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Formulation & Evaluation of Microsponge Loaded Emulgel Form for Current use of Luliconazole

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ABSTRACT:
The Main aim of the review is to do the detail study regarding the topical delivery of the luliconazole drug by using the microsponge method to increase the efficacy of the drug. It includes the detail study of the Gel, Types of gel & different types of skin derma layers & the mechanism of action of the drug on the infected part. It also includes the detail study regarding the fungal infection. Microsponge containing Luliconazole (API) with different proportion of drug polymer were obtained efficiently using Quasi-emulsion solvent diffusion method this helps to minimise the side effects ,reduce the skin secretions and to get better action in the minimum dose and ultimately the drug delivery system. Qausi-emulsion solvent diffusion method was used with the different of polymers such as HPMC, Polyvinyl Ethyl cellulose and other.

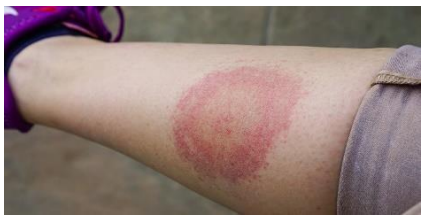
Key Words: Microsponge, polymer, Quasi emulsion, drug delivery.

I. INTRODUCTION:

Microsponges are the microscopic spherical, sponge like structures analyzed by mercury intrusion porosimetry method which control the release of the drug to the skin by the tropical preparations and thereby reducing the oily layers and shine from the skin.these are usually used to exert the prolonged drug action by regulating it's secretion in the minimal amount of the dose.the main aim of these microsponge application is to enhance the stability and diminishing the side effects of the drug. In this review article we have to study Microsponges of LCZ were formulated by utilizing Ethyl Cellulose as a control discharge polymer.

Fungal Infection :

When the body's defence system is weakened or when there's a high concentration of harmful microorganisms, an infection can occur. Most of the time, infections go unnoticed but sometimes they trigger a response from the body, causing visible signs and symptoms, which we call infectious diseases. These diseases can be caused by various agents like bacteria, viruses, parasites, fungi, and others. In the past, bacterial infections were the most feared, but as treatments improved, fungal infections became more dangerous, especially for patients with weakened immune systems.



Fungi, including yeasts and molds are opportunistic pathogens, meaning they only cause infection when the body's natural defences are weakened. Factors like aggressive medical treatments make it easier for fungi to invade the body. Fungal infections are now among the top causes of illness in intensive care units, and they're often difficult to detect because their symptoms aren't always obvious.

So why are fungi such formidable foes for seriously ill patients Despite their roles in making bread rise or fermenting beverages, fungi are fundamentally decomposers. They thrive on decaying organic matter, including human bodies. Once triggered by signals of decay, fungi grow relentlessly, even in the face of medical

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interventions meant to prolong life. In fact, some treatments can inadvertently aid fungal growth by further compromising the immune system.

In essence, fungi are unique infective agents, and understanding their behaviour is crucial in combating fungal infections in medical settings.

Pathophysiology Of Fungal Infection :

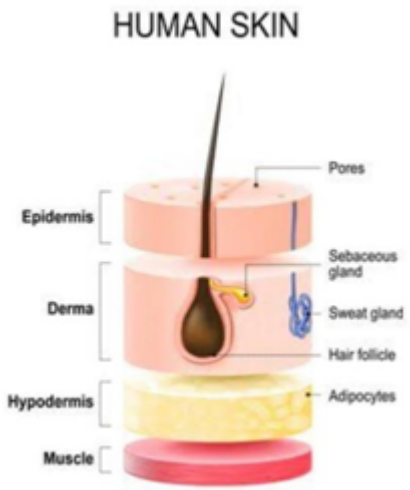
Only a few types of fungi are really strong enough to cause harm to healthy individuals. Usually, they're not much of a threat unless they come into contact with someone whose immune system isn't working well, which gives the fungi a chance to get inside the body.

