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FORMULATION AND EVALUATION OF ANTIFUNGAL GEL

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1. ABSTRACT

Fungal infections of the skin and nails, caused by dermatophytes (e.g., Trichophyton) and yeasts (e.g., Candida), pose a significant health burden, especially in immunocompromised individuals. Traditional treatments with topical antifungal creams often suffer from limitations like poor drug penetration, prolonged treatment needs, and inconsistent patient adherence, driving the need for more effective options. This study explores a novel gel-based antifungal formulation designed to improve drug delivery, efficacy, and patient convenience while reducing side effects. The gel, containing active ingredients like clotrimazole or ketoconazole in a bioadhesive and biocompatible base, is optimized for sustained drug release directly at the infection site. Bioadhesive properties enhance drug retention and localized action, minimizing systemic absorption. The formulation, created using gelling agents like HPMC and chitosan, underwent extensive testing to ensure stability, appropriate viscosity, and controlled drug release. In vitro tests against Trichophyton rubrum and Candida albicans showed strong antifungal effects, outperforming conventional formulations. Stability and skin compatibility studies also indicated safe, effective use in topical applications. This gel-based formulation promises a superior alternative for treating fungal infections, with potential to improve therapeutic outcomes and patient quality of life. Future clinical trials are necessary to validate its effectiveness further.

KEYWORDS: Antifungal Gels, Drug Delivery System, Topical Treatment.

2. INTRODUCTION

2.1. Background and Evolution

Fungi are eukaryotic organisms that can cause a range of infections, collectively known as mycoses. Historically, fungal infections were seen primarily as skin or superficial infections. However, advances in microbiology and medical

technology have revealed that many fungi can cause serious and systemic infections, especially in immunocompromised individuals. Conditions like HIV/AIDS and advancements in organ transplants and cancer treatments led to marked increase in invasive fungal infections. Notably, diseases like candidiasis, aspergillosis, and mucormycosis became prominent in medical literature due to their life-threatening potential. In particular, mucormycosis gained international attention during the COVID-19 pandemic due to increased cases associated with immune suppression therapies.[1,2,3,4]

2.1.1. Prevalence and Types of Fungal Infections

- **Skin and Nail Infections**: Common worldwide, particularly in humid conditions and among those wearing tight clothing, skin and nail infections are primarily caused by dermatophytes like *Trichophyton* and *Epidermophyton*.
- **Systemic Infections**: In immunocompromised individuals, fungi such as *Candida* and *Aspergillus* can lead to serious infections, including candidemia and pulmonary aspergillosis. *Candida albicans* often causes mucosal infections (e.g., thrush) and can become systemic in those with weakened immunity.[6]

2.1.2. Challenges with Conventional Treatments

- **Topical Treatments:** Topical antifungal creams or ointments (e.g., clotrimazole, terbinafine) are commonly used for skin infections. However, these treatments may not penetrate the deeper layers of the skin or nail beds effectively, limiting their success in treating more stubborn infections.[5]
- **Oral Antifungal Drugs:** Oral antifungals (e.g., terbinafine, fluconazole, itraconazole) are often required for more extensive or resistant infections.
- **Adherence Issues**: One significant issue with oral antifungal treatments is patient adherence, particularly when the treatment duration is long. Non-compliance leads to incomplete eradication of the infection, increasing the likelihood of recurrence.[5]

2.1.3. Need for Improved Treatment Strategies

- **Drug Resistance**: This underscores the need for alternative therapies with better efficacy and fewer side effects.
- **Research into New Treatments:** Innovations in drug delivery systems are also being explored to improve the effectiveness of current treatments.[6]

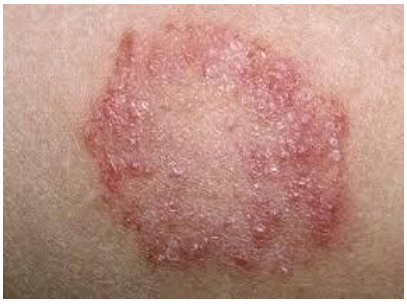

Figure 2.1: Fungal infection in skin.

2.2. Need for Novel Dosage Forms: Antifungal Gel

2.2.1. Challenges with Conventional Topical Antifungal Treatments

- Traditional Forms (Creams, Sprays, and Ointments): Conventional antifungal treatments, such as creams, sprays, and ointments, have limitations regarding ease of use, patient compliance, and penetration of the active ingredients.[7,10]

- Localized Application Issues: These formulations may also be challenging to apply in areas like the nails or scalp, where skin permeability is different from that of other regions.[9]

2.2.2. Improved Patient Compliance with Gel Formulations

- Convenience and Accessibility: Gel formulations are compact and easy to store, making them a more practical choice for patients on the go.[7]
- Reduced Risk of Contamination: Gels in tube or pump formats minimize the risk of contamination compared to open jars of creams or ointments.[11]

2.2.3. Potential for Enhanced Efficacy with Gels

- Sustained Release: Gels can be engineered to provide sustained release of the antifungal agent over time, allowing for prolonged action at the site of infection.[12]
- Targeted Action: Gels allow for targeted delivery of the antifungal agent to the infected areas, ensuring that the drug remains localized and effective for a longer period without being diluted or spread too thin.[10]

3. AIM AND OBJECTIVES OF THE STUDY

AIM: To formulate and evaluate a novel antifungal gel dosage form that enhances drug bioavailability, provides controlled drug release, and shows effective antifungal activity.

