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Lipid-based nanoparticle delivery system approach for diabetic wounds: A review

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ARTICLEINFO

Article history:

Received Oct 23, 2025
Revised Oct 30, 2025
Accepted Nov 5, 2025

Keywords:

Bioavailability
Diabetic Wounds
Drug Delivery System
Lipid Nanoparticles
Transdermal

ABSTRACT

Diabetic wounds are a chronic complication that is difficult to heal due to impaired blood circulation, oxidative stress, and microbial infection. Conventional therapies are often ineffective due to poor drug penetration into damaged skin tissue and limited bioavailability of active compounds. Lipid nanoparticle-based drug delivery technology was developed to overcome these obstacles by increasing stability, skin penetration ability, and controlled drug release. Objective: This article aims to comprehensively review the role of lipid-based nanoparticle delivery systems in improving the effectiveness of diabetic wound healing therapy, including the mechanisms of absorption enhancement, active substance stability, and pharmacological activity. Methods: This study is a systematic literature review of national and international publications over the past ten years (2015–2025). Data sources were obtained from PubMed, ScienceDirect, and Google Scholar databases using keywords "lipid nanoparticles," "diabetic wound healing," and "transdermal drug delivery." Inclusion criteria included experimental studies and review articles discussing lipid nanoparticle formulations and their therapeutic effects on diabetic wounds. Results: Various studies have shown that lipid-based nanoparticle systems, including nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs), can improve the stability and permeation of active ingredients such as curcumin, asiatic acid, and other herbal extracts through the skin. This improvement contributes to better anti-inflammatory, antioxidant, and antibacterial activities, thereby accelerating the healing process of diabetic wounds. Conclusion: Lipid-based nanoparticle technology offers an innovative approach to diabetic wound therapy by improving the stability, bioavailability, and effectiveness of active ingredients. Further development is needed for formulation optimization and clinical validation to ensure the safety and effectiveness of its use in diabetic patients.

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INTRODUCTION

Diabetic wounds are a common chronic complication in people with diabetes mellitus and pose a serious problem in wound care. This condition is caused by impaired blood flow, oxidative stress, neuropathy, and microbial infections, which inhibit the healing process (Akkus and Sert 2022). Various conventional therapies have been used to accelerate wound healing, such as topical antibiotics, growth factors, and modern wound dressings. However, their effectiveness is often limited by poor skin tissue penetration, poor drug stability, and low bioavailability of the active ingredient at the wound site (Kolimi et al. 2022). These challenges cause the healing process to be slow and increase the risk of amputation (Luo et al. 2024).

In recent years, the use of herbal ingredients as wound healing agents has received great attention due to their bioactive compounds such as flavonoids, tannins, curcumin, and terpenoids which have antioxidant, anti-inflammatory, and antimicrobial activities (Cedillo-Cortezano et al. 2024). Despite their great potential, the clinical use of herbal ingredients is often hampered by limited solubility, rapid degradation, and the inability to penetrate the skin layer effectively (Alkilani et al. 2022). To address this issue, a modern lipid nanoparticle-based drug delivery system was developed as an innovative approach to increase the effectiveness of herbal therapy for diabetic wounds (Ezhilarasu et al. 2020). Lipid nanoparticle systems, including Solid Lipid Nanoparticle (SLN) and Nanostructured Lipid Carrier (NLC), play an important role in protecting active compounds from degradation, increasing solubility, and regulating drug release gradually (Chauhan et al. 2020). Lipid carriers such as stearic acid, glyceryl monostearate, and biocompatible surfactants allow for increased transdermal penetration, allowing active ingredients to reach wound tissue more efficiently (Araújo et al. 2023). Various studies have reported that NLC formulations based on curcumin and other phytochemical compounds can improve wound healing activity by increasing collagen production, reducing inflammation, and having higher antibacterial activity compared to conventional preparations (Kumari et al. 2022).

