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FORMULATION AND EVALUATION OF LULICONAZOLE LOADED MICROSPONGE EMULGEL FOR ENHANCED THERAPEUTIC APPLICATION

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Abstract:
The primary objective of this review is to conduct a comprehensive study on the topical delivery of luliconazole using the microsponge method to enhance the drug's efficacy. The study encompasses a detailed examination of gels, various types of gels, different layers of the skin dermis, and the mechanism of action of the drug on infected areas. Additionally, it explores fungal infections in depth. Microsponges containing Luliconazole (API) with varying proportions of drug polymers were efficiently prepared using the quasi-emulsion solvent diffusion method. This approach aims to minimize side effects, reduce skin secretions, and enhance therapeutic efficacy at lower doses, thereby optimizing the drug delivery system. The quasi-emulsion solvent diffusion method utilized different polymers such as HPMC, Polyvinyl Ethyl cellulose, and others to achieve these objectives.

Key Words: Microsponge, polymer, Quasi emulsion, drug delivery.

INTRODUCTION

Microsponges are microscopic spherical structures analyzed using the mercury intrusion porosimetry method. They are designed to control the release of drugs in topical preparations, thereby reducing oily layers and skin shine. These microsponges are used to achieve prolonged drug action by regulating drug release at minimal doses. Their primary objective is to enhance drug stability and minimize side effects. In this review, we focus on the formulation of Microsponges containing LCZ (Luliconazole) using Ethyl Cellulose as a controlled release polymer[1].

Fungal Infection:

When the body's immune system is compromised or when harmful microorganisms are highly concentrated, infections can occur. Often, infections may be asymptomatic, but they can sometimes provoke a response from the body, leading to visible signs and symptoms, collectively known as infectious diseases[2]. These diseases can be caused by various agents such as bacteria, viruses, parasites, fungi, and others. Historically, bacterial infections were the most concerning, but with advancements in treatment, fungal infections have become increasingly perilous, especially for individuals with weakened immune systems[3].

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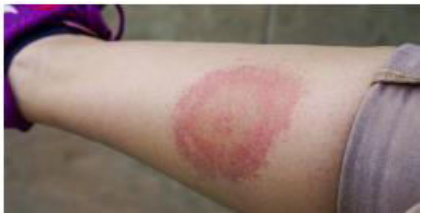

Figure 1: Fungal Infection

Fungi, encompassing yeasts and molds, are opportunistic pathogens, causing infections when the body's natural defense are weakened, often due to aggressive medical treatments. These infections have become significant contributors to illness in intensive care units, characterized by symptoms that can be challenging to identify[4].

Despite their roles in processes like fermenting beverages or leavening bread, fungi are fundamentally decomposers. They thrive on decaying organic matter, including human tissues. Once activated by signals of decay, fungi grow vigorously, even resisting medical interventions intended to sustain life. In some cases, these treatments inadvertently promote fungal growth by further compromising the immune system[5].

Understanding the unique nature of fungi as infective agents is crucial for effectively combating fungal infections in medical environments[6].

Pathophysiology of Fungal Infection: Only a select few types of fungi possess the capability to harm healthy individuals significantly. Typically, they pose minimal threat unless they encounter someone with a compromised immune system, providing an opportunity for the fungi to penetrate the body[7].

Under normal circumstances, our gastrointestinal and respiratory systems are fortified with barriers that protect against fungal cells and spores. However, damaged tissues can create favourable conditions for infections to develop. Therefore, fungal infections that become severe are often considered opportunistic, taking advantage of weakened defenses. Recent research has suggested that genetic variations in certain immune response genes could influence susceptibility to invasive fungal infections. Factors like variations in IL-10 production, Toll-like receptor variants, and differences in the plasminogen gene are being explored in this context. Nevertheless, severe impairment of the immune system remains the primary risk factor for these infections, especially in conditions such as hematological malignancies.

Skin: The skin is a vital organ, constituting approximately 16% of our body weight and serving as the largest organ in the body. Its comprehensive coverage across the body underscores its fundamental physiological role. In addition to providing a protective barrier, the skin interfaces with mucous membranes at body openings and includes specialized structures such as glands, hair follicles, and nails in specific regions.

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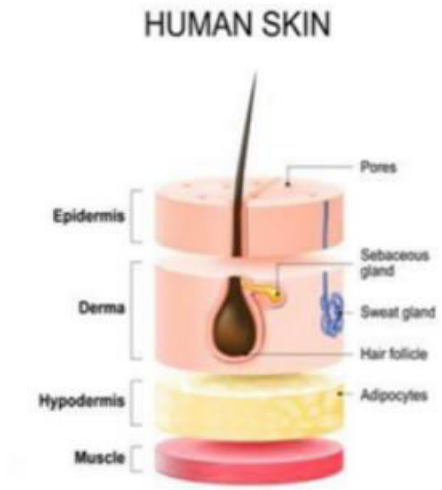

Figure 2: Human Skin

Gel: In simpler terms, a gel can be likened to a sponge structured in a three-dimensional network, composed of solid materials intertwined with a significant amount of liquid. This mesh-like structure traps the liquid within, creating a firm consistency. The solid components can range from tiny particles to large molecules, primarily polymers. The connections between these solid parts can be chemical bonds or physical interactions, defining whether the gel is categorized as chemical or physical. Luliconazole, a medication used to combat fungal infections, works by inhibiting the synthesis of ergosterol, a crucial component of fungal cell membranes. This inhibition causes the fungal cells to lose integrity and eventually die.

