FORMULATION AND EVALUATION OF NANOSTRUCTURED LIPID CARRIERS (NLCS) OF REPAGLINIDE

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Abstract

The study was designed to formulate Repaglinide-loaded Nanostructured Lipid Carriers (NLCs) and assess their ability to improve the drug's solubility and dissolution characteristics, with the ultimate aim of enhancing its oral delivery potential. Five formulations of Repaglinide-loaded NLCs (F1-F5) were developed by employing a combination of hot homogenization and ultrasonication. Compritol 888 ATO and Miglyol 812 were selected as the solid and liquid lipid components, respectively, while different concentrations and ratios of surfactants were investigated. Following optimization, the selected NLC formulation was lyophilized and converted into a tablet dosage form. The optimized formulation was further subjected to accelerated stability testing. Pre-formulation characterization established the identity and purity of Repaglinide and confirmed its lipophilic nature, as indicated by a log P value of 2.56. Comparative evaluation of the prepared NLCs identified F5 as the most promising formulation. F5 produced nanoparticles with a mean particle size of 79.3 ± 1.6 nm and a polydispersity index of 0.182, reflecting a relatively uniform particle-size distribution. The formulation exhibited a zeta potential of −31.2 ± 0.8 mV and achieved an entrapment efficiency of 92.1 ± 1.2%. The tablet prepared from F5 demonstrated markedly improved in-vitro drug release, reaching 95.4 ± 2.0% within 60 min, whereas the marketed conventional tablet exhibited only 64.2% release over the same period. The developed Repaglinide NLC system demonstrated substantial improvement in drug entrapment and dissolution performance compared with the conventional marketed formulation. Formulation F5, in particular, showed favorable nanoscale characteristics, high entrapment efficiency, enhanced drug release, and satisfactory stability. These findings support the potential of NLC technology as an effective lipid-based strategy for improving the oral delivery of Repaglinide and may contribute to improved therapeutic performance in Type 2 Diabetes Mellitus.

Keywords: *Repaglinide, Nanostructured Lipid Carriers (NLCs), Type 2 Diabetes Mellitus, In-vitro Dissolution*

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1. Introduction

Diabetes mellitus is a long-term metabolic disease marked by a steady rise in blood sugar levels brought on by either insufficient insulin production, poor insulin action, or a combination of the two. The most prevalent kind of the illness is type 2 diabetes mellitus (T2DM), which commonly need pharmaceutical intervention to attain adequate glycaemic control. Repaglinide is a meglitinide class short-acting insulin secretagogue that is frequently used to treat type 2 diabetes. Its pharmacological activity is mainly linked to the closure of ATP-sensitive potassium channels, which stimulates insulin production from pancreatic β-cells.

Repaglinide offers quick postprandial blood glucose control, however its pharmacological characteristics make oral administration difficult. According to Wu et al. (2020), the drug's oral bioavailability is claimed to be less than 55% due to its poor water solubility and substantial hepatic first-pass metabolism. Additionally, it has a biological half-life of around one hour, which can need repeated administration and affect patient compliance (Sharma et al., 2015; Wu et al., 2020). Therefore, developing a suitable delivery method that may enhance Repaglinide's solubility and absorption properties continues to be a crucial field of formulation research.

The use of lipid-based drug delivery systems to enhance the biopharmaceutical performance of medications that are poorly soluble in water has attracted a lot of attention. These systems can promote interaction with biological membranes, improve therapeutic dispersion in gastrointestinal fluids, and improve the integration of lipophilic compounds into appropriate lipid matrices. Lipid nanocarriers are adaptable platforms for enhancing the solubility, stability, drug loading, controlled release, and biological performance of poorly soluble therapeutic drugs, according to recent pharmaceutical study (Singh and Srivastava, 2026).

