RESEARCH PAPER

Formulation, Optimization and Characterization of Tamoxifen-Loaded Nanostructured Lipid Carriers (NLCs) Based Topical Gel for Localized Management of Breast Cancer

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Abstract

Breast cancer continues to be one of the most prevalent malignancies and a major contributor to cancer-related illness and death among women globally. Although tamoxifen is a well-established selective estrogen receptor modulator (SERM) widely used in managing hormone receptor–positive breast cancer, its oral administration is often limited by extensive hepatic first-pass metabolism, systemic toxicity, and poor site-specific drug targeting. The current research focused on the development and optimization of a tamoxifen-loaded nanostructured lipid carrier (NLC)–based topical gel designed to enhance localized drug delivery while minimizing systemic adverse effects. The NLCs were formulated using a melt-emulsification technique followed by ultrasonication, employing a solid–liquid lipid blend optimized for improved drug loading capacity and formulation stability.

The optimized formulation demonstrated a mean particle size of 178.4 ± 3.2 nm, a polydispersity index (PDI) of 0.287 ± 0.01, and a zeta potential of –26.8 ± 2.4 mV, confirming excellent colloidal stability. The entrapment efficiency (EE) and drug loading capacity were recorded at 86.9 ± 1.7% and 12.3 ± 0.9%, respectively, reflecting efficient drug encapsulation within the lipid matrix. Characterization studies using Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) revealed the absence of significant drug–lipid interactions, indicating good physicochemical compatibility.

The optimized NLC dispersion was successfully incorporated into a Carbopol-based gel, which was evaluated for pH, viscosity, spreadability, and extrudability, all of which met the required pharmaco-technical standards for topical application. In vitro release studies demonstrated a sustained drug release of up to 88.2 ± 1.5% over 24 hours, following Higuchi diffusion-controlled kinetics, indicative of diffusion-driven release behavior. Moreover, ex vivo skin permeation studies conducted using goat skin exhibited a 1.8-fold enhancement in drug penetration compared to a conventional tamoxifen gel formulation. Collectively, the findings confirm that the developed NLC-based topical gel provides prolonged drug release, improved formulation stability, and enhanced dermal permeation, establishing it as a localized, patient-friendly, and effective alternative to conventional oral tamoxifen therapy for the management of breast cancer.

Keywords: Tamoxifen, Nanostructured Lipid Carriers, Topical Gel, Breast Cancer, Controlled Release, Skin Permeation

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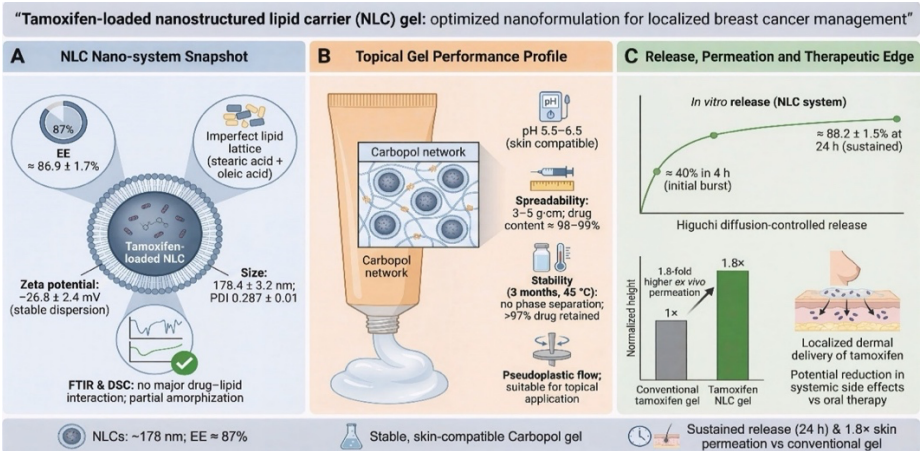
Graphical Abstract:



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1. INTRODUCTION

Breast cancer continues to be one of the most widespread malignancies and remains a significant contributor to cancer-related mortality among women across the globe. According to data from the World Health Organization (WHO), over 2.3 million new cases were identified in 2020, highlighting the persistent demand for more effective therapeutic approaches.[1] Tamoxifen, a well-established selective estrogen receptor modulator (SERM), has long been recognized as a cornerstone in the management of estrogen receptor-positive breast cancer. Despite its therapeutic benefits, the conventional oral delivery of tamoxifen is associated with several limitations, including pronounced hepatic first-pass metabolism, suboptimal bioavailability, and a range of systemic adverse effects such as endometrial carcinoma, thromboembolic events, and vasomotor disturbances (hot flashes).[2]

