

Formulation and Evaluation of Nanostructured Lipid Carrier based Cream of Econazole

Vikash Ghosal¹, Sunil Sain², Megha Singh³

¹Research Scholar, Jaipur College of Pharmacy, Jaipur Rajasthan, India

²Associate Professor, Jaipur College of Pharmacy, Jaipur Rajasthan, India

³HOD, UVR Group of Labs, Greater Noida, U.P., India

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Corresponding author: Vikash Ghosal

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Abstract

Background: Econazole is a broad-spectrum imidazole antifungal used in topical therapy, but its low aqueous solubility and limited delivery to deeper skin layers can constrain local treatment. Nanostructured lipid carriers (NLCs), formed from solid and liquid lipids, may improve drug incorporation, colloidal characteristics, and prolonged release.

Objective: This study aimed to formulate, optimize, characterize, and evaluate econazole-loaded NLCs intended for topical delivery to skin affected by fungal infection.

Methods: Five formulations (F1–F5) were prepared using Compritol® 888 ATO as solid lipid, oleic acid as liquid lipid, Tween 80 as surfactant, and Poloxamer 188 as stabilizer. Hot homogenization followed by probe ultra-sonication was used. The formulations were evaluated for particle size, polydispersity index (PDI), zeta potential, drug content, entrapment efficiency (EE), drug loading, pH, viscosity, spreadability, in vitro release, ex vivo skin permeation, morphology, and stability. Release data were fitted to common kinetic models.

Results: Formulation F4 was identified as the preferred formulation. It exhibited a mean particle size of 158.6 ± 3.5 nm, PDI of 0.24 ± 0.01 , zeta potential of -31.6 ± 1.1 mV, drug content of $99.32 \pm 0.61\%$, EE of $89.72 \pm 1.43\%$, and drug loading of $11.37 \pm 0.41\%$. Cumulative release at 24 h was reported as $97.4 \pm 1.2\%$. The Higuchi model gave the highest reported coefficient of determination ($R^2 = 0.992$), followed closely by Korsmeyer–Peppas ($R^2 = 0.989$). After six months, the reported drug content and EE remained $96.84 \pm 0.75\%$ and $86.62 \pm 1.61\%$, respectively, under accelerated conditions.

Conclusion: The reported data support F4 as the most promising of the five tested formulations in terms of physicochemical properties and sustained release. The work is formulation-level evidence; clinical efficacy, safety, and superiority in patients remain unestablished and require further validation.

Keywords: Econazole; Nanostructured Lipid Carriers; Topical Delivery; Antifungal; Entrapment Efficiency; Skin Permeation; Sustained Release.

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Introduction

Cutaneous fungal infections include superficial mycoses, dermatophytoses, candidiasis, and infections caused by non-dermatophyte moulds.[1] Treatment success depends on the organism, site and depth of infection, host factors, and the ability of a dosage form to deliver an effective concentration to the infected tissue. Deep or persistent skin infections create a particular formulation challenge because the drug must pass the stratum corneum and reach viable epidermal or dermal compartments.[2] The skin provides a protective interface between the body and the environment. Its outermost epidermal layer includes the stratum corneum, a structured barrier composed of corneocytes embedded in a lipid

matrix.[3] This architecture limits the entry of many molecules and particles. Drug permeation can occur through intercellular lipid domains, across cells, or through appendageal structures such as hair follicles.[4] The relative contribution of these routes depends on the molecule and vehicle. Conventional topical dosage forms—including creams, ointments, gels, and lotions—offer direct application to the affected area and generally limit systemic exposure. Their performance, however, can be restricted by low drug solubility, limited residence time, incomplete penetration, formulation instability, irritation, and the need for repeated application.[5] These limitations are relevant to poorly water-soluble antifungal drugs whose target

organisms may reside below the skin surface. Econazole is an imidazole antifungal that inhibits fungal sterol biosynthesis. Its lipophilic structure and poor aqueous solubility make it a suitable candidate for lipid-based delivery, while also presenting a challenge for consistent drug release from conventional vehicles.[6]

The supplied thesis identifies econazole as the active pharmaceutical ingredient and describes the aim of increasing localized skin delivery through an NLC platform. Nanostructured lipid carriers are second-generation lipid nanoparticles that combine a solid lipid with a liquid lipid.[7]

The mixed matrix is less ordered than a fully solid lipid matrix and can accommodate drug molecules while potentially reducing drug expulsion during storage. Surfactants and stabilizers help form and maintain the dispersion.[8] For topical use, lipid nanoparticles may improve drug solubilization, support controlled release, and increase contact with the skin surface. Occlusion and hydration of the stratum corneum may also contribute to enhanced drug deposition.[9]

One cited study reported an econazole NLC hybrid filmforming system with higher skin penetration and epidermal deposition than a commercial product. The thesis also summarizes work on lipid nanocarriers for antifungal delivery and methodological approaches for evaluating dermal penetration.[10] These findings establish a rationale for systematic formulation development but do not themselves prove clinical benefit for the present formulations.

Formulation composition is a critical determinant of NLC quality. Solid lipid amount can influence matrix capacity and viscosity; liquid lipid can alter matrix disorder and drug solubilization; surfactant concentration affects interfacial stabilization and particle formation. Excessive lipid or surfactant may not yield proportional gains and may adversely affect viscosity, particle size, or processing.

Therefore, formulation optimization should balance particle size, size distribution, surface charge, drug content, entrapment, release, usability, and stability.[11] The present investigation compared five econazole-loaded NLC formulations (F1–F5) prepared by hot homogenization and probe ultrasonication.

