

FORMULATION AND EVALUATION OF LULICONAZOLE AND TOCOPHEROL BASED SKINCARE FOR TREATING SKIN DISORDERS: A Review

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ABSTRACT

Skin-related disorders, particularly superficial fungal infections, continue to represent a significant challenge in dermatological practice and pharmaceutical research due to their widespread prevalence, recurrent nature, and adverse impact on quality of life. Luliconazole, a newer-generation imidazole antifungal agent, has emerged as an effective therapeutic option owing to its potent fungicidal activity against dermatophytes, broad antifungal spectrum, shorter treatment duration, and improved patient compliance compared to conventional antifungal drugs. Tocopherol (vitamin E), a lipid-soluble antioxidant, is well recognized for its ability to protect the skin against oxidative stress, reduce inflammation, enhance skin barrier function, and support tissue repair and hydration. Although the individual pharmacological and dermatological benefits of luliconazole and tocopherol are well documented, their combined application in topical skincare formulations has not been extensively investigated. This review critically examines the pharmacological properties and mechanism of action of luliconazole, along with the dermatological significance of tocopherol in maintaining skin health. Various formulation strategies for topical delivery, including creams, gels, and advanced delivery systems, are discussed with emphasis on formulation compatibility, stability, and skin permeation. Additionally, key evaluation parameters such as antifungal efficacy, antioxidant potential, safety, stability, and skin irritation studies are summarized. By identifying existing research gaps and outlining future research directions, this review highlights the scientific rationale and therapeutic potential of luliconazole–tocopherol based topical formulations as a promising approach for advanced antifungal therapy and multifunctional skincare applications.

KEY WORDS

Luliconazole, Tocopherol, Vitamin E, Antifungal Agents, Topical Drug Delivery, Skincare Formulation

INTRODUCTION

The skin is the largest organ of the human body and functions as a protective interface between the body and the external environment. It safeguards against microbial invasion, ultraviolet radiation, chemical exposure, and physical injury. However, disruption of the skin barrier or prolonged exposure to pathogens often leads to dermatological disorders such as fungal

infections, inflammation, and oxidative damage. Superficial fungal infections, mainly caused by dermatophytes, are among the most prevalent skin diseases worldwide and significantly affect quality of life^[1].

Topical drug delivery is the preferred route for managing such infections due to localized action, reduced systemic toxicity, and improved therapeutic outcomes. However, fungal infections are often associated with inflammatory responses and oxidative stress, which delay healing and promote recurrence. Therefore, incorporating antioxidants into antifungal formulations has emerged as a promising strategy. This review focuses on the scientific basis, formulation approaches, and evaluation aspects of combining luliconazole with tocopherol for effective skincare therapy^[2].

LULICONAZOLE: PHARMACOLOGICAL PROFILE

Luliconazole is a synthetic imidazole antifungal agent with high lipophilicity, enabling strong interaction with fungal cell membranes. It acts by inhibiting lanosterol 14 α -demethylase, a key enzyme involved in ergosterol biosynthesis.^[3] Ergosterol is an essential component of fungal cell membranes, and its depletion leads to increased membrane permeability and fungal cell death.^[4]

Clinically, luliconazole is indicated for the treatment of superficial fungal infections such as tinea pedis, tinea cruris, and tinea corporis.^[5] Compared to conventional azole antifungals, luliconazole exhibits higher potency, rapid onset of action, and once-daily dosing.^[6] Despite these advantages, its poor aqueous solubility and limited penetration through the stratum corneum necessitate formulation optimization for improved therapeutic efficacy.^[7]

Luliconazole cream is a highly potent, broad-spectrum azole antifungal showing excellent efficacy and safety for treating dermatophyte infections like ringworm (tinea corporis/cruris/pedis) and potentially onychomycosis, with studies highlighting its superiority or non-inferiority to other antifungals like fluconazole, rapid action, and good tolerability, though mild side effects like itching or irritation can occur.^[8] Reviews emphasize its strong fungicidal activity, favorable penetration, and potential for short-duration treatment, making it a promising first-line option, with research exploring advanced nanoformulations for better delivery.^[9]

Key features:

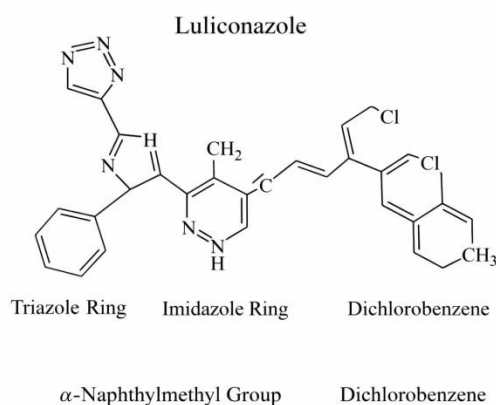
- **High Efficacy:** Luliconazole demonstrates significant clinical and mycological cure rates in short treatment periods (e.g., 1-2 weeks for tinea).
- **Broad-Spectrum & Potent:** It's effective against various fungi, including dermatophytes (like *Trichophyton*, *Microsporum*) and has fungicidal (killing) and fungistatic (inhibiting growth) properties.
- **Superiority/Non-Inferiority:** It is as good as or better than older antifungals like fluconazole and amorolfine, with faster results and lower relapse rates.^[10]

- **Good Safety Profile:** Generally well-tolerated, with mild application site reactions (itching, redness, contact dermatitis) being the most common adverse events, rarely leading to discontinuation.^[11]
- **Favorable Pharmacokinetics:** Its unique structure allows for deep penetration, especially into nails (as a solution), making it a strong candidate for onychomycosis.
- **Advanced Formulations:** Research focuses on Nano-formulation to overcome its low solubility and improve skin permeation for enhanced efficacy.^[12]

Applications & Future Directions:

- **Current Use:** Approved for tinea infections (ringworm, jock itch, athlete's foot) and under investigation for nail fungus (onychomycosis).
- **Future Research:** Focuses on long term efficacy, resistance pattern and systemic application.
- In essence, reviews position luliconazole as a significant advance in topical antifungal therapy due to its potency, rapid action, and good tolerability, making it a valuable tool against common fungal skin infections.^[13]

Luliconazole is an imidazole antifungal API with a unique skeleton, since the imidazole molecule is absorbed into the ketene dithioacetate configuration. The potent antifungal activity of luliconazole may be due to a combination of potent in-vitro antifungal activity and favorable pharmacokinetic properties in the skin. Even when used only once per day, luliconazole 1% cream is effective. It was former official in Japan in 2005 and was approved by the FDA in November 2013. The enzyme lanosterol demethylase is thought to be inhibited by luliconazole. Lanosterol demethylase is required for the formation of ergosterol, which is the primary component of fungal cell membranes. It is available as a 1% topical cream. Topical drug delivery techniques are restricted drug distribution strategies.^[14]

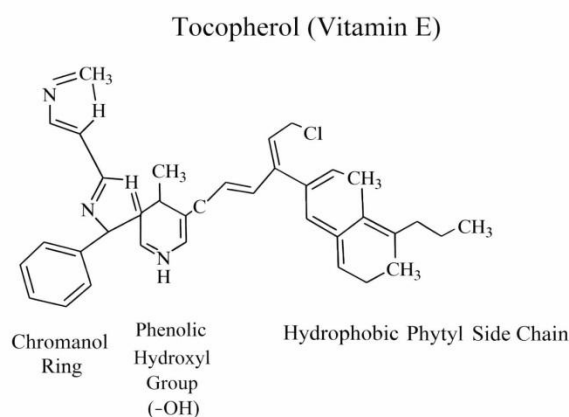


Luliconazole is a synthetic imidazole antifungal agent with a complex heterocyclic structure. It contains an imidazole ring, which is essential for antifungal activity through inhibition of ergosterol synthesis. The molecule also possesses a triazole ring that enhances binding with fungal cytochrome P450 enzymes. An α -naphthylmethyl group and a dichlorobenzene ring increase lipophilicity and skin penetration. This structural composition contributes to the high potency and prolonged antifungal action of luliconazole in topical formulations.^[15]

TOCOPHEROL (VITAMIN E): DERMATOLOGICAL SIGNIFICANCE

Tocopherol, commonly known as vitamin E, is a naturally occurring lipid-soluble antioxidant present in the skin's sebaceous secretions and stratum corneum. Among its various isoforms, α -tocopherol is the most biologically active and widely utilized in topical formulations. Tocopherol protects cellular membranes by scavenging reactive oxygen species and preventing lipid peroxidation.^[16]