Classification of Gel: Gels are classified into various categories based on their ingredients, the type of liquid used, their behaviour, and physical properties.

1. **Types based on the liquid used**:
    - Hydrogels primarily use water as the liquid medium. Examples include bentonite, cellulose derivatives, and synthetic poloxamer gels.
    - Organogels are semi-solid gels where an oily liquid is trapped within the structure through specific compound interactions.
    - Xerogels are solid gels with minimal liquid content. They are created by removing the liquid, leaving a gel structure that can re-swell upon contact with fluid.
2. **Types based on ingredients**:
    - Inorganic gels have distinct phases that determine their structure and properties.
    - Single-phase system gels involve large organic molecules dissolved in a continuous phase.
3. **Types based on behaviour**:
    - Gels typically exhibit non-flowing behaviour like water and can be:
        - Plastic gels, behaving like Bingham bodies or suspensions with a yield value.
        - Pseudoplastic gels, changing viscosity under pressure.

- Thixotropic gels, whose viscosity decreases over time when agitated.

4. **Types based on physical properties**:
    - Elastic gels, such as agar, guar gum, and alginates, can return to their original shape due to weak bonds.
    - Rigid gels have a strong structure, comparable to colloid or silicic acid gels.

Formation of Gels: Gels are typically manufactured at room temperature in factories, although certain polymers, both synthetic and natural, may require additional processing steps before gel formation. Various methods are employed to create gels, including temperature adjustments, particle flocculation, and chemical reactions.

Luliconazole: Luliconazole belongs to the imidazole class of antifungal medications known for its efficacy against various fungi, especially dermatophytes responsible for skin infections. This review focuses on the pharmacodynamics of luliconazole when applied topically, discussing its mechanism of action in treating fungal infections.

Clinical Studies: Clinical studies have evaluated the efficacy of luliconazole in treating cutaneous dermatophyte infections. In a study comparing 1% luliconazole cream applied once daily for two weeks with 1% bifonazole cream applied daily for four weeks in tinea pedis patients, 489 participants were involved. The results showed comparable clinical effectiveness between the two treatments after four weeks, with approximately 91.5% of patients in the luliconazole group and 91.7% in the bifonazole group demonstrating at least moderate improvement. Both treatments also showed similar efficacy in achieving negative results in KOH microscopy. Regarding mycologic cure (negative culture), luliconazole cream exhibited superior efficacy compared to bifonazole, with 73% of patients treated with luliconazole showing negative cultures versus 50% in the bifonazole group. Another study assessed different strengths of luliconazole cream (1%, 0.5%, and 0.1%) applied once daily for two weeks in 213 tinea pedis patients.

Mechanism of Action of Luliconazole: Luliconazole, an imidazole derivative with potent antifungal activity, incorporates into the fungal cell membrane by inhibiting lanosterol demethylase. This enzyme is crucial for ergosterol synthesis, a key component of fungal cell membranes. By disrupting ergosterol production, luliconazole inhibits fungal growth, leading to the reduction and eventual elimination of fungal infections.

Microsponge Method: The microsponge delivery system employs tiny porous microspheres resembling sponges, designed for controlled and targeted drug delivery. These microspheres feature a large porous surface that enables gradual drug release onto the skin's epidermis. This innovative method enhances drug efficacy while minimizing adverse effects and optimizing cost-effectiveness in drug delivery systems. Microsponges are composed of microscopic polymer-based spheres with micropores (10-25 µm in diameter), capable of encapsulating a wide range of active substances.

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Microsponge technology not only enhances drug stability and formulation flexibility but also reduces irritability and allergenicity. It is widely applicable in cosmetics, skincare products, sunscreens, and clinical care formulations due to its non-irritating, non-allergenic, and self-sterilizing properties. This approach is particularly advantageous for controlled release and targeted delivery, ensuring drugs remain localize in skin cells or tissues, thereby minimizing systemic exposure and associated side effects.