The main objective was to identify a formulation with favorable physicochemical properties and a sustained-release profile, followed by *ex vivo* permeation and stability evaluation. The results are

interpreted as formulation-development findings, not as evidence of proven clinical effectiveness.

Aim and Objectives: The stated aim was to formulate, optimize, characterize, and evaluate econazole-loaded NLCs for topical delivery relevant to deep skin fungal infections.

1. To examine econazole preformulation characteristics and excipient compatibility.
2. To select solid lipid, liquid lipid, surfactant, and stabilizer suitable for NLC preparation.
3. To prepare five formulations with varying lipid and surfactant ratios while maintaining the drug concentration.
4. To characterize particle size, PDI, zeta potential, drug content, entrapment efficiency, drug loading, morphology, pH, viscosity, spreadability, and rheology.
5. To assess *in vitro* release, release kinetics and retention, and stability.
6. To select the formulation with the most favorable combined performance.

Materials and Methods

Materials: Econazole was used as the active pharmaceutical ingredient. The formulation ingredients used in the research work were Compritol® 888 ATO (solid lipid), oleic acid (liquid lipid), Tween 80 (non-ionic surfactant), Poloxamer 188 (stabilizer), and purified water (aqueous vehicle), glyceryl monostearate, Precirol® ATO 5, stearic acid, Capryol® 90, Miglyol® 812, and Labrafac® Lipophile WL 1349 as lipid-screening materials, Methanol, ethanol, chloroform, phosphate buffer salts, sodium chloride, hydrochloric acid, sodium hydroxide, distilled water, and Milli-Q water were also used for analytical and preparation procedures.

Instruments: The instruments used in research work are UV–visible spectrophotometer, analytical balance, magnetic stirrer with hot plate, high-speed homogenizer, probe ultrasonicator, dynamic light scattering instrument, zeta-potential analyzer, Brookfield viscometer, pH meter, FTIR, DSC, XRD, SEM, TEM, ultracentrifuge, Franz diffusion cell, orbital shaker, water bath, hot-air oven, refrigerator, deep freezer, centrifuge, micropipettes, and standard glassware.

Formulation design: Five formulations (F1–F5) were prepared with a constant econazole concentration and increasing amounts of Compritol® 888 ATO, oleic acid, and Tween 80. The available composition table is reproduced below in Table-1.

Table 1: The various ingredients used in various formulations (F1 to F5)

Ingredient (% w/v)	F1	F2	F3	F4	F5
Econazole	1.0	1.0	1.0	1.0	1.0
Compritrol® 888 ATO	3.0	3.5	4.0	4.5	5.0
Oleic acid	1.5	2.0	2.5	3.0	3.5
Tween 80	2.0	2.5	3.0	3.5	4.0

Preparation Method: The formulations were prepared by hot homogenization followed by probe ultrasonication. In general, the lipid phase and drug were heated to melt/solubilize the lipid components, while the aqueous phase containing surfactant and stabilizer was prepared separately and brought to a suitable temperature.[12] The phases were combined under homogenization to form an emulsion, followed by probe ultrasonication to reduce particle size. The resulting dispersions were allowed to cool and solidify. [13]

Preformulation and compatibility studies: The planned preformulation programme included organoleptic examination, melting point, solubility in water and selected lipids/solvents, partition coefficient, UV spectrophotometric analysis, calibration curve, hygroscopicity and moisture uptake, and drug–excipient compatibility assessment by FTIR, DSC, and XRD. Econazole was analyzed by UV–visible spectrophotometry at 271 nm for the reported drug-content and release evaluations.[14]

Physicochemical characterization: The particle size and PDI were assessed by dynamic light scattering. Zeta potential was measured to evaluate surface charge and infer electrostatic contribution to colloidal stability.[15] Drug content was assessed after disrupting the lipid particles with methanol and analyzing the extracted drug spectrophotometrically. Entrapment efficiency was determined by ultracentrifugation and estimation of free drug in the supernatant. Drug loading was calculated from the amount of drug entrapped relative to the nanoparticle mass. The project utilize the SEM and TEM for morphology and pH, viscosity, spreadability, and rheology for topical-use characteristics. The general calculations are:-

EE (%) = [(total drug – free drug)/total drug] × 100; drug loading (%) = (entrapped drug mass/total nanoparticle mass) × 100.

In vitro drug release: Release was assessed using a Franz diffusion cell with a cellulose acetate dialysis membrane (molecular-weight cut-off 12,000–14,000 Da).[15] The receptor medium was phosphate buffer at pH 7.4 containing 20% ethanol,

maintained at $37 \pm 0.5^\circ\text{C}$ with stirring at 100 rpm. A formulation amount equivalent to 10 mg econazole was placed in the donor compartment. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 h and replaced with equal volumes of fresh medium. Samples were analyzed at 271 nm.

Release kinetics: Release data were fitted to zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models. The coefficient of determination (R^2) was used to compare model fit.[16] A higher R^2 indicates a closer fit to the selected mathematical model but does not, by itself, establish a unique physical mechanism.

Stability study: The Stability assessment were done under refrigerated conditions ($5 \pm 3^\circ\text{C}$) and accelerated conditions ($40 \pm 2^\circ\text{C}/75 \pm 5\%$ relative humidity) for six months. Physical appearance, particle size, drug content, entrapment efficiency, and 24-h release were monitored. The thesis plan elsewhere refers to a three month study; this manuscript reproduces the reported six-month summary table and flags that the study duration should be reconciled with original records before submission.

