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Utilizing Microsponge Technology in Topical Drug Delivery Systems

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ABSTRACT

Microsponges are tiny, sponge-like spheres used in drug delivery. These microscopic carriers hold and release medication into the skin over time. This system offers several advantages, including controlled release with reduced irritation, improved stability against heat, light, and chemical breakdown. The main goal of any drug delivery system is to safely deliver the right amount of medication to the bloodstream or target tissue for an extended period. This review explores various methods for designing microsponge drug delivery systems. It also highlights the benefits of this approach compared to traditional methods. With ongoing advancements in drug delivery, microsponges offer a promising approach with reduced side effects, enhanced stability, improved aesthetics, and greater formulation flexibility. Studies have confirmed that microsponge systems are non-irritating, non-mutagenic, non-allergenic, and safe for use. Currently, this technology is being utilized in cosmetics, over-the-counter skincare products, sunscreens, and even prescription medications.

INTRODUCTION

A Microsponges Delivery System (MDS) represents a breakthrough in skincare technology, featuring intricately designed, permeable polymeric microspheres within a protective, highly interconnected framework. Ranging from 10 to 25 microns in size, these miniature sponge-like polymers have the remarkable ability to encapsulate a diverse array of active ingredients, gradually releasing them into the skin over time or in response to specific triggers. This innovative system offers numerous advantages, including enhanced product effectiveness, gentleness, tolerability, and prolonged efficacy across a wide range of skincare treatments.(1-2)

While traditional transdermal delivery systems (TDS) have been successful in enhancing the efficacy and safety of various medications by utilizing the skin as a gateway for systemic absorption, they are not suitable for delivering

substances whose primary target is the skin itself. Consequently, there is a pressing need for a delivery system that maximizes the duration of active ingredient presence on the skin surface or within the epidermis while minimizing their systemic absorption. The MDS addresses this need by providing a tailored solution for targeted skincare applications, promising superior performance and safety profiles.(3)

The groundbreaking microsponge technology was pioneered by Won in 1987, with the initial patents being assigned to Advanced Polymer Systems, Inc. This company spearheaded the development of numerous iterations of the system, which have found applications in both therapeutic and over-the-counter (OTC) as well as prescription drug products. Currently, this innovative technology has been licensed to Cardinal Health, Inc., for incorporation into effective products.(4)

The scanning electron microscopy of the microsponge molecule reveals its internal structure resembling a "pack of marbles," with porosity resulting from the interstitial spaces between these marbles. These interstitial pores have the capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, anti-infective, and anti-inflammatory agents. These entrapped microsponges can then be incorporated or formulated into various product forms, including creams, lotions, powders, cleansers, capsules, and tablets. Upon application of these products, the entrapped material is delivered to the skin in a controlled time-release pattern or a pre-programmed manner utilizing various triggers such as rubbing or pressing the microsponge after it has been applied to the skin. This action elevates the skin surface temperature, thereby exposing solvents for the entrapped materials such as water, alcohol, or even sweat, while controlling the rate of evaporation. Active ingredients entrapped within the porous polymeric structure exhibit modified behavior concerning their delivery, characterized by restriction and prolonged release. (5-6)

POTENTIAL FEATURES OR CHARACTERISTIC OF MICROSPONGE DRUG DELIVERY SYSTEMS [7]

1. Microsponges demonstrate satisfactory stability across a wide pH range from 1 to 11 and at high temperatures (up to 130°C).
2. Microsponges exhibit significant similarity with various carriers and ingredients.
3. Microsponges possess high entrapment efficiency, reaching up to 50 to 60%.Microsponges are characterized by their free-flowing properties.
4. The average pore size of microsponges is small (0.25 μm), serving as a method to prevent the ingress of microbes, thus obviating the need for cleansing or additional preservatives.
5. Microsponges are non-allergenic, non-irritating, non-mutagenic, and non-toxic.
6. Microsponges can absorb oil up to several times their own weight without losing their structural integrity.