Nanostructured Lipid Carriers (NLCs) are a second-generation lipid nanoparticle system among lipid-based nanocarriers that were created to get around a number of issues with traditional Solid Lipid Nanoparticles (SLNs). Solid and liquid lipids are combined to form NLCs. The highly organised crystalline structure of the solid lipid is disrupted by the presence of liquid lipid, creating an imperfect lipid matrix that can hold more medication and lessen drug ejection during storage. Because of this structural characteristic, NLCs are especially appealing for the delivery of substances that are poorly soluble in water (Müller et al., 2000; Mehnert and Mäder, 2001). NLCs are lipid systems in which the mix of solid and liquid lipids enhances drug-loading capacity and reduces drug ejection related to lipid crystallisation, according to recent GJPSR literature (Musharraf et al., 2026).

Because of their nanoscale size, NLCs have a comparatively high surface area, which can increase medication solubility and make it easier for them to interact with biological membranes. NLCs may potentially offer higher absorption of lipophilic medicines, better physical stability, and controlled or extended drug release, depending on formulation composition and delivery method. By lessening the effect of hepatic first-pass metabolism for appropriate pharmacological compounds, their capacity to promote intestinal transport and lipid-associated lymphatic absorption may further enhance systemic exposure (Pardeike et al., 2009; Khan et al., 2023). Similar benefits of lipid nanocarriers, such as improved encapsulation, controlled release, drug molecule preservation, and increased transport efficiency, have been highlighted by recent GJPSR study (Singh and Srivastava, 2026).

Because the addition of liquid lipid results in a less organised interior structure, NLCs also have a number of benefits over SLNs. This may enhance entrapment efficiency and release properties, as well as offer more flexibility in accommodating drug compounds. Higher drug-loading capacity and better formulation performance are significant benefits of NLCs over more highly crystalline lipid systems, according to comparative discussions in the GJPSR literature (Musharraf et al., 2026).

Lipid nanocarriers are now widely used for poorly soluble medications, including oral and various pharmaceutical dose forms. Nanocarrier-based solutions can be especially helpful for BCS Class II medications, for which dissolution is often a significant issue limiting oral absorption, according to current GJPSR literature. As a result, solid lipid nanoparticles, nanoemulsions, nanostructured lipid carriers, and similar systems have drawn more interest as methods for enhancing medication dispersion and dissolution (Prajapati et al., 2026).

The promise of NLC technology has also been shown in earlier studies that particularly used repaglinide. When compared to traditional formulations, repaglinide-loaded NLCs with particle sizes of around 79 nm have been linked to improved intestinal permeability and absorption (Wu et al., 2020). Repaglinide NLCs produced up to a 3.02-fold increase in the area under the plasma concentration-time curve (AUC) when compared to commercial formulations, according to pharmacokinetic assessment (Wu et al., 2020). Repaglinide NLCs with high entrapment efficiencies of around 96-98% and particle sizes between 79 and 325 nm have been described in other studies, indicating that these systems can enhance drug absorption and assimilation (Kumar et al., 2021).

Repaglinide transdermal delivery has also been studied using NLC technology. When compared to traditional dosage forms, these formulations have shown prolonged drug release and a roughly two-fold increase in bioavailability (Patel et al., 2020). All of these results

suggest that Repaglinide's low water solubility may be addressed by modifying it into a lipid-based nanosystem, which would also improve drug release and absorption.

Despite these promising results, the kind and ratio of solid and liquid lipids, surfactant content, processing conditions, and drug-excipient interactions all have a significant impact on an NLC system's performance. To produce nanoparticles with appropriate particle size, narrow size distribution, sufficient surface charge, high drug-entrapment efficiency, good release properties, and acceptable stability, thorough formulation optimisation is thus required.

In light of these factors, the current study was conducted to create and assess Repaglinide-loaded Nanostructured Lipid Carriers as a method for enhancing the drug's oral delivery efficacy. The formulation optimisation and characterisation of the produced NLCs in terms of particle size, polydispersity index, zeta potential, drug-entrapment efficiency, and in-vitro drug-release properties were the main objectives of the study. The physicochemical and mechanical characteristics of the optimised NLC formulation were then assessed after it was integrated into a tablet dosage form. In order to evaluate the created system's appropriateness for possible oral administration of repaglinide, stability testing was also conducted under accelerated storage conditions.

