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A Review on Formulation and Evaluation of Antifungal Activity of Ketoconazole Emulgel

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ABSTRACT

Fungal skin infections are prevalent in humid and tropical regions, often requiring effective topical treatment. Ketoconazole, a widely used antifungal agent, is commonly formulated in creams and ointments; however, these conventional forms often exhibit poor skin absorption and limited therapeutic performance. To address these limitations, emulgels — which merge the advantages of emulsions and gels — have emerged as a promising drug delivery system. This study explores the formulation and evaluation of ketoconazole-based emulgel using Carbopol 940 as the gelling agent. The final formulation was assessed for pH, viscosity, drug content, physical appearance, in vitro drug release, and swelling index. Results indicated that the dual-phase emulgel structure supports enhanced skin retention and antifungal efficacy. These findings highlight emulgels as a valuable approach for improving topical delivery of lipophilic antifungal agents such as ketoconazole.

Keywords: Ketoconazole, Emulgel, Topical delivery, Antifungal therapy, Drug formulation, Evaluation

Introduction

Fungal infections of the skin, such as dermatophytosis and candidiasis, are commonly encountered in tropical and humid environments. These infections can cause irritation, inflammation, and secondary complications, often impacting the patient's quality of life. Treatment generally involves topical or systemic antifungal agents, depending on the severity and location of the infection. Ketoconazole is an imidazole-class antifungal agent known for its broad-spectrum activity against dermatophytes, yeasts, and some molds. It acts by inhibiting the synthesis of ergosterol, an essential component of the fungal cell membrane, thereby increasing membrane permeability and inducing fungal cell death. Although effective, conventional ketoconazole formulations like creams and ointments often present limitations such as poor penetration, greasy texture, and reduced stability in moist conditions. To enhance the delivery and efficacy of such lipophilic drugs, emulgel systems have gained popularity. These systems combine the structural properties of emulsions and gels, offering better drug stability, improved skin penetration, and increased patient compliance. The gel component provides a pleasant texture and easy application, while the emulsion facilitates drug solubilization and controlled release. This review aims to explore the formulation strategies, evaluation parameters, and therapeutic effectiveness of ketoconazole emulgels. Emphasis is placed on the potential of emulgels to overcome the challenges associated with conventional topical therapies and their promising role in the management of superficial fungal infections.

Emulgel as a Topical Drug Delivery System

An emulgel is a novel topical drug delivery system that merges the characteristics of both emulsions and gels. Structurally, it involves the dispersion of an emulsion—either oil-in-water (O/W) or water-in-oil (W/O)—within a gel matrix formed by gelling agents such as Carbopol, hydroxypropyl methylcellulose (HPMC), or xanthan gum. This combination offers a semi-solid formulation that is ideal for topical application, particularly for drugs with poor water solubility. The gel network serves multiple roles: it stabilizes the emulsion droplets, enhances spreadability, and improves the residence time of the formulation on the skin. Meanwhile, the emulsion component aids in solubilizing lipophilic drugs and facilitates their gradual release. Emulgels are non-greasy, easy to apply, and aesthetically more acceptable to patients compared to traditional ointments or creams. Due to their unique structure and favorable physicochemical properties, emulgels have proven especially beneficial for delivering hydrophobic drugs like ketoconazole. They allow better skin penetration, reduced irritation, and improved drug bioavailability at the site of infection.

Components of Emulgels

Component	Role
Oil phase	Solubilizes lipophilic drug (e.g., ketoconazole)
Surfactants	Stabilize the emulsion (e.g., Span 20, Tween 80)
Gelling agents	Provide structure and viscosity (e.g., Carbopol)
Co-solvents	Enhance solubility/permeation (e.g., ethanol)
Penetration enhancers	Improve skin absorption (e.g., propylene glycol)
Preservatives	Prevent microbial growth (e.g., methylparaben)

Advantages of Emulgels

- Improved drug penetration through the stratum corneum
- Non-greasy and easily washable
- Enhanced patient compliance
- Suitable for hydrophobic drugs like ketoconazole
- Good stability and aesthetic appeal

Types of emulgels

- **Oil-in-Water (O/W)** Emulgel: More suitable for hydrophobic drugs; better patient acceptability
- **Water-in-Oil (W/O)** Emulgel: Better emollient and occlusive properties

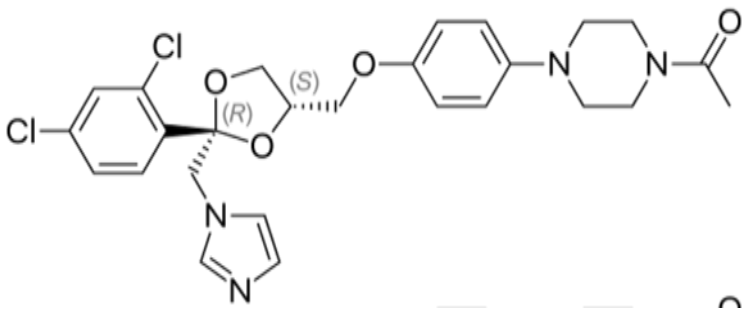
Emulgels represent a smart delivery system, particularly for lipophilic drugs with limited aqueous solubility and skin permeability. Their unique structure allows sustained drug release, making them an effective alternative for antifungal therapy

