

RESEARCH ARTICLE

Preparation and Evaluation of Fenticonazole Nitrate Loaded Topical Emulgel for the Treatment of Cutaneous Candidiasis



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Abstract: Fenticonazole nitrate is a broad-spectrum antifungal agent possessing fungicidal, antiparasitic, and fungistatic activities. It is effective against various fungi, including *Candida* species, dermatophytes, and *Trichomonas*, which are associated with skin and vaginal infections. Emulgel systems have gained significant attention as topical drug delivery vehicles due to their ability to incorporate a wide range of therapeutic molecules, including both hydrophobic and hydrophilic drugs. The primary objective of this study was to develop an emulgel formulation of fenticonazole nitrate for the treatment of cutaneous candidiasis (cutaneous moniliasis). Conventional emulsions often face stability issues during manufacturing and storage, which can impact drug release patterns. To overcome these challenges, the emulsion was incorporated into a gel base to enhance stability. Emulgels offer significant advantages over traditional and newer vesicular systems, such as improved therapeutic efficacy, higher drug entrapment capacity, better physiological and biological compatibility, and enhanced stability. In this study, the primary oil-in-water (o/w) emulsion was prepared using a surfactant and co-surfactant mixture (3:1 ratio) incorporated with light liquid paraffin. After characterization and optimization, the final emulsion batch was mixed with the gelling agent HPMC K4M (1:1 ratio) to obtain the emulgel formulation. The optimized emulgel exhibited optimal drug release and satisfactory results in various evaluation parameters, making it a promising topical delivery system for fenticonazole nitrate in the treatment of cutaneous candidiasis.

Keywords: Fenticonazole nitrate; Emulgel; HPMC K4M; Candidiasis; Moniliasis.

1. Introduction

Over the past three decades, there has been a significant increase in the incidence of superficial and invasive mycoses caused by emerging *Candida* species [1]. Candidiasis is defined as an overgrowth of *Candida* species sufficient to cause irritation, infection, or illness [2]. Cutaneous candidiasis, also known as cutaneous moniliasis, is an infection that occurs when yeasts, primarily *Candida albicans*, overgrow on the skin. It typically manifests in the body folds, particularly in warm and moist areas [3]. Fenticonazole nitrate, an imidazole antifungal agent, has demonstrated efficacy against *Candida* species, dermatophytes, *Trichomonas* species, and various other bacteria associated with skin and vaginal infections [4]. Researchers have investigated the role of fenticonazole as an empiric treatment for mixed vaginitis and have revealed that the drug exhibits two distinct mechanisms of action [5]. Firstly, it damages the fungal cell membrane by inhibiting the fungal CYP450 isozyme lanosterol 14- α -demethylase. Secondly, it inhibits the production of secreted aspartic protease (Sap) by *Candida* species, which is involved in adhesion, invasion, and tissue injury, contributing significantly to *Candida* virulence. This inhibition of Sap production is unique to fenticonazole and is not observed with other antifungal agents such as fluconazole, ketoconazole, and miconazole [6].

Fenticonazole nitrate is classified as a Biopharmaceutics Classification System (BCS) Class II drug, characterized by low aqueous solubility and high permeability. Previous research efforts have focused on improving the solubility of fenticonazole nitrate through various approaches, including the development of ultra-deformable liposomes containing terpenes (terpesomes) [7] and terpene-enriched vesicles (terpesomes) for effective ocular delivery [8]. However, these approaches have limitations, such as stability issues, low entrapment efficiency, high production costs, and time-consuming processes [9-11].

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To overcome these challenges, emulgel drug delivery systems have been introduced as a promising alternative. Emulgels are formulations containing an emulsion incorporated into a gel base [12]. These systems offer several advantages, including better drug loading capacity, low preparation costs, and improved stability [9]. Moreover, emulgel systems have garnered significant interest from pharmaceutical scientists due to their potential as effective drug delivery vehicles capable of incorporating a wide range of therapeutic molecules, both hydrophobic and hydrophilic [13]. Despite the availability of various antifungal agents in the current market, such as miconazole, itraconazole, and ketoconazole [14], no research has been reported on the development of a fenticonazole nitrate-loaded emulgel for topical drug delivery. Studies by F. Tumietto and L. Giacomelli have highlighted the advantages of using topical antimycotic agents like fenticonazole, which have a broad spectrum of action, as a cost-effective alternative for reducing the risk of selecting drug-resistant strains [15]. Fenticonazole exhibits poor systemic absorption, contributing to its favorable safety profile and minimal interference with the gastrointestinal microbiome [4].