In dermatology, tocopherol is extensively used for its anti-inflammatory, photoprotective, and wound-healing properties. Oxidative stress plays a crucial role in the pathogenesis of several skin disorders, including fungal infections and inflammatory dermatoses. Topical application of tocopherol enhances skin barrier function, accelerates tissue repair, and reduces irritation caused by active pharmaceutical ingredients.^[17]



Tocopherol is a lipid-soluble compound consisting of a chromanol ring attached to a long hydrophobic phytyl side chain. The chromanol ring contains a phenolic hydroxyl ($-OH$) group, which is responsible for its antioxidant activity. This hydroxyl group donates hydrogen atoms to neutralize free radicals. The phytyl side chain enhances lipophilicity and facilitates integration into skin lipids and cell membranes. Due to this structural arrangement, tocopherol is well suited for topical dermatological formulations.^[18]

Tocopherol: Indication

Tocopherol can be used as a dietary supplement for patients with a deficit of vitamin E; this is mainly prescribed in the alpha form. Tocopherol can be used as a dietary supplement for patients with a deficit of vitamin E; this is mainly prescribed in the alpha form. Vitamin E deficiency is rare, and it is primarily found in premature babies of very low birth weight, patients with fat malabsorption or patients with abetalipoproteinemia.^[19]

MECHANISM OF ACTION

Tocopherol acts as a radical scavenger. It mainly acts as an antioxidant for lipid bilayers. Tocopherol's functions depend on the H-atom donating ability, location, and movement within the membrane, as well as the efficiency in the radical recycling by some cytosolic reductants such

as ascorbate. Tocopherol actions are related to the trap of radicals, and it has been shown that even in the absence of substituents in the ortho-positions, tocopherol can trap more than two radicals. The types of radicals available for tocopherol are alkyl and peroxy.^[20]

ADVANTAGES OF TOCOPHEROL IN TOPICAL ANTIFUNGAL FORMULATIONS

The incorporation of tocopherol into topical antifungal formulations offers several therapeutic and formulation-related benefits:

Reduction of Drug-Induced Skin Irritation

Tocopherol helps counteract dryness, erythema, and irritation that may occur with prolonged use of antifungal agents, thereby improving patient comfort.^[21]

Enhanced Skin Tolerability

Its moisturizing and barrier-repair properties make formulations suitable for sensitive or damaged skin commonly seen in fungal infections.^[22]

Supportive Role in Antifungal Therapy

Although tocopherol does not possess direct antifungal activity, it supports antifungal treatment by maintaining healthy skin conditions that favor effective drug action and recovery.

Improved Patient Compliance

Reduced irritation and enhanced skin feel lead to better adherence to treatment regimens, especially in long-term or recurrent fungal infections.^[23]

Stabilization of Formulation Components

Tocopherol acts as an antioxidant stabilizer, protecting active pharmaceutical ingredients and excipients from oxidative degradation, thereby improving formulation stability and shelf life.^[24]

Synergistic Therapeutic Outcome

When combined with antifungal agents such as luliconazole, tocopherol provides a synergistic therapeutic effect by simultaneously treating infection and repairing skin damage.^[25]

SCIENTIFIC RATIONALE FOR COMBINATION THERAPY

Superficial fungal infections are multifactorial conditions involving microbial proliferation, inflammation, and oxidative stress. While luliconazole effectively targets fungal pathogens, it does not directly address oxidative damage or barrier impairment. Tocopherol complements antifungal therapy by reducing inflammation, protecting against oxidative injury, and supporting skin regeneration.^[26]

The combination of luliconazole and tocopherol in a single topical formulation may result in synergistic therapeutic benefits, including enhanced antifungal efficacy, improved skin tolerability, faster healing, and better patient compliance. Such combination therapy aligns with modern pharmaceutical approaches that emphasize holistic management of skin disorders.^[28]

MATERIALS AND METHOD

Active pharmaceutical ingredients: Luliconazole, Tocopherol (Vitamin E)

