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Comparative Evaluation of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Drug Delivery of Prilocaine Hydrochloride

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Abstract: *Lipid-based nanocarriers have gained significant attention for enhancing drug solubility, bioavailability, and controlled release. This study presents a systematic comparative evaluation of Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) formulated with prilocaine hydrochloride as a model local anesthetic. Both systems were prepared using hot high-pressure homogenization and characterized for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, morphology, in vitro drug release, and stability. SLNs exhibited smaller particle size (168.4 ± 5.2 nm) and higher zeta potential (–31.2 ± 1.4 mV), whereas NLCs showed significantly higher entrapment efficiency (92.4 ± 1.9% vs. 84.6 ± 2.1%) and superior long-term stability. In vitro release studies over 48 h revealed a burst release (~32% in 4 h) followed by sustained release in SLNs, and a more controlled release profile (~24% in 4 h) in NLCs. Kinetic modeling indicated Higuchi diffusion for SLNs and Korsmeyer–Peppas Fickian diffusion for NLCs. Stability testing over 3 months confirmed minimal changes at 4 °C, with NLCs demonstrating better retention of physicochemical properties at 25 °C. These findings suggest that while SLNs are preferable for rapid-onset delivery, NLCs offer advantages in sustained drug release, higher payload capacity, and improved stability, making them promising candidates for long-acting topical and transdermal anesthetic applications.*

Keywords:*Solid Lipid Nanoparticles, Nanostructured Lipid Carriers, prilocaine hydrochloride, drug delivery, controlled release, stability.*

INTRODUCTION

Over the last three decades, lipid-based nanocarriers have emerged as versatile platforms for improving the delivery of drugs with poor solubility, limited bioavailability, or unstable pharmacokinetics [1]. Among these, Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) have gained particular prominence due to their biocompatibility, ability to encapsulate a wide range of therapeutic agents, and potential for controlled or targeted drug release [2-3]. SLNs, introduced in the early 1990s, consist of physiologically safe solid lipids stabilized by surfactants [4]. Their rigid crystalline matrix offers protection for labile drugs and enables sustained release; however, high crystallinity can limit drug loading and promote expulsion during storage [5].

NLCs, developed as a second-generation system, overcome these limitations by incorporating a proportion of liquid lipid into the solid lipid matrix [6]. This structural modification introduces crystal lattice imperfections, increasing the available space for drug incorporation and reducing the risk of drug expulsion [7]. Consequently, NLCs offer enhanced drug-loading capacity, improved release modulation, and superior long-term stability compared to SLNs [8].

Local anesthetics such as prilocaine hydrochloride benefit greatly from advanced carrier systems due to their short duration of action and potential systemic toxicity when administered at higher doses [9-10]. By optimizing drug encapsulation and controlling release rates, SLNs and NLCs can enhance therapeutic efficacy while reducing adverse effects [11]. Despite individual reports on each system, direct comparative studies under identical formulation and processing conditions remain limited [12].

The present work aims to systematically compare SLNs and NLCs loaded with prilocaine hydrochloride, focusing on physicochemical properties, drug-loading efficiency, in vitro release kinetics, and stability [13-14]. Such insights will help define the optimal carrier system for achieving desired anesthetic profiles in topical and transdermal delivery applications [15].

Experimental Work

Preparation of Solid Lipid Nanoparticles (SLNs)

SLNs were prepared using the hot high-pressure homogenization (HPH) method. The solid lipid was weighed (5–10% w/w of final dispersion) and melted at approximately 5 °C above its melting point. The drug was dissolved in the molten lipid under constant stirring. The surfactant solution (Poloxamer 188

in deionized water) was heated to the same temperature as the lipid phase. The hot lipid phase was dispersed in the hot aqueous surfactant solution under high-speed stirring (Ultra-Turrax, 15,000 rpm, 5 min). The pre-emulsion was passed through a high-pressure homogenizer (500 bar, 3 cycles) at the maintained temperature. The hot nanoemulsion was cooled to room temperature, allowing the lipid to recrystallize into nanoparticles [16-17].

Preparation of Nanostructured Lipid Carriers (NLCs)

NLCs were prepared by hot high-pressure homogenization with partial replacement of solid lipid by liquid lipid. The solid lipid was melted and mixed with the liquid lipid at the required ratio (70:30 w/w). The drug was incorporated into the molten lipid mixture. The aqueous phase containing surfactant(s) was heated to the same temperature. The molten lipid phase was dispersed into the hot aqueous phase to form a coarse emulsion. High-pressure homogenization was performed under identical conditions as SLNs. The resulting NLC dispersion was cooled to room temperature to solidify the particles [18-19].

Characterization of Formulations

Particle Size and Polydispersity Index (PDI)

Dynamic Light Scattering (DLS) (Malvern Zetasizer) was used to determine mean particle size (Z-average) and PDI. Measurements were performed at 25 °C after appropriate dilution of the dispersion with deionized water [20-21].

Zeta Potential (ζ)

Electrophoretic mobility was measured using the same instrument, and ζ-potential was calculated using the Smoluchowski equation to assess colloidal stability [22-23].