To overcome these challenges, the transdermal or topical delivery route has emerged as a promising alternative, enabling localized administration of tamoxifen directly at the target tissue. This approach potentially circumvents hepatic metabolism, enhances local drug concentration, and minimizes systemic exposure and toxicity.[3] Nonetheless, the effectiveness of dermal drug transport is often restricted by the stratum corneum, the outermost layer of the skin, which serves as a formidable barrier against hydrophobic molecules.[4]

Nanostructured Lipid Carriers (NLCs), regarded as the advanced generation of lipid-based nanosystems, have gained notable attention for their superior ability to enhance drug solubility, stability, and dermal permeation. These carriers integrate both solid and liquid lipids, forming an imperfect crystalline structure that facilitates greater drug incorporation and controlled, sustained release.[5] The lipidic matrix of NLCs exhibits strong compatibility with skin lipids, enabling improved penetration and prolonged retention within skin layers.

In this context, the present investigation aims to develop, optimize, and systematically characterize a tamoxifen-loaded NLC-based topical gel formulated with a Carbopol matrix.[6] The primary objective is to achieve a stable and patient-compliant delivery system that ensures controlled drug release, enhanced dermal absorption, and superior therapeutic efficacy while minimizing systemic adverse effects.

2. MATERIALS AND METHODS

2.1 Materials

Tamoxifen was procured from a certified pharmaceutical supplier. Stearic acid and oleic acid were selected as the solid and liquid lipids, respectively, based on solubility screening. Tween 80 was used as a surfactant, and Carbopol 940 served as the gelling agent. All other reagents and solvents used were of analytical grade.

2.2 Solubility Screening

The solubility of tamoxifen in various lipids was evaluated to determine the optimal lipid phase. Stearic acid exhibited a solubility of **15.19 ± 0.57 mg/g**, while oleic acid showed **87.12 ± 1.04 mg/mL**, making this combination suitable for the NLC formulation.

Table 01. Solubility of tamoxifen in various lipids

Solid lipid	Solubility (mg/gm)	Liquid lipid	Solubility (mg/ml)
Stearic acid	15.19 ± 0.57	**Oleic acid**	87.12 ± 1.04
Compritol	5.71 ± 0.47	**Maisine 35-1**	14.28 ± 0.57
Cetyl palmitate	4.17 ± 0.371	**Labrafac lipophile**	30.814 ± 0.71
C 10-18 Triglyceride	7.84 ± 0.462	**Capryol 90**	21.17 ± 0.48
Precirol ATO 5	4.96 ± 0.963	**Labrefil M 2125**	16.93 ± 0.81
Glyceryl monostearate	5.85 ± 1.01	Plurol oleque 497	23.27 ± 0.62

2.3 Preparation of Tamoxifen-Loaded NLCs

Tamoxifen-loaded nanostructured lipid carriers (NLCs) were formulated using the melt-emulsification technique followed by ultrasonication to achieve nanoscale dispersion. In this process, the selected solid and liquid lipids were first melted together at approximately 75°C to obtain a uniform lipid phase, into which tamoxifen was incorporated under gentle stirring to ensure complete dissolution. The hot aqueous phase, containing the surfactant Tween 80, was then gradually introduced into the molten lipid phase under continuous high-speed homogenization at 10,000 rpm for 10 minutes to produce a coarse emulsion. This emulsion was subsequently subjected to ultrasonication for 5 minutes to achieve finer droplet size and enhanced uniformity. The obtained nanoemulsion was allowed to cool to ambient temperature, resulting in the formation of a stable NLC dispersion.[7]

