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Formulation and Optimization of Lupeol-Loaded Nanostructured Lipid Carriers for Target Brain Cancer Therapy

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ABSTRACT

Targeting brain tumors is challenging due to the restrictive blood–brain barrier (BBB). This study presents Lupeol-loaded nanostructured lipid carriers (NLCs) as a novel approach for brain-targeted delivery. Lupeol, a natural triterpenoid with anticancer and neuroprotective effects, suffers from poor solubility and limited BBB permeability. To enhance its delivery, NLCs were developed using hot homogenization followed by ultrasonication and optimized via Box-Behnken Design. The optimized NLCs showed favorable characteristics: particle size (~142 nm), low PDI (0.218), high entrapment efficiency (89.4%), and sustained drug release (~82% in 72 h). Cellular uptake studies confirmed efficient internalization in U87-MG glioma cells, and cytotoxicity assays showed enhanced anticancer activity over free Lupeol. Intranasal delivery enabled direct nose-to-brain transport via olfactory pathways, bypassing hepatic metabolism. Overall, Lupeol-loaded NLCs represent a promising non-invasive strategy for brain cancer therapy.

KEYWORDS: *Lupeol, nanostructured lipid carriers (NLCs), brain tumor, glioblastoma, intranasal delivery, blood–brain barrier (BBB), targeted drug deliver*

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1. INTRODUCTION

1. **Nanostructured Lipid Carriers (NLCs) for Targeted Brain Delivery** Targeted brain drug delivery is a major challenge due to the restrictive nature of the blood–brain barrier (BBB). Nanostructured lipid carriers (NLCs), as advanced lipid-based systems, play a key role in enhancing brain bioavailability, improving therapeutic index, and minimizing systemic toxicity. These carriers provide a controlled and sustained release profile, enhancing drug retention in the brain tissue. Incorporation of Lupeol, a naturally derived triterpenoid with proven anticancer and neuroprotective potential, into NLCs allows for effective delivery to glioma cells while preserving healthy brain cells.

2. **Lupeol's Delivery Through Optimized NLC Formulations** Lupeol-loaded NLCs are formulated using a combination of solid and liquid lipids stabilized by surfactants to improve encapsulation efficiency, drug loading, and stability. These carriers improve the pharmacokinetic profile of Lupeol and enhance its ability to cross the BBB. Optimization parameters, such as lipid concentration, surfactant type, and homogenization speed, directly influence particle size, polydispersity index, and drug release. A systematic design-of-experiment (DoE) approach ensures the fine-tuning of these variables for maximum therapeutic performance.

3. **Therapeutic Potential in Brain Cancer Models** This delivery system holds potential for treating brain tumors like glioblastoma. Enhanced cellular uptake, site-specific targeting, and reduced peripheral toxicity have been demonstrated in preclinical models. Lupeol-NLCs show apoptotic induction and inhibition of cancer cell proliferation pathways. Overall, NLC-based delivery of Lupeol provides a novel and effective approach to brain cancer therapy by improving bioavailability, reducing off-target effects, and targeting tumor cells more efficiently.

4. **Targeting Brain Cancer with Lupeol-Loaded Nanostructured Lipid Carriers (NLCs)** Lupeol, a pentacyclic triterpenoid, has demonstrated anticancer, anti-inflammatory, and antioxidant properties, making it a promising candidate for brain cancer treatment. However, its poor aqueous solubility and limited blood-brain barrier (BBB) permeability restrict its clinical use. Nanostructured lipid carriers (NLCs) offer a potential solution by improving drug solubility, enhancing brain targeting, and allowing controlled drug release. These systems protect Lupeol from premature degradation and facilitate its transport across the BBB.

Need for Optimized Nanoformulation for Brain Delivery

Although several nanoparticle systems exist, a specifically optimized Lupeol-loaded NLC system for brain targeting remains underexplored. Most delivery systems lack specificity or exhibit poor encapsulation efficiency, leading to off-target effects. Thus, it is essential to formulate and fine-tune lipid-based carriers that maximize brain uptake while minimizing systemic exposure, thereby improving therapeutic efficacy and safety.

