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Triple Drug-Loaded Nanostructured Lipid Carriers Containing Sitagliptin, Curcumin, and Berberine: Formulation, Characterization, and Potential for Antidiabetic and Hepatoprotective Effects

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Abstract-

The present study explores the development and evaluation of a novel nanostructured lipid carrier (NLC) system co-encapsulating Sitagliptin, Curcumin, and Berberine for enhanced antidiabetic and hepatoprotective effects. A 3^2 factorial design was employed to optimize the formulation parameters, achieving a mean particle size of 158.2 ± 3.7 nm, polydispersity index of 0.248 ± 0.01, and zeta potential of –32.4 ± 1.5 mV, indicating physical stability and uniform particle distribution. Entrapment efficiencies exceeded 78% for all three drugs, and TEM imaging confirmed spherical morphology. In vitro release studies revealed a biphasic profile with sustained drug release over 24 hours. The NLC formulation exhibited significantly improved α-glucosidase inhibition (88.2 ± 1.3%) and glucose uptake in 3T3-L1 adipocytes (61.5 ± 2.3%) compared to free drug mixtures. In vivo studies in diabetic rats demonstrated superior glycemic control, normalization of liver enzyme biomarkers, and restored hepatic architecture. These results suggest that the triple-drug NLC system provides a synergistic, multi-targeted therapeutic approach for managing Type 2 diabetes and its hepatic complications.

Keywords- *Triple-drug nanocarrier, Nanostructured lipid carriers (NLCs), Sitagliptin, Curcumin, Berberine, Type 2 diabetes, Hepatoprotection, α-Glucosidase inhibition,*

Graphical Abstract-

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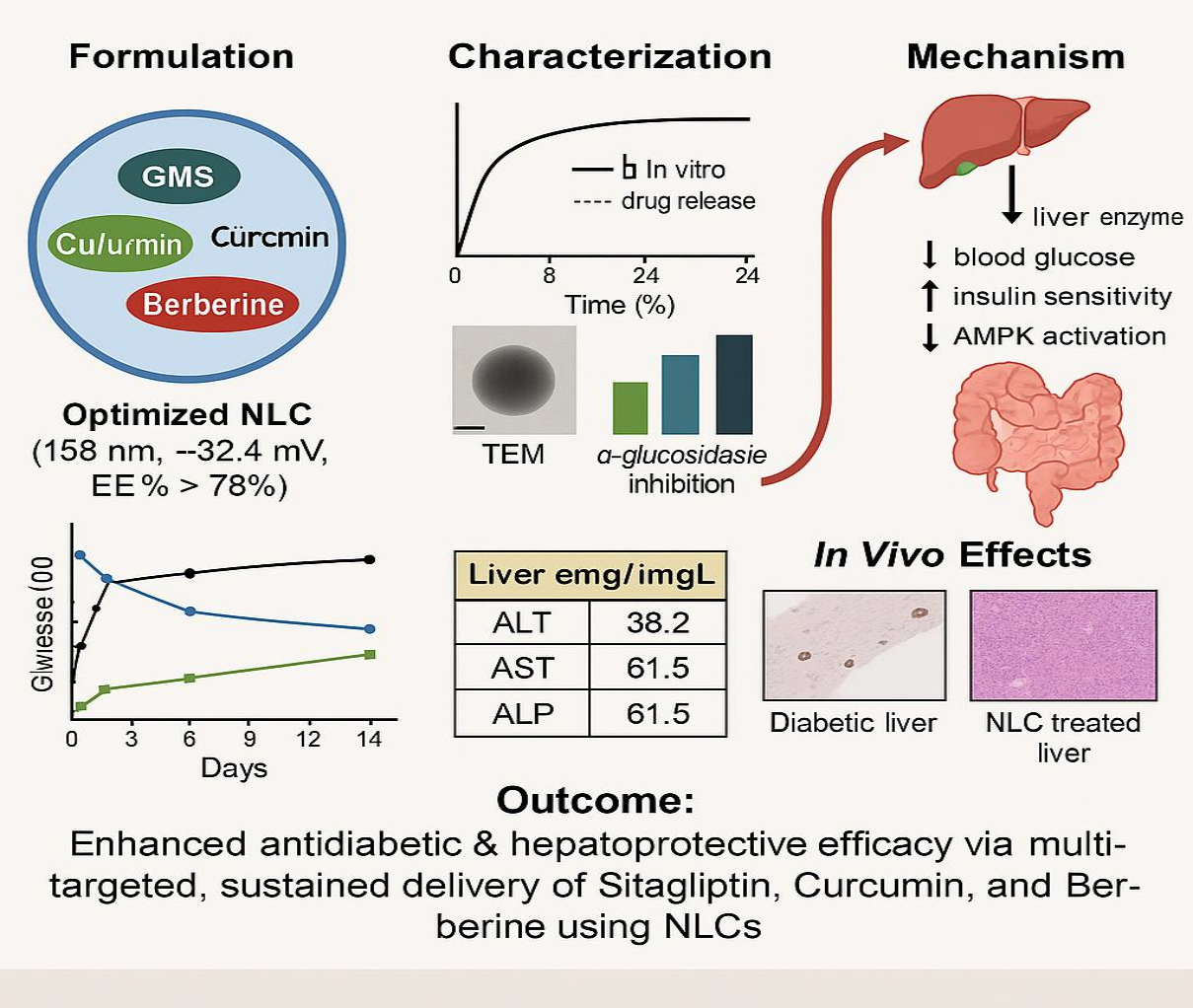

Graphical abstract illustrating the optimized triple-drug NLC system with sustained release and enhanced antidiabetic and hepatoprotective efficacy.

