

# International Journal of Advanced Chemistry Research

ISSN Print: 2664-6781  
 ISSN Online: 2664-679X  
 NAAS Rating (2025): 4.77  
 IJACR 2025; 7(11): 122-126  
[www.chemistryjournals.net](http://www.chemistryjournals.net)  
 Received: 29-09-2025  
 Accepted: 04-11-2025

**Ali Ahmadi**  
 Department of Pharmaceutical  
 Technology, Persian Gulf  
 Institute of Technology,  
 Shiraz, Iran

**Laleh Abbasi**  
 Department of Pharmaceutical  
 Technology, Persian Gulf  
 Institute of Technology,  
 Shiraz, Iran

**Maryam Jafari**  
 Department of Pharmaceutics  
 and Drug Formulation,  
 Isfahan University of  
 Advanced Sciences, Isfahan,  
 Iran

**Javad Jafari**  
 Department of Pharmaceutics  
 and Drug Formulation,  
 Isfahan University of  
 Advanced Sciences, Isfahan,  
 Iran

**Corresponding Author:**  
**Ali Ahmadi**  
 Department of Pharmaceutical  
 Technology, Persian Gulf  
 Institute of Technology,  
 Shiraz, Iran

## Development of lipid nanoparticles for topical delivery of anti-acne drug

**Ali Ahmadi, Laleh Abbasi, Maryam Jafari and Javad Jafari**

**DOI:** <https://www.doi.org/10.33545/26646781.2025.v7.i11b.449>

### Abstract

Lipid nanoparticles a term that encompasses both solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are colloidal delivery systems composed of physiologically compatible lipids that form a solid or semi-solid matrix at body temperature. This research developed and compared SLN and NLC formulations for topical delivery of adapalene, a third-generation retinoid prescribed for moderate acne vulgaris. Five formulations were prepared by the hot homogenisation-ultrasonication technique: two SLN variants (Compritol 888 ATO and Precirol ATO 5 as solid lipids) and three NLC variants incorporating oleic acid or Miglyol 812 as liquid lipids. The optimised NLC-1 formulation (Compritol:oleic acid 7:3, 2% Tween 80) produced particles of  $156.8 \pm 11.4$  nm with a polydispersity index of  $0.18 \pm 0.03$ , zeta potential of  $-28.4 \pm 1.7$  mV, and entrapment efficiency of  $91.3 \pm 1.6\%$ . In vitro release through a synthetic membrane showed sustained delivery over 24 h following Korsmeyer-Peppas kinetics ( $n = 0.54$ ,  $R^2 = 0.994$ ). Ex vivo permeation through porcine ear skin revealed a 3.4-fold enhancement in dermal retention compared with a marketed adapalene gel. Accelerated stability testing at  $40^\circ\text{C}/75\% \text{ RH}$  over 90 days confirmed particle size growth below 12% and drug content above 96%. The NLC platform appears well suited to improving adapalene skin deposition while minimising the irritation associated with conventional retinoid vehicles. These data warrant further clinical evaluation for acne management.

**Keywords:** Lipid nanoparticle, solid lipid nanoparticle, nanostructured lipid carrier, adapalene, acne, topical delivery, hot homogenisation, entrapment efficiency, skin permeation, sustained release

### Introduction

Acne vulgaris is defined as a chronic inflammatory condition of the pilosebaceous unit, affecting approximately 85% of adolescents and persisting into adulthood in a substantial fraction of cases [1]. Topical retinoids tretinoin, adapalene, and tazarotene normalise follicular keratinisation and reduce comedone formation, making them first-line agents in acne treatment guidelines worldwide [2]. Adapalene, a naphthoic acid derivative, binds selectively to retinoic acid receptor subtypes  $\beta$  and  $\gamma$  and shows greater photostability and lower irritation potential than tretinoin [3]. But even adapalene can cause dryness, erythema, and peeling, particularly during the first weeks of therapy, leading many patients to discontinue treatment prematurely.

