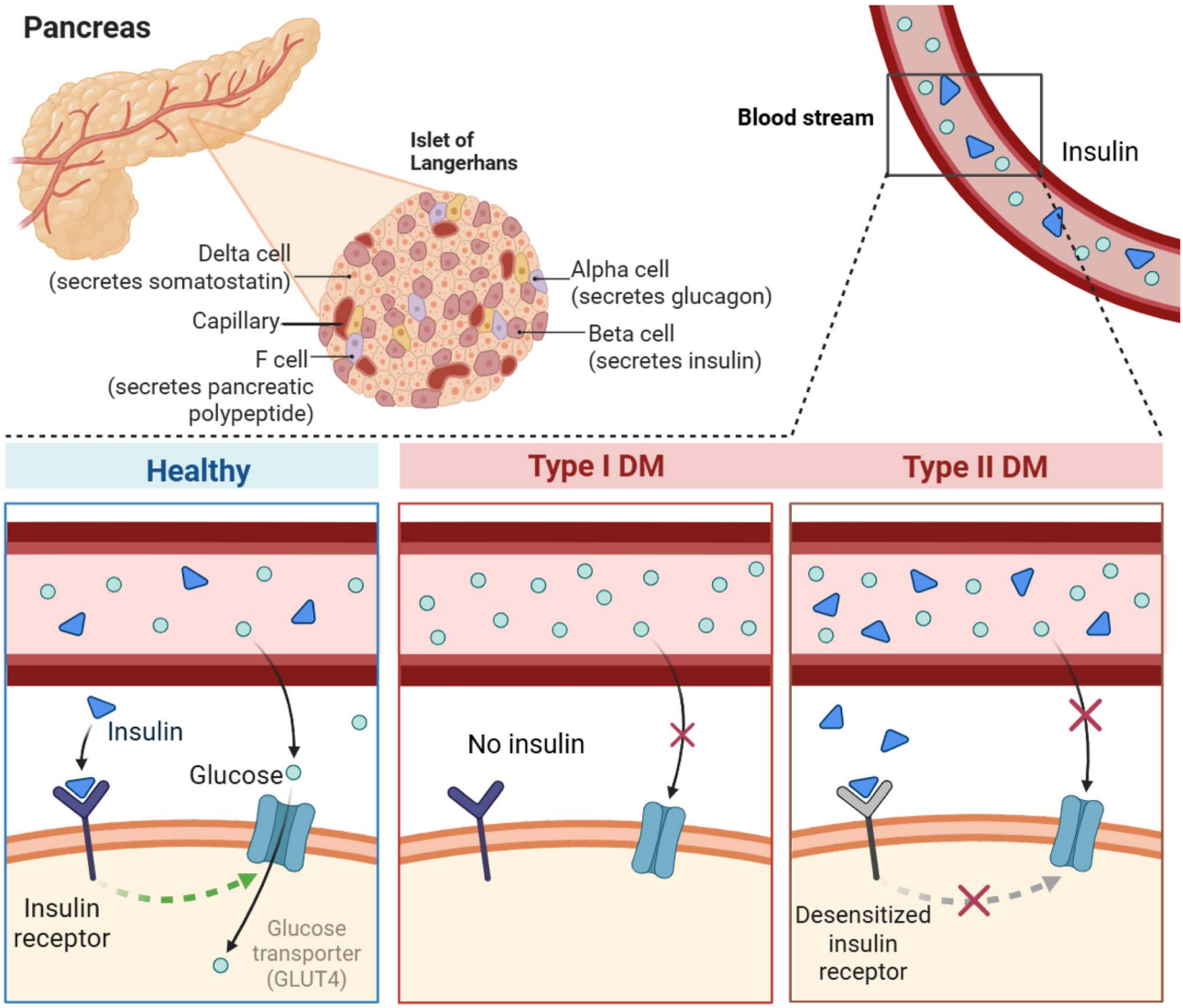

Fig. 3 Overview of processes involved in type 1 and type 2 diabetes (figure was created with BioRender.com (http://BioRender.com)).

scale, gestational DM is becoming more common and accounts for 1–28% of pregnancies.[24] This type of diabetes is one of the most common pregnancy-related medical problems. It is characterized as glucose intolerance that first appears during pregnancy. Although it can occur at any point during pregnancy, this ailment usually manifests in the second or third trimester.[25] It poses significant risks to both maternal and fetal health. Potential complications include pre-eclampsia and the need for cesarean delivery in the mother, as well as fetal distress, birth injuries, and an increased likelihood of metabolic disorders or mortality later in the child's life.[26,27] There are a few less common types of diabetes that are divided into monogenic and secondary diabetes in addition to type 1 diabetes, type 2 diabetes, and gestational diabetes. Monogenic diabetes is caused by a genetic error in a single gene of β cells in pancreas, which limits the function of β cells or a decrease in cell count. Secondary diabetes can develop as a side effect of other diseases, such as hormone imbalances, pancreatic disorders (like pancreatitis), endocrine dysfunctions, medications or chemicals (like steroids) and genetic syndromes linked to DM like Turner syndrome and Down syndrome.[20]

3. Diabetes management

3.1. Conventional approaches

The conventional mode of treatment of type 1 DM is subcutaneous insulin administration, typically delivered *via* multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) using insulin pumps. Dosages are patient-specific but generally range from 0.5 to 1.0 units per kg per day, divided into basal (long-acting) and bolus (short-acting) components.[28] The therapeutic goal is to maintain glycemic targets fasting glucose levels between 80–130 mg dL^{-1} and postprandial levels below 180 mg dL^{-1}. These methods can successfully lower blood sugar levels and avoid acute problems like diabetic ketoacidosis, but they cannot stop the evolution of

autoimmune diseases or stop long-term damage to the microvascular and macrovascular systems. The key limitation of using insulin is its short half-life, which renders it susceptible to rapid degradation in the gastrointestinal tract and prevents its oral delivery. Moreover, it also triggers hypoglycemia, weight gain, allergies, and injection anxiety.[29] Even though new types of technology, such as insulin provided by hybrid closed-loop systems and continuous glucose monitors (CGMs), have emerged, the injection of insulin remains a challenge, as does the need to administer it at the exact time and in the exact amount.[30] The Type 2 DM is treated with oral and injectable drugs. Metformin, an oral biguanide, is typically used at a dose of 500–1000 mg twice daily as an initial form of treatment. It can also decrease the HbA1c concentration by 1.0–1.5%. In the event of unattainable glycemic goals, additional oral pharmaceuticals include sulfonylureas (*e.g.*, glimepiride 1–4 mg per day), DPP-4 blockers (*e.g.*, sitagliptin 100 mg per day), and SGLT2 blockers (*e.g.*, empagliflozin 10–25 mg per day).[31] The success of these oral interventions in minimizing hemoglobin A1c (HbA1c) by 0.5–1.5% is notable. The risks related to sulfonylureas include hypoglycemia, as well as weight gain, and genitourinary infections might be an issue with SGLT2 inhibitors.[32] Patients require injections when the condition of type 2 diabetes progresses and the use of oral medications loses its effect. These tend to be the long-acting insulins, like insulin glargine, at a dose between 10 and 50 units per day, or agents that activate the glucagon-like peptide-1 (GLP-1) receptor, like liraglutide, usually dosed by subcutaneous injection at the dose 1.2 to 1.8 mg per day. These therapies help maintain glycemic control when oral agents alone are insufficient to achieve this goal. Agents that reduce GLP-1 levels increase HbA1c by 1.0–1.6% and additionally minimize body weight and cardiovascular health.[33] These conventional therapies for DM are often limited by poor bioavailability, short half-life, and the need for frequent dosing, leading to low patient compliance. Importantly, these approaches provide only symptomatic glycemic control without preventing β-cell exhaustion or disease progression. Such dilemmas demonstrate the dire necessity to develop new delivery platforms (nano-based systems, in particular), which may enhance therapeutic index, drug delivery, and reduce side effects within the system.

3.2. Nanotechnology: modern approach in diabetes management

A product is considered nanotech-based, according to Food and Drug Administration (FDA) regulation, if at least one of its dimensions is within the nanoscale range of 1–100 nm. But in some cases never exceed from 1000 nm, provided their functional properties align with nanoscale characteristics. The scientific community continues to debate the precise definitions of nanotechnology and its associated terms, such as nanoparticles, nanosystems, and nanomaterials, highlighting an ongoing lack of consensus on the exact parameters that qualify something as 'nano-scale'.[34] Typically, these materials are synthesized either top-down or bottom-up processes (Fig. 4(a)). The top-down process converts bulk material into nanoscale particles. In this method, the bonds between the layers of material are broken through a physical or chemical exfoliation process. This method offers broader-scale nanomaterial production under ambient conditions. Bottom-up

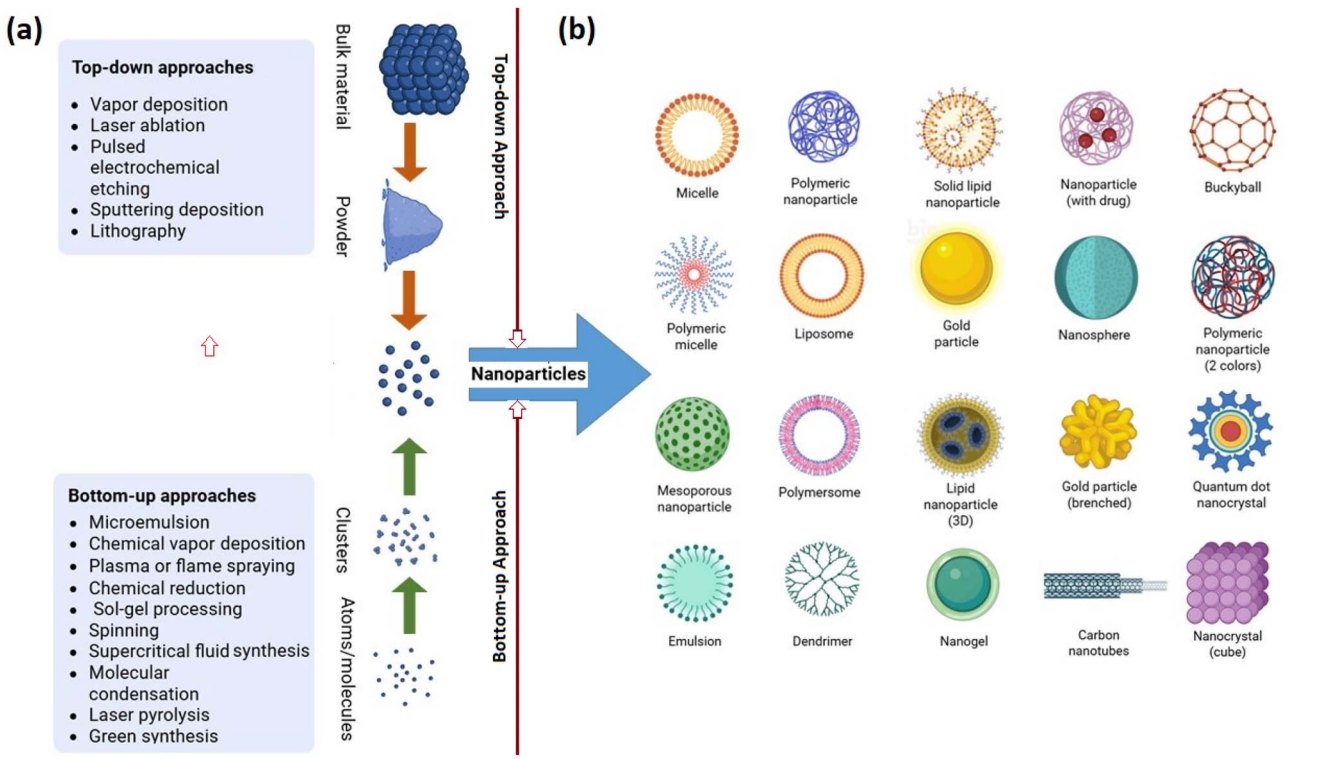

Fig. 4 Synthetic approaches of nanomaterial (a), and synthesized nanomaterials used for drug delivery (b).

process is a constructive approach that uses atoms and molecules as building units to grow and assemble into nanoparticles with precise size, shape, and chemical makeup. This process uses wet-synthesis techniques or chemical and physical vapor deposition, which favor to control the size and shape of the nanoparticles.