2. Methodology

2.1 Materials

Repaglinide, used as the active pharmaceutical ingredient (API) and model drug in the present investigation, was selected for the development of the nanostructured lipid carrier system. Different solid and liquid lipids were screened for preparation of the lipid matrix. The solid lipid phase comprised Glyceryl Monostearate, Stearic Acid, and Compritol 888 ATO, whereas Oleic Acid, Caprylic-Capric Triglyceride, and Miglyol 812 were investigated as liquid lipid components. Tween 80, Poloxamer 188, and Soy Lecithin were employed as surfactants during formulation development. For preparation of the tablet dosage form, Microcrystalline Cellulose (MCC PH 102), Lactose Monohydrate, Croscarmellose Sodium, PVP K-30, Colloidal Silicon Dioxide, and Magnesium Stearate were used as formulation excipients. These materials were procured from the college laboratory. All remaining chemicals and reagents utilized during the study were of analytical grade and were used without further purification.

2.2 Instrumentation

The major instruments employed throughout the study included an electronic analytical balance (Shimadzu) for accurate weighing of drug and formulation components, a rotary

evaporator (Heidolph/Buchi) for solvent removal, a pH meter (Eutech) for determination of formulation pH, a Brookfield viscometer for viscosity measurements, and a magnetic stirrer equipped with a hot plate (Remi Instruments) for controlled mixing and heating during formulation development.

The particle characteristics of the developed nanostructured lipid carriers were assessed using Dynamic Light Scattering (DLS) for determination of particle size and polydispersity, along with a zeta potential analyzer for evaluation of surface charge. The prepared tablets were subjected to standard quality-control tests using a Monsanto hardness tester, Electrolab friability tester, and USP dissolution apparatus for assessment of mechanical strength, friability, and in-vitro drug-release characteristics, respectively.

2.3 Pre-formulation Studies of Repaglinide

2.3.1 Physical Characterization

Under carefully monitored laboratory circumstances, the organoleptic properties of Repaglinide, such as its colour, odour, and taste, were assessed using visual and sensory analysis. The observed traits were recorded and contrasted with the drug's claimed literature specifications. To ensure that the observations were consistent, each evaluation was conducted three times.

2.3.2 Melting Point Determination

A digital capillary melting point device (Mel-Temp) was used to investigate the melting behaviour of repaglinide. A little amount of the finely powdered drug sample was added to a capillary tube. After the loaded capillary was placed within the device, the temperature was gradually raised. The melting-point range was then recorded after the temperatures that corresponded to the start and finish of the melting process were documented. To guarantee repeatability, the analysis was carried out three times.

2.3.3 Solubility Analysis

The shake-flask method was used to examine the solubility profile of repaglinide in various solvents at 25°C and 37°C. To achieve equilibrium, an excess amount of the medication was added to each solvent system and stirred constantly for 48 hours. The samples were filtered to remove any drug particles that had not dissolved during equilibration. To measure the amount of medication dissolved, the filtrates were suitably diluted and subjected to UV-visible spectrophotometric analysis. Every solubility test was carried out three times.

2.3.4 Determination of Loss on Drying

The moisture content of Repaglinide was determined by the loss-on-drying (LOD) method. A predetermined quantity of the drug was accurately weighed and transferred to a suitable

container before being placed in a hot-air oven maintained at 105°C. The sample was dried until a constant weight was achieved. The percentage loss in weight relative to the initial sample weight was calculated and expressed as the moisture content. The determination was carried out in triplicate.

2.4 Evaluation of Powder Flow Properties

Conventional micromeritic measurements were used to evaluate the flow properties of both the final powder blend and the pure medication. While tapped density was acquired after mechanical tapping using a tapped-density device running at 300 drops per minute, bulk density was calculated from the starting volume occupied by a known amount of powder. Carr's compressibility index and Hausner ratio were computed to describe the flowability and packing behaviour of powder based on the bulk and tapped density data. The fixed-funnel approach was also used to estimate the angle of repose. This parameter was utilised to evaluate the powder material's flow behaviour and frictional properties. The material's eligibility for further formulation and tableting was assessed using the findings of all micromeritic measurements, which were carried out in triplicate.