ADVANTAGES OF MICROSPONGE DRUG DELIVERY SYSTEM [8,9]

- Microcapsules often lack the ability to precisely regulate the release rate of active pharmaceutical ingredients (APIs). Upon rupture of the barrier, the API enclosed within the microcapsules is released. The question arises: Can MDS (Microsponge Delivery System) achieve this control.
- Liposomes suffer from drawbacks such as lower payload capacity, complex formulation, limited chemical stability, and susceptibility to microbial degradation. Are MDS capable of offering a broad range of chemical stability and ease of formulation
- MDS exhibit stability across a pH range of 1-11 and can withstand temperatures up to 130°C. They boast a payload capacity of up to 50-60%. Additionally, they are characterized by their free-flowing nature and cost-effectiveness. Microsponges, being small spheres capable of absorbing skin secretions, contribute to reducing skin oiliness and shine
- Improved product efficacy
- Prolonged drug delivery.
- Reduced irritation leading to improved patient adherence.
- Enhanced product sophistication.

- Enhanced oil absorption capability, able to absorb oil up to six times its weight without causing dryness
- Enhances effectiveness in treatment.Achieve prompt confirmation of cure or control.
- Advance the management of the condition.
- Enhance the bioavailability of existing medications
- Versatility to promote the creation of new product configurations.
- Non-irritating, non-mutagenic, non-allergenic, and non-toxic.
- Enhances stability, thermal, physical, and chemical security.
- Allows for the combination of immiscible items.
- Enhances material processing, such as transforming liquids into powders.

APPLICATION OF MICROSPONGE [10,11]

Microsponge delivery systems are employed to enhance the safety, efficacy, and aesthetic appeal of topical medications, over-the-counter products, and personal care items. Products under development or already in the market utilize topical microsponge systems in three primary ways:

1. Serving as reservoirs for gradual release of active ingredients over an extended period,
2. Acting as reservoirs for sequestering undesirable substances, such as excess skin oils, or
3. Functioning as closed compartments to retain ingredients on the skin for surface-level action.

Delivering active ingredients from conventional topical formulations over an extended period is challenging. Cosmetics and skincare solutions are typically designed to act superficially on the skin's outer layers. In traditional products, the active ingredient is often present in a relatively high concentration and can be rapidly absorbed upon application, leading to potential overmedication followed by a period of under-medication until the next application. This can result in adverse effects such as rashes and more serious complications when the active ingredients penetrate rapidly below the skin's surface.

Microsponge technology aims to address this issue by enabling a prolonged release of active ingredients, thereby potentially reducing the occurrence of adverse effects while maintaining therapeutic efficacy. Microsponges are porous, polymeric microspheres primarily utilized for topical application and more recently for oral administration. They are designed to efficiently deliver a drug's active ingredient at a minimal dose, as well as to enhance stability, reduce side effects, and modulate drug release.

Category	Description
Anti-acne	Maintaining effectiveness while minimizing skin irritation.
Anti-inflammatory	Providing long-lasting relief with decreased skin allergic reactions and dermatoses.
Anti-fungals	Ensuring sustained release of active ingredients.
Anti-dandruffs	Reducing unpleasant odor while enhancing safety and efficacy.
Antipruritics	Extending and improving relief from itching sensations.
Sunscreens	Ensuring reliable effectiveness, with enhanced protection against sunburns and related injuries, even at higher concentrations, while minimizing irritation.
Skin depigmenting agents	Offering improved protection against oxidation with increased effectiveness and a less oily texture.
Rubefacients	Providing prolonged relief with decreased irritation, greasiness, and odor.

