Nano Nexus & Applications

www.nna.reapress.com

Nano. Nex. App. Vol. 1, No. 1 (2026) 58–66.

Paper Type: Original Article

Development and Optimization of Glipizide Nanoliposomes for Enhanced Oral Delivery

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Citation:

Received: 12 May 2025 *Revised: 23 July 2025* *Accepted: 14 September 2025*	Pourqasem, M. (2026). Development and optimization of glipizide nanoliposomes for enhanced oral delivery. *Nano nexus & applications, 1*(1), 58-66.

Abstract

Glipizide is a sulfonylurea drug widely prescribed for the management of type II diabetes; however, its therapeutic efficiency is limited by significant degradation in the acidic gastric environment, resulting in reduced bioavailability. To address this limitation, glipizide-loaded nanoliposomes were prepared using the thin-film hydration method. A time-variant optimization strategy was applied to evaluate the influence of formulation parameters, including the lecithin-to-cholesterol ratio, the organic-to-aqueous solvent ratio, and the duration of liposome formation. The optimized values for these parameters were determined to be 7:1, 4:1, and 2 hours and 20 minutes, respectively, yielding an Encapsulation Efficiency (EE) of 90.12%. Particle size and morphology were examined using Scanning Electron Microscopy (SEM). The resulting nanoliposomes exhibited a uniform spherical shape with particle diameters ranging from 50 to 95 nm and a mean size of approximately 82 nm, indicating successful formation of nanoscale vesicles suitable for drug delivery applications. The nanosized structure is expected to enhance mucosal interaction and improve intestinal transport. Stability assessments performed at physiological pH (7.4) demonstrated a marked increase in the structural and chemical stability of glipizide following encapsulation. This improvement highlights the liposomal membrane's protective role against premature degradation in the gastrointestinal environment. Overall, the findings suggest that liposomal encapsulation provides an effective strategy to enhance the stability and potential oral bioavailability of glipizide. The optimized nanocarrier system developed in this study represents a promising platform for the controlled delivery of hydrophilic antidiabetic agents. It may contribute to improved therapeutic outcomes in future pharmaceutical formulations.

Keywords: Diabetes type II, Glipizide, Encapsulation percentage, Nanoliposome.

1 | Introduction

Type II Diabetes Mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance, impaired pancreatic β-cell function, and chronic hyperglycemia. It represents one of the major global health challenges, with increasing prevalence due to sedentary lifestyles, obesity, and aging populations [1]. Glipizide,

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https://doi.org/10.48314/nna.vi.62

a sulfonylurea drug, is widely prescribed as first-line therapy for patients with type II diabetes due to its ability to stimulate insulin secretion from pancreatic β-cells and lower blood glucose levels [2]. Despite its clinical efficacy, glipizide exhibits limited oral bioavailability and undergoes significant degradation in the acidic gastric environment, which reduces its therapeutic potential [3], [4]. Moreover, the short biological half-life and hydrophilic nature of glipizide often necessitate repeated dosing, which may lead to gastrointestinal side effects and reduced patient compliance [5], [6].

Recent advances in drug delivery strategies have highlighted the importance of modifying glipizide's pharmacokinetic profile to enhance its stability, bioavailability, and patient adherence. Among these strategies, nanocarrier-based delivery systems, particularly liposomes, offer a promising approach to improve the stability, solubility, and controlled release of hydrophilic drugs such as glipizide [7]. Liposomes are biocompatible phospholipid vesicles that can encapsulate both hydrophilic and hydrophobic molecules, thereby protecting active agents from premature degradation and modulating their release profiles [8]. The physicochemical properties of liposomes, including lipid composition, membrane rigidity, size distribution, surface charge, and Encapsulation Efficiency (EE), directly influence their biological performance, biodistribution, and therapeutic efficacy [9].

