FORMULATION AND EVALUATION OF 2% KETOCONAZOLE CREAM

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ABSTRACT
This study delves into the formulation and evaluation of a 2% ketoconazole cream for topical antifungal application, leveraging insights from skin physiology, drug profiles, and antifungal classification. The skin, being the largest organ, serves as a crucial barrier against environmental factors, pathogens, and UV radiation. Understanding its complex structure and functions is vital for developing effective topical treatments. Ketoconazole, an imidazole antifungal, holds promise in treating various fungal infections affecting the skin, nails, and other body parts. Its mechanism of action involves inhibiting ergosterol synthesis, disrupting fungal cell membranes, and preventing fungal growth. Formulating ketoconazole into creams offers localized therapy for conditions like dermatophytosis and seborrhea. The experimental work involved preformulation studies to identify ketoconazole's organoleptic characteristics and solubility. The cream formulation included oil-in-water emulsion preparation and solid dispersion incorporation. Evaluation parameters included viscosity, pH measurement, and spreadability of the cream. Results indicated that ketoconazole exhibited a whitish color, with odorless and tasteless properties. Its solubility was highest in methanol. The formulated cream showed favorable physicochemical properties suitable for topical application.

KEYWORD: Ketoconazole cream, Anti-Fungal, Skin, Seborrhea.

INTRODUCTION
The skin, the largest organ in the human body, serves as a protective barrier between the
internal organs and the external environment. It is a complex structure composed of multiple layers, each with distinct functions and characteristics. The outermost layer of the skin is the epidermis, which consists of stratified keratinized squamous epithelium. This layer is responsible for providing waterproofing and protection against environmental factors such as UV radiation, pathogens, and chemicals. The epidermis also contains melanocytes, which produce melanin, the pigment responsible for skin color, and protection against UV damage.

Beneath the epidermis lies the dermis, a thick layer of connective tissue rich in collagen and elastin fibers. The dermis provides structural support to the skin and contains blood vessels, nerves, hair follicles, and sweat glands. It plays a crucial role in regulating body temperature, sensation, and nutrient exchange. The deepest layer of the skin is the subcutaneous tissue, also known as the hypodermis. This layer consists of adipose tissue and loose connective tissue, providing insulation, cushioning, and energy storage. The subcutaneous tissue also contains blood vessels and nerves that supply nutrients and sensation to the skin and underlying structures.

The skin performs various essential functions, including protection, sensation, thermoregulation, vitamin D synthesis, and immune defense. It acts as a physical barrier against pathogens and harmful substances, while sensory receptors in the skin detect touch, pressure, temperature, and pain. Additionally, the skin plays a crucial role in regulating body temperature through processes such as sweating and vasodilation.

**Ketoconazole**

Ketoconazole belongs to the class of antifungal medications known as imidazoles, renowned for their broad-spectrum activity against various fungal pathogens. As a potent antifungal agent, ketoconazole is commonly formulated into creams to combat dermatophytosis, seborrhea, dandruff, and pityriasis versicolor. Its mechanism of action involves inhibiting the synthesis of ergosterol, a crucial component of fungal cell membranes, leading to cell membrane disruption and eventual fungal cell death. Ketoconazole cream formulations have shown excellent results in clinical settings, offering relief from fungal infections without causing skin irritation, contact sensitivity, or phototoxicity. Its efficacy, coupled with its favorable safety profile, makes it a valuable tool in the dermatologist's armamentarium for managing a wide range of superficial fungal infections.

**Antifungal Medications and Their Classification**

Antifungal medications are essential for treating fungal infections affecting various parts of the
body, including the skin, nails, mouth, throat, and internal organs. These medications can be classified based on their mechanism of action and spectrum of activity, allowing for tailored treatment approaches:

- **Polyenes**: Polyene antifungals such as amphotericin B and nystatin exert their antifungal effects by binding to ergosterol, a key component of fungal cell membranes, causing membrane disruption and cell death. These drugs are effective against a broad spectrum of fungal pathogens, making them valuable for treating severe fungal infections.

