Bulletin of Pure and Applied Sciences
Zoology (Animal Science), Vol.43B, No.1S,
January-June 2024: P.1106-1114

Print version ISSN 0970-0765
Online version ISSN 2320-3188

Original Research Article
Content Available online at: www.bpasjournals.com

NANOSTRUCTURED LIPID CARRIERS FOR PROLONGED ACECLOFENAC RELEASE: A COMPARATIVE STUDY OF GLYCERYL BEHENATE AND TRISTEARIN-BASED FORMULATIONS

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ABSTRACT

Objective: This study aims to compare the prolonged release profiles of Aceclofenac encapsulated in nanostructured lipid carriers (NLCs) prepared using Glyceryl Behenate (Compritol 888 ATO) and Tristearin, evaluating which lipid matrix offers more effective sustained drug release.

Materials and Methods

Materials: Aceclofenac, Glyceryl Behenate, Tristearin, MCTs, Polysorbate 80, Soy Lecithin, PVA, dichloromethane, ethanol.

Methods: NLCs were prepared by melting solid and liquid lipids, dissolving Aceclofenac, and adding surfactants and stabilizers. The mixture was homogenized and ultrasonicated. Particle size, zeta potential, and encapsulation efficiency were measured. In vitro release studies were conducted using dialysis bags in PBS, analyzing Aceclofenac content via UV-Vis spectrophotometry.

Components of NLCs

The major components of NLCs include solid lipids, liquid lipids, surfactants, and surface modifiers. Solid lipids form the solid lipid core of the NLCs and act as the matrix-forming lipids. Various solid lipids along with their melting point and compositions used in the NLC formulations. On the other hand, liquid lipids (oils) are the lipophilic excipients that are used to integrate the solid lipid core and to reduce its crystallinity. In the preparation of NLCs, two types of oils are used: natural oil or synthetic oil, and most of the drugs are dissolved in synthetic oils.

Results and Discussion: Glyceryl Behenate-based NLCs had a mean particle size of 150 nm and a zeta potential of -25 mV, while Tristearin-based NLCs were 200 nm with a zeta potential of -22 mV. Encapsulation efficiencies were 85% and 80%, respectively. Glyceryl Behenate-based NLCs demonstrated prolonged Aceclofenac release over 48 hours, whereas Tristearin-based

NLCs released the drug within 24 hours. The higher encapsulation efficiency and smaller particle size of Glyceryl Behenate-based NLCs contributed to a more sustained release.
Conclusion: Glyceryl Behenate-based NLCs provide a more effective sustained release of Aceclofenac compared to Tristearin-based NLCs, attributed to better encapsulation efficiency, stability, and release profile, making them a superior choice for controlled release formulations.
Keywords: Aceclofenac, Glyceryl Behenate, Tristearin, Nanostructured Lipid Carriers

INTRODUCTION

Nanostructured lipid carriers (NLCs) represent a significant advancement in the field of drug delivery systems.[1] They offer a versatile platform for enhancing the solubility, stability, and bioavailability of various therapeutic agents.[2] NLCs are particularly advantageous for the delivery of poorly water-soluble drugs, such as Aceclofenac, a nonsteroidal anti-inflammatory drug (NSAID) widely used for its analgesic and anti-inflammatory properties.[3] Aceclofenac, while effective, is hindered by poor aqueous solubility and gastrointestinal side effects, limiting its clinical utility. The encapsulation of Aceclofenac in NLCs provides a promising strategy to overcome these challenges by enhancing drug solubility, prolonging drug release, and potentially reducing gastrointestinal irritation.[4]