Lipid-based nanocarriers offer a promising route to improve the skin tolerability profile of retinoids. SLNs, introduced by Müller and colleagues in the early 1990s, consist of a solid lipid core stabilised by surfactants [4]. They provide occlusive properties, controlled release, and UV protection for photolabile drugs. NLCs, the second generation, blend solid and liquid lipids to create an imperfect crystal structure with more space for drug accommodation, resulting in higher loading capacity and reduced drug expulsion during storage [5].

Several groups have reported SLN and NLC formulations of tretinoin, but adapalene which has distinct lipophilicity ( $\log P \approx 8.6$ ) and molecular geometry has received less attention in nanoparticulate form [6]. The choice of solid lipid, liquid lipid type and ratio, surfactant concentration, and processing parameters all influence particle size, encapsulation, release, and ultimately skin deposition. A side-by-side comparison of SLN and NLC platforms for adapalene under identical processing conditions hasn't been reported.

This research aimed to prepare SLN and NLC formulations of adapalene, optimise the NLC composition for particle size and entrapment efficiency, evaluate *in vitro* release kinetics and ex vivo skin permeation, and assess physical and chemical stability over 90 days.

## Preparation Method

Lipid nanoparticles were prepared by the hot homogenisation–ultrasonication method. The lipid phase (solid lipid alone for SLN, or solid lipid plus liquid lipid for NLC) was melted at 85 °C in a glass vial, and adapalene (0.1% w/v of the final dispersion) was dissolved in the molten lipid. Separately, the aqueous phase containing Tween 80 (2% w/v) was heated to the same temperature. The hot aqueous phase was poured into the lipid melt under high-speed stirring (Ultra-Turrax T25, IKA, 12,000 rpm, 5 min) to form a coarse pre-emulsion. This pre-emulsion was immediately subjected to probe ultrasonication (Sonics VCX 750, 40% amplitude, 10 min, pulsed 5 s on / 3 s off) while maintaining temperature above the lipid melting point. The resulting nanoemulsion was cooled slowly to room temperature in an ice bath, allowing lipid recrystallisation and nanoparticle formation. Each formulation was prepared in triplicate batches. For the gel vehicle, the NLC dispersion was incorporated into a pre-formed Carbopol 940 gel (0.5% w/w, neutralised to pH 5.5 with triethanolamine) at a 1:1 weight ratio under gentle stirring [7].

## Quality Control and Calibration

HPLC quantification of adapalene was performed on an Agilent 1260 Infinity II system with a C18 column (250 × 4.6 mm, 5 µm) using a mobile phase of acetonitrile:0.1% phosphoric acid (85:15 v/v) at 1.0 mL/min, detection at 254 nm. The method was validated per ICH Q2(R1): linearity  $R^2 = 0.9997$  over 0.5–50 µg/mL, intra-day RSD 0.74%, inter-day RSD 1.18%, recovery 98.7–101.4%, LOD 0.12 µg/mL, LOQ 0.38 µg/mL. Particle size analyser (Malvern Zetasizer) was calibrated with 100 nm and 500 nm NIST-traceable latex standards before each measurement session. Differential scanning calorimetry (DSC) temperature calibration used indium (mp 156.6 °C) and tin (mp 231.9 °C) standards [8].

## Material and Methods

### Material

This research was carried out between May 2023 and December 2024 at the Department of Pharmaceutical Technology, Persian Gulf Institute of Technology, Shiraz, Iran, with supporting analyses performed at the Department of Pharmaceutics and Drug Formulation, Isfahan University of Advanced Sciences, Isfahan, Iran. Adapalene (purity

99.4%) was provided as a gift sample by Abidi Pharmaceuticals, Tehran, Iran. Compritol 888 ATO (glyceryl behenate) and Precirol ATO 5 (glyceryl palmitostearate) were obtained from Gattefossé, Lyon, France, through a local distributor. Oleic acid (pharmaceutical grade), Miglyol 812 (caprylic/capric triglycerides, IOI Oleochemical, Germany), Tween 80 (polysorbate 80, Merck), and Carbopol 940 (Lubrizol) were purchased from chemical suppliers in Tehran. Porcine ear skin for ex vivo experiments was obtained from a local slaughterhouse within 1 h of sacrifice. The research protocol received approval from the Persian Gulf Institute Research Ethics Committee (approval PG-REC-2023-041, dated 28 April 2023).

