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FORMULATION AND EVALUATION OF ECONAZOLE NITRATE NANOEMULSION FOR TOPICAL ANTIFUNGAL THERAPY

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Abstract: The present study aimed to formulate and evaluate an Econazole Nitrate nano emulsion for topical antifungal therapy in order to enhance drug solubility, stability, skin permeation, and sustained drug release. Eight nano emulsion formulations (F1–F8) were prepared by the high-speed homogenization followed by ultrasonication technique. The preformulation studies confirmed the purity and compatibility of Econazole Nitrate with the selected excipients. The prepared nano emulsions exhibited pH values ranging from 5.9 to 6.8, indicating compatibility with normal skin pH. Drug entrapment efficiency ranged from 81.19% to 93.56%, while viscosity values ranged from 72.91 to 101.01 cP. SEM analysis revealed spherical, uniformly distributed nano-sized droplets without aggregation. Particle size analysis showed droplet sizes between 186 and 243 nm, whereas zeta potential values ranged from −21 to −28 mV, indicating satisfactory physical stability. Among all formulations, F5 was identified as the optimized formulation with the highest drug entrapment efficiency (93.56%), smallest particle size (186 nm), suitable viscosity (98.56 cP), and cumulative drug release of 96.78% after 12 hours. Drug release kinetic analysis demonstrated that the optimized formulation followed the Higuchi diffusion model ($R^2 = 0.993$), indicating diffusion-controlled sustained drug release. Accelerated stability studies conducted for three months according to ICH guidelines confirmed that the optimized formulation remained physically and chemically stable without significant changes in drug release. The optimized formulation has significant potential for improving the therapeutic efficacy of topical antifungal treatment and may provide better patient compliance compared with conventional dosage forms. Further in vivo and clinical studies are warranted to confirm its therapeutic performance.

Keywords: Econazole Nitrate, FTIR Studies, High-speed homogenization Nano emulsion, In Vitro drug release studies

INTRODUCTION

Nanotechnology-based drug delivery systems have emerged as a promising strategy to overcome these drawbacks. Among them, nano emulsions have gained significant attention for topical antifungal therapy due to their unique physicochemical properties.1 Nano emulsions are thermodynamically or kinetically stable colloidal dispersions consisting of oil, water, surfactant, and often a co-surfactant, with droplet sizes typically ranging from 20 to 200 nm.2 The small droplet size provides a large surface area, enhancing drug solubilization and improving permeation through the skin. Fungal skin infections are among the most common superficial infections worldwide and represent a significant therapeutic challenge because of their recurrent nature, prolonged treatment requirements, and the ability of pathogenic fungi to persist within the superficial layers of the skin.3 Econazole nitrate is a broad-spectrum imidazole antifungal agent commonly used for the topical treatment of superficial fungal infections.4 Topical nano emulsion systems can offer several advantages over conventional formulations, including improved drug solubility, enhanced drug release, increased skin deposition, reduced variability in drug delivery, and the possibility of prolonged residence at the site of application.5 The presence of surfactants and co-surfactants may further modify the barrier

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properties of the stratum corneum and facilitate the transport of drug molecules into the skin. Consequently, nano emulsions have attracted considerable attention for the topical delivery of antifungal, anti-inflammatory, antibacterial, and other poorly water-soluble therapeutic agents. Therefore, the development of an econazole nitrate-loaded nano emulsion may provide a rational approach for overcoming the limitations associated with conventional topical delivery of econazole nitrate.6 By improving drug solubilization and increasing the interfacial contact between the formulation and skin, the nano emulsion system may enhance drug availability at the site of fungal infection and provide more effective and consistent topical therapy.7 The present study was consequently designed to formulate and evaluate an econazole nitrate nano emulsion for topical antifungal therapy, with emphasis on optimization of formulation variables and characterization of its physicochemical properties, drug-release behavior, and stability to establish its potential as an improved topical drug-delivery system.8

MATERIALS

Econazole Nitrate was procured from Hetero Labs, HYD. Oleic acid, Tween 80 and Propylene glycol was obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Formulation development