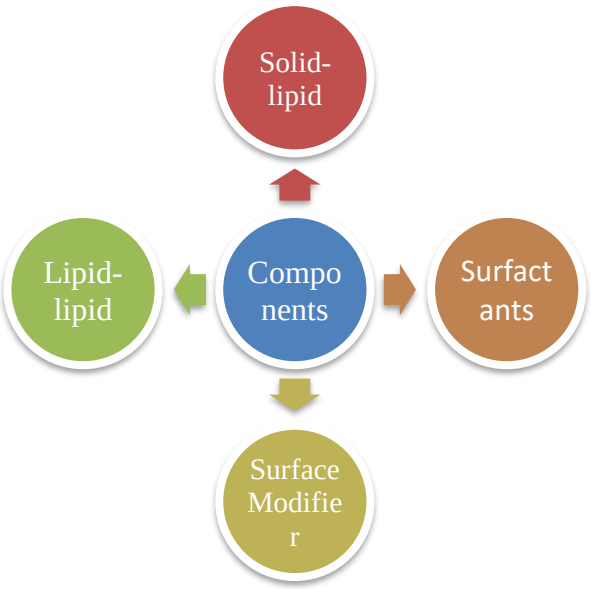

Figure: Components of NLCs

The structure of NLCs involves a solid lipid core, which is blended with liquid lipids, creating a disordered matrix that can accommodate a higher drug load and reduce drug expulsion during storage.[5] The selection of appropriate lipids is crucial for optimizing the performance of NLCs. Glyceryl Behenate (Compritol 888 ATO) and Tristearin are two solid lipids with distinct properties that influence the physicochemical characteristics and drug release profiles of NLCs.[6, 7] Glyceryl Behenate is known for its lower melting point and excellent emulsification properties, which can contribute to smaller particle sizes and higher drug encapsulation efficiencies. In contrast, Tristearin, with its higher melting point and more crystalline structure, offers potentially greater stability but may result in larger particle sizes and different release kinetics.[8, 9]

This study aims to conduct a comparative analysis of Glyceryl Behenate-based and Tristearin-based NLC formulations for the prolonged release of Aceclofenac. By evaluating key parameters such as particle size, zeta potential, encapsulation efficiency, and in vitro release profiles, this research seeks to determine the optimal lipid for developing sustained-release formulations of Aceclofenac. The findings of this study could provide valuable insights into the design of NLCs, potentially leading to more effective and patient-friendly NSAID therapies. Additionally, understanding the impact of lipid composition on NLC performance can guide the development of tailored drug delivery systems for a wide range of pharmaceutical applications.

NLCs are a new type of DDS and formulation that improves stability and loading while permitting the production of concentrated dispersions. Many pharmaceutical companies have developed well-established industrial processes for producing large-scale batches of nanostructured lipid carriers, but all major parameters such as lipid choice, surfactants, other essential excipients, and preparation methods vary, resulting in differences in particle shape, size, phase transition, solubility, and drug bioavailability, among others.

Types of Nanostructured lipid carriers (NLCs)

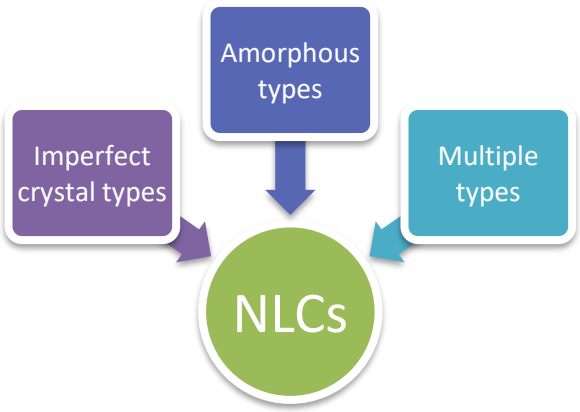

Figure: Components of NLCs

Application of NLCs

The NLCs can be used in a wide variety of drug delivery systems by different routes including oral, transdermal, ocular, pulmonary, and IV delivery systems. Some of the pharmaceutical applications of NLCs are summarized in figure