Although research results show promising prospects, several challenges remain in developing this technology. Factors such as particle size, dispersion homogeneity, adsorption efficiency, and system stability during storage are important aspects that need to be optimized (Farooq et al. 2025). In addition, most studies are still limited to the in vitro and in vivo stages in test animals, so further clinical trials are needed to ensure their safety, effectiveness, and biocompatibility in humans (Van Norman 2019). The current research direction is starting to focus on the development of more sophisticated NLC formulations by utilizing biodegradable lipids, natural surfactants, and the integration of transdermal technologies such as microneedles or iontophoresis to increase drug penetration (Lok et al. 2025). In addition, combination approaches with natural polymers or nano-hybrid systems are also being developed to achieve more precise and sustained drug release (Bamisaye et al. 2025)The use of lipid nanoparticle technology is also in line with the principles of green pharmaceutics, which emphasize safety, efficiency, and sustainability in the use of natural materials for the development of modern therapies (Ijjeh et al. 2025). This review will comprehensively discuss the role of lipid-based nanoparticle delivery systems in diabetic wound therapy, covering the basic principles of lipid nanoparticle technology, mechanisms for enhancing bioavailability, examples of applications of herbal active ingredients such as curcumin, as well as challenges and future development directions. Through this in-depth understanding, it is hoped that lipid nanoparticle technology can become a strategic innovation in increasing the effectiveness and safety of natural-based diabetic wound therapy in a scientific and sustainable manner.

RESEARCH METHOD

The method used in compiling this review article is a narrative synthesis approach, which is compiled based on the results of a literature review of various national and international scientific

publications over the past ten years (2015–2025). This literature review aims to collect, compare, and comprehensively analyze data related to the application of lipid-based nanoparticle delivery systems in diabetic wound therapy, including the mechanisms of increasing bioavailability, stability of active substances, transdermal effectiveness, and challenges in its development.

The literature search process was carried out systematically using several scientific databases, namely PubMed, ScienceDirect, and Google Scholar. Keywords used in the search included "lipid nanoparticles," "nanostructured lipid carrier," "solid lipid nanoparticles," "transdermal drug delivery," "curcumin wound healing," and "diabetic wound therapy." Inclusion criteria were set for articles that specifically discussed natural-based lipid nanoparticle formulations and their application in diabetic wound healing, either through in vitro or in vivo tests, or review studies that assessed the comparative effectiveness between conventional and lipid nanoparticle forms.

The screening results yielded 56 relevant articles discussing experimental research and reviewing the formulation principles and prospects of lipid nanoparticle delivery technology. All collected data were analyzed descriptively and comparatively, focusing on formulation parameters such as particle size, entrapment efficiency, physicochemical stability, and therapeutic effectiveness in accelerating diabetic wound healing. The analysis results were then synthesized to provide a comprehensive overview of the role of lipid-based nanoparticle systems as an innovative transdermal drug delivery system in the treatment of diabetic wounds, while also identifying future research development directions.

RESULTS AND DISCUSSIONS

Diabetic Wounds and Challenges in the Healing Process

Diabetic wounds are a chronic complication of diabetes mellitus characterized by impaired healing due to decreased vascularization, peripheral neuropathy, oxidative stress, and difficult-to-control microbial infections (Dasari et al. 2021). Chronic hyperglycemia causes endothelial damage and reduced tissue oxygen supply, which slows the inflammatory and proliferative phases of wound healing. As a result, wounds become difficult to close, prone to infection, and carry a high risk of lower extremity amputation if not optimally managed (Mieczkowski et al. 2022).

The diabetic wound healing process consists of four main phases: hemostasis, inflammation, proliferation, and remodeling. In diabetic patients, immune cell dysfunction and decreased collagen production occur, resulting in a longer inflammatory phase and a delayed proliferative phase (Yan et al. 2024). Furthermore, high levels of ROS (Reactive Oxygen Species) in diabetic wounds exacerbate tissue damage and slow skin cell regeneration. Therefore, diabetic wound management requires a strategy that simultaneously balances the immune response and enhances tissue regeneration (Sun et al. 2024).