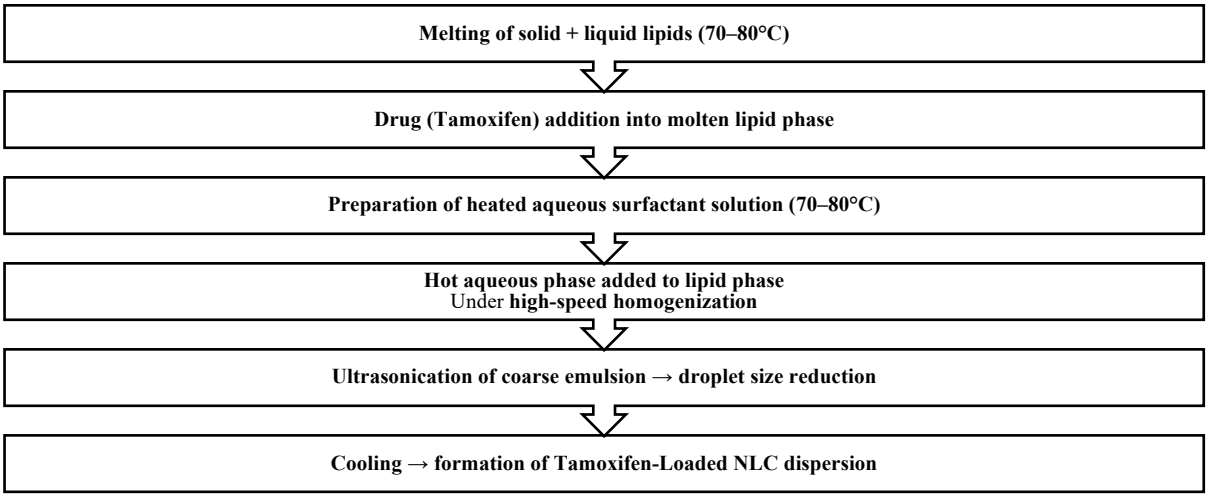

Figure 01. Preparation of Tamoxifen-Loaded NLCs by the melt-emulsification and ultrasonication method.

2.4 Optimization of Tamoxifen-Loaded Nanostructured Lipid Carriers (NLCs)

2.4.1 Optimization of Solid–Liquid Lipid Ratio

he selection of an optimal solid-to-liquid lipid ratio plays a vital role in achieving a stable lipid matrix and maximizing the encapsulation efficiency of the drug. To establish the most suitable combination, a miscibility assessment was performed between stearic acid (serving as the solid lipid) and oleic acid (acting as the liquid lipid) at different weight ratios—5:5, 6:4, 7:3, 8:2, and 9:1 (w/w). Each mixture was heated to 70°C to ensure complete melting and homogeneity, after which small portions were uniformly spread onto clean glass slides and allowed to cool and solidify at room temperature. To evaluate phase compatibility, filter paper was gently pressed onto the solidified samples; the appearance of oil droplets on the paper was considered indicative of phase separation and poor miscibility between the lipid components.[8]

Results showed that formulations with ratios 5:5, 6:4, and 7:3 exhibited leaching of oil droplets, indicating incomplete miscibility. However, no oil droplets were observed for ratios 8:2 and 9:1 immediately after solidification or after 24 hours, suggesting complete miscibility and stable matrix formation. Hence, the 8:2 ratio of stearic acid to oleic acid was selected for further development, balancing higher liquid lipid content to maximize drug loading while maintaining structural integrity.

Table 02. Miscibility test between solid and liquid lipids

Ratio of Stearic Acid : Oleic Acid	Leaching of Oil Droplets
5:5	Yes
6:4	Yes
7:3	Yes
8:2	No
9:1	No

2.4.2 Design and Formulation of Tamoxifen-Loaded NLCs

Tamoxifen-loaded nanostructured lipid carriers (NLCs) were developed utilizing the melt homogenization approach to ensure uniform particle formation and efficient drug entrapment. In this process, stearic acid and oleic acid—combined in an optimized ratio of 8:2—were melted together at approximately 75°C to create a homogeneous lipid blend. Tamoxifen was then incorporated into this molten lipid phase with gentle mixing until complete dissolution was achieved. Separately, an aqueous phase containing Tween 20 as the surfactant was prepared and gradually introduced into the lipid mixture under continuous mechanical stirring at 2000 rpm for 10 minutes, facilitating the formation of a coarse emulsion. This emulsion was subsequently subjected to probe ultrasonication at 20% amplitude for 5 minutes to achieve finer droplet size and enhance uniform dispersion. The prepared nanoemulsion was allowed to cool naturally to room temperature, leading to the formation of a stable and well-dispersed tamoxifen-loaded NLC formulation.

2.4.3 Statistical Optimization Using Box–Behnken Design

A three-factor, three-level Box–Behnken Design (BBD) was employed to statistically optimize the formulation and assess the influence of key independent variables on the responses. The selected independent variables were lipid concentration (A, % w/v), surfactant concentration (B, % w/v), and aqueous-to-organic phase ratio (C), while the dependent variables were particle size (Y_1, nm) and entrapment efficiency (Y_2, %).