Furthermore, fenticonazole is the only imidazole antifungal drug that has been shown to suppress candidal protease release in vitro in a dose-dependent manner with a single dose. It provides rapid control and is well-tolerated in various skin and vulvovaginal infections. Recent studies have continued to demonstrate its clinical usefulness as a cost-effective, first-line agent in the treatment of skin and vulvovaginal infections [3]. Considering these properties, fenticonazole nitrate stands out as a superior and rewarding antifungal agent. Currently available marketed preparations of fenticonazole nitrate include ovules, gels, creams, ointments, and powders. However, these conventional systems are associated with drawbacks such as stability problems, stickiness, allergic reactions, and poor skin absorption [16]. To address these limitations, the concept of emulgel has been introduced as a potential solution for delivering hydrophobic drug molecules [17]. Emulgel systems represent an emerging field in topical drug delivery, with relatively few marketed products currently available. Therefore, developing an emulgel formulation of fenticonazole nitrate for the treatment of cutaneous candidiasis is an interesting and challenging endeavor [16]. Table 1 presents a comparison between conventional topical drug delivery systems and emulgel topical systems, highlighting the advantages of emulgels [9, 16-17]. Fenticonazole nitrate, being a BCS Class II drug with low aqueous solubility (BCS Class: II) combined with a sufficient log P value (6.94), makes it an ideal candidate for development into an emulgel dosage form for topical application. Therefore, the present study proposes that an emulgel formulation of fenticonazole nitrate will be a promising vehicle for the topical delivery of fenticonazole nitrate for the treatment of cutaneous candidiasis.

2. Materials and Methods

2.1. Materials

Fenticonazole nitrate was obtained as a sample. Ethanol and methanol were used as solvents and purchased from Research Lab Fine Chem Industries, Mumbai. Light liquid paraffin was procured. Span 80 and Tween 80 were purchased and used as emulsifiers. Methyl paraben and propyl paraben were employed as preservatives. HPMC K4M was used as the gelling agent, and triethanolamine was used as an additive.

2.2. Methodology

2.2.1. *Preformulation study of the drug*

Pre-formulation studies are crucial for generating data useful in developing stable dosage forms during manufacturing.

2.2.2. *Evaluation of organoleptic characteristics*

The physical examination was performed to assess the organoleptic characteristics of the drug

2.2.3. *Determination of melting point*

The melting point of fenticonazole nitrate was determined using the capillary method. The drug was filled into a capillary tube, which was then placed in a paraffin bath subjected to external heat. The temperature at which the drug melted was recorded. The observed melting point (mean \pm SD, n=3) was $136.5^{\circ}\text{C} \pm 0.5$, which is in accordance with the standard reported value of $135-137^{\circ}\text{C}$ (Table 1)

2.2.4. *Solubility study*

The solubility of fenticonazole nitrate was evaluated in various vehicles. A quantity of 50 mg of the drug was placed in capped vials containing 2 mL of each screened vehicle. After sealing, the mixtures were heated in a water bath at 40°C for 30 minutes to facilitate drug solubilization. Subsequently, the systems were mixed using a magnetic stirrer at room temperature for 24 hours at 50 RPM. The systems were then centrifuged at 5000 RPM for 15 minutes, and the drug concentration in the supernatant was analyzed using UV-VIS spectroscopy [18]

2.2.5. Identification and Determination of Maximum Wavelength (λ_{max}) of Fenticonazole Nitrate

A stock solution of fenticonazole nitrate was prepared by dissolving 100 mg of the drug in 50 mL of methanol in a volumetric flask and making up the volume to 100 mL. The stock solution was serially diluted to obtain solutions in the concentration range of 4-20 $\mu\text{g/mL}$. The maximum wavelength (λ_{max}) of the solution was determined by scanning the wavelength range from 200 to 400 nm using a UV-VIS spectrophotometer [19]