However, conventional liposomes may be rapidly cleared by the Mononuclear Phagocyte System (MPS), particularly in the liver and spleen, underscoring the need to optimize liposomal composition and surface characteristics to prolong systemic circulation [10]. Several studies have explored various encapsulation platforms to enhance the oral delivery of antidiabetic drugs. For instance, chitosan-coated microcomplexes and pectin-based microspheres have been reported to improve mucosal adhesion, gastric protection, and sustained-release behavior, thereby reducing gastrointestinal irritation and enhancing therapeutic outcomes [11], [12].

Additionally, liposomal drug delivery systems such as PEGylated liposomes for chemotherapeutics, RGD-functionalized pH-sensitive liposomes, and dextran cyanoacrylate nanocapsules illustrate the versatility of liposomes in improving drug stability, reducing toxicity, and enabling targeted delivery [13–20]. These findings collectively emphasize the importance of optimizing liposomal physicochemical properties, including particle size, morphology, and lipid composition, to achieve desirable pharmacological outcomes. Nanoscale liposomes (typically 50–150 nm) are particularly advantageous for enhancing interaction with intestinal epithelial surfaces, promoting transcellular and paracellular transport, and improving oral absorption [20–24].

Characterization techniques, such as Scanning Electron Microscopy (SEM), are essential for confirming vesicle morphology, assessing structural integrity, and ensuring appropriate nanoscale dimensions for effective drug delivery [18]. Encapsulation of glipizide within nanosized liposomal carriers represents a promising strategy to protect the drug from gastric degradation, prolong its release, reduce dosing frequency, and improve patient tolerability. Given the limitations of conventional glipizide therapy and the growing interest in nanocarrier-mediated drug delivery, the development and optimization of a stable liposomal formulation of glipizide are of significant clinical and pharmaceutical relevance.

This study aims to synthesize glipizide-loaded nanoliposomes using a controlled methodological approach, evaluate their physicochemical properties, including particle size, morphology, and EE, and assess their potential for improved stability in physiological conditions. The findings are expected to advance oral nanocarrier systems capable of enhancing the therapeutic profile of glipizide and improving the management of type II diabetes.

2|Materials and Methods

2.1|Materials and Equipment

Lipid materials, including lecithin and cholesterol, as well as Butylated Hydroxytoluene (BHT) and Glipizide, were obtained from Sigma-Aldrich. Organic solvents, including chloroform and ethanol, were purchased

from Merck. Laboratory equipment included a magnetic stirrer (FALC-F60, Italy), a UV–visible spectrophotometer (UV1800-DP2000A, Taiwan), a pH meter (ISTEK INC, Korea), and a rotary evaporator (STEROGLASS STRIKE 202, Germany).

2.2 | Preparation of Glipizide Liposomes

Glipizide liposomes were prepared using a modified thin-film hydration method. Initially, accurately weighed amounts of lecithin and cholesterol were dissolved in a chloroform-ethanol mixture (2:1 v/v) in a volumetric flask. BHT (0.2% w/w of the total lipid content) was added as an antioxidant. The mixture was stirred on a magnetic stirrer at room temperature for 24 hours to ensure complete dissolution. The organic solvents were subsequently removed using a rotary evaporator at controlled temperature and rotation speed, forming a thin lipid film on the inner wall of the flask. This film constituted the lipid phase. For the aqueous phase, a specific amount of glipizide was dissolved in phosphate buffer (pH 7.4) and stirred at room temperature for 1 hour until fully dissolved. The aqueous phase was added to the flask containing the lipid film, and the mixture was stirred at room temperature until a homogeneous suspension formed. The resulting liposomal suspension was stored at 4°C for further analysis [24].

