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Design Development And Formulation Of Ketoconazole Ointment For Fungal Infection Of Athlete Foot

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Abstract:

The goal of this study is to treat fungal infections, which include eczema, itching, and skin irritations, after producing an oleaginous ointment successfully. Our primary objective is to create an ointment base that is optimally consistent and has favourable antifungal and antibacterial properties in order that promote optimum diffusion. In order to achieve this, we carefully consider a number of characteristics, paying close attention to the systematic produce of the ointment base, which serves as a foundation of future formulation attempts. In order to ensure effectiveness against fungal infections while minimising side effects, we incorporate the active component, ketoconazole, into the base using the fusion method at the lowest possible effective ratio. Additionally, our evaluation goes beyond composition to include a thorough appraisal of the ointments' physical attributes. Spreadability, homogeneity, stability, and pH are examples of such parameters.

Keywords: Eczema, antifungal, Spreadability.

INTRODUCTION

Medication for skin conditions such as eczema, fungal infections induced itching, and irritations is quite difficult. As a result, it is imperative to provide efficient solutions that address these particular issues. Preparing specialised ointments to fight these many skin problems is one interesting answer. Oleaginous components serve as crucial to these ointment formulations as they enhance dermatological treatments' usability and effectiveness. Natural oils, plant-based oils, and waxes are examples of oleaginous materials that have inherent features that make them extremely beneficial in dermatological applications. Because of their occlusive characteristics, they protect the skin from loss of moisture and make it easier for active pharmaceutical ingredients (APIs) penetrate deeper tissue layers. This barrier protects the skin from dangerous ultraviolet (UV) radiation and aids in keeping the skin moisturised. In addition, oleaginous materials add desirable properties including smoothness, spreadability, and emollience to ointment compositions by contribute to the product's overall rheological profile. Formulators may modify the physical attributes of ointments to meet the specific requirements of various skin related conditions by varying the concentration and kind of oleaginous components. For example, thicker, more occlusive oils

may be used in formulas meant for dry or scaly skin types to offer extreme moisturization and barrier protection. Moreover, oleaginous materials serve as vehicles for the solubilization and dispersion of active medicinal components, guaranteeing their even distribution throughout the ointment matrix. This function enhances the bioavailability and therapeutic efficacy of the contained APIs while boosting the formulation's stability and shelf life.

Types of ointments:

In earlier times, the phrase "ointment" was frequently used to describe the two different subclasses of oleaginous semisolids as well as the general name of the class for all semisolids meant for external application. Ointments, for example, are quite broadly defined as “semisolid preparations intended for external application to the skin or mucous membranes”. However, the term "ointment" is more accurately used by pharmaceutical companies to denote the mixing of a medication into an oleaginous ointment basis; an example of this would be the name Hydrocortisone. Hydrocortisone is introduced to an oil-like semisolid basis to create an ointment. This scenario would be explained under the proposed nomenclature; the general class would be named using the term semisolid, and the term ointment would be specified specifically as “a viscous oleaginous or polymeric semisolid dosage form”. The USP states that ointment bases can be classified into four categories: hydrocarbon, absorption, water-removable, and water-soluble..The main four categories are as follows:

1. Hydrocarbon.

2. Absorption.

3. Water-removable.

4. Water-soluble.

The term "oleaginous" typically indicates products that have an oily or greasy appearance. Oleaginous ointments are classified as hydrocarbon bases when it comes to ointment bases. These bases, which include things like mineral oil and petrolatum, commonly referred to as petroleum jelly, are distinguished by their high lipid content.

Advantages and disadvantages of ointments

Advantages

- Formulation Provides a barrier for wound protection
- Allows controlled release of medication
- Suitable for localized treatment
- Can be formulated for various skin types
- Typically, stable formulations
- Long shelf life
- Patient Compliance
- Easy to apply
- Less frequent dosing
- Can be formulated without preservatives
- Less risk of systemic side effects

Disadvantages

- May feel greasy or sticky.
- Difficult to apply on hairy areas.
- Can be messy, especially in warm weather.
- Potential for contamination if not properly stored.
- Susceptible to oxidation and degradation.
- Risk of microbial growth if not properly preserved.
- Requires manual application.
- May require reapplication throughout the day.
- Not suitable for all types of skin conditions.
- Potential for allergic reactions to components.
- Some specialized formulations can be expensive.
- May require frequent reapplication.
- Increasing overall cost.