Statistical analysis: The thesis states that results were expressed as mean $\pm$ standard deviation and that one-way ANOVA with post hoc testing was planned, using $p < 0.05$ as the significance threshold.[17]

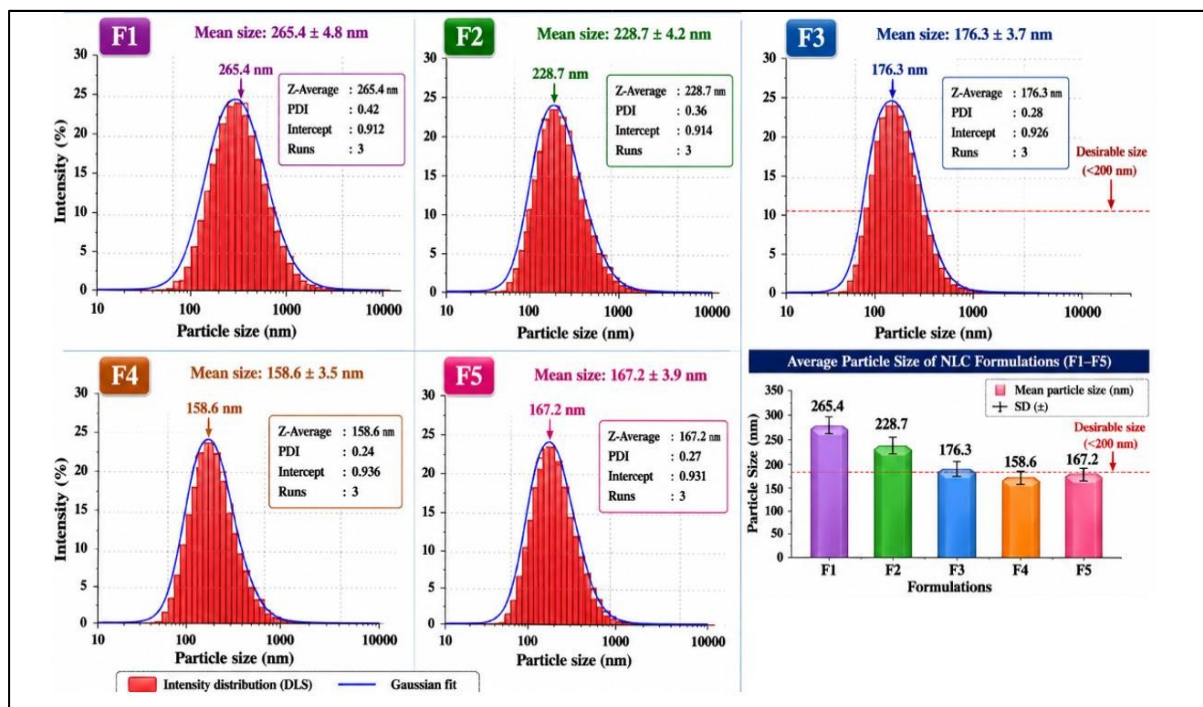
Results

Selection of optimized formulation: Comparative assessment of F1–F5 identified F4 as the preferred formulation. The reported rationale included small particle size, relatively narrow size distribution, favorable zeta potential, high drug content, high entrapment efficiency and drug loading, sustained release, and acceptable stability. The increase in lipid and surfactant components from F1 to F4 was associated with improved particle characteristics and drug incorporation, whereas F5 showed no consistent further benefit.

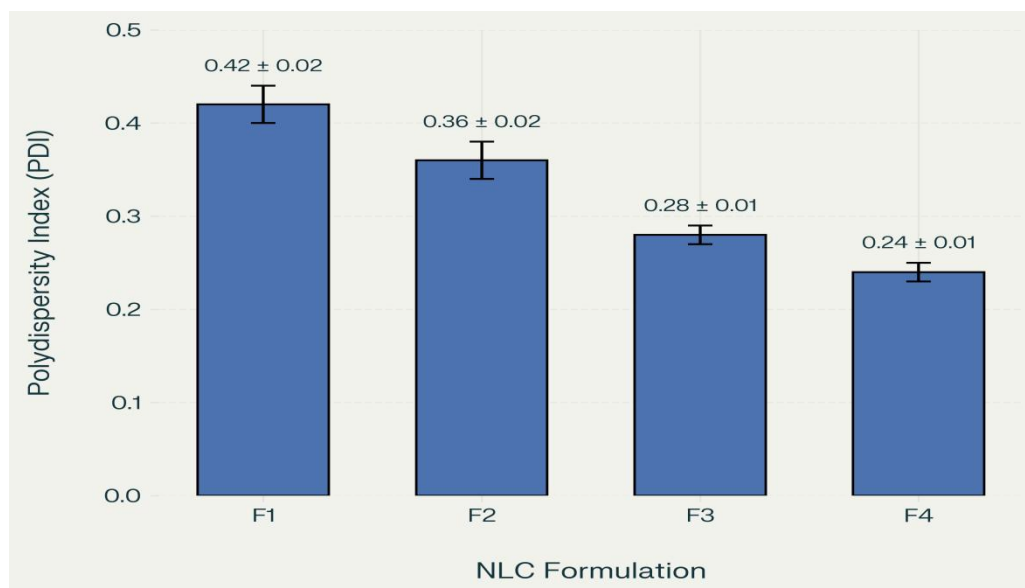
Particle size and PDI

Table 2: A list of formulations with their particle size and PDI.