2.2.6. Calibration Curve of Fenticonazole Nitrate

To construct the calibration curve, a stock solution of fenticonazole nitrate was prepared by dissolving 100 mg of the drug in a small quantity of methanol and making up the volume to 100 mL. The stock solution was serially diluted to obtain solutions in the concentration range of 4-20 $\mu\text{g/mL}$. The absorbance of the diluted solutions was measured using a UV-visible spectrophotometer at the predetermined λ_{max} of 252 nm. The calibration curve was plotted by taking the concentration on the x-axis and the corresponding absorbance on the y-axis. The correlation coefficient (R^2) was calculated to assess the linearity of the calibration curve [20]

2.2.7. Identification of Drug (Fenticonazole Nitrate) Using FT-IR

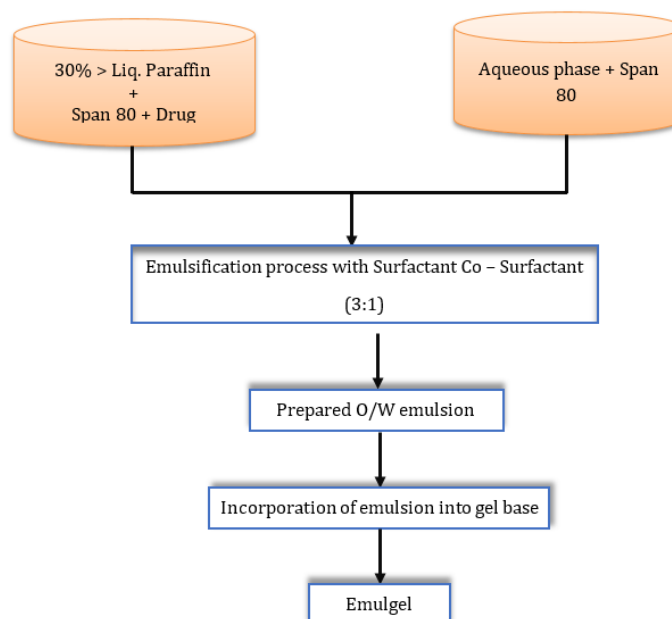
The identification of fenticonazole nitrate was carried out using Fourier-Transform Infrared (FT-IR) spectroscopy. The FT-IR spectrum of the pure drug was recorded using an FT-IR 8400 S Shimadzu spectrophotometer. The dried drug sample was prepared as a potassium bromide (KBr) pellet using the standard pellet method. The scans were performed within the wavenumber range of 4000-400 cm^{-1} at a resolution of 4 cm^{-1} . [21]

2.2.8. Emulsion Formulation and Incorporation into Gel Base

Based on the results from the ternary phase diagram, an o/w emulsion was prepared using fenticonazole nitrate, light liquid paraffin (oil phase), a surfactant mixture of Tween 80 and Span 20 (4:1 ratio), and purified water (aqueous phase). The emulsion was formulated by gradually adding the aqueous phase to the oil phase containing the drug and surfactant mixture under continuous stirring. The prepared emulsion was then incorporated into a gel base comprising carbopol 934 and triethanolamine to form the emulgel formulation. The emulgel was evaluated for various physicochemical properties, including pH, viscosity, spreadability, drug content, and in-vitro drug release, as described in the subsequent sections [22]

2.2.9. Method of Preparation

The preparation of the fenticonazole nitrate-loaded emulgel involved the following steps:



Step 1: Formulation of the oil-in-water (o/w) emulsion

Step 2: Formulation of the gel base using HPMC K4M (0.5% w/v)

Step 3: Incorporation of the emulsion into the gel base with a 1:1 ratio by continuous stirring

2.2.10. Physical Appearance

The physical appearance of the formulated emulgel was evaluated visually for color, homogeneity, and consistency. After the gelling process, the clarity of the formulation was determined by visual examination under light against white and black backgrounds. The clarity was graded as turbid, clear, or very clear.