Drug profile: Ketoconazole

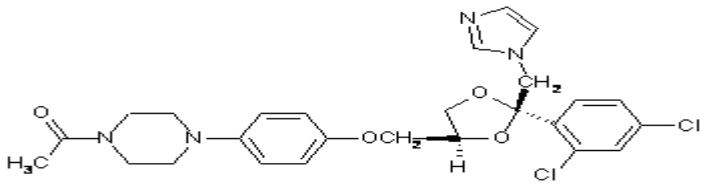

Fig no.1Chemical Structure & formula :$C_{26}H_{28}Cl_2N_4O_4$

IUPAC name: 1-[4-(4-{[2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]ethan-1-one

- Generic name: ketoconazole
- Trade/Brand name: Extina, Ketodan, Ketoderm, Nizoral, Xolegel

. • Mechanism of action: 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.

- Weight: Average: 531.431 Monoisotopic: 530.148760818
- Melting point: 146-153°C
- Chemical Formula: C26H28Cl2N4O4
- PUBCHEM ID: CID 47576

• Adverse Drug effects: Burning, itching, and dryness on the place of application site are common adverse effects. Severe skin reactions or allergic reaction are examples of uncommon but potentially hazardous reactions. Adrenal insufficiency can arise from systemic absorption, particularly after prolonged or excessive use.

Dosage and Topical Route Administration:

Topical ketoconazole dose and administration are dependent upon the particular formulation and disease being handled. It is usually used once or twice a day to the affected area shortly after the skin has been thoroughly cleansed and dried. To ensure its secure and effective use, it's important to carefully follow the directions provided on the medication label or as given by a medical professional.

Preformulation study:

Ketoconazole's physicochemical properties:

- Solubility: Ketoconazole soluble easily in organic solvent such as methanol, ethanol and chloroform but is basically insoluble I water.
- Melting point: The melting point of ketoconazole is around 146-1530oC.
- Stability: While ketoconazole is stable when stored normally ,it may break down when exposed to high temperature ,light or moisture.
- pKa : Ketoconazole has a pKa that is roughly 6.5,that indicates acidic in nature.

Compatibility studies:

- Beeswax: In ointment composition , beeswax is frequently employed as an emulsifying & thickening agent. It is unlikely to result in significant interaction with ketoconazole and is generally compatible with it.
- Mineral oil: Often utilized as the base in ointment composition , mineral oil, is a nonpolar hydrocarbon oil . It can be used to deliver ketoconazole and is safe with it.
- Tocopherol in or vitamin E:
  Because of its antioxidant qualities vitamin E is frequently include in skincare products. It may help in keep stay hydrated and retains moisture . It can be added to the formulation without having a major impact with ketoconazole since it is compatible with it.
- Glycerol: Also known as glycerin, glycerol is a humectant that is frequently used to topical treatments to help skin stay hydrated and retains moisture. It can be added to the formulation without having a major impact with ketoconazole since it is compatible with it,
- Propylene glycol: It is a commonly used solvent and humectant in pharmaceutical and cosmetic formulation. It is generally compatible with ketoconazole and is often used in topical formulation to enhance drug solubility and skin penetration.
  Propylene glycol can improve the solubility of ketoconazole in the formulation and may also contribute to its stability. When propylene glycol is added in formulation within acceptable limit for avoid any potential irritation or adverse effect to the skin.

Material & Method

Antifungal drug Ketoconazole was available by institutional resources as free sample, other ingredients like beeswax, mineral oil , glycerol, & propylene glycol used of analytical grade available in institute for the purpose of research. Vitamin E (tocopherol) had purchased from local market .

