

Development, Optimization and In-Vitro Evaluation of Tranexamic Acid-Loaded Nanostructured Lipid Carrier Gel for Enhanced Topical Delivery in the Management of Hyperpigmentation

Meenakshi Verma¹, Priya Gupta¹, Monika Dhiman², Payal Sharma³, Atul Kumar Gupta^{1*}

¹School of Pharmaceutical Sciences, Bahra University, Wakhnaghat, Shimla Hills, Himachal Pradesh-173234

Department: Pharmaceutics

²Himalayan Institute of Pharmacy, Kala-Amb, Himachal Pradesh-173030

Department: Pharmaceutics

³Himalayan Institute of Pharmacy, Kala-Amb, Himachal Pradesh-173030

Department: Pharmacognosy

AUTHOR DETAILS

Meenakshi Verma

Assistant Professor, Department of Pharmaceutics, School of Pharmaceutical Sciences, Bahra University, Wakhnaghat, Shimla Hills, Himachal Pradesh-173234

Email: verma.meenakshi1999@gmail.com

ORCID: 0009-0000-6532-5613

Priya Gupta

Research Scholar, Department of Pharmaceutics, School of Pharmaceutical Sciences, Bahra University, Wakhnaghat, Shimla Hills, Himachal Pradesh-173234

Monika Dhiman

Assistant Professor, Department of Pharmaceutics, Himalayan Institute of Pharmacy, Kala-Amb, Himachal Pradesh-173030

Email: monikadhiman5807@gmail.com

ORCID: 0009-0004-3574-9545

Payal Sharma

Assistant Professor, Department of Pharmacognosy, Himalayan Institute of Pharmacy, Kala-Amb, Himachal Pradesh-173030

Email: payalsharma10660@gmail.com

ORCID: 0009-0004-4383-7246

***Corresponding Author:** Atul Kumar Gupta, Professor, Department of Pharmaceutics, School of Pharmaceutical Sciences, Bahra University, Wakhnaghat, Shimla Hills, Himachal Pradesh-173234

Email: prof.akg1979@gmail.com

ABSTRACT

Hyperpigmentation is a common skin disorder caused by the overproduction of melanin. It can be triggered by UV exposure, hormonal changes, inflammation, and aging. Tranexamic acid (TXA) exhibits potential anti-hyperpigmentary activity, but its conventional topical delivery approach may be hindered by inadequate skin penetration and retention. NLCs can enhance drug stability, controlled release, skin penetration, and localized drug deposition. Thus, the incorporation of TXA in an NLC based gel may enhance its topical delivery and therapeutic potential. The present study deals with development, optimization and in-vitro evaluation of TXA loaded NLC gel for better management of hyperpigmentation.

Keywords: Tranexamic acid; Nanostructured lipid carrier; Melasma; Hyperpigmentation; Topical delivery; Solvent diffusion; Sustained release; Carbopol 980.

How to cite this article: Meenakshi Verma¹ Priya Gupta¹ Monika Dhiman² Payal Sharma³ Atul Kumar Gupta^{1*}. Development, Optimization and In-Vitro Evaluation of Tranexamic Acid-Loaded Nanostructured Lipid Carrier Gel for Enhanced Topical Delivery in the Management of Hyperpigmentation. *Int J Drug Deliv Technol.* 2026;16(83s):1477-1487. DOI: 10.25258/ijddt.16.83s.160.

Source of support: Nil.

Conflict of interest: None

1. Introduction

The skin is the largest organ of the human body and is the main barrier to microbial invasion, ultraviolet

radiation, chemical insult and mechanical injury, and a regulator of body temperature and transepidermal water loss (Yousef et al., 2024). It is composed of three functional layers: the superficial, stratified epidermis (stratum corneum) determines the speed of which molecules are delivered topically into the skin; the dermis layer is the site of sweat and sebaceous glands and is also present; and the hypodermis layer is underneath the dermis. The stratum corneum is a tightly packed “brick and mortar” structure with corneocytes surrounded by an intercellular matrix that is densely packed with ceramides, cholesterol and long chain free fatty acids and represents the rate limiting step for both dermal and transdermal drug absorption (Trommer & Neubert, 2006; Yousef et al., 2024). Therefore, the requirement of an active agent to be delivered into the viable layer of the skin is an important criterion for the success of the cutaneous therapeutic agents and this can only be achieved if the carrier is capable in temporarily disturbing the lipid barrier of the skin.

Localized acquired hypermelanosis; brown to greyish brown symmetrical macules on sun-exposed areas is called melanism. It is more common in females, and is reported to be present in between 1.5 % and 33.3 % of the populations, and virtually a large proportion of pregnancies (Nouveau et al., 2016; Pahadiya et al., 2024). It is a multi-factorial disease caused due to relapsing and often refractory pigmentation due to the combination of factors such as ultraviolet exposure, genetic predisposition and hormonal influence with increased dermal vascularity (Ghasemiyeh et al., 2024). The pharmacotherapy of the pigmentary disorders is difficult because pigment is deposited at both the epidermal and mixed/dermal levels and these layers must be sufficiently permeable to the active molecule.

Tranexamic acid (TXA; trans-4-aminomethylcyclohexanecarboxylic acid) is a synthetic lysine analogue that reversibly, and competitively, inhibits the binding of plasminogen to fibrin and thus has anti-fibrinolytic properties. is used in cyclic heavy bleeding, for decreasing surgical and traumatic blood loss (off-label use) and for short-term prophylaxis in haemophilia (Chauncey & Patel, 2026; Karaman, 2015). In dermatology TXA has been shown to be a promising depigmenting agent that not only interferes with the interaction between keratinocytes and melanocytes, but also inhibits plasmin activity induced by the UV radiation, thereby reducing the synthesis and transfer of melanin and helping restore the function of the skin barrier (Jaiswal et al., 2025; Pahadiya et al., 2024). The limitations are that TXA has been used orally, topically and as a microinjection into the lesions. Conventional topical therapy is safe, well tolerated, but has its own intrinsic hydrophilicity, leading to poor partitioning in lipid-rich stratum corneum, poor skin retention and efficacy, and requires competent clinician administration with risk of

infection and is invasive and painful (Jaiswal et al., 2025; Zhang et al., 2024).

There are strategies which have been studied that can be used to overcome these; the nanocarrier approach. Lipid nanoparticles were developed from the solid lipid nanoparticles (SLN) which was developed as an aqueous and organic solvent free alternative to polymeric nanoparticles and liposomes in the 1990s and are known for their physical stability and controlled release and physiological tolerability (Müller et al., 2011; Teeranachaideekul et al., 2007). However, “the drawback of the SLN was their limited drug loading capacity as well as a decrease in drug content during storage because of the drug being crystallized in an ordered lipid core, which led to the development of a second generation of lipid nanoparticles, called nanostructured lipid carriers (NLCs) (Müller et al., 2004; Radtke et al., 2005). NLCs are composed of solid and liquid lipids, creating an imperfect crystal-lattice packing which allows more drug molecules to enter the lattice, leading to higher loading capacity, low leakage and greater stability over time (Battaglia & Gallarate, 2012; Mehnert & Mäder, 2012). As applied topically, NLCs bind to and form film on the surface of the skin, which helps to keep the skin moist; interaction of their lipids with skin lipids facilitates the penetration of substances and enables the release of targeted substances for a long time (Czajkowska-Kośnik et al., 2023; Trommer & Neubert, 2006).