The wide range of synthesis of nanomaterials and their practical applications across the industrial and clinical worlds enable nanotechnology to provide the best solutions to clinical and industrial issues.[35] Notably, it has reshaped the world of medical sciences by introducing innovations in the diagnosis and treatment of diseases. Presently, nanotechnology has revolutionized the medical field in all aspects. The development of medication delivery systems based on nanotechnology is a key objective. Metals, lipids, bio- and synthetic polymers are among the materials which are reported frequently to address the drug delivery challenges.[36,37] Modern advancements in nanomedicine have greatly enhanced the management of health issues like autoimmune diseases, cancer, cardiac conditions, and inflammatory diseases. All this make it convenient for effective drug dispensation and controlled release to obtain precise therapeutic outcome.[38]

In the case of diabetes management, there is an urgent need to address the key limitations associated with conventional approaches, such as the risk of hypoglycemia, poor bioavailability, short half-life, and the requirement for frequent dosing. The effective outcomes, in managing the DM using nanotechnology, are the lowering of the risk of hypoglycemia, increasing the drug half-life and bioavailability by administering encapsulated insulin nanomoieties.[39] The significant breakthrough was reported when stem or pancreatic cells were transduced successfully with nanoparticles containing oligonucleotides in the form of non-viral vectors for the activation of genes associated with insulin production or the suppression of the faulty genes related to DM.[40] Numerous nanomaterials, including lipid-based particles, hydrogel-based nanosystems, fibrous nanomaterials, polymer-based systems, micelles, gold and magnetic nanoparticles, cyclodextrin complexes, dendrimers, nanogels, and liposomes, are being investigated as drug carriers (Fig. 4(b)).

4. Nanoliposomes: structure and properties

Lipid based delivery systems fall into a number of categories, including solid lipid nanoparticles, liposomes, and nanostructured lipid carriers. Liposomes are gaining considerable attention as a carrier for advanced drug delivery. The term "liposome" originated from two Greek words "lipos" which means "fat", and "soma", which means "body of"; so liposome means "body of fat".[41] In 1961, Dr Alec Douglas Bangham at the Babraham Institute in Cambridge was the first person to introduce the term "Liposomes".[42] Gregory Gregoriadis first proposed in the early 1970s that liposomes can be employed as drug delivery carriers to cross the cell membrane.[43] These are tiny, man-made spherical carriers that vary in size from a few nanometers up to several micrometers.

Liposomes are mostly composed of phospholipids and cholesterol.[44,45] The behavior of these carriers largely depends on the specific chemical properties of the lipids from which they are made. The fundamental component of liposomes is phospholipid bilayers (Fig. 5). Both synthetic and naturally derived phosphatidylcholine, are among the top choices for producing liposomes.[46] Phospholipids derived from natural sources, such as egg yolk or soybeans, tend to be less stable than their synthetic counterparts, largely because they contain a higher proportion of polyunsaturated fats.[47]

Phospholipids make up between 55 and 100% of the total liposomal component by molar proportion. The most common phospholipid constituent is called 1,2-distearoyl-*sn*-glycerophosphocholine (DSPC) (see Fig. 6(a)).[48] This molecule is composed of a phosphate group head, which is polar, and a hydrophobic hydrocarbon chain. The polar head makes up the outward face of the liposome bilayer, whereas the hydrocarbon chain makes up the interior face of the bilayer. Other functional groups can be connected to the head section for surface modification. Another useful phospholipid frequently used in drug delivery is 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (DSPE), which actively contributes to the stabilization and functionalization of the lipid structure by incorporating polymers such as polyethylene glycol (PEG)

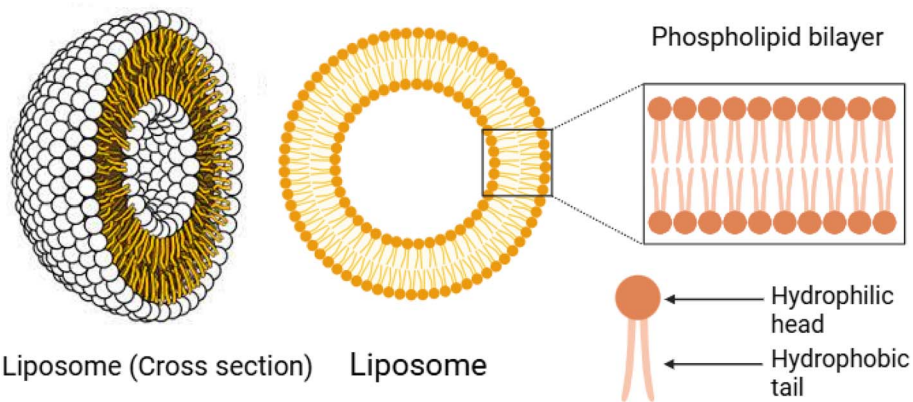

Fig. 5 Schematic representation of the structure of a liposome that is composed of a phospholipid bilayer.

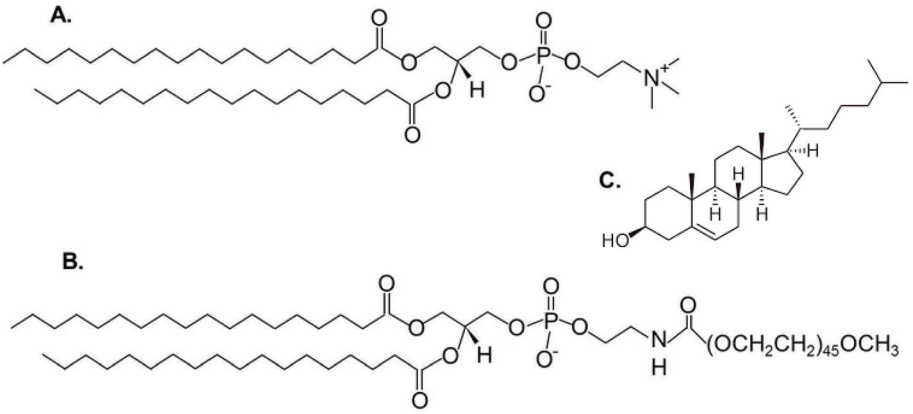

Fig. 6 Chemical structures of common components of nanoliposomes (A) DSPC, (B) DSPE-PEG and (C) cholesterol.

(Fig. 6(b)).[49,50] The size and shape of a liposome are eventually determined by the type of phospholipids and their molar percentage. The bilayer structure of phospholipids is also dependent on the length of the lipid and the size of the groups.[51]

Cholesterol is the primary component used in liposomal formulations to stabilize the liposome bilayer, as the flip-flop motions of phospholipids permit rotational freedom, which can result in leaky liposomes. Because cholesterol provides the fluidity, elasticity, permeability, and stability of liposome membranes, its molar fraction of total liposome components ranges from 30 to 40%, depending on the bilayer's fluidity and rigidity.[52] In a lipid bilayer, the polar heads of the phospholipids and cholesterol are in alignment. Cholesterol fills the void left by improper phospholipid packing in lipid bilayers by existing in the interior due to its hydrophobic characteristics.[53] Some research has indicated that cholesterol also aids in preventing the hydrolytic breakdown of the lipid bilayer.

4.1. Liposomal architectures and classification

Liposomes are often classified based on their size, lamellarity, composition, and functional characteristics. Based on lamellarity, they divided them into unilamellar, multilamellar, and multivesicular vesicles (Fig. 7(a)). Unilamellar vesicles (ULVs) are characterized by the presence of a single phospholipid bilayer enclosing an aqueous phase. ULVs can be broadly categorized based on their size; some are quite small, known as small unilamellar vesicles (SUVs), while others are significantly larger and referred to as large unilamellar vesicles (LUVs). SUVs may range in size from 20 to 100 nm.

LUVs have a size between 100 and 1000 nm. Multilamellar vesicles (MLVs) are made up of several layers of phospholipid membranes arranged like nested spheres, with thin spaces of water separating each membrane. In MLVs, one unilamellar vesicle typically grows inside another in decreasing size, resulting in an onion-like structure. These are large, maybe reaching a size of 5 μm, and are ideal for incorporating hydrophobic drugs.[54] Multivesicular vesicles (MVVs) contain multiple internal vesicles within a lipid bilayer, measuring 1 to several microns in size.

Lipid membranes separate these internal vesicles, allowing them to encapsulate both hydrophilic and hydrophobic agents. While based on composition and functional properties, they are classified as conventional, PEGylated, stimuli-responsive or theranostic, and ligand-targeted liposomes (Fig. 7(b)). Conventional liposomes are the simplest form, primarily made from phospholipids and cholesterol. They can be neutral, anionic, or cationic. The main limitation of these liposomes is the rapid clearance from the body by the mononuclear phagocyte system (MPS), which reduces the circulation time of these carriers. In order to minimize the rapid clearance, PEGylated liposomes are used. These liposomes are modified by incorporating polyethylene glycol (PEG) chains to their surface. This coating forms a hydrophobic shield around liposomes, helping them stay longer in the body by avoiding opsonization. Ligand-targeted liposomes are advanced surface-modified with targeting ligands such as peptides, antibodies, or small molecules that bind to specific receptors on target cells. Stimuli-responsive liposomes are specifically engineered to release medication in response to specific *in vivo* and *in vitro* stimuli, such as changes in pH, light, and temperature. Briefly, nanoliposomes combine the biocompatibility and drug-loading versatility of liposomes with the advantages of nanoscale systems, including improved cellular uptake, prolonged circulation, and controlled release. These properties make them promising carriers for diabetes therapy, particularly for insulin, oral antidiabetics, and bioactive natural compounds.