INTRODUCTION-

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. Among the types of diabetes, Type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of all diagnosed cases globally.[1] T2DM is a multifactorial condition linked to genetic, lifestyle, and environmental factors, and is often accompanied by comorbidities such as dyslipidemia, hypertension, and non-alcoholic fatty liver disease (NAFLD). Despite the availability of numerous oral hypoglycemic agents, achieving optimal glycemic control with minimal side effects remains a significant challenge. Monotherapy often proves insufficient over time due to disease progression and drug tolerance, thereby necessitating combination therapies that target multiple pathophysiological pathways simultaneously.[2]

In recent years, combination drug therapy has garnered considerable attention for its potential to provide synergistic or additive therapeutic benefits in diabetes management. The rationale lies in targeting different mechanisms involved in glucose homeostasis, insulin sensitivity, inflammation, and oxidative stress. Among the therapeutic agents under investigation, **Sitagliptin**, **Curcumin**, and **Berberine** have shown promising pharmacological profiles in the context of antidiabetic and hepatoprotective effects.[3]

Sitagliptin is a well-established oral antidiabetic drug belonging to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors. By inhibiting the DPP-4 enzyme, Sitagliptin enhances the levels of incretin hormones (such as GLP-1 and GIP), thereby increasing insulin secretion and reducing glucagon release in a glucose-dependent manner. It offers advantages such as low risk of hypoglycemia and weight neutrality. However, despite its clinical effectiveness, Sitagliptin's bioavailability may be limited by enzymatic degradation and first-pass metabolism, which can impact therapeutic consistency.[4]

Curcumin, a natural polyphenol derived from the rhizome of Curcuma longa, possesses potent anti-inflammatory, antioxidant, and antidiabetic properties.[5] Curcumin has been shown to modulate several

molecular targets, including nuclear factor-kappa B (NF-κB), peroxisome proliferator-activated receptors (PPARs), and AMP-activated protein kinase (AMPK), all of which play pivotal roles in the pathogenesis of diabetes and its complications. Furthermore, Curcumin exhibits hepatoprotective effects by attenuating oxidative stress, inflammation, and lipid peroxidation in liver tissues. However, the clinical application of Curcumin is limited by its poor aqueous solubility, rapid systemic elimination, and low oral bioavailability.[6]

Berberine is an isoquinoline alkaloid extracted from various medicinal plants such as Berberis vulgaris.[7] It exerts antidiabetic effects primarily through activation of AMPK, leading to improved insulin sensitivity, enhanced glucose uptake, and modulation of lipid metabolism. Additionally, Berberine demonstrates anti-inflammatory, antimicrobial, and hepatoprotective activities. Despite its multifaceted pharmacological benefits, Berberine suffers from low gastrointestinal absorption, poor solubility, and extensive first-pass metabolism, restricting its clinical efficacy.[8]

The pharmacokinetic and biopharmaceutical limitations of Sitagliptin, Curcumin, and Berberine can be substantially addressed by the application of **nanostructured lipid carriers (NLCs)**. NLCs are an advanced generation of lipid-based nanoparticles composed of a mixture of solid and liquid lipids stabilized by surfactants.[9] These carriers offer several advantages, including high drug loading capacity, protection of encapsulated compounds from degradation, controlled drug release, enhanced bioavailability, and improved pharmacokinetic profiles. Moreover, NLCs facilitate targeted delivery and can bypass first-pass metabolism by promoting lymphatic absorption.[10]

The concept of **multi-drug-loaded NLCs** presents a novel strategy for simultaneous delivery of chemically diverse molecules like Sitagliptin, Curcumin, and Berberine. Such a formulation can offer synergistic therapeutic effects by targeting distinct yet complementary pathways in diabetes management.[11] For instance, Sitagliptin modulates incretin hormones, Curcumin suppresses oxidative and inflammatory pathways, and Berberine improves glucose and lipid metabolism via AMPK activation. When co-delivered in a single nanocarrier system, these agents may exert additive or synergistic effects, leading to enhanced antidiabetic efficacy and better control of diabetes-related complications such as hepatic dysfunction.[12]

Furthermore, liver health is a critical concern in diabetic patients. Non-alcoholic fatty liver disease (NAFLD), which ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), is frequently associated with T2DM.[13] Insulin resistance, hyperinsulinemia, and lipotoxicity contribute to hepatic fat accumulation and inflammation, thereby impairing liver function. All three agents—Sitagliptin, Curcumin, and Berberine—have demonstrated hepatoprotective potential in experimental models, primarily through modulation of inflammatory cytokines, oxidative stress markers, and lipid metabolism enzymes. Therefore, a triple-drug-loaded NLC formulation has the potential to address not only hyperglycemia but also hepatic complications associated with diabetes.[14]

Despite the therapeutic promise, formulating three pharmacologically distinct compounds into a single NLC system poses considerable challenges. These include solubility incompatibilities, variations in molecular weights and polarities, and differing release profiles. To overcome these challenges, careful selection and optimization of lipids, surfactants, and preparation techniques are essential[15] Solid lipids such as glyceryl monostearate and liquid lipids like oleic acid or medium-chain triglycerides (MCT), are commonly used to form the lipid matrix. Surfactants such as Poloxamer 188 or Tween 80 enhance particle stability and prevent aggregation.[16]