NLC dispersions are naturally low-viscous, poorly substantivity, and when combined with an appropriate semisolid vehicle, this mixture provides both the benefits in terms of penetration and controlled release of a nanocarrier and it is easily applied to the skin and maintains a long skin-residence time of a gel (Czajkowska-Kośnik et al., 2023; Rajinikanth & Chellian, 2016). Carbomers like Carbopol 980 are commonly used as a hydrophilic rheology modifier which forms low viscosity colloidal dispersion in water but thickens significantly on neutralization and thus are well suited for use as gelling agents in topical NLC systems (Rajinikanth & Chellian, 2016; Rowe et al., 2009a). Several nanocarrier systems have been recently developed to improve the dermal delivery and depigmenting efficacy of TXA including polymeric micellar hydrogels, transthesomes, solid lipid nanoparticles and microneedle patches which can be both used in the dermal and transdermal delivery of various actives (Chevala et al., 2022; Jaiswal et al., 2025; Rajput et al., 2025; Shaji & Parab, 2022; Toksoy et al., 2025); nanostructured lipid carriers in particular have enhanced the dermal and transdermal delivery of a wide range of actives. To this end, the present invention was carried out to develop and optimize a TXA-loaded NLC dispersion, transform the optimized dispersion to a Carbopol 980 gel and assess the developed formulation in vitro. The optimization of drug loading of the hydrophilic drug in the lipid

nanocarrier and the optimization of the drug release profile suitable for topical application of hyperpigmentation were the specific optimization targets.

2. Materials and Methods

2.1 Materials

The tranexamic acid was bought from BLD Pharmatech. Stearic acid was bought from Otto Chemie Pvt. Ltd. and the other chemicals, namely Ethyl oleate, Oleic acid, Methanol, Disodium hydrogen orthophosphate (anhydrous), Potassium dihydrogen orthophosphate and Sodium hydroxide were obtained from Finar. Propylene glycol monocaprylate and medium-chain triglyceride were both obtained from Gattefossé and AMS Enterprises, respectively. Except carbopol 980, all the other reagents used were analytical grade and carbopol 980 was of cosmetic grade. An electronic balance (Centurion Scientific), a pH-meter (Electrolab, Mumbai), a UV-visible spectrophotometer (Shimadzu) and a particle-size analyzer and a zeta analyzer (Malvern, UK), a probe sonicator, and a Brookfield viscometer were used.

2.2 Preformulation studies

The bulk TXA was tested organoleptically. The melting point was obtained by the open-capillary method with a melting-point apparatus and repeated three times in the capillary method. A stock solution (1000 µg/mL) of TXA in water was prepared and a working solution was prepared and scanned against a water blank, to find the absorption maximum for the TXA in working solution. The value of λ_{max} obtained was used to make a calibration curve for the range 20 – 200 µg/mL and each concentration was measured three times using linear regression.

Apparent partition coefficient was measured after contacting the 1:1 n-octanol/1:1 water mixture for 24 h at 100 rpm, shaking at 37 °C, separating and centrifuging (5000 rpm for 15 min), and calculating log P as the ratio of the drug concentration in n-octanol to that in water. In 1 mL of the various media, excess amount of the drug was added and the mixture was shaken for 24 h at 37 °C at 100 rpm and then centrifuged for 10 min at 1000 x g and the supernatant was measured at λ_{max} , the measurements were repeated thrice (Bachhav et al., 2019).

2.3 Preparation of TXA-loaded NLCs

2.3.1 Melt-emulsification method

Weighed stearic acid was added to the beaker which was then placed in a water bath (magnetic-stirrer bath) and the melting was conducted at approximately 70 °C. The molten lipid liquid was added to the beaker. The TXA and Tween 80 were simultaneously dissolved in 10 mL of water and then heated at 70 °C. The hot aqueous phase was added to the lipid phase and the mixture was stirred continuously at 100 rpm for 30 min and then probe-sonicated (40 % amplitude, 1 min) and cooled to room temperature (Yuan et al., 2007).

2.3.2 Solvent-diffusion method

Stearic acid and the liquid lipid were dissolved under stirring with 10 mL of a 1:1 mixture of acetone and ethanol by heating at 70 °C and TXA and Tween 80 were dissolved with 10 mL of water by heating at 70 °C. The aqueous phase was stirred with the organic lipid solution for 30 min at 70 °C and then probe-sonicated (Hu et al., 2005) for 1 min at 40 % amplitude and then cooled to room temperature. For 10 batches (TS1–TS10) the amount of drug (300 mg) and the amount of Tween 80 (1 % w/v) and the entrapment efficiency were kept constant while the amount of stearic acid (50, 100, 200, 400 mg) and the amount of liquid lipid (25, 50, 100, 125 mg) were varied (Table 1).

Table 1: Composition of TXA-loaded NLC batches (total volume 10 mL; Tween 80 fixed at 1 % w/v)

Code	Method	Stearic acid (mg)	Liquid lipid (mg)	Variable studied
TS1	Melt emulsification	200	50	Method
TS2	Solvent diffusion	200	50	Method / stearic acid
TS3	Solvent diffusion	50	50	Stearic acid
TS4	Solvent diffusion	100	50	Stearic acid
TS5	Solvent diffusion	300	50	Stearic acid / liquid lipid
TS6	Solvent diffusion	400	50	Stearic acid
TS7	Solvent diffusion	300	25	Liquid lipid
TS8	Solvent diffusion	300	75	Liquid lipid
TS9	Solvent diffusion	300	100	Liquid lipid
TS10	Solvent diffusion	300	125	Liquid lipid

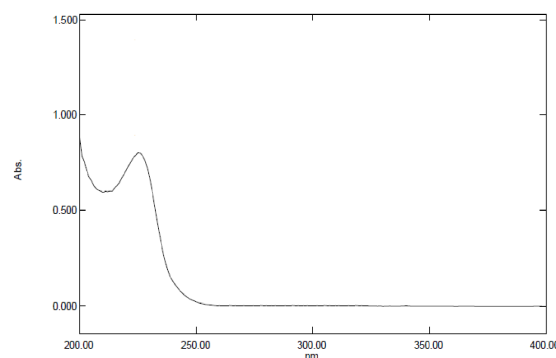


Figure 1: UV absorption spectrum of tranexamic acid working solution (180 µg/mL) in water, showing the absorption maximum at 221 nm.

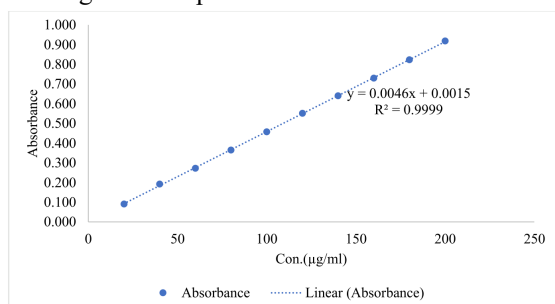


Figure 2: Standard calibration curve of tranexamic acid in water at 221 nm (20–200 µg/mL).