2.5 Formulation of Nanostructured Lipid Carriers

Repaglinide-loaded Nanostructured Lipid Carriers (NLCs) were produced by combining high-shear homogenization and probe ultrasonication. The required quantities of the selected solid and liquid lipids were combined and heated to 70-80°C until a homogeneous molten lipid phase was obtained. Repaglinide (25 mg) was incorporated into the molten lipid mixture and allowed to dissolve completely to produce a uniform drug-containing lipid phase.

In parallel, the aqueous phase was prepared by dissolving Tween 80 and Soy Lecithin in purified water. The aqueous phase was subsequently heated to approximately the same temperature as the lipid phase to minimize premature lipid solidification during emulsification.

The molten lipid phase was gradually introduced into the preheated aqueous phase while maintaining high-shear homogenization at 10,000-15,000 rpm for 3-5 min. This process resulted in the formation of a coarse lipid emulsion. The preliminary emulsion was then subjected to probe ultrasonication at 50-70% amplitude for 3-7 min to reduce the size of the dispersed lipid droplets and obtain a nanosized dispersion. An ice bath was used during sonication to minimize excessive temperature elevation and protect the formulation from potential thermal degradation.

Following ultrasonication, the resulting NLC dispersion was allowed to cool gradually to room temperature. Cooling facilitated recrystallization of the lipid matrix and formation of the final Repaglinide-loaded nanostructured lipid carrier dispersion.

2.6 Characterization of Repaglinide-Loaded Nanostructured Lipid Carriers

2.6.1 Particle Size and Polydispersity Index

The mean particle size and polydispersity index (PDI) of the developed Repaglinide-loaded NLC formulations were determined by **Dynamic Light Scattering (DLS)** using a particle size analyzer. Prior to measurement, each formulation was suitably diluted with distilled water to minimize particle-particle interactions and multiple-scattering effects. Measurements were performed at **room temperature** under appropriate instrumental conditions.

Particle size was expressed as the mean hydrodynamic diameter of the dispersed NLC particles, whereas the PDI was used to assess the breadth and uniformity of the particle-size distribution. A **PDI value below 0.3** is generally indicative of a relatively narrow and homogeneous particle population. Each formulation was analyzed in **triplicate**, and the results were recorded as mean values with appropriate variation.

2.6.2 Zeta Potential

The surface charge characteristics of the Repaglinide-loaded NLCs were assessed by determining their **zeta potential** using a zeta potential analyzer based on electrophoretic mobility. The NLC dispersions were appropriately diluted with distilled water and transferred into a suitable zeta-potential measurement cell before analysis at room temperature. Zeta potential provides an indication of the electrical charge present at the particle-liquid interface and is an important parameter for assessing the physical stability of colloidal systems. A sufficiently high positive or negative surface potential promotes electrostatic repulsion among particles and can minimize aggregation. In general, an absolute zeta-potential value of approximately **30 mV or greater** is considered favorable for electrostatic stabilization of colloidal dispersions. Measurements were performed in **triplicate**.

2.6.3 Entrapment Efficiency and Drug Loading

The entrapment efficiency (EE%) and drug loading (DL%) of the Repaglinide NLC formulations were determined by quantifying the amount of drug incorporated into the lipid nanoparticles. Free or unentrapped Repaglinide was separated from the NLC dispersion by ultracentrifugation. Following centrifugation, the supernatant containing the unentrapped drug was carefully separated and suitably diluted for quantitative estimation using UV-Visible spectrophotometry.

The quantity of Repaglinide incorporated within the NLCs was obtained from the difference between the total amount of drug initially introduced into the formulation and the amount of free drug detected in the supernatant.

The entrapment efficiency was calculated using the following equation:.

$$\textbf{EE (\%) = [(Total drug - Free drug) / Total drug] × 100}$$

$$\textbf{DL (\%) = [(Entrapped drug) / Total weight of nanoparticles] × 100}$$

2.7 Preparation of NLC-Loaded Tablets

The optimized lyophilized NLC powder, corresponding to 2 mg of Repaglinide, was accurately weighed and mixed with the selected tablet excipients. Microcrystalline cellulose (MCC), lactose, and croscarmellose sodium were initially blended with the NLC powder. The resulting mixture was passed through a #40 mesh sieve to improve particle-size uniformity and facilitate efficient mixing. The sieved material was subsequently mixed in a tumble blender to obtain a homogeneous powder blend.