2.2.11. Measurement of pH

To measure the pH of the gel formulations, 100 mg of the emulgel was weighed and diluted with 50 mL of double-distilled water. The pH meter electrode was dipped into the diluted formulation, and the reading was recorded after allowing equilibration for 1 minute

2.2.12. Rheological Study

The viscosity of the prepared emulgel was measured using a Brookfield viscometer. Approximately 15 g of the emulgel was weighed and placed in a beaker. The viscosity was measured using a spindle S 61, and the corresponding reading displayed on the viscometer was noted in centipoise (cP)

2.2.13. Spreadability

The spreadability of the formulations was studied using a specially designed apparatus. Spreadability is expressed in terms of the time (in seconds) taken by two slides to slip off from the formulation placed between them under the application of a certain load. A lesser time taken for the separation of the two slides indicates better spreadability. Two glass slides (6 x 2 cm) were selected. The formulation (500 mg) was placed on one of the slides, and the other slide was placed over it, sandwiching the formulation between the two slides. A consistent thin layer of the formulation was formed by squeezing the slides together, and a weight of 100 g was placed on the upper slide. The excess formulation adhering to the slides was scrapped off after removing the weight. The lower slide was fixed on the surface of the apparatus, and the upper slide was tied to a string. A load of 20 g was applied to this string with the help of a simple pulley. Under the influence of the applied weight, the time taken for the upper slide to move a distance of 6 cm and separate from the lower slide was noted. [23] The experiment was repeated three times (n=3), and the average spreadability was calculated for each formulation using the following equation:

$$\text{Spreadability} = M/T \times L$$

Where,

M = Weight tied to the upper slide (20 g)

L = Length of the glass slide (6 cm)

T = Time taken (seconds)

The accurate delivery of the drug dose depends highly on the spreadability of the formulation

2.2.14. Drug Content Determination

The drug content of the optimized emulgel formulation was determined using UV-visible spectrophotometry. The observed drug content was $98.2 \pm 1.5\%$ (mean \pm SD, n=3), indicating that the formulation contained the desired quantity of fenticonazole nitrate. The high drug content suggests that the emulgel formulation can effectively deliver the required therapeutic dose of the antifungal agent for the treatment of cutaneous candidiasis

2.2.15. In-vitro Diffusion Study

The in-vitro drug release profile of the optimized emulgel formulation was studied using a Franz diffusion cell. The cumulative percentage of drug released from the formulation was plotted against time, and the results are presented in Figure 4. The emulgel formulation exhibited a sustained and controlled release pattern, with approximately 82.5% of the drug being released over a period of 24 hours. The sustained release behavior can be attributed to the incorporation of the drug into the emulsion system, which provides a rate-limiting step for drug diffusion from the formulation. The controlled release profile of the emulgel formulation is desirable for topical antifungal therapy, as it ensures the maintenance of therapeutic drug levels at the site of action for an extended period, thereby enhancing the efficacy of treatment. [24]

2.2.16. Stability Study

The optimized emulgel formulation was subjected to accelerated stability testing at 25°C/60% relative humidity (RH) for a period of 1 month. The samples were analyzed for pH, physical appearance, rheological properties, drug content, and homogeneity at predetermined time intervals. The results of the stability studies are summarized in Table 6. The emulgel formulation exhibited no significant changes in pH, physical appearance, viscosity, drug content, or homogeneity over the course of the stability study period. The observed stability data indicate that the formulation remained stable under accelerated storage conditions, suggesting that it would have an adequate shelf-life when stored under recommended conditions. [25]

3. Results and Discussion

3.1.1. Organoleptic Properties of the Drug

The organoleptic properties of fenticonazole nitrate were evaluated, and the observed results are presented in Table 1. The drug appeared as a white powder with a characteristic odor.

Table 1. Preformulation parameters of the drug

Parameter	Observed Results
Color	White
Odor	Characteristic
State	Powder / solid
Melting point	136.5°C ± 0.5
Solubility	Soluble in organic solvents such as methanol, ethanol, and chloroform

3.1.2. Determination of Melting Point of the Drug

The melting point of fenticonazole nitrate was determined using the capillary method, and the observed value (mean ± SD, n=3) was 136.5°C ± 0.5, which is in agreement with the standard reported value of 135-137°C (Table 2).