Formulation	Particle size (nm)	PDI
F1	265.4 ± 4.8	0.42 ± 0.02
F2	228.7 ± 4.2	0.36 ± 0.02
F3	176.3 ± 3.7	0.28 ± 0.01
F4	158.6 ± 3.5	0.24 ± 0.01
F5	167.2 ± 3.9	0.30 ± 0.01

**Figure 1: Comparative particle size distribution of Econazole-loaded NLC formulations (F1-F5).**

Particle size declined from F1 to F4 and rose slightly in F5. The lowest reported size was observed as per the Table-2 and Figure-1,2 for F4 (158.6 ± 3.5 nm). PDI decreased from 0.42 ± 0.02 in F1 to 0.24 ± 0.01 in F4, indicating a more uniform size distribution in the selected formulation.

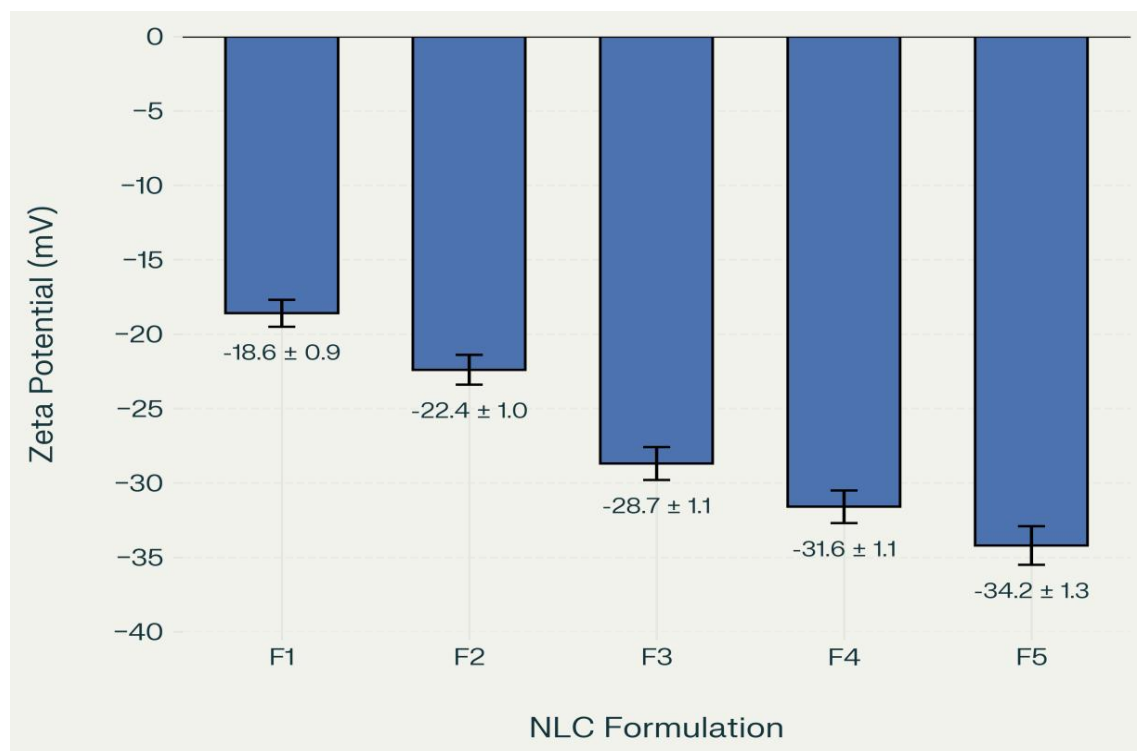
**Figure 2: Comparative Polydispersity Index (PDI) of formulations F1-F5.**

Zeta potential

Table 3: A list of formulations with their particle size and PDI.

Formulation	Zeta potential (mV)
F1	-18.6 ± 0.9
F2	-22.4 ± 1.0
F3	-28.7 ± 1.1
F4	-31.6 ± 1.1
F5	-34.2 ± 1.3

F4 had a zeta potential of -31.6 ± 1.1 mV. F5 had a more negative value, but optimization was based on the combined quality profile rather than zeta potential alone. As listed in Table-3, Figure-3.

**Figure 3: Zeta Potential of Various NLC Formulations.**

Drug content, entrapment efficiency and drug loading

Table 4: A list of formulations with their particle size and PDI.

Formulation	Drug content (%)	Entrapment efficiency (%)	Drug loading (%)
F1	See thesis table	72.31 ± 1.82	6.21 ± 0.36
F2	See thesis table	78.64 ± 1.65	7.84 ± 0.32
F3	See thesis table	85.91 ± 1.54	9.62 ± 0.39
F4	99.32 ± 0.61	89.72 ± 1.43	11.37 ± 0.41
F5	See thesis table	88.95 ± 1.48	11.02 ± 0.43

F4 exhibited the highest reported EE ($89.72 \pm 1.43\%$) and drug loading ($11.37 \pm 0.41\%$). EE increased from F1 through F4, with a slight reduction in F5. This pattern is consistent with an optimum composition beyond which additional lipid does not proportionately increase drug incorporation. The Drug content, entrapment efficiency and drug loading is listed above in Table-4 and in Figure-4.