Table-1: Composition of Nano emulsion

F. no	Drug (mg)	Oleic acid (ml)	Tween 80 (ml)	PEG (ml)	Propylene glycol (ml)	Water (ml)
F1	100	2.5	2	2	1	Q. S
F2	100	5	4	2	1	Q. S
F3	100	7.5	6	2	1	Q. S
F4	100	10	8	2	1	Q. S
F5	100	12.5	10	2	1	Q. S
F6	100	15	12	2	1	Q. S
F7	100	17.5	14	2	1	Q. S
F8	100	20	16	2	1	Q. S

The Econazole nitrate nano emulsions (F1–F8) were prepared by the high-speed homogenization followed by ultrasonication method.9

Step 1: Preparation of Oil Phase

The required quantity of Econazole nitrate (100 mg) was accurately weighed and dissolved in the specified volume of oleic acid (2.5–20 mL according to the formulation). The mixture was stirred using a magnetic stirrer until a clear solution was obtained.

Step 2: Preparation of Surfactant Mixture (Smix)

The required volume of Tween 80 and PEG 400 was measured and mixed thoroughly. Propylene glycol (1 mL) was then added to the mixture and stirred for 5–10 minutes to obtain a homogeneous surfactant mixture (Smix).

Step 3: Formation of pre-emulsion

The oil phase containing the dissolved drug was slowly added to the Smix under continuous magnetic stirring at 800–1000 rpm for about 10–15 minutes. Distilled water was then added dropwise while stirring continuously to form a coarse emulsion.

Step 4: High-Speed Homogenization

The coarse emulsion was homogenized using a high-speed homogenizer at 10,000–15,000 rpm for 10–15 minutes. This process reduced the droplet size and produced a uniform emulsion.

Step 5: Ultrasonication

The homogenized emulsion was subjected to probe ultrasonication for 5–10 minutes (30–50% amplitude) with intermittent cooling to prevent temperature rise. Ultrasonication further reduced the droplet size into the nanometer range and produced a stable nano emulsion.

Step 6: Final Volume Adjustment

The formulation volume was adjusted with distilled water (q.s.), and the nano emulsion was stirred gently for 5 minutes to ensure complete uniformity.

Step 7: Storage

The prepared nano emulsions were transferred into clean, amber-colored glass bottles, tightly sealed, and stored at 25 ± 2°C until further evaluation.

CHARACTERIZATION

Evaluation Procedures for Econazole Nitrate Nano emulsion

pH Measurement

The pH of the prepared Econazole nitrate nano emulsion was determined using a calibrated digital pH meter. Before measurement, the pH meter was calibrated using standard buffer solutions of pH 4.0, 7.0, and 9.2. Approximately 10 mL of the nano emulsion was transferred into a clean beaker, and the electrode was immersed completely in the formulation. The pH was recorded after the reading became stable. All measurements were performed in triplicate at 25 ± 2°C, and the mean value was calculated.10

Viscosity Measurement

The viscosity of the nano emulsion formulations was measured using a Brookfield Digital Viscometer fitted with an appropriate spindle (e.g., Spindle No. 62 or 64). Approximately 50 mL of the formulation was transferred into the sample container, and the spindle was immersed without entrapping air bubbles. The viscosity was measured at 25 ± 2°C at a rotational speed of 50 rpm. The readings were recorded in centipoise (cP) after stabilization, and the average of three determinations was reported.11

Particle Size Analysis

The average particle size and particle size distribution of the nano emulsion were determined by Dynamic Light Scattering (DLS) using a Malvern Zetasizer Nano ZS. A small quantity of the nano emulsion was diluted with filtered distilled water (1:100) to avoid multiple scattering effects. The diluted sample was transferred into a disposable cuvette and analyzed at 25°C with a scattering angle of 173°. The mean particle size and polydispersity index (PDI) were recorded as the average of three measurements.12

Zeta Potential Determination

The zeta potential of the nano emulsion was measured using a Malvern Zetasizer Nano ZS based on electrophoretic light scattering. The formulation was diluted with deionized water (1:100) and filled into a folded capillary cell. Measurements were carried out at 25°C after equilibration. The zeta potential values were expressed in millivolts (mV), and the average of three readings was reported. A high absolute zeta potential value indicates good physical stability of the nanoemulsion.13