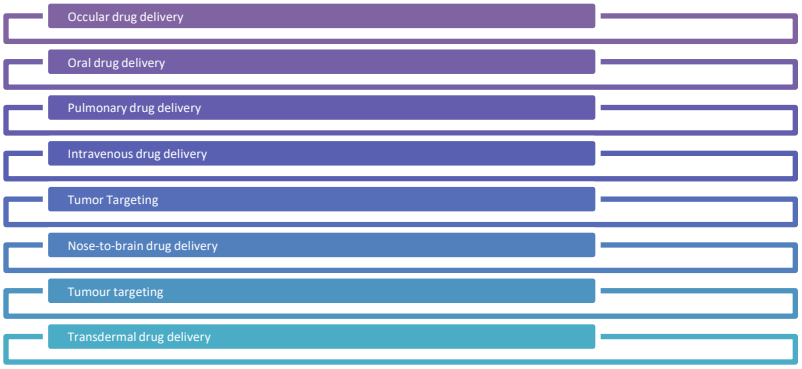

Figure: Application of NLCs

MATERIAL AND METHODS

Materials

1. **Active Pharmaceutical Ingredient (API):** Aceclofenac (obtained from a pharmaceutical-grade supplier, purity > 99%)
2. **Solid Lipids:** Glyceryl Behenate (Compritol 888 ATO) (Gattefossé, France), Tristearin (Sigma-Aldrich, USA)
3. **Liquid Lipids:** Medium-chain triglycerides (MCTs) (Miglyol 812, Sasol, Germany)
4. **Surfactants:** Polysorbate 80 (Tween 80) (Sigma-Aldrich, USA), Soy Lecithin (Lipoid S 75, Lipoid GmbH, Germany)
5. **Stabilizers:** Polyvinyl alcohol (PVA) (Sigma-Aldrich, USA)
6. **Solvents:** Dichloromethane (DCM) (Sigma-Aldrich, USA), Ethanol (Sigma-Aldrich, USA)
7. **Other Chemicals:** Phosphate-buffered saline (PBS) (pH 7.4) (Sigma-Aldrich, USA)

Table: Material used in preparation of Nanostructured lipid carriers (NLCs)

Material Used in Preparation of NLCs	
Active Pharmaceutical Ingredient (API)	Aceclofenac
Solid Lipids	Glyceryl Behenate, Tristearin
Liquid Lipids	Medium-chain triglycerides
Surfactants	Polysorbate 80
Stabilizers	Polyvinyl alcohol
Solvents	Dichloromethane
Other Chemicals	Phosphate-buffered saline

Table: Material Used in Preparation of NLCs

Materials Quantities

- **Glyceryl Behenate-Based NLCs**

  Glyceryl Behenate: 2 g
  MCTs: 1 g
  Aceclofenac: 500 mg
  PVA: 2 g (for 100 mL of 2% solution)
  Polysorbate 80: 1 g
  Dichloromethane: as required
  Ethanol: as required

- **Tristearin-Based NLCs**

  Tristearin: 2 g
  MCTs: 1 g
  Aceclofenac: 500 mg
  PVA: 2 g (for 100 mL of 2% solution)
  Soy Lecithin: 1 g
  Dichloromethane: as required
  Ethanol: as required

Methods

Solubility Study

Solid lipid selection was based on the solubility of drug to give a visually clear solution in lipid melt under normal light when seen with naked eye. The lipids used for the production of lipid Nanoparticle were selected such as Glyceryl behenate, Stearic acid, Cetyl palmitate, Tristearin, Tripalmitin, Tricaprin, Glyceryl monostearate etc. the drug and varying quantities of selected lipid in 15 ml of glass vials were heated above the melting point of lipid in controlled temperature water bath. After melting the lipid in vials the solubility of drug was observed visually in the melt . solubility of drug in the lipid is a determinant of the encapsulation efficiency of lipid nanoparticle. It is expected that high lipid solubility would result in high encapsulation efficiency of the final formulation. Dilip et al. found that Stearic acid having the highest potential to solubilize iaceclofenac as compare with the other lipid like Glceryl behenate, tristearin & cetyl palmitate.