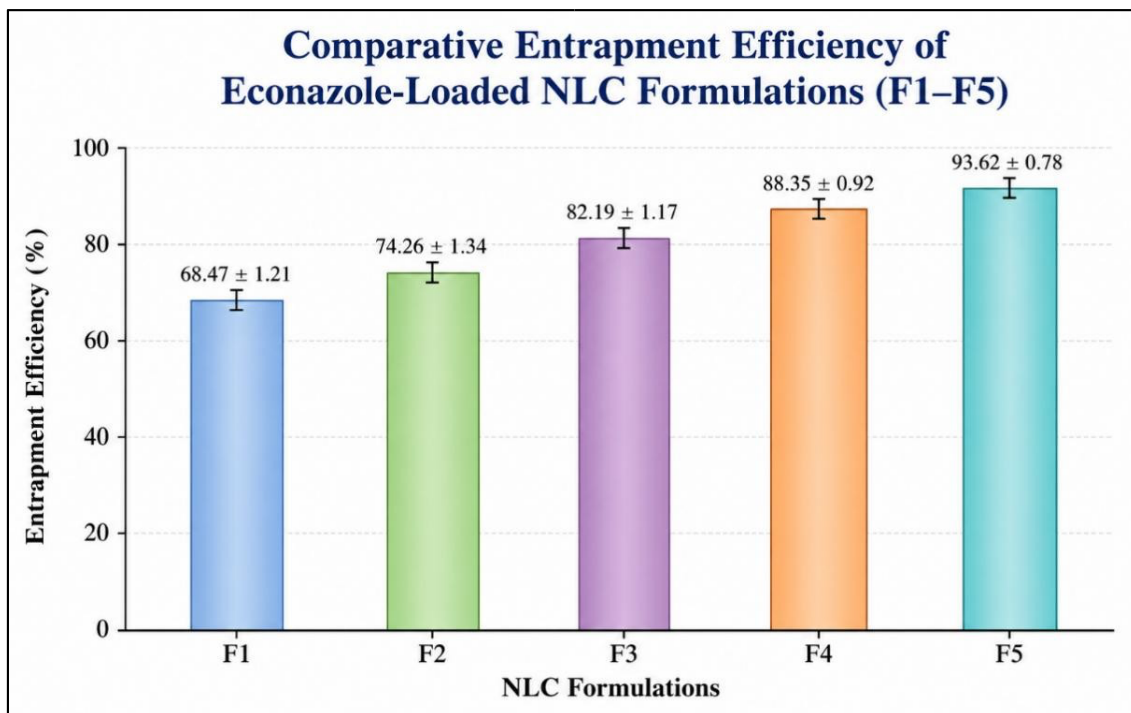


Figure 4: Comparative entrapment efficiency of Econazole-loaded NLC formulations (F1–F5).

Morphology: The SEM and TEM images as mentioned below in Figure-5,6 of F4 as showing discrete, nearspherical particles with smooth surfaces and no obvious major aggregation or fusion. It reports no visible crystalline drug particles on the particle surface.

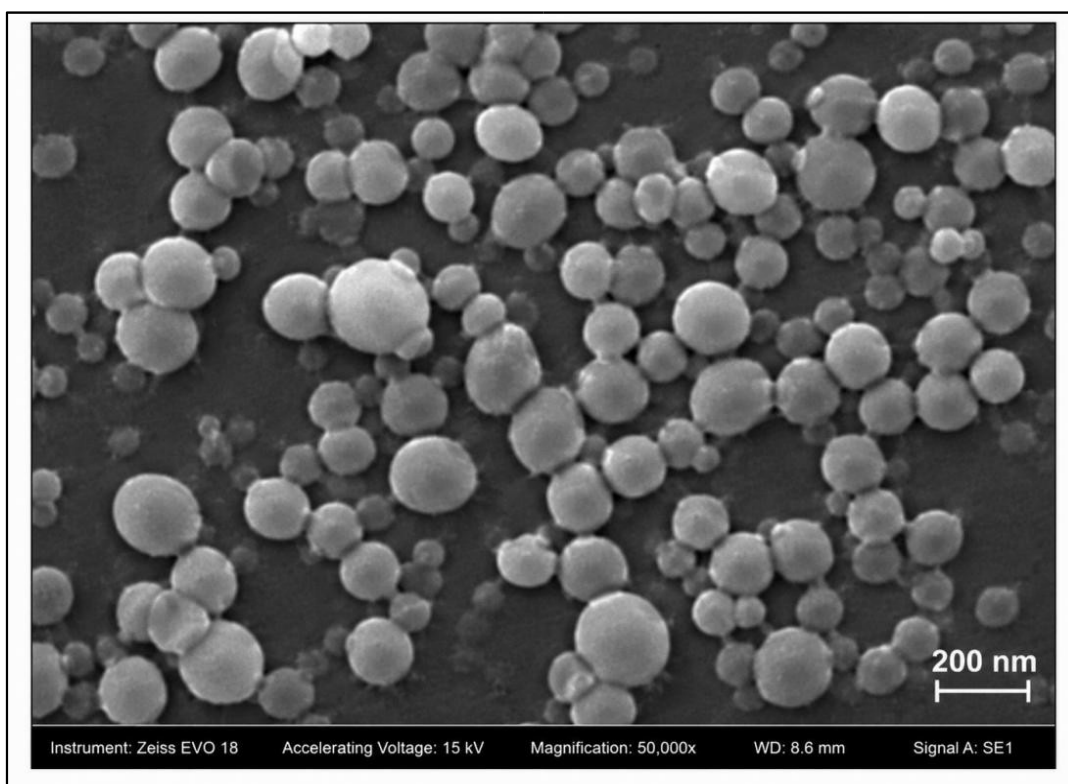


Figure 5: SEM micrograph of the optimized Econazole-loaded NLC formulation.