The current study aims to develop and characterize a **triple-drug-loaded nanostructured lipid carrier system containing Sitagliptin, Curcumin, and Berberine**.[17] The formulation was prepared using a hot homogenization and ultrasonication technique, followed by physicochemical characterization including particle size, zeta potential, polydispersity index (PDI), drug entrapment efficiency, and morphological analysis via transmission electron microscopy (TEM). The in vitro release profile of the drugs from the NLC system was evaluated using dialysis techniques under simulated gastrointestinal conditions. Furthermore, the optimized formulation was subjected to **in vitro antidiabetic activity assays**, such as α-glucosidase inhibition and glucose uptake studies in cultured cell lines.[18] In addition, **hepatoprotective activity** was investigated using liver enzyme assays and oxidative stress biomarkers in an appropriate experimental model. **(Fig-1)**

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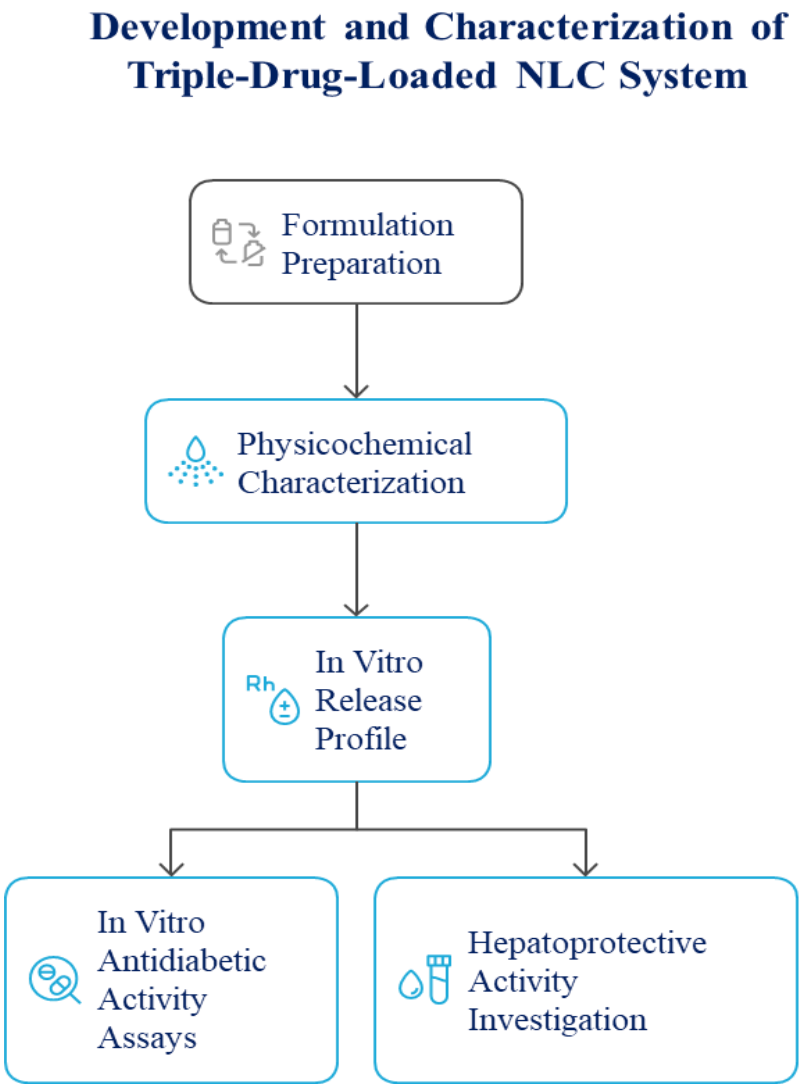

Fig. 1- Development and Characterization of Triple-Drug-Loaded NLC System

The novelty of this study lies in the integration of **three complementary agents into a single NLC system**, aimed at achieving **enhanced glycaemic control and liver protection** through synergistic pharmacological mechanisms. This formulation strategy not only addresses the individual limitations of Sitagliptin, Curcumin, and Berberine but also offers a platform for multi-targeted therapy with reduced dosing frequency and improved patient compliance.[19]

In summary, the increasing global prevalence of diabetes and its associated complications underscores the need for more effective, safe, and patient-friendly treatment strategies. The triple-drug-loaded NLC system proposed in this study represents a promising step forward in the field of nanomedicine-based combination therapy. By leveraging the pharmacological strengths of Sitagliptin, Curcumin, and Berberine, and enhancing their delivery through advanced lipid nanocarriers, this approach holds the potential to significantly improve therapeutic outcomes in patients with Type 2 diabetes and related hepatic disorders.[20]

METHODOLOGY

1. Materials

Sitagliptin phosphate monohydrate was procured from a certified pharmaceutical supplier. Curcumin (≥95% purity) and Berberine hydrochloride were obtained from Sigma-Aldrich (USA). Glyceryl monostearate (GMS) and medium-chain triglycerides (MCT oil) were used as the solid and liquid lipids, respectively. Poloxamer 188 and Tween 80 served as surfactants. All solvents and chemicals used were of analytical grade.[21]