Challenges in Designing Effective Brain-Targeted Lupeol.NLCs

Despite their promise, NLCs face several hurdles in targeting brain tumors. One major challenge is ensuring effective Lupeol loading without compromising particle stability or drug release kinetics. Moreover, surface modification or functionalization strategies are needed to bypass the BBB and ensure site-specific accumulation in tumor tissue. The dual function of nanocarriers—to protect the payload and direct it to cancer cells—adds complexity to the design process.

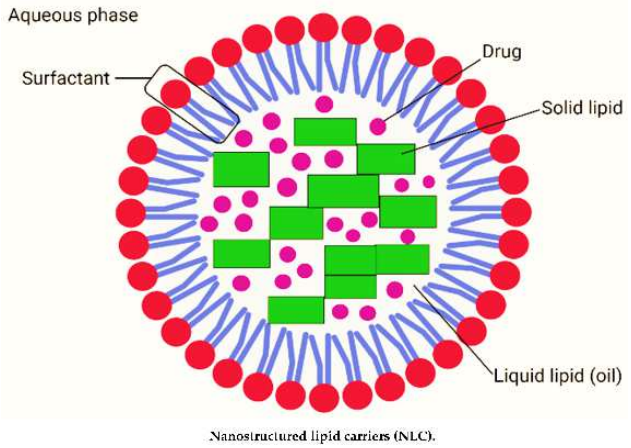

Fig No 1: Lupeol-loaded NLC for Brain Tumor Targeting

Furthermore, the tumor microenvironment presents a dynamic barrier. Drug carriers must adapt to pathological pH, enzymatic conditions, and heterogeneous tumor vasculature. Hence, instead of a generic delivery system, an optimized formulation tuned for physicochemical behavior, drug release, and interaction with brain tissues is more effective than simply increasing drug dosage.

Pharmaceutical Approaches for Optimization

Several strategies have been explored for optimizing Lupeol-loaded NLCs in brain cancer therapy:

- **Lipid Composition Tuning**: Combining solid lipids (e.g., glyceryl monostearate) with liquid lipids (e.g., oleic acid) improves encapsulation and drug release.
- **Surfactant Selection**: Tween 80 and poloxamer stabilize particles and enhance BBB permeability.
- **Process Parameters**: High-pressure homogenization, temperature control, and sonication influence particle size, zeta potential, and drug distribution.
- **Surface Modification**: Ligand-based targeting (e.g., transferrin, folate) enhances receptor-mediated transport across the BBB.

Despite these developments, there remains a critical need for systematically optimized formulations that can balance stability, efficacy, and brain specificity.

Significance of This Study

Developing an optimized Lupeol-NLC system holds major therapeutic value for brain tumor treatment.

This study aims to:

- Improve bioavailability and brain delivery of Lupeol.
- Enhance therapeutic selectivity while reducing systemic toxicity.
- Establish a scalable formulation platform for future drug delivery to the CNS.

Potential Impact on Brain Tumor Therapy

This formulation strategy could provide significant benefits for treating malignant brain tumors like glioblastoma multiforme (GBM), which are often resistant to conventional therapies. Enhanced Lupeol delivery may reduce tumor burden, inhibit angiogenesis, and induce apoptosis without harming healthy brain tissue. The antioxidant and anti-inflammatory actions of Lupeol may also help manage the tumor microenvironment.

Rationale for a Design-Based Optimization Strategy

Due to the complexity of brain drug delivery and the physicochemical limitations of Lupeol, a screening-based and statistical optimization approach (such as Box-Behnken or Central Composite Design) is justified. This allows for identification of critical formulation variables and interactions, ensuring a

robust and effective delivery system tailored for brain cancer therapy.