Table 1 : Application of microsponge

COMPOSITION OF MICROSPONGE

Various polymers are utilized in the manufacture of microsponges to facilitate effective application, resulting in the formation of a microsponge 'cage'. According to published literature, polymers investigated thus far include polymethacrylates or Eudragit© polymers (such as Eudragit RS100, Eudragit RSPO, and Eudragit S100), polylactide-co-

glycolic acid, polylactic acid, polydivinyl benzene, polyhydroxy butyrate, and ethyl cellulose. Among these, Eudragit RS100 is the most extensively studied polymer due to its versatile nature. (12)

The wide range of Eudragit polymers, varying in control, solubility, and water permeability, allows for highly tailored delivery characteristics in this system, providing a wide range of options to achieve the desired performance. Polymers belonging to the polymethacrylate class are FDA-approved, safe, non-toxic, and cost-effective excipients commonly used in the pharmaceutical industry. The ability to combine different polymethacrylate polymers offers improved control over drug release behavior, particularly due to drug-methacrylate-polymer interactions. Ethyl cellulose, as a fundamental material for microsponges, is also employed in their design due to its non-irritating, non-toxic, and non-allergenic nature.(13)

Additionally, polydivinyl benzene has been reported for the production of porous microspheres through liquid suspension polymerization. While several polymers have been explored recently, only a few studies have reported the use of biodegradable polymers. These biodegradable polymers have the potential to serve as excipients for the development of microsponge carriers for drug targeting, highlighting the strong need to investigate biodegradable polymers for this delivery system. Furthermore, the choice of polymer should take into account the potential for skin irritation and dermal toxicity, which is a significant concern in dermatological formulations and has been addressed by several groups of researchers working in the field of microsponge-based delivery systems.(14)

Properties of the actives for the entrapment into microsponges

1. It should either be fully miscible in a monomer or capable of being made miscible by the addition of a small amount of a water-immiscible solvent.
2. It should be water-immiscible or at most only marginally soluble.
3. It should be inert to monomers and should not alter the viscosity of the mixture during formulation.
4. It should remain stable when in contact with the polymerization catalyst and under conditions of polymerization

The circular construction of the microsponges ought not to fall.(15)

Microsponges can be engineered to release specific amounts of active ingredients over time in response to one or more external stimuli

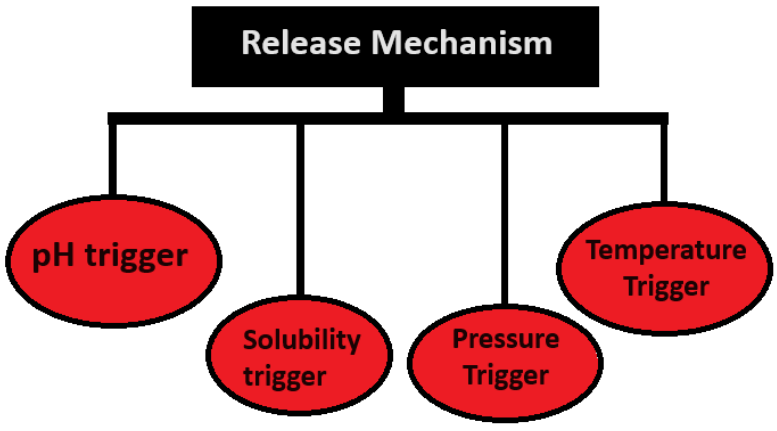

Figure 1: Release mechanism of microsponge triggered systems

i) **Pressure:** Application of rubbing or strain can release active ingredients from the microsponge onto the skin surface.

ii) **Solubility**: Microsponges containing water-soluble ingredients, such as anti-precipitants, release their contents in the presence of water. Release can also be triggered by diffusion, considering the partition coefficient of the ingredient between the microsponge and the external environment.

iii) **Temperature change**: Some complex active ingredients may be too viscous at room temperature to flow readily from the microsponge onto the skin. Increased skin temperature can result in enhanced flow rate and subsequent release. The drug release from the skin semi-solid formulation can be investigated using Franz-type static diffusion cells.