5. Liposomes: selection, fabrication and stabilization

The type of liposome to be used depends on several factors, including the desired particle size and stability, the nature of the drug, the administration route, and the target site, which make them highly suitable delivery systems for the delivery of antidiabetic medications. The specified size of 50–200 nm allows for efficient intestinal absorption, with prolonged

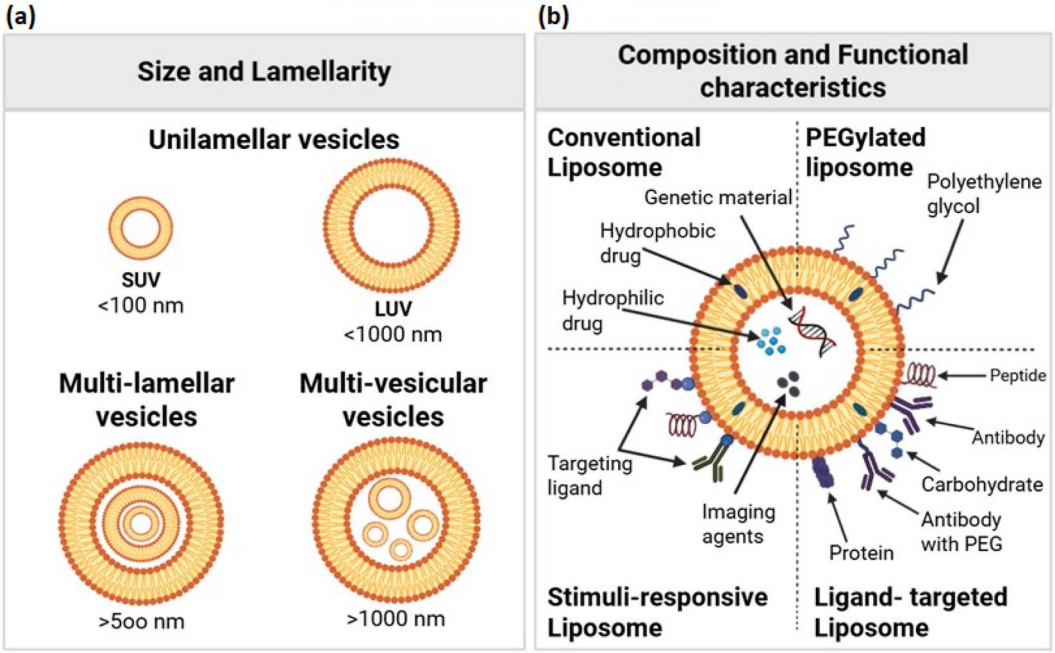

Fig. 7 Classification of liposome based on size and lamellarity (a), composition and functional characteristics (b).

circulation, and enables it to reach the target tissue, as well as evade rapid renal clearance (<10 nm) or spleen filtration (>200 nm). Indicatively, the oral bioavailability of insulin-loaded bile salt liposomes (120 nm) led to a 15–20% increase when compared to that of free insulin in diabetic rats.[55] Another important parameter is stability, as the inclusion of cholesterol and pegylated lipids reduces aggregation, prevents premature leakage, and provides a longer duration of systemic retention. For instance, conventional liposomes are used for short-term and passive delivery, while PEGylated liposomes are used when prolonged circulation and stability are required. In particular, pegylated insulin liposomes remained in circulation for more than 48 hours, which significantly decreases rapid plasma clearance.[56] Formulation is also governed by the nature of the drug, where hydrophilic medications, such as insulin, GLP-1 agonists, or growth factors, are entrapped in the aqueous core. In contrast, hydrophobic medicines, such as curcumin, quercetin, or resveratrol, are loaded into the lipid bilayer. Curcumin loaded liposomes (approximately 100 nm) made using long circulation lipid improved insulin sensitivity and reduced inflammatory cytokines in diabetic mice with type 2 diabetes.[57] The route of administration also influenced the design, as oral administration requires protection against enzymatic breakdown in the gastrointestinal system. At the same time, transdermal delivery involves the use of nanosized, stable particles to penetrate the skin, and intravenous administration can be enhanced with pegylated liposomes to prevent elimination by the reticuloendothelial system. Liposomes that are ligand-specific, such as those targeting peptides, folate, and vitamin B-12, are best for delivering the drug with high specificity by targeting therapy to specific cells and tissues, thereby minimizing off-target effects. Stimuli-responsive liposomes are used when controlled and on demand release of drug is required, typically in response to specific internal or external stimuli such as temperature, pH, and enzymes, allowing precise drug release. All these features improve drug bioavailability, deliver sustained release, decreased dosing frequency, and enhanced therapeutic outcomes in the management of DM.

5.1. Fabrication

The fabrication strategy defines the size, stability, and encapsulation effectiveness necessary for nanoliposomes in diabetes drug delivery. It has been reported that various methods generate different characteristics and therefore, some methods are better suited to a specific type of antidiabetic drugs.

Thin-film hydration (TFH) or the Bangham technique is commonly used for encapsulating lipophilic compounds. It is the most straightforward, ancient, and popular technique for producing MLVs. SUVs are created when this procedure is followed by sonication.[58] The primary phospholipid components are dissolved in an organic solvent (such as ethanol, dichloromethane, chloroform, or a combination of chloroform and methanol with a 2 : 1 v/v ratio). The organic solvent is eliminated successively by evaporating under a vacuum pump at a temperature between 45 and 60 °C using a rotary evaporator, which rotates at 60 rpm. This results in a thin, dry, and uniform lipid film of bilayers being created. When water is added, the dry film begins to absorb moisture and expand, eventually forming multilamellar vesicles as it is gently stirred or shaken. The process is followed by sonication to create SUVs (see Fig. 8A). The encapsulation efficiency (EE%) of nanoliposomes created from this method for metformin is approximately 93.04%. Indicatively, liposomes loaded with curcumin made by TFH (~100 nm) showed long-term stability of over 30

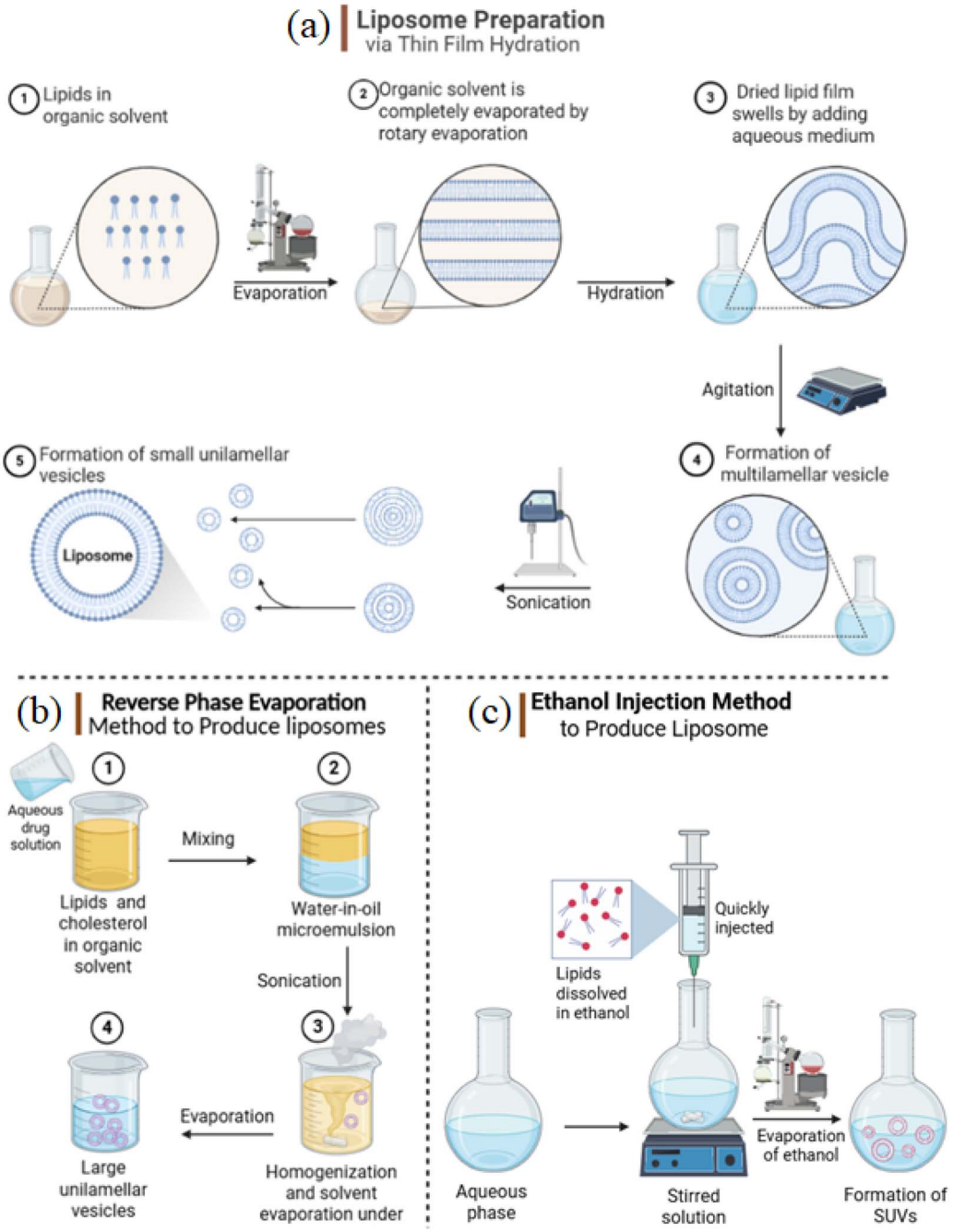

Fig. 8 Fabrication methods of liposomes used for diabetes management: thin film hydration method (a), reverse phase evaporation method (b), and ethanol injection method (c).

days at 4 °C and remarkably enhanced sensitivity in diabetic mice with type 2.[57] However, less encapsulation efficacy is observed with hydrophilic drugs, such as insulin, unless remote or active loading methods are used.