2.3 | Method for Determining the Optimal Values of Design Variables

After identifying the key design variables, the One Variable at A Time (OVAT) approach was applied to determine the optimal conditions. In this method, one variable is varied while the others are held constant. The experiments are performed iteratively to find the value of the selected variable that yields the highest EE. Once this optimal value is determined, it is fixed, and the next variable is varied in a proportional range to identify its optimum. This process is repeated sequentially for all design variables until the overall optimal combination is achieved. In this study, the design variables included the ratio of phosphatidylcholine (lecithin) to cholesterol, the ratio of organic-phase solvent to aqueous-phase solvent, and liposome formation time. The ranges investigated for the lecithin to cholesterol ratio were 1:14, 10:10, 7:1, 4:1, and 2:1; for the organic to aqueous solvent ratio, 6:1, 5:1, 4:1, 3:1, and 2:1; and for liposome formation time, 4.50, 4.00, 3.10, 2.20, and 1.30 hours. Using this systematic approach, the optimal combination of design variables that maximizes the EE of Glipizide hydrochloride liposomes was determined [25–28].

2.4 | Encapsulation Efficiency of Glipizide in Liposomes

Initially, 10 mg of glipizide was accurately weighed and dissolved in phosphate buffer (pH 7.4) to a final volume of 100 mL in a volumetric flask. From this stock solution, aliquots of 1, 2.5, 4, 5.5, 7, 8.5, and 10 mL were taken, and each was diluted to 50 mL in separate volumetric flasks, yielding solutions with concentrations ranging from 4 to 20 μg/mL. The absorbance of each solution was measured at the maximum wavelength for glipizide (276 nm) using a UV–visible spectrophotometer. A calibration curve of absorbance versus concentration was constructed to determine the concentration of glipizide in each sample based on the measured absorbance [29–31]. The EE (EE%) of the liposomal formulations was then calculated using the following *Eq. (1)*:

$$\mathrm{EE\%} = \frac{C_1 - C_2}{C_1} \times 100, \quad \textbf{(1)}$$

where C_1 is the total (initial) concentration of Glipizide and C_2 is the concentration of free (unencapsulated) glipizide in the liposome suspension. This method allowed accurate quantification of the fraction of glipizide successfully encapsulated within the liposomal carriers, providing a reliable assessment of formulation efficiency.

2.5 | Morphological Analysis of Liposomal Nanocapsules Using Scanning Electron Microscopy

The morphology of Glipizide-loaded liposomal nanocapsules was evaluated using SEM. A small amount of the liposomal suspension was placed on a clean glass slide and allowed to air dry at room temperature. The dried samples were then mounted on aluminum stubs using double-sided conductive carbon tape and coated with a thin layer of gold via sputter coating to enhance conductivity. SEM imaging was performed at 15 kV to examine the shape, surface characteristics, and approximate size of the liposomal vesicles. Micrographs were captured at various magnifications to assess the uniformity, surface morphology, and structural integrity of the nanocapsules [32–35].

3 | Results and Discussion

3.1 | Single Variable Experiments

The design variables significantly influenced glipizide EE, and optimal values were determined through single-variable experiments. The ratio of coating material to the encapsulated component is a key factor affecting EE.

In the first series of experiments, the lecithin to cholesterol ratios of 2:1, 4:1, 7:1, 10:1, and 14:1 were tested while keeping the organic to aqueous phase solvent ratio constant at 5:1 and the liposome formation time at approximately 2 hours (*Fig. 1*). The optimal lecithin to cholesterol ratio was found to be 7:1, resulting in an EE of 84.91%.

In the second series, the organic to aqueous phase solvent ratio was varied (2:1, 3:1, 4:1, 5:1, 6:1) while maintaining the lecithin to cholesterol ratio at 7:1. A formation time of approximately 2 hours (*Fig. 2*). The optimal solvent ratio was determined to be 4:1, achieving an EE of 88.65%.

In the final series, the liposome formation time was varied (1.30, 2.20, 3.10, 4.00, and 4.50 hours) while maintaining the optimal lecithin to cholesterol ratio (7:1) and the optimal organic to aqueous solvent ratio (4:1) (*Fig. 3*). The optimal formation time was 2.20 hours, yielding the highest EE of 90.12%. These results indicate that careful optimization of formulation parameters is essential to maximize glipizide EE in liposomal nanocarriers.