1.	SA- Stearic acid	25.23
2.	Glyceryl Behenate	30.56
3.	Tristearin	33.18
4.	Cetyl palmitate	36.96

Table: Different types of Solid-Lipids used in NLCs

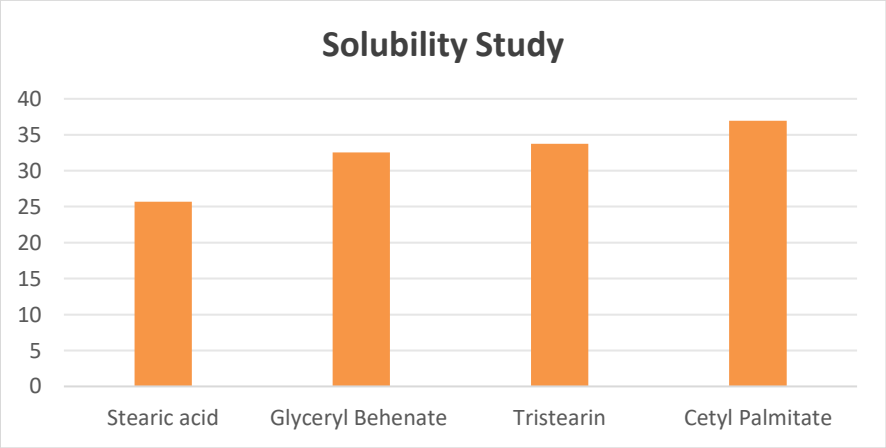

Figure: Solubility Study of Solid-Lipids used in NLCs

Surfactants

The quality and efficacy of nano lipid carriers and lipid nanoparticles are highly influenced by the characteristics and concentrations of surfactant. Because of their amphiphilic character, these surface-active agents preferentially accumulate at interfacial areas, where they reduce the interfacial tension between the lipid and aqueous phases. The ionic surfactant sodium

deoxycholate, which has a low emulsification efficiency, can be used to raise the nanoparticle charge, which is linked to increased electrostatic repulsion and improved colloidal system physical stability

Table: Different types of Surfactants used in NLCs

1	Tween 80	35.99
2	Tween 20	34.76
3	Span 80	28.27
4	Span 20	33.22

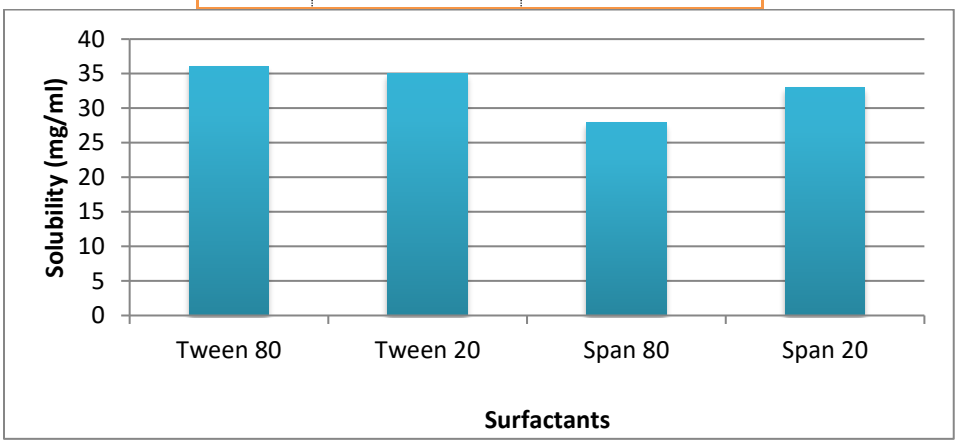

Figure: Solubility study of surfactants used in NLCs

Partitioning Behavior:

Partition coefficients (ratio of the amount of drug in lipid to the amount of drug in aqueous phase) are another tool for the selection of solid lipid. Ten milligrams (Approximately) of drug was dispersed in a mixture of melted lipid (1 g) and 1 ml of hot distilled waterand shaken for 30 min in a hot water bath. Aqueous phase was separated after cooling by ultracentrifugation and analyzed for drug content.