Normally, the layers in our gut protect us from invaders, and the respiratory system's defences keep out fungal cells and spores. But if there's damaged tissue, it can create a good environment for an infection to start. Because of all these things, fungal infections that get serious are often seen as opportunistic, meaning they take advantage of weakened defences. Recently, some researchers have suggested that genetic differences in certain immune response genes could affect how susceptible people are to invasive fungal infections. These genes might affect things like IL-10 production, Toll-like receptor variations, plasminogen gene differences, and so on. These findings are interesting, but currently, the most significant risk factor for these infections seems to be severe damage to one or more parts of the immune system. When the body's natural defense systems are weakened due to treatment, like in the case of hematological malignancies, it becomes easier for invasive fungal infections to occur.

Skin :

The skin is a vital organ, making up about 16% of our body weight and serving as the body's largest organ. Since it wraps around the entire body, it's crucial for all surgeons to grasp its fundamental physiology. Additionally, the skin is connected to the membranes lining body openings and includes extra features like glands, hair follicles, and nails in specific regions.

Physiology of Skin :



Gel :

In simpler terms, a gel is like a sponge made of two parts that are connected in a three-dimensional way. This spongey structure is made up of solid materials mixed with a lot of liquid, creating a sort of firm mesh that traps the liquid inside. The solid parts can be tiny particles or large molecules, mostly polymers. These solid parts are linked together either by chemical bonds or physical connections, which determines if the gel is a chemical or physical type. Luliconazole is a type of medicine that fights fungal infections by stopping the fungus from making a key component of its cell membrane called ergosterol. Without this component, the fungus's cells become leaky and die.

Classification of Gel :

Gels can be sorted into different groups based on their ingredients, the liquid used, how they behave, and their physical properties.

1. **Types based on the liquid used:**

- Hydrogels are made with water as the main liquid. Examples include bentonite, cellulose derivatives, and synthetic poloxamer gel.
- Organogels are like semi-solid gels made with an oily liquid trapped inside. The structure is formed by the interaction of certain compounds.
- Xerogels are solid gels with very little liquid. They're made by removing the liquid, leaving behind the gel structure, which can swell again when in contact with fluid.

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. **Types based on the ingredients:**

- Inorganic gels have two phases, determining their structure and properties.
- Single-phase system gels contain large organic molecules dissolved in a continuous phase.

. **Types based on how they behave:**

- Gels usually don't flow like water. They can be:
- Plastic gels which behave like Bingham bodies or suspensions with a yield value.
- Pseudoplastic gels which can change viscosity when pressure is applied.
- Thixotropic gels whose viscosity decreases over time when stirred.

. **Types based on physical properties:**

- Elastic gels like agar, guar gum, and alginates can bounce back to their original shape. They're held together by weak bonds.
- Rigid gels have a strong structure, like colloid or silic acid gels.

Formation Of Gels :

Gels are typically made in factories at room temperature, but some types of polymers, like synthetic and natural ones, require extra steps before they can be made into gels. There are several methods for making gels, including:

1. Using changes in temperature.
2. Causing particles to clump together (flocculation).
3. Using chemical processes or reactions.

Luliconazole :

Luliconazole is a type of antifungal medication belonging to the imidazole class. It's known for being effective against different types of fungi, particularly dermatophytes which cause skin infections. This review is based on evidence and discusses how luliconazole works in the body (pharmacodynamics) when applied topically, as well as its role in treating fungal infections.

Clinical Studies :

Luliconazole in treating cutaneous dermatophyte infections based on various clinical studies. In one study, the effectiveness of 1% luliconazole cream applied once daily for two weeks was compared to 1% bifonazole cream applied once daily for four weeks in patients with tinea pedis. The study included 489 patients and found comparable clinical efficacy between the two groups after four weeks of treatment, with around 91.5% of patients in the luliconazole group and 91.7% in the bifonazole group showing at least moderate improvement. Both medications also showed comparable efficacy in achieving negative results in KOH microscopy.In terms of mycologic cure (negative culture), luliconazole cream demonstrated higher efficacy compared to bifonazole, with 73% of patients treated with luliconazole showing negative cultures compared to 50% of patients treated with bifonazole.Another study tested different strengths of luliconazole cream (1%, 0.5%, and 0.1%) applied once daily for two weeks in 213 patients with tinea pedis.

Mechanism Of Action Of Luliconazole :

As previously mentioned,LCZ is an imidazole having antifungal activity and has a structure of combination of imidazole incorporated into the ketene dithioacetate which acts as more potent for giving the desired clinical outcomes.