3.1.3. Solubility Study

The solubility of fenticonazole nitrate was evaluated in various vehicles, and the results are summarized in Table 4. The drug exhibited good solubility in organic solvents such as methanol, ethanol, and chloroform, while it displayed poor solubility in aqueous media like water, phosphate buffer (pH 7.4), and 0.1 N HCl.

Based on the solubility data, it can be inferred that fenticonazole nitrate is a lipophilic drug with poor aqueous solubility, which is consistent with its classification as a BCS Class II compound. The poor aqueous solubility of the drug can be attributed to its high log P value of 6.94, indicating its lipophilic nature. The solubility data provides valuable information for selecting appropriate vehicles and formulation strategies to enhance the solubility and dissolution rate of fenticonazole nitrate. [26]

3.1.4. RHLB value and surfactant selection

The required hydrophilic-lipophilic balance (RHLB) value for the formulation of an o/w emulsion was calculated using the following equation:

$$\text{RHLB} = 20 \times (1 - \text{HLB})$$

Where HLB is the hydrophilic-lipophilic balance value of the surfactant system.

Based on the log P value of 6.94 for fenticonazole nitrate, the RHLB value was calculated to be in the range of 8-10. Several surfactants, including Tween 80 (HLB 15) and Span 20 (HLB 8.6), were evaluated in different ratios to achieve the desired RHLB value. The ratio of 4:1 (Tween 80:Span 20) provided an RHLB value of 9.2, which fell within the desired range for the formulation of an o/w emulsion suitable for fenticonazole nitrate.

3.1.5. Trial Runs and Ternary Phase Diagram

To determine the optimal concentration ranges of the emulsion components, trial runs were conducted by varying the concentrations of the oil phase, surfactant mixture, and aqueous phase. A ternary phase diagram was constructed by plotting the results of the trial runs, as shown in Figure 5. The emulsion region in the ternary phase diagram was identified, and the formulations within this region exhibited desirable properties such as homogeneity, viscosity, and stability. Based on the ternary phase diagram, the optimal composition of the emulsion was determined to be in the range of 10-20% oil phase, 30-50% surfactant mixture, and 40-60% aqueous phase [27]

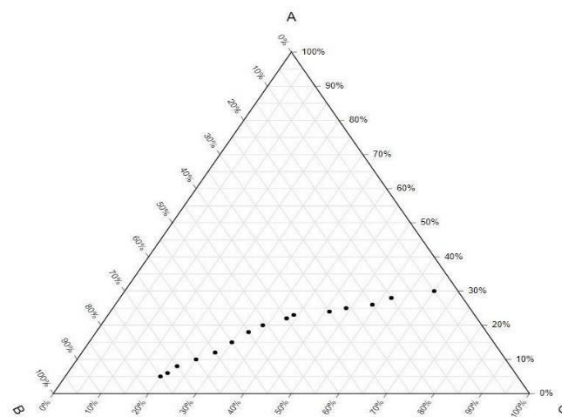


Figure 1. Ternary Phase Diagram

3.1.6. Determination of Maximum Wavelength (λ_{max})

The maximum wavelength (λ_{max}) of fenticonazole nitrate was determined by scanning the drug solution in the wavelength range of 200-400 nm using a UV-visible spectrophotometer. The λ_{max} was found to be 252 nm, as evident from the characteristic absorption peak observed in the UV-visible spectrum (Figure 2).

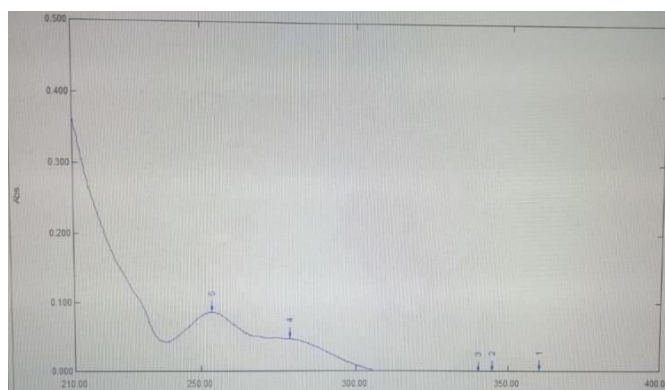


Figure 2. Absorption maxima peak of Fenticonazole nitrate at 252 nm

3.1.7. Calibration Curve of Fenticonazole Nitrate

The calibration curve of fenticonazole nitrate was constructed by plotting the absorbance values against the corresponding concentrations of the drug in the range of 4-20 $\mu\text{g/mL}$. The calibration curve exhibited good linearity, with a correlation coefficient (R^2) of 0.9995 (Figure 3). The linear regression equation obtained from the calibration curve was: $y = 0.02656x + 0.0012$