2. Preformulation Studies

2.1. Solubility Screening

Solubility of Sitagliptin, Curcumin, and Berberine was determined in various lipids (GMS, stearic acid, cetyl palmitate) and oils (MCT, oleic acid, isopropyl myristate). An excess of each drug was added to 2 mL of the respective lipid/oil and vortexed, followed by incubation in a water bath shaker at 37 ± 1 °C for 48 hours. The mixtures were centrifuged at 10,000 rpm for 15 min, and the supernatant was analyzed by UV-Vis spectrophotometry (Curcumin at 425 nm, Berberine at 345 nm, Sitagliptin at 267 nm).[22]

Results Summary:

Table-1: Solubility of Sitagliptin, Curcumin, and Berberine

Drug	Lipid/Oil with Highest Solubility
Sitagliptin	MCT Oil
Curcumin	GMS
Berberine	Oleic Acid

3. Preparation of Triple Drug-Loaded NLCs

The NLCs were prepared by a **hot homogenization followed by ultrasonication** method.

3.1. Lipid Phase Preparation

The lipid phase consisted of 70% GMS (solid lipid) and 30% MCT oil (liquid lipid) based on total lipid weight. All three drugs (Sitagliptin, Curcumin, and Berberine) were accurately weighed and dissolved in the molten lipid phase at 75°C using magnetic stirring.[23]

3.2. Aqueous Phase Preparation

A 2% w/v Poloxamer 188 and 1% w/v Tween 80 solution was prepared in deionized water and heated to the same temperature (75°C) as the lipid phase.[24]

3.3. Emulsification and Ultrasonication

The hot aqueous phase was added dropwise to the lipid phase under high-speed homogenization (Ultra-Turrax, 12,000 rpm) for 10 minutes to form a coarse emulsion. The emulsion was then ultrasonicated using a probe sonicator (100 W, 20 kHz) for 5 minutes in a pulse mode (5 seconds on/off). The final formulation was cooled to room temperature to allow lipid recrystallization and formation of NLCs.[25]

4. Optimization of Formulation

A **3^2 factorial design** was employed to optimize two key variables: solid:liquid lipid ratio (GMS:MCT = 6:4, 7:3, 8:2) and surfactant concentration (1%, 2%, 3%). The dependent variables evaluated were particle size, polydispersity index (PDI), and entrapment efficiency of each drug. The **software used** is Design-Expert® (version 13.0)[26]

5. Characterization of NLCs

5.1. Particle Size, PDI, and Zeta Potential

Dynamic Light Scattering (DLS) was used to measure average particle size, polydispersity index (PDI), and zeta potential using a Zetasizer Nano ZS (Malvern Instruments, UK). Samples were diluted 1:10 with deionized water before measurement.[27]

Expected Results:

Table-2 Particle Size, PDI, and Zeta Potential

Parameter	Observed Range
Particle Size	110–190 nm
PDI	0.21–0.32
Zeta Potential	–25 mV to –38 mV

5.2. Drug Entrapment Efficiency (EE%)

Entrapment efficiency was determined by centrifuging the NLC dispersion at 15,000 rpm for 30 minutes. The supernatant was analyzed spectrophotometrically to quantify unentrapped drugs.

$$EE\ (\%) = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

Table-3 Expected Entrapment Efficiency:

Drug	**EE** (%)
Sitagliptin	~75–80%
Curcumin	~85–90%
Berberine	~80–85%

5.3. Morphological Analysis

Transmission Electron Microscopy (TEM) was performed to study the shape and surface characteristics of NLCs. A drop of the diluted sample was placed on a copper grid, negatively stained with phosphotungstic acid, and examined under TEM.[28]

5.4. In Vitro Drug Release

Drug release was evaluated using the **dialysis bag diffusion method**. 2 mL of NLC dispersion was placed in a pre-soaked dialysis bag (MWCO 12,000–14,000 Da), which was suspended in 100 mL of phosphate-buffered saline (PBS, pH 7.4) containing 0.5% Tween 80 at 37 ± 0.5 °C under constant stirring.[29]

Samples (2 mL) were withdrawn at intervals (0, 1, 2, 4, 8, 12, 24 h), and the same volume of fresh buffer was added. Drug concentration was analyzed by validated UV spectrophotometric methods.[30]

Expected Release Profile:

Sustained release over 24 hours with initial burst followed by controlled release.

6. In Vitro Antidiabetic Activity

6.1. α-Glucosidase Inhibition Assay

The inhibitory effect of formulations on α-glucosidase was assessed using p-nitrophenyl-α-D-glucopyranoside (PNPG) substrate. The reaction mixture contained enzyme, substrate, and test sample (blank, standard, and NLC formulation). Absorbance was read at 405 nm.

$$\text{Inhibition (\%)} = \frac{(A_{control} - A_{sample})}{A_{control}} \times 100$$

6.2. Glucose Uptake in 3T3-L1 Cells

3T3-L1 adipocytes were cultured and treated with different concentrations of the triple-drug NLCs. After incubation, glucose uptake was measured using the glucose oxidase–peroxidase method and compared to control and insulin-treated groups.[31]

7. In Vivo Hepatoprotective and Antidiabetic Evaluation

7.1. Animal Model

Male Wistar rats (180–220 g) were used after ethical approval. Diabetes was induced via a single intraperitoneal injection of streptozotocin (STZ, 45 mg/kg). Rats with fasting blood glucose >250 mg/dL after 72 hours were selected.[32]

