

NANOSPONGE HYDROGEL SYSTEMS IN ANTIFUNGAL THERAPY: CURRENT PERSPECTIVES AND THERAPEUTIC APPLICATIONS

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1. INTRODUCTION

Fungal infections have emerged as a major global health concern due to the increasing prevalence of superficial and systemic mycoses, particularly among immunocompromised individuals, diabetic patients, cancer patients undergoing chemotherapy, and organ transplant recipients. Common fungal pathogens such as *Candida albicans*, *Aspergillus* species, *Cryptococcus neoformans*, and dermatophytes are responsible for a wide range of infections affecting the skin, nails, mucosal tissues, and internal organs.^[1] Although several antifungal agents including azoles, polyenes, allylamines, and echinocandins are available for clinical use, their therapeutic efficacy is often limited by poor aqueous solubility, low bioavailability, inadequate skin penetration, systemic toxicity, frequent dosing, and the emergence of antifungal resistance. These limitations have encouraged researchers to explore

advanced drug delivery systems capable of improving antifungal therapy outcomes.^[2] Nanotechnology-based drug delivery systems have gained considerable attention in recent years due to their ability to enhance drug solubility, improve targeted delivery, provide controlled drug release, and reduce adverse effects. Among various nanocarrier systems, nanosponges represent a promising and versatile platform for antifungal drug delivery. Nanosponges are nanosized, porous, three-dimensional structures composed mainly of biodegradable and biocompatible polymers crosslinked to form a cavity-like network capable of encapsulating both hydrophilic and lipophilic drugs.^[3] Their unique porous architecture provides high drug loading capacity, enhanced stability, and sustained release characteristics,

making them highly suitable for topical and transdermal antifungal therapy.^[4] Hydrogels are another important class of drug delivery systems characterized by their hydrophilic polymeric network capable of retaining a large amount of water or biological fluids. Hydrogels offer several advantages such as excellent biocompatibility, ease of application, prolonged residence time, enhanced patient compliance, and controlled drug release. When nanosponges are incorporated into hydrogel matrices, the resulting nanosponge hydrogel systems combine the advantages of both technologies, leading to improved drug retention at the site of infection, enhanced skin permeation, and sustained antifungal activity. Such hybrid systems have demonstrated significant potential in overcoming the limitations associated with conventional topical antifungal formulations such as creams, ointments, and gels.^[2] Nanosponge hydrogel systems have been extensively investigated for the delivery of various antifungal agents including fluconazole, itraconazole, ketoconazole, terbinafine, voriconazole, and amphotericin B. These systems not only improve drug solubility and stability but also facilitate controlled and localized drug release, thereby minimizing systemic exposure and toxicity. Furthermore, the nanoscale size of nanosponges enhances penetration into deeper skin layers and infected tissues, resulting in improved therapeutic efficacy against resistant fungal strains.^[5] The growing interest in nanosponge hydrogel technology has led to substantial advancements in formulation strategies, polymer selection, fabrication methods, characterization techniques, and therapeutic applications. Therefore, this review aims to comprehensively discuss the current perspectives of nanosponge hydrogel systems in antifungal therapy, including their formulation approaches, mechanisms of drug release, characterization parameters, recent therapeutic applications, advantages, limitations, and future prospects in the management of fungal infections.^[6]

1.1 Overview of Fungal Infections

Fungal infections, also known as mycoses, are infectious diseases caused by pathogenic fungi that invade various tissues of the human body. These infections may range from mild superficial conditions affecting the skin and mucosal membranes to severe systemic infections involving internal organs. The incidence of fungal infections has increased significantly over the past few decades due to the growing population of immunocompromised individuals, widespread use of broad-spectrum antibiotics, increased prevalence of diabetes mellitus, cancer chemotherapy, organ transplantation, and human immunodeficiency virus (HIV) infection. Fungal diseases are now considered an important public health concern because of their high morbidity, mortality, and economic burden