After achieving adequate blend uniformity, magnesium stearate and colloidal silicon dioxide were incorporated as lubricant and glidant, respectively. The lubricants were mixed for a short, controlled period to ensure uniform distribution while minimizing the possibility of excessive lubrication. The final blend was compressed using a rotary tablet compression machine equipped with 8-10 mm punches. Compression conditions were adjusted to produce tablets with a target hardness of 4-8 kgf, providing sufficient mechanical integrity for subsequent handling and evaluation.

2.8 Evaluation of NLC-Loaded Tablets

The prepared NLC-loaded tablets were subjected to a series of post-compression quality-control tests. Weight variation was assessed by individually weighing 20 tablets and determining their mean weight and deviation from the average. Tablet hardness was measured using a Monsanto hardness tester to determine the mechanical strength of the compressed tablets. The resistance of the tablets to abrasion was evaluated by performing a friability test using an Electrolab friabilator. The percentage loss in tablet weight was calculated after the specified testing procedure, with a value below 1% considered acceptable. Disintegration time was determined using a standard disintegration apparatus to establish the time required for the tablets to break down into smaller particles under the prescribed test conditions.

2.8.1 In-vitro Drug Release Study

The release behavior of Repaglinide from the NLC-loaded tablets was investigated using USP Apparatus II (paddle method). The dissolution medium consisted of simulated gastric and intestinal fluids maintained at 37 ± 0.5°C throughout the experiment. At predetermined sampling intervals, aliquots of the dissolution medium were withdrawn and appropriately filtered. The samples were analyzed by UV-Visible spectrophotometry, and the percentage of Repaglinide released at each time point was calculated to generate the dissolution profile.

2.8.2 Stability Study

The stability of the optimized NLC-loaded tablets was investigated in accordance with applicable ICH stability-testing conditions. Samples were stored under both long-term conditions of 25°C ± 2°C/60% ± 5% RH and accelerated conditions of 40°C ± 2°C/75% ± 5% RH for a period of up to 6 months. At predetermined intervals, the stored tablets were examined for changes in relevant physicochemical characteristics and drug content.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation Studies of Repaglinide

3.1.1 Physical Appearance

The preliminary examination of Repaglinide included assessment of its physical and organoleptic characteristics. The drug was observed as a white to off-white crystalline powder with an odorless character. Its taste was described as practically tasteless to slightly bitter. The observed characteristics were consistent with the expected physical properties of Repaglinide and supported its preliminary identification.

3.1.2 Identification of Repaglinide by Melting Point

The melting-point determination was performed as a preliminary assessment of the identity and purity of the drug. Repaglinide exhibited a sharp melting range of 130-131°C. The absence of any apparent decomposition or unusual change during melting indicated satisfactory thermal behavior of the drug sample. The narrow melting range also supported the identity and relative purity of the Repaglinide used in the formulation study.

3.1.3 Solubility Study

The solubility investigation demonstrated the characteristic poor aqueous solubility of Repaglinide. The drug was found to be practically insoluble in purified water and exhibited limited solubility in 0.1 N HCl and phosphate buffer at pH 6.8. In contrast, appreciable solubility was observed in organic solvents, including methanol, ethanol, and acetone, while

the drug showed comparatively higher solubility in chloroform and dimethyl sulfoxide (DMSO).

The observed solvent-dependent solubility behavior indicates the predominantly lipophilic nature of Repaglinide. Its poor aqueous solubility represents an important formulation challenge because dissolution is a critical step in the oral absorption of poorly water-soluble drugs. Accordingly, incorporation of Repaglinide into a lipid-based nanocarrier system was considered a suitable approach for improving its dispersion and dissolution characteristics.

3.1.4 Loss on Drying

The moisture content of the Repaglinide sample was evaluated by determining its Loss on Drying (LOD). A value of 1.0% was obtained, indicating a relatively low level of moisture or volatile components in the drug sample. The low LOD value suggests that the material was adequately dry and suitable for further formulation development.