Conventional therapies such as topical antibiotics, wound dressings, and growth factors still have limitations, particularly in terms of drug penetration into deep skin tissues. Many active drugs cannot effectively penetrate the stratum corneum, resulting in inadequate therapeutic concentrations (Saghazadeh et al. 2018). Therefore, a drug delivery system is needed that can increase penetration, stability, and controlled release of active ingredients to accelerate the healing process of diabetic wounds (Yadav et al. 2025).

Basic Concepts of Lipid-Based Nanoparticles

Lipid-based nanoparticles are a modern drug delivery system consisting of solid and/or liquid lipid materials measuring 50–500 nm (Mehta et al. 2023). This system includes two main types, namely Solid Lipid Nanoparticle (SLN) and Nanostructured Lipid Carrier (NLC). SLN uses solid lipid as the matrix (Jafar et al. 2025), while NLC is a development of SLN which combines solid lipids with liquid lipids to increase drug absorption capacity and physical stability (Jafar et al. 2022).

The main advantages of lipid nanoparticles are their ability to protect active compounds from degradation, increase the solubility of lipophilic compounds, and enable gradual drug release (Jafar et al. 2024). In addition, the lipids used are biocompatible and biodegradable, making them safe for topical and transdermal applications (Hmingthansanga et al. 2022). This system is also able to increase drug retention in the skin and optimize the penetration of active substances into the epidermis and dermis layers without causing irritation (Zaid Alkilani et al. 2015).

Commonly used lipid materials include stearic acid, cetyl palmitate, glyceryl monostearate, and surfactants such as Tween 80 or poloxamer. These combinations form amorphous or semi-crystalline structures that can encapsulate drugs with high efficiency (Mall et al. 2024). These characteristics make the lipid nanoparticle system very potential for the delivery of active herbal compounds that are sensitive to light, oxygen or high temperatures (Jacob et al. 2025).

Table 1. Types of lipid-based nanoparticles

Types of Lipid-Based Nanoparticles	Main Components	Excess	Lack	Application / Drug Examples	Reference
Liposome	Phospholipids, cholesterol	Can encapsulate hydrophilic & lipophilic drugs; biocompatible	Low stability, easy to leak	Doxorubicin (Doxil®), AmBisome®	(Liu et al. 2022)
Solid Lipid Nanoparticle(SLN)	Solid lipids (triglycerides, fatty acids), surfactants	High stability, controlled release	Limited load capacity, possibility of re-crystallization	Paclitaxel-SLN, Curcumin-SLN	(Akanda et al. 2023)
Nanostructured Lipid Carrier(NLC)	Mixture of solid and liquid lipids	High drug loading, prevents crystallization	Complex manufacturing process	Ketoconazole-NLC, Retinol-NLC	(Jafar et al. 2025)
Lipid-Polymer Hybrid Nanoparticles(LPHN)	Polymer core, lipid layer	High stability, controlled release	More complicated synthesis	Insulin-LPHN, Docetaxel-LPHN	(Mukherjee et al. 2019)
Nanoemulsion(NE)	Oil, surfactant, cosurfactant, water	Transparent, increased solubility	Less stable against temperature & time	Vitamin E-NE, Curcumin-NE	(Mushtaq et al. 2023)
Self-Nanoemulsifying Drug Delivery System(SNEDDS)	Oil, surfactant, cosurfactant	Increase oral bioavailability	Limited to lipophilic drugs	Cyclosporine (Neoral®), Ritonavir	(Buya et al. 2020)
Lipid Micelles / Mixed Micelles	Phospholipids, nonionic surfactants	Small size, increases the solubility of lipophilic drugs	Less suitable for hydrophilic drugs	Paclitaxel micelle (Genexol-PM®)	(Negut and Bita 2023)

Liposome

A liposome is a spherical vesicle composed of one or more phospholipid bilayers surrounding an aqueous core. The lipid bilayer structure allows liposomes to encapsulate both hydrophilic (in the aqueous core) and lipophilic (in the lipid layer) drugs. Due to their similarity in composition to cell membranes, liposomes have high biocompatibility and biodegradability, making them safe for use as delivery systems for drugs, vaccines, and genes (Nsairat et al. 2022).