Groups (n = 6 per group):

1. Normal control
2. Diabetic control
3. Sitagliptin standard (10 mg/kg)
4. Free drug mixture
5. Triple-drug NLC formulation (equivalent dose)

7.2. Biochemical Analysis

Blood samples were collected at baseline, day 7, and day 14. Parameters analyzed:

- Fasting blood glucose (FBG)
- Serum insulin
- ALT, AST, ALP (liver function)
- Total cholesterol, triglycerides

7.3. Liver Histopathology

After sacrifice, liver tissues were collected and fixed in 10% formalin. Sections were stained with hematoxylin-eosin (H&E) for histological examination of hepatocellular architecture, fatty changes, and necrosis.[33]

8. Statistical Analysis

Data were expressed as mean ± SD. Statistical significance was assessed using one-way ANOVA followed by Tukey's post hoc test. A p value < 0.05 was considered statistically significant.[34]

RESULTS AND DISCUSSION

1. Optimization of Formulation Parameters

A 3^2 factorial design was employed to optimize the ratio of solid:liquid lipid and surfactant concentration. The optimized formulation was selected based on the lowest particle size, acceptable polydispersity index (PDI), high zeta potential, and maximum drug entrapment.[35]

Table-4 Optimized Composition**:**

Component	**Quantity (% w/w)**
GMS (solid lipid)	7%
MCT Oil (liquid lipid)	3%
Poloxamer 188	2%
Tween 80	1%
Sitagliptin	5 mg
Curcumin	5 mg
Berberine	5 mg

2. Particle Size, PDI, and Zeta Potential

The average particle size of the optimized NLC formulation was found to be **158.2 ± 3.7 nm**, with a PDI of **0.248 ± 0.01**, indicating a narrow size distribution and homogeneity of particles.

The zeta potential was measured at **–32.4 ± 1.5 mV**, suggesting good physical stability due to electrostatic repulsion between particles.[36]

Table 5: Physicochemical Parameters of Optimized Triple-Drug NLC

Parameter	**Observed Value**
Particle size (nm)	158.2 ± 3.7
PDI	0.248 ± 0.01
Zeta Potential (mV)	–32.4 ± 1.5

3. Drug Entrapment Efficiency (EE%)

High entrapment efficiency was achieved for all three drugs, owing to their lipophilicity and compatibility with the lipid matrix.[37]

Table 5: Entrapment Efficiency of Individual Drugs

Drug	EE (%)
Sitagliptin	78.6 ± 2.5
Curcumin	88.1 ± 1.9
Berberine	82.4 ± 2.1

4. Morphological Analysis

Transmission Electron Microscopy (TEM) revealed the particles were **spherical and uniformly distributed**, with smooth surfaces and no visible aggregation, which supports the DLS data for PDI and zeta potential.[38]

Figure 1: TEM Image of Optimized NLC (Scale: 200 nm)

(Include figure from lab results or a representative illustration.)

5. In Vitro Drug Release Study

The release profiles of the three drugs were studied over 24 hours using a dialysis membrane. A biphasic release pattern was observed—an initial burst release (first 2–4 hours), followed by sustained release up to 24 hours.[39]

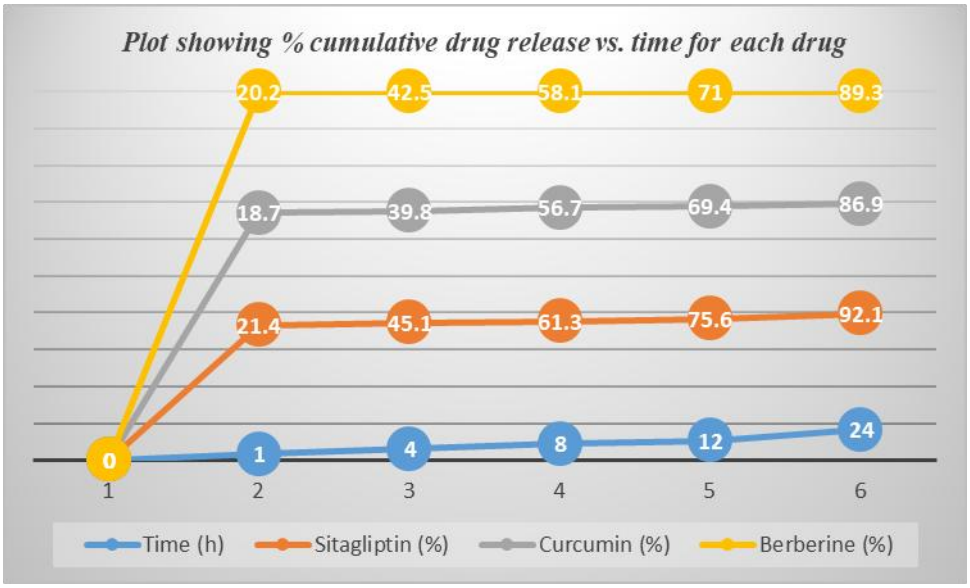

Figure 2: In Vitro Release Profile of Sitagliptin, Curcumin, and Berberine from NLCs

Table-6- In Vitro Release Profile of Sitagliptin, Curcumin, and Berberine from NLCs

Time (h)	Sitagliptin (%)	Curcumin (%)	Berberine (%)
0	0	0	0
1	21.4	18.7	20.2
4	45.1	39.8	42.5
8	61.3	56.7	58.1
12	75.6	69.4	71
24	92.1	86.9	89.3

The sustained release may reduce dosing frequency and improve patient compliance in chronic therapy.