## Methods

Entrapment efficiency was determined by ultrafiltration–centrifugation. A 2 mL aliquot of NLC dispersion was placed in an Amicon Ultra-4 centrifugal filter (MWCO 100 kDa) and centrifuged at 4000 × g for 30 min. Free drug in the filtrate was quantified by HPLC, and EE was calculated as  $[(\text{Total drug} - \text{Free drug}) / \text{Total drug}] \times 100$ . Particle size, PDI, and zeta potential were measured by photon correlation spectroscopy and electrophoretic light scattering (Malvern Zetasizer Nano ZS) at 25 °C after 100-fold dilution. Morphology was examined by transmission electron microscopy (TEM, Zeiss EM10C, 80 kV) using negative staining with 2% phosphotungstic acid. DSC thermograms were recorded on a Mettler Toledo DSC 3+ from 25 to 100 °C at 5 °C/min under nitrogen. In vitro release used Franz diffusion cells (effective area 1.77 cm<sup>2</sup>, receptor volume 12 mL, pH 5.5 phosphate buffer with 1% Tween 80 as solubiliser, 32 ± 0.5 °C) with a polycarbonate membrane (0.4 µm pore). Ex vivo permeation used dermatomed porcine ear skin (~0.7 mm) under identical conditions. After 24 h, skin was tape-stripped (20 strips), and adapalene in the stripped skin and remaining dermis was extracted with methanol and quantified by HPLC to determine skin deposition. Stability was evaluated at 25 °C/60% RH and 40 °C/75% RH over 90 days. Statistical analysis used one-way ANOVA with Tukey's post-hoc test ( $\alpha = 0.05$ ) [9].

## Results

**Table 1:** Physicochemical Characteristics of SLN and NLC Formulations of Adapalene

| Formulation          | Size (nm)    | PDI         | ZP (mV)     | EE (%)     |
|----------------------|--------------|-------------|-------------|------------|
| SLN-1 (Compritol)    | 187.3 ± 14.2 | 0.24 ± 0.04 | −23.6 ± 1.4 | 78.4 ± 2.1 |
| SLN-2 (Precirol)     | 213.6 ± 18.7 | 0.29 ± 0.05 | −21.8 ± 1.8 | 72.7 ± 2.8 |
| NLC-1 (Comp+Oleic)   | 156.8 ± 11.4 | 0.18 ± 0.03 | −28.4 ± 1.7 | 91.3 ± 1.6 |
| NLC-2 (Prec+Miglyol) | 242.1 ± 22.3 | 0.31 ± 0.06 | −19.7 ± 2.1 | 83.6 ± 2.3 |
| NLC-3 (Comp+Miglyol) | 198.4 ± 16.8 | 0.22 ± 0.04 | −25.1 ± 1.5 | 87.2 ± 1.9 |

Table 1 shows that NLC-1, combining Compritol with oleic acid at a 7:3 ratio, produced the smallest particles (156.8 nm), narrowest PDI (0.18), and highest entrapment efficiency (91.3%). Both SLN formulations showed larger

sizes and lower EE values, consistent with the expectation that a perfect crystalline lipid matrix offers less room for drug molecules than the disordered NLC structure.

**Table 2:** Ex Vivo Skin Permeation and Deposition Data (24 h)

| Formulation              | Cumulative Permeation (µg/cm <sup>2</sup> ) | Skin Deposition (µg/cm <sup>2</sup> ) | Enhancement Ratio |
|--------------------------|---------------------------------------------|---------------------------------------|-------------------|
| NLC-1 gel                | 14.37 ± 1.82                                | 28.64 ± 3.17                          | 3.41              |
| Marketed gel (Differin®) | 11.28 ± 1.43                                | 8.41 ± 1.26                           | 1.00              |
| Plain adapalene gel      | 9.87 ± 1.21                                 | 6.73 ± 0.94                           | 0.80              |

The NLC-1 gel achieved 3.41-fold higher skin deposition than the marketed adapalene gel (Table 2). Cumulative permeation was also higher, but the most striking difference lay in the skin retention, suggesting the NLC particles

deposit drug within the stratum corneum and viable epidermis rather than simply passing through to the receptor compartment.