The reverse-phase evaporation (REV) approach is a flexible technique for creating nanoliposomes, particularly helpful when encapsulating a hydrophilic medication with high efficiency. In this technique, lipids are dissolved in an organic solvent, such as a mixture of diethyl ether and chloroform (1 : 1 v/v) or chloroform and methanol (2 : 1 v/v), which results in the development of inverted micelles. Adding an aqueous buffer containing the appropriate drug results in a water-in-oil (W/O) microemulsion. This buffer is frequently phosphate or citrate-based. Through mechanical mixing or sonication, the emulsion is homogenized. Under reduced pressure, the solvent is evaporated by using rotary evaporation which leads to a gel-like phase. The structure transforms into LUVs as the solvent evaporates and phospholipids self-assemble into bilayers around water droplets (see Fig. 8B).[59] These vesicles are smaller than those of other conventional methods, with an

encapsulation efficiency (EE%) of approximately 50.1% for lactoferrin. In a published study, insulin-loaded liposomes synthesized using the REV method had encapsulation efficiencies of 50–60%, resulting in a 45% decrease in blood glucose in diabetic rats 4 hours after oral administration.[60] This underscores the fact that it prevents enzymatic breakdown of insulin and improves the oral bioavailability. This technique is inappropriate for delicate (bio-)drugs as it involves organic solvent and sonication, which can degrade the drug structure.[61]

The ethanol injection technique produces evenly distributed nanoliposomes (50–150 nm) with a narrow diameter distribution, making them ideal for systemic and transdermal delivery. Using this method, the lipids were first dissolved in ethanol and quickly injected into a stirred aqueous buffer. When ethanol is mixed with water, it becomes diluted, allowing the lipids present in the water-based solution to naturally organize themselves into bilayer structures that can trap and surround the surrounding water content.[62,63] In the evaporation phase, ethanol depletion promotes the fusion of lipid fragments, resulting in the formation of closed unilamellar vesicles (Fig. 8C) with a particle size of 80–170 nm. For hydrophobic drugs, these nanoliposomes achieve 100% encapsulation efficiency, whereas for hydrophilic drugs, the efficiency is 16%.[64] The ethanol injection preparation of GLP-1 analogs demonstrated improved circulation time and enhanced glucose regulation in diabetic models. Systemic half-life was further enhanced by pegylated preparations.[56,65] Nonetheless, the encapsulation of hydrophobic molecules is still not that high and it necessitates secondary loading or the addition of stabilizers. This is due to the fact that the ethanol injection method produces small unilamellar vesicles with a minimal aqueous core volume, and the fast self-assembly procedure does not allow for the efficient entrapment of water-soluble drugs, resulting in most hydrophilic biomolecules not being incorporated into the vesicles.

Supercritical carbon dioxide-assisted liposome synthesis technique, as the antioxidants and plant-based polyphenols, which are commonly used to treat DM, are examples of heat-sensitive, fragile compounds that respond particularly well to this approach. It involves dissolving lipids and the medication (such as anthocyanins, which have been shown to have antidiabetic properties) in a small amount of ethanol before introducing them into a chamber that contains supercritical CO_2, at pressures of 73.8 bar and temperatures above its critical point of 31.1 °C.[66] Under these conditions, CO_2 behaves both like a gas and a liquid, facilitating the uniform distribution of lipid and drug molecules. When the pressure is gradually reduced, the CO_2 transitions back to a gas and exits the system, leaving behind self-assembled liposomes containing the drug. The resulting liposomes tend to be small (~160 nm) and exhibit good encapsulation efficiency, with a value of around 52%.[67]

Importantly, there is no universal fabrication method that can have all the desired characteristics in diabetes therapy. REV and modified TFH techniques are more compatible with oral insulin and peptide delivery owing to their greater aqueous encapsulation capacity.[55,60] TFH is more compatible with lipophilic phytochemicals, such as curcumin and resveratrol, and ethanol injection is the most effective method for fabricating intravenous or transdermal delivery, owing to its reproducibility and nanosizing.[57] Thus, the best approach is not limited to one approach but is instead based on adapting the physicochemical nature of the drug, its route of administration, and the therapeutic objective.

5.2. Stabilization

Lyophilization is a critical technique that maintains the physicochemical stability of nanoliposomes, especially where long-term storage and transportation are necessary. Despite the ability of methods like thin-film hydration, reverse-phase evaporation, and ethanol injection to produce nanoliposomes of the required particle size and encapsulation efficiency, such preparations tend to aggregate, fuse the membranes and leak the drug during storage due to chemical reactions like oxidation in aqueous suspension.[68,69] The use of freeze-drying overcomes these shortcomings by eliminating water at low temperatures and under vacuum, which in turn converts the liposomal dispersion into a stable dry powder that can be easily reconstituted prior to use. It consists of three stages including freezing, primary drying and secondary drying. The process begins by freezing the liposomal suspension, typically in vials, and in order to protect the structure and integrity of liposomes during freezing, cryoprotectants such as sucrose, lactose, or trehalose are added followed by applying a deep vacuum to remove ice through sublimation. In secondary drying phase, remaining unfrozen moisture is removed. To prevent moisture reabsorption, the final product is sealed under vacuum or dry nitrogen in airtight containers.[70,71] When optimized, freeze-dried liposomes typically remain below 200 nm in size, with reduced polydispersity and enhanced longevity. It has been shown that nanoliposomes that are insulin-loaded and then lyophilized with a cryoprotectant like trehalose or sucrose retained more than 80% of their initial encapsulation efficiency and retained particle size distribution on rehydration.[72,73] This becomes especially important with hydrophilic and peptide-based drugs such as insulin that are likely to be degraded in solution. Moreover, nanoliposomes that are lyophilated exhibit a better shelf life, less hydrolytic degradation of phospholipid and physical stability in transportation.[69,74] Therefore, according to the best-fit approach, lyophilization is a necessary complementary strategy to produce nanoliposomes with good stability, uniform size, and acceptable biocompatibility, thereby delivering antidiabetic drugs effectively. On glance summary of the key methods for the fabrication and stabilization of nanoliposomes is shown in Table 1.

6. Mechanisms of drug encapsulation and delivery

Drugs are delivered by loading *via* encapsulation into the liposome cavity which mainly carried out passive and active encapsulation techniques. Drug incorporation into liposomes during their formation is known as passive loading. In this method, water-soluble (hydrophilic) drugs are blended with the

Table 1 Summary of the key methods for the fabrication and stabilization of nanoliposomes

Method	Particle size (nm)	Encapsulation efficiency (EE%)	Types of nanoliposomes	Advantages	Disadvantages	Cost effectiveness	References
Thin film hydration method	~52	Upto 93.04% (metformin)	MLVs, SUVs after sonication	Simple process, high EE both with small and large molecules	Time-consuming, low scalability, requires sonication, low EE% for water-soluble drugs, small-scale production	Moderate	58
Reverse phase evaporation method	Smaller than other methods	~50.1% (lactoferrin)	LUVs	Suitable for hydrophilic drugs	Complex setup, unsuitable for fragile (bio-) drugs, use organic solvents	Moderate	61
Ethanol injection method	80–170	100% (hydrophobic) 16% (hydrophilic)	SUVs	Simple, reproducible, rapid, cost-effective	Low EE% for water-soluble drugs, removal of ethanol is difficult as it forms azeotrope with water	High	64
Supercritical CO_2 method	~160	52% (anthocyanins)	ULVs	Solvent-free, stable, green method	High equipment cost, less accessible	Expensive	67
Freeze-drying method	Below 200	80% with cryoprotectants	Lyophilized liposomes MLVs, ULVs	Improved storage stability, low organic solvent residue, suitable for large-scale production, and prevents physical degradation	May induce structural and size alterations, time and energy consuming, sterilization issue	Low	75

hydration solution used to moisten the thin lipid film, allowing the drug to be naturally drawn into the inner core of the liposomes during their formation. When a thin, dry lipid film is being prepared, lipophilic medications are combined with other liposome constituents and then put into lipid bilayers.[76] The drug molecules that are not entrapped are extracted from the liposome suspension using gel-filtration chromatography or dialysis. The size of the liposomes and the kind and quantity of lipids utilised are some of the main elements that affect how well encapsulation works. Generally, larger vesicles tend to have better encapsulation capacity compared to smaller ones.[54,77] Typically, drugs that interact with lipid bilayers, like lipophilic compounds, have higher encapsulation rates. To increase the effectiveness of drug encapsulation, several methods have been developed. One popular strategy is to add a lipophilic chain to the drug molecule, which facilitates its incorporation into the lipid bilayer and enhances its overall lipophilicity.[78] Passive loading yields lower drug encapsulation efficiency compared to active loading.

Active (Remote) loading strategy allows specific drug to load into manufactured liposomes, and is also known as remote loading. To achieve high drug encapsulation efficiency within the nanoliposomes, it is utilized. This type of loading strategy involves an electrochemical potential generated by the pH or ion gradient formed across the lipid bilayer. It consists of creating a pH difference between the outside and inside of the liposome. During the liposome preparation process, a buffer with a certain pH and ion concentration is used to establish the pH or ion gradient. Dialysis, size exclusion chromatography, or another buffer with a different pH is then used to change the liposome's external pH. Once the pH gradient across the membranes has been established, the drug is loaded by mixing it with the liposomes, usually at a temperature higher than the phase transition temperature, ensuring fluidity and effective transport across the bilayer. The drug molecules become charged as a result of their interactions with ions inside liposomes. The liposome core traps the charged drug molecules, preventing them from escaping.[78] Active loading tends to have a higher encapsulation efficiency (EE%) compared to passive loading. A study reported that active loading of protein into a liposome using the freeze–thaw (FT) technique achieved an EE% of $7.2 \pm 0.8\%$, whereas passive loading showed an EE% of $4.57 \pm 0.2\%$. Active loading is particularly used for the delivery of chemotherapeutics, as it can lower toxicity and boost efficacy.

7. Cross-study analysis of nanoliposomal drug formulations in diabetes therapy

Across published research, a comparative analysis of nanoliposomal systems indicates that there are distinct performance differences between insulin, metformin, peptide and phytochemical nanoliposomal systems. Insulin liposomes have the quickest glycemic response. Chitosan-coated carriers reduced blood glucose by 84–85% in 15 minutes,[79] while biotin-conjugated liposomes resulted in a 38.4% reduction in 5.28-

fold higher bioavailability,[80] and PEGylated folate-targeted insulin liposomes kept glucose at around half of baseline in 24 hours. Oral uptake was further increased by 2.3 times using vitamin B12-functionalized liposomes.[81] Systems with metformin demonstrate moderate but consistent increases, with HDCA-modified liposomes reducing the fasting glucose level by 37.8 percent and glucose tolerance by 28.3 percent.[82] The peptide-carrying nanoliposomes like multivesicular liraglutide preparations provide enhanced activity and provide 144-hour sustained release and 4.5-fold higher bioavailability.[83] Phytochemical-loaded liposomes, on the contrary, have slower onset and wider metabolic correction. Betanin liposomes decreased glucose levels to the range of about 375 mg dL^{-1} to about 185 mg dL^{-1} and increased antioxidant enzymes,[84–86] whereas quercetin, silibinin, and daidzein liposomes had a significant positive effect on oxidative stress levels, decreased inflammatory factors, and increased GLUT2/GLUT4 expression.[87,88] PEGylated resveratrol and Rg3 liposomes were reported to have 24-hour protection of antioxidants, reinforcement of β-cell structure and insulin sensitivity.[89,90] Together, insulin-based nanoliposomes are more effective in glucose reduction within a short period of time, and phytochemical and peptide-based systems provide metabolic repair in the long-term, such as antioxidant stabilization, b-cell repair, and improved insulin signaling.