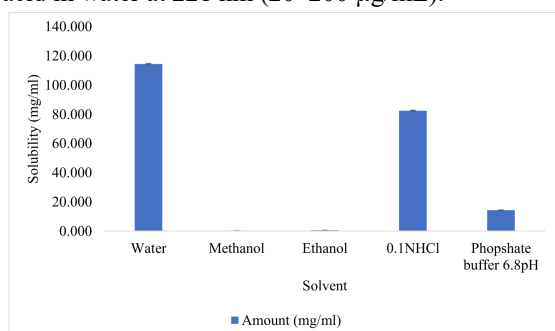


Figure 3: Equilibrium solubility of tranexamic acid in water, water-miscible solvents and buffers.

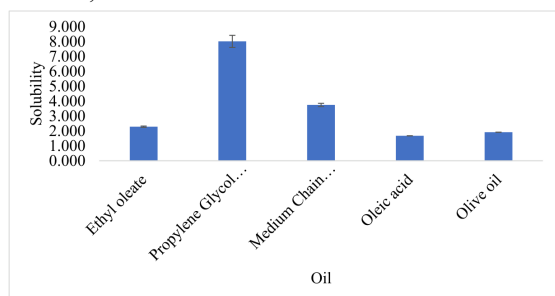


Figure 4: Equilibrium solubility of tranexamic acid in the candidate liquid lipids (oils).

2.4 Characterization of TXA-loaded NLCs

Visual examinations were conducted to determine if the drug particles, aggregation and phase separation were present in the prepared dispersions. Free (unentrapped) drug was determined by measuring the amount of drug dispersed after centrifugation (15 000 rpm for 30 min, cooling centrifuge) and by assaying the supernatant drug using λ_{max} against a methanol blank and subtracting the percentage of free drug from the theoretical drug content to calculate the percentage of drug entrapment. The mean particle size and PDI for the optimized batch were measured using dynamic light scattering at 25 °C while the zeta potential was measured in a capillary zeta cell mounted on Nano ZS Zetasizer. Particles were deposited on carbon-coated copper grid and negatively stained with 1 % phosphotungstic acid and subsequently observed by TEM (Gaba et al., 2015; Mendes et al., 2019).

2.5 Preparation of TXA-loaded NLC gel

Optimized NLC dispersion was gelled by dispersing the Carbopol 980 (1.0, 1.5, 2.0 and 2.5 % w/w) directly in the dispersion and letting it

hydrate overnight. Methyl paraben (0.01 % w/w) was incorporated into the gel to maintain the gel, and the pH was maintained around 6 by drop-wise addition of triethanolamine, stirring continuously. The TXA equivalent concentration of all four gels was 3 % (TS9G1, TS9G2, TS9G3 and TS9G4) (Mendes et al., 2019; Rajinikanth & Chellian, 2016).

2.6 Evaluation of TXA-loaded NLC gel

The colour, aggregation and precipitation was checked in gels and homogeneity and grittiness was done by rubbing a small amount of gel between fingers. The pH was measured by measuring the pH of 100 mg/50 mL aqueous dispersion of the gel in a pH meter at room temperature (25 °C), triplicates. The spreading behavior was evaluated by slip and drag method in which 1 g of gel sample was squeezed between two glass plates under the pressure of 10 g and the time (T) required for the top glass plate to move the prescribed distance (L) under the above pressure was measured and spreadability was expressed as $S = (M \times L)/T$, where M is the applied weight, L is the length of the slide and T is the time. The absorbance of the drug solution was then determined by dispersing 1 g of the gel in 100 mL of the drug solution (1:1 methanol–water) and subsequently centrifugation at λ_{max} . The viscosity was measured three times on a Brookfield viscometer (spindle 62, speed 50 rpm, temperature 25 ± 2 °C) (Czajkowska-Kośnik et al., 2023; Khot et al., 2024).

In-vitro drug release studies were carried out at 37 °C and 100 rpm using Franz diffusion cell system with activated dialysis membrane with receptor medium phosphate buffer (pH 6.8, 30 mL). 1.0 g of the gel was placed in the donor compartment and 1.0 mL samples were taken at 0.25, 0.5, 1, 2, 4, 8, 10, 12 and 24 h and were replaced with fresh medium and measured at λ_{max} compared with the corresponding control gel, triplicated (Mendes et al., 2019; Patwekar & Pedewad, 2017). The data were fitted to the zero-order, first-order, Higuchi and Korsmeyer–Peppas model and the model with the largest R^2 value was used for the best fit. Lastly, Fourier-transform infrared (FTIR) spectroscopy method was used to investigate the interaction between drug and excipients using pure TXA and optimized gel ($400\text{--}4000\text{ cm}^{-1}$).

3. Results and Discussion

3.1 Preformulation characterization

Bulk TXA was found to be a white to almost white crystalline powder as described in the Pharmacopoeia. It was found that its melting point was at 305.34 ± 0.58 °C and 309 ± 1.00 °C respectively which are in accordance with the reported melting point value of approximately 305 °C (Vijayakumar et al., 2016). The working solution with 180 µg/mL ultraviolet spectrum showed an absorption max at 221 nm in water, to which all subsequent absorption measurements were made. The absorption maximum of the working solution (180 µg/mL) was 221 nm in water and this was used in all other absorption

measurements thereafter. The Beer–Lambert law was found to be obeyed within the working range as the calibration curve was linear with a slope of 0.0046 and a regression coefficient of 0.9999 in the range of 20–200 µg/mL (Figures 1 and 2). The apparent partition coefficient (log P) of the studied compound was -1.598 ± 0.014 which is acceptable with the reported value of -1.6 (Karaman, 2015; Karaman et al., 2013) and is in accordance with the high hydrophilicity of the molecule.

The solubility data (Table 2) revealed that TXA is freely soluble in water (114.46 mg/mL), highly soluble in 0.1 N HCl (82.43 mg/mL), sparingly soluble in phosphate buffer pH 6.8 and only very slightly soluble in methanol and ethanol again indicating its hydrophilic nature. Thus, the solubility was screened in five oils and the oil which provided the highest solubility (8.018 ± 0.407 mg/mL; Figures 3 and 4) was used as liquid lipid for formulation, propylene glycol monocaprylate.

Table 2: Equilibrium solubility of tranexamic acid in aqueous/organic solvents and in candidate liquid lipids

Medium	Solubility (mg/mL)	Inference
Water	114.457 ± 0.377	Freely soluble
0.1 N HCl	82.428 ± 0.332	Soluble
Phosphate buffer pH 6.8	14.322 ± 0.112	Sparingly soluble
Ethanol	0.527 ± 0.009	Very slightly soluble
Methanol	0.231 ± 0.005	Very slightly soluble
Propylene glycol monocaprylate	8.018 ± 0.407	Selected liquid lipid
Medium-chain triglyceride	3.750 ± 0.109	—
Ethyl oleate	2.286 ± 0.045	—
Olive oil	1.916 ± 0.008	—
Oleic acid	1.678 ± 0.007	—

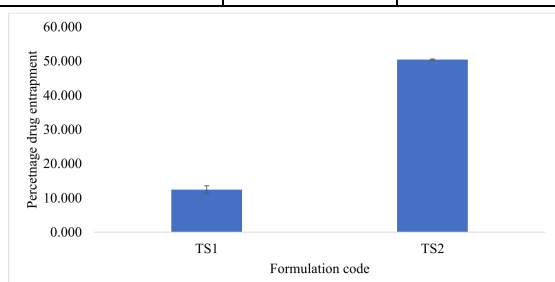


Figure 5: Effect of the preparation method (melt-emulsification vs. solvent-diffusion) on the entrapment efficiency of TXA-loaded NLCs.