worldwide.^[7] Fungal infections are generally classified into superficial, cutaneous, subcutaneous, and systemic mycoses based on the site and severity of infection. Superficial fungal infections primarily affect the outermost layers of the skin, hair, nails, and mucosal tissues. Dermatophytosis, candidiasis, and pityriasis versicolor are among the most common superficial fungal infections. Dermatophytes such as *Trichophyton*, *Microsporum*, and *Epidermophyton* species are responsible for infections commonly known as ringworm or tinea infections. Similarly, *Candida albicans* is a major opportunistic fungal pathogen causing oral thrush, vaginal candidiasis, and cutaneous candidiasis.^[8] Systemic fungal infections are more severe and potentially life-threatening, particularly in immunocompromised patients. Opportunistic fungi such as *Aspergillus fumigatus*, *Cryptococcus neoformans*, and *Candida* species can invade deep tissues and vital organs including the lungs, bloodstream, brain, and kidneys. Invasive fungal infections are associated with high mortality rates because of delayed diagnosis, limited therapeutic options, and increasing antifungal resistance. The emergence of multidrug-resistant fungal strains has further complicated antifungal treatment and highlighted the urgent need for novel therapeutic strategies.^[9] Conventional antifungal therapy involves the use of polyenes, azoles, echinocandins, and allylamines. Although these drugs have shown clinical effectiveness, their therapeutic use is often associated with several limitations such as poor water solubility, low permeability, inadequate drug retention at the site of infection, systemic toxicity, hepatotoxicity, nephrotoxicity, and frequent dosing requirements. Topical antifungal formulations such as creams, ointments, and lotions often exhibit poor penetration through the stratum corneum, leading to reduced therapeutic efficacy and recurrence of infection.^[10] Additionally, fungal biofilm formation has emerged as a significant challenge in antifungal therapy. Biofilms protect fungal cells from host immune responses and antifungal agents, thereby contributing to chronic and recurrent infections. The increasing resistance of fungal pathogens to commonly used antifungal drugs has further necessitated the development of advanced drug delivery systems capable of improving drug targeting, enhancing penetration, and providing sustained antifungal activity.^[11] Recent advances in nanotechnology have provided new opportunities for improving antifungal treatment through the development of nanoscale drug delivery systems. Among these, nanosponge hydrogel systems have attracted considerable interest due to their ability to improve drug solubility, enhance skin permeation, prolong drug release, and minimize systemic side effects. These innovative delivery systems hold significant promise in overcoming the limitations of conventional antifungal therapy and improving patient outcomes in the management of fungal infections.^[12]

1.1.1 Types of Fungal Infections

Fungal infections are categorized based on the depth of tissue involvement and the type of pathogenic fungi responsible for the infection. They are broadly classified into superficial, cutaneous, subcutaneous, systemic, and opportunistic fungal infections. Each category differs in terms of causative organisms, site of infection, severity, and therapeutic management.^[13]

1. Superficial Fungal Infections

Superficial fungal infections are limited to the outermost layers of the skin, hair, nails, and mucous membranes. These infections are generally non-life-threatening but may cause discomfort, itching, inflammation, and cosmetic concerns. The most common superficial fungal infections include dermatophytosis, candidiasis, and pityriasis versicolor.^[14] Dermatophytosis, commonly known as ringworm or tinea infection, is caused by dermatophytes such as *Trichophyton*, *Microsporum*, and *Epidermophyton* species. Depending on the affected body site, dermatophytosis may be classified as tinea corporis, tinea pedis, tinea capitis, tinea cruris, and tinea unguium. *Candida albicans* is another common fungal pathogen responsible for oral thrush, vaginal candidiasis, and cutaneous candidiasis. Pityriasis versicolor is caused by *Malassezia* species and is characterized by discolored patches on the skin.^[15]

2. Cutaneous Fungal Infections

Cutaneous fungal infections involve deeper layers of the epidermis, hair follicles, and nails. These infections are mainly caused by dermatophytes and may lead to inflammation, scaling, redness, and nail deformities. Factors such as poor hygiene, excessive sweating, humid climate, immunosuppression, and diabetes increase susceptibility to cutaneous fungal infections. Chronic or recurrent cutaneous infections often require prolonged antifungal therapy because of poor drug penetration into keratinized tissues.^[16]

