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A REVIEW ON FORMULATION AND EVALUATION OF TOPICAL HYDROGEL OF TERBINAFINE HCL FOR EFFECTIVE MANAGEMENT OF DERMATOPHYTE

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ABSTRACT :

Fungal infections of the skin, collectively termed dermatophytosis and primarily etiologically linked to dermatophytes, constitute one of the most highly prevalent dermatological conditions encountered globally, where efficacious therapeutic intervention is paramount to preclude both recurrence and systemic dissemination. While Terbinafine Hydrochloride (HCl) is recognized as a potent, broad-spectrum antifungal agent extensively employed in the clinical management of these infections, the conventional and highly effective oral route of administration is frequently correlated with a propensity for systemic adverse effects, including hepatotoxicity and gastrointestinal disturbances, which necessitates rigorous therapeutic monitoring and may compromise patient safety and adherence. Consequently, this comprehensive review examines the development of topical hydrogels incorporating Terbinafine HCl as a demonstrably superior alternative for localized, targeted therapy that maximizes drug concentration at the infection site while minimizing systemic exposure. These hydrogel systems afford considerable advantages over conventional preparations like ointments and creams due to unique physicochemical characteristics: an elevated water content that imparts a cooling sensation and promotes rehydration, biocompatibility that minimizes skin irritation, improved patient compliance due to a non-greasy aesthetic, and a specialized polymeric matrix that enables controlled drug release kinetics. Recent pharmaceutical investigations have meticulously explored diverse polymers for these matrices, including Hydroxypropyl Methylcellulose (HPMC) for viscosity regulation, Carboxymethylcellulose (CMC) for mucoadhesion, Carbopol 934 for its outstanding gelling efficiency and pseudoplastic flow, and Guar Gum as an economically viable gelling agent. The efficacy of these formulations is systematically scrutinized through key evaluation parameters, including pH determination to ensure compatibility with the skin's physiological range (4.5–6.5), spreadability assessment for patient comfort, rigorous viscosity measurement to ensure optimal skin residence, and in-vitro drug release studies using Franz diffusion cells to determine permeation kinetics. The prevailing consensus unequivocally supports that hydrogel formulations—particularly those utilizing Carbopol 934 and HPMC—constitute an exceptionally promising strategy to customize drug release, maximize therapeutic efficacy, and mitigate the systemic risks of oral therapy, thereby offering a safer, patient-centric treatment paradigm for dermatophytosis.

Keywords: Terbinafine HCl, Hydrogel, Dermatophytes, Topical Drug Delivery, Carbopol, HPMC, Antifungal.

1. Introduction

Terbinafine hydrochloride hydrogels were the focus of research aiming for formulation, evaluation, and in-vitro antifungal activity assessment.

Topical Drug Delivery and Hydrogels

The topical route is utilized for both localized treatment of skin diseases and for systemic drug effects. Hydrogels are commonly prepared for both cosmetic and pharmaceutical purposes. Gels, compared to creams and ointments, often offer superior drug release, independent of the drug's water solubility. Local application presents several advantages over oral and parenteral systems, including:

- Ease of application to the skin.
- Selective delivery of drugs to the site of action.
- Elimination of hepatic first-pass metabolism.
- Improved patient compliance.

Hydrogels are favored in topical systems due to properties such as controllable and prolonged drug release. Upon contact with the skin, these formulations form a semi-occlusive film, allowing for controlled drug release. While lipophilic drugs can penetrate the Stratum corneum, their diffusion rate slows as they reach the more aqueous lower regions of the epidermis.

Antifungal Medications and Terbinafine Hydrochloride

Fungal infections are classified into superficial and systemic types. Antifungal drugs are categorized by their chemical structure: azoles, polyenes, allylamines, and echinocandins.

Terbinafine hydrochloride, an allylamine antifungal drug, is used to treat superficial skin infections like jock itch and athlete's foot. It is primarily effective against the dermatophyte group of fungi and exhibits a broad spectrum of antimycotic activity even at low concentrations. Its mechanism involves inhibiting fungal sterol biosynthesis, leading to ergosterol deficiency and intracellular accumulation of squalene, which causes fungal cell death. Terbinafine has been reported not to interfere with the metabolism of hormones or other drugs.