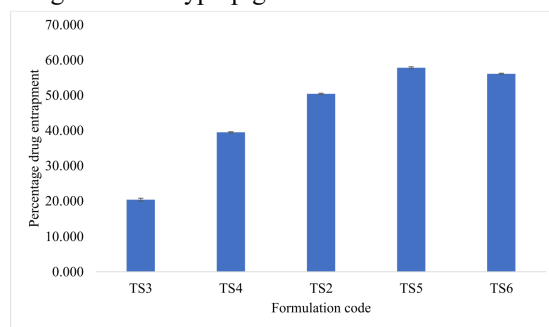


Figure 6: Effect of the amount of solid lipid (stearic acid) on the entrapment efficiency of TXA-loaded NLCs.

3.2 Preparation and optimization of NLCs

The two methods of preparation were quite different. The phase separation was visible macroscopically in the dispersion obtained by melt-emulsification (TS1) whereas the nanodispersions obtained by the other 10 solvent-diffusion methods (TS2 to TS10) were white, translucent and uniform and showed no phase separation. This rapid diffusion of the water soluble organic solvent into the water phase creates interfacial turbulence (Marangoni effect) which naturally forms submicron-sized droplets, thus giving the finer and more uniform product (Hu et al., 2005; Dora et al., 2012). Both the colloidal dispersions were milky, homogeneous after preparing them with the lipid melt at 70 °C and after probe-sonicating them to achieve a nanometric range of particles.

The entrapment efficiency was because of these observations. Substantially higher percentage of entrapped drug was achieved in the solvent-diffusion batch (50.40 ± 0.19 %) as compared to the melt-emulsification batch (12.44 ± 1.11 %) (Figure 5). The main reason for the lower efficiency of the melt-emulsification method is the poor solubility of the hydrophilic drug in the molten lipid, and the fact that the drug is incorporated into the aqueous phase during the emulsification process (Yuan et al., 2007). In all subsequent development, thus solvent-diffusion was employed.

Varying the solid lipid at a fixed liquid-lipid level showed that entrapment rose progressively as stearic acid increased from 50 mg (TS3, 20.41 %) through 100 mg (TS4, 39.51 %) and 200 mg (TS2, 50.40 %) to 300 mg (TS5, 57.79 %), but did not increase further at 400 mg (TS6, 56.10 %). The increase in mass of solid-liquid phase also leads to increase in the number of solid particles to enclose the drug and more imperfections in the matrix to accommodate the drug content, but after a certain optimum, the benefit becomes levelled, hence 300 mg of stearic acid (Figure 6) (TS5) was advanced (Gaba et al., 2015).

With the solid lipid fixed at 300 mg, increasing the liquid lipid from 25 mg (TS7, 35.88 %) through 50 mg (TS5, 57.79 %) and 75 mg (TS8, 68.08 %) to 100 mg (TS9, 73.01 %) markedly improved entrapment, whereas a further increase to 125 mg

Development, Optimization and In-Vitro Evaluation of Tranexamic Acid-Loaded Nanostructured Lipid Carrier Gel for Enhanced Topical Delivery in the Management of Hyperpigmentation

(TS10, 72.26 %) produced no additional gain. Incorporation of liquid lipid disrupts the ordered crystalline lattice of the solid lipid creating space for the drug molecules and decreasing the interfacial tension and stabilizing the emulsion against drug leakage into the aqueous phase (Hu et al., 2005; Khot et al., 2024). From this study, it was concluded that the optimized formulation found to be batch TS9 (300 mg stearic acid, 100 mg propylene glycol monocaprylate) had the highest EE of 73.01 ± 0.29 % (Figure 7; Table 3).

Table 3: Effect of formulation variables on entrapment efficiency of TXA-loaded NLCs

Variable	Code	Level	Entrapment efficiency (%)
Method	TS1	Melt emulsification	12.440 ± 1.107
Method	TS2	Solvent diffusion	50.399 ± 0.192
Stearic acid	TS3	50 mg	20.411 ± 0.418
Stearic acid	TS4	100 mg	39.505 ± 0.182
Stearic acid	TS5	300 mg	57.790 ± 0.290
Stearic acid	TS6	400 mg	56.099 ± 0.151
Liquid lipid	TS7	25 mg	35.882 ± 0.182
Liquid lipid	TS8	75 mg	68.080 ± 0.192
Liquid lipid	TS9	100 mg	73.007 ± 0.290
Liquid lipid	TS10	125 mg	72.258 ± 0.327

3.3 Particle size, PDI and zeta potential

A small particle size is desirable as this increases the skin surface area of the interface and thus drug partitioning and absorption will be improved. The mean particle size of the optimized batch TS9 was 230.4 nm (Figure 8) and PDI of 0.123. A PDI value of 0.1–0.7 is considered as monodisperse system, whereas PDI value > 0.7 is considered as broadly distributed system, hence, low PDI value means homogeneous and monodisperse system (Gaba et al., 2015). The surface charge and electrostatic repulsive force responsible for maintaining the stability of a colloidal dispersion, called the zeta potential, was found to be -28.3 mV for TS9 (Figure 9). The characteristic of this magnitude is its negative value, which is typical for the particle surface ionization of stearic acid, and it is considered to provide good interparticle stabilization by repulsion (Hu et al., 2005; Mendes et al., 2019; Rowe et al., 2009b). The transmission electron microscopy results showed that the size and morphology of the nanoparticles were discrete

and spherical (Figure 10), which was consistent with the light-scattering results.

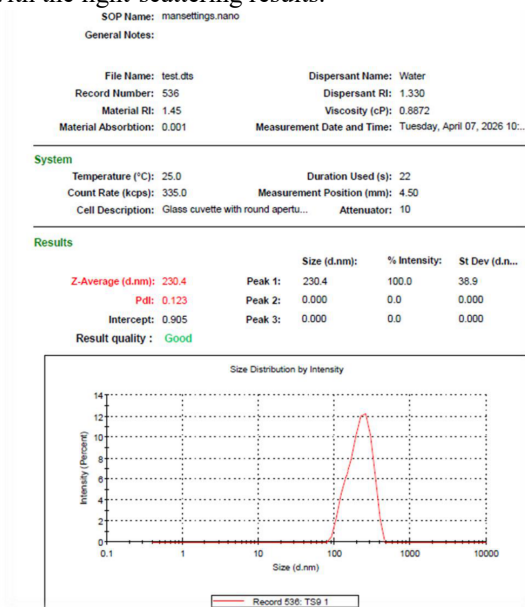


Figure 7: Particle-size distribution and polydispersity index of the optimized formulation TS9 (Z-average 230.4 nm, PDI 0.123).

