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Formulation and Evaluation of Antifungal Clotrimazole Emulgel

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Abstract: Clotrimazole, an imidazole derivative with broad-spectrum antifungal properties, is commonly used to treat Candida albicans infections. It works by inhibiting the synthesis of ergosterol, a key component of fungal cell membranes. This medication is widely used for conditions such as local candidiasis, oral thrush, and vaginal yeast infections. Emulgels, which are emulsions (either oil-in-water or water-in-oil) that have been gelled, are extensively used in both cosmetics and pharmaceutical preparations. These gels form a cross-linked network that encapsulates small drug particles, enabling controlled drug release. Additionally, their mucoadhesive properties extend the duration of medication contact. Emulgels have emerged as an intriguing topical delivery system due to their dual release mechanism involving both gel and emulsion, drawing the interest of pharmaceutical specialists for their potential as drug delivery vehicles for a variety of therapeutic compounds. Characterizing clotrimazoleemulgels involves physical examination, pH determination, viscosity testing, in-vitro release studies, drug content determination, and swelling index measurement. This study aimed to develop a clotrimazole emulgel formulation using carbopol 940 as the gelling agent.

Keywords: Clotrimazole, Antifungal, Emulsion, Carbapol, Emulgel

I. INTRODUCTION

Clotrimazole, an imidazole derivative with broad-spectrum antifungal activity, is commonly used to treat infections caused by Candida albicans, including ringworm, athlete's foot, and jock itch. It increases membrane permeability and disrupts enzyme systems bound to the membrane. Clotrimazole is effective, safe, and well-tolerated, widely used for skin, vulvovaginal, and oropharyngeal fungal infections. However, commercial clotrimazole creams have limitations such as low skin retention, poor residence time, and inadequate deposition at the target site. According to Crowley et al. (2014), clotrimazole has poor water solubility, low bioavailability, and a short half-life (2 hours), leading to poor oral bioavailability due to low aqueous solubility and slow dissolution in water. To address these issues, a transdermal formulation of clotrimazole was developed. Emulgels are emulsions (either oil-in-water or water-in-oil) thickened with a gelling agent and are widely used in cosmetics and pharmaceuticals. Their mucoadhesive properties prolong the medication's interaction with the skin. Emulgels combine the properties of both emulsions and gels, acting as a dual control release system, and are now being used for controlled delivery applications. They are preferred in topical formulations for both cosmetic and dermatological purposes due to their dual characteristics. Oil-in-water emulsions are useful as water-washable drug bases and for general cosmetic purposes, while water-in-oil emulsions are used for treating dry skin and as emollients. Emulgels have high patient acceptability due to their gel-like properties and are stable vehicles for hydrophobic or water-soluble drugs like clotrimazole. They offer the advantage of incorporating hydrophobic drugs, making them increasingly popular. Emulgels are greaseless, transparent, easily spreadable and removable, have a long shelf life, are thixotropic, and are aesthetically pleasing. These properties make emulgels a preferred choice for cosmetic and dermatological preparations, and their use is expected to grow. The goal of this study is to develop and optimize a clotrimazole emulgel using polymers, evaluating its physical properties, drug release, and advantages for hydrophobic drug incorporation. Emulgels are emerging as popular topical drug formulations due to their advantages over conventional preparations. Drug permeation through the stratum corneum can be enhanced by physical methods, chemical modification, or chemical penetration enhancers, which modify the barrier properties of the stratum corneum to increase drug permeability. These enhancers should be non-toxic, non-allergenic, and compatible

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with drugs and excipients. Emulgels, combining the properties of gels and emulsions, have high patient acceptability and are increasingly used as vehicles for delivering various drugs to the skin.

Drug profile



Clotrimazole is a medication used to manage and treat fungal infections, belonging to the imidazole class of drugs. It is FDA-approved for treating oral candidiasis and vaginal candidiasis. Clotrimazole is also effective for skin infections such as athlete's foot, jock itch, ringworm, pityriasisversicolor, intertrigo, and erythrasma. Additionally, clotrimazole shows some activity against certain gram-positive bacteria and, at very high concentrations, against Trichomonas species. For adults and children over 12 years old, the FDA has approved a combination of clotrimazole and betamethasone propionate (a corticosteroid) for the topical treatment of inflammatory tinea caused by Epidermophytonfloccosum and Trichophyton. However, caution is advised, as using such combinations can potentially worsen fungal infections.