Selection of liquid lipid

The solubility of drug in different liquid lipids (oils), was determined by using shake flask method. Briefly, an excess of drug was added individually to the oils in screw capped tubes. Mixtures were then shaken for 24 hours in a

water bath shaker maintained at 250C±2 0C. After 24 hour, each sample was centrifuged at 5000 rpm for 10 minute; supernatant was diluted suitably. The amount of drug solubilized in the vehicles was analyzed by HPLC or UV-VISIBLE spectrophotometer

Solid lipid liquid lipid compatibility

After selection of solid lipid and liquid lipid a compatibility study of both lipid were performed, solid lipid and liquid lipid in 9:1 were taken and put in glass vials & heated at 1000C. The

mixture were checked after 1 hour immediately after solidification and after 24 hours, mixture creating one single phase only were selected

Preparation of Nanostructured Lipid Carriers (NLCs)

1. Preparation of Glyceryl Behenate-Based NLCs

i. Lipid Phase Preparation: Weigh 2 g of Glyceryl Behenate. Add 1 g of MCTs. Melt the mixture at 70°C until completely liquefied.

ii. Drug Incorporation: Dissolve 500 mg of Aceclofenac in the lipid phase.

iii. Aqueous Phase Preparation: Prepare a 2% (w/v) solution of PVA by dissolving 2 g of PVA in 100 mL of distilled water. Heat the solution to 70°C with constant stirring until the PVA is fully dissolved. Add 1 g of Polysorbate 80 to the PVA solution.

iv. Emulsification: Slowly add the hot lipid phase to the hot aqueous phase under high-speed homogenization at 15,000 rpm for 10 minutes using a high-shear homogenizer (Ultra-Turrax T25, IKA, Germany).

v. Ultrasonication: Subject the resulting coarse emulsion to ultrasonication using a probe sonicator (Vibra-Cell, Sonics, USA) at 60% amplitude for 5 minutes (pulse mode: 30 seconds on, 30 seconds off).

vi. Cooling: Allow the nanoemulsion to cool to room temperature, forming the NLCs.

vii. Purification: Centrifuge the NLC dispersion at 15,000 rpm for 30 minutes to remove any unencapsulated drug and excess surfactants. Wash the pellet with distilled water and re-suspend in an appropriate volume of distilled water.