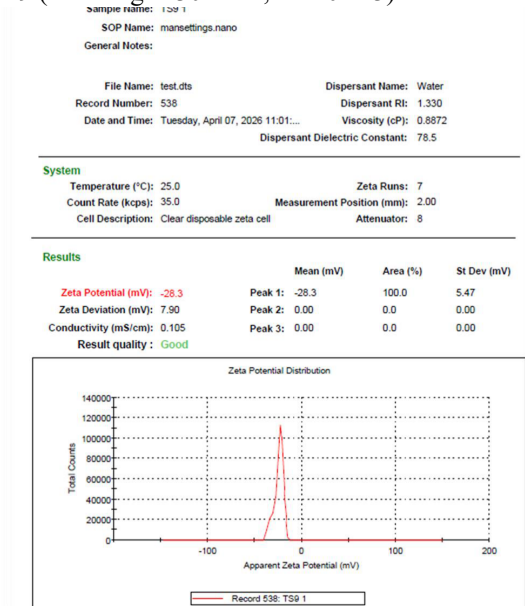


Figure 8: Zeta-potential distribution of the optimized formulation TS9 (-28.3 mV).

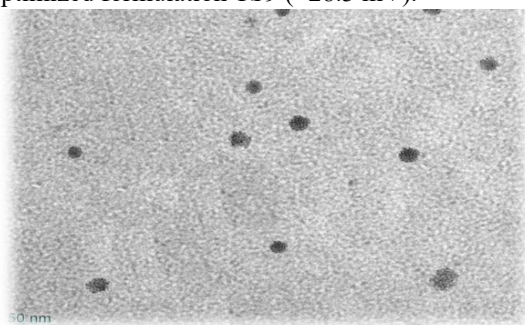


Figure 9: Transmission electron micrograph (TEM) of the optimized formulation TS9 showing discrete, spherical nanoparticles.

3.4 Physicochemical evaluation of the NLC gel

The optimized dispersion had low viscosity and low substantivity, which was neutralized by adding the hydrophilic polyacrylic-acid polymer, Carbopol 980, which is a low viscosity dispersion of water, which thickens when neutralized by a base such as triethanolamine as in the case of Czajkowska-Kośnik et al. (2023) and Rajinikanth & Chellian (2016). The four gels (TS9G1 to TS9G4) were white, translucent and devoid of any grittiness and the absence of powder particles meant that the drug loaded NLCs were evenly distributed through the gel matrix, but the least viscous was TS9G1 (1 % Carbopol) (Figure 11). The pH levels of all the gels were in the range of $5.570 \pm 0.044 - 5.800 \pm 0.046$ which is slightly acidic (Figure 12), desirable for the skin to avoid disrupting the barrier function, drying the skin, or causing an increase in sebum production (Czajkowska-Kośnik et al., 2023).

The spreadability was found to be inversely proportional to the concentration of the gelling agent, e.g., TS9G1 with 12.844 ± 0.149 g·cm/s and TS9G4 with 3.309 ± 0.015 g·cm/s were considered ideal for the topical application (Khot et al, 2024). Drug content of all gels was high and uniform (95.05–99.16 %), with TS9G3 highest at 99.155 ± 0.418 %. The viscosity of both the formulations, TS9G3 (3690 cP) and TS9G4 (5104 cP) were found to be good and were adequate for providing the required consistency as the viscosity increased with the increase in concentration of Carbopol from 1486.33 ± 2.52 cP (TS9G1) to 5104.00 ± 2.00 cP (TS9G4) which enhanced the skin adhesion, residence time and modulated the release profile (Figures 13–15; Table 4). A balance of spreadability, drug content and viscosity led to the choice of TS9G3 and TS9G4 for release testing.

Table 4: Physicochemical properties of TXA-loaded NLC gels (TS9G1–TS9G4)

Gel (Carbopol 980)	pH	Spreadability (g·cm/s)	Drug content (%)	Viscosity (cP)
TS9G1 (1.0 %)	5.65 ± 0.076	12.844 ± 0.149	95.048 ± 1.107	1486.33 ± 2.52
TS9G2 (1.5 %)	5.57 ± 0.044	9.653 ± 0.056	98.188 ± 0.725	2563.00 ± 1.73
TS9G3 (2.0 %)	5.71 ± 0.026	4.698 ± 0.029	99.155 ± 0.418	3690.00 ± 1.00
TS9G4 (2.5 %)	5.80 ± 0.046	3.309 ± 0.015	97.464 ± 1.255	5104.00 ± 2.00



Figure 10: Physical appearance of the optimized TXA-loaded NLC gel (TS9G3).

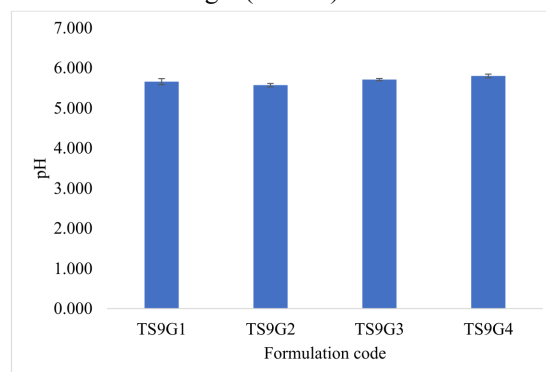


Figure 11: pH of the prepared TXA-loaded NLC gels (TS9G1–TS9G4).

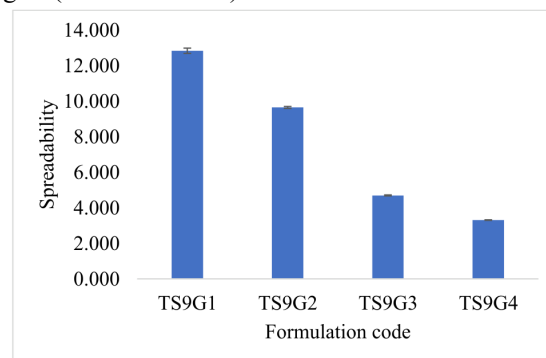


Figure 12: Spreadability of the prepared TXA-loaded NLC gels (TS9G1–TS9G4).

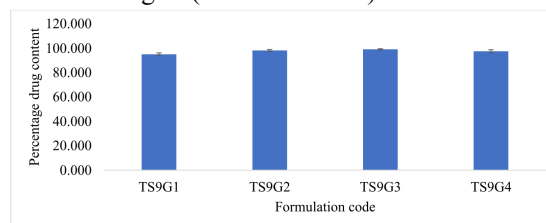


Figure 13: Drug content of the prepared TXA-loaded NLC gels (TS9G1–TS9G4).

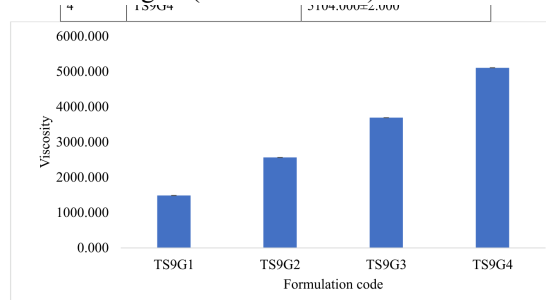


Figure 14: Viscosity of the prepared TXA-loaded NLC gels (TS9G1–TS9G4).