Identification of Ketoconazole:

Identification test for Ketoconazole, a widely used antifungal agent, involve several methods to confirm its presence and purity. One common test is the melting point determination. Ketoconazole has a melting point range between 145-151oC and this range can be checked against a known standard to verify its identity.

Formulation of Ketoconazole ointment:

Sr.No.	Ingredients	F1	F2	F3	F4	F5
1.	Ketoconazole	2gm	2gm	2gm	2gm	2gm
2.	Beeswax	10gm	8gm	6gm	8gm	10gm
3.	Liquid Paraffin	30gm	35gm	27gm	30gm	35gm
4.	Vitamin E	0.5gm	0.5gm	0.5gm	0.5gm	0.5gm
5.	Glycerol	1.5gm	1.5gm	1.5gm	1.5gm	1.4gm
6.	Propylene glycol	1gm	1gm	1gm	1gm	1gm
7.	Ketoconazole	-	2%	-	-	-

Table no. 2 Formulation of Ketoconazole ointment

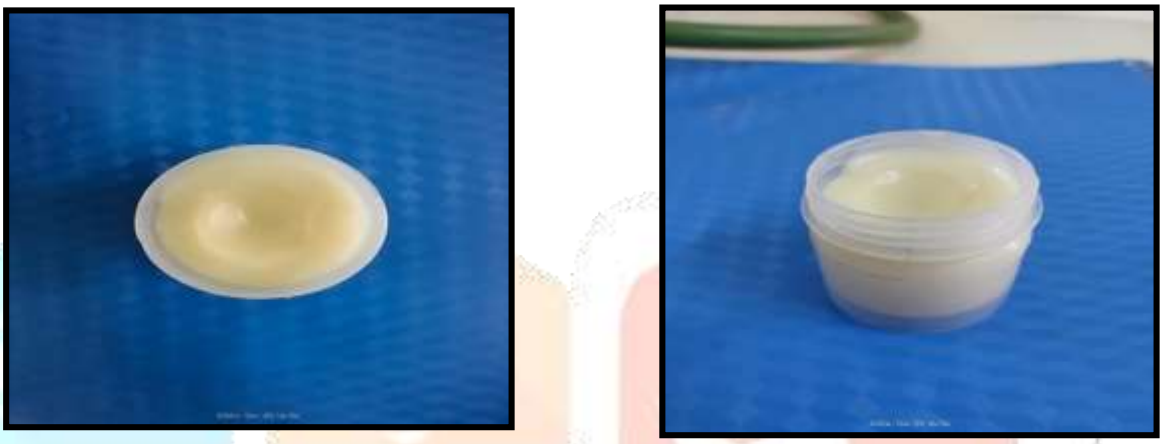

Fig:2 Ketoconazole Ointment 2%w/w in Formulation 2

Method of Oleaginous Ointment preparation:

1. Weighing of all ingredients according to formulations required.
2. Melting of beeswax by using heat resistant container, stirred gently to ensured uniform melting.
3. Incorporation of other ingredients sequentially like liquid paraffin, vitamin E, glycerol, then propylene glycol at measured quantity.
4. Stirred the mixture thoroughly to ensure even distribution of all components.
5. Allowed to mixture cool gradually while stirring gently to prevent the formulation of air bubbles.
6. Once the mixture reaches a suitable temperature continued stirring until it begins to thicken and form an ointment like consistency.
7. On the basis of good appearance texture consistency & spreadibility preferred formulation no.2 for mixing of drug. added drug ketoconazole 2%w/w in ointment base by using tiles and spatula for gradually mixing.
8. Transferred the prepared oleaginous ointment into suitable containers (e.g. Jars or tubes) while it is still warm and malleable.
9. Sealed the container tightly to prevent contamination and stored in cool & dry place away from direct sunlight.