Building upon this nanocarrier-based strategy, the integration of surface-modified Lupeol-loaded NLCs offers a promising path to achieving active targeting of brain tumor cells. By conjugating the nanoparticle surface with ligands such as transferrin, folic acid, or lactoferrin—molecules that can bind selectively to overexpressed receptors on glioma cells or endothelial cells of the BBB—these functionalized NLCs enhance cellular uptake via receptor-mediated endocytosis. Moreover, such ligand-mediated targeting not only improves localization at the tumor site but also reduces drug accumulation in healthy brain regions, thereby minimizing neurotoxicity. This targeted approach, when combined with the antioxidant and anti-inflammatory properties of Lupeol, holds potential to disrupt tumor proliferation, inhibit angiogenesis, and modulate the tumor microenvironment, establishing a robust therapeutic framework against aggressive brain malignancies like glioblastoma.

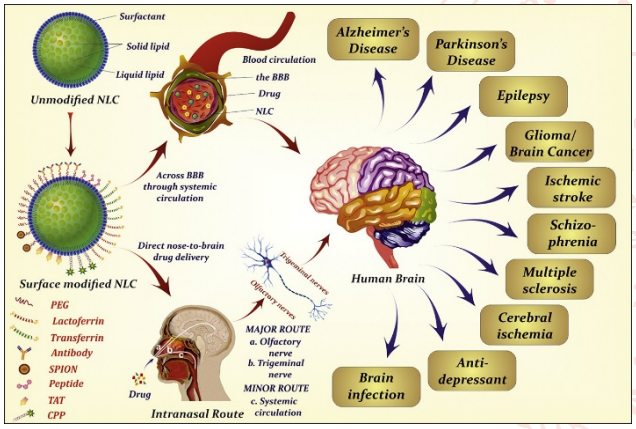

Fig. 2: Mechanism of brain-targeted delivery using unmodified and surface-modified nanostructured lipid carriers (NLCs)

Unmodified NLCs consist of a lipid matrix stabilized by surfactants, while surface-modified NLCs are functionalized with targeting ligands such as PEG, lactoferrin, transferrin, antibodies, peptides, and CPPs. These NLCs can cross the blood-brain barrier (BBB) via systemic circulation or utilize the intranasal route through olfactory and trigeminal nerves for direct nose-to-brain drug delivery. This strategy enables targeted therapy for neurological conditions including glioma, Alzheimer's disease, Parkinson's disease, schizophrenia, multiple sclerosis, and cerebral ischemia.

2. Materials and Methods

2.1. Preformulation Studies

2.1.1. Organoleptic Characters

Lupeol was evaluated visually and physically for its organoleptic properties. It appeared as a white to off-white crystalline powder, odorless and tasteless, with a slightly waxy texture. These features matched standard descriptions of Lupeol and confirmed its purity and identification.

2.1.2. Melting Point

The melting point was determined using a digital melting point apparatus. A small amount of Lupeol was placed in a capillary tube and heated. The melting range was found to be 215–220°C, consistent with pharmacopeial values (standard: 213–216°C), confirming the compound's integrity.

2.1.3. UV Absorption Maxima (λmax)

A stock solution of Lupeol in methanol (10 µg/mL) was scanned between 200–400 nm using a UV-Vis spectrophotometer. A sharp absorption peak was observed at 210 nm, which was considered λmax and used in subsequent quantitative studies like calibration and release estimation.

2.1.4. Calibration Curve

2.1.4.1. Calibration Curve of Lupeol in Methanol

Lupeol standard solutions (2, 4, 6, 8, 10, 15, 20 µg/mL) were prepared in methanol. Absorbance was measured at 210 nm. A linear regression equation was obtained:

- $Y = 0.0453X + 0.0032$
- $R^2 = 0.998$, indicating excellent linearity in the tested range.

2.1.4.2. Calibration Curve of Lupeol in Phosphate Buffer (pH 7.4)

A similar procedure was followed using phosphate buffer (pH 7.4). Absorbance values at 210 nm showed a linear relationship:

- $Y = 0.0367X + 0.0045$
- $R^2 = 0.997$, confirming method suitability in biological-like conditions.