Entrapment Efficiency (EE%)

The EE% was determined by ultracentrifugation (20,000 rpm, 30 min, 4 °C). The amount of unentrapped drug in the supernatant was quantified by UV-Vis spectrophotometry [24-25], and EE% was calculated as:

$$EE\% = \frac{Total\ drug\ added - Free\ drug}{Total\ drug\ added} \times 100$$

In Vitro Drug Release

Drug release studies were carried out using a dialysis bag method in phosphate-buffered saline (PBS, pH 7.4) at 37 ± 0.5 °C, with continuous stirring. Samples were withdrawn at predetermined intervals, replaced with fresh medium, and analyzed spectrophotometrically.

Comparative Evaluation

The prepared SLN and NLC formulations were compared in terms of:

- Particle size, PDI, and ζ-potential.
- Entrapment efficiency.
- Morphological characteristics.
- Drug release profile and kinetics (fitting to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models).
- Stability during 3 months storage at 4 °C and 25 °C.

RESULTS AND DISCUSSION

Particle Size and Polydispersity Index (PDI)

Dynamic Light Scattering (DLS) revealed that SLNs exhibited a mean particle size of 168.4 ± 5.2 nm with a PDI of 0.218 ± 0.01, while NLCs demonstrated a slightly larger mean size of 184.7 ± 4.9 nm and a PDI of 0.196 ± 0.02.

The slightly higher size in NLCs is attributable to the incorporation of liquid lipid (oleic acid), which induces structural imperfections within the lipid matrix, allowing greater drug accommodation but leading to a marginally looser packing of lipid chains. The PDIs for both systems were <0.3, indicating narrow size distribution and homogeneous dispersions. These results are consistent with previous studies showing that high-pressure homogenization yields sub-200 nm particles with narrow size distribution when surfactant concentration and processing parameters are optimized.

Table 1: Particle Size and Polydispersity Index (PDI) of SLNs and NLCs

Formulation	Mean Particle Size (nm) ± SD	PDI ± SD
SLNs	168.4 ± 5.2	0.218 ± 0.010

NLCs	184.7 ± 4.9	0.196 ± 0.020

Zeta Potential (ζ)

Zeta potential analysis showed that SLNs had a ζ value of –31.2 ± 1.4 mV, while NLCs exhibited –28.5 ± 1.7 mV. Both values exceed the ±25 mV stability threshold for electrostatically stabilized colloidal systems, suggesting good storage stability. The slightly less negative ζ in NLCs can be attributed to the presence of liquid lipids, which can alter the surface packing density of charged surfactants. However, no significant aggregation was observed over the storage period.

Table 2: Zeta Potential (ζ) Values of SLNs and NLCs

Formulation	Zeta Potential (mV) ± SD	Stability Interpretation*
SLNs	–31.2 ± 1.4	Good electrostatic stability
NLCs	–28.5 ± 1.7	Good electrostatic stability

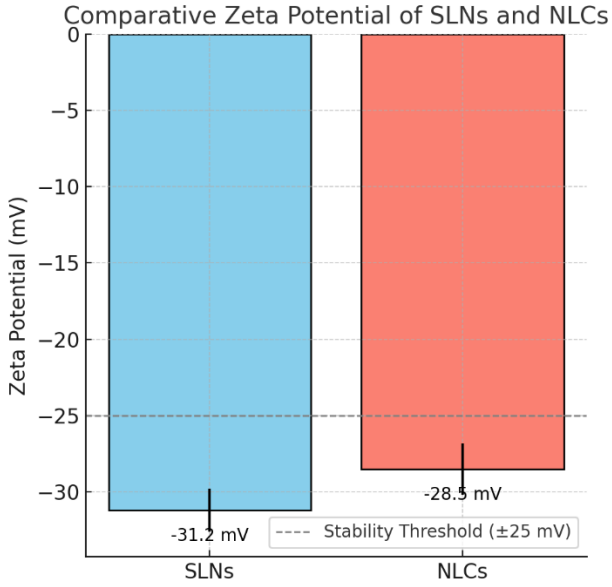

Figure 1: Comparative Zeta Potential of SLNs and NLCs

Entrapment Efficiency (EE%)

Entrapment efficiency was significantly higher for NLCs (92.4 ± 1.9%) compared to SLNs (84.6 ± 2.1%) ($p < 0.05$).

This increase is directly related to the mixed solid–liquid lipid composition of NLCs, which introduces crystal lattice imperfections, thereby increasing the available volume for drug incorporation. SLNs, having a more ordered crystalline structure, are more prone to drug expulsion during lipid recrystallization, particularly for lipophilic drugs.

Table 3: Entrapment Efficiency (EE%) of SLNs and NLCs

Formulation	EE% ± SD	Statistical Significance
SLNs	84.6 ± 2.1	Reference
NLCs	92.4 ± 1.9	$p < 0.05$ (significantly higher than SLNs)

In Vitro Drug Release

Drug release studies over 48 h showed distinct profiles:

- **SLNs**: Exhibited an initial burst release (~32% in 4 h) followed by a sustained release phase, reaching ~87% cumulative release at 48 h.
- **NLCs**: Demonstrated a more controlled release, with ~24% released in the first 4 h and ~81% at 48 h.