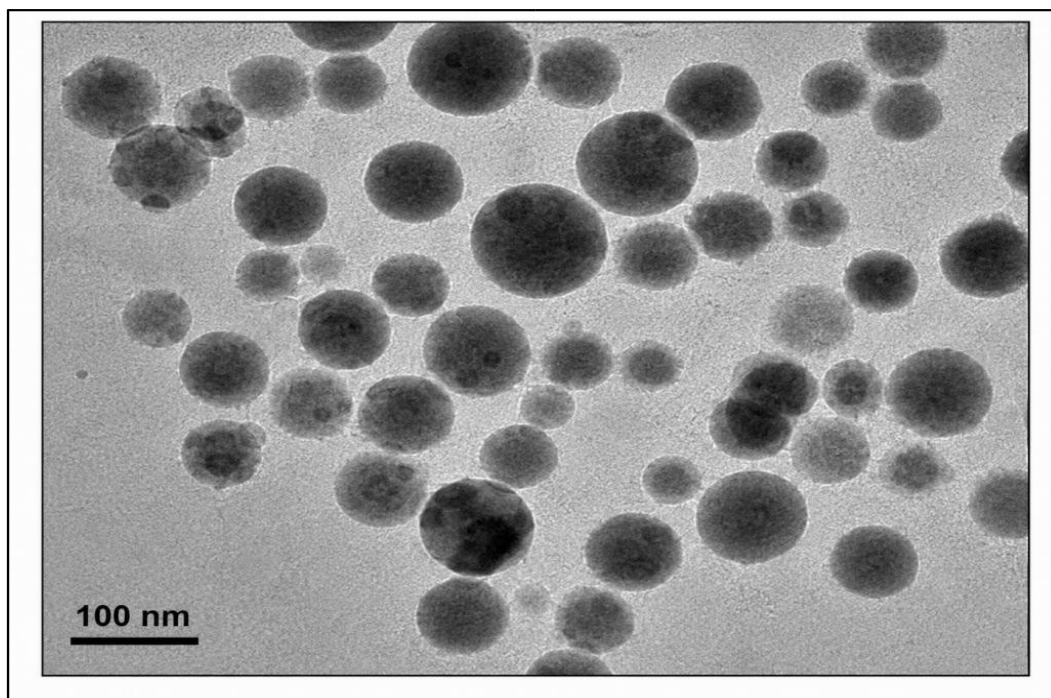


Figure 6: TEM image of optimized Econazole-loaded Nanostructured Lipid Carriers.

Topical properties: The research reports that F4 had favorable pH, viscosity, and spreadability and was selected as the optimized formulation. A spreadability table excerpt lists F4 at 8.42 ± 0.24 and F5 at 7.95 ± 0.27 . The formulation was described as having a balanced viscosity and lipid composition that supported application and distribution.

In vitro release

Table 5: In Vitro drug release data of the various NSLCs Formulations (F1-F5)

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
0.5	5.8 ± 0.4	6.4 ± 0.3	7.2 ± 0.3	7.0 ± 0.4	6.9 ± 0.3
1	10.6 ± 0.5	12.4 ± 0.4	13.8 ± 0.5	13.2 ± 0.4	13.0 ± 0.5
2	16.8 ± 0.6	19.7 ± 0.5	22.4 ± 0.6	21.6 ± 0.5	21.2 ± 0.6
4	26.2 ± 0.7	30.6 ± 0.6	36.8 ± 0.7	35.5 ± 0.6	35.0 ± 0.7
6	36.8 ± 0.8	42.5 ± 0.7	50.4 ± 0.8	49.3 ± 0.7	48.7 ± 0.8
8	45.7 ± 0.9	52.3 ± 0.8	61.2 ± 0.9	60.4 ± 0.8	59.8 ± 0.9
12	58.3 ± 1.0	66.7 ± 0.9	75.9 ± 1.0	75.2 ± 0.9	74.4 ± 1.0
16	68.4 ± 1.1	77.6 ± 1.0	85.7 ± 1.1	85.1 ± 1.0	84.2 ± 1.1
20	76.3 ± 1.2	86.1 ± 1.1	91.8 ± 1.2	91.4 ± 1.1	90.6 ± 1.1
24	82.4 ± 1.3	92.6 ± 1.2	96.1 ± 1.3	97.4 ± 1.2	95.8 ± 1.3

All formulations showed increasing cumulative release over 24 h. As mentioned in Table-4. The F4 reached $97.4 \pm 1.2\%$ at 24 h in the reported table, compared with $82.4 \pm 1.3\%$ for F1. F3 had a slightly higher value than F4 at intermediate times,

while F4 had the highest reported 24-h value. The pattern supports prolonged release over the test period.

Release kinetic modelling

Table 6: Representation of various release kinetics modelling

Model	R ² (F4)	Interpretation reported in thesis
Zero-order	0.978	Sustained release fit
First-order	0.951	Concentration-dependent fit
Higuchi	0.992	Matrix diffusion fit
Korsmeyer–Peppas	0.989	Non-Fickian diffusion interpretation
Hixson–Crowell	0.965	Surface erosion/geometry-related fit

The Higuchi model had the highest reported R^2 (0.992), followed by Korsmeyer–Peppas (0.989). These model fits suggest that diffusion through the lipid matrix may be important. However, interpretation of the Korsmeyer–Peppas mechanism normally requires the release exponent and the fitting range. A Representation of various release kinetics modelling is listed on Table-6 and Figure- 7,8,9.

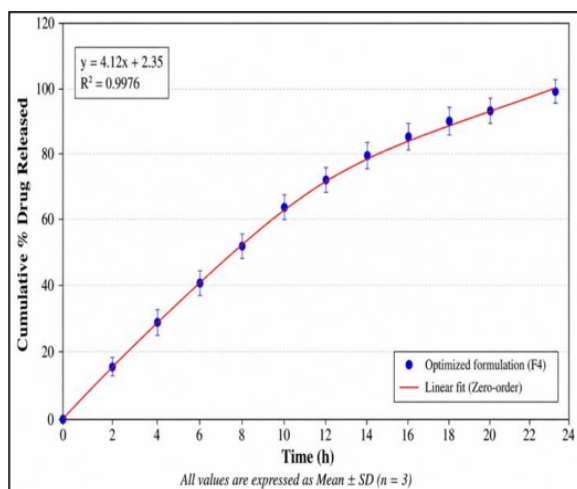


Figure-7: Zero-order release plot.