Scanning Electron Microscopy (SEM) Analysis

The surface morphology of the optimized nano emulsion was examined using Scanning Electron Microscopy (SEM). A drop of the diluted nano emulsion was placed on a clean aluminum stub and allowed to dry under vacuum. The dried sample was coated with a thin layer of gold using a sputter coater to improve electrical conductivity. The sample was then observed under the scanning electron microscope at suitable accelerating voltage and magnifications. The obtained micrographs were used to evaluate the shape, surface characteristics, and homogeneity of the nano emulsion droplets.14

Drug Entrapment Efficiency

The entrapment efficiency of the nano emulsion was determined by the ultracentrifugation method. Approximately 5 mL of the nano emulsion was transferred into centrifuge tubes and centrifuged at 15,000 rpm for 30 minutes at 4°C. The supernatant containing the free (unentrapped) drug was carefully separated and suitably diluted with methanol or phosphate buffer (pH 7.4). The amount of free Econazole nitrate was determined using a UV–Visible spectrophotometer at its λmax (approximately 271 nm). The entrapment efficiency was calculated using the following equation:15

Entrapment Efficiency (%)=Total Drug Total /Drug−Free Drug ×100

In Vitro Drug Release Studies

The in vitro drug release of the prepared Econazole nitrate nano emulsion was carried out using a Franz diffusion cell. A cellophane membrane (or dialysis membrane, molecular weight cut-off 12,000–14,000 Da) was soaked overnight in phosphate buffer (pH 7.4) before use. The membrane was mounted carefully between the donor and receptor compartments of the diffusion cell. Approximately 1 g of the nano emulsion was placed in the donor compartment. The receptor compartment was filled with phosphate buffer (pH 7.4) containing 20% ethanol to maintain sink conditions and continuously stirred with a magnetic stirrer at 100 rpm. The temperature was maintained at 37 ± 0.5°C throughout the study. At predetermined time intervals (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h), 5 mL of the receptor medium was withdrawn and immediately replaced with an equal volume of fresh dissolution medium maintained at the same temperature. The samples were filtered, suitably diluted, and analyzed using a UV–Visible spectrophotometer at 271 nm. The cumulative percentage drug release was calculated and plotted against time.16

Kinetics of Drug Release Studies17

The drug release data obtained from the in vitro diffusion study were fitted into different mathematical kinetic models to determine the mechanism of drug release. The cumulative drug release data were analyzed using Zero-order, First-order, Higuchi, and Korsmeyer–Peppas kinetic models.

Zero-order model: Cumulative percentage drug released versus time.

First-order model: Log percentage drug remaining versus time.

Higuchi model: Cumulative percentage drug released versus square root of time.

Korsmeyer–Peppas model: Log cumulative percentage drug released versus log time.

The regression coefficient (R^2) for each model was calculated, and the model showing the highest R^2 value was considered the best fit. The release exponent (n) obtained from the Korsmeyer–Peppas model was used to determine the mechanism of drug release, such as Fickian diffusion, anomalous transport, or Case II transport.

Stability Studies18

The stability studies of the optimized nano emulsion formulation were performed according to ICH Q1A(R2) guidelines. The optimized formulation was packed in airtight amber-colored glass containers and stored under the following conditions:

25 ± 2°C / 60 ± 5% RH (Long-term condition)

40 ± 2°C / 75 ± 5% RH (Accelerated condition)

RESULTS AND DISCUSSION

EVALUATION PARAMETERS:

Table-2: Drug entrapment efficiency of all formulation

F.no	Drug entrapment efficiency	pH	Viscosity (cp)
F1	88.57	6.2	72.91
F2	82.26	5.9	82.36
F3	81.19	6.3	93.58
F4	89.88	6.5	101.01
F5	93.56	6.2	98.56
F6	91.49	6.4	89.87
F7	92.18	6.7	79.43
F8	90.13	6.8	95.48