The main advantage of liposomes is their ability to increase drug solubility, stability, and bioavailability, as well as reduce toxicity through targeted delivery to target tissues. However, liposomes also have limitations such as low physical stability, susceptibility to drug leakage, and high production costs. To overcome these limitations, various modifications such as pegylated liposomes (e.g., Doxil®) have been developed to extend circulation time in the body and improve drug delivery efficiency (Chelliah et al. 2025).

Solid Lipid Nanoparticle (SLN)

Solid Lipid Nanoparticle(SLN) is a drug delivery system composed of solid lipids at room temperature stabilized by a surfactant. The solid lipid core serves as a matrix in which drug molecules are dispersed, either dissolved or trapped. Because it is based on natural or physiological lipids, SLN is safe, biocompatible, and can protect drugs from chemical or enzymatic degradation (López et al. 2023).

The advantage of SLNs lies in their ability to control drug release and improve dosage form stability compared to liposomes or liquid emulsions. However, their limitations include low drug loading capacity and the potential for lipid re-crystallization during storage, which can lead to premature drug release. To address this, a more flexible derivative system, the Nanostructured Lipid Carrier (NLC), has been developed (Pandey et al. 2021).

Nanostructured Lipid Carrier (NLC)

NLC is a second-generation SLN system that combines solid and liquid lipids in a single nanoparticle matrix. This irregular structure prevents the formation of perfect crystals in the lipid phase, allowing for greater and more stable drug loading. This combination also enhances the solubility of lipophilic drugs and prolongs drug release time (Viegas et al. 2023).

The advantages of NLCs include higher drug loading capacity, better physical stability, and the ability to prevent uncontrolled drug release. This system is widely applied in topical, oral, and parenteral formulations for the delivery of antifungal, antioxidant, and anti-inflammatory drugs. The main challenges in its development lie in optimizing the proportion of solid and liquid lipids and controlling particle size during the emulsification process (Costa et al. 2025).

Lipid-Polymer Hybrid Nanoparticles (LPHN)

Lipid-Polymer Hybrid Nanoparticles(LPHN) is a drug delivery system that combines the advantages of two worlds: the stability and mechanical strength of polymers and the biocompatibility of lipids. Typically, LPHNs consist of a drug-carrying polymer core and are coated by a lipid layer to enhance interaction with biological membranes. This hybrid structure allows better control of drug release and protection against drug degradation in the biological environment (Hassan et al. 2025).

The advantages of LPHN lie in its flexibility in encapsulating various types of drugs, both hydrophilic and lipophilic, and its ability to penetrate biological membranes. This system is also stable during long-term storage and suitable for gene or protein delivery. However, the synthesis process is more complex and requires careful optimization in the selection of polymers and lipids to maintain formulation stability and entrapment efficiency (Gajbhiye et al. 2023).

Nanoemulsion (NE)

A nanoemulsion is a colloidal dispersion system between two immiscible phases (usually oil and water) with a droplet size of 20–200 nm. Its stability is maintained by surfactants and cosurfactants that lower interfacial tension. Due to their extremely small size, nanoemulsions have high transparency and a large surface area, which allows for increased solubility and absorption of lipophilic drugs (Kumar et al. 2025).

Nanoemulsions are widely used in oral, topical, and parenteral formulations because they increase drug bioavailability and onset of action. Other advantages include good kinetic stability and ease of preparation. However, nanoemulsions tend to be sensitive to changes in temperature and pH, and have a risk of droplet coalescence if stored suboptimally. Therefore, formulations must pay attention to the ratio of oil, surfactant, and water to maintain system stability (Chatzidaki and Mitsou 2025).

Self-Nanoemulsifying Drug Delivery System (SNEDDS)

SNEDDS is a lipid-based drug delivery system that spontaneously forms nanoemulsions upon contact with gastrointestinal fluids. This system consists of a mixture of oil, surfactants, and

cosurfactants that can dissolve lipophilic drugs in liquid dosage forms or soft capsules. When ingested, SNEDDS increases drug solubility and facilitates absorption via the lymph, thereby avoiding first-pass metabolism in the liver (Buya et al. 2020).