7.1. Insulin-loaded liposome

Researchers have made tremendous progress in reducing drug toxicity and increasing both safety and effectiveness by employing liposomal formulations to deliver therapies to targeted cells and organs. Several factors must be taken into account in order to improve the particle size and efficiency of insulin encapsulation within the liposomal core, such as the water to oil emulsion state ratio, the pH of buffering agent during hydration and the ratios of phospholipids and cholesterol. To maintain membrane fluidity, allow the maximum number of insulin molecules to be integrated, and prevent insulin leakage, the right ratio is essential. Lower temperature and smaller unilamellar liposomes are the ideal conditions for insulin attachment to liposomes. Gradual development has yielded promising achievements in the oral delivery strategy, with encouraging outcomes, such as the development of insulin-packed liposomes augmented with biotin, a vitamin considered a targeted ligand to enhance intestinal absorption. The liposomes were fabricated using the reverse-phase evaporation method, followed by sonication, with a lipid-to-cholesterol ratio of 3 : 1. Their lipid membranes contained a specific compound, biotin-DSPE. The nanoliposomes having size of 153.7 ± 6 nm were developed and showed the EE% of 78.3 ± 3.1%. The preclinical trials were performed on normal Sprague Dawley rats by oral administration of biotin-modified liposomes loaded with insulin (20 IU per kg). The nanoliposomal formulation showed a maximum glucose reduction of 38.4%.[80] In comparison to subcutaneous insulin, these nanoliposomes had a pharmacological bioavailability of 11.04%, which was 5.28 times greater than that of conventional liposomes. The biotin formulation significantly improved the absorption of insulin compared to the unmodified liposomes. This study highlights the potential of biotin-modified liposomes as a promising strategy for oral insulin delivery.

Furthermore, Agrawal *et al.* developed the functionalized multilayered liposomes (layersomes) structure covered with the two oppositely charged polymers, *i.e.*, polyacrylic acid (PAA) and polyallyl amine hydrochloride (PAH) and integrated with folic acid to direct the system to desired targets.[91] These liposomes were fabricated by the thin-film hydration method followed by sonication and layer-by-layer polyelectrolyte coating (PAA/PAH). The freeze-dried layersomes were 266 nm in size with a zeta potential of +25.4 ± 2.6 mV and had an EE% of 92.9 ± 1.4%. The preclinical experiments were conducted on streptozotocin-induced diabetic Sprague–Dawley rats. After six 6 hours of oral administration, glucose levels dropped by 77.7%, remaining below 50% of baseline for twelve hours. When compared to conventional insulin solution delivered subcutaneously, studies showed nearly twofold hypoglycemia and a 19.3% relative bioavailability because of FA receptor-mediated absorption and GI stability.

Yazdi and colleagues developed folate-targeted PEGylated liposomes using the thin-film hydration method followed by extrusion.[92] The liposomes were surface-functionalized with stealth-stabilizer $Mpeg_{200}$-DSPE (4%) and targeting ligand DSPE-PEG_{3400}-folate (1%) to simultaneously increase the stability and penetration effectiveness of liposomes. The modified liposomes had 208 ± 2 nm particle size, a zeta potential of −6.8 mV and 66% EE% of insulin. By oral administration (50 IU per Kg) to diabetic Wistar rats, the blood glucose level was reduced by ∼50% of the baseline within 4 h. The hypoglycemic activity sustained for 24 hours. Compared to non-targeted liposomes, the pharmacologically availability of targeted liposome was 19.08%, which was 2.1 times greater than the previous ones. The findings also showed that PEGylated liposomes targeted with FA had longer residence time in the gut and stomach. Further development revealed that the layer-by-layer chitosan–insulin–chitosan coated nanoliposomes (Fig. 9) achieved high insulin loading (10.7% by weight) and offered superior protection with limited release in simulated gastric fluid. Furthermore, 40–60 μg of insulin was attached hydrophobically to 1 μmol of phospholipids in a liposome.[93]

The nanoliposomes were fabricated by the reverse-phase evaporation method. To achieve a chitosan coating, the liposomal suspensions were incubated with a chitosan solution. The coated liposomes were 202.4 nm in diameter with a zeta potential of +6.7 mV and had an encapsulation efficiency (EE%) of 75.9%. By oral administration of insulin (250 IU per kg) coated with 0.2% chitosan to Kunming mice, the blood glucose level was reduced by 84.9% (to 15.1% of the baseline) in just 15 minutes. The hypoglycemic effect persisted for four hours after administration.

Additionally, the chitosan layer helped conceal the insulin from digestive enzymes such as trypsin and pepsin by forming a barrier around the liposomes, especially at neutral pH. Stabilization of the newly insulin-coated nanoliposomes remains a challenge. Sarhadi and co-workers developed

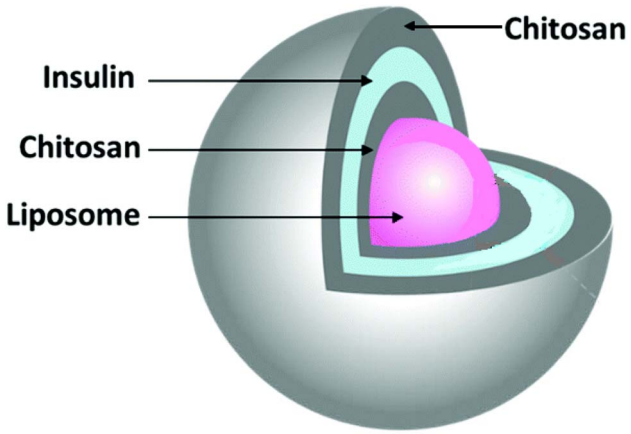

Fig. 9 Lyer-by-layer coating of chitosan–insulin–chitosan over nanoliposome, adopted from ref. 93 licensed under CC-BY 4.0.

PEGylated liposomes functionalized with vitamin B_{12} (cyanobalanin), to improve the stability of insulin in GI conditions and enhance their uptake into intestinal epithelial cells to facilitate transcytosis.[81] The functionalized liposomes were 154 nm in size, with a zeta potential of −11.2 mV, and had 63% EE% of insulin. By oral administration (100 IU per kg) to STZ-induced Wistar rats, the glucose level was reduced by 28% within 30 min, and the hypoglycemic effect persisted for 4 h. B_{12}-functionalized liposomes showed 12.4% relative bioavailability, which was 2.3 times higher than non-targeted liposomes with no toxicity on Caco-2 cells. *In vitro* results demonstrate the notable and effective potential of B_{12}-functionalized liposomes for oral insulin delivery.

In another study, Wu *et al.* developed the insulin encapsulated liposomes incorporated into alginate hydrogels to improve the oral bioavailability of insulin.[94] Prior to encapsulation in liposomes, insulin was first complexed with arginine (1 : 3 molar ratio) to enhance its permeability and make it water soluble. The produced liposomes loaded with arginine–insulin complexes (AINS) exhibited a particle size of 100–300 nm, a zeta potential of −22.8 mV, and an encapsulation efficiency (EE%) of 75.9%. AINS-Lip was then incorporated into cysteine-modified alginate hydrogel to enhance its adherence to the small intestine and boost resistance against gastric degradation. Compared to AINS-Lip (7% at 60 UI per kg) and free AINS (1%), the oral dose of AINS-Lip-Gel (40 IU per kg) in mice showed effective pharmacokinetics, lowering blood glucose level over a period of more than 12 hours while reaching a relative bioavailability of about 11% with increased intestinal penetration. Shafiq and colleagues fabricated insulin-encapsulated liposomes using camel milk fat globule membrane (MFGM) phospholipids and a thin-film hydration method.[95] The liposomes showed a particle size of 292.9 nm in the blank and 1294 nm in the insulin-encapsulated sample, and a zeta potential of −23.8 mV and −13.1 mV, respectively, which indicated successful encapsulation of insulin. *In vitro* study experiment indicated long-term insulin release (77.44% after 24 hours) and excellent biocompatibility (more than 90 percent viability in HEK-293 cells). Oral dose (40 IU per kg) showed a marked effect on lowering blood glucose level in diabetic rats ($p < 0.0001$), similar to subcutaneous insulin. Importantly, the biomarkers of liver dysfunction (ALP, ALT, and bilirubin; $p < 0.01$) were normalized, indicating restored liver function. The research highlights the use of camel MFGM as a source of natural phospholipids and a therapeutic accelerator that reduces the hepatotoxicity linked to diabetes while improving oral insulin absorption.

7.2. Metformin-encapsulated nanoliposomes

One of the first-line medications for the clinical management of type 2DM is metformin. To mitigate the limitations associated with metformin, it was loaded onto nanoliposomes. The results of various investigations have shown an increase in therapeutic impact. Notably, Hu *et al.* (2023) developed metformin-encapsulated liposomes modified with hyodeoxycholic acid (HDCA) to address its limited bioavailability and gastrointestinal degradation.[82] Nanoliposomes were fabricated using the thin-film dispersion technique, with lecithin as the primary phospholipid and HDCA serving as a bioactive stabilizer. Three formulations with different molar ratios of HDCA and metformin (0.5 : 1, 1 : 1, 2 : 1) were prepared. In addition to forming a structural element by acting as a structural component in place of cholesterol in the bilayer, HDCA serves as a glucose regulator. The HDCA : ME (1 : 1) formulation was the most effective when administered orally to STZ-induced type 2 diabetic mice. It increased glucose tolerance by 28.3%, exhibited sustained-release characteristics, and reduced fasting glucose by 37.8% after 21 days, a result that exceeded that of plain metformin by 5.2% (32.6% *vs.* 37.8%). Mechanistically, it decreased oxidative stress, improved insulin sensitivity, and raised GLP-1 secretion. Histopathology demonstrated reduced inflammation and necrosis in comparison to unmodified metformin, confirming the improved hepatoprotection.