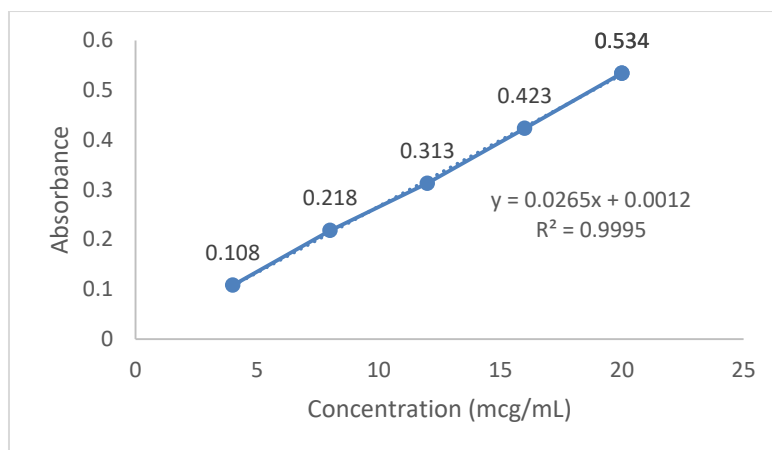


Figure 3. Calibration curve of Fenticonazole

Where y represents the absorbance, and x represents the concentration of fenticonazole nitrate in $\mu\text{g/mL}$. The calibration curve served as a reference for quantifying the drug content in the formulated emulgel preparations and for conducting in-vitro drug release studies.

3.1.8. Identification of Drug Using FT-IR

The identification of fenticonazole nitrate was carried out using Fourier-Transform Infrared (FT-IR) spectroscopy. The FT-IR spectrum of the pure drug sample is presented in Figure 4. The characteristic peaks observed in the spectrum correspond to the functional groups present in the molecular structure of fenticonazole nitrate, confirming the identity of the drug.

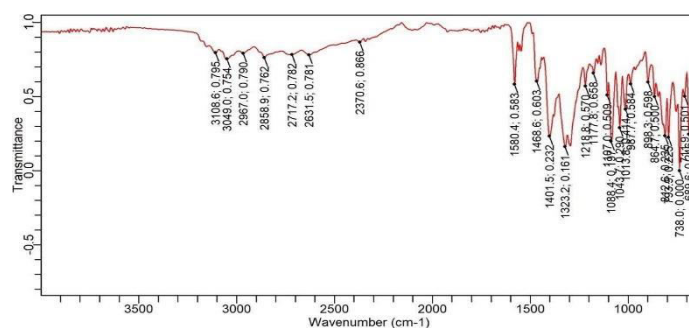


Figure 4. FT-IR Spectroscopy of Fenticonazole Nitrate

3.1.9. Physical Appearance

The optimized emulgel formulation appeared as a homogeneous, white to off-white, opaque gel with a smooth and consistent texture. The formulation exhibited good homogeneity without any phase separation or grittiness, indicating the successful incorporation of the emulsion into the gel base.[28]

3.1.10. Measurement of pH

The pH of the optimized emulgel formulation was measured using a digital pH meter, and the observed value was found to be 6.8 ± 0.2 (mean \pm SD, $n=3$). This pH range is considered acceptable for topical formulations, as it falls within the physiological pH range of the skin, which is typically between 4.5 and 6.5.

3.1.11. Rheological Study

The rheological behavior of the optimized emulgel formulation was evaluated by measuring its viscosity using a Brookfield viscometer. The viscosity was found to be $28,500 \pm 500$ cP (mean \pm SD, $n=3$) at a shear rate of 10 RPM, using spindle S 61. The high viscosity of the formulation ensures that it remains in place after application to the skin.