Evaluations of Ketoconazole ointment 2%w/w:

Appearance : creamy consistency, glossy appearance.
Color: Pearl white
Odor: odorless
Texture: smooth oily
Uniformity: Homogenous preparation
Spreadability: 202.7g.cm/sec.
pH 6.92

Antifungal susceptibility testing of ketoconazole ointments (AFST)
It is a crucial step in determining the efficacy of antifungal agent against fungal pathogens. During the research we had target to evaluated the effectiveness of a formulated Ketoconazole ointments against Trichophyton rubrum, a common causative agent of athlete foot.

Methods : (A) Incubation & Inoculation of Fungal strain : Trichophyton rubrum, obtained from dry infected skin surface of a human.
Culture media: Prepared Sabouraud Dextrose Agar (SDA) was used due to its efficacy growing dermatophytes.
Incubation : the fungal spores were inoculated on the SDA plates & incubated at 28 to 30oC for 7days to ensure optimal fungal growth.

(B) **Antifungal Activity completed by cup plate method**:
After proper development of fungal in SDA media , prepared proper cups by using sterile disc to removed surface in the media and placed and filled prepared ketoconazole ointment in the empty area . Plates were incubated again at 28 to 30oC for 72 hrs.

(C) **Measurement of Zone of inhibition**:
Post incubation, the plates were examined for zone of inhibition, which are clear areas around the discs where fungal growth was inhibited. The diameter of these zone was measured in millimetres using a calibrated ruler.
Figure of zone of inhibition by cup plate method.


Fig no 3: Fungal developed in SDA media


Fig no.4: Cup plate method F2

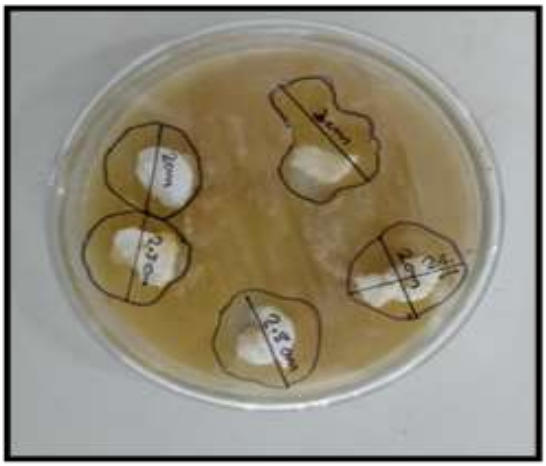

Fig no.5:Zone of Inhibition

The observed zones of inhibition clearly demonstrate the efficacy of the Ketoconazole ointment against Trichophyton rubrum. The lack of inhibition around the control discs confirms that the antifungal activity is specifically due to Ketoconazole. This finding supports the potential use of this ointment formulation in treating athlete's foot, as it effectively inhibits the growth of the fungal pathogen responsible for the infection.

Result & discussion

This research marked the successful development of an ointment specially treatment for athlete foot, a dermatophyte infection predominantly caused by Trichophyton rubrum and Trichophyton mentagrophytes. The formulated ointment integers ketoconazole, a broad-spectrum azole antifungal agent known for its mechanism of action involving inhibition of ergosterol synthesis in fungal membrane. This mode of action disrupts membrane integrity, thereby impeding fungal growth and replication. Recent studies have highlighted ketoconazole efficacy against various dermatophyte, demonstrating its MIC (minimum inhibitory concentration) values in the range of 0.03-0.5% microgram/ml against Trichophyton species.

The formulation and evaluation of ketoconazole ointments 2%w/w provided significant result including appearance, homogeneity, pH, & spreadibility. Most important it gave the significant inhibition of fungal growth, which validating its effectiveness in treatment of fungal infection. The ointment not only facilitated the delivery of ketoconazole but also provide a moisturizing effect, which is beneficial for maintaining skin integrity during treatment.

The AFST conducted in this study showed that the formulated Ketoconazole ointment 2%w/w has significant antifungal activity against Trichophyton rubrum, as evidenced by the clear zones of inhibitors observed. This inference suggested that the ointment can be promising treatment for athlete's foot, offering effective management of the fungal infection.

Future studies, including clinical trials would be beneficial to confirm these findings and established the ointment's efficacy and safety in human subjects.

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