7.3. Liposomes loaded with peptide-based antidiabetic agents

Incorporating other protocols to combat DM challenges, the fabrication of multivesicular liposomes loaded with liraglutide *via* a two-step water-in-oil-in-water double emulsification technique.[83] With a mean particle size of 6.69 μm, large MLVs showed a high EE% of approximately 82.23% for liraglutide. After a single subcutaneous administration to alloxin-induced diabetic Sprague–Dawley rats, large-MLVs produced a sustained drop in blood glucose level for 144 hours. The pharmacokinetic analysis demonstrated a 4.5-fold increase in relative bioavailability of large-MLVs compared to liraglutide solution and yielded an MRT_{0-t} of 88.224 ± 3.893 h and a C_{max} of 81.979 ± 12.140 pg mL^{-1}. All these findings suggest that MLV is a promising carrier that can be efficiently used to obtain sustained administration of liraglutide. Recently, Khopade and coworkers (2025) fabricated a liposomal hydrogel system loaded with human glucagon-like peptide-1 (HuGLP-1) for the management of type 2DM.[96] Nanoliposomes were developed using the ethanol injection technique, with a particle size of

179.2 nm and an entrapment efficiency of 47 ± 2.18%. Nanoliposomes were incorporated into a thermosensitive hydrogel, made of poloxamer 188 and poloxamer 407. HuGLP-1-NLs-loaded hydrogel administered sublingually in STZ-induced diabetic rats resulted in a sustained (24 hours) decrease in blood glucose and notable weight loss due to the gradual release of the drug.

7.4. Phytochemicals-loaded liposomes with antidiabetic potential

Phytochemicals such as flavonoids, stilbenes, isoflavones and ginsenosides have high antioxidant, anti-inflammatory and β-cell protective properties; however, limited clinical applications are due to its low bioavailability and poor solubility.[97] Key members of different phytochemical classes have been investigated by loading them over a variety of nano-carrier systems to enhance its bioavailability.[98] Therefore, different phytochemicals with antidiabetic potential were loaded over nanoliposomes to prevent the destruction of compounds in the gastrointestinal tract and allow prolonged release at disease cells. Flavonoid loaded liposomes exhibit some of the most significant enhancements. Equivalent, cyanidin and delphinidin loading formulation (approximately 94 nm; EE 85–89%) decreased the albumin glycation to 8–14% *versus* 30–46% in the free forms.[99] Silibinin liposomes (EE of around 96%) enhanced the structure of the pancreatic islet, lowered serum glucose and triglycerides levels, and lowered the level of inflammatory markers.[88] The COX-2; PGE2 and NF-κB activity were reduced successfully using quercetin liposomes (120 nm; EE 93%) or improved hepatic insulin resistance control.[87] There are other plant derived compounds which are also immensely benefiting in liposomal encapsulation. PEGylated liposomes of resveratrol (215–226 nm) offered antioxidant protection in 24 hours and increased the resistance of β-cells to hyperglycemic stress.[89,90] One of the greatest glycemic improvements was observed when using betanin-loaded liposomes (40 nm; EE% 80) that reduced glucose levels, elevated insulin levels, and boosted antioxidant enzyme activity, dropping glucose levels (approximately 375 mg dL^{-1}) to lower glucose levels (approximately 185 mg dL^{-1}).[84–86] The Daidzein liposomes (approximately 293 nm) enhanced the expression of GLUT2/GLUT4 and lipid profile and decreased the oxidative markers like iNOS.[100–103] The antioxidant and anti-inflammatory properties of polydatin liposomes were high with a diameter of 107 nm of loaded drug, which enhanced the hepatic and pancreatic integrity.[104–107] PEGylated gisenoside Rg3 liposomes (PEGylated liposomes, 140 nm) showed significant advantages among the bioactives with low inherent bioavailability in terms of glucose tolerance, β-cell reserve and peripheral insulin sensitivity.[108–110]

Together, the liposomal phytochemicals have presented a multimodal therapeutic benefit with glycemic control alongside antioxidant and anti-inflammatory properties with pancreatic tissue regeneration potential. Their functionality is determined by particle size, lipid content and surface changes like PEGylation. The future may involve co-delivery systems (*e.g.* phytochemicals with insulin), stimuli-responsive release systems and clinical scale formulation approaches to diabetic to take these promising nano-therapeutics to practical management. Some other salient studies are summarized in Table 2.

7.5. Translational gap between rodent models and human diabetic pathophysiology

Majority of liposomal-based antidiabetic campaign/reported in literature base on rodent-models. Significant gaps in translating rodent study to clinical practice need to be address. Such as in mice, liposomes tend to undergo rapid hepatic and splenic uptake and foreseeable clearance by the mononuclear phagocyte system but in humans biodistribution is much more diverse because of diverse metabolisms, vascular layout and disease burden.[112,113] This discrepancy adds to the reality that a negligible percentage of rodent-proven antidiabetic drug loaded liposomal compounds fail during patient trials. This highlights the significant variation in drug handling approach in rodent and human biological system and variation definitely a barrier in shifting from rodent to human.[114]

Furthermore, there is another issue is recognized with immune response and general diabetic pathophysiology. The immune responses of rodents particularly in NOD or STZ-induced diabetic models to lipid carriers are not as predictable as in humans, tend to be more tolerogenic or anti-inflammatory.[115,116] As an example, phosphatidylserine liposomes that carry insulin peptides can suppress autoimmunity in NOD mice, but remain unable to trigger activation thresholds of human immune cells and antigen-processing pathways.[117] Moreover, human diabetes is a multifaceted metabolic–immune interaction that cannot be perfectly recreated in rodent models in few days of developing diabetes. Therefore, although preclinical evidence is promising, translation of liposomal therapies in mice to human beings should be done with caution and better model systems that more closely mimic to human diabetic physiology. Some significant studies regarding the therapeutic agents loaded over nanoliposomes for the treatment of DM complications using animal models are given in Table 3.

8. Nanoliposomal formulation for the management of diabetic complications

Despite the potential of medication formulations involving nanoliposomes to regulate blood glucose levels, there is a rapid increase in their application to address various aspects linked to diabetes. Besides disrupting the insulin signaling pathways, chronic hyperglycemia leads to the progressive damage of multiple organ systems, with the most significant damage occurring to the kidneys, retina, and cardiovascular systems.[118] Recent advancement in the nanoliposomal formulations show strong therapeutic potential in managing diabetic complications beyond glycemic control, including cardiomyopathy, nephropathy, retinopathy, and neuropathy. They provide targeted drug delivery, enhance bioavailability, reduce oxidative stress, and improve tissue repair and remodeling. The following

Table 2 Liposome-encapsulated therapeutics in DM management

Sr no.	Therapeutic agent	Liposome preparation method	Liposomal composition and modifications	Particle size/zeta potential/EE%	Animal model	Therapeutic effect	References
1	Insulin	Reverse-phase evaporation	Lecithin, cholesterol (4 : 1 ratio)	202.4 nm/+6.7 mV/ 75.9%	Kunming mice	↓ Glucose level (85%), sustained hypoglycemic effect for 4 h, ↑ permeability and insulin absorption, 73% insulin retention after trypsin	79
2	Insulin	Reverse-phase evaporation/sonication	Biotinylated liposomes (lipid : cholesterol ratio 3 : 1, biotin-DSPE), chitosan-coated	153.7 ± 6.2 nm/78.3 ± 3.1%	Sprague–Dawley rats	↓ Blood glucose level, improved oral insulin bioavailability, sustained hypoglycemic effect, and enzymatic protection in the GI tract	80
3	Insulin	Thin-film hydration/ sonication + layer-by-layer proelectrolyte coating	Multilayered liposomes (polyacrylic acid + polyallyl amine hydrochloride), with folic acid	266 nm/+25.4 ± 2.6 mV/ 92.9 ± 1.4%	STZ-induced diabetic SD rats	Delayed and sustained glycemic control; ↓ hypoglycemic risk; ↑ intestinal permeability	91
4	Insulin	Thin-film hydration/ extrusion + freeze drying	Hydrogenated soya phosphatidylcholine (HSPC), cholesterol; $mPEG_{2000}$-DSPE, DSPE-PEG_{3400}-Folate	∼150–210 nm/−6.8 mV/ 60–75%	STZ-induced diabetic Wistar rats	↓ Blood glucose level within 4 h, sustained hypoglycemic effect for 24 h, 75% insulin retained in GI fluid	92
5	Insulin	Thin-film hydration/ extrusion + freeze drying	HSPC, cholesterol; DSPE-PEG_{2000}, DSPE-PEG_{3400}-B_{12}	153.6 ± 0.3 nm (100 nm filtered), 235.1 ± 2.2 nm (200 nm filtered)/−11.2 ± 3.4 mV/63 ± 2%	STZ-induced diabetic Wistar rats	↓ Glucose level 28% within 30 min, sustained hypoglycemia for 4 h, no cytotoxicity in Caco-2 cells, 12.4% relative bioavailability	81
6	Insulin (complexed with L-arginine)	Thin-film hydration/ extrusion	Phosphatidylethanolamine, cholesterol (3 : 1)	100–300 nm/−22.8 mV/ 75.9%	STZ-induced diabetic mice	Decreased glucose level, ↓ drug bioavailability, prolonged hypoglycemic effect up to 12 h	94
7	Insulin	Thin-film hydration	Phospholipids extracted from camel milk MFGM	1294 nm/−23.8 mv/34%	STZ-induced diabetic Wistar albino rats	Significant hypoglycemic effect, ↓ ALP, ALT, bilirubin	95
8	Metformin	Thin-film dispersion method	HDCA-based nanoliposomes (ratios: 0.5 : 1, 1 : 1, 2 : 1)	196.36–332.40 nm/ optimal EE at 1 : 1 ratio	STZ-induced type 2 diabetic Kunming mice	Enhanced glucose tolerance, ↓ hepatic oxidative stress, improved liver histology, and enhanced GLP-1 secretion	82
9	Liraglutide	Two-step water-in-oil-in-water double emulsification	Soybean phospholipids, cholesterol, triolein	6.69 μm/82.23 ± 4.78%	Alloxan-induced diabetic SD rats	Sustained reduction in glucose level for 144 h, no initial boost release, high relative bioavailability	83
10	HuGLP-1	Ethanol injection method	Soybean phosphatidylcholine (SPC), cholesterol (2 : 1)	179.2 ± 1.65 nm/47.27 ± 2.18%	STZ-induced diabetic SD rats	Significant weight loss, hepatic tissue recovery, sustained hypoglycemia for 24 h	96
11	Delphinidin & cyanidin (flavonoids)	Thin-film hydration followed by extrusion	Phosphatidylcholine & cholesterol, pH-neutral buffer	∼94 nm/EE: 89.05 ± 0.18% (delphinidin), 85 ± 0.15% (cyanidin)	Diabetic mice	Lower HbA1c, serum glucose, and cholesterol; improved glycogen storage in diabetic rats, delphinidin > cyanidin efficacy	99

Table 2 (*Contd.*)