Discussion

The prepared Econazole Nitrate nano emulsion formulations (F1–F8) were evaluated for drug entrapment efficiency, pH, and viscosity to determine their suitability for topical administration. The drug entrapment efficiency ranged from 81.19% to 93.56%, indicating efficient incorporation of the drug into the nano emulsion droplets. Formulation F5 exhibited the highest entrapment efficiency (93.56%), which may be attributed to the optimum concentration of oleic acid and Tween 80 that enhanced the solubilization of Econazole Nitrate within the oil phase. Formulations containing lower or higher concentrations of oil and surfactant showed comparatively lower entrapment efficiency due to insufficient or excessive surfactant concentration affecting drug incorporation. The pH values of all formulations ranged between 5.9 and 6.8, which is within the normal physiological pH of the skin. These values indicate that the prepared nano emulsions are suitable for topical application without causing irritation or discomfort. The viscosity of the formulations varied from 72.91 to 101.01 cP. The viscosity initially increased with increasing oil and surfactant concentration and reached an optimum value in formulation F4. Further changes in the composition resulted in a slight decrease in viscosity, probably due to changes in droplet organization within the nano emulsion system. The viscosity values obtained are appropriate for easy spreading and application on the skin.

Determination of globule size and morphology

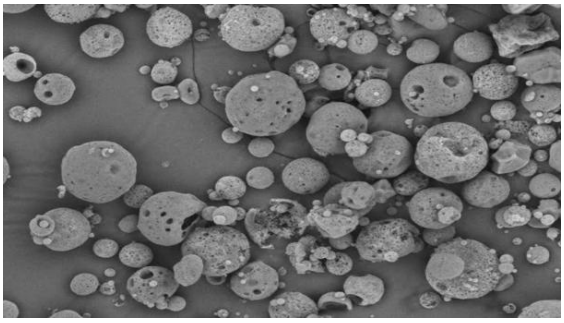


Fig-1: SEM analysis of Optimized Nano emulsion

Discussion

Scanning Electron Microscopy (SEM) was carried out to examine the morphology of the optimized nano emulsion (F5). The SEM images revealed that the nano emulsion droplets were uniformly distributed, spherical in shape, and free from aggregation. The smooth surface morphology confirmed successful formation of the nano emulsion system. The absence of cracks or agglomeration suggested good physical stability of the optimized formulation. The small and uniform globules are expected to improve drug penetration through the skin and enhance antifungal activity.

Particle size

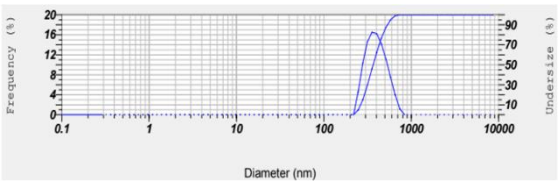


Fig-2: Particle size analysis of Optimized Nano emulsion

Zeta potential

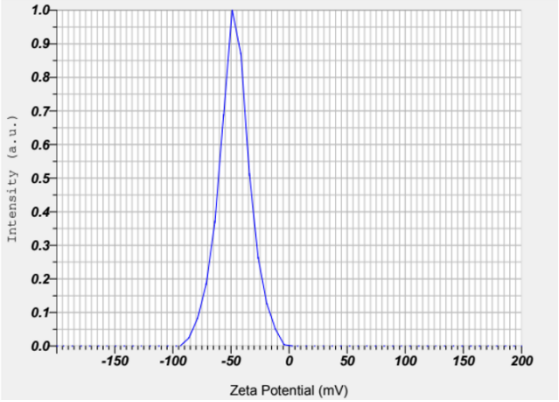


Fig-3: Zeta potential of Econazole Nitrate nano emulsion

Table-3: Evaluation Studies of Econazole Nitrate Nano emulsion particle size and Zeta potential

F. No	Particle size (nm)	Zeta potential (-mV)
F1	239	-25
F2	224	-28
F3	231	-27
F4	243	-26
F5	186	-21
F6	198	-23
F7	200	-22
F8	215	-24