OBJECTIVES

- To formulate a stable antifungal gel using a suitable bioadhesive and biocompatible base.
- To assess the physicochemical properties of the gel, including pH, viscosity, spreadability, and stability.
- To perform in vitro drug release studies to determine the release profile of the antifungal agent from the gel matrix.
- To evaluate the antifungal efficacy of the gel formulation against clinically relevant fungal pathogens.

4.1. Fungal Skin Infections and Treatment

Fungal skin infections are commonly caused by dermatophytes such as *Trichophyton*, *Microsporum*, and *Epidermophyton*, as well as yeasts like *Candida*. Examples include athlete's foot, ringworm, and nail infections.

- **Common Fungal Skin Infections**

Dermatophyte Infections: Ringworm: Athlete's Foot.[22]

Yeast Infections: Candida Infections, Malassezia Infections.[22]

- **Traditional Treatments for Fungal Skin Infections:** Traditional treatments typically consist of topical antifungal agents such as creams, ointments, powders, and sprays.
- **Topical Antifungals:** Creams and Ointments: Medications like *clotrimazole*, *miconazole*, *ketoconazole*, and *terbinafine* are widely used to treat dermatophyte and yeast infections.
- **Powders:** useful for infections in areas with excess moisture, such as the groin.[24]
  Sprays: Antifungal sprays, such as *Lamisil* (terbinafine) and *Lotrimin*.[24]
- **Oral Antifungals:** In more severe cases, oral antifungals like *fluconazole*, *itraconazole*, and *terbinafine* may be prescribed.

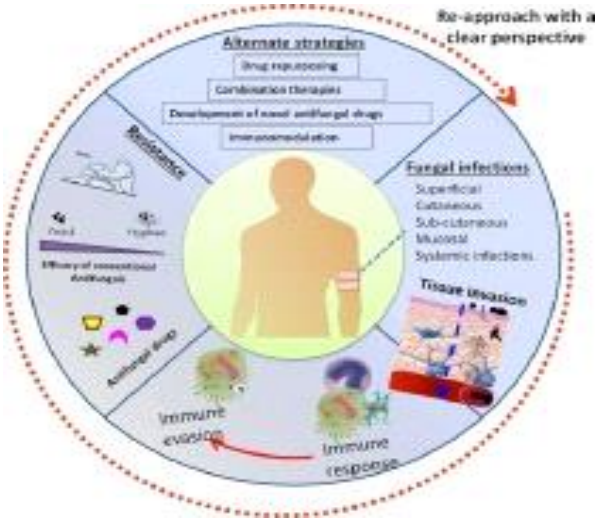

Fig. 2: Life cycle of fungal infection and treatment.[57]

- **Limitations of Traditional Treatment**

Poor Patient Adherence: Patients often fail to complete the full treatment regimen, especially when symptoms improve before the infection is completely eradicated, leading to recurrence.[24]

Prolonged Treatment Periods: Fungal infections typically require weeks of treatment, which can be difficult for patients to adhere to, leading to the risk of reinfection.[23]

Incomplete Drug Penetration: Topical treatments may struggle to penetrate the skin in areas with thick skin, like the soles of the feet, or in nail infections. This can result in suboptimal therapeutic outcomes.[24]

Side Effects: Although generally safe, topical antifungals may cause irritation, and systemic antifungals can have side effects like liver toxicity or gastrointestinal distress.[22]

4.2. Antifungal Agents

Table 01: Antifungal agents.[22,24,25,26,26,27]

Class of Antifungal	Mechanism of Action	Examples	Side Effects	Common Use
Azoles	Inhibit ergosterol synthesis in the fungal cell membrane	Clotrimazole, Miconazole, Fluconazole.	Liver toxicity, GI disturbances, skin irritation	Superficial and systemic fungal infections
Polyene Antifungals	Bind to ergosterol and disrupt fungal cell membrane integrity.	Amphotericin B, Nystatin	Nephrotoxicity (Amphotericin B), fever, chills	Severe systemic infections, superficial Candida infections
Echinocandins	Inhibit glucan synthesis in the fungal cell wall.	Caspofungin, Micafungin, Anidulafungin	Mild liver enzyme elevations, GI upset	Invasive Candida and Aspergillus infections
Allylamines	Inhibit squalene epoxidase, disrupting ergosterol synthesis.	Terbinafine	Liver toxicity, skin reactions, GI disturbances	Dermatophyte infections (ringworm, athlete's foot, nail)
Griseofulvin	Disrupts mitosis by binding to tubulin.	Griseofulvin	GI upset, photosensitivity, liver toxicity	Dermatophyte infections, especially involving nails and hair
Topical Antifungals	Various mechanisms (e.g., inhibition of ergosterol synthesis).	Terbinafine cream, Clotrimazole cream	Mild skin irritation	Localized skin infections like athlete's foot, ringworm