3.5 In-vitro drug release

Development, Optimization and In-Vitro Evaluation of Tranexamic Acid-Loaded Nanostructured Lipid Carrier Gel for Enhanced Topical Delivery in the Management of Hyperpigmentation

The Table 5 shows the release profiles over 24 h that clearly showed the difference between the nanostructured gels and the control gel. The control gel released 100.69 ± 0.70 % of TXA in only 2 h while TS9G3 and TS9G4 released only 36.20 ± 0.58 % and 24.67 ± 0.58 % at 2 h and continued releasing throughout 24 h (Figure 16). The characteristic biphasic nature with a first relatively more rapid phase and a second slower phase, was observed in both NLC gels. The early burst is attributed to the drug that diffused to the outer layers of the cooling process, while the sustained phase is attributed to the drug entrapped in the deep part of the solid-lipid core and the oil droplets precipitated in the matrix which delayed the diffusion (Czajkowska-Kośnik et al., 2023; Gaba et al., 2015). The drug release in 24 h from the TS9G3 formulation was 99.53 ± 0.13 % while for the TS9G4 formulation, it was 82.86 ± 0.45 %; this difference in drug release between the two formulations may be attributed to higher viscosity of the TS9G4 formulation which reduces the ability of the drug to diffuse out of the matrix. TS9G3 was thus thought to be optimized with a sustained profile and almost 100% release and was considered to be the optimized gel.

Table 5: Cumulative in-vitro release of TXA from the control gel and NLC gels

Time (h)	Control gel (%)	TS9G3 (%)	TS9G4 (%)
0.25	31.775 ± 0.547	5.181 ± 0.332	3.949 ± 0.332
0.5	48.587 ± 0.217	12.210 ± 0.502	14.167 ± 0.330
1	77.790 ± 0.763	20.978 ± 0.377	18.514 ± 0.547
2	100.688 ± 0.699	36.196 ± 0.575	24.674 ± 0.575
4	—	48.442 ± 0.251	33.080 ± 0.453
8	—	63.949 ± 0.232	53.080 ± 0.233
10	—	86.268 ± 0.453	69.094 ± 1.197
12	—	99.457 ± 0.217	81.341 ± 0.628
24	—	99.529 ± 0.126	82.862 ± 0.453

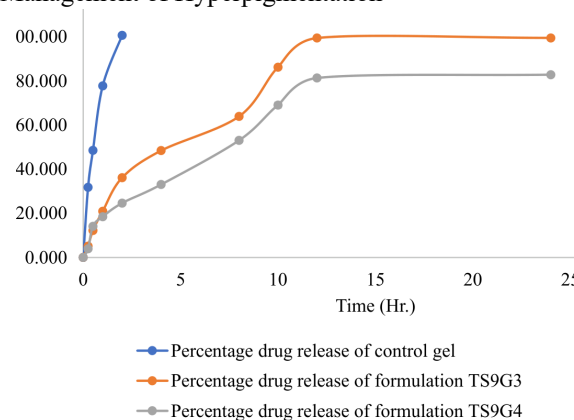


Figure 15: Cumulative in-vitro release of tranexamic acid from the control gel and the NLC gels (TS9G3 and TS9G4) over 24 h.

3.6 Release kinetics

The data were fitted to four models to better understand the release mechanism and the best fit was chosen by R^2 . The Korsmeyer–Peppas model gave the highest correlation ($R^2 = 0.957$), followed by the Higuchi model ($R^2 = 0.927$), and the zero-order ($R^2 = 0.776$) and first-order ($R^2 = 0.817$) models fitted less well. The predominant fits of the Korsmeyer–Peppas and Higuchi indicate that the release process is diffusion-controlled from the lipid matrix, and the value of the release exponent of the Korsmeyer–Peppas model, $n \approx 0.64$, suggests an abnormal (non-Fickian) drug release mechanism, during which the drug is released simultaneously by diffusion and relaxation of the polymeric gel network (Figures 17–20) (Czajkowska-Kośnik et al., 2023). The behaviour is similar to that of sustained release profile observed, attributing the suitability of using the NLC gel as a controlled release topical carrier.

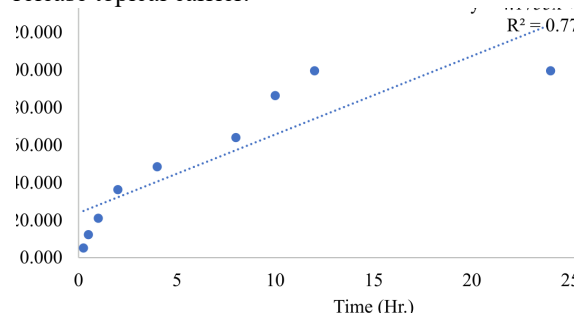


Figure 16: Zero-order release kinetic plot for the optimized NLC gel TS9G3.

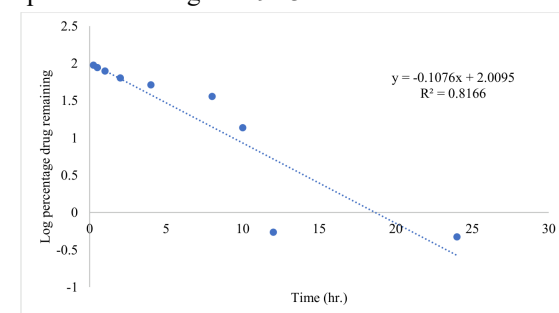


Figure 17: First-order release kinetic plot for the optimized NLC gel TS9G3.

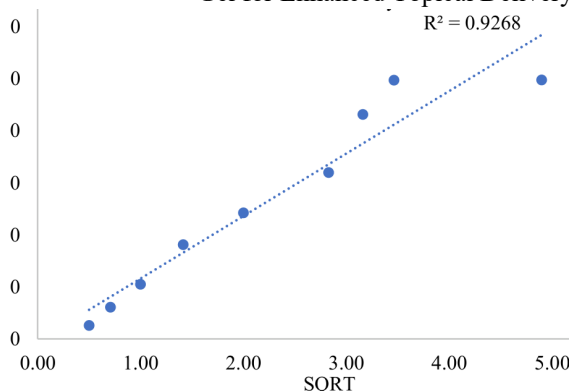


Figure 18: Higuchi release kinetic plot for the optimized NLC gel TS9G3.

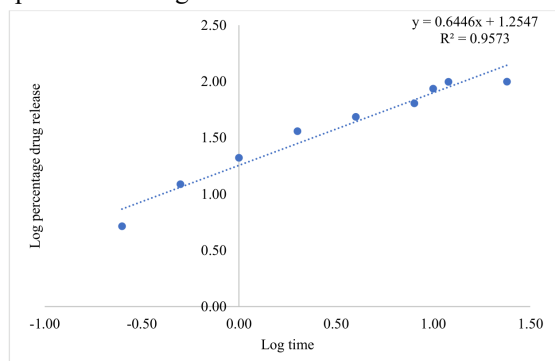


Figure 19: Korsmeyer–Peppas release kinetic plot for the optimized NLC gel TS9G3.