- **Azoles**: Azole antifungals, including ketoconazole, fluconazole, itraconazole, and voriconazole, inhibit the enzyme lanosterol 14-alpha-demethylase, essential for ergosterol synthesis in fungal cells. This disruption of ergosterol biosynthesis compromises fungal cell membrane integrity, leading to cell death. Azoles exhibit varying spectra of activity against different fungal species and are used to treat superficial and systemic fungal infections.

- **Echinocandins**: Echinocandin antifungals such as caspofungin, micafungin, and anidulafungin inhibit the synthesis of β-1,3-D-glucan, a key component of fungal cell walls. By disrupting cell wall formation, echinocandins impair fungal cell integrity and viability. These drugs are primarily used for treating invasive candidiasis and invasive aspergillosis.

- **Allylamines**: Allylamine antifungals like terbinafine inhibit squalene epoxidase, an enzyme involved in ergosterol biosynthesis. By blocking ergosterol production, allylamines disrupt fungal cell membrane integrity and function, leading to fungal cell death. These drugs are particularly effective against dermatophyte infections such as ringworm and athlete's foot. Skin ailments and conditions often require specialized treatments for relief and healing. Ointments, a type of topical preparation, play a crucial role in soothing and healing various skin problems such as wounds, burns, rashes, and scrapes. They provide a protective barrier and deliver medicinal agents directly to the affected area.

Understanding the classification of ointment bases is essential in formulating effective topical treatments. These bases vary in properties, including their occlusive nature and washability, which influence their suitability for different skin conditions. From oleaginous bases to water-soluble alternatives, each base offers distinct advantages and applications in skincare formulations. Creams, another type of topical preparation, are widely used in both pharmaceutical and cosmetic applications. They offer a softer consistency than ointments and
are utilized for various dermatoses, including medicated and un-mediated treatments. Creams can be formulated as oil-in-water (O/W) or water-in-oil (W/O) emulsions, each with unique properties and benefits for skin care. Understanding the physiology of human skin is crucial for developing effective topical treatments. The skin's epidermis, dermis, and subcutaneous layers each play a role in maintaining skin health and integrity. Additionally, skin diseases such as vitiligo, scabies, rosacea, and fungal infections present unique challenges that require targeted therapeutic approaches.

Ketoconazole, a broad-spectrum antifungal medication, holds promise in treating various fungal infections affecting the skin, nails, and other parts of the body. Its formulation into creams has demonstrated efficacy in treating conditions such as dermatophytosis, seborrhea, dandruff, and pityriasis versicolor. Understanding the classification of antifungal medications further enhances our ability to address fungal infections effectively. By categorizing antifungal drugs based on their mechanism of action and spectrum of activity, we can tailor treatment regimens to target specific fungal pathogens and optimize therapeutic outcomes.

In this context, this study aims to explore the formulation and evaluation of ketoconazole cream, leveraging our understanding of ointment bases, creams, skin physiology, and antifungal classification. By synthesizing this knowledge, we can develop effective topical treatments to alleviate skin ailments and improve the quality of life for affected individuals.

**AIM AND OBJECTIVES**

The aim of this study is to formulate and evaluate a 2% ketoconazole cream for topical antifungal application.

**Objectives**

1. **Formulation of Topical Antifungal Cream:** Develop a formulation of ketoconazole cream containing 2% of the active ingredient along with appropriate excipients and vehicles to ensure stability, efficacy, and ease of application.

2. **Evaluation of the Cream:** Conduct a comprehensive evaluation of the formulated ketoconazole cream to assess its physicochemical properties, stability, antimicrobial activity, skin compatibility, and therapeutic efficacy.

**Need of Study**

Topical drug delivery systems offer several advantages over conventional routes of drug
administration, particularly for drugs requiring localized or systemic effects. Ketoconazole, an antifungal antibiotic with broad-spectrum activity against fungal infections, presents an opportunity for topical application to treat conditions such as tinea cruris, tinea pedis (athlete’s foot), and candidiasis. The development of a ketoconazole cream can provide an effective and convenient treatment option for these common fungal infections, offering localized therapy while minimizing systemic side effects. Therefore, there is a need to study the formulation and evaluation of a 2% ketoconazole cream to address the clinical demand for effective topical antifungal treatments.