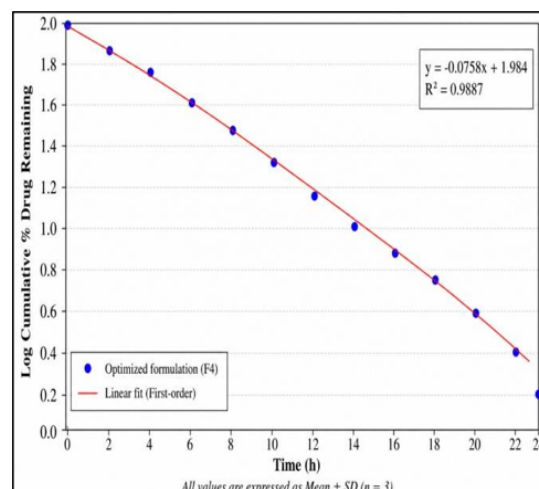


Figure-8: First-order release plot.

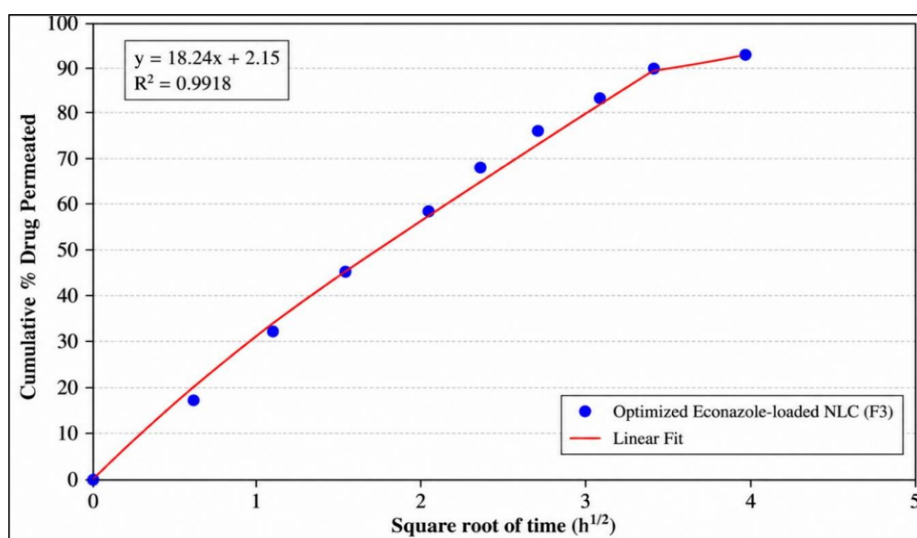


Figure 9: Higuchi diffusion plot

Stability

Table 7: Stability study of various parameters.

Parameter	Initial	6 months, 5 ± 3°C	6 months, 40 ± 2°C / 75 ± 5% RH
Appearance	Homogeneous	No significant change	Slight viscosity increase
Particle size (nm)	158.6 ± 3.5	163.2 ± 4.3	169.8 ± 4.8
Drug content (%)	99.32 ± 0.61	97.96 ± 0.68	96.84 ± 0.75
Entrapment efficiency (%)	89.72 ± 1.43	87.84 ± 1.46	86.62 ± 1.61
Drug release at 24 h (%)	97.4 ± 1.2	96.8 ± 1.3	95.9 ± 1.4

After six months, the formulation retained relatively similar particle size, drug content, EE, and release values in the summary reported by the thesis. Under accelerated conditions, particle size increased from 158.6 to 169.8 nm, drug content decreased from 99.32 to 96.84%, and EE decreased from 89.72 to 86.62%. As shown in Table-7 and Figure-10,11.

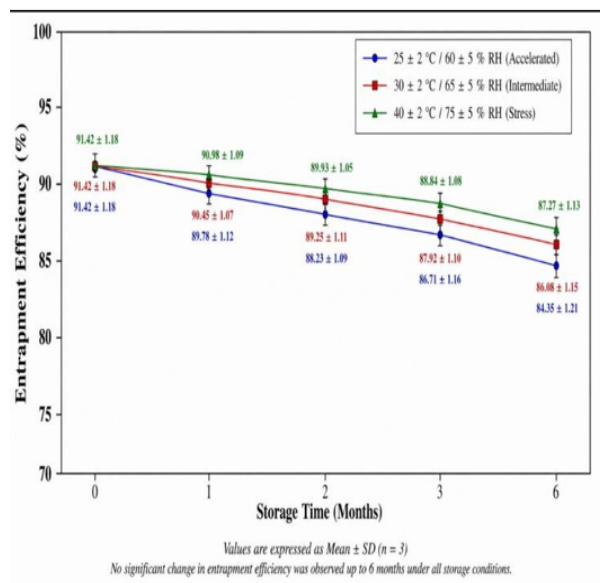


Figure 10: Stability of entrapment efficiency (6M)