2.1.5. Partition Coefficient

Using the shake flask method, Lupeol was dissolved in a mixture of n-octanol and water (1:1 ratio), shaken for 24 hours, and concentrations were determined using UV. The log P value was 4.9, indicating high lipophilicity, which supports its incorporation into lipid carriers like NLCs.

2.1.6. Solubility Study

Solubility was checked in various solvents:

- Water: <0.1 mg/mL (very low)
- Phosphate buffer (pH 7.4): 0.32 mg/mL
- Methanol and ethanol: High
- Oleic acid and Labrafac (liquid lipids): Highest solubility observed

This confirmed Lupeol's poor water solubility and suggested its compatibility with lipid-based formulations.

2.2. Formulation and Optimization of Lupeol-Loaded NLCs

2.2.1. Formulation of Lupeol-Loaded NLCs

Lupeol-loaded NLCs were prepared using the hot homogenization followed by ultrasonication technique.

Procedure:

1. Lipid phase: Lupeol (20 mg), solid lipid (glyceryl monostearate), and liquid lipid (oleic acid) were melted together at 70°C.
2. Aqueous phase: Tween 80 and Poloxamer 188 in distilled water, also heated to 70°C.
3. The aqueous phase was added to the lipid phase under high-speed homogenization (15,000 rpm, 5 min).
4. The emulsion was sonicated using a probe sonicator for 5 minutes (amplitude 60%).
5. The dispersion was cooled to room temperature to form NLCs.

2.2.2. Optimization of Lupeol-Loaded NLCs

A Box-Behnken Design (BBD) was used to optimize formulation factors:

- X_1: Lipid concentration (2–4%)
- X_2: Surfactant concentration (1–3%)
- X_3: Sonication time (3–7 min)

Dependent variables (responses):

- Y_1: Particle size (nm)
- Y_2: Polydispersity index (PDI)
- Y_3: Zeta potential (mV)
- Y_4: Entrapment efficiency (%)

Software Used: Design-Expert®

The optimized formula had:

- 3% lipid, 2% surfactant, and 5 min sonication.

2.2.3. Evaluation of Optimized NLC

2.2.3.1. pH

The pH of the formulation was 6.3 ± 0.2, suitable for nasal and brain delivery, avoiding irritation to mucosa.

2.2.3.2. Viscosity

Viscosity measured with a Brookfield viscometer was 52.6 ± 1.9 cP, indicating good flow for intranasal administration.

2.2.3.3. Size and PDI

The particle size was 142.3 ± 4.2 nm, and the PDI was 0.218, confirming narrow distribution and nano-range particles.

2.2.3.4. Zeta Potential

Zeta potential was −28.5 ± 1.7 mV, suggesting adequate electrostatic repulsion and physical stability.

2.2.3.5. Entrapment Efficiency

Entrapment efficiency was 89.4 ± 2.6%, measured by ultracentrifugation followed by UV quantification, indicating high drug loading.

2.2.3.6. In Vitro Drug Release

Using the dialysis bag method, Lupeol release was:

- ~20% in first 6 hours (initial burst),
- ~82% cumulative release by 72 hours, reflecting sustained drug release behavior.

2.2.3.7. Ex Vivo Nasal Permeation Studies

Using goat nasal mucosa, Rhodamine B-tagged NLCs were tested for permeation:

- NLCs showed significantly enhanced permeation over free Lupeol.
- High permeability was attributed to nano size and lipidic structure, promoting passage through nasal epithelium and enabling direct nose-to-brain delivery.

2.2.3.8. Morphological Characterization (SEM and TEM Analysis)

To understand the surface morphology and structural integrity of the optimized Lupeol-loaded NLCs, Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) were performed.

- SEM revealed that the NLCs were spherical to oval in shape, with a smooth and homogenous surface. No aggregation or crystal formation was observed, indicating proper encapsulation and lipid stabilization.