3. Subcutaneous Fungal Infections

Subcutaneous mycoses occur when fungal organisms enter the body through traumatic injury or skin puncture. These infections affect the dermis, subcutaneous tissues, muscles, and lymphatic system. Common subcutaneous fungal infections include sporotrichosis, chromoblastomycosis, and mycetoma. *Sporothrix schenckii* is the causative organism of sporotrichosis, which commonly affects gardeners and agricultural workers due to contact with contaminated soil or plant materials. Subcutaneous fungal infections are usually chronic in nature and may require long-term antifungal treatment or surgical intervention.^[17]

4. Systemic Fungal Infections

Systemic fungal infections are severe infections involving internal organs such as the lungs, bloodstream, brain, liver, and kidneys. These infections are generally caused by pathogenic fungi capable of invading deep tissues and disseminating throughout the body. Systemic mycoses are particularly common among immunocompromised patients, including individuals with HIV/AIDS, cancer, organ transplants, or prolonged corticosteroid therapy.^[18] Major systemic fungal pathogens include *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides* species. Invasive candidiasis and aspergillosis are among the most life-threatening fungal infections associated with high mortality rates. Early diagnosis and effective antifungal therapy are essential for successful management of systemic mycoses.^[19]

5. Opportunistic Fungal Infections

Opportunistic fungal infections are caused by fungi that normally do not produce disease in healthy individuals but become pathogenic in immunocompromised conditions. These infections have increased significantly due to the rise in immunosuppressive diseases and therapies. Common opportunistic fungal pathogens include *Candida* species, *Aspergillus* species, *Pneumocystis Jirovecii*, and *Mucor* species.^[20] Mucormycosis gained global attention during the COVID-19 pandemic, particularly among diabetic and immunocompromised patients receiving corticosteroid therapy. Opportunistic fungal infections are difficult to treat because of rapid disease progression, limited drug penetration, toxicity of antifungal agents, and increasing antifungal resistance.^[21] The diverse nature and severity of fungal infections necessitate the development of advanced and targeted drug delivery systems. Novel nanosponge hydrogel formulations offer promising potential for improving antifungal drug delivery, enhancing localized action, and minimizing systemic adverse effects in various types of fungal infections.^[22]

1.1.2 Challenges in Antifungal Therapy

Despite the availability of several antifungal agents, the effective management of fungal infections remains a major therapeutic challenge. Conventional antifungal therapy is often associated with limited efficacy, adverse drug reactions, poor patient compliance, and increasing resistance among fungal pathogens. These challenges significantly affect treatment outcomes and necessitate the development of advanced drug delivery approaches for improved antifungal therapy.^[11] One of the major limitations of antifungal drugs is their poor