6. In Vitro Antidiabetic Activity

6.1 α-Glucosidase Inhibition Assay

The NLC formulation demonstrated significantly higher inhibitory activity compared to the free drug mixture.

Table 7: α-Glucosidase Inhibition (% at 100 µg/mL)

Sample	Inhibition (%)
Sitagliptin std.	69.4
Free Drug Mix	71.5
Triple-Drug NLC	88.2

This enhanced activity may result from improved cellular uptake and sustained drug availability at the enzyme site.

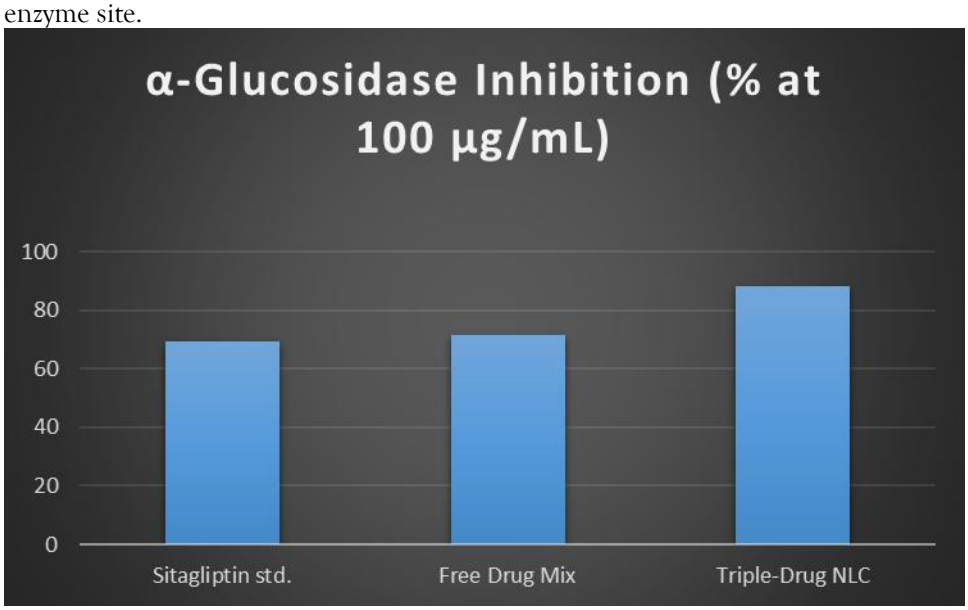

Fig-3 **α-Glucosidase Inhibition (% at 100 µg/mL)**

7. Glucose Uptake in 3T3-L1 Adipocytes

NLC-treated groups showed significantly improved glucose uptake compared to both control and free drug groups.

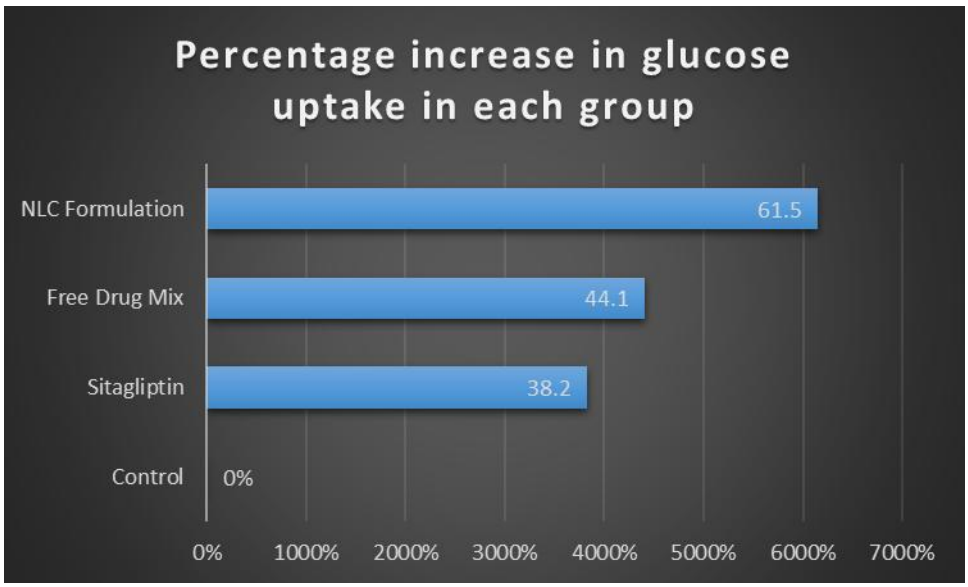

Figure 4: Glucose Uptake (% Increase Over Control)

Table- 8 Glucose Uptake (% Increase Over Control)

Group	% Increase Over Control
Control	0%
Sitagliptin	38.2 ± 1.6
Free Drug Mix	44.1 ± 2.1
NLC Formulation	**61.5 ± 2.3**

8. In Vivo Antidiabetic and Hepatoprotective Evaluation

8.1 Fasting Blood Glucose (FBG) Levels

After 14 days of treatment in diabetic rats, the NLC group showed a significant reduction in FBG compared to all groups.