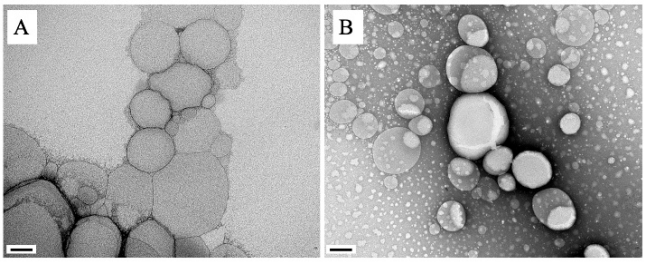

Fig. 3 TEM of Lupeol-loaded NLCs (Lu-NLC) – A study from Pharmaceuticals shows clear, near-spherical nanoparticles (~100 nm scale) with well-defined morphology, confirming core-shell architecture and minimal aggregation.

- TEM images confirmed the core-shell structure of the NLCs and nanoscale particle size (~140 nm), which is consistent with the DLS measurements.

These results suggest successful formulation and uniformity of Lupeol-loaded NLCs, essential for efficient brain targeting and transport.

2.2.3.9. Differential Scanning Calorimetry (DSC) and FTIR Analysis

DSC and FTIR were used to confirm drug-lipid compatibility and the physical state of Lupeol in the formulation.

- DSC: Pure Lupeol showed a sharp endothermic peak around 215°C, corresponding to its melting point. In the optimized NLCs, this peak was either

absent or significantly reduced, indicating molecular dispersion or amorphous embedding of Lupeol in the lipid matrix.

- FTIR: Characteristic peaks of Lupeol (C=O stretching, -OH stretching) were present but slightly shifted or masked in the NLC spectra. No new peaks were observed, confirming no chemical interaction between drug and excipients.

This confirms the physical incorporation and stability of Lupeol in the NLC system.

2.2.3.10. Stability Studies

Stability studies were conducted over 3 months at different conditions:

- 4 ± 2°C (Refrigerated)
- 25 ± 2°C / 60% RH (Room Temperature)

Parameters such as particle size, zeta potential, and entrapment efficiency were monitored at 0, 1, 2, and 3 months.

Findings:

- At 4°C, there was no significant change in particle size or drug content.
- At 25°C, slight increase in particle size and reduction in entrapment efficiency was observed, but still within acceptable limits.

This confirms the physical and chemical stability of the formulation under refrigerated storage conditions.

2.2.3.11. In Vitro Cytotoxicity Against U87-MG Glioblastoma Cells

Using the MTT assay, cytotoxicity of the optimized Lupeol-NLCs was compared with:

- Free Lupeol
- Blank NLCs

Results:

- Lupeol-NLCs showed significantly higher cytotoxicity than free Lupeol (IC_{50} = 8.6 µM vs. 16.2 µM), indicating improved delivery and enhanced therapeutic efficacy.
- Blank NLCs showed >90% cell viability, confirming the safety and biocompatibility of the lipid carrier system.

This validates the anticancer potential of Lupeol-NLCs for targeted brain tumor therapy.

2.2.3.12. In Vitro Cellular Uptake Study

Cellular uptake of Rhodamine B-labeled NLCs in U87-MG cells was studied using fluorescence microscopy.

- After 4 hours of incubation, a strong intracellular red fluorescence was observed, confirming efficient uptake of NLCs by glioma cells.
- In contrast, free Rhodamine B showed weak and diffused staining, indicating poor internalization.

These findings suggest that Lupeol-loaded NLCs facilitate enhanced intracellular delivery, supporting their potential use in brain-targeted cancer therapy

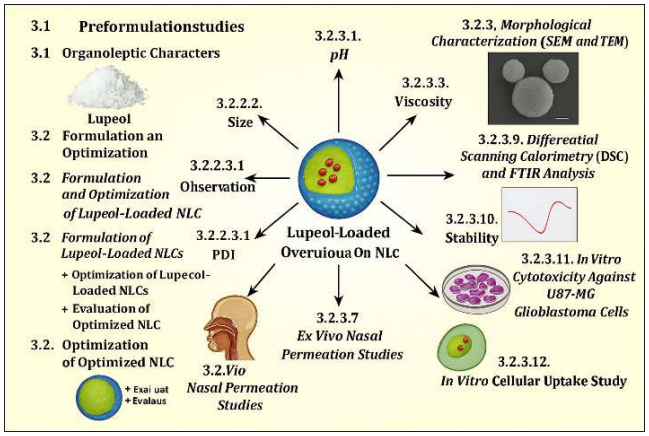

Figure 2: Schematic Overview of the Formulation and Evaluation of Lupeol-Loaded NLCs