Sr no.	Therapeutic agent	Liposome preparation method	Liposomal composition and modifications	Particle size/zeta potential/EE%	Animal model	Therapeutic effect	References
12	Silibinin	Thin-film hydration/ sonication	Phospholipon 90 G (phosphatidylcholine from soybean)	2024.7 ± 22.1 nm/ −26.2 ± 0.6 mV/96%	Nicotinamide/STZ-induced diabetic Wistar albino rats	↑ Insulin level, restored islet cell morphology; ↓ glucose, GlyHb, creatine levels	88
13	Quercetin	Thin-film hydration/ extrusion	Soybean L-*a*-phosphatidylcholine, cholesterol; DSPE- $mPEG_{2000}$ (8 : 1.5 : 0.5)	120 nm/93%	HePG2 cells (*in vitro* study)	↓ Oxidative stress enhanced insulin sensitivity. Suppressed inflammation	87
14	Resveratrol	Thin-film hydration	Dipalmitophosphatidylcholine (DPPC), cholesterol; DSPE-PEG_{2000}	226 nm/−45.3 ± 2.1 mV/EE not specified	STZ-induced diabetic	Increased insulin secretion; ↑ SOD, ↑ GSH-Px; reduced oxidative stress over 24 hours	89
15	Betanin	Thin-film hydration followed by sonication	Lecithin	40.06 ± 6.21 nm/ −17.04 ± 2.03 mV/EE ≈ 80.35 ± 1%	STZ-induced diabetic Wistar rats	Significant reduction in blood glucose level; ↑ insulin levels; reduced pancreatic and renal tissue damage, ↓ oxidative stress	86
16	Curcumin	Thin-film hydration	DPPC, cholesterol; PEG_{2000}-DSPE (9.5 : 1 : 0.5)	140 nm/−50 mV	STZ-induced diabetic Wistar–Bratislava rats	↑ Hypoglycemic activity, hepatoprotective effect, ↓ oxidative stress	111
17	Curcumin	Ethanol injection method	HSPC, cholesterol	124.3 nm/−22.9 mV	STZ-induced type 1 diabetic SD rats	↓ Blood glucose level, oxidative stress, and cellular inflammation	100
18	Daidzein	Simple dispersion method followed by sonication	Lecithin	293.0 ± 46.5 nm/ −27.22 mV	Alloxan-induced diabetic Balb/c mice	Improved cholesterol concentration, suppressed iNOS gene expression in the pancreas, and enhanced CAT gene expression	103
19	Polydatin	Membrane dispersion method	Lecithin, cholesterol; DSPE-PEG_{2000}	107.15 ± 5.43 nm/ −23.19 ± 0.18 mV/ 93.31 ± 1.86%	SD rats, C57bl/6 mice	↓ Blood sugar level, ↓ oxidative stress, repair damage to pancreas and spleen, improved weight loss in obese mice	107
20	Ginsenoside G-Rg3	Ethanol injection method/extrusion	Egg yolk phosphatidylcholine (ePC), cholesterol; DSPE-PEG_{2000}	140.5 ± 1.4 nm/−0.10 ± 0.05 mV/99.8%	STZ-induced diabetic C57BL/6 mice	Improved glucose tolerance and food intake, enhanced fasting insulin and insulin sensitivity index. Improve body weight	110

Table 3 Therapeutic agents loaded over nanoliposomes for the therapy of DM complications

Diabetic complication	Therapeutic agent	Nanoliposome details	Animal model	Administration route	Observed benefits	References
Cardiomyopathy	FGF1 (liposomes + UTMD)	Size: <100 nm; PDI < 0.15; EE: 73.52 ± 3.25%; zeta: −3.06 ± 0.01 mV	STZ-induced diabetic SD rats	IV + ultrasound	Heart protection, ↓ apoptosis & fibrosis	125
	NM-aFGF (PEG-liposomes + UTMD)	Size: 125 nm; EE: 87.9 ± 2.1%; zeta: −23.7 ± 1.1 mV	STZ-induced diabetic SD rats	IV + ultrasound	↓ Oxidative stress, ↓ fibrosis, preserved mitochondria	126
	Semaglutide (PEG-liposomes + UTMD)	Size: 109 nm; EE: 89 ± 1.5%; zeta: −12.82 mV	STZ-induced diabetic SD rats	Intravenous (IV) + ultrasound	↓ Blood glucose, ↑ heart function, ↓ fibrosis	127
	GFFs-liposomes	Size: 142 nm; EE: 82%; zeta: −3.8 mV	C57BL/6 STZ-induced diabetic mice	Intraperitoneal	↑ LVEF by 81.3%, ↑ LVIDs by 69.2%, ↓ cardiac fibrosis, ↓ cardiomyocyte apoptosis	128
Nephropathy	bFGF (liposomes + UTMD)	Size: 171 ± 14.2 nm; EE: 79.8 ± 2.6%; zeta: −5.15 ± 2.08 mV	STZ-induced SD rats	IV (tail vein) + ultrasound	↓ Kidney swelling, ↑ blood flow, ↓ and inflammation	135
	Quercetin (PEGylated liposome)	Size: ∼129 nm/EE: 87%	STZ-induced diabetic SD rats	Oral administration	Amelioration of diabetic nephropathy; reduced TNF-α, IL-1β, AGEs; ↓ kidney damage	136
	Calycosin (PEGylated liposome)	Size: 134 ± 21.44 nm; EE: 88.37%; zeta: −20.53 mV; DL: 7.48%; slow-release at pH 7.4; stable up to 2 months	STZ-induced diabetic SD rats	Intraperitoneal	↓ ROS, ↓ MDA, ↑ mitochondrial respiration, ↑ ATP, ↓ lipid peroxidation	137
Retinopathy	Naringenin-liposomes	Size: 148 to 215 nm; EE: 43% to 66%; zeta: 15 mV	Alpha-aminoadipic acid (α-AAA) induced retinopathy in the rabbit	Eye drops	↓ Neovascularization, ↓ retinal damage	148
	Curcumin (ozonated liposomes)	Size: 84.77 ± 0.7 nm; EE: 94.73 ± 0.66%; zeta: −16.8 mV	No animal (*in vitro* study)	Eye drops (intended)	Sustained drug release over 24 h	149
Neuropathy	Chrysin (PEGylated liposome)	Size: 134.6 ± 21.45 nm; EE: 90.48 ± 7.75%; zeta: −21.1 ± 1.72 mV	Alloxan-induced diabetic rats	Intraperitoneal injection	↓ Blood glucose level by 67.7%, ↑ 40% serum acetylcholinesterase levels, and inhibit sciatic nerve degeneration	158

subsection will outline the recent and effective developments in managing these complications.

8.1. Nanoliposomal therapies for treatment of diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is a severe and characteristic cardiac complication connected with DM that proceeds with the structural and functional changes of the myocardium without coronary artery disease, hypertension, or valvular pathology.[119,120] It occurs with diastolic and subsequent systolic malfunction, myocardial fibrosis, apoptosis and metabolic disproportion. In its persistent state, hyperglycemia leads to the induction of oxidative stress and inflammatory responses with the impairment of the mitochondrial activity in the heart, which contributes to the development of DCM.[121,122] More broadly, the term cardiomyopathy refers to diseases of the heart muscle that alter the efficiency of blood pumping. Insulin resistance, biosynthesis, and chronic hyperglycemia have a direct impact on cardiac cells during diabetes, causing cardiac cell death, impairing contractility, and promoting intestinal fibrosis.[123] The occurrence of these pathophysiological events causes heart failure.[124]

Nanoliposome-based drug delivery system has become an effective measure in managing the DCM by enhancing the accuracy and effectiveness of medical intervention. In a study, Zheng and co-workers used fibroblast growth factor-loaded nanoliposomes (FGF1-nlip) along with ultrasound targeted microbubble destruction (UTMD) using ultrasound examination to assess the cardioprotective effects of FGF1 on DCM.[125] Using the reverse phase evaporation process, nanoliposomes were created with a particle diameter of less than 100 nm and a polydispersity index of less than 0.15. Regular echocardiography and velocity vector imaging revealed a substantial improvement in LVEF and LVFS, confirming an enhancement of systolic function. Transmission electron microscopy and light microscopy demonstrated that the myocardium's perfusion and structural integrity were unaltered. Effectively transporting FGF1 to the myocardium, FGF1-nlip + UTMD therapy significantly reduced interstitial fibrosis and myocardial apoptosis. These therapeutic advantages were mechanistically linked to reduced oxidative stress and improved cardiac remodeling, primarily due to increased local bioavailability of FGF1 at the target site.

Furthermore, Zhang and co-workers employed non-mitogenic NM-aFGF-PEG-liposomes, along with UTMD, and observed significant cardioprotective outcomes in a diabetic rat model.[126] These loaded liposomes had a mean particle size of 125 ± 2.14 nm with an EE of $87.9 \pm 2.1\%$. Myocardial structure of diabetic rats significantly improved and the myocardium had less fibrosis, preserved the integrity of the mitochondria, and had diminished myofibrillar degeneration after 12 weeks of receiving NM-aFGF-PEG-lips with UTMD. These structural advantages were associated with lower levels of malondialdehyde (MDA) and higher levels of antioxidant enzymes (SOD, GSH-Px), indicating less oxidative stress. It was observed that the therapy worked by activating the AKT/GSK-3b/Nrf2 cascade, which strengthens the cell's defences and prevents fibrosis and apoptosis. This was further supported by a significant decrease in collagen volume percentage, as well as fibrosis markers such as TGF-beta 1 and collagen I and III levels. In another study, it was found that STZ-induced diabetic rats administered semaglutide-loaded PEGylated nanoliposomes (Sem-PEG-nlips) in combination with UTMD exhibited a significantly enhanced metabolic and cardiac profile.[127] With an average particle size of 108.9 nm and an EE of 89.1%, the Sem-PEG-nlips demonstrated targeted and prolonged administration. Compared with diabetic controls who were not treated, the combined treatment resulted in reduced fasting blood glucose and restored body weight. Echocardiography revealed a significant improvement in LVEF and fractional shortening, indicating improved cardiac systolic function. The involved molecular mechanism was the activation of the PI3K/Akt/Nrf2 pathway because of up-regulated expression of Nrf2, SOD2 and NQO1 proteins, which play an important role in response to oxidative stress.

Recently, Gao and colleagues studied the therapeutic role of Ginkgo Flavone Glycosides in treating DCM.[128] The results indicated that administration of GFFs encapsulated with nanoliposomes significantly improved cardiac performance in diabetic mice. Three variables were enhanced in the tested mice compared to the untreated diabetic mice: LVEF increased by 81.3%, LVIDs decreased by 69.2%, and LVIDd decreased by 56.1%. Histological studies demonstrated a significant reduction in cardiac fibrosis, and the TUNEL test indicated a considerable reduction in cardiomyocyte apoptosis. Mechanically, the cardioprotective effects of the defense were achieved through the activation of SIRT1, which inhibited TSPAN4 by deacetylating the transcription factor FOSL1, leading to elevated energy metabolism and autophagic homeostasis. Notably, liposomal encapsulation has increased the drug release to 72 hours, which is a potential advantage of liposomes as a selective and sustainable mode of drug delivery in the treatment of DCM.