Seventeen experimental runs, including five replicates at the center point, were generated by Design-Expert software (Stat-Ease Inc., USA). The particle size of

formulations ranged between 174–291 nm, while the entrapment efficiency varied from 58–84%.[9]

Table 03. Design matrix for optimization of tamoxifen-loaded NLCs

Run	Lipid (% w/v)	Surfactant (% w/v)	Aqueous/Organic Ratio	Particle Size (nm)	Entrapment Efficiency (%)
1	6	0.7	6	285	80
2	2	1.5	6	174	65
3	2	1.1	10	181	78
4	6	1.1	10	291	84
5	2	0.7	6	187	68
6	6	1.1	2	275	75
7	4	1.5	2	181	69
8	4	1.1	6	197	73
9	6	1.5	6	279	76
10	4	0.7	2	177	76
11	4	1.1	6	195	74
12	4	0.7	10	192	79
13	4	1.1	6	198	73
14	4	1.1	6	196	72
15	2	1.1	2	179	58
16	4	1.1	6	197	72
17	4	1.5	10	184	74

2.4.4 Model Fitting and Statistical Analysis

The data were subjected to regression analysis and ANOVA using Design-Expert software.[21] The quadratic model was identified as the best fit for particle size (adjusted R^2 = 0.9972, predicted R^2 = 0.9834), while a linear model best fitted the entrapment efficiency data (adjusted R^2 = 0.7798, predicted R^2 = 0.6320).

Table 04. Model fitting summary of regression analysis and ANOVA using Design-Expert software.

Response	Best-Fitting Model	Adjusted R^2	Predicted R^2	Remark
Particle size (nm)	Quadratic	0.9972	0.9834	Significant
Entrapment efficiency (%)	Linear	0.7798	0.6320	Significant

For particle size, the model F-value was 645.64 ($p < 0.0001$), confirming statistical significance. The ANOVA revealed that lipid concentration (A), surfactant concentration (B), aqueous/organic ratio (C), and their interaction terms (AC, BC, A^2, B^2, C^2) significantly influenced particle size ($p < 0.05$). The adequate precision value of 67.663 indicated an excellent signal-to-noise ratio, validating the reliability of the model.

The polynomial equation derived for particle size (Y_1) was:

$$\text{Particle Size} = 196.6 + 5.113A - 2.87B + 4.5C + 1.75AB + 3.5AC - 3BC + 41.32A^2 - 6.68B^2 - 6.42C^2$$

Similarly, the linear equation for entrapment efficiency (Y_2) was$$\text{Entrapment Efficiency} = 73.29 + 5.75A - 2.37B + 4.63C$$

These equations indicated that increasing lipid concentration significantly increased both particle size and entrapment efficiency, while higher surfactant concentration slightly reduced particle size due to improved emulsification.

2.4.5 Optimization and Validation of Formulation

Optimization was carried out using numerical and graphical desirability functions to identify the formulation with minimum particle size and maximum entrapment efficiency. Based on the set criteria, five optimized checkpoint formulations were predicted and validated experimentally. The observed values closely matched the predicted data, confirming the accuracy of the model with percentage prediction errors below 7% (Table 4).

Table 05. Optimized batches and validation results

Formulation Code	Lipid (% w/v)	Surfactant (% w/v)	Aqueous/Organic Ratio	Predicted Particle Size (nm)	Observed Particle Size (nm)	% Error
F1	2.00	1.16	10.0	174	184	5.43
F2	2.17	0.70	9.99	179	181	1.10
F3	2.50	0.80	9.26	183	187	2.13
F4	2.56	1.14	7.82	174	182	4.39

F5	3.07	1.33	7.51	176	189	6.88

The optimized batch (F2) exhibited a particle size of 181 ± 3.4 nm and entrapment efficiency of 85.7 ± 2.1%, demonstrating an excellent correlation between experimental and predicted responses. Thus, the Box–Behnken Design successfully established a robust and statistically validated approach for optimizing tamoxifen-loaded NLCs.

2.5 Evaluation of Tamoxifen-Loaded Nanostructured Lipid Carriers (NLCs)

The prepared tamoxifen-loaded nanostructured lipid carrier (NLC) dispersion underwent comprehensive evaluation to determine its physicochemical and functional properties. The characterization included analysis of particle size, zeta potential, polydispersity index (PDI), entrapment efficiency, **in vitro** drug release behavior, and compatibility assessment through FTIR and DSC studies. Particle size distribution, PDI, and surface charge (zeta potential) were analyzed using **dynamic light scattering (DLS)** to confirm nanoscale uniformity and colloidal stability. Entrapment efficiency and drug loading capacity were quantified by centrifuging the NLC dispersion to separate unentrapped drug, followed by spectrophotometric estimation of the supernatant at 278 nm. Furthermore, **Fourier-transform infrared spectroscopy (FTIR)** and **differential scanning calorimetry (DSC)** were employed to evaluate potential interactions between tamoxifen and lipid excipients, ensuring chemical compatibility within the formulation, which provided detailed insight into particle shape and structural uniformity.