The exact mechanism of LCZ in not known till now.It is considered to be act by inhibiting the enzyme lanosterol demethylase. Which is needed for the synthesis of ergosterol, a major component of the fungus cell membranes. Since the production of major component of the fungal cell membrane get depressed the fungal growth and hence the overall fungal infectious activity will get diminished and eventually infection get cured in such way.

Microsponge Method :

The microsponge is a clever way of delivering drugs, made up of tiny porous microspheres that resemble sponges. These spheres have a large porous surface, allowing for controlled release and targeted delivery of drugs. It's a newer method that's gaining traction because it optimizes drug efficacy and cost-effectiveness. In the world of drug delivery systems, many methods are being explored, but microsponge delivery systems (MDS) stand out for their ability to release drugs slowly onto the skin's outer layer (epidermis). These drug-loaded microsponges are small beads with micropores, about 10-25 µm in diameter, which can hold a wide range of active agents. They're essentially microscopic, polymer-based spheres that can trap various substances.

Microsponge technology not only helps trap drugs, reducing their harmful effects, but also improves stability, smoothness, and formulation flexibility. Studies have shown that microsponges are non-irritating and non-allergenic, making them suitable for use in cosmetics, skincare, sunscreens,

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and clinical care products. They're even self-sterilizing and useful for oral drug delivery, bone, and tissue engineering.The main goal of microsponges is to minimize drug doses and side effects while enhancing stability. They're particularly popular for controlled release and targeted drug delivery, as they can stay in skin cells or tissues and prevent rapid release into the bloodstream, thus reducing side effects.

Microsponges also offer improved stability, reduced side effects, and enhanced formulation flexibility.Various studies have confirmed that microsponge systems are non-allergic, non-irritating, non-mutagenic, and non-toxic. This versatile method is now widely used in cosmetics, skincare, sunscreens, and clinical products.

Characteristics of Microsponge drug delivery system :

- Microsponges remain stable across a wide pH range, from 1.5 to 11.
- They can withstand temperatures up to 130°C without losing stability.
- Microsponges work well with many active therapeutic substances and other ingredients.
- The average pore size of microsponges is 25µ, eliminating the need for specific sterilization processes.
- Around 38 to 62% of drugs can be trapped within microsponges.
- Microsponges need to be fully mixable with a monomer or be able to mix well with the addition of a small amount of a water-immiscible solvent.
- They shouldn't react with monomers, and they shouldn't increase the viscosity of the mixture or formulation.
- Microsponges should remain stable when in contact with polymerization catalysts and during the polymerization process.

Advantages of Microsponges :

- Enhances the flexibility of the formulation.

Extends the drug release duration, allowing for continuous release for up to 12 hours.

- Microsponges are hypoallergenic.
- Improves patient compliance.
- Enables direct application of the drug to target organs or areas.
- Offers a higher drug loading capacity compared to other topical preparations.
- Demonstrates stability even at temperatures up to 130°C. Preparation Of Microsponges :

Methods :

There are two main methods for loading drugs into microsponges. One is a single-step process, which involves liquid-liquid suspension polymerization. The other is a two-step process called the quasi-emulsion solvent diffusion method. These methods rely on the specific characteristics of the drug being used. If the drug is typically an inert, non-polar substance, it will help create a porous structure within the microsponge, acting as what's called a porogen. Porogen drugs don't interfere with the polymerization process or get activated by it, and they remain stable to free radicals. These porogen drugs are captured within the microsponge using the one-step process.

1. Liquid-liquid suspension polymerization :

First the building blocks (called monomers) are mixed with active ingredients in a liquid solvent. Then, this mixture is stirred into a watery solution with additives like surfactants and dispersants to help spread everything evenly. Once the mixture forms tiny droplets of the right size, we start the process of turning those droplets into solid particles by triggering the monomers to link up using either a catalyst, heat, or light. As this linking process happens, it forms a round structure with lots of tiny holes inside, kind of like a sponge. These structures clump together, forming a network of connected spaces inside. After the process is done, we clean the solid particles and store them for later use.

. Quasi Emulsion Technique :

When the drug is sensitive they uses a two-step process. Basically, they dissolve the drug along with a different substance called a polymer in a liquid (inner phase).

