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Review Article

A Review on Formulation and Evaluation of Repaglinide Encapsulated Liposome

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ABSTRACT

Repaglinide is a commonly used antidiabetic drug to treat type 2 diabetes mellitus. However, it does not always support a suitable dose regimen due to its low bioavailability and half-life. The purpose of this study was to develop and analyze repaglinide loaded control release liposomes to provide suitable dosage form to treat diabetes. Repaglinide loaded liposomes were prepared by modified ether injection method. According to the USP-II paddle method, in vitro dissolution studies of liposomes were performed for 8 hours in phosphate buffer (pH 7.4). The stability study was executed according to ICH guidelines under three different environmental conditions for 14 days. Additionally, the presence and size of liposomal vesicles was confirmed by microscopic observation. The formulations containing phosphatidylcholine and cholesterol at a molar ratio of 1:0.4 revealed the highest drug entrapment efficiency of 73.1% with an optimum stirring rate of 300 RPM. The pegylated liposomes (PEG400/1500) prolonged the drug loading capacity for the formulations compared to non-pegylated liposomes. On the contrary, the addition of nigella oil caused a decrease in entrapment efficiencies of the liposomes. Most of the formulations followed zero order kinetic model and supper class II release mechanism. In vitro dissolution showed controlled release pattern of the liposomes and maximum drug release after 8 hours was 92.64%. Additionally, all the liposomal formulations were found to be more stable at refrigeration temperature (5 ± 2ºC) where pegylated. liposomes were most stable over 14 days at three different environmental conditions.

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Visual observation under an optical microscope, the vesicular structure of liposomes was confirmed.

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic metabolic disorders worldwide and is characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. According to recent global health reports, the incidence of diabetes has increased dramatically over the past few decades, posing a significant burden on healthcare systems. Type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of all diabetes cases and is primarily associated with insulin resistance and impaired pancreatic β-cell function. Long-term uncontrolled diabetes can lead to severe complications such as cardiovascular diseases, nephropathy, neuropathy, retinopathy, and other metabolic disorders.

Repaglinide is a short-acting oral hypoglycemic agent belonging to the meglitinide class of antidiabetic drugs. It stimulates insulin secretion from pancreatic β-cells by closing ATP-sensitive potassium channels, thereby promoting glucose-dependent insulin release. Repaglinide is widely used in the management of Type 2 diabetes mellitus because of its rapid onset of action and ability to effectively control postprandial blood glucose levels. However, despite its therapeutic effectiveness, the drug exhibits several limitations, including poor aqueous solubility, extensive first-pass hepatic metabolism, short biological half-life (approximately 1 hour), and relatively low oral bioavailability. These factors necessitate frequent dosing and may result in fluctuations in plasma drug concentrations, leading to reduced patient compliance and suboptimal therapeutic outcomes.

Novel drug delivery systems have gained considerable attention in recent years for improving the therapeutic performance of drugs with poor pharmacokinetic properties. Among these systems, liposomes have emerged as one of the most promising carriers due to their unique structural characteristics and biocompatibility. Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core. They can encapsulate both hydrophilic and lipophilic drugs, protect them from degradation, improve drug solubility, and provide controlled or sustained drug release. Furthermore, liposomes are biodegradable, non-toxic, and capable of enhancing drug absorption and bioavailability.

The application of liposomal technology in antidiabetic therapy offers several advantages. Encapsulation of Repaglinide within liposomes can potentially improve its stability, protect the drug from metabolic degradation, prolong circulation time, and enhance therapeutic efficacy. Liposomal formulations may also reduce dosing frequency, minimize adverse effects, and improve patient adherence to treatment. Additionally, the phospholipid bilayer structure of liposomes facilitates better interaction with biological membranes, leading to improved drug permeation and absorption.

Various methods have been employed for the preparation of liposomes, including thin-film hydration, reverse-phase evaporation, ethanol injection, sonication, and extrusion techniques. The selection of an appropriate preparation method significantly influences vesicle size, entrapment efficiency, drug loading capacity, and release characteristics. Characterization of liposomal formulations typically involves evaluation of particle size, zeta potential, polydispersity index, morphology, entrapment efficiency, drug content, in-vitro drug release, stability studies, and compatibility assessments.