3.7 Drug–excipient compatibility (FTIR)

The FTIR spectrum of pure TXA displayed its characteristic absorptions: a methylene/ CH_2 band at 1450.56 cm^{-1} and a C–N band at 1009.12 cm^{-1} , carbonyl (C=O) bands at 1532.12 , 1635.12 and 2209.25 cm^{-1} , and C–H stretching at 2862.19 and 2920.05 cm^{-1} (Figure 21) (Chevala et al., 2022; Huang et al., 2024). The characteristic peaks of the drug were absent or reduced in the spectrum of the optimized gel TS9G3 indicating that there was no negative chemical reaction involved in the drug with this optimized gel (Figure 22), but it was successfully entrapped in the lipid matrix and masked by the excipients. No new peaks appearing show that there is no incompatibility between the drug and the excipients; the drug–excipient association is therefore not chemical, but physical.

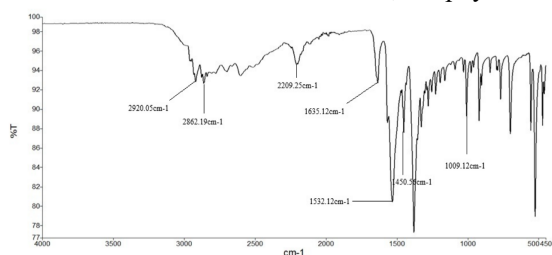


Figure 20: FTIR spectrum of pure tranexamic acid.

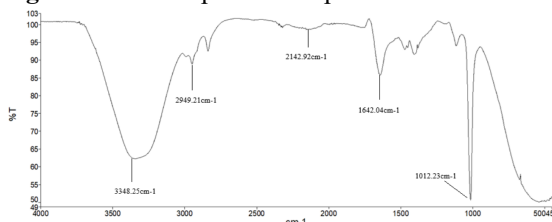


Figure 21: FTIR spectrum of the optimized formulation TS9G3.

4. Conclusion

NLC based gel loaded with tranexamic acid has been successfully developed and optimized for better and sustained topical delivery. The preformulation studies, which confirmed the identity of the drug, its characteristic melting point and the maximum of its UV absorption at 221 nm , showed that the drug was highly soluble in water and had a high hydrophilic/lipophilic character ($\log P \approx -1.6$), thus making it the most appropriate liquid lipid for the preparation of nanocrystals. The outcome of the two preparation methods studied clearly showed that the dispersion quality (homogeneity and entrapment) was significantly higher for the solvent diffusion method than for the melt-emulsification method. The optimized batch of nanocarriers was TS9 with a maximum entrapment efficiency of 73.01% , a nanometric particle size of 230.4 nm , low PDI of 0.123 and a favourable zeta potential of -28.3 mV along with spherical morphology, suggesting a stable and uniform nanocarrier.

The optimized dispersion was incorporated into the gel, Carbopol 980, to prepare skin compatible semisolids with suitable pH, spreadability, drug content and viscosity, of which the TS9G3 (optimized dispersion at 2% of Carbopol 980) formulation was found to have the best overall balance of properties. The NLC gels exhibited a controlled release of the drug, with 99.53% of release over 24 h (TS9G3) which was due to diffusion mechanism, governed by the Korsmeyer–Peppas model, while conventional control gel released the drug within 2 h . FTIR analysis also indicated the non-incompatibility of the drug with the lipid matrix. All these results indicate that optimized NLC gel can enhance the loading capacity and give sustained release, thus it could be used as a carrier system to deliver tranexamic acid to the skin for treatment of melasma and hyperpigmentation. Ex-vivo permeation, in-vivo efficacy and stability testing are recommended to support the potential of the drug for clinical use.

References

1. Bachhav, A. A., Ahire, S. A., & Jadhav, A. G. (2019). Preformulation study of piroxicam. *International Journal of Pharmaceutical Sciences and Research*, *10*(2), 811–818.
2. Battaglia, L., & Gallarate, M. (2012). Lipid nanoparticles: State of the art, new preparation methods and challenges in drug delivery. *Expert Opinion on Drug Delivery*, *9*(5), 497–508.
3. Chauncey, J. M., & Patel, P. (2026). Tranexamic acid. In StatPearls. StatPearls Publishing.
4. Chevala, N. T., Dsouza, J. A., Saini, H., & Kumar, L. (2022). Design and development of tranexamic acid loaded film-forming gel to alleviate melasma. *Journal of Cosmetic Dermatology*, *21*(12), 6863–6874.