Types of Fungal Infections

Superficial fungal infections of the skin, hair, and nails are highly prevalent globally. These infections are broadly classified based on the depth of fungal penetration:

- **Superficial Fungal Infections:** Confined to the stratum corneum (the outermost layer of the epidermis), such as tinea versicolor and some cases of pityriasis versicolor.
- **Cutaneous Mycoses:** Infections that penetrate deeper into the epidermis or dermis, including tinea corporis, tinea pedis, and onychomycosis (fungal nail infections).

The depth of penetration is crucial for determining the necessary treatment approach and the effectiveness of topical antifungal therapies.

Dermatophytosis

Dermatophytes are filamentous fungi that cause tinea infections. They parasitize and infect keratinized tissues, including hair, nails, and the stratum corneum, causing severe itching, erythema, and scaling due to a triggered inflammatory response. The pathogenesis involves infectious spores adhering to surface cells, invading keratin layers by releasing keratinase, and causing inflammation. Keratinases break down hard keratin into low-molecular-weight components that dermatophytes can utilize. Dermatophytes are subcategorized based on:

- **Microscopic traits:** *Microsporum*, *Epidermophyton*, and *Trichophyton* species.
- **Typical habitats:** Anthropophilic (infects only humans), zoophilic (primarily infects animals), and geophilic (found in soil) species.

Pityriasis Versicolor

Pityriasis versicolor, also known as tinea versicolor, is the second most common fungal infection after dermatophytosis. It is caused by the yeast species *Malassezia*, a non-dermatophytic fungus. *Malassezia globosa* is a major cause of infections in the microbiology of skin, soft tissue, bone, and joints. These lipophilic yeasts are skin commensals, naturally inhabiting seborrheic areas, and can contribute to the pathophysiology of seborrheic dermatitis, dandruff, Malassezia folliculitis, and potentially exacerbate psoriasis (head/neck) and atopic dermatitis. *Malassezia* organisms grow more easily *in vitro* with the addition of oil.

Terbinafine:

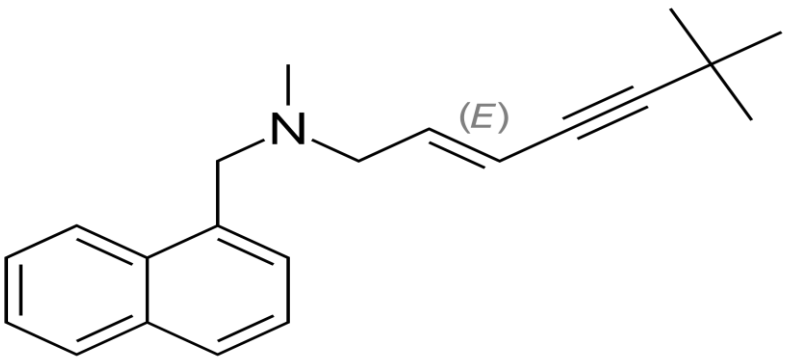

Fig. 1: Chemical structure of Terbinafine

Formula	$C_{21}H_{25}N$
Molar Mass	291.438 $g \cdot mol^{-1}$
Routes of administration	By mouth, topical
Bioavailability	Readily absorbed: 70–90%
Protein binding	>99%
Metabolism	Liver
Elimination half-life	Highly variable

Terbinafine hydrochloride, an allylamine derivative and a BCS class II drug, is a widely recognized lipophilic antifungal agent effective against a broad spectrum of fungal pathogens, including dermatophytes, certain dimorphic fungi, yeasts, and molds.
It is a popular topical treatment for various fungal infection diseases, such as tinea pedis ("athlete's foot"), tinea corporis ("ringworm"), tinea cruris ("jock itch"), and infections affecting fingernails and toenails. Its broad spectrum of activity covers infections caused by organisms like *Trichophyton*, *Microsporum*, and *Epidermophyton*, as well as Tinea versicolor and cutaneous candidiasis (skin yeast infections).
Despite its efficacy, oral therapy with terbinafine hydrochloride is associated with significant drawbacks, including severe side effects, toxicity, drug interactions, and a high risk of recurrence. Consequently, there is a pressing need to develop an effective, safe, and patient-compliant topical formulation that can deliver and sustain the drug's action.