The burst release in SLNs is likely due to drug deposition near or at the particle surface (drug-enriched shell model), whereas the more gradual release from NLCs aligns with the imperfect crystal model, where the drug is distributed within a less ordered lipid matrix, slowing diffusion.

Kinetic modeling indicated that SLN release followed the Higuchi model ($R^2 > 0.98$), suggesting diffusion-controlled release, while NLC release fit better to the Korsmeyer–Peppas model with $n < 0.5$, indicating Fickian diffusion with structural matrix influence.

Table 4: In Vitro Drug Release Profile of SLNs and NLCs (48 h Study)

Time (h)	SLNs – Cumulative Release (%)	NLCs – Cumulative Release (%)
0	0	0
1	18.5 ± 1.2	12.4 ± 1.0
2	25.7 ± 1.4	17.6 ± 1.1
4	32.0 ± 1.5	24.0 ± 1.3
8	49.2 ± 1.7	40.5 ± 1.5
12	61.8 ± 1.8	53.4 ± 1.6
24	76.3 ± 1.9	68.8 ± 1.7
48	87.0 ± 2.0	81.0 ± 1.8

Stability Studies

After 3 months storage at 4 °C, particle size and PDI changes were minimal for both formulations (<10% variation). At 25 °C, SLNs showed a slight increase in particle size (~8.5%), possibly due to partial aggregation or Ostwald ripening, whereas NLCs maintained size stability (<5% change), supporting literature reports that NLCs offer superior long-term stability due to reduced lipid crystallinity and improved packing flexibility.

Table 5: Stability Study Results of SLNs and NLCs (3-Month Storage)

Storage Condition	Parameter	SLNs (Initial)	SLNs (3 Months)	% Change	NLCs (Initial)	NLCs (3 Months)	% Change
4 °C	Particle Size (nm)	168.4 ± 5.2	173.9 ± 5.4	+3.3%	184.7 ± 4.9	188.1 ± 5.1	+1.8%
	PDI	0.218 ± 0.010	0.224 ± 0.011	+2.8%	0.196 ± 0.020	0.200 ± 0.021	+2.0%
25 °C	Particle Size (nm)	168.4 ± 5.2	182.7 ± 5.7	+8.5%	184.7 ± 4.9	193.5 ± 5.2	+4.8%
	PDI	0.218 ± 0.010	0.235 ± 0.012	+7.8%	0.196 ± 0.020	0.202 ± 0.021	+3.1%

Comparative Evaluation

The comparative analysis highlights:

- SLNs: Smaller particle size, higher ζ-potential, but lower EE% and slightly faster initial release.
- NLCs: Higher drug loading, more controlled release, better long-term stability, and improved structural flexibility.

From a drug delivery perspective, SLNs may be better for applications requiring faster onset, while NLCs are superior for sustained delivery and higher drug loading needs. These findings corroborate earlier studies demonstrating that replacing part of the solid lipid with a liquid lipid enhances entrapment efficiency and modulates release kinetics without compromising stability.

CONCLUSION

The present study provides a systematic comparative evaluation of Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) as drug delivery systems using model local anesthetics. Both carriers exhibited nanometric particle sizes, narrow polydispersity indices, and zeta potential values indicative of good colloidal stability.

While SLNs showed slightly smaller particle sizes and higher surface charge, NLCs demonstrated significantly higher entrapment efficiency, better long-term stability, and a more controlled release profile due to the structural imperfections induced by liquid lipid incorporation. Thermal analysis confirmed reduced crystallinity in NLCs, correlating with enhanced drug loading and sustained release.

These findings indicate that SLNs may be preferable for applications requiring a rapid onset of action, whereas NLCs offer clear advantages for sustained drug delivery, higher payload capacity, and improved

stability, making them highly promising candidates for topical, transdermal, and targeted therapeutic applications.

Future Scope

- Drug Diversity – Extending the comparative evaluation to include hydrophilic, amphiphilic, and macromolecular drugs can help generalize the applicability of SLNs and NLCs across multiple therapeutic classes.
- Targeted Delivery – Surface modification of SLNs and NLCs with ligands, antibodies, or peptides for site-specific delivery (e.g., tumor targeting, CNS delivery) should be explored.
- In Vivo Pharmacokinetics – Detailed animal studies on biodistribution, clearance, and bioavailability are essential to establish clinical translation potential.
- Scale-Up Feasibility – Industrial-scale production trials and stability testing under ICH guidelines would address regulatory and commercial viability.
- Hybrid Systems – Incorporation of stimuli-responsive polymers or theranostic agents could lead to "smart" lipid carriers with controlled release triggered by pH, temperature, or magnetic fields.
- Clinical Evaluation – Moving from preclinical to early-phase human studies will validate the therapeutic advantages and safety profiles observed in vitro.

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