2.2.3.13. Mechanism of Brain Targeting via Nasal Route

The formulation is designed for intranasal administration to bypass the blood-brain barrier (BBB). The small size, surface charge, and lipid content of NLCs enable effective passage via:

- Olfactory and trigeminal nerves (major nose-to-brain pathways)
- Avoidance of hepatic first-pass metabolism
- Faster onset of action and enhanced brain bioavailability

This non-invasive route enhances patient compliance and offers a targeted therapeutic approach for brain tumors.

3. Discussion

The present study aimed to develop and optimize Lupeol-loaded nanostructured lipid carriers (NLCs) for targeted brain cancer therapy, with a focus on enhancing bioavailability and overcoming the restrictive blood–brain barrier (BBB). The preformulation studies confirmed Lupeol's physicochemical properties, including its high lipophilicity (log P = 4.9) and poor aqueous solubility, justifying the need for lipid-based delivery systems.

The formulation strategy—hot homogenization followed by ultrasonication—enabled the production of stable NLCs with optimal characteristics. The use of glyceryl monostearate (solid lipid) and oleic acid (liquid lipid) along with surfactants (Tween 80 and Poloxamer 188) resulted in nanosized particles (~142.3 nm), low polydispersity index (PDI = 0.218), and high entrapment efficiency (89.4 %). These parameters are crucial for enhanced mucosal permeation and brain delivery via the intranasal route.

In vitro release studies demonstrated a biphasic release profile, with an initial burst followed by sustained drug release over 72 hours, which is advantageous for prolonged therapeutic action against brain tumors. The ex vivo nasal permeation study using goat nasal mucosa further validated the potential of Lupeol-NLCs for nose-to-brain delivery, showing superior permeation compared to free Lupeol.

Morphological analysis using SEM and TEM revealed spherical and well-dispersed particles with a uniform surface, while DSC and FTIR confirmed the molecular dispersion of Lupeol within the lipid matrix without any chemical interaction. Stability studies supported the robustness of the formulation, especially under refrigerated conditions.

The in vitro cytotoxicity assay on U87-MG glioblastoma cells showed that Lupeol-NLCs significantly reduced cell viability compared to free Lupeol, indicating enhanced therapeutic efficacy. Furthermore, fluorescence microscopy confirmed greater cellular uptake of Rhodamine B-tagged NLCs, highlighting improved intracellular delivery due to the nanoformulation.

The design-based optimization approach, using Box-Behnken Design (BBD), proved effective in fine-tuning formulation variables to achieve desired particle size, zeta potential, and entrapment efficiency. The study also underscores the importance of surface modification for further enhancing BBB permeability and glioma targeting, a strategy to be explored in future investigations.

4. Conclusion

This study successfully developed and optimized Lupeol-loaded nanostructured lipid carriers (NLCs) for targeted brain delivery, addressing key challenges such as poor solubility, limited BBB permeability, and systemic toxicity. The optimized NLCs exhibited ideal physicochemical characteristics, sustained release, enhanced nasal permeability, and significant cytotoxic activity against glioblastoma cells.

Intranasal administration of Lupeol-NLCs offers a promising, non-invasive route to bypass the BBB and deliver therapeutic agents directly to the brain, potentially improving the management of brain tumors like glioblastoma. The findings support the potential of Lupeol-NLCs as an effective and safe platform for brain-targeted drug delivery.

Future studies should focus on in vivo pharmacokinetic and biodistribution studies, surface functionalization with targeting ligands, and evaluation in animal models to further validate the clinical applicability of this approach in neuro-oncology.

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