8.2. Nanoliposomal therapies for treatment of diabetic nephropathy

Among the numerous microvascular disorders that DM can induce, diabetic nephropathy (DN), which primarily affects the kidneys, is the most common and severe.[129] It is characterized by albuminuria, a persistent decrease in glomerular filtration rate (GFR), and high blood pressure.[130] The primary factors influencing the development of DN include inflammation, oxidative stress, and hyperglycemia-induced activation of the renin-angiotensin-aldosterone system (RAAS).[131,132] When left untreated, structural changes, including the glomerular basal membrane's thickness, mesangial growth, and podocyte loss, result in end-stage renal disease (ESRD) and chronic kidney injury.[133,134] Another group utilized bFGF-loaded nanoliposomes (bFGF-nlips) combined with UTMD to enhance the therapeutic effects and targeted delivery of bFGF for the treatment of DN.[135] The developed nanoliposomes had a particle diameter of 171.1 nm with a zeta potential of −5.15 mV. STZ-induced DN rats were treated with bFGF-nlips with and without UTMD for eight weeks. The bFGF-nlip + UTMD group

showed significant improvement in the structure and functions of the kidney. A considerable decrease in kidney swelling was observed, which led to increased blood flow in the kidneys. The combined treatment resulted in a significant downregulation of NF-κB signalling in kidney tissues, subsequently decreasing the level of inflammatory cytokines.

Afterward, encapsulation of quercetin in PEGylated nanoliposomes showed encouraging therapeutic efficacy against STZ-induced DN rats.[136] These nanoliposomes were of 129 nm in size on average. According to pharmacokinetic investigations, nanoliposomal quercetin led to a significant improvement in fasting blood glucose levels, as well as a reduction in kidney hypertrophy. Additionally, nanoliposomal quercetin had increased the antioxidant proteins and decreased oxidative stress. A reduced morphological damage was observed in the histological analysis of kidney tissue, indicating the high renoprotective potential of Q-PEGL in managing DN.

In another study, Huang and co-workers synthesized calycosin-loaded liposomes to target mitochondrial dysfunction in diabetic kidneys.[137] PEGylated nanoliposomes had a particle size of 134 nm with a zeta potential of −20.53 mV. Pharmacokinetic studies revealed that nanoliposomal calycosin showed a much higher systemic exposure of nearly 2.3 times than that of the free drug formulation. The mean residence time and half-life ($t_{\frac{1}{2}}$) were also prolonged 1.54 and 1.33 times, respectively. In addition to their capacity to reduce active oxygen species (ROS), the results demonstrated that calycosin-loaded nanoliposomes improved the potential of mitochondrial membrane, restored the rate of oxygen consumption (OCR), and increased ATP production. Based on these finding, calycosin when administered *via* nanoliposomal delivery system, it effectively combats oxidative damage as well as increase cellular bio energy in kidneys in DN.

8.3. Nanoliposomal therapies for management of diabetic retinopathy

Diabetic retinopathy (DR) is an eye disorder characterized by retinal damage resulting from diabetes.[138] Long-term high blood glucose destroys the retina's small blood vessels, causing DR; however, the precise mechanism is unknown.[139,140] Increased retinal blood vessel permeability, changed retinal blood flow, and capillary cell death are all associated with the progression of DR and can all lower the amount of oxygen that reaches the retina.[141] DR is divided into two primary stages. In the first stage of diabetic eye disease, known as non-proliferative diabetic retinopathy (NPDR), small blood vessels weaken and leak, causing the retina to swell.[142] Improper oxygenation of tissues leads to the formation of new blood vessels across the retina, causing proliferative retinopathy (PDR).[143] These new vessels are prone to rupturing, which can result in retinal or macula injury, scarring, and internal bleeding.[144] According to recent data, inflammation and diabetic retinopathy are strongly correlated.[145,146] Nearly all diabetics have some degree of retinopathy. Although many novel medications and improved treatments are available to help people with diabetes, it remains one of the primary causes of sight loss and blindness worldwide.[147] In a study, Salimi and co-workers fabricated naringenin encapsulated nanoliposomes *via* the thin-film hydration technique and assessed their effect on α-AAA-induced DR in an albino rabbit model.[148] Liposomal naringenin had a particle size between 148 and 215 nm, with a zeta potential of 15 mV and an EE of 43% to 66%. After one hour of administration, two liposomal formulations demonstrated appropriate drug release of 5.5% and 3.1%, and after twenty-four hours, 72.93% and 52.01%. Histological findings showed that three liposomal naringenin doses, particularly 800 μg mL^{-1}, reduced retinal damage caused by α-AAA and demonstrated prevention of neovascularization. The results showed that liposomal naringenin might be a useful treatment for retinopathy that prevents neovascularization.

Furthermore, Kaydan and co-workers effectively created and described a curcumin-encapsulated ozonated nanoliposomal formulation for ocular medication delivery that targets DR in particular.[149] Nanoliposomes exhibited an EE of 94.7% and a particle size of 84.77 nm. The formulation demonstrated a cumulative release of 82.09% of curcumin over 24 hours. The formulation remained stable during three months at room temperature, as indicated by stability experiments, with only minor changes in key parameters. The antimicrobial properties of ozonated oil combined with the therapeutic advantages of curcumin provide a novel method for ocular drug delivery (ODD), overcoming the difficulties caused by curcumin's low bioavailability and solubility. Curcumin administration using the ozonated liposomes shows promising properties that could increase the medication's therapeutic effectiveness in ocular applications.

8.4. Nanoliposomal therapies for management of diabetic neuropathy

Diabetic neuropathy (DN) is a severe complication of DM, affecting over 50% of diabetic individuals.[150–152] DN is characterized by gradual nerve damage due to prolonged hyperglycemia.[153] The nerves in the hands and feet are primarily affected, resulting in muscle weakness, tingling, pain, numbness, and foot ulcers, which lower the quality of life for affected individuals.[154,155] It is diagnosed following the exclusion of other sources of nerve damage and, in some cases, can be asymptomatic. The most prevalent one is peripheral neuropathy, which usually affects the feet and legs. The core causes include metabolic changes in the body, such as inflammation, mitochondrial dysfunction, and oxidative stress, which impair nerve functions.[156] The primary goals of controlling diabetes involve maintaining blood sugar levels within normal ranges and managing symptoms.[157] Development of PEGylated nanoliposomes loaded with Chrysin (Chr-PLs), a natural flavonoid, revealed 134 nm in size with an EE of 90.48% showing sound development in controlling DN.[158] By intraperitoneal administration, Chr-PLs effectively raised serum acetylcholinesterase levels by 40% and lowered blood glucose levels by 67.7%. Furthermore, Chr-PLs suppressed the expression of genes linked to endoplasmic reticulum stress. Additionally, Chr-PLs increased the sciatic nerve's autophagic marker expression

and prevented sciatic nerve degeneration, according to the histological examination. According to the results, Chr-PLs may help guard against DN *via* regulating autophagy and endoplasmic reticulum stress.

9. Barriers to clinical translation and future perspective

Although nanoliposomes-based diabetes treatment has shown good preclinical results, there are various challenges to translating the therapy into clinical application. One significant issue, as mentioned in previous section is the uncertainty of *in vivo* behavior because biodistribution, and pharmacokinetics in rodents do not necessarily mirror in humans. Differences in the architecture of the vascular system, immune surveillance, metabolic rate, and progression of end-organ disease in species make it difficult to predict the outcome of drug administration and pharmacokinetics. Also, immunological reactions of lipid carrier differ greatly between species, liposomes that are tolerogenic or anti-inflammatory in rodents may induce alternative activation patterns in human immune responses, making therapeutic responses less predictable. Besides, more disease-relevant models, including humanized mice, organoids, and microfluidic systems on diabetes on a chip, are required to better reflect the human diabetic pathophysiology and interactions of lipid-nanocarriers. Other critical issues might be the production under Good Manufacturing Practice (GMP) conditions, stability and reproducibility.

Secondly, there should be the creation of stimulus responsive liposomes, co-delivery systems to deliver synergistic therapy and customized nanomedicine systems as determined by patient metabolic and immunological phenotype. Finally, the translation of clinical research will rely on the ability to make rodents models mimic to human system, scale manufacturing optimally, and implement standardized test systems. The three stakeholders, academia, industry, and regulatory agencies, need to collaborate with each other to hasten the safe and effective translation of nanoliposome-based antidiabetic therapies into clinical practice.

10. Conclusion

The nanoliposome drug delivery system uses the encapsulation of various forms of therapeutic agents such as synthetic drugs, peptides and phytochemicals. The strategy has greatly enhanced the treatment of diabetes through increased drug bioavailability, controlled release of the therapeutic agents and precisely targeting the disease cells. Therefore, glycemia and complications of diabetes could be managed by loading wide array of synthetic drugs, synthetic molecules and phytochemicals. Further, beyond glycemic regulation, nanoliposome loaded antidiabetic therapeutic utility has expanded toward addressing diabetic complications such as cardiomyopathy, nephropathy, retinopathy, and neuropathy. However, it requires intense research in the area of nanoliposomes, focusing on drug stability, efficacy, controlling oxidative stress, inflammation, and apoptosis. Under the light of reported studies, nanoliposomal formulations significantly improve therapeutic outcomes while minimizing systemic toxicity. Presently, a huge number of published reports on the incorporation of antidiabetic phytochemicals further broadens their therapeutic potential and multi-targeted interference in DM and its complications.

Furthermore, co-delivery of various drugs into a single nanoliposome might provide a more feasible way of dealing with the complexity of DM. It can also withstand GI breakdown, which consequently enhances the bioavailability of insulin and improves patient compliance. According to recent breakthrough studies, it is possible that nanoliposomes can be combined with gene editing technology and personalized medicine to create new potential treatments for insulin resistance reversal or pancreatic beta cell regeneration. Recent developments indicate that personalized medicine methods based on genetic causes of diabetes might be made possible by integration with gene editing technology, including CRISPR-Cas9. This would be done experimentally through development of nanoliposome-based vectors that give high delivery efficiency, tissue specificity and safety *in vivo*. Conclusively, though the existing developments in gene-editing technologies are still reinforcing their association with the personalized medicine, further developments will require well-outlined experimental pathways and multidisciplinary approaches. However, *in vitro* and *in vivo* experiments should be conducted specifically to confirm the accuracy of editing, long-term genomic stability and treatment of specific patients in using human model. It would only be possible to strengthen interdisciplinary collaboration among the molecular biologists, clinicians, bioinformaticians, and biomedical engineers. Such combined strategy will not only sharpen the clinical usefulness of gene editing but also help in translating the agents from rodents to human within due time frame.

Conflicts of interest

All the authors declare no conflict of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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