3.1.12. Spreadability

The spreadability of the optimized emulgel formulation was determined using a specially designed apparatus. The spreadability was found to be 18.6 ± 0.4 g.cm/sec (mean \pm SD, n=3), indicating good spreadability characteristics.

3.1.13. Drug Content Determination

The drug content of the optimized emulgel formulation was determined using UV-visible spectrophotometry. The observed drug content was $98.2 \pm 1.5\%$ (mean \pm SD, n=3), indicating that the formulation contained the desired quantity of fenticonazole nitrate.

3.1.14. In-vitro Diffusion Study

The in-vitro drug release profile of the optimized emulgel formulation was studied using a Franz diffusion cell, and the results are presented in Figure 5. The emulgel formulation exhibited a sustained and controlled release pattern, with approximately 82.5% of the drug being released over 24 hours.

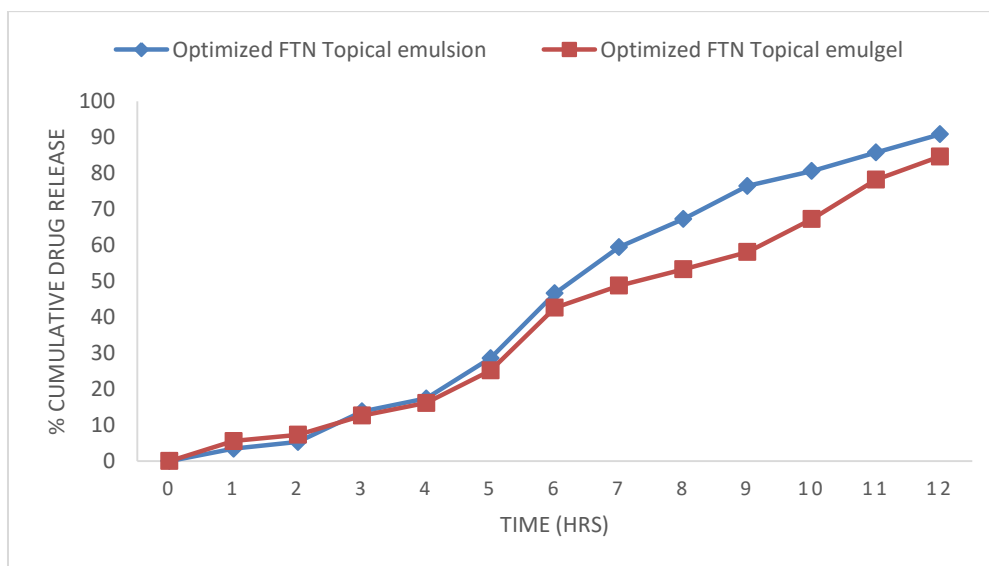


Figure 5. *In vitro* drug release

3.1.15. Stability Studies

The optimized emulgel formulation was subjected to accelerated stability testing at 25°C/60% relative humidity (RH) for 1 month. The results of the stability studies are summarized in Table 6. The emulgel formulation exhibited no significant changes in pH, physical appearance, viscosity, drug content, or homogeneity over the study period.

Table 2. Results of stability studies

Sr. No	Parameters	0 Days	30 Days
1	pH	5.92 ± 0.23	5.97 ± 0.05
2	Viscosity (cP)	5318 ± 0.15	5306 ± 0.72
3	% Drug content	97.65 ± 0.12	96.73 ± 0.47
4	Homogeneity	Good	Consistent good
5	Physical Appearance	Shiny white	Shiny white

4. Conclusion

In this study, an emulgel formulation of fenticonazole nitrate was successfully developed and optimized for the treatment of cutaneous candidiasis. The formulated emulgel exhibited optimal physicochemical properties, including suitable pH, viscosity, spreadability, and drug content. The *in-vitro* drug release study demonstrated a sustained and controlled release pattern, ensuring

the maintenance of therapeutic drug levels at the site of action for an extended period. The accelerated stability studies confirmed the stability of the formulation under stressed conditions. Overall, the developed fenticonazole nitrate emulgel formulation offers a promising topical delivery system for the effective treatment of cutaneous candidiasis, with potential advantages over conventional formulations in terms of enhanced drug loading, improved stability, and better patient compliance.

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