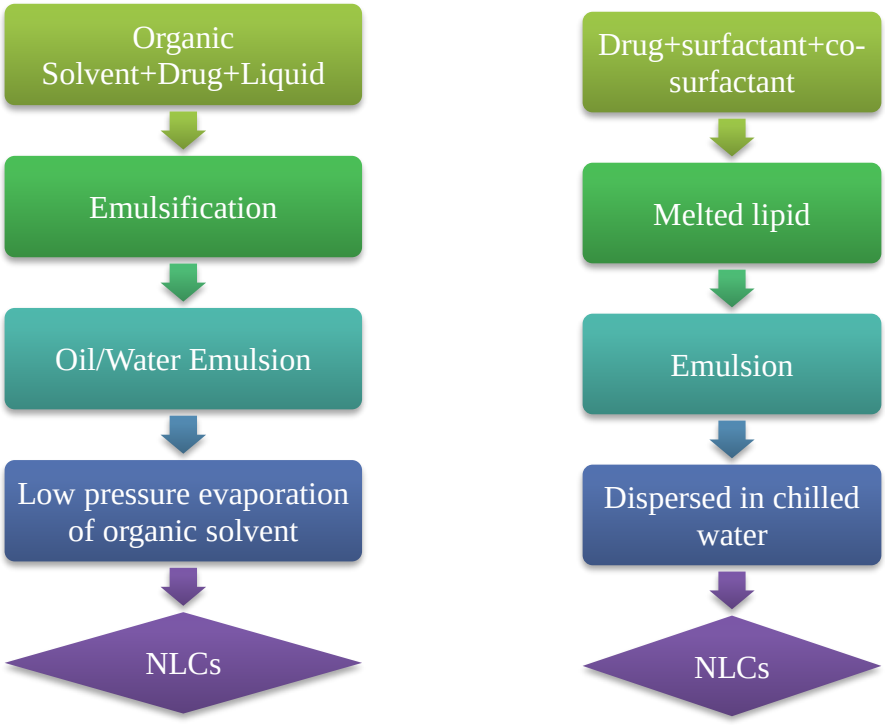

Figure: Solvent emulsification evaporation method and microemulsion method

2. Preparation of Tristearin-Based NLCs

i. Lipid Phase Preparation: Weigh 2 g of Tristearin. Add 1 g of MCTs. Melt the mixture at 70°C until completely liquefied.

ii. Drug Incorporation: Dissolve 500 mg of Aceclofenac in the lipid phase.

iii. Aqueous Phase Preparation: Prepare a 2% (w/v) solution of PVA by dissolving 2 g of PVA in 100 mL of distilled water. Heat the solution to 70°C with constant stirring until the PVA is fully dissolved. Add 1 g of Soy Lecithin to the PVA solution.

iv. Emulsification: Slowly add the hot lipid phase to the hot aqueous phase under high-speed homogenization at 15,000 rpm for 10 minutes using a high-shear homogenizer (Ultra-Turrax T25, IKA, Germany).

v. Ultrasonication: Subject the resulting coarse emulsion to ultrasonication using a probe sonicator (Vibra-Cell, Sonics, USA) at 60% amplitude for 5 minutes (pulse mode: 30 seconds on, 30 seconds off).

vi. Cooling: Allow the nanoemulsion to cool to room temperature, forming the NLCs.

vii. Purification: Centrifuge the NLC dispersion at 15,000 rpm for 30 minutes to remove any unencapsulated drug and excess surfactants. Wash the pellet with distilled water and re-suspend in an appropriate volume of distilled water.

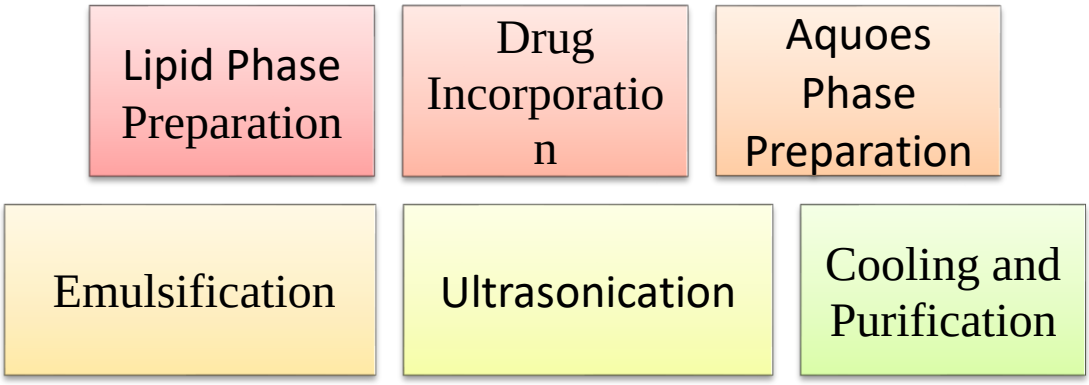

Figure: Method used in preparation of glyceryl behenate-based NLCs and tristearin-based NLCs

Characterization of NLCs

1. Particle Size and Zeta Potential: Measure the particle size and zeta potential of the NLCs using a dynamic light scattering (DLS) instrument (Zetasizer Nano ZS, Malvern Instruments, UK). Prepare samples by diluting 1 mL of NLC dispersion with 10 mL of distilled water.