Ketoconazole A broad Spectrum antifungal agent

Ketoconazole is a synthetic, broad-spectrum antifungal agent belonging to the imidazole class. It was first introduced in the 1980s and has since been widely used in both systemic and topical antifungal therapies. Its primary mechanism of action involves the inhibition of lanosterol 14-α-demethylase, a cytochrome P450-dependent enzyme responsible for converting lanosterol to ergosterol — a key component of fungal cell membranes. The inhibition of ergosterol biosynthesis disrupts the fungal membrane structure and function, leading to cell lysis and death.

Pharmacological Profile

- **Molecular formula**: $C_{26}H_{28}Cl_2N_4O_4$
- **Molecular weight**: 531.43 g/mol
- **Solubility**: Practically insoluble in water; soluble in alcohol, polyethylene glycol, and oils



Antifungal Spectrum

Ketoconazole exhibits strong fungistatic and fungicidal activity against:

- **Dermatophytes**: *Trichophyton rubrum, T. mentagrophytes, Microsporum canis*
- **Yeasts**: *Candida albicans, Malassezia furfur*
- **Molds**: *Aspergillus* species (limited activity)

Clinical Applications

Topically, ketoconazole is used to treat:

- Tinea corporis, cruris, and pedis
- Seborrheic dermatitis
- Cutaneous candidiasis
- Pityriasis versicolor.

Formulation Strategies for Ketoconazole Emulgel

The preparation of ketoconazole emulgel involves three key stages: gel base formation, emulsion preparation, and incorporation of the emulsion into the gel. Each step is designed to ensure a stable formulation with effective drug dispersion and skin penetration.

Step 1: Preparation of Gel Base

A gelling agent, such as Carbopol 934, is dispersed in purified water under continuous mechanical stirring to form a uniform gel base. The dispersion is allowed to swell, and the pH is adjusted to approximately 6.0–6.5 using triethanolamine, ensuring compatibility with skin and drug stability.

Step 2: Formulation of the Emulsion

Oil Phase Preparation:

Span 20 (a lipophilic surfactant) is mixed with light liquid paraffin to form the oil phase.

Aqueous Phase Preparation:

In a separate container, Tween 20 (a hydrophilic surfactant) is dissolved in purified water. Ketoconazole is separately dissolved in methanol, while preservatives like methylparaben and propylparaben are dissolved in propylene glycol. These solutions are then added to the aqueous phase with continuous stirring.

Emulsion Formation:

Both the oil and aqueous phases are heated separately to around 70–80°C. The oil phase is gradually added to the aqueous phase with continuous stirring until a stable emulsion is formed, which is then cooled to room temperature.

Step 3: Incorporation of Emulsion into Gel

The prepared emulsion is added gradually into the gel base in a 1:1 ratio with constant stirring to ensure uniform distribution and consistency. The final formulation is stored in airtight containers to maintain stability.

Preformulation Study

1. Evaluation of Organoleptic Characteristics:

The physical attributes of pure ketoconazole were examined, including its color, smell, taste, crystalline nature, and pH. These properties provide preliminary insights into the material's identity and handling behavior.

2. Melting Point Determination:

The melting point of ketoconazole was assessed using a melting point apparatus. The sample was introduced into a capillary tube sealed at one end. This tube was placed inside the instrument, and the temperature was increased gradually until the sample melted. The temperature at which complete liquefaction occurred was recorded as the melting point.

3. Angle of Repose (θ):

The angle of repose indicates the flow properties of powdered substances. It is defined as the steepest angle formed between a conical heap of powder and a flat surface. To measure it, powder was allowed to fall freely from a fixed height through a funnel. The height (h) and radius (r) of the formed pile were recorded, and the angle was calculated using the formula:

$$\theta = \tan^{-1}(h/r)$$

This helps assess the interparticulate friction and ease of flow of the powder.