3.2 Flow Properties of Pure Repaglinide

The flow characteristics of the pure drug were investigated to assess its handling and processing behavior during formulation development. The measured micromeritic parameters, including bulk density, tapped density, Carr's compressibility index, Hausner ratio, and angle of repose, were used to characterize the packing and flow behavior of the powder. Overall, the observed flow characteristics indicated that Repaglinide possessed acceptable powder-flow behavior, suggesting that the drug could be handled and incorporated into the formulation without major processing difficulties. These characteristics were considered favorable for subsequent blending with formulation components and preparation of the Repaglinide-loaded NLC system.

Table 1: Flow Properties of Pure Repaglinide

Parameter	Observed Value (Mean ± SD)	Interpretation
Angle of Repose (°)	28.6° ± 0.5	Good flow (<30°)
Bulk Density (g/mL)	0.421 ± 0.003	-
Tapped Density (g/mL)	0.487 ± 0.004	-
Carr’s Index (%)	13.6% ± 0.4	Good (<15%)
Hausner’s Ratio	1.15 ± 0.01	Good (<1.25)

3.3 Evaluation Repaglinide Nanostructured Lipid Carriers

3.3.1 Physical Appearance of Repaglinide NLCs

The Repaglinide-loaded NLCs were characterized as a smooth, homogeneous, milky-white colloidal dispersion. The formulation appeared odorless and exhibited a neutral taste, with no evidence of lumps, sedimentation, or phase separation. These observations confirm the physical stability and uniform consistency of the nanosuspension, making it suitable for subsequent evaluation.

3.3.2 Particle Size Determination of Repaglinide NLCs

The particle size, polydispersity index (PDI), and zeta potential of repaglinide-loaded NLCs (F1-F5) were evaluated. Particle size decreased from 118.6 ± 2.4 nm (F1) to 79.3 ± 1.6 nm (F5), indicating successful optimization. PDI values ranged from 0.286 to 0.182, confirming a uniform size distribution. Zeta potential values (−24.3 to −31.2 mV) indicated good colloidal stability. Among all formulations, F5 showed the best characteristics with minimum particle size, low PDI, and highest stability.

Table 1: Particle Size Analysis of Repaglinide NLCs (F1-F5)

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)
F1	118.6 ± 2.4	0.286 ± 0.01	−24.3 ± 0.5
F2	104.9 ± 2.1	0.241 ± 0.02	−26.5 ± 0.6
F3	92.4 ± 1.8	0.218 ± 0.02	−28.6 ± 0.7
F4	86.7 ± 1.5	0.196 ± 0.01	−29.8 ± 0.6
F5	79.3 ± 1.6	0.182 ± 0.01	−31.2 ± 0.8
Fenofibrate Nanocrystal (Marketed)	**80-200**	**0.20-0.30**	**−20 to −30**

3.3.3 Entrapment Efficiency (EE%) and Drug Loading (DL%)

The entrapment efficiency (EE%) and drug loading (DL%) of Repaglinide in formulations F1-F5 were evaluated to assess drug incorporation within the lipid matrix. Results showed a progressive increase in EE% from 72.4% (F1) to 92.1% (F5), while DL% improved from 4.2% to 5.8%. Formulation F5 achieved the highest encapsulation and loading capacity, indicating an optimized lipid composition and superior potential for enhanced bioavailability and sustained drug release.

Table 2: Entrapment Efficiency (EE%) and Drug Loading (DL%)

Formulation	Entrapment Efficiency	Drug Loading

	(EE%)	**(DL%)**
F1	72.4 ± 1.8	4.2 ± 0.14
F2	78.9 ± 1.5	4.6 ± 0.12
F3	84.3 ± 1.7	4.9 ± 0.15
F4	88.6 ± 1.4	5.3 ± 0.16
F5	92.1 ± 1.2	5.8 ± 0.18

3.4 Preparation of Repaglinide-loaded nanostructured lipid carrier (NLC) tablets

3.4.1 Physical appearance

The formulated Repaglinide-loaded NLC tablets were evaluated to ensure quality and suitability for oral administration. The tablets appeared off-white to creamy, were odorless, and exhibited a slightly bitter taste. Physically, they were flat, round, and possessed a smooth, non-gritty surface texture. All batches demonstrated a uniform appearance with no visible defects such as cracks, mottling, or capping, indicating consistent formulation and successful compression across all batches.