Oil phase: Stearic acid, liquid paraffin, cetostearyl alcohol

Aqueous phase: Purified water, glycerin/propylene glycol

Emulsifier: Polysorbate 60 or suitable non-ionic surfactant

Preservatives: Methyl paraben, propyl paraben

pH adjuster: Triethanolamine / sodium hydroxide solution

METHOD OF PREPARATION

1. Preparation of Oil Phase (Tocopherol Incorporation)

Stearic acid, liquid paraffin, and cetostearyl alcohol were accurately weighed and transferred into a clean beaker. Tocopherol was added to this mixture and the contents were heated on a water bath at 70–75 °C until complete melting and formation of a clear, homogeneous oil phase. Incorporation of tocopherol in the oil phase ensured its uniform distribution and stability due to its lipid-soluble nature.^[29]

2. Preparation of Aqueous Phase (Luliconazole Incorporation)

Purified water was heated separately to the same temperature (70–75 °C). Glycerin or propylene glycol was added as a humectant, followed by the complete dissolution of preservatives under continuous stirring. Luliconazole was dissolved or uniformly dispersed in a suitable solvent and then incorporated into the aqueous phase with constant stirring to ensure uniform drug distribution.^[30]

3. Emulsification

The hot oil phase containing tocopherol was slowly added to the hot aqueous phase containing luliconazole with continuous mechanical stirring. Emulsification was continued until a stable oil-in-water emulsion was obtained. Proper temperature control and stirring speed were maintained to prevent phase separation and ensure uniform droplet size.^[31]

4. Cooling and Cream Formation

The formed emulsion was allowed to cool gradually to room temperature with gentle stirring. During cooling, viscosity increased, resulting in the formation of a smooth and homogeneous cream. Homogenization was performed, if required, to improve texture and physical stability.^[32]

5. pH Adjustment

The pH of the prepared combination cream was measured and adjusted to a skin-compatible range of 5.5–6.5 using triethanolamine or suitable neutralizing agents, thereby reducing the risk of skin irritation.^[33]

6. Filling and Storage

The final luliconazole–tocopherol combination cream was filled into clean, sterilized containers, properly labeled, and stored at controlled room temperature for further evaluation studies.

SIGNIFICANCE OF COMBINATION APPROACH

The combination of luliconazole and tocopherol in a single cream formulation offers synergistic benefits by simultaneously addressing fungal infection and associated skin damage. Tocopherol enhances skin hydration and barrier repair, which may reduce drug-induced irritation and improve patient adherence, while luliconazole ensures potent antifungal efficacy. This combination approach represents a promising strategy for advanced topical antifungal therapy.^[34]

FORMULATION STRATEGIES FOR TOPICAL DELIVERY

Effective co-delivery of luliconazole and tocopherol requires careful selection of formulation components and delivery systems. Conventional semisolid dosage forms such as creams and ointments are widely used due to their ease of application and patient acceptability. Gels and emulgels offer additional advantages, including non-greasy texture, better spreadability, and enhanced drug release.^[35]

Advanced drug delivery systems such as nanoemulsions, liposomes, and solid lipid nanoparticles have shown promise in improving skin penetration, drug stability, and controlled release. These systems are particularly beneficial for protecting tocopherol from oxidation and enhancing luliconazole retention within the skin layers.^[36]

EVALUATION PARAMETERS

Topical formulations should be evaluated using comprehensive physicochemical and biological parameters. These includes-

- a) Appearance,
- b) Homogeneity
- c) pH
- d) Viscosity
- e) Spreadability
- f) Drug content uniformity
- g) Ensure consistent dosing

While in-vitro drug release studies provide insight into drug availability and release kinetics.

Antifungal efficacy is assessed using microbiological assays such as zone of inhibition and minimum inhibitory concentration studies. Stability testing under different storage conditions is essential to ensure formulation integrity and shelf life. Skin irritation and safety studies further confirm suitability for topical application.^[38]

FUTURE PROSPECTS

Despite extensive research on luliconazole-based formulations and tocopherol-containing skincare products individually, limited studies have investigated their combined use. Future research should focus on preformulation compatibility studies, optimization of co-delivery

systems, in-vitro and in-vivo evaluations, and clinical trials. Such studies may lead to the development of innovative and effective dermatological products.

CONCLUSION

Luliconazole and tocopherol possess distinct yet complementary roles in the management of skin disorders. Luliconazole provides potent antifungal activity, while tocopherol enhances skin protection and healing through its antioxidant properties. The development of a combined topical formulation represents a promising approach for effective and holistic skincare therapy. Further pharmaceutical and clinical research is required to validate this strategy and translate it into clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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