Discussion

Particle size is one of the most important parameters influencing the stability and drug release characteristics of nano emulsions. The particle size of the prepared formulations ranged from 186 to 243 nm. Among all formulations, F5 showed the smallest particle size (186 nm), indicating efficient emulsification and better stabilization by the selected surfactant concentration. The reduction in particle size increases the total surface area available for drug release and enhances permeation through the skin. The narrow particle size distribution also indicates uniformity of the prepared nano emulsion system The zeta potential values of the prepared nano emulsions ranged from −21 mV to −28 mV. The negative zeta potential values indicate electrostatic repulsion between the droplets, thereby preventing aggregation and improving formulation stability. Although all formulations exhibited acceptable stability, formulation F5 (-21 mV) showed adequate electrostatic stabilization along with the smallest particle size and highest entrapment efficiency. These results suggest that the optimized formulation possesses satisfactory colloidal stability suitable for topical drug delivery.

In vitro drug release studies:

Table-4: Results of Econazole Nitrate Nano emulsion of all formulations

Time (hr.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	19.86	18.59	20.18	21.59	22.25	23.19	24.79	17.49
2	32.46	29.86	33.56	35.49	38.79	37.48	38.46	33.58
3	43.19	42.52	45.87	47.49	49.87	46.38	47.89	41.53
4	52.57	53.78	55.69	56.81	58.43	57.86	55.19	56.78
6	61.49	62.59	63.48	65.48	67.84	66.49	64.81	65.47
8	73.10	72.18	75.49	74.57	75.42	74.58	72.50	72.15
10	82.49	83.20	85.57	84.75	89.67	83.27	82.16	80.25
12	92.48	93.60	94.50	95.12	96.78	94.28	93.56	91.53

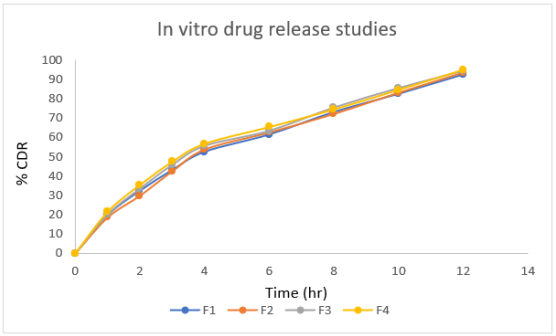


Fig-4: Drug release studies of (F1-F4) formulations

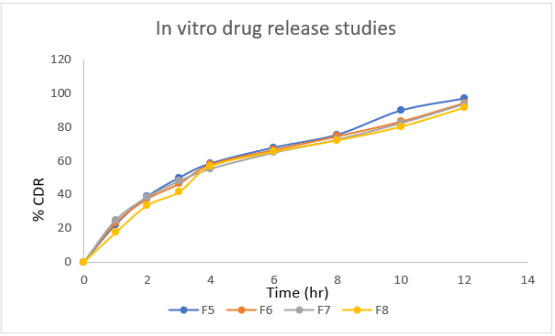


Fig-5: Drug release studies of (F5-F8) formulations

Discussion

The in vitro drug release study was carried out using phosphate buffer (pH 7.4) for 12 hours. All formulations exhibited a gradual and sustained release of Econazole Nitrate throughout the study period. The cumulative drug release after 12 hours ranged from 91.53% to 96.78%. Among all formulations, F5 showed the highest cumulative drug release (96.78%), indicating the optimum balance between oil phase and

surfactant concentration. The smaller particle size of F5 increased the surface area available for diffusion, resulting in faster and more complete drug release. Formulations with larger particle size or lower drug entrapment efficiency exhibited comparatively slower release profiles. The sustained release behavior demonstrates the capability of the nano emulsion system to maintain therapeutic drug levels over an extended period, thereby reducing the frequency of application.