2. Literature Review

Topical gels are preferred for local infections and skin problems due to their direct application to the site of action, which enhances drug bioavailability by avoiding gastrointestinal irritation and first-pass metabolism, and eliminates the risk of drug-drug or food-drug interactions. Gels also offer better penetrating power because of their two-phase composition (Prem samundre et al., 2020).

Terbinafine hydrochloride, an antifungal drug, is commonly used to treat fungal infections. However, its oral use is discouraged because of potential side effects and hepatic first-pass metabolism. T. Praveen Kumar et al. (2020) formulated a hydrogel using various gelling agents like HPMC, Sodium CMC, and Poloxamer at different concentrations. The prepared formulations were assessed for physicochemical characteristics (physical appearance, pH, skin irritation, drug release, drug content) and rheological properties (spreadability, extrudability).

In a different approach, Vij N.N. et al. (2014) developed a 'film-forming gel' of Terbinafine hydrochloride (TH), which creates a thin, transparent film upon skin application. This formulation utilized Eudragit RS PO and hydroxypropyl cellulose in combination to form a matrix film for prolonged antifungal agent release. A 3^2 full factorial design was employed for preparation, and the gels were evaluated for drying time, drug release, antifungal activity, skin irritation, and stability. Further characterization included pH, viscosity, drug content, effective dosage volume, mechanical properties of the film, bioadhesion, and water vapor permeability.

Furthermore, Sunita Rani et al. (2018) highlighted the utility of stimuli-sensitive hydrogels, which can alter their swelling and drug release profiles in response to environmental changes. A key example is the temperature-sensitive hydrogel. Poloxamers, as tri-block copolymers, exhibit thermoreversible properties, transitioning from a liquid to a gel state above a specific sol-gel transition temperature.

V.S. et al. (2017) explored the formulation and evaluation of a Terbinafine hydrochloride-loaded microsponge-based gel for achieving sustained topical delivery. Terbinafine hydrochloride is an allylamine-class antifungal, effective against dermatophytes and Candida fungi, used both orally and topically.

3. Ingredients and Formulation

I. Introduction and Materials

This study focuses on the development and evaluation of a topical hydrogel system containing Terbinafine Hydrochloride (HCl), a well-established synthetic allylamine antifungal agent, for the management of dermatophyte infections.

The analytical grade materials used include Terbinafine Hydrochloride (Mecleods pharmaceutical, Baddi), Sodium CMC (ultratech pharmaceutical

Baddi), Poloxamer (Signet Chemicals), HPMC (Qualikem chemicals, Delhi), and Glycerin, Propylene glycol, Methyl paraben, and Propyl paraben (S.D Fine chemical, Mumbai).

II. Role of Components

Component	Function in Hydrogel Formulation
Terbinafine HCl	Primary active ingredient with fungicidal action.
	Inhibits the fungal enzyme squalene epoxidase, preventing ergosterol production, which leads to toxic squalene accumulation and ultimately fungal cell destruction.
Poloxamers	Provide thermo-reversible gelling properties (liquid to gel at body temperature), act as solubilizers, enhance mucoadhesion, and are used for controlled drug delivery.
HPMC	Acts as a gelling, thickening, and swelling agent, providing structural integrity, controlled release, and bioadhesion.
Sodium CMC	Key component for forming the network structure, enhancing mechanical strength, and controlling swelling.
Glycerin	Humectant/Plasticizer.
Propylene Glycol	Solvent/Penetration Enhancer.
Methyl/Propyl Paraben	Preservatives.