Then, they pour this mixture into another liquid called polyvinyl alcohol (outer phase) whil,. the inner phase is processed for by ultra sonication or probe sonication technique at certain temperature for dissolving. Then this inner phase is poured into external organic phase to get rid of the first liquid with stirring at 500 rpm for an hour so that microsponges will get obtain after filtration.these microsponges are then dried at 40°C in a hot air oven for 12-24 hrs this step will entrap the API into the microsponges which is the main purpose of this formulation to give the desired outcomes.

[Probe sonication is the nanotechnology for dispersing the nanoparticles evenly in the medium.]

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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

Preparation method:

- **Gel -:**

Corbapol 971 is scattered into the water with medium agitation , 1% w/w LCZ microspnge is added into it and the pH is maintained to neutral by using triethanolamine until the gel shape is formed.thenPlane medication gel was set up By utilizing drug in that capacity without fused in microsponges in the gel base .

- **Evaluation of gel :**

-Brookfield computerized viscometer and texture profile analysis is done to evaluate the physical parameters.
This is carried out by using Franz Diffusion Cell.

- **Determination of drug dose -:**

-1 gm of microsponge loaded in gel is taken and then make up the volume upto 100 ml with methanol solution is weaken in such a way and then absorbance is checked at 296 nm
utilizing Shimadzu-1650 UV spectrophotometer, for the determination of drug content.
-In vitro drug release is observed.

- **Evaluation of the formulated preparation:**
- IR spectroscopy analysis.

It is done by FTIR spectrophotometer.The pure medication and polymers only are utilized in this study.The FTIR spectroscopy and phantom investigation is done on the theory paraffin oil film in th range of 4000 to 4000 cm^{-1}

•Differential Scanning Calorimetry.
The unadulterated medication under test is weighed and warmed in a shut punctured
aluminium container at 100C/min scanning rate and between 300 and 3000C and 40 ml/min of nitrogen stream by using DSC.

•Drug –Excipients Compatibility Study and Determination of the Effect of Drug/Polymer Ratio (table)
According to practical studies,it is observed that increiin the drug : polymer ratio shows increment in the production yield, entrapment efficiency and drug content.

Morphology and Particle Size Analysis of Microsponges.
The resultant microsponges are observed under SEM and analysed as spherical and porus.after this the microsponges containg drug is compared with the formulation containing drug only and the result shows that drug containing microsponges is bulging indicating that the drug is fully incorporated into the MS.

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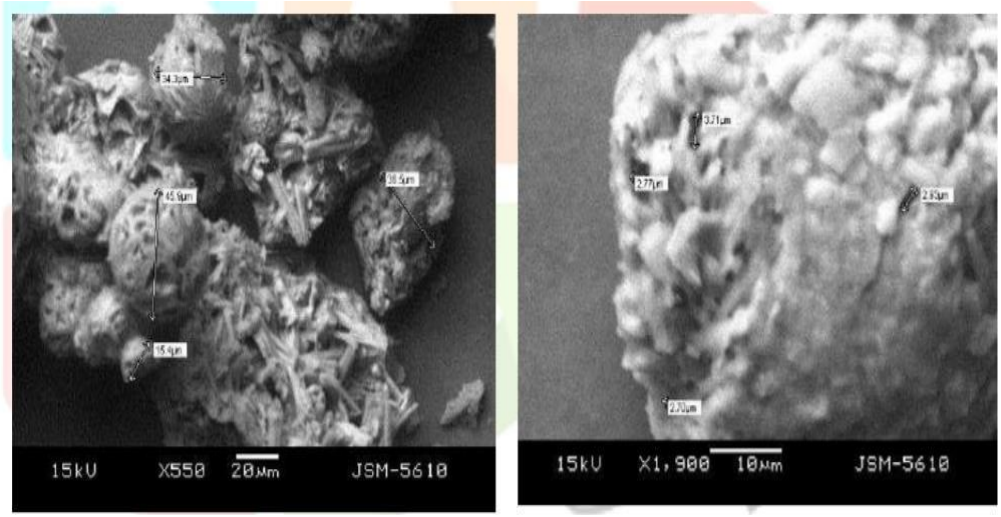

•Determination of Porosity Parameter.

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

Different porosity parameters such as % Porosity, Average pore diameter, total cumulative value, mass and apparent density are determined by mercury intrusion porosimetry and the resultant data is tabulated as shown above.