4. Bulk Density Measurement:

Bulk density (Db) was determined by measuring the mass of a known volume of powder without tapping. About 50 cm^3 of sieved ketoconazole powder was transferred to a 100 ml graduated cylinder, and the following formula was used:

$$Db = M / Vp$$

Where,
Db = Bulk density (g/cm^3)

M = Mass of the powder (g)

Vp = Apparent volume (cm^3)

5. Tapped Density Assessment:

Tapped density (Dt) was measured by tapping the cylinder containing the powder 100 times at 2-second intervals from a height of 1 inch. The powder volume after tapping was used in the equation:

$$Dt = M / Vp$$

Where,
Dt = Tapped density (g/cm^3)

M = Weight of powder (g)

Vp = Volume after tapping (cm^3)

6. Flow Property Indicators – Carr's Index & Hausner Ratio:

To further evaluate flow characteristics, Carr's compressibility index and Hausner ratio were calculated:

- **Carr's Index (%)** = [(Dt - Db) / Dt] × 100
- **Hausner Ratio** = Dt / Db

A lower Carr's Index and Hausner Ratio denote better flow behavior, which is crucial for consistent drug formulation.

7. λmax Determination via UV-Visible Spectrophotometry:

A primary solution was prepared by dissolving 10 mg of ketoconazole in methanol (40 ml), then sonicated for 15 minutes. The final volume was made up to 100 ml to get a 100 µg/ml solution. From this, 1 ml was further diluted to 10 ml with methanol to obtain a 10 µg/ml solution. The solution was scanned from 200 to 400 nm using a UV-Vis spectrophotometer (Jasco V-630, Japan), and the maximum absorbance wavelength (λmax) was recorded.

8. Preparation of Calibration Curve:

From the stock solution, volumes of 1, 2, 3, 4, and 5 ml were each diluted to 10 ml with methanol to yield concentrations from 10 to 50 µg/ml. Absorbance was measured at the determined λmax (204 nm), and a calibration curve was plotted. The linearity was verified by calculating the correlation coefficient.

9. Solubility Study:

Ketoconazole's solubility profile was tested in multiple solvents, including methanol, ethanol, dichloromethane, chloroform, ether, and distilled water. An excess amount of drug was added to each solvent and stirred manually to observe the extent of solubility.

10. FTIR Spectroscopic Analysis:

Fourier-transform infrared (FTIR) spectroscopy was conducted using a Shimadzu FTIR-8400S instrument. The drug sample was blended with potassium bromide (KBr) in a 1:100 ratio and compressed into a pellet. The spectrum was recorded in the range of 4000–400 cm^{-1} to identify functional groups and confirm drug identity.

Evaluation Parameters of Ketoconazole Emulgels

To ensure the quality, stability, and efficacy of the formulated ketoconazole emulgel, a series of physicochemical and biological evaluations were carried out.

1. Physical Appearance

The emulgel was visually assessed for color, consistency, homogeneity, and the presence of any phase separation. A uniform appearance with no signs of grittiness or separation indicated good formulation stability.

2. pH Measurement

The pH of the formulation was determined using a digital pH meter. The electrode was immersed directly into the emulgel sample, and readings were recorded to ensure compatibility with skin (ideal range: 5.5–6.5).

3. Spreadability

Spreadability was evaluated by placing a fixed quantity of emulgel between two glass slides. A specific weight was applied on the upper slide, and the time required for the slides to separate was measured. Spreadability (S) was calculated using the formula:

$S = M \times L / T$

Where:

M = weight on upper slide (g)

L = length moved by slide (cm)

T = time taken to separate (sec)

4. Viscosity

The viscosity was measured using a Brookfield viscometer at 25°C using spindle no. 2 at a speed of 6 rpm. This helps determine the consistency and application suitability of the emulgel.

5. Antifungal Activity

The formulation's antifungal efficacy was evaluated using the agar cup diffusion method against Candida albicans. Sterile Potato Dextrose Agar was inoculated with fungal suspension, and wells were created in the solidified agar. The emulgel was filled in the wells and incubated at 35–37°C for 48 hours. The zone of inhibition around the wells was measured to assess antifungal effectiveness.

Future Scope

- Nano-emulgel development for enhanced skin penetration and efficacy.
- Use of natural polymers (e.g., chitosan, aloe vera) for biocompatibility.
- Combination therapy with antibacterial or anti-inflammatory agents.
- Stimuli-responsive emulgels for controlled drug release.
- Clinical trials to evaluate safety, efficacy, and patient compliance.
- Application in cosmeceuticals for dandruff and fungal acne.
- Development of film-forming emulgels or transdermal patches for sustained release.

Conclusion:-

The formulation of ketoconazole into an emulgel system offers a promising approach for effective topical antifungal therapy. Emulgels combine the advantages of both emulsions and gels, providing enhanced drug penetration, ease of application, improved patient compliance, and sustained release of the active ingredient. Ketoconazole, a broad-spectrum antifungal agent, demonstrates significant efficacy against dermatophytes and yeasts, and its incorporation into an emulgel enhances its therapeutic potential. Various evaluation parameters such as pH, viscosity, drug content, in vitro drug release, and antifungal activity confirm the stability and effectiveness of the formulation. Overall, ketoconazole emulgel stands out as a novel and efficient dosage form for the management of superficial fungal infections, with further research and clinical trials paving the way for its optimization and commercial application.

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