pH activation: Initiating the pH-dependent release of the active ingredient can be achieved by modifying the coating on the microsponge. This has various applications in drug delivery.(16)

Fungal infections: Typically, humans coexist peacefully with the microorganisms surrounding them, and it's only when the immune system is compromised or the concentration of microbes reaches a particularly high density that an infection may occur. While most infections go unnoticed, sometimes the infecting agents elicit a response from the body, leading to clinically observable signs and symptoms, a condition known as infectious disease. Various microorganisms such as bacteria, viruses, parasites, fungi, prions, worms, and 207elminthes have all been implicated in infectious diseases, with common viruses being the most frequent culprits and, until recent years, bacteria being the most feared. As strategies for controlling bacterial infections in patients improved, fungi became the most dangerous microorganisms. Yeasts and molds now rank among the top 10 most frequently isolated organisms among patients in Intensive Care Units. About 7% of all febrile episodes occurring during neutropenia can be attributed definitively to invasive fungal infections. Candida has become the fourth most common bloodstream isolate in hospitals in the USA, surpassing many traditionally notorious bacterial pathogens. Since the 1980s, an increased incidence of invasive fungal infections in patients who are not in the end stage of their underlying illness has been observed. Furthermore, due to the universally low autopsy rate, their incidence is likely underestimated because signs and symptoms are rarely characteristic, leading to many invasive fungal infections going undetected while the patient is alive.(17)

Mycology: Parasites are significant organisms and constitute a distinct realm for classification purposes. Eukaryotes, fungi possess a membrane enclosing their nucleus, their cells are significantly larger than microorganisms, and their molecular processes closely resemble those of plants and animals. However, unlike mammalian cells, fungi almost always feature a rigid cell wall composed of chitin products surrounding their plasma membrane. Fungi are vegetative organisms and are not classified as plants because they do not produce chlorophyll. They are non-motile entities, and their fundamental structural unit consists of either a chain of cylindrical cells (hyphae) or a unicellular structure, or both. Common species such as Aspergillus and Candida are ubiquitous worldwide, being found in gardens, playgrounds, houses, hotels, hospitals, and even on the skin and mucous membranes, where they have been identified as sources of potentially dangerous infections(18)