- **Kinetics of drug release.**

It is carried out by using first order kinetics, second order kinetics and Higuchi's equation.
The graph clearly shows that zero order kinetics has the highest r^2(drug release)value .The kinetics of the drug release is hence determined here.

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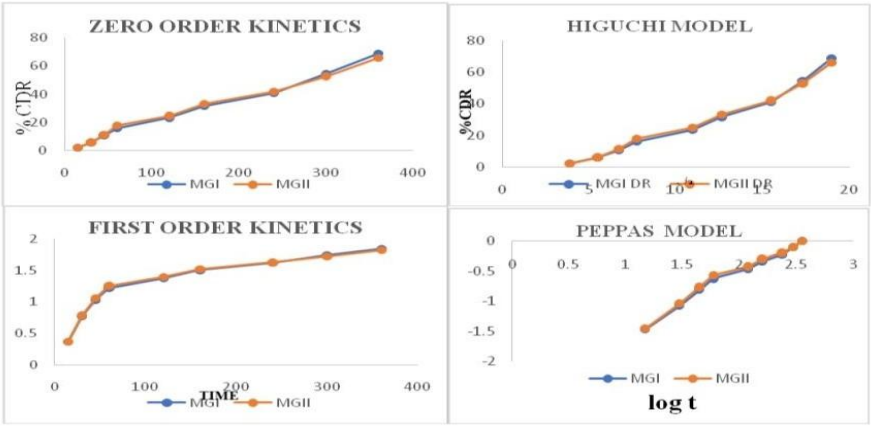
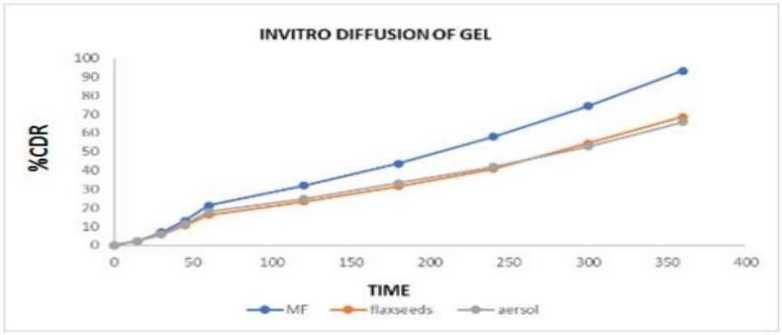


Fig. 17: Graph showing Zero order, Higuchi, first order and peppas model kinetics of microsponge gels MGI and MGII

- **In-Vitro Drug Release.:**



•Physical Parameters of Gel and Stability Analysis.

- Hardness- It is having moderate hardness value therefore exhibits good spreadability.

-pH - 6.7 to 6.8 which is suitable.

- **Another approach :**

The Polymer HPMC is also used widely in topical preparations as it is having properties like swelling, forming thik film on drying, cooling effect and gelling properties.Due to this it increases bioadhesion and thus drug delivery by enhancing the clinical outcome along with reduced side effects and low frequency of adminstration.

As I previously mentioned the formulation that is using LCZ and microsponges with polymer EC if we incorporate HPMC into this formulation we would get the synergistic effect of our preparation as both the polymers will exert their effect to its best to show the p'logical action.

The cause behind using only HPMC polymer rather than other existing polymers such as Eudragit RSPO ,PVA is explained by practical studies (FTIR spectrophotometer,SEM analysis , in vitro diffusion, physical parameters diffusion) of combination of EC with other polymers which gives better effect in comparison to other combinations.

-For the final evaluation of this microsponge preparation ,the controlled formulation (i. e. HPMC + EC in a measured quantity) was incorporated into the gel base [F1] and is compared with the marketed preparation.

And it is found that F1 preparation is more efficient in production yield, antifungal activity, drug release kinetics than marketed preparation.

II. CONCLUSION :

It is practically determined that, increase in the drug : polymer ratio shows increased production of yield, entrapment efficiency of microsponges with ethyl cellulose.

On the basis of this research article it shows that microsponges itself exhibit a way better action when used in the tropical preparations and in

it is used along with the polymer, especially ethyl cellulose found to be the best for controlled release of drug for 12 hrs and followed zero order kinetics which is used to treat fungal infections.
For best activity the combination of polymers EC and HPMC can be used into the LCZ microsponge containing topical application.

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