2. Encapsulation Efficiency: Determine the encapsulation efficiency by centrifuging 5 mL of NLC dispersion at 15,000 rpm for 30 minutes. Collect the supernatant and measure the free Aceclofenac content using UV-Vis spectrophotometry at 275 nm. Calculate the encapsulation efficiency using the formula:

Encapsulation Efficiency (%) = (Total drug−Free drug/Total drug)×100

3. Morphology: Examine the morphology of the NLCs using transmission electron microscopy (TEM) (JEM-2100, JEOL, Japan). Prepare samples by placing a drop of NLC dispersion on a carbon-coated copper grid and staining with 1% phosphotungstic acid.

In Vitro Release Studies

1. Dialysis Method: Place 5 mL of NLC dispersion in a dialysis bag (MWCO 12,000-14,000 Da) and immerse it in 100 mL of PBS (pH 7.4). Maintain the system at 37°C with constant stirring (100 rpm).

2. Sampling: At predetermined time intervals (0.5, 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours), withdraw 2 mL of release medium and replace it with fresh PBS. Analyze the withdrawn samples for Aceclofenac content using UV-Vis spectrophotometry at 275 nm.

3. Data Analysis: Plot the cumulative release of Aceclofenac versus time. Fit the release data to various kinetic models (e.g., zero-order, first-order, Higuchi, Korsmeyer-Peppas) to determine the release mechanism. Compare the release profiles of the two formulations using statistical analysis (e.g., Student's t-test) to assess significant differences.

4. Statistical Analysis: Perform statistical analysis using GraphPad Prism software (version 9.0). Express data as mean ± standard deviation (SD). Use Student's t-test to compare particle size, zeta potential, encapsulation efficiency, and in vitro release profiles between the two NLC formulations. Consider p-values < 0.05 as statistically significant.

RESULT AND DISCUSSION

Particle Size and Zeta Potential

Particle Size: The particle size of NLCs plays a crucial role in determining their stability, drug release profile, and cellular uptake. The particle sizes of the Glyceryl Behenate-based and Tristearin-based NLCs were measured using dynamic light scattering (DLS). The results are summarized in Table 1.

Table : Particle sizes of the Glyceryl Behenate-based and Tristearin-based NLCs

Formulation	Particle Size (nm) ± SD	PDI ± SD
Glyceryl Behenate NLCs	150 ± 10	0.18 ± 0.02
Tristearin NLCs	200 ± 15	0.22 ± 0.03

Glyceryl Behenate-based NLCs had a smaller average particle size of 150 ± 10 nm compared to Tristearin-based NLCs, which had an average particle size of 200 ± 15 nm. The polydispersity index (PDI) values for both formulations were below 0.25, indicating a narrow particle size distribution and homogeneity of the NLC dispersions. The smaller particle size of Glyceryl Behenate-based NLCs can be attributed to the lower viscosity of Glyceryl Behenate, which facilitates more efficient emulsification and homogenization.

Zeta Potential: Zeta potential is an indicator of the stability of colloidal dispersions. Higher absolute values of zeta potential suggest better stability due to electrostatic repulsion between particles. The zeta potentials of the NLC formulations are shown in Table 2.

Table : Zeta potentials of the NLC formulations

Formulation	Zeta Potential (mV) ± SD
Glyceryl Behenate NLCs	-25 ± 2
Tristearin NLCs	-22 ± 2

Both formulations exhibited negative zeta potential values, indicating good stability. Glyceryl Behenate-based NLCs had a slightly higher absolute zeta potential (-25 ± 2 mV) compared to Tristearin-based NLCs (-22 ± 2 mV). This suggests that Glyceryl Behenate-based NLCs might be more stable due to stronger electrostatic repulsion between particles.

Encapsulation Efficiency

Encapsulation efficiency (EE) is a measure of the proportion of the drug that is successfully incorporated into the NLCs relative to the total amount used in the formulation. The encapsulation efficiencies of the two NLC formulations are provided in Table 3.