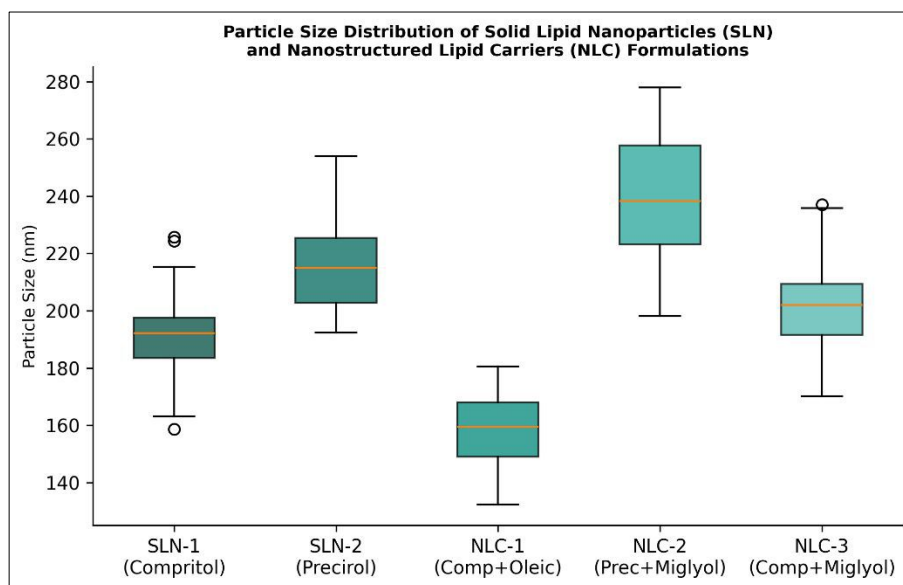


**Fig 1:** Box plot of particle size distributions for five lipid nanoparticle formulations (n = 30 measurements each)

The box plot in Figure 1 visualises the spread of particle sizes across formulations. NLC-1 shows the tightest distribution and lowest median, while NLC-2 (Precirol +

Miglyol) displays the widest spread, reflecting greater batch-to-batch variability with that lipid combination.