Formulation:

Sr. No.	Ingredients	MSG1	MSG2	MSG3	MSG4
1	MS eq.to (%)	1	1	1	1
2	Carbopol 971 (%)	0.5	1	1.5	1.5
3	Triethanolamine (ml)	1	2	2.5	3
4	Water (ml)	100	100	100	100

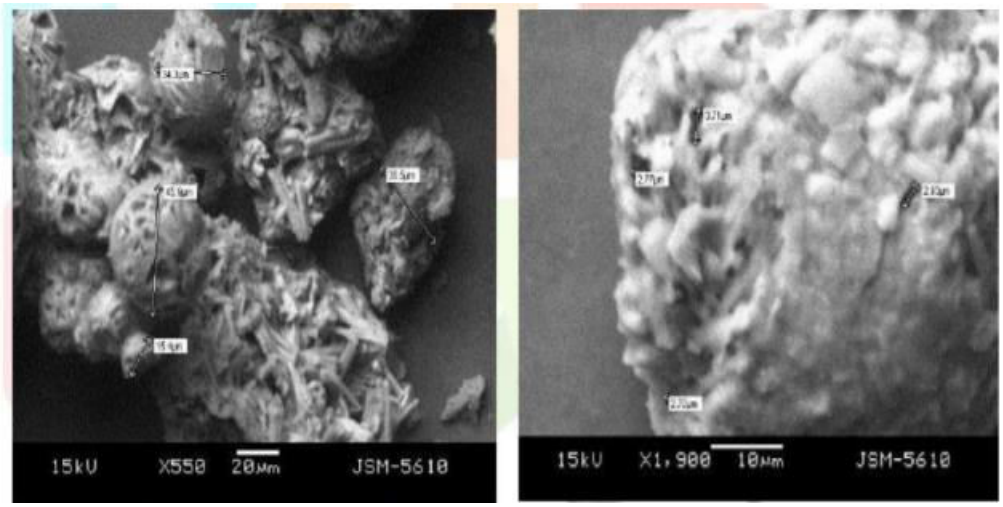

Figure 3: Morphological Structure Determination

•Determination of Porosity Parameter

Sr. no.	Parameters	Observation
1	Total cumulative volume (cc/g)	0.2284
2	Total specific surface area (m^2/gm)	15.097
3	3. Average pore diameter (µ)	0.3431
4	Total porosity (%)	13.162
5	Bulk density (g/cm^3)	0.5761
6	Apparant density (g/cm^3)	0.6635

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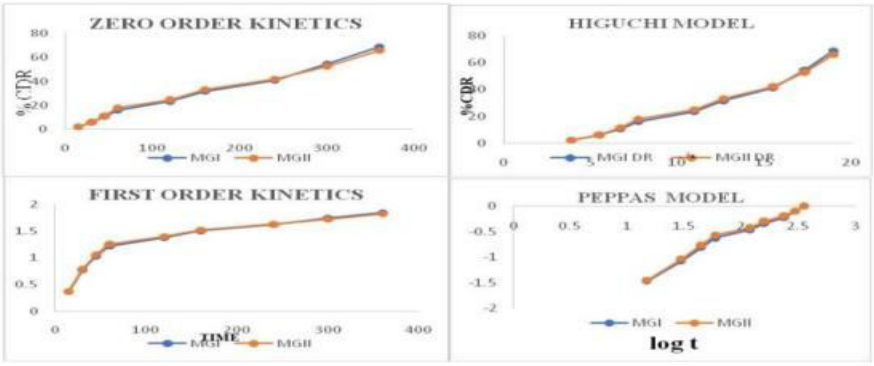

Figure 4: Model Kinetics of Microsponge gels MGI & MGH

In-Vitro Drug Release:

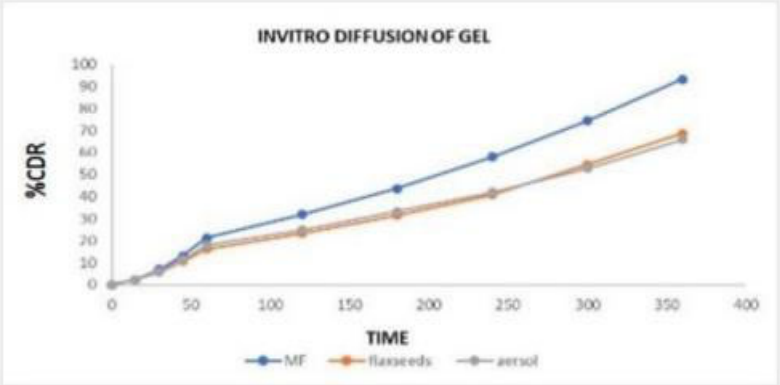

Figure 5: In-vitro drug release

Conclusion:

This study conclusively demonstrates that increasing the ratio of drug to polymer enhances the yield and entrapment efficiency of microsponges containing ethyl cellulose. The research underscores the superior performance of microsponges in topical formulations, especially when combined with ethyl cellulose polymer. This combination facilitates controlled drug release over 12 hours, following zero-order kinetics, which is ideal for treating fungal infections. For optimal efficacy, a combination of polymers such as ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) can be recommended for formulating luliconazole (LCZ) microsponges for topical application.

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