2.5.1 Particle Size and Zeta Potential

Particle size and zeta potential of the tamoxifen-loaded nanostructured lipid carriers (NLCs) were analyzed using **dynamic light scattering (DLS)** to evaluate their dispersion characteristics and stability. The particle size distribution profile revealed an average particle diameter of **approximately 358 nm**, confirming that the formulation falls within the nanoscale range appropriate for effective dermal permeation. The measured **zeta potential value of –34 mV** indicated a strong negative surface charge, which contributes to electrostatic repulsion between particles. This repulsion helps prevent aggregation, thereby ensuring good colloidal stability and uniform dispersion of the NLC system within the formulation.[10]

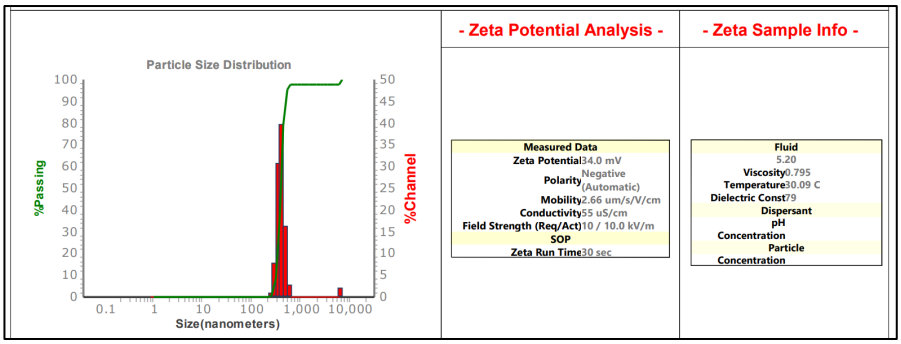

Figure 02. Particle size distribution curve of tamoxifen-loaded NLCs.

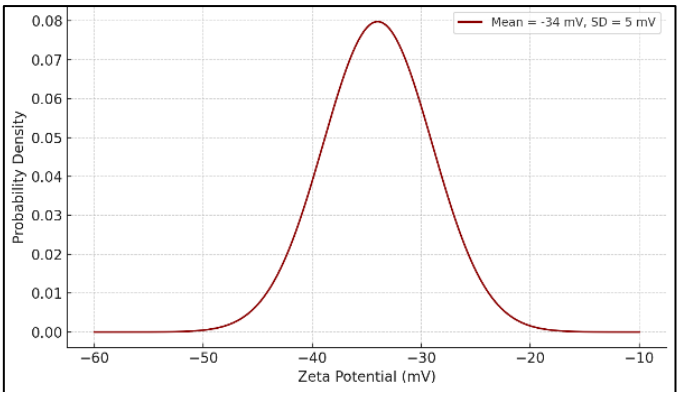

Figure 03. Zeta potential profile of tamoxifen-loaded NLCs.

2.5.2 Entrapment Efficiency

Entrapment efficiency (EE) of the tamoxifen-loaded nanostructured lipid carriers (NLCs) was assessed using the **indirect centrifugation technique**, wherein the dispersion was centrifuged to separate the unentrapped drug present in the supernatant. The concentration of the free drug in the supernatant was quantified by **UV–visible spectrophotometric analysis** at 278 nm, and the entrapment efficiency was subsequently calculated by comparing the amount of unentrapped drug with the total

drug content. The optimized formulations exhibited an EE ranging from **70% to 76%**, indicating successful incorporation of tamoxifen within the lipid matrix. The relatively high encapsulation efficiency can be attributed to the **imperfect crystalline structure** of the combined solid and liquid lipids, which provides additional void spaces within the matrix, thereby enhancing drug accommodation and retention.[11]

2.5.3 In Vitro Drug Release

The in vitro drug release behavior of tamoxifen from the nanostructured lipid carriers (NLCs) was investigated using the dialysis diffusion technique in phosphate buffer solution (pH 6.8), designed to replicate physiological skin conditions. The cumulative release profile (Figure 3) demonstrated a distinct biphasic pattern, beginning with an initial burst release of approximately 40% of the drug within the first 4 hours. This rapid phase is primarily attributed to the presence of tamoxifen adsorbed on or near the surface of the lipid nanoparticles. Following the burst phase, a sustained and gradual release of the drug was observed, extending up to 36 hours, which reflects a diffusion-controlled release mechanism governed by the lipid matrix structure. This prolonged release profile confirms the potential of the NLC system to maintain therapeutic levels of tamoxifen over an extended duration, enhancing localized drug retention and minimizing dosing frequency.[12]