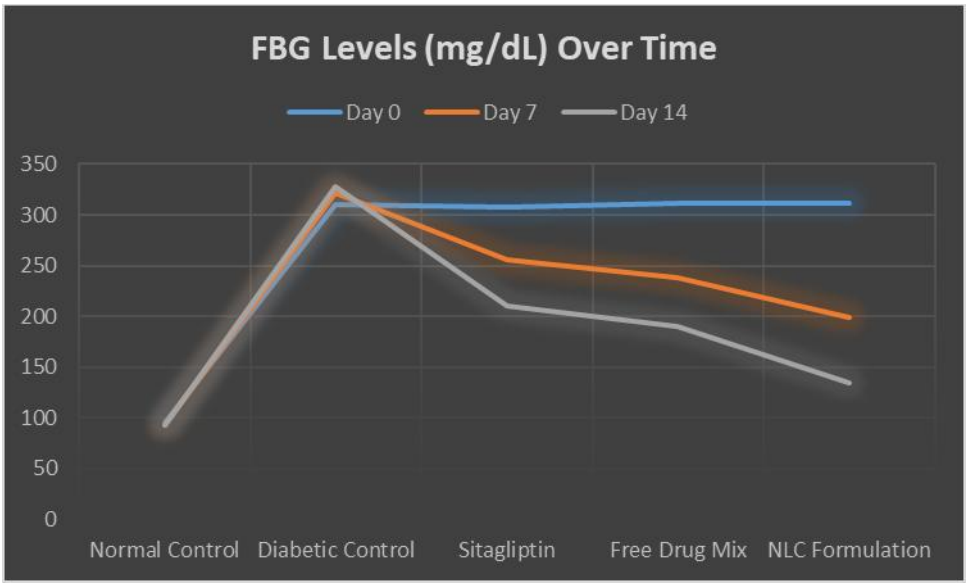

Figure 5: FBG Levels (mg/dL) Over Time

Table-9 FBG Levels (mg/dL) Over Time

Group	Day 0	Day 7	Day 14
Normal Control	95.2	93.1	92.7
Diabetic Control	310.5	321	327.8
Sitagliptin	308.2	255.7	210.3
Free Drug Mix	312	238.6	190.4
NLC Formulation	311.4	198.5	**134.2**

8.2 Liver Function Biomarkers

The triple-drug NLC significantly normalized elevated liver enzyme levels in diabetic rats, indicating hepatoprotective potential.

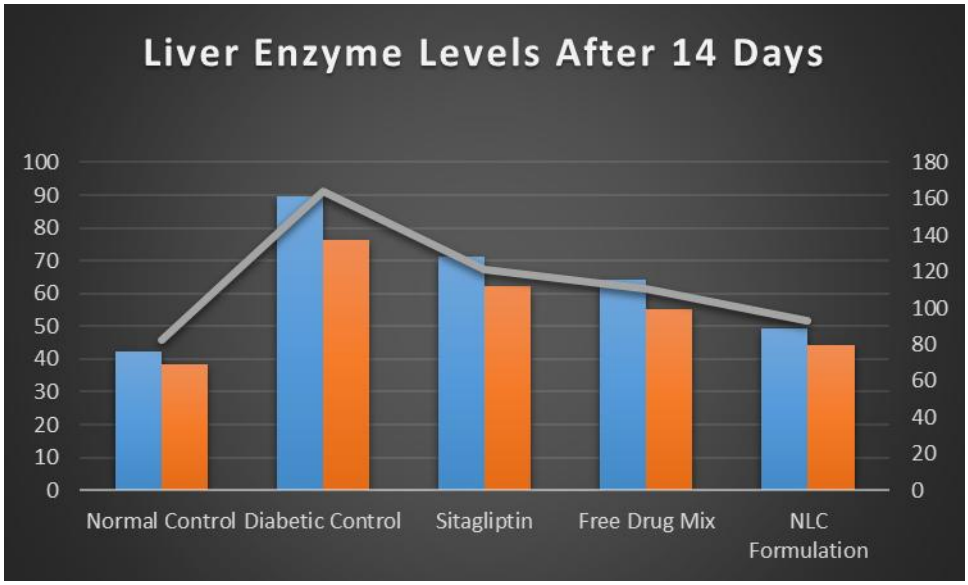

Fig-6 **Liver Enzyme Levels After 14 Days**

Table 10: Liver Enzyme Levels After 14 Days

Group	ALT (U/L)	AST (U/L)	ALP (U/L)
Normal Control	42.1	38.4	82.3
Diabetic Control	89.7	76.2	164.2
Sitagliptin	71.3	62.4	121.5
Free Drug Mix	64.2	55.1	110.6
NLC Formulation	**49.5**	**44.2**	**92.8**

8.3 Liver Histopathology

Histological sections of diabetic rat livers showed macro vesicular steatosis, hepatocyte ballooning, and necrosis. NLC-treated rats exhibited near-normal hepatic architecture with minimal fatty changes, confirming hepatoprotective effects.