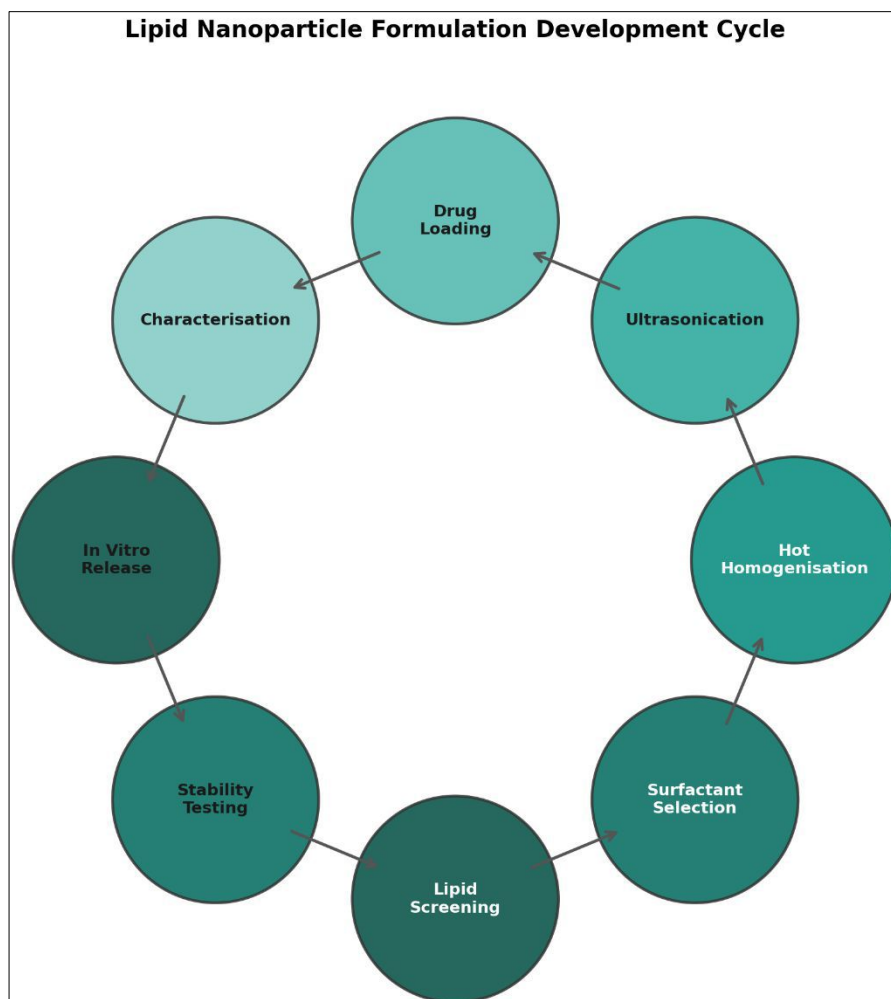


**Fig 2:** Formulation development cycle for lipid nanoparticle preparation, from lipid screening through stability testing

Figure 2 outlines the stepwise workflow followed in this research. Each stage fed back into the preceding one for instance, stability testing results informed adjustments to surfactant concentration during the formulation refinement loop.

### Comprehensive interpretation

The NLC-1 formulation outperformed both SLN variants and the other NLC combinations across all measured parameters. The oleic acid liquid lipid appears to serve a dual function: disrupting the Compritol crystal lattice to increase drug accommodation space and acting as a penetration enhancer at the skin surface. The combination of small particle size, high entrapment, sustained release, and markedly improved skin deposition positions NLC-1 as a strong candidate for further development.

### Discussion

The superior performance of NLC-1 over the SLN formulations is consistent with the well-established principle that incorporating a liquid lipid into the solid matrix creates crystal imperfections that prevent drug expulsion during polymorphic transitions<sup>[5]</sup>. Adapalene's high lipophilicity ( $\log P \sim 8.6$ ) favours its partitioning into the lipid core, and the disordered NLC structure retains it more effectively than the more ordered SLN lattice<sup>[10]</sup>.

The 3.41-fold skin deposition enhancement observed for NLC-1 over the marketed gel is promising. Similar or slightly lower enhancement ratios (2.0–3.0) have been reported for NLC formulations of other retinoids such as tretinoin and isotretinoin<sup>[11]</sup>. The mechanism likely involves occlusive film formation on the skin surface, which hydrates the stratum corneum and widens intercellular channels, as well as direct nanoparticle–skin interaction at the follicular orifice<sup>[12]</sup>.

Stability data at 40 °C/75% RH showed less than 12% growth in particle size over 90 days, which is within acceptable limits for lipid nanoparticle dispersions<sup>[13]</sup>. Drug content remained above 96%, confirming adequate chemical stability of adapalene within the lipid matrix. The slightly negative zeta potential (–28.4 mV) provides sufficient electrostatic repulsion to minimise aggregation, though the presence of the Tween 80 steric layer is likely the dominant stabilisation mechanism<sup>[14]</sup>.

A limitation of this work is the use of porcine ear skin as a surrogate for human skin. While porcine skin is widely accepted as the closest animal model, differences in follicular density and stratum corneum thickness may affect quantitative extrapolation. Clinical trials with the NLC-1 gel formulation are the logical next step to confirm tolerability and efficacy in acne patients<sup>[15]</sup>.