5. Czajkowska-Kośnik, A., Szymańska, E., & Winnicka, K. (2023). Nanostructured lipid carriers (NLC)-based gel formulations as etodolac delivery: From gel preparation to permeation study. *Molecules*, 28(1), 235.
6. Dora, C. L., Putaux, J. L., Pignot-Paintrand, I., Dubreuil, F., Soldi, V., Borsali, R., & Lemos-Senna, E. (2012). Physicochemical and morphological characterizations of glyceryl tristearate/castor oil nanocarriers prepared by the solvent diffusion method. *Journal of the Brazilian Chemical Society*, 23(11), 1972–1981.
7. Elmowafy, M., Shalaby, K., Ali, H. M., Alruwaili, N. K., Salama, A., Ibrahim, M. F., Akl, M. A., & Ahmed, T. A. (2019). Impact of nanostructured lipid carriers on dapsone delivery to the skin: In vitro and in vivo studies. *International Journal of Pharmaceutics*, 572, 118781.
8. Gaba, B., Fazil, M., Khan, S., Ali, A., Baboota, S., & Ali, J. (2015). Nanostructured lipid carrier system for topical delivery of terbinafine hydrochloride. *Bulletin of Faculty of Pharmacy, Cairo University*, 53(2), 147–159.
9. Ghasemiyeh, P., Fazlinejad, R., Kiafar, M. R., Rasekh, S., Mokhtarzadegan, M., & Mohammadi-Samani, S. (2024). Different therapeutic approaches in melasma: Advances and limitations. *Frontiers in Pharmacology*, 15, 1337282.
10. Hu, F. Q., Jiang, S. P., Du, Y. Z., Yuan, H., Ye, Y. Q., & Zeng, S. (2005). Preparation and characterization of stearic acid nanostructured lipid carriers by solvent diffusion method in an aqueous system. *Colloids and Surfaces B: Biointerfaces*, 45(3–4), 167–173.
11. Huang, C., Wang, M., Yu, S., Yu, D.-G., & Bligh, S. W. A. (2024). Electrospun fenoprofen/polycaprolactone @ tranexamic acid/hydroxyapatite nanofibers as orthopedic hemostasis dressings. *Nanomaterials*, 14(7), 646.
12. Imran, M., Iqbal, M. K., Imtiyaz, K., Saleem, S., Mittal, S., Rizvi, M. M. A., Ali, J., & Baboota, S. (2020). Topical nanostructured lipid carrier gel of quercetin and resveratrol: Formulation, optimization, in vitro and ex vivo study for the treatment of skin cancer. *International Journal of Pharmaceutics*, 587, 119705.
13. Jaiswal, S., Ahmed, B., Naryal, S., Rana, M., Kaur, S., & Kaur, I. P. (2025). Tranexamic acid-based polymeric micellar hydrogel for enhanced dermal delivery and melanin reduction. *Molecular Pharmaceutics*, 22(8), 4567–4586.
14. Karaman, R. (2015). From conventional prodrugs to prodrugs designed by molecular orbital methods. In *Frontiers in Computational Chemistry* (Vol. 2, pp. 187–249). Bentham Science Publishers.
15. Karaman, R., Ghareeb, H., Dajani, K. K., Scrano, L., Hallak, H., Abu-Lafi, S., Mecca, G., & Bufo, S. A. (2013). Design, synthesis and in vitro kinetic study of tranexamic acid prodrugs for the treatment of bleeding conditions. *Journal of Computer-Aided Molecular Design*, 27(7), 615–635.
16. Khot, C., Kolekar, K., Dabhale, S., Mohite, A., Nadaf, S., Kumbhar, P. S., & Disouza, J. (2024). Optimized albendazole-loaded nanostructured lipid carrier gel: A redefined approach for localized skin cancer treatment. *RSC Pharmaceutics*, 1, 1042–1058.
17. Mehnert, W., & Mäder, K. (2012). Solid lipid nanoparticles: Production, characterization and applications. *Advanced Drug Delivery Reviews*, 64(Suppl.), 83–101.
18. Mendes, I. T., Ruela, A. L. M., Carvalho, F. C., Freitas, J. T. J., Bonfílio, R., & Pereira, G. R. (2019). Development and characterization of nanostructured lipid carrier-based gels for the transdermal delivery of donepezil. *Colloids and Surfaces B: Biointerfaces*, 177, 274–281.
19. Mikled, P., Chavasiri, W., & Khongkow, M. (2024). Development of dihydroxyresveratrol-loaded nanostructured lipid carriers for safe and effective treatment of hyperpigmentation. *Scientific Reports*, 14, 29211.
20. Müller, R. H., Radtke, M., & Wissing, S. A. (2004). Solid lipid nanoparticles and nanostructured lipid carriers. In *Encyclopedia of Nanoscience and Nanotechnology*. American Scientific Publishers.
21. Müller, R. H., Rainer, S., & Keck, C. M. (2011). 20 years of lipid nanoparticles (SLN & NLC): Present state of development and industrial applications. *Current Drug Discovery Technologies*, 8(3), 207–227.
22. Nouveau, S., Agrawal, D., Kohli, M., Bernerd, F., Misra, N., & Nayak, C. S. (2016). Skin hyperpigmentation in Indian population: Insights and best practice. *Indian Journal of Dermatology*, 61(5), 487–495.
23. Pahadiya, P., Sharma, V. K., Patil, S. B., & Patil, B. K. (2024). A clinico-epidemiological study of melasma at a tertiary care centre in India. *International Journal of Academic Medicine and Pharmacy*, 6(6), 868–871.
24. Pardeike, J., Hommoss, A., & Müller, R. H. (2009). Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. *International Journal of Pharmaceutics*, 366(1–2), 170–184.
25. Patwekar, S. L., & Pedewad, S. R. (2017). Development and evaluation of nanostructured lipid carriers based gel of isotretinoin. *Particulate Science and Technology*, 37(3), 296–304.
26. Radtke, M., Souto, E. B., & Müller, R. H. (2005). Nanostructured lipid carriers: A novel generation of solid lipid drug carriers.

Development, Optimization and In-Vitro Evaluation of Tranexamic Acid-Loaded Nanostructured Lipid Carrier Gel for Enhanced Topical Delivery in the Management of Hyperpigmentation

- Pharmaceutical Technology Europe, 17(4), 45–50.
27. Rajinikanth, P. S., & Chellian, J. (2016). Development and evaluation of nanostructured lipid carrier-based hydrogel for topical delivery of 5-fluorouracil. *International Journal of Nanomedicine*, 11, 5067–5077.
28. Rajput, D., Rathee, S., Sahu, A., Sen, D., Jain, S. K., & Patil, U. K. (2025). Integrating nanotechnology and phytochemicals: Innovative approaches for the management of melasma. *The Natural Products Journal*, 16(1).
29. Rehman, A., Iqbal, M., Khan, B. A., Khan, M. K., Huwaimel, B., Alshehri, S., Alamri, A. H., Alzhrani, R. M., Bukhary, D. M., Safhi, A. Y., & Hosny, K. M. (2022). Fabrication, in vitro, and in vivo assessment of eucalyptol-loaded nanoemulgel as a novel paradigm for wound healing. *Pharmaceutics*, 14(9), 1971.
30. Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009a). Carbomer. In *Handbook of pharmaceutical excipients* (6th ed., pp. 110–114). Pharmaceutical Press.
31. Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009b). Stearic acid. In *Handbook of pharmaceutical excipients* (6th ed., pp. 737–739). Pharmaceutical Press.
32. Shaji, J., & Parab, S. S. (2022). Formulation development of tranexamic acid loaded transethosomal patch for melasma. *Research Journal of Pharmaceutical Dosage Forms and Technology*, 14(1), 7–16.
33. Teeranachaideekul, V., Müller, R. H., & Junyaprasert, V. B. (2007). Encapsulation of ascorbyl palmitate in nanostructured lipid carriers (NLC): Effects of formulation parameters on physicochemical stability. *International Journal of Pharmaceutics*, 340(1–2), 198–206.
34. Toksoy, M. O., Aşır, F., & Sabancılar, İ. (2025). Development and characterization of tranexamic acid-loaded solid lipid nanoparticles for enhanced permeability: Release kinetics, in vitro cytotoxicity, and histological evaluation. *Journal of Dispersion Science and Technology*, 1–13.
35. Trommer, H., & Neubert, R. H. H. (2006). Overcoming the stratum corneum: The modulation of skin penetration. *Skin Pharmacology and Physiology*, 19(2), 106–121.
36. Vijayakumar, A., Baskaran, R., & Yoo, B. K. (2016). Skin permeation and retention of topical bead formulation containing tranexamic acid. *Journal of Cosmetic and Laser Therapy*, 19(2), 102–108.
37. Yousef, H., Alhaji, M., Fakoya, A. O., & Sharma, S. (2024). Anatomy, skin (integument), epidermis. In *StatPearls*. StatPearls Publishing.
38. Yuan, H., Wang, L. L., Du, Y. Z., You, J., Hu, F. Q., & Zeng, S. (2007). Preparation and characteristics of nanostructured lipid carriers for control-releasing progesterone by melt-emulsification. *Colloids and Surfaces B: Biointerfaces*, 60(2), 174–179.
39. Zhang, C., Song, X., Ma, C., Wang, M., Deng, H., Yuan, M., Zhu, W., Shen, L., Li, Y., & Shi, L. (2024). Hyaluronic acid dissolving microneedle patch loaded with tranexamic acid for melasma treatment. *International Journal of Biological Macromolecules*, 270(Pt 2), 132255.
40. Zhong, Q. K., Wu, Z. Y., Qin, Y. Q., Hu, Z., Li, S. D., Yang, Z. M., & Li, P. W. (2019). Preparation and properties of carboxymethyl chitosan/alginate/tranexamic acid composite films. *Membranes*, 9(1), 11.