Table 3: Physical Appearance of Repaglinide-Loaded NLC Tablets

Parameter	**Observation**
Colour	Off-white to creamy
Odour	Odourless
Taste	Slightly bitter (due to excipients and drug)
Shape	Flat/round tablets
Surface Texture	Smooth, uniform, non-gritty
Appearance	No cracks, no mottling, no capping
Overall Uniformity	Uniform in appearance across all batches

3.4.2 Hardness

The Repaglinide-loaded NLC tablets (F1-F5) exhibited hardness values from 5.2 to 6.2 kg/cm², demonstrating superior mechanical strength compared to the conventional marketed tablet (5.0 kg/cm²). Formulation F5 showed the highest robustness, ensuring all batches possess the durability required for handling and packaging while maintaining optimal disintegration properties.

Table 4: Hardness of Repaglinide NLC Tablets (F1-F5)

Formulation	Hardness (kg/cm²) (Mean ± SD)
F1	5.2 ± 0.12
F2	5.5 ± 0.10
F3	5.8 ± 0.11
F4	6.0 ± 0.12
F5	6.2 ± 0.10
Marketed Product (Prandin)	**5.0 ± 0.11**

3.4.3 Friability test

The friability of Repaglinide-loaded NLC tablets (F1-F5) was evaluated to assess their resistance to mechanical stress. The tablets exhibited low friability values, ranging from 0.42% (F1) to 0.31% (F5), which are well within the pharmacopeial limit of <1%. In comparison, the marketed conventional tablet showed a friability of 0.40%.

Table 5: Friability of Repaglinide NLC Tablets

Formulation	Friability (%) (Mean ± SD)
F1	0.42 ± 0.02
F2	0.38 ± 0.01
F3	0.35 ± 0.01
F4	0.33 ± 0.01
F5	0.31 ± 0.01
Marketed Product (Prandin)	**0.40 ± 0.02**

3.4.4 Weight variation

The weight variation of Repaglinide-loaded NLC tablets (F1-F5) was evaluated to ensure dosage uniformity. Average weights ranged from 498 ± 2.0 mg (F3) to 502 ± 1.8 mg (F2), with percentage deviations between 0.8% (F5) and 1.2% (F1). These results are comparable to the marketed conventional tablet (500 ± 2.0 mg; 1.1% deviation) and fall well within the pharmacopeial limit of ±7%. Formulation F5 exhibited the least deviation, confirming superior batch-to-batch consistency and high-quality manufacturing standards.

Table 6: Weight Variation of Repaglinide NLC Tablets

Formulation	Average Weight (mg) (Mean ± SD)
F1	500 ± 2.1
F2	502 ± 1.8

F3	498 ± 2.0
F4	501 ± 1.5
F5	500 ± 1.2
Marketed Product (Prandin)	**500 ± 2.0**

3.4.5 Flow Properties of Repaglinide-Loaded NLC Tablets

The flow characteristics of Repaglinide-loaded NLC tablet formulations (F1-F5) were evaluated to assess their compressibility and suitability for direct compression or encapsulation processes.

Table 7: Flow Properties of Repaglinide-Loaded NLC Tablet (F1-F5)

Parameter	F1	F2	F3	F4	F5	Acceptable Limit
Angle of Repose (°)	30.2 ± 0.6	29.4 ± 0.5	28.7 ± 0.4	27.9 ± 0.5	27.2 ± 0.4	< 30° (Good Flow)
Bulk Density (g/mL)	0.41 ± 0.02	0.42 ± 0.01	0.43 ± 0.02	0.44 ± 0.01	0.45 ± 0.02	—
Tapped Density (g/mL)	0.49 ± 0.01	0.50 ± 0.02	0.51 ± 0.01	0.52 ± 0.01	0.53 ± 0.02	—
Carr's Index (%)	16.3 ± 0.5	15.0 ± 0.4	14.0 ± 0.3	13.4 ± 0.4	12.8 ± 0.3	5-15% (Good)
Hausner's Ratio	1.19 ± 0.02	1.17 ± 0.01	1.16 ± 0.01	1.15 ± 0.01	1.14 ± 0.01	1.00-1.25 (Good)

3.4.6 Dissolution Testing

The in-vitro dissolution profiles of Repaglinide-loaded NLC tablets (F1-F5) were compared with the marketed conventional tablet to evaluate the effect of NLC formulation on drug release. These results indicate that the NLC-based tablets can provide enhanced dissolution and potentially improved bioavailability over conventional formulations.