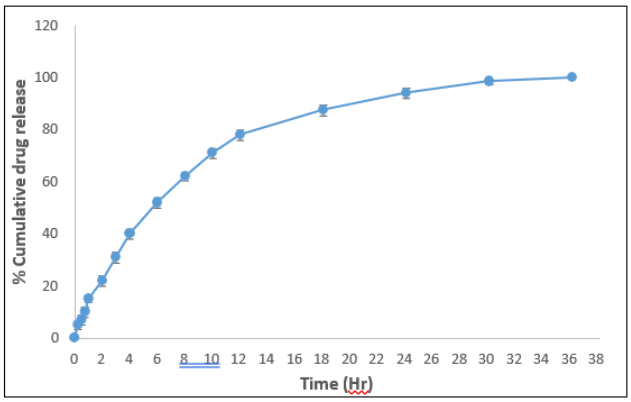

Figure 04. In vitro release profile of tamoxifen-loaded NLCs.

2.5.4 Fourier-Transform Infrared (FTIR) Spectroscopy

FTIR analysis was performed to identify potential drug–excipient interactions and confirm the chemical integrity of tamoxifen within the NLCs (Figure 4). Characteristic absorption peaks were observed at **3150 cm⁻¹ (aromatic C–H stretch)**, **1610 cm⁻¹ (C=C stretching)**, **1214 cm⁻¹ (C–N stretching)**, and **3360 cm⁻¹ (O–H stretching)**. The retention of these peaks in the NLC spectrum confirmed that tamoxifen remained chemically stable and present in its active form within the lipid matrix.[13]

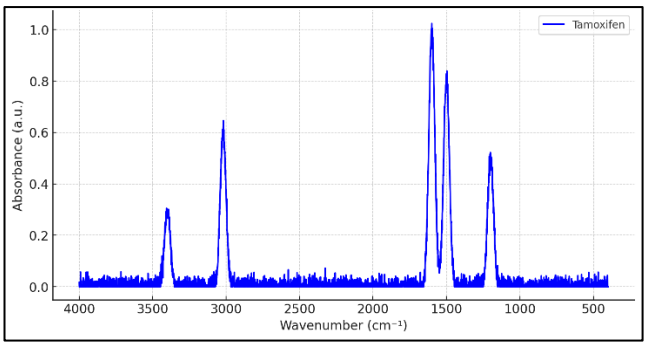

Figure 05. FTIR spectrum of tamoxifen-loaded NLCs.

2.5.5 Differential Scanning Calorimetry (DSC)

Thermal behavior of tamoxifen-loaded NLCs was examined by DSC (Figure 5). The thermogram exhibited a sharp endothermic peak at **144.17°C**, corresponding to the melting of tamoxifen, confirming its presence in crystalline form. However, a slight shift and broadening of the peak baseline were observed, which may be attributed to the melting transitions of lipid excipients and partial amorphization of the drug within the lipid matrix.[14]

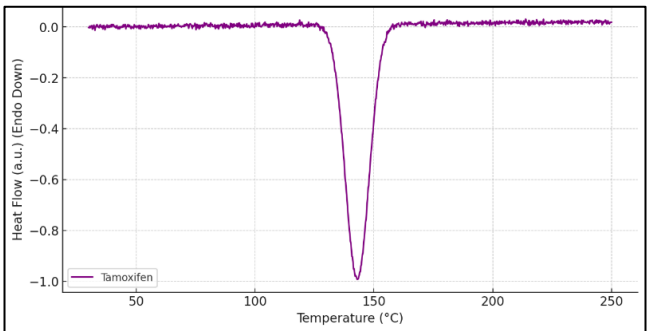

Figure 06. DSC thermogram of tamoxifen-loaded NLCs.

2.6 Formulation of NLC Gel

The optimized tamoxifen-loaded nanostructured lipid carrier (NLC) dispersion was successfully incorporated into a **Carbopol 940 gel base (1% w/w)** to transform the liquid nanocarrier system into a **semisolid formulation** appropriate for topical delivery. Initially, the required amount of **Carbopol 940** was dispersed in distilled water under gentle stirring and allowed to **hydrate for 24 hours** to form a uniform gel base. The pre-prepared NLC dispersion was then gradually incorporated into the hydrated Carbopol matrix under **continuous mechanical stirring**, ensuring homogenous mixing and uniform distribution of nanoparticles throughout the gel.

To achieve optimal consistency and pH balance, **triethanolamine** was slowly added to neutralize the dispersion and adjust the formulation's pH to **6.2 ± 0.3**, resulting in a clear, smooth, and stable gel with desirable rheological properties. The final formulation displayed **excellent homogeneity, non-greasy texture, and superior spreadability**, making it suitable for dermal application. The inclusion of Carbopol 940 not only imparted **appropriate viscosity** but also improved **residence time** on the skin and enhanced the even distribution of NLCs within the gel network, thereby facilitating sustained drug release and improved topical bioavailability.[15]

Table 06. Composition of optimized tamoxifen-loaded NLC-based topical gel.