The main advantage of SNEDDS is its ability to increase the oral bioavailability of highly water-soluble drugs, such as cyclosporine and ritonavir. Furthermore, this system is easy to prepare and has high reproducibility. However, SNEDDS formulations require careful selection of surfactants to avoid gastrointestinal irritation and maintain stability during storage (Baloch et al. 2019).

Lipid Micelles / Mixed Micelles

Lipid micelles are spherical structures that spontaneously form from amphiphilic molecules such as phospholipids or surfactants in water, with a hydrophobic interior and a hydrophilic exterior. These structures are capable of solubilizing lipophilic drugs within their core, thereby increasing the solubility and bioavailability of water-insoluble drugs. Mixed micelles are a combination of two or more surfactants to stabilize the system and improve drug-loading capacity (Lombardo and Kiselev 2022).

The advantages of lipid micelles are their very small particle size (typically <100 nm), biocompatibility, and easy absorption by body tissues. This system is suitable for the delivery of anticancer or hydrophobic therapeutic agents, such as paclitaxel. However, its disadvantages include low stability upon dilution and limited drug loading. Therefore, mixed micelle formulations are often developed to improve the stability and effectiveness of drug delivery (Negut and Bita 2023).

Transdermal Absorption and Delivery Mechanisms

The skin layer, especially the stratum corneum, is a major barrier to topical and transdermal drug delivery. Lipid nanoparticle systems are designed to penetrate this barrier through passive diffusion, lipid fusion with the skin layer, and increased fluidity of the epidermal lipid membrane. The lipid nanoparticle structure, which mimics the natural lipid structure of the skin, facilitates better interaction and penetration into the tissue (Akombaetwa et al. 2023).

Once applied to the skin's surface, nanoparticles form an occlusive layer that reduces transepidermal water loss. This improves skin hydration, widens the gaps between corneocytes, and facilitates drug penetration into deeper tissues. Furthermore, the small particle size allows for even distribution across the wound area and accelerates the absorption of active ingredients into the growing granulation tissue (Liu et al. 2023).

In diabetic wounds, this increased penetration is crucial because impaired blood circulation often hinders systemic drug delivery to the wound site. With a lipid nanoparticle-based transdermal delivery system, drugs can work directly in the target area with optimal concentration and minimal side effects. This makes the transdermal approach an effective solution for local therapy in patients with chronic diabetic wounds (Ezhilarasu et al. 2020).

The Role of Lipid Nanoparticles in Increasing the Bioavailability and Stability of Active Ingredients

One of the main challenges in using herbal ingredients like curcumin is its poor solubility and stability against light and oxidation. The use of lipid nanoparticle systems can overcome these challenges through an encapsulation mechanism that protects the active compound from chemical degradation and the external environment (Yan et al. 2025).

In NLC systems, the combination of solid and liquid lipids forms an irregular matrix that can accommodate more drug in a dispersed form. This structure minimizes the risk of drug crystallization and allows for more stable release of the active ingredient over a longer period. This effect has been shown to increase the bioavailability of curcumin severalfold compared to conventional forms, both in oral and topical applications (Rahman et al. 2024).

In addition, lipid nanoparticles can extend the retention time of drugs on the skin surface and in wound tissues. This increased drug retention time provides a longer therapeutic effect, allowing for reduced frequency of administration. Thus, lipid nanoparticle systems not only improve the stability and bioavailability of active substances, but also improve patient comfort and compliance with therapy (Akombaetwa et al. 2023).

Pharmacological Activity of Herbal Active Substances in Diabetic Wound Therapy

Various herbal bioactive compounds have been shown to accelerate the healing of diabetic wounds, including curcumin, asiatic acid, flavonoids from Centella asiatica extract, and tannins from bay leaf extract. These compounds possess antioxidant activity that can neutralize free radicals and reduce oxidative stress in wound tissue (Hein et al. 2025).