Table 8: In-vitro Dissolution Profile of Repaglinide NLC Tablets vs. Marketed Tablet

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	Marketed Tablet (%)

10	24.5 ± 1.2	28.3 ± 1.1	32.6 ± 1.3	36.9 ± 1.4	41.2 ± 1.5	18.4 ± 1.0
20	38.6 ± 1.4	44.7 ± 1.5	51.8 ± 1.6	57.6 ± 1.7	63.5 ± 1.8	29.3 ± 1.3
30	52.3 ± 1.6	58.8 ± 1.7	66.2 ± 1.8	73.4 ± 1.9	79.6 ± 2.0	41.7 ± 1.5
45	63.7 ± 1.7	71.2 ± 1.8	79.8 ± 1.9	87.6 ± 2.1	92.4 ± 2.3	54.6 ± 1.6
60	72.3 ± 1.8	81.5 ± 2.0	88.7 ± 2.0	92.1 ± 2.2	95.4 ± 2.4	64.2 ± 1.8

3.4.7 Stability studies as per the ICH guidelines

The stability of optimized Repaglinide NLC tablets (F5) was evaluated under accelerated conditions (40°C/75% RH) for three months. The tablets showed no significant changes in appearance and maintained good mechanical properties, with slight variations in hardness (5.8 to 5.5 kg/cm²) and friability (0.33% to 0.36%). Drug content remained above 98%, and in-vitro dissolution showed minimal reduction (95.4% to 93.8%), indicating good stability of the formulation.

Table 9: Observations of Stability studies

Parameter	Initial	1 month	2 month	3 month
Physical Appearance	Off-white, smooth	No change	No change	No change
Hardness (kg/cm²)	5.8 ± 0.11	5.7 ± 0.10	5.6 ± 0.12	5.5 ± 0.13
Friability (%)	0.33	0.34	0.35	0.36
Disintegration (min)	4.6 ± 0.2	4.7 ± 0.2	4.8 ± 0.3	4.9 ± 0.3
Drug Content (%)	99.2 ± 1.1	98.9 ± 1.2	98.5 ± 1.3	98.0 ± 1.4
Dissolution (%)	95.4 ± 2.0	94.9 ± 1.9	94.2 ± 2.1	93.8 ± 2.2

Observation: No significant changes were observed, indicating **good physical and chemical stability** of F5 under accelerated conditions.

4. Conclusion

The present study successfully developed and evaluated Repaglinide-loaded Nanostructured Lipid Carriers (NLCs) to address the drug's inherent challenges of poor aqueous solubility and low bioavailability. Among the five formulations (F1-F5) prepared via the hot homogenization-ultrasonication method, F5 emerged as the optimized batch.

Formulation F5 exhibited superior physicochemical properties, including the smallest particle size (79.3 nm), a narrow polydispersity index (0.182), and high zeta potential (−31.2 mV), ensuring excellent colloidal stability. Furthermore, it achieved the highest entrapment efficiency (92.1%) and drug loading (5.8%). When compressed into tablets, F5 demonstrated a significantly enhanced *in-vitro* release profile, reaching 95.4% drug dissolution within 60 minutes, which was markedly higher than the marketed product (64.2%).

Stability studies conducted under ICH guidelines confirmed that the optimized formulation maintains its physical and chemical integrity over time. In summary, the NLC-based oral delivery system specifically the F5 formulation represents a promising strategy to improve the therapeutic efficacy of Repaglinide in the management of Type 2 Diabetes Mellitus, providing a solid foundation for future *in-vivo* pharmacokinetic evaluations.

5. Acknowledgements

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6. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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