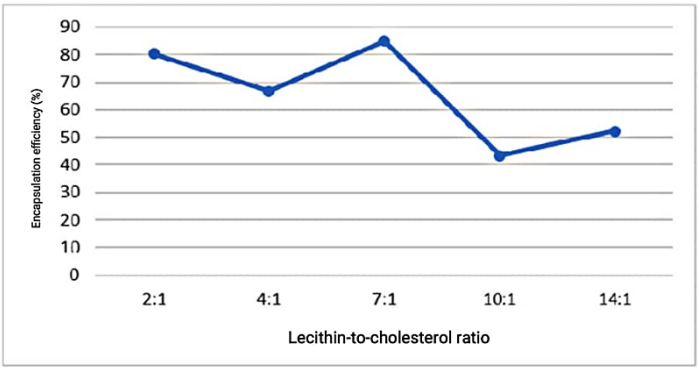

Fig. 1. Effect of lecithin on the cholesterol operating parameter at specified rates with an organic phase solvent to the aqueous phase solvent ratio of 5:1 and liposome formation time of 1.30.

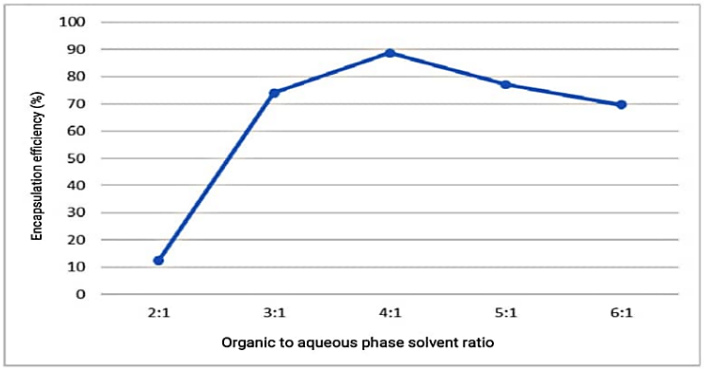

Fig. 2. Effect of operating parameter ratio of organic phase solvent to aqueous phase solvent at specified rates for a lecithin to cholesterol ratio of 7:1 and a liposome formation time of 1.30.

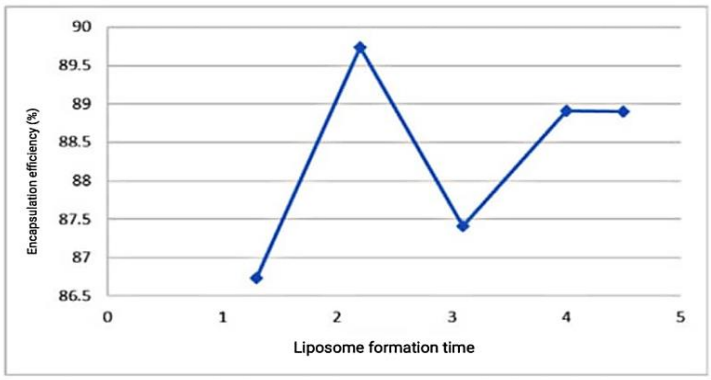

Fig. 3. Effect of operating parameters on liposome formation time at specified rates for the optimal ratio of lecithin to cholesterol of 7:1 and the optimal ratio of organic phase solvent to aqueous phase solvent of 4:1.

3.2 | Morphological Analysis of Liposomes by Scanning Electron Microscopy

The morphology of Glipizide-loaded liposomal nanocapsules was evaluated using SEM. SEM images revealed that the liposomal particles were predominantly spherical, with smooth, well-defined surfaces, indicating uniform vesicle formation.

Particle size analysis of SEM images showed that the nanocapsules ranged from 57 to 95 nm, with an average diameter of approximately 83 nm. These results demonstrate that the thin-film hydration method effectively produces liposomal nanocarriers with a narrow, uniform size distribution.

Furthermore, the SEM images indicated that the liposomal nanocapsules were free from irregular aggregates or oversized clusters, suggesting structural integrity and physical stability under laboratory conditions. Such characteristics are essential for the efficient delivery of Glipizide hydrochloride, as they can enhance cellular uptake and provide controlled drug release [36].