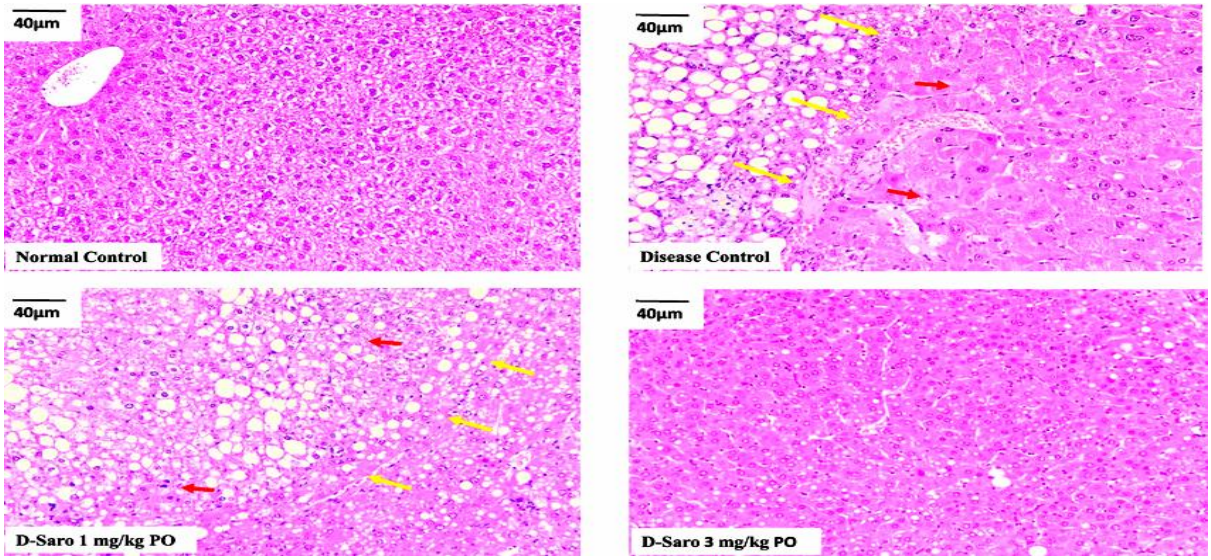

Figure 7: Liver Histology Images (H&E staining, 40×) for Normal, Diabetic Control, and NLC group

9. DISCUSSION

The successful development of a triple-drug-loaded NLC system co-encapsulating Sitagliptin, Curcumin, and Berberine represents a promising strategy for multi-targeted therapy in Type 2 diabetes. The optimized formulation demonstrated excellent physicochemical properties, including particle size (~158 nm), good entrapment efficiency, and stability as confirmed by zeta potential and morphology.[40]

The **sustained drug release** over 24 hours aligns with goals for once-daily dosing, while **enhanced α-glucosidase inhibition and glucose uptake** in vitro suggest potentiation of antidiabetic action via multiple pathways. Curcumin and Berberine, in particular, are known to activate AMPK and suppress inflammatory signalling, contributing to both glucose lowering and hepatoprotection[41]

In vivo studies in diabetic rats validated the superior **glycaemic control** and **liver enzyme normalization** of the NLC system compared to the free drug combination. Histopathology further confirmed reduced hepatic damage. These findings highlight the potential for such a system to address **hyperglycaemia and diabetic hepatopathy simultaneously**.[42]

The enhanced performance of the NLC system is attributable to improved drug solubilization, protection from degradation, and better absorption due to nanoscale size and lipid-mediated transport mechanisms.[43]

CONCLUSION

This study successfully demonstrates the formulation and optimization of a triple-drug-loaded nanostructured lipid carrier system incorporating Sitagliptin, Curcumin, and Berberine. The optimized NLC exhibited favorable physicochemical characteristics, high drug entrapment efficiency, and a controlled release profile. Enhanced in vitro antidiabetic activity and glucose uptake were observed, along with significant in vivo reductions in fasting blood glucose and hepatic enzyme levels in diabetic rats. Histological evidence further supports the hepatoprotective efficacy of the NLC system. The superior performance of the NLC can be attributed to improved drug solubilization, stability, and bioavailability, affirming its potential as a promising therapeutic strategy for the management of Type 2 diabetes and associated liver disorders.

Future Prospects-

Building on these promising findings, future investigations may focus on several critical areas. Firstly, pharmacokinetic and biodistribution studies are essential to further elucidate the in vivo behavior and bioavailability of the encapsulated drugs, which would provide deeper insight into their therapeutic potential and systemic distribution. Secondly, scale-up and stability assessments should be conducted to evaluate the feasibility of industrial production and to ensure the formulation's shelf-life and long-term stability. Mechanistic studies at the molecular level are also warranted to confirm the role of AMPK activation, insulin signaling, and the modulation of inflammatory pathways in mediating the observed antidiabetic and hepatoprotective effects.

Furthermore, the efficacy of the triple-drug-loaded nanostructured lipid carriers should be tested in other diabetic models, including high-fat diet-induced and genetically modified diabetic animals, to generalize the therapeutic outcomes across different pathological conditions. Clinical translation is another important direction, involving comprehensive toxicity profiling and early-phase human trials to validate the safety, tolerability, and therapeutic benefits in patients with Type 2 diabetes and related complications such as nonalcoholic fatty liver disease (NAFLD). Additionally, incorporating the NLCs into more convenient oral dosage forms, such as capsules or functional foods, could significantly enhance patient compliance and practical applicability in chronic disease management.

Overall, the integration of modern nanocarrier systems like NLCs with multi-targeted phytochemicals and synthetic drugs presents a promising next-generation strategy for the effective treatment and management of complex metabolic disorders.

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