4.2.1. Advantages of Gel-based drug delivery systems

To making them an attractive option for both topical and systemic treatments. Below are the key benefits of using gels as a drug delivery system,

1. **Localized Delivery and Targeting:** Gels are often applied directly to the site of infection or disease, which provides the advantage of localized drug delivery. This minimizes systemic side effects by focusing the therapeutic action on the affected area. For example, in the treatment of fungal skin infections, gels can target the infection site more effectively than oral drugs, which may require higher doses to achieve sufficient tissue concentrations.[28]
2. **Enhanced Permeation and Skin Penetration:** Gel formulations are known to enhance the permeability of the skin due to their high water content and ability to form a thin, uniform layer. This improves the **penetration of the active pharmaceutical ingredient (API)** into deeper layers of the skin or mucous membranes.[29] This is particularly beneficial for antifungal agents that need to reach the deeper skin layers or nails.
3. **Controlled and Sustained Release:** Gel formulations can provide controlled drug release, ensuring a sustained effect over time. The gel matrix can be designed to release the drug in a slow and steady manner, reducing the need for frequent applications and improving patient compliance.[30] This is beneficial in treating chronic fungal infections that require prolonged therapy.
4. **Ease of Application:** Gels are generally easy to apply, with a non-greasy and non-sticky texture that is more acceptable to patients compared to creams and ointments. The transparency of gels also makes them less noticeable, which can enhance cosmetic acceptability.[31]
5. **Reduced Systemic Side Effects:** Because gels are applied topically, the potential for systemic side effects is reduced. This is especially important in the treatment of conditions like fungal skin infections, where oral antifungals may have adverse effects on the liver or kidneys.[32]
6. **Improved Patient Compliance:** Due to their easy application, gel-based formulations may increase patient compliance, especially for children or elderly patients who may find creams or ointments messy or difficult to apply regularly.[28]
7. **Aesthetic Appeal:** Gels are often clear, odorless, and non-greasy, which contributes to their cosmetic appeal. Patients are more likely to use a product that is visually unobtrusive and does not leave a greasy residue.[31]

4.2.2. NOVEL DRUG DELIVERY SYSTEMS (NDDS)

1. **Nanoemulsions:** Nanoemulsions are stable colloidal systems that consist of water, oil, and surfactants, and are typically in the size range of 20 to 200 nm making them an ideal choice for antifungal treatments, as they enhance the solubility and bioavailability of drugs like clotrimazole and ketoconazole. Nanoemulsions provide targeted delivery and sustained release.[33,34]
2. **Liposomes:** Liposomes are spherical vesicles made up of lipid bilayers that can encapsulate both hydrophilic and lipophilic drugs, Liposomes can increase the residence time of antifungal agents, making them a promising formulation for chronic skin infections.[33,34]
3. **Hydrogels:** Hydrogels are water-based systems that can retain a significant amount of water, making them ideal for wound healing and skin infections. Hydrogels can also be combined with other systems like nanoparticles for improved performance.[36]
4. **Microspheres:** prolonging the release of antifungal agents, microspheres reduce the need for frequent applications and improve patient adherence to treatment. They are particularly beneficial in cases where the antifungal treatment needs to be delivered over extended periods.[37,3]

5. **Transdermal Drug Delivery Systems (TDDS)**: Transdermal drug delivery systems use patches or devices that facilitate the passage of drugs through the skin via passive or active mechanisms (such as iontophoresis).. The use of permeation enhancers and micro-needling technologies has further improved the efficacy of TDDS in topical treatments.[38,39]
6. **Iontophoresis:** This technique enhances the permeability of the skin, allowing for the efficient delivery of hydrophilic drugs. Iontophoresis is particularly useful when combined with antifungal agents, ensuring deeper penetration of the active compound into the skin layers.[40]

4.2.3. ADVANTAGES OF NOVEL DRUG DELIVERY SYSTEMS

- Improved Skin Penetration: Systems like nanoemulsions and liposomes enhance drug absorption into the skin, overcoming the stratum corneum barrier.
- Sustained Drug Release: Hydrogels, microspheres, and transdermal systems allow for continuous drug release, reducing the frequency of application and improving patient compliance.
- Targeted Delivery: These systems deliver the drug directly to the site of infection, ensuring effective therapy while minimizing side effects.
- Enhanced Bioavailability: By overcoming issues like solubility and permeability, NDDS increase the bioavailability of active agents, improving their therapeutic outcomes.