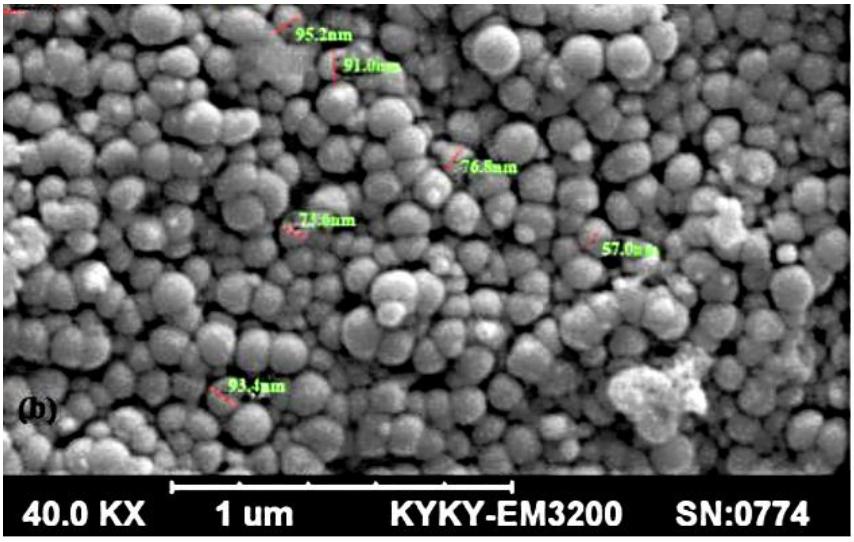

Fig. 4. SEM image of glipizide-loaded nanoliposomes.

4 | Conclusion

In this study, glipizide-loaded liposomal nanocapsules were successfully developed using the thin-film hydration technique, and a systematic optimization of formulation parameters was performed. The effects of key design variables, including the lecithin-to-cholesterol ratio, the organic-to-aqueous solvent ratio, and liposome formation time, were investigated using single-variable experiments. The optimal conditions were identified as a lecithin-to-cholesterol ratio of 7:1, an organic-to-aqueous solvent ratio of 4:1, and a liposome formation time of 2.20 hours, yielding a maximum EE of 90.12%. These findings indicate that careful tuning of formulation parameters is essential to maximize drug loading and ensure consistent liposome quality [24–26].

Morphological analysis using SEM revealed that the liposomal nanocapsules were predominantly spherical, with smooth surfaces and a uniform structural arrangement. Particle size analysis showed diameters ranging from 57 to 95 nm, with an average size of 83 nm, demonstrating a narrow size distribution. Such characteristics suggest that the prepared liposomes possess high structural integrity, stability, and uniformity, which are critical for enhancing cellular uptake and ensuring predictable drug release profiles. The absence of aggregation or irregular particles further confirms the robustness of the preparation method and the reproducibility of the formulation [37].

The encapsulation of Glipizide hydrochloride within liposomes provides multiple advantages over conventional drug administration. Liposomal coating can protect the drug from degradation in the acidic gastric environment, improve its stability in the intestinal milieu, and enable sustained, controlled release, potentially reducing dosing frequency and minimizing gastrointestinal side effects commonly associated with Glipizide therapy. Moreover, the nanoscale size and uniform morphology of liposomes may enhance bioavailability, pharmacokinetics, and tissue distribution, thereby improving therapeutic outcomes [3], [38], [39].

Overall, this study demonstrates that liposomal nanocarriers are a promising strategy for delivering hydrophilic antidiabetic drugs such as Glipizide hydrochloride. The combination of high EE, controlled particle size, structural stability, and potential for targeted and sustained release underscores the applicability of liposomal formulations as advanced drug delivery systems. These findings provide a strong foundation for further preclinical and clinical investigations to enhance the efficacy, safety, and patient compliance of Glipizide therapy in type II diabetes.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

All data are included in the text.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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