Kinetic modelling of drug release

Zero order kinetics



Fig-5: Zero order kinetics of optimized formulation

First order kinetics

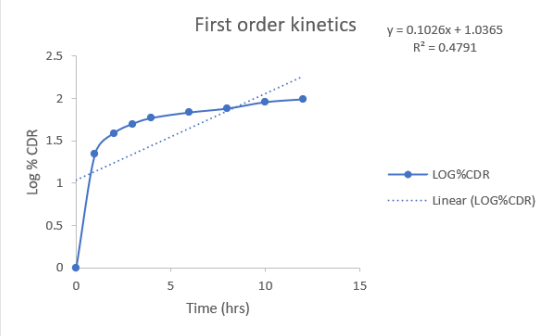


Fig-6: First order kinetics of optimized formulation

Higuchi model

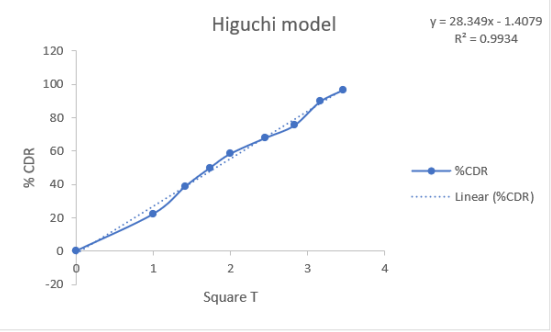


Fig-7: Higuchi model of optimized formulation

Korsmeyer peppas

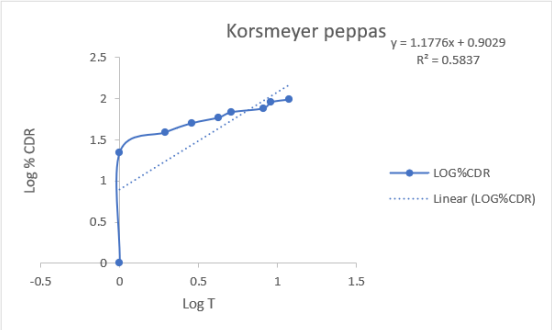


Fig-8: Korsmeyer peppas of optimized formulation

Discussion

The Higuchi model (R^2 = 0.993) exhibited the highest regression coefficient among all the models, indicating that the release of Econazole Nitrate from the optimized nano emulsion predominantly follows a diffusion-controlled mechanism. Drug molecules diffuse gradually from the dispersed oil droplets into the release medium, resulting in sustained drug release. The comparatively lower R^2 values obtained for the First-order and Korsmeyer–Peppas models suggest that these models do not adequately describe the release behavior of the formulation.

Stability studies

Optimized formulations F5 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for drug release for a period of three months.

Table-5: Stability studies of optimized formulations at 40 ± 2 0C and 75 ± 5% RH for 3 months

Formulation Code	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	96.78	95.81	94.48	93.67	Not less than 85 %
F-5	96.78	95.37	94.32	93.15	Not less than 85 %
F-5	96.78	95.26	94.26	93.20	Not less than 85 %

Discussion

The optimized formulation F5 was subjected to accelerated stability studies at 40 ± 2°C and 75 ± 5% RH for three months according to ICH guidelines. Drug release was evaluated periodically during the study. The cumulative drug release showed only a slight reduction from 96.78% initially to approximately 93% after three months, while remaining well above the specified acceptance limit of 85%. No significant changes in appearance, phase separation, or drug release behavior were observed during storage. These findings indicate that the optimized nano emulsion maintained its physical

integrity, chemical stability, and therapeutic performance throughout the study period.

CONCLUSION

The present investigation successfully developed and evaluated an Econazole Nitrate nano emulsion for topical antifungal therapy. The formulated nano emulsions exhibited satisfactory physicochemical properties, high drug entrapment efficiency, suitable pH, acceptable viscosity, nano-sized droplets, good colloidal stability, and sustained drug release characteristics. Among the eight formulations, F5 was identified as the optimized formulation because it demonstrated the highest drug entrapment efficiency (93.56%), the smallest particle size (186 nm), satisfactory zeta potential (−21 mV), and the highest cumulative drug release (96.78%). The optimized formulation also remained stable under accelerated storage conditions for three months without significant changes in its performance. Drug release followed the Higuchi diffusion-controlled model, confirming sustained release behavior. Overall, the developed Econazole Nitrate nano emulsion represents a promising topical drug delivery system with the potential to enhance skin penetration, improve therapeutic efficacy, reduce dosing frequency, and increase patient compliance in the management of fungal skin infections.

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