4. Evaluation Parameters for Topical Gel

The developed topical gel formulations were assessed using the following parameters:

- **Appearance and Homogeneity:** Evaluated by visual inspection.
- **pH of the Gel:** Measured using a digital pH meter after dissolving 1g of gel in a suitable medium.
- **Viscosity:** Measured using the Brookfield Viscometer.
- **Spreadability:** Determined by measuring the increase in diameter after applying 0.5g of gel between two glass plates under a 500g weight for 10 minutes.
- **Extrudability:** Measured as the weight (in grams) required to expel a 0.5 cm ribbon of the gel from a collapsible tube in 10 seconds.
- **Skin Irritation Test:** Conducted using the swiss albino mice strain or Guinea pig (400-500gm), applying normal saline, blank gel, and the formulation to the shaven, spirit-cleaned skin.
- **Stability Studies:** Conducted as per ICH guidelines, storing the gel at 30ºC± 2ºC/ 60% ± 5% RH and 40ºC± 2ºC/ 75% ± 5% RH, and analyzing for changes in physical appearance, pH, spreadability, and viscosity.

- **In vitro Diffusion Studies:** Performed using a Franz diffusion cell with 0.5g of gel sample on a membrane, employing phosphate buffer (pH 7.4) as the dissolution medium at 37 ± 1ºC. Samples were withdrawn periodically, replaced with fresh buffer, and analyzed spectrophotometrically.
- **Drug Content:** Determined by dissolving 1g of gel in a suitable medium, filtering, and examining the filtrate under a spectrophotometer. The drug content was calculated using the regression linear analysis of a calibration curve.

5. Discussion

The development of a topical hydrogel system for Terbinafine HCl is highly advantageous for treating dermatophyte infections. Terbinafine HCl's mechanism—potent inhibition of fungal squalene epoxidase—leads to fungicidal action. The hydrogel formulation offers a controlled and prolonged release profile, ease of application, localized action, and avoids hepatic first-pass metabolism, enhancing patient compliance. The lipophilic nature of Terbinafine HCl further supports its effective accumulation in the skin.

Terbinafine HCl gel formulations prepared with gelling agents such as HPMC, Sodium CMC, and Poloxamer demonstrated acceptable physical, chemical, rheological properties, and antifungal activity, including satisfactory color, homogeneity, consistency, spreadability, and pH.

In conclusion, the Terbinafine HCl antifungal hydrogel represents a promising advancement in topical drug delivery. By using a polymeric gel base, the formulation achieves improved drug solubility, controlled release, and enhanced patient compliance compared to conventional treatments.

6. Future Scope

The future of Terbinafine HCl hydrogels lies in revolutionary advancements in topical antifungal therapy, including:

- **Nanotechnology Integration:** Incorporating nanogels or lipid-based carriers for deeper skin penetration and highly controlled drug release.
- **Smart Hydrogels:** Developing gels responsive to stimuli like pH or temperature for targeted delivery, minimizing side effects.
- **Multifunctional Gels:** Combining Terbinafine with wound-healing or anti-inflammatory agents to broaden therapeutic applications.

This focus on localized, non-systemic treatments positions Terbinafine HCl hydrogels to become the preferred choice for dermatophytic infections and potentially expand into specialized areas like ophthalmic or vaginal antifungal therapies.

7.Conclusion :

The development of a terbinafine HCl antifungal hydrogel represents a considerable advancement in the field of topical drug delivery for dermatophytic infections. This sophisticated formulation is engineered through the seamless incorporation of terbinafine hydrochloride, a potent antifungal agent, into an advanced polymeric gel matrix. Typical choices for the gelling base include pharmaceutical-grade polymers such as Carbopol (a family of polyacrylic acid polymers) or Hydroxypropyl Methylcellulose (HPMC), which are highly regarded for their biocompatibility and favorable rheological characteristics.