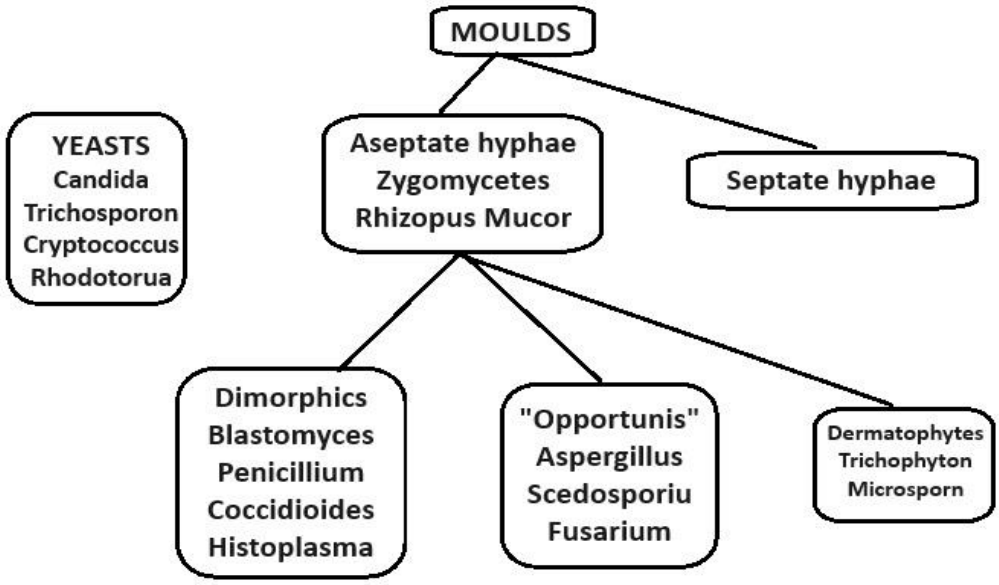

Figure 2: Classification of fungus

Pathophysiology of fungal infections: A few fungal pathogens that are harmful to humans can infect a healthy host. However, most fungi are relatively harmless unless they encounter an immune-compromised patient, where a weakened immune system allows them to invade the body. Under normal circumstances, the intact epithelial surfaces of the gastrointestinal tract prevent invasion by microorganisms, and the mucociliary barrier of the respiratory tract prevents the entry of fungal cells and spores. Conversely, dead or damaged tissue may become a conducive environment for infection. Therefore, invasive fungal infections must be classified among the typically insidious infections.(19)

Method of preparation of microsponges:

Microsponges can be formulated using either a one-step process or a two-step process, which are discussed in liquid-liquid suspension polymerization and the quasi-emulsion solvent diffusion method, respectively. These methods are based on the physicochemical properties of the drug.

1) **Liquid-liquid suspension polymerization**: In this method, a solution is prepared containing monomers and the active ingredient, which are immiscible with water. This solution is then suspended with agitation in an aqueous phase, typically containing additives such as surfactants and dispersants, to form a suspension. Once the suspension is established with discrete beads of the desired size, polymerization is initiated by activating the monomers through catalysis, increasing temperature, or exposure to light. During the polymerization process, thousands of microsponge particles are formed, which are round in structure and interconnected with each other, resembling a cluster of grapes. Upon completion of polymerization, solid particles are recovered from the suspension. These particles are then washed and dried for further use.(20-21)

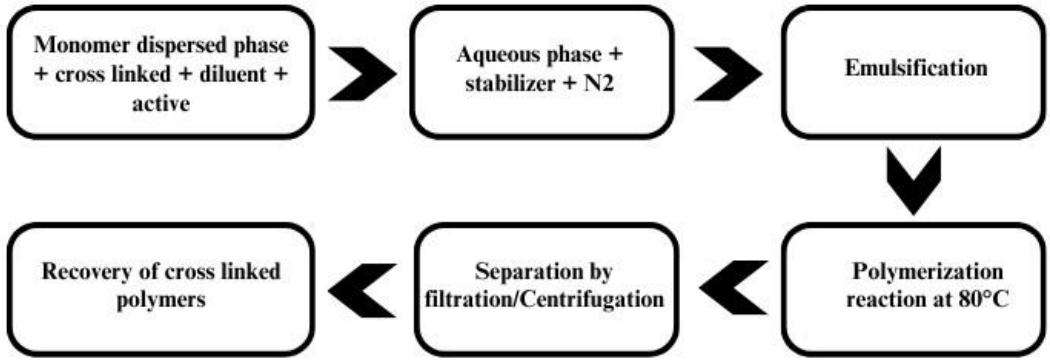

Figure 3 :- Liquid-liquid suspension polymerizarion

2) **Quasi-emulsion solvent diffusion**: This technique typically involves two stages: the first step is the preparation of the internal phase, and the second step is the formation of the external phase. It is commonly used for the preparation of oral and topical microsponges. In the internal organic phase, the polymer is dissolved in ethyl alcohol, and the drug is dissolved in this solution using ultrasonication at room temperature. The external phase consists of a polyvinyl alcohol (PVA) solution in water. The solutions are mixed and filtered for further use. The internal phase is then added dropwise into the external phase with the assistance of a mechanical stirrer. After mixing, semi-emulsion droplets are formed, facilitating the evaporation of the organic solvent and producing solid microsponge particles. The pre-formed microsponges are filtered and dried in an oven for 12 hours.(22)