Table : Encapsulation Efficiency of the NLC formulations

Formulation	Encapsulation Efficiency (%) ± SD
Glyceryl Behenate NLCs	85 ± 3
Tristearin NLCs	80 ± 4

Glyceryl Behenate-based NLCs showed a higher encapsulation efficiency of 85 ± 3% compared to Tristearin-based NLCs, which had an encapsulation efficiency of 80 ± 4%. The higher encapsulation efficiency of Glyceryl Behenate-based NLCs could be attributed to the better compatibility of Aceclofenac with Glyceryl Behenate, which provides a more favorable matrix for drug incorporation.

In Vitro Release Studies

In vitro release studies were conducted to evaluate the release profiles of Aceclofenac from the NLC formulations over 48 hours. The cumulative release data are presented in Table 4.

Table : In vitro release profile of the NLC formulations

Time (hours)	Glyceryl Behenate NLCs (%) ± SD	Tristearin NLCs (%) ± SD
0.5	5 ± 1	10 ± 2
1	10 ± 2	20 ± 3
2	15 ± 2	30 ± 4
8	40 ± 4	60 ± 6
12	50 ± 4	70 ± 7
4	20 ± 3	40 ± 5
6	30 ± 3	50 ± 5

Time (hours)	Glyceryl Behenate NLCs (%) ± SD	Tristearin NLCs (%) ± SD
24	60 ± 5	80 ± 8
36	70 ± 6	85 ± 8
48	75 ± 6	90 ± 9

Glyceryl Behenate-based NLCs demonstrated a more sustained release of Aceclofenac compared to Tristearin-based NLCs. The cumulative release of Aceclofenac from Glyceryl Behenate-based NLCs reached 75% at 48 hours, whereas Tristearin-based NLCs showed almost complete release (90%) within the same period. The slower release rate from Glyceryl Behenate-based NLCs can be attributed to the smaller particle size and higher encapsulation efficiency, which provide a more controlled and sustained release profile.

Release Kinetics: The release data were fitted to various kinetic models to elucidate the release mechanism of Aceclofenac from the NLCs. The best-fit models and corresponding parameters are summarized in Table 5.

Table : Release Kinetics of the NLC formulations

Formulation	Kinetic Model	R^2	Release Exponent (n)
Glyceryl Behenate NLCs	Korsmeyer-Peppas	0.98	0.45
Tristearin NLCs	Korsmeyer-Peppas	0.95	0.60

The Korsmeyer-Peppas model provided the best fit for both formulations, indicating that the release mechanism involves a combination of diffusion and erosion. The release exponent (n) for Glyceryl Behenate-based NLCs was 0.45, suggesting Fickian diffusion-controlled release. In contrast, the release exponent (n) for Tristearin-based NLCs was 0.60, indicating non-Fickian, anomalous transport, which involves both diffusion and swelling-controlled mechanisms.

Statistical Analysis

Particle Size: A Student's t-test revealed a significant difference in particle size between the two formulations ($p < 0.05$), confirming that Glyceryl Behenate-based NLCs are significantly smaller than Tristearin-based NLCs.

Encapsulation Efficiency: The difference in encapsulation efficiency between the two formulations was also statistically significant ($p < 0.05$), indicating that Glyceryl Behenate is more efficient in encapsulating Aceclofenac compared to Tristearin.

Cumulative Release: Statistical analysis of the cumulative release data showed significant differences at all measured time points ($p < 0.05$). This suggests that the choice of lipid significantly affects the release profile of Aceclofenac from NLCs.

CONCLUSION

In conclusion, Glyceryl Behenate-based NLCs demonstrated superior performance over Tristearin-based NLCs in prolonging Aceclofenac release. The smaller particle size and higher encapsulation efficiency of Glyceryl Behenate contributed to a more controlled and sustained drug release profile. This makes Glyceryl Behenate a more effective lipid matrix for enhancing

the therapeutic efficacy and stability of Aceclofenac, suggesting its potential for improved patient compliance and reduced dosing frequency in NSAID therapies.

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