Advantages and Mechanisms of the Hydrogel System

The hydrogel system confers a multitude of clinical and pharmacokinetic advantages when compared with conventional treatment modalities, such as traditional antifungal creams, ointments, or oral tablets:

1. **Enhanced Drug Solubilization and Bioavailability:** The gel matrix, particularly with the inclusion of specific excipients, is capable of effectively solubilizing terbinafine HCl, resulting in improved thermodynamic activity and subsequent bioavailability at the precise site of infection.
2. **Controlled and Sustained Release:** The polymeric network functions as a controlled reservoir, meticulously regulating the drug's release rate. This controlled-release profile guarantees a consistent and prolonged therapeutic concentration of terbinafine at the infection site, thereby offering the potential to reduce the required frequency of application and enhance overall treatment efficacy.
3. **Localized Action and Minimised Systemic Exposure:** By administering the drug directly to the infected dermal area, the hydrogel maximizes the local drug concentration while simultaneously minimizing the quantity of drug absorbed into the systemic circulation. This mechanism is crucial for mitigating the risk of systemic adverse effects, which are commonly associated with oral terbinafine therapy (e.g., hepatotoxicity). Furthermore, it successfully bypasses the first-pass metabolism that orally administered drugs typically undergo.
4. **Superior Patient Adherence:** The intrinsic physical characteristics of the hydrogel formulation directly contribute to improved patient compliance. Its non-greasy, cosmetically appealing texture is rapidly absorbed, leaving minimal residue, making it significantly more palatable to patients than viscous, oleaginous creams or ointments, especially when applied to intertriginous areas or large body surface areas. The simplicity of application further reinforces adherence.

Physicochemical and Performance Evaluation

Rigorous pharmaceutical testing is mandatory to confirm the quality and performance attributes of these hydrogel formulations. Various formulations prepared utilising diverse gelling agents, such as HPMC, Sodium Carboxymethylcellulose (Sodium CMC), and Poloxamer, have demonstrated an acceptable profile across critical evaluation parameters:

- **Physical Attributes:** All successful gel formulations must exhibit satisfactory physical properties, including a uniform colour, perfect homogeneity (absence of discernible aggregates), appropriate consistency (firm yet easily spreadable), and an acceptable spreadability index, which is essential for user-friendliness.
- **Chemical Stability:** The pH value must be scrupulously controlled to ensure it is non-irritating to the skin and provides the optimal environment for the chemical stability of terbinafine HCl. All measured parameters must consistently conform to prescribed regulatory limits.
- **Rheological Properties:** The rheological profile (the characteristics of flow and deformation) is paramount for both efficient manufacturing and practical application. An acceptable viscosity ensures that the gel remains adherent to the application site while simultaneously permitting easy extrusion from the container and uniform spreading across the skin.
- **Antifungal Activity:** Most critically, the resultant gels must exhibit robust and sustained *in vitro* and *in vivo* antifungal activity against common dermatophytes (e.g., *Trichophyton*, *Microsporum*, and *Epidermophyton* species), thereby unequivocally confirming that the drug's therapeutic potency is successfully retained within the final formulation.

Future Therapeutic Trajectories

The foundational success achieved with the terbinafine HCl hydrogel establishes a platform for next-generation advancements that hold the promise of further enhancing its therapeutic utility. Future research and development endeavours are anticipated to concentrate on:

- **Nanotechnology-Based Hydrogels:** The incorporation of the antifungal agent into nanocarriers (e.g., liposomes, solid lipid nanoparticles) within the hydrogel matrix has the potential to significantly improve drug penetration into the deeper strata of the epidermis and the nail plate, likely leading to a more rapid resolution of the infection.
- **Bioadhesive Systems:** The formulation of bioadhesive hydrogels that can adhere more strongly and for extended durations to the infected skin would prolong the drug's contact time, thus augmenting efficacy, particularly in anatomically challenging areas.
- **Multifunctional Formulations:** The creation of hydrogels possessing dual-action capabilities—for example, combining the antifungal agent with a low-dose corticosteroid to concurrently manage the inflammation and pruritus frequently associated with dermatophyte infections.

In summation, the terbinafine HCl antifungal hydrogel is strategically positioned as a next-generation topical antifungal treatment, offering a high-performance, patient-centric, and therapeutically significant alternative to current standards of care, thereby ensuring its considerable clinical and commercial viability in the management of dermatophytic diseases.

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