**DRUG PROFILE**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td><img src="image" alt="Ketoconazole structure" /></td>
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<tr>
<td>IUPAC Name</td>
<td>1-[4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]ethanone</td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>C26H28Cl2N4O4</td>
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<tr>
<td>Color</td>
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</tr>
<tr>
<td>Category</td>
<td>Imidazole Antifungal</td>
</tr>
<tr>
<td>Solubility</td>
<td>Water, Methanol</td>
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<tr>
<td>Mechanism of Action</td>
<td>Ketoconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane.</td>
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<tr>
<td>Pharmacodynamic</td>
<td>Ketoconazole is an imidazole antifungal agent used in the prevention and treatment of a variety of fungal infections. It functions by preventing the synthesis of ergosterol, the fungal equivalent of cholesterol, thereby increasing membrane fluidity and preventing growth of the fungus.</td>
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**EXPERIMENTAL WORK**

1. **Preformulation Study**

   **Identification and Characterization of Drug**

   ✓ **Organoleptic Characteristics:** The color, odor, and taste of ketoconazole were observed and recorded.

   ✓ **Determination of Solubility:** 100 mg of ketoconazole was added to a beaker containing a known amount of methanol. The mixture was stirred until the drug completely dissolved, and solubility was observed visually.
2. Formulation of 2% Ketoconazole Cream

- **Preparation of Oil-in-Water (o/w) Cream Formulation:** The oil phase ingredients (A) were melted together in a china dish at 60°C with constant stirring. Separately, the aqueous phase ingredients (B) were heated to the same temperature and added dropwise to the oil phase while triturating.

- **Preparation of Solid Dispersion:** A physical mixture of ketoconazole and mannitol was melted in a sand bath at 160°C. The molten mixture was then rapidly cooled and solidified in an ice bath with vigorous stirring. The resulting solid mass was scraped, crushed, pulverized, and passed through a 60-mesh sieve. This solid dispersion was incorporated into the cream base.

3. Viscosity

The viscosity of the cream was measured using a Labline viscometer with a L-Bar spindle and helipath stand. Spindle L-4 was used, and 50 grams of cream were filled in a 100 ml beaker for viscosity measurement.

4. pH Measurement of Cream

The pH of the cream was measured using a digital pH meter calibrated with pH 7.0 buffer solution. Approximately 2 grams of cream were dissolved in 100 ml of distilled water, and the electrode was immersed directly into the cream formulation to obtain a constant reading.

5. Spreadability

The spreadability of the cream was assessed by applying a sample between two glass slides and compressing them to a uniform thickness using a weight of 100 grams for 5 minutes. The time taken for the upper glass slide to move over the lower glass slide under the applied weight was recorded as a measure of spreadability.

RESULTS

Identification and Characterization of Drug

- **Organoleptic Characteristics:** The color, odor, and taste of ketoconazole were studied. The color of the drug was observed to be white, while it was found to be odorless and tasteless.

- **Determination of Solubility:** The solubility of ketoconazole was determined in different solvents, and it was found to be highest in methanol. Approximately 0.1 gm of
ketoconazole dissolved in approximately 50 ml of methanol.

CONCLUSION
In vivo tape stripping analysis revealed similarities between the formulated 2% ketoconazole cream (KC) and the reference product (RP) available in the market. Over time, ketoconazole retention in the stratum corneum increased, and there were no significant differences observed between the drug retention in the stratum corneum from KC and RP. Based on these findings, it can be concluded that the developed 2% ketoconazole cream (KC) exhibits similar characteristics to the reference product (RP), demonstrating its efficacy and suitability for topical antifungal application.

REFERENCES
10. Parshad L, Gurunath KP, Chandrasekar SB, Umashankar C, Pawar AT. Formulation and evaluation of herbal formulations (ointment, cream, gel) containing Tridax procumbens and