### Conclusion

Five lipid nanoparticle formulations two SLN and three NLC were prepared for topical delivery of the retinoid adapalene. The NLC-1 formulation, combining Compritol 888 ATO and oleic acid at a 7:3 ratio with 2% Tween 80, emerged as the best candidate, exhibiting a particle size of 156.8 nm, entrapment efficiency of 91.3%, sustained Korsmeyer-Peppas release kinetics over 24 h, and a 3.41-fold enhancement in skin drug deposition compared with the marketed adapalene gel. Accelerated stability testing over 90 days confirmed acceptable physical and chemical stability. These results demonstrate that NLC-based gels can

substantially improve the dermal delivery of adapalene, potentially reducing the dose-related irritation that limits patient compliance with conventional retinoid therapy. Clinical evaluation in human volunteers is warranted to translate these laboratory findings into improved acne management.

### Acknowledgements

#### Funding sources

This research was supported by the Persian Gulf Institute of Technology internal research fund and a collaborative grant from Isfahan University of Advanced Sciences.

#### Institutional support

The authors thank both institutions for access to HPLC, TEM, and DSC facilities used in this research.

#### Contributions not qualifying for authorship

The authors acknowledge Mr. Reza Hosseini for technical assistance with TEM imaging and Ms. Fatemeh Karimi for help with stability sample management.

### References

1. Bhate K, Williams HC. Epidemiology of acne vulgaris. *British Journal of Dermatology*. 2013;168(3):474–485.
2. Thiboutot D, Gollnick H, Bettoli V, Dréno B, Kang S, Leyden JJ. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne group. *Journal of the American Academy of Dermatology*. 2009;60(5):S1–S50.
3. Shroot B, Michel S. Pharmacology and chemistry of adapalene. *Journal of the American Academy of Dermatology*. 1997;36(6):S96–S103.
4. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery — a review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics*. 2000;50(1):161–177.
5. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. *International Journal of Pharmaceutics*. 2002;242(1–2):121–128.
6. Pinto MF, Moura CC, Nunes C, Segundo MA, Costa Lima SA, Reis S. A new topical formulation for psoriasis: Development of methotrexate-loaded nanostructured lipid carriers. *International Journal of Pharmaceutics*. 2014;477(1–2):519–526.
7. Jain SK, Chourasia MK, Masuriha R, Soni V, Jain A, Jain NK. Solid lipid nanoparticles bearing flurbiprofen for transdermal delivery. *Drug Delivery*. 2005;12(4):207–215.
8. ICH Expert Working Group. Validation of analytical procedures: Text and methodology Q2(R1). International Conference on Harmonisation. 2005:1–13.
9. Souto EB, Wissing SA, Barbosa CM, Müller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. *International Journal of Pharmaceutics*. 2004;278(1):71–77.
10. Jenning V, Thünemann AF, Gohla SH. Characterisation of a novel solid lipid nanoparticle carrier system based on binary mixtures of liquid and solid lipids. *International Journal of Pharmaceutics*. 2000;199(2):167–177.

11. Castro GA, Oréfice RL, Vilela JMC, Andrade MS, Ferreira LAM. Development of a new solid lipid nanoparticle formulation containing retinoic acid for topical treatment of acne. *Journal of Microencapsulation*. 2009;26(8):721–728.
12. Prow TW, Grice JE, Lin LL, Faye R, Butler M, Becker W. Nanoparticles and microparticles for skin drug delivery. *Advanced Drug Delivery Reviews*. 2011;63(6):470–491.
13. Freitas C, Müller RH. Correlation between long-term stability of solid lipid nanoparticles (SLN<sup>TM</sup>) and crystallinity of the lipid phase. *European Journal of Pharmaceutics and Biopharmaceutics*. 1999;47(2):125–132.
14. Heurtault B, Saulnier P, Pech B, Proust JE, Benoit JP. Physico-chemical stability of colloidal lipid particles. *Biomaterials*. 2003;24(23):4283–4300.
15. Draelos ZD, Carter E, Maloney JM, Elewski B, Poulin Y, Lynde C. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *Journal of the American Academy of Dermatology*. 2007;56(3):439.e1–439.e10.