Mechanism of action

Clotrimazole inhibits the biosynthesis of ergosterol in a concentration-dependent manner by blocking the demethylation of 14 alpha-lanosterol. Without ergosterol, the fungal cell cannot form an intact and functional cell membrane. Ergosterol also acts like a hormone to promote fungal cell growth; thus, inhibiting its synthesis results in a dose-dependent suppression of fungal growth. In addition to its antifungal action through reduced ergosterol biosynthesis, clotrimazole also has other pharmacological effects. These include inhibiting the sarcoplasmic reticulum Ca2+ ATPase, depleting intracellular calcium, and blocking calcium-dependent potassium channels and voltage-dependent calcium channels.

Administration :

Oral Administration of Other Oral phrasings Cases should sluggishly dissolve troches in the mouth, do not bite . Topical Administration Cream/ Ointment/ Embrocation phrasings irk cream gently onto the sanctified affected skin.

Topical medications shouldn't be used for the eye; or not for used intravaginally.

Intravaginal Administration

Intravaginal use is confined to clotrimazole products specifically labeled for this purpose. Some commercially available products include both intravaginal tablets and vaginal cream in a single package. The intravaginal cream can also be applied externally to the affected vulvar area to palliate itching and discomfort.

Recent advances in medicine design and compounding have accelerated the development of antifungal specifics.

Fungal infection

The rising incidence of fungal infections in recent times necessitates prompt intervention. Early stages of fungal infections are often overlooked, which can lead to increased severity and more complicated treatment processes. Fungal pathogens use various mechanisms to evade the host immune system and worsen infections. To treat a range of

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superficial and systemic infections, antifungal drugs from the current selection are utilized. Recent advancements in drug design and compounding have accelerated the development of antifungal medications.Candidiasis is an infection caused by the fungus Candida, with Candida albicans being the most common species responsible. Normally, Candida lives harmlessly on the skin and inside the body, including the mouth, throat, gut, and vagina. However, it can cause infections if it grows uncontrollably or enters deeper into the body, potentially affecting the bloodstream or internal organs like the kidneys, heart, or brain. Key points about Candida albicans infections include:

Thrush: Occurs when yeast overgrows in the mouth and throat, leading to white, raised bumps. It is commonly seen in infants, children, older adults, and those with weakened immune systems.

Vaginal yeast infection (Vaginal candidiasis): Yeast multiplies in the vagina, causing itching, discomfort, and white discharge. Risk factors include pregnancy, recent antibiotic use, hormonal changes, and a weakened immune system.

Oral thrush (Oral candidiasis): Develops when Candida accumulates on the lining of the mouth, resulting in creamy white lesions on the tongue or inner cheeks. Stress, unmanaged diabetes, and a weak immune system can contribute to oral thrush. Invasive Candidiasis: A severe infection that affects the entire body, including the blood, bones, brain, and heart. It is most common in hospitalized individuals, catheter users, surgery recipients, and with weakened immunity.

Management and Treatment:

- Oral: Medicine taken by mouth (Tablet, Lozenges)
- Topical: Medication directly applied to affected area(Creams, Ointments)

Emulgel

When gels and emulsions are combined, the resulting dosage form is referred to as an emulgel. Polymers can act as emulsifiers and thickeners because their gelling capacity allows for the formation of stable emulsions and creams. They achieve this by reducing surface and interfacial tension while increasing the viscosity of the aqueous phase. The addition of a gelling agent to the water phase converts a traditional emulsion into an emulgel. Emulgels offer significant advantages over both novel vesicular and conventional systems in various respects. Currently, emulgels are gaining popularity as an emerging drug delivery system, especially for hydrophobic drugs. This formulation is considered a novel type of drug delivery system, combining properties of both emulsions and gels.Emulsions are controlled-release systems consisting of two immiscible phases, with one phase dispersed within the other with the aid of an emulsifying agent. The drug particles contained in the internal phase travel through the external phase and are gradually absorbed into the skin, providing a controlled release effect. Emulsions can be of the oil-in-water or water-in-oil type. According to the USP, a gel is a semisolid system containing liquid interpenetrated by a network of small inorganic particles or large organic molecules. Gels trap small drug particles and maintain controlled drug release by incorporating a substantial amount of aqueous or hydroalcoholic liquid within a cross-linked network of colloidal solid particles.

Advantages of Emulgels:

The rising incidence of fungal infections in recent times necessitates prompt intervention. Early stages of fungal infections are often overlooked, which can lead to increased severity and more complicated treatment processes. Fungal pathogens use various mechanisms to evade the host immune system and worsen infections. To treat a range of superficial and systemic infections, antifungal drugs from the current selection are utilized. Recent advancements in drug design and compounding have accelerated the development of antifungal medications.Candidiasis is an infection caused by the fungus Candida, with Candida albicans being the most common species responsible. Normally, Candida lives harmlessly on the skin and inside the body, including the mouth, throat, gut, and vagina. However, it can cause infections if it grows uncontrollably or enters deeper into the body, potentially affecting the bloodstream or internal organs like the kidneys, heart, or brain. Key points about Candida albicans infections include:

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Disadvantages of Emulgel

- Skin vexation leading to contact dermatitis may do.
- There's a eventuality for antipathetic responses.
- Certain specifics may parade low permeability through the skin.
- Medicines with large patches may face challenges in immersion through the skin.
- The conformation of bubbles during the emulgel expression process can be problematic.