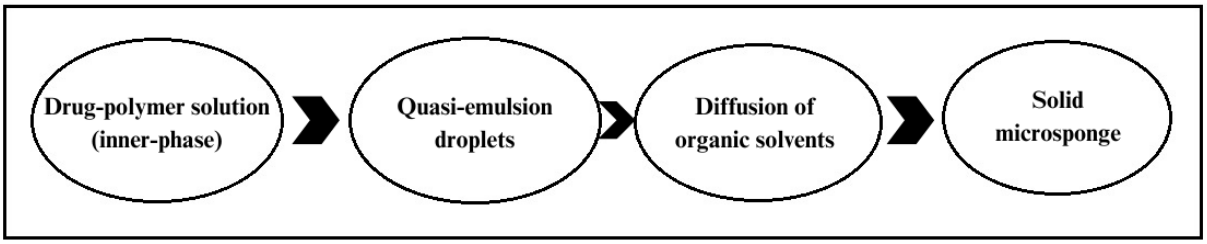

Figure 4 : Quasi-emulsion solvent method

MECHANISM OF ACTION:

To achieve the predetermined release rate of the active material from the matrix of the Microsponge particle, several parameters can be adjusted, considering the physical and chemical characteristics of the active agent and the environment. The vehicle in which the polymer resides plays a crucial role in determining the release rate of the active agent from the system. Initially, there is an equilibrium between the concentration of the active agent in the polymer and in the vehicle. As the skin depletes the concentration of the active agent from the vehicle. (23)

The Microsponge Delivery System (MDS) releases more active agent in response to the demand caused by the shift in equilibrium. This system achieves a continuous and steady release of active agent onto the skin. Furthermore, unlike conventional topical formulations, the MDS can act as a reservoir, continuously releasing active agent to the skin even after the vehicle has been absorbed by the skin or has dried out.(24)

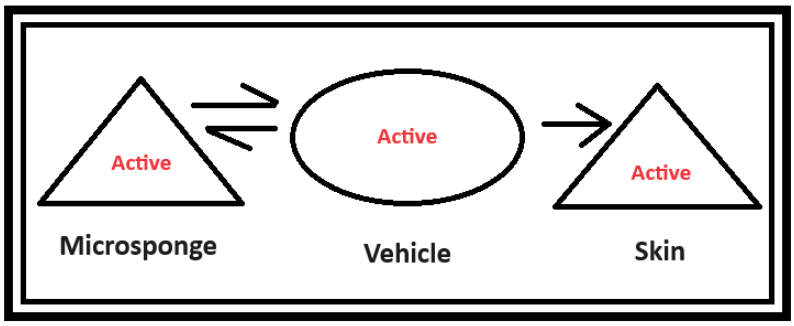

Figure 5 : Schematic representation of the distribution of the loaded material (active) on skin

EVALUATION OF MICROSPONGES [25,26,27]

Particle size and size distribution analysis: This determines the size and distribution of microsponge particles, which can affect their performance in drug delivery.

Drug content: This assesses the amount of drug present in the microsponges, ensuring that they meet the intended dosage requirements.

Entrapment efficiency: This measures the effectiveness of the microsponges in trapping and retaining the drug within their matrix.

Angle of repose: This evaluates the flow properties of the microsponge particles, which is important for their handling and processing.

Compressibility index and Hausner's ratio: These parameters assess the compressibility and flowability of the microsponges, providing insight into their physical characteristics.

Determination of density: Bulk density and tapped density measurements help to determine the density of the microsponges, which can influence their behavior during manufacturing and use

Production yield (PY) is calculated using the following formula:
Production yield (PY)=Practical mass of microsponge×100/Theoretical mass (Polymer + Drug)

This calculation determines the efficiency of the microsponge production process by comparing the actual mass of microsponges obtained to the theoretical mass that should have been produced based on the amount of polymer and drug used.