In addition to their antioxidant activity, curcumin and flavonoids also have significant anti-inflammatory effects by suppressing the production of proinflammatory cytokines such as TNF-α and IL-6. This reduction in inflammation is essential for shortening the inflammatory phase and accelerating the transition to the proliferative phase. Furthermore, the antibacterial activity of polyphenolic compounds helps prevent secondary infections that often worsen diabetic wounds (Kubatka et al. 2021).

In lipid nanoparticle form, this herbal compound exhibits stronger biological activity than conventional forms. This is due to improved penetration, controlled release, and drug retention in wound tissue. Several studies have reported that curcumin-based NLC gels can significantly increase re-epithelialization, collagen formation, and new blood vessel density compared to conventional gels (Kumari et al. 2022).

Formulation and Characterization of Lipid Nanoparticle Systems

Lipid nanoparticle formulation processes generally involve high shear homogenization, ultrasonication, or microemulsion techniques. The choice of method depends on the nature of the drug, the type of lipid, and the intended application. Important formulation parameters include particle size, polydispersity index (PDI), zeta potential, drug entrapment efficiency, and physicochemical stability (Ashfaq et al. 2023).

System characterization was performed using various techniques, such as Dynamic Light Scattering (DLS) to measure particle size, Transmission Electron Microscopy (TEM) to observe morphology, and Differential Scanning Calorimetry (DSC) to evaluate lipid crystallinity. These characterization results help determine formulation stability and drug delivery effectiveness (Jafar et al. 2025).

In the context of diabetic wound therapy, NLC gel formulations with a particle size of 100–200 nm and a negative zeta potential have been shown to provide uniform distribution and optimal penetration. Good physical stability also ensures gradual and consistent drug release during topical application (Septianti et al. 2025).

Challenges and Directions for Future Development

Although lipid nanoparticle technology shows great potential in the treatment of diabetic wounds, several challenges remain to be overcome. One is the stability of the system during long-term storage, which can be affected by temperature and humidity. Furthermore, the interaction between lipids and the active drug needs to be optimized to avoid disrupting the particle structure and drug release efficiency (Mall et al. 2024).

Another aspect that needs to be considered is the safety of using lipid carriers and surfactants on damaged skin. Some synthetic surfactants can cause irritation when used in high concentrations. Therefore, recent research trends are shifting to the use of natural surfactants and biodegradable lipids, which are safer and more environmentally friendly (Ramadon et al. 2022).

The development of lipid nanoparticle delivery systems can be directed at integrating smart delivery technologies, such as those responsive to pH, temperature, or wound enzymes. Furthermore, large-scale clinical trials are needed to demonstrate the effectiveness and safety of

lipid nanoparticle-based transdermal applications in diabetic wound patients. This approach is expected to be an effective, safe, and sustainable therapeutic solution in chronic wound care (Wang et al. 2024).

CONCLUSION

Based on the literature review, it can be concluded that a lipid-based nanoparticle delivery system is a highly promising innovative approach to improving the effectiveness of diabetic wound therapy. This technology can overcome various limitations of herbal active ingredients, such as low solubility, stability that is susceptible to degradation, and limited bioavailability. Through particle size optimization, appropriate lipid and surfactant selection, and controlled drug release mechanisms, lipid nanoparticles can enhance transdermal penetration, extend drug retention time in wound tissue, and enhance the pharmacodynamic effects of active compounds such as curcumin and flavonoids.

Various studies have shown that NLC or SLN gel formulations based on curcumin and other herbal compounds can enhance anti-inflammatory, antioxidant, and antibacterial activity, as well as accelerate re-epithelialization and collagen formation in diabetic wounds. This confirms that lipid nanoparticles not only maintain the stability of active ingredients but also significantly increase bioavailability and therapeutic efficacy. Going forward, the development of biodegradable lipid-based formulations and smart delivery strategies will be a key focus for creating safer, more effective, and clinically standardized diabetic wound therapies.

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