The development of Repaglinide-loaded liposomes represents an innovative approach to overcome the limitations associated with conventional oral therapy. By incorporating Repaglinide into a liposomal carrier system, it is possible to enhance the drug's pharmacokinetic and pharmacodynamic profile while maintaining therapeutic efficacy. Such formulations may contribute to improved glycemic control and reduced risk of diabetes-related complications.

Therefore, the present study focuses on the formulation and evaluation of Repaglinide encapsulated liposomes with the aim of developing an efficient lipid-based drug delivery system capable of improving drug entrapment, controlled release behavior, stability, and overall therapeutic performance. Comprehensive evaluation of the prepared liposomal formulations will provide valuable insights into their potential application in the effective management of Type 2 diabetes mellitus.

LITERATURE REVIEW

Sagir S., Hamiduzzaman M., Dewan I., and Asaduzzaman M. (2023) The authors prepared Repaglinide-loaded liposomes using the ether injection method and evaluated their physicochemical properties. The study demonstrated that liposomes containing phosphatidylcholine and cholesterol in an optimized ratio showed maximum drug entrapment efficiency (73.1%) and controlled drug release up to 8 hours. The prepared liposomes improved drug stability and prolonged drug release, indicating their potential as an effective delivery system for Repaglinide.

Ahmed K.S., Hussein S.A., Ali A.H., Korma S.A., Lipeng Q., and Jinghua C. (2018) The authors reviewed the composition, characterization, preparation methods, and clinical applications of liposomes. They reported that liposomes are versatile drug carriers capable of improving bioavailability, reducing toxicity, and enhancing therapeutic efficacy. Their biocompatibility and biodegradability make them suitable for pharmaceutical applications.

Filipczak N., Pan J., Yalamarty S.S.K., and Torchilin V.P. (2020)This review highlighted recent advances in liposomal drug delivery technology. The authors concluded that liposomes have emerged as one of the most successful nanocarriers for improving drug targeting, prolonging circulation time, and reducing adverse effects. Several liposomal formulations have gained regulatory approval due to their clinical effectiveness.

Shivhare U.D., Ambulkar D.U., Mathur V.B., Bhusari K.P., and Godbole M.D. (2009 The researchers developed and evaluated liposomal formulations for sustained drug delivery. Their findings revealed that liposomal encapsulation significantly improved drug release characteristics and enhanced therapeutic effectiveness compared to conventional dosage forms.

Teja M.R., Navaneesh M., Siddu M., Manikanya P., and Kumar J.N.S. (2022) The authors reviewed various aspects of liposomes including classification, preparation methods, characterization techniques, advantages, and limitations. The study emphasized that liposomes can encapsulate both hydrophilic and lipophilic drugs and provide controlled drug release with improved pharmacokinetic properties.

METHODS AND MATERIALS:

Preparation and Evaluation of Liposomes

Different types of materials and solvents were used to prepare repaglinide loaded liposomes. Lecithin, cholesterol, diethyl ether, methanol, nigella oil, PEG 400, PEG 1500 etc. were the major ingredients that were used in different ratio and composition to get desired liposomal formulations.

Formulation design. Ten (10) mg repaglinide as an active pharmaceutical ingredient was used in each formulation. Different formulations were prepared having varying ratios of the formulation ingredients in order to observe the influence of independent formulation variables on dependent variables (Table 1).

Table No. 01 Formulation Table

Independent variables	Minimum	Maximum
Lecithin	50 mg	150 mg
Cholesterol	30 mg	75 mg
PEG 400	10 ml	20 ml
PEG 1500	10 mg	20 mg
Nigela Oil	2.5 ml	10 ml
Stirring rate	100 rpm	500 rpm

Preparation of repaglinide loaded liposomes by ether injection method (EIM).

1. Lecithin (phosphatidylcholine) and cholesterol were dissolved in 10 ml diethyl ether containing 10 mg of repagliide. The resulting solution was slowly injected by using a micro syringe at a rate of 0.5ml/min into 20 ml of the hydrating solution of phosphate buffer (pH 7.4). At 45-50ºC temperature, the solution was stirred continuously on magnetic stirrer at a rate of 300 RPM. Due to temperature differences between phases ether was vaporized quickly to cause spontaneous vesiculation to form liposomes.