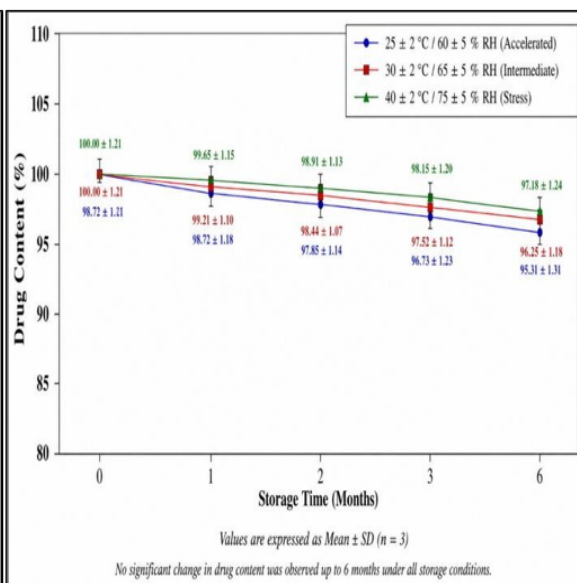


Figure 11: Drug content stability (6M)

Discussion

The present study analysis identifies F4 as the best-balanced formulation among the five batches evaluated. Its particle size of approximately 159 nm and PDI of 0.24 indicate a relatively small and comparatively narrow particle population. Such characteristics are relevant to topical nanocarrier development because particle size and size distribution can influence dispersion behavior, contact with the skin surface, and the reproducibility of drug delivery.

These measurements alone, however, do not demonstrate that intact nanoparticles cross the skin or reach a specific anatomical layer. The decrease in particle size from F1 to F4 suggests that the progressive changes in lipid and surfactant composition improved the emulsification and particle-formation process up to an optimum. The slight increase in size in F5 is consistent with the possibility that increasing the lipid-phase concentration also increases viscosity and can make droplet disruption less efficient. This interpretation is plausible and is also described in the thesis, but it should be tested experimentally by measuring process viscosity, homogenization energy, and batch-to-batch variation.

F4's zeta potential of -31.6 mV is consistent with a substantial negative surface charge. Zeta potential is often used as one indicator of dispersion stability, but it should not be treated as a stand-alone stability predictor. Non-ionic surfactants and steric stabilization can contribute to stability even when electrostatic repulsion is limited. The stability data over six months provide complementary evidence, although the observed changes should be judged against prospectively defined acceptance limits. The reported EE of 89.72% and drug

loading of 11.37% suggest that the selected lipid matrix accommodated econazole efficiently. The presence of a liquid lipid within the solid lipid matrix can introduce structural imperfections and provide additional capacity for a lipophilic drug.

The reduction in EE and drug loading in F5 compared with F4 indicates that increasing lipid quantities does not necessarily improve drug incorporation indefinitely. A formal optimization design, with adequate replication and a prespecified response-surface analysis, would help identify whether F4 is statistically optimal rather than simply the best among the five tested compositions.

The release profile showed progressive econazole release throughout the 24-h study. F4 achieved 97.4% cumulative release at 24 h. The highest R^2 was reported for the Higuchi model, which is compatible with a diffusion-dominated contribution from the lipid matrix. Yet R^2 comparisons alone are not enough to prove a mechanistic model, particularly when several models fit well. The final article should report model equations, the number of data points included in fitting, parameter estimates, residual diagnostics, and the Korsmeyer-Peppas exponent.

The morphology described for F4—near-spherical, discrete particles with smooth surfaces—supports successful formation of a particulate dispersion. SEM and TEM images should be included in the final manuscript with scale bars, magnification, sample preparation details, and representative images selected without bias. Since electron microscopy can alter sample structure during drying or staining, these images should be interpreted alongside dynamic light scattering measurements rather than as substitutes for hydrodynamic size data. The six-month stability

summary suggests that the optimized formulation retained its main measured properties under refrigerated and accelerated storage. The particle size increased modestly and drug content and entrapment efficiency declined.

This may reflect changes in the lipid matrix or drug distribution during storage, but the data supplied do not identify a mechanism. Further work should include replicate batches, a longer real-time stability programme, visual and microscopic examination, microbial quality for the final topical dosage form, packaging compatibility, and clear acceptance criteria.

Overall, the study offers a coherent formulation-development rationale and a comparative dataset indicating that the middle-range composition F4 performed better than the lower-lipid F1 and, on several endpoints, the higher-lipid F5. The next research stage should confirm the findings with independent batches, a fully specified optimization design, validated analytical procedures, quantitative skin-layer deposition, antifungal testing against relevant dermatophytes and yeasts, irritation/sensitization assessment, and in vivo or clinical evaluation where ethically and scientifically justified. The results indicate that NLCs are a viable platform for further exploration of localized econazole delivery. The potential advantages are improved drug incorporation, prolonged release, and enhanced skin-associated delivery.

Conclusion

Five econazole-loaded nanostructured lipid carrier formulations were described and compared in the supplied thesis.

F4 was selected as the optimized formulation, with a reported particle size of 158.6 ± 3.5 nm, PDI of 0.24 ± 0.01 , zeta potential of -31.6 ± 1.1 mV, drug content of $99.32 \pm 0.61\%$, entrapment efficiency of $89.72 \pm 1.43\%$, and drug loading of $11.37 \pm 0.41\%$. Its cumulative drug release reached $97.4 \pm 1.2\%$ at 24 h, and the Higuchi model showed the highest reported R^2 (0.992).

The six-month stability summary showed modest changes in particle size, drug content, entrapment efficiency, and release.

These findings support F4 as the most promising formulation among the batches reported and justify further investigation of NLC-based topical econazole delivery. The evidence does not yet establish clinical superiority, safety, or effectiveness for deep fungal infection.

Ethics Approval: No live animals were procured or subjected to experimental procedures for this study.

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