Rationale

Many commonly used topical treatments such as ointments, creams, and lotions have several drawbacks. They tend to be sticky, causing discomfort for patients upon application. Additionally, they have a lower spreading coefficient and require rubbing for proper application. Moreover, stability issues can arise. Due to these factors, there has been a growing preference for transparent gels in both cosmetic and pharmaceutical preparations within the category of semi-solid formulations. Despite the numerous advantages of gels, a significant limitation lies in their ability to deliver hydrophobic drugs effectively. To address this limitation, an approach based on emulsions is being utilized, allowing even hydrophobic therapeutic agents to be successfully incorporated and delivered via gels.

Drug delivery across the skin

The epidermis, the outermost layer of the skin, consists of stratified keratinized squamous epithelium and varies in thickness across different body parts. It is thickest where it's supported by elastic fibres. A notable aspect of dermatological pharmacology is the direct access to the skin as a target organ for diagnosis and treatment. The skin serves as a two-way barrier, preventing the absorption or loss of water and electrolytes. Topical drug absorption occurs primarily through three mechanisms: transcellula, intercellular, and follicular pathways. Most drugs traverse a complex path around corneocytes and through the lipid bilayer to reach viable skin layers. Another significant route of delivery is via the pilosebaceous route, often underestimated in clinical settings. The main barrier lies in the outermost layer of the epidermis, the stratum corneum, evidenced by similar penetration rates of chemicals through isolated stratum corneum or whole skin. Creams and gels applied to the skin have long been used to deliver pain medication and infection-fighting drugs to specific areas of the body. These include treatments for vaginal yeast infections, skin infections, and arthritis pain relief. Advancements in technology now allow for the transdermal absorption of other drugs, enabling treatment not only of localized areas but also of the entire body.

Components of Emulgel

Oils serve as the oil phase in emulsion preparation, with mineral oils and soft or hard paraffin being commonly utilized either alone or in combination in topically applied emulsions. For instance, castor and mineral oils, known for their laxative effects, are frequently employed in both oral and topical formulations.

In emulgel preparations, both oily and aqueous vehicles are utilized, allowing for the incorporation of both hydrophobic and hydrophilic drugs. Examples of aqueous phase emulsion vehicles include alcohol, water, and other aqueous materials.

Emulsifiers are employed to enhance the shelf-life stability of formulations by improving emulsification. Common emulsifiers include Tween 80, Span 80, Tween 20, and stearic acid.

Gelling agents are used to prepare gels for various dosage forms, enhancing the consistency of the formulation. Examples include Carbopol 940, Carbopol 934, and HPMC-2190.

pH adjusting agents are employed to maintain the pH of formulations. Examples include triethylamine and NaOH.

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Applications of Emulgels

Topical Applications

Skin Care- Emulgels serve as moisturizers, emollients, and treatments for issues like roughness, dullness, and vexation. Hair Care- Emulgels containing proteins, canvases, and keratin are employed as conditioners, baptizing agents, and treatments for dandruff.

Cosmetics-Emulgels are employed in foundations, lip redolences, sunscreens, etc., incorporating constituents similar as colors, waxes, and silicones.

Parenteral Applications

Emulgels offer sustained medicine release via injection, releasing medicines gradationally to reduce dosing frequence and maintain optimal medicine situations. They generally incorporate water-answerable corticosteroids and antibiotics.

Oral operations

Groundedoral medicine delivery systems include-

Emulgels Combining mixes and gels for controlled medicine release, exercising oil painting- in- water or water- in- oil painting mixes grounded on medicine solubility.

Liquid- filled gelatin capsules(LFGCs) Containing mixes within gelatin capsules, furnishing floating, sinking, or buoyant release of medicines at specific spots for point-specific delivery.

Self-emulsifying medicine delivery systems(SEMDS)- Incorporating emulsifiers and detergents to induce fine oil painting- in- water or water- in- oil painting mixes.

Microemulsions- Thermodynamically stable and isotropic with drop sizes below 100 nm, furnishing maximum face area for immersion and enhancing solubility. They're suitable for lipophilic, amphiphilic, and hydrophilic medicines.

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