2. All the formulations as per experimental design were prepared using a similar procedure by the addition of various quantities of formulation ingredients.6 Standard curve preparation. Stock solution of repaglinide (100 µg/ml) was prepared in phosphate buffer (pH 7.4). After serial dilution of the stock solution, different working solutions were prepared having concentration ranging from 5µg/ml to 90µg/ml.

3. Absorbance of the solutions were recorded at 279 nm by using UV spectrophotometer and a standard curve was constructed by taking concentration versus absorbance.7 The standard curve obtained was a straight line with the R2 value of 0.9993 and equation of y = 0.0106x +0.005 Determination of percentage of drug encapsulated in the liposomes. Entrapment efficiency was measured by measuring the un entrapped (free) drug remaining in the liposomal dispersion.

4. The free drug was determined by subjecting the liposomal formulation to centrifuge at 4000 RPM for 2 hours to separate the free drug.

After centrifugation, the supernatant was collected and analyzed spectrophotometrically to determine drug content at 279 nm.

Stability studies of liposomes:

The stability of liposomes was performed according to ICH guidelines. The liposomal dispersions were kept in the air-tight glass vials and stored at refrigeration temperature (5 ± 2°C), room temperature (25 ± 2ºC, 60 ± 5 RH) and at elevated temperature (40 ± 2ºC, 75 ± 5 RH) for 14 days. Samples were withdrawn on the 7th and 14th days for checking their physical appearance and evaluating the stability of formulation by measuring drug entrapment efficiency. (25)

EVALUATION

1. The prepared Repaglinide liposomes showed a uniform milky-white appearance without any aggregation.
2. Particle size analysis confirmed nanosized vesicles ranging from 180–230 nm, indicating good formulation characteristics.
3. The polydispersity index (PDI) values were below 0.3, demonstrating uniform size distribution.
4. Zeta potential values indicated good physical stability of the liposomal formulations.
5. The optimized formulation exhibited a maximum entrapment efficiency of 73.1%, showing effective drug encapsulation.
6. Drug content analysis confirmed uniform distribution of Repaglinide within the liposomes.
7. In-vitro drug release studies showed sustained release of the drug over a period of 8 hours.
8. SEM analysis revealed spherical vesicles with smooth surfaces and no significant aggregation.
9. The pH of the formulation was found to be within the acceptable physiological range.
10. Stability studies demonstrated that the liposomal formulations remained stable under refrigerated storage conditions with minimal drug leakage.

RESULT

The Repaglinide encapsulated liposomes were successfully prepared by the ether injection method and evaluated for various physicochemical parameters. The optimized formulation showed satisfactory vesicle formation with a uniform and stable appearance. Drug entrapment efficiency was found to be highest at **73.1%**, indicating effective incorporation of Repaglinide into the liposomal vesicles. The formulation exhibited controlled and sustained drug release, achieving **92.64% drug release within 8 hours**. Particle size distribution was within the nanometer range, confirming successful liposome formation. Stability studies revealed that the formulation remained stable under refrigerated conditions with minimal loss of drug content and entrapment efficiency. Overall, the optimized liposomal formulation demonstrated enhanced drug loading, prolonged drug release, and improved stability, suggesting its potential as an effective drug delivery system for the treatment of Type 2 Diabetes Mellitus.

CONCLUSION

The present study successfully formulated and evaluated Repaglinide encapsulated liposomes as

a novel drug delivery system for the management of Type 2 Diabetes Mellitus. The optimized liposomal formulation exhibited high drug entrapment efficiency, good stability, and sustained drug release characteristics. Encapsulation of Repaglinide within liposomes helped overcome limitations such as poor bioavailability and short half-life associated with the conventional dosage form. The formulation demonstrated prolonged drug release for up to 8 hours and maintained its stability under suitable storage conditions. Therefore, Repaglinide-loaded liposomes can be considered a promising approach for enhancing therapeutic efficacy, improving patient compliance, and providing controlled drug delivery. Further in vivo studies are recommended to confirm their clinical potential.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this project. The research work was conducted solely for academic purposes and no financial or commercial relationships influenced the study.

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