Fig 3: Popular markted gel formulation.[58]

4.2.4. CHALLENGES IN FORMULATING EFFECTIVE ANTIFUNGAL GELS

- Ensuring Consistent Viscosity One of the most significant challenges in formulating antifungal gels is achieving consistent viscosity. Gels need to have an optimal consistency for easy application while also ensuring that they adhere well to the skin or nails.[41]
- Stability Issues The physical and chemical stability of antifungal gels over time is another major concern. Antifungal drugs are sensitive to factors like temperature, pH, and light exposure, which can degrade their active components.[44]
- Drug Penetration through Keratinized Tissues The skin, especially the stratum corneum, acts as a significant barrier to the penetration of drugs, particularly those used in the treatment of fungal infections.[43]
- Compatibility of Excipients and Active Ingredients The compatibility of the antifungal agent with other excipients in the gel formulation is critical. Some excipients may affect the solubility or stability of the antifungal drug, reducing its effica.[42]
- Microbial Contamination and Preservation Since antifungal gels are topical formulations, microbial contamination is another critical concern.[43]

4.3. METHODOLOGY

Active Pharmaceutical Ingredients (APIs)

- Clotrimazole, Miconazole, and Ketoconazole are widely used antifungal agents known for their broad-spectrum activity against dermatophytes, yeasts like *Candida*, and molds. They inhibit ergosterol synthesis in fungal cell membranes, leading to cell death.[39]

Excipients

- Starch and Cellulose are used as gelling agents that form a matrix for the gel. These ingredients help provide structure, improve the texture of the gel, and control the release of the active ingredient.[45]
- Hydroxypropyl Methylcellulose (HPMC) is commonly employed as a gelling agent that imparts viscosity and stability to the gel, ensuring sustained drug release.[43]
- Glycerin and Propylene Glycol: These act as humectants and penetration enhancers, improving moisture retention and enhancing the drug's penetration through the skin.[45]
- Citric Acid is used to adjust the pH of the gel, optimizing the gel's compatibility with the skin and ensuring stability.[46]
- **Preservatives** like Phenoxyethanol are incorporated to prevent microbial growth and ensure that the gel remains free of contaminants during its shelf life and usage.[43]

4.4. FORMULATION PREPARATION

- **Gel Preparation**: HPMC is dissolved in water under continuous stirring to form the gel base. Once the gel matrix is formed, the active pharmaceutical ingredients (APIs).[45]
- **Incorporation of Excipients**: After the APIs are incorporated, excipients like glycerin and propylene glycol are added for moisture retention and enhanced drug penetration.[39]
- **Homogenization**: The mixture is homogenized to achieve uniformity.[46]
- **Characterization**: Several tests are conducted to evaluate the final gel formulation:

- Viscosity: Ensures the gel is of a desirable consistency for application.
- pH: Confirms the gel’s skin compatibility.
- Drug Release: In vitro studies to assess the release of the active ingredient.[43]

4.5. EVALUATION TESTS

- **Physical Appearance and Homogeneity**: Check gel’s color, texture, and uniformity for any lumps or separation.[48]
- **pH Measurement**: Ensure gel pH aligns with skin's natural pH (~5.5) to prevent irritation.[49]
- **Viscosity Measurement**: Use a Brookfield viscometer to confirm the gel's consistency for proper application.[50]
- **Spreadability Test**: Assess gel spreadability by measuring spread area under a specified weight.[51]
- **Drug Content Uniformity**: Ensure even distribution of the antifungal agent using spectrophotometry or HPLC.[52]
- **In Vitro Drug Release**: Analyze drug release rate with a dialysis membrane to determine bioavailability.[53]
- **Antifungal Efficacy**: Test gel’s activity against fungi (e.g., *Candida albicans*) using agar diffusion or MIC assay.[55]
- **Stability Studies**: Store gel under varied conditions to check for changes in pH, viscosity, and drug content over time.[55]

- **Skin Irritation Study**: Conduct patch tests to confirm skin safety.[56]

5. CONCLUSION

In conclusion, antifungal gel formulations offer a promising and effective alternative for treating fungal skin infections. Unlike traditional creams and ointments, gels provide controlled and sustained drug release, enhancing patient adherence and improving therapeutic outcomes. The use of polymers and excipients, such as HPMC and glycerin, allows for better drug penetration and stability. While challenges remain in optimizing viscosity and drug delivery through skin, advancements in formulation techniques and delivery systems make antifungal gels a valuable option for managing infections caused by dermatophytes and yeasts. Continued research will further refine these formulations, benefiting patient care.

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