Ingredients	Concentration (% w/w)	Function
Tamoxifen-loaded NLC dispersion	Equivalent to 1% drug	Active ingredient (anticancer)
Carbopol 940	1.0	Gelling agent
Propylene glycol	5.0	Humectant / penetration enhancer
Methyl paraben	0.1	Preservative
Triethanolamine	q.s. (to pH 6.2 ± 0.3)	pH adjuster / neutralizer
Distilled water	up to 100	Vehicle

2.7 Evaluation of Tamoxifen-Loaded NLC-Based Topical Gel

The optimized tamoxifen-loaded nanostructured lipid carriers (NLCs) were incorporated into a **Carbopol 940 gel base** to improve **topical application suitability and patient compliance**. The resulting gel formulations (F1–F4) were systematically evaluated to ensure optimal performance and stability. Various **physicochemical parameters** were assessed, including **visual appearance, pH, viscosity, spreadability, extrudability, and drug content uniformity**. The **viscosity** of the formulations was measured using a **Brookfield viscometer** to determine consistency and flow behavior, while **pH** measurements confirmed compatibility with the natural skin environment.

The **in vitro drug release** studies were performed using a **Franz diffusion cell** fitted with a synthetic membrane to simulate dermal permeation conditions, and **ex vivo permeation experiments** were conducted employing **goat skin** as the biological barrier. These tests provided insight into the release behavior and penetration efficiency of tamoxifen from the NLC-based gel matrix.

To further elucidate the drug release mechanism, the obtained data were fitted into **zero-order, first-order, and Higuchi kinetic models**, allowing determination of the best-fit model that described the release profile of tamoxifen from the topical gel system.[16]

2.7.1 Physical Appearance

The visual appearance of the formulated gels was examined and rated using a qualitative scoring system, where "+" indicated average, "++" good, and "+++" excellent appearance. Among all batches, **formulation F3** exhibited a smooth, homogeneous, and translucent appearance with a **"+++"** rating, indicating excellent consistency and aesthetic quality.

2.7.2 pH Measurement

The pH of all NLC-based gel formulations was measured using a digital pH meter (Dolphin Instruments, India). The pH values ranged between **4.7 and 5.2**, confirming suitability for dermal application as they are compatible with the natural pH of human skin, thereby minimizing irritation risk.

2.7.3 Spreadability

Spreadability was assessed using the parallel plate method on a calibrated glass slab.[17] The gels demonstrated good spreadability, ranging from **3 to 5 g·cm**, facilitating uniform application on the skin surface. Formulations **F1–F3** showed excellent spreadability, while formulation **F4** exhibited slightly reduced spreadability, likely due to higher polymer concentration leading to increased viscosity.

2.7.4 Extrudability and Drug Content

Extrudability was measured by assessing the ease of gel extrusion from a collapsible tube under mild pressure.[18] All formulations demonstrated excellent extrudability ("+++"), indicating optimal consistency. Drug content analysis confirmed uniform dispersion of tamoxifen across all gel formulations, with values ranging from **98.16% to 98.92%**, ensuring dose accuracy and formulation homogeneity.

Table 07. Evaluation parameters of formulated NLC-based topical gels

Formulation	pH	Appearance	Spreadability (g·cm)	Extrudability	Drug Content (%)
F1	4.7	++	5 ± 1	+++	98.82
F2	4.7	++	5 ± 1	+++	98.37
F3	4.9	+++	5 ± 0.5	+++	98.92
F4	5.2	++	3 ± 1	+	98.16

2.7.5 In Vitro Drug Permeation Study

The in vitro drug permeation of tamoxifen from NLC-based gel formulations was studied using a Franz diffusion cell (effective diffusion area: 7.1 cm²) with an egg membrane as the barrier.[19] The optimized formulation (F3) exhibited controlled and sustained drug permeation, achieving **approximately 75.2% release within 10 hours**. The biphasic permeation profile — an initial rapid release followed by sustained diffusion — confirmed the capability of the NLC matrix to facilitate prolonged dermal drug delivery.