Scanning electron microscopy: The surface topography and morphology of the prepared microsponges were analyzed using a scanning electron microscope. Samples were mounted on a metal stub using double adhesive tape and coated with a platinum/palladium alloy under vacuum conditions to enhance conductivity and image quality.

Particle size analysis: Particle size analysis of the microsponges was conducted using a particle size analyzer. Prior to analysis, the prepared microsponges were dispersed in double distilled water to ensure that the light scattering signal fell within the sensitivity range of the instrument. The analysis was performed at room temperature, with the angle of detection set at 90 degrees.

Infrared spectroscopy: Infrared spectroscopy was carried out using a Fourier-transform infrared spectrophotometer with the KBr pellet method. This technique helps to identify functional groups and chemical bonds present in the microsponge samples.

Differential scanning calorimetry (DSC): Differential scanning calorimetry (DSC) is a vital technique for investigating interactions between the drug and excipients. Changes in the thermogram can indicate such interactions. The DSC analysis involved heating a powder sample of microsponges at a constant rate of 10°C per minute over a temperature range of 30°C to 300°C, under a nitrogen atmosphere with a flow rate of 20 ml/min.

EVALUATION OF MICROSPONGE-LOADED GEL FORMATION [28,29,30]

Appearance : The appearance of the gel, including clarity, color, and the presence of particles, is visually inspected. A transparent gel indicates proper dispersion of microsponges in the gel base.

pH : The pH of the gel formulation is measured by dissolving it in water and using a digital pH meter. This helps determine the acidity or alkalinity of the gel, which can impact its stability and skin compatibility.

Spreadability studies : Spreadability of the gel is assessed by placing it between two horizontal glass slides of standard dimensions. A weight is placed on top to ensure uniform spreading, and the time taken for the formulation to spread is measured. This parameter indicates the ease of application and uniform coverage on the skin.

Viscositry : The viscosity of the microsponge-loaded gel is determined using a Brookfield viscometer with specific settings. This measurement reflects the gel's resistance to flow and affects its consistency and ease of application.

Drug content : The amount of drug present in the gel formulation is quantified by extracting a known quantity of gel and analyzing it using UV spectrophotometry. This ensures that the intended dosage of the drug is present in the formulation.

In vitro release study of microsponge gel

Formulations was conducted using a modified Franz diffusion cell equipped with a Spectra Pore dialysis membrane with a molecular weight cutoff and an effective diffusion area of 3 cm. The release medium consisted of 100 ml acetate buffer at pH 4, supplemented with 1% sodium lauryl sulfate (SLS).

In the experimental setup, one gram of either gel or powder was placed onto the previously soaked dialysis membrane, which had been submerged overnight in the release medium. The receptor medium was stirred at 50 rpm and maintained at a temperature of 34°C to simulate physiological conditions.

At predetermined time intervals over a duration of 6 hours, 3 ml aliquots of the release medium were withdrawn and replaced with an equal volume of fresh medium to maintain sink conditions. Subsequently, the withdrawn samples were analyzed spectrophotometrically at a wavelength of 270 nm to measure the drug content and calculate the drug flux through the membrane.

To elucidate the mechanism of drug release from the microsponge gel, various mathematical models including zero order, first order, Higuchi, and Korsmeyer-Peppas models were applied to analyze the release profile. These models help in understanding the kinetics and mechanisms governing the release of the drug from the microsponge gel formulation over time(31)

In vitro

In vitro antifungal activity was assessed against Candida albicans using the disc diffusion method. Initially, 100 µL of a yeast suspension was spread evenly onto Sabouraud dextrose agar (SDA) plates, which were then allowed to cool and solidify. Subsequently, circular discs impregnated with 100 mg of microsponge gel, a commercial product, gel without the drug, and gel containing unencapsulated drug were placed on the agar surface. Control discs impregnated with solutions at a concentration of 50 mg/mL were also included. The plates were then incubated for 24 hours at 37°C, following which the diameter of the zone without fungal growth around each disc, indicating antifungal activity, was measured in millimeters.(32)

For the in vivo evaluation of therapeutic efficacy:

Animal Model: Adult Wistar rats weighing 280 ± 10 g, of both sexes, were utilized. These animals were housed in spacious, open polyacrylic cages at room temperature with a 12-hour light/12-hour dark cycle. They had access to water and standard rodent pellet diet ad libitum.

IN ACUTE TOXICITY TESTING

Female rodents were chosen as the subjects. The dorsal surface of each animal, measuring 2 x 2 cm, was cleared of hair using a hair remover and cleansed with alcohol. A designated area of 1 x 1 cm was demarcated for testing purposes. Subsequently, 0.5 g of a microsponge-enhanced gel was applied topically to the marked area of the animal's skin for the observation period, which lasted for 14 days. During this period, signs such as erythema and edema were carefully assessed and recorded.(33)

The evaluation of therapeutic efficacy involved the use of male rodents, which were divided into four groups: a normal control group (Group I), a Candida glabrata control group (Group II), a standard treatment group (Group III), and a group treated with microsponge-enhanced gel (Group IV). For Groups II to IV, intravenous methylprednisolone (5 mg/kg) was administered for 3 days to induce and maintain cell-mediated immune suppression. Candida glabrata culture was prepared by streaking organisms from stock isolates onto nutrient agar, which was then incubated at 37°C for 24 hours. The resulting culture was utilized for further experimentation.

The Candida glabrata culture was diluted with phosphate-buffered saline (PBS) and inoculated into the smooth muscle of the rodents' penises, where it was allowed to grow for 3 days until Candida growth was visible. Colonization was confirmed by counting colony-forming units. Animals with colony-forming unit values exceeding 3 cfu/mL were included in the study. The animals were treated for a week, during which their physical changes were observed regularly.

Swab cultures were collected on the initial day, the fourth day, and the seventh day of the experiment for microscopic assessment. At the end of the trial, the animals were euthanized, and the ischiocavernosus smooth muscle was harvested from each trial animal and preserved in 10% formalin for further analysis.(34)

DISCUSSION

Microsponges represent a significant advancement in the treatment of dermatological conditions compared to traditional topical formulations. This innovative Microsponge Delivery System offers the ability to encapsulate a wide range of active ingredients and release them onto the skin gradually over time or in response to specific triggers. It is a versatile technology designed for controlled release of active agents, applicable not only in topical applications but also in oral and biopharmaceutical drug delivery.

The benefits of Microsponge technology are multifaceted. It allows for the conversion of liquids into free-flowing powders, enhancing formulation flexibility. Originally developed for delivering drugs such as anti-acne, anti-inflammatory, antifungal, anti-dandruff, anti-itch, and skin-reddening agents, Microsponges can accommodate incompatible ingredients while ensuring prolonged stability without the need for preservatives. Moreover, it enhances the safety of potentially irritating or sensitizing drugs, and the customizable release profiles enable precise control over drug delivery to targeted areas.

Overall, the Microsponge drug delivery system represents a significant advancement in controlled drug delivery technology with promising potential for future developments. It is a highly sophisticated field that warrants further exploration and research to unlock its full capabilities and applications in various therapeutic areas.

CONCLUSION

In conclusion, the microsponge delivery system represents a remarkable innovation for controlled release of porous particles containing active ingredients, offering the potential to minimize side effects while maintaining therapeutic

effectiveness. This technology allows for the encapsulation of ingredients and is expected to contribute to reduced side effects, improved safety, enhanced aesthetic appeal, and increased formulation flexibility. Moreover, numerous studies have demonstrated that microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. Currently, this technology is utilized in cosmetics, over-the-counter skincare products, sunscreens, and prescription medications. Such drug delivery systems hold promise for advancing the treatment of various diseases, suggesting that microsponge-based drug delivery innovation will play a significant role in future therapeutic applications.

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