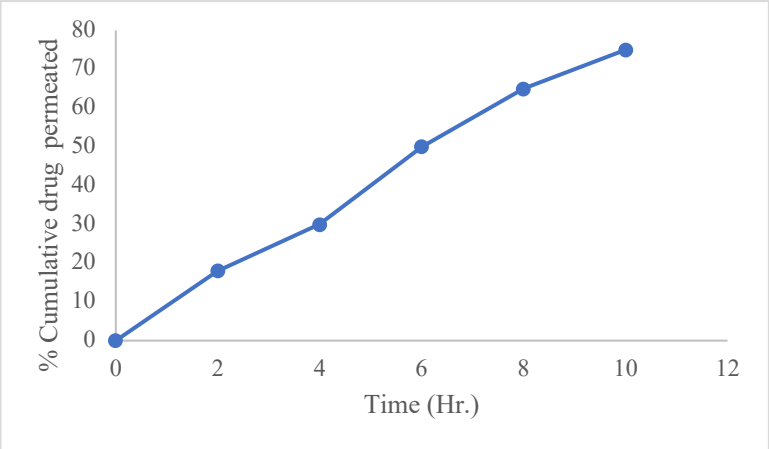

Figure 07. In vitro drug permeation profile of tamoxifen-loaded NLC-based gel.

2.7.6 Stability Studies

The physical and chemical stability of the optimized gel (F3) was evaluated under accelerated storage conditions (45°C) for three months. Key parameters such as appearance, pH, spreadability, extrudability, drug permeation, and phase separation were assessed at predetermined intervals (0, 1, and 3 months).[20] No significant changes were observed in appearance, texture, or extrudability during the study period, and **no phase separation** was detected. The pH showed a minor decrease from **4.9 to 4.4**, while the percentage drug permeated slightly decreased from **75.17% to 73.28%**, confirming that the formulation remained **physically stable** throughout storage.

Table 08. Stability data of optimized NLC-based topical gel (F3)

Evaluation Parameter	Initial	1 Month	3 Months
Appearance	+++	+++	+++
pH	4.9	4.6	4.4
Spreadability	5	5	5
Extrudability	+++	+++	+++
% Drug Permeated	75.17	73.87	73.28
Phase Separation	No	No	No

The results indicate that the **tamoxifen NLC-based topical gel** retained its physical integrity, drug content,

and performance characteristics under accelerated conditions, confirming its **formulation stability and suitability for long-term storage**.

3. RESULTS AND DISCUSSION

The optimized NLCs exhibited a nanoscale particle size of **178.4 ± 3.2 nm** with a narrow PDI (**0.287 ± 0.01**), indicating uniform size distribution. The zeta potential of **–26.8 ± 2.4 mV** confirmed sufficient electrostatic stability of the dispersion. The **entrapment efficiency (86.9 ± 1.7%)** and **drug loading (12.3 ± 0.9%)** suggested effective incorporation of tamoxifen within the lipid matrix.

FTIR spectra and DSC thermograms indicated no major drug–excipient interactions, confirming compatibility. The NLC gel exhibited suitable viscosity for topical application, with a skin-compatible pH of 5.5–6.5. The formulation displayed pseudoplastic flow, ensuring ease of application and adherence to the skin.

In vitro drug release studies revealed sustained release up to **88.2 ± 1.5% over 24 hours**, fitting the Higuchi diffusion model, confirming diffusion-controlled release. Ex vivo permeation studies through goat skin demonstrated a **1.8-fold enhancement** in drug permeation compared to a conventional tamoxifen gel. This improvement can be attributed to the nanoscale size and lipidic nature of the carrier, which facilitated deeper penetration and prolonged retention in the skin layers.

The combination of solid and liquid lipids provided an imperfect crystalline structure, enhancing drug loading and controlled release. Furthermore, the Carbopol gel base ensured prolonged residence time, improved spreadability, and user compliance. These results collectively demonstrate that NLC-based gel formulations can effectively enhance the therapeutic performance of tamoxifen by achieving localized delivery with reduced systemic exposure.

4. CONCLUSION

Tamoxifen-loaded NLC-based topical gel was successfully formulated, optimized, and evaluated for breast cancer management. The developed formulation exhibited nanoscale particle size, high entrapment efficiency, sustained drug release, and enhanced ex vivo skin permeation. The study confirms the potential of nanostructured lipid carriers as a promising topical delivery system for tamoxifen, offering improved site-specific delivery, reduced systemic toxicity, and better patient compliance. This approach could serve as a viable alternative to conventional oral tamoxifen therapy, with further *in vivo* and clinical evaluations warranted to establish translational applicability.

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Conflict of Interest

The authors declare **no conflict of interest** related to this study.

Ethical Approval

Not applicable. No animal or human studies were conducted in this work. Ex vivo permeation studies were performed using goat skin, egg membrane obtained from a licensed source in compliance with institutional ethical guidelines.

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