aqueous solubility and low bioavailability. Many commonly used antifungal agents such as itraconazole, ketoconazole, amphotericin B, and voriconazole exhibit poor water solubility, resulting in inadequate absorption and limited therapeutic effectiveness. Poor solubility often requires the use of high drug doses or toxic solubilizing agents, which may increase the risk of systemic side effects.^[23] Another important challenge is the limited penetration of antifungal drugs through biological barriers, particularly the stratum corneum of the skin and keratinized tissues such as nails. Topical formulations including creams, ointments, and gels frequently fail to deliver sufficient drug concentrations into deeper layers of infected tissues. As a result, prolonged therapy and repeated application are often required, which may reduce patient adherence and increase the risk of recurrence.^[24] Systemic toxicity is also a significant concern in antifungal therapy. Polyene antifungals such as amphotericin B are associated with nephrotoxicity, infusion-related reactions, and electrolyte imbalance, whereas azole antifungals may cause hepatotoxicity, gastrointestinal disturbances, and drug-drug interactions. Long-term administration of systemic antifungal drugs can further increase the risk of organ toxicity and adverse effects, especially in elderly and immunocompromised patients.^[25] The emergence of antifungal resistance has become a global healthcare challenge. Fungal pathogens develop resistance through several mechanisms including alteration of drug targets, overexpression of efflux pumps, biofilm formation, enzymatic drug degradation, and genetic mutations. Resistant strains of *Candida*, *Aspergillus*, and *Cryptococcus* species have been increasingly reported worldwide, reducing the effectiveness of existing antifungal therapies. Biofilm-associated fungal infections are particularly difficult to eradicate because biofilms act as protective barriers that limit drug penetration and enhance fungal survival.^[26] Another challenge is the prolonged duration of antifungal treatment. Chronic and recurrent fungal infections often require long-term therapy lasting several weeks or months. Extended treatment duration may lead to poor patient compliance, increased healthcare costs, and higher chances of treatment failure. Inadequate adherence to therapy may further contribute to the development of resistant fungal strains.^[27] Drug instability and rapid degradation also limit the therapeutic performance of many antifungal agents. Certain antifungal drugs are sensitive to environmental conditions such as light, heat, and oxidation, which may reduce their stability during storage and administration. Additionally, rapid drug metabolism and clearance from the site of infection can result in subtherapeutic drug concentrations and reduced efficacy.^[28] Conventional dosage forms also lack site-specific targeting capabilities, leading to non-selective drug distribution and systemic exposure. This not only decreases drug concentration at the infected site but also increases the possibility of off-target effects

and toxicity. Therefore, there is a growing need for novel drug delivery systems capable of improving drug targeting, enhancing penetration, prolonging drug release, and reducing systemic adverse effects.^[29] In recent years, nanotechnology-based delivery systems such as liposomes, solid lipid nanoparticles, nanoemulsions, and nanosponges have shown promising potential in overcoming the limitations of conventional antifungal therapy. Among these, nanosponge hydrogel systems have emerged as an innovative approach for enhancing antifungal drug delivery through improved solubility, controlled release, prolonged retention, enhanced permeation, and localized therapeutic action. These advanced systems may provide an effective strategy for improving antifungal efficacy while minimizing toxicity and resistance-related complications.^[2]

1.2 Limitations of Conventional Topical Formulations

Conventional topical formulations such as creams, ointments, lotions, powders, and gels are widely used for the treatment of superficial fungal infections due to their ease of application and localized therapeutic action. These formulations are commonly employed for managing dermatophytosis, candidiasis, and other cutaneous fungal infections. Although topical therapy offers advantages such as reduced systemic toxicity and direct drug delivery to the infected site, conventional formulations often exhibit several limitations that compromise their therapeutic effectiveness.^[30] One of the major drawbacks of conventional topical formulations is poor drug penetration through the stratum corneum, which is the primary barrier of the skin. The highly organized lipid structure of the stratum corneum restricts the permeation of many antifungal agents, especially lipophilic drugs with poor aqueous solubility. As a result, inadequate drug concentration reaches the deeper layers of the skin and infected tissues, leading to incomplete eradication of fungal pathogens and recurrence of infection.^[2] Another significant limitation is the short residence time of topical formulations at the site of application. Conventional creams, lotions, and gels are easily removed by sweating, washing, friction from clothing, or natural skin movements. This results in reduced contact time between the drug and infected tissue, thereby decreasing therapeutic efficacy and necessitating frequent reapplication. Repeated dosing may reduce patient compliance, particularly during long-term antifungal therapy.^[27] Poor drug solubility and stability further limit the effectiveness of conventional formulations. Many antifungal drugs such as itraconazole, ketoconazole, and amphotericin B possess low aqueous solubility, which hinders uniform drug distribution within the formulation and reduces bioavailability. In addition, certain antifungal agents are susceptible to degradation by light, oxidation, heat, or

moisture, leading to reduced stability and therapeutic activity during storage and application.^[28]

Conventional topical systems also often exhibit uncontrolled and rapid drug release patterns. Immediate release of the drug may result in an initial burst effect followed by rapid decline in drug concentration below therapeutic levels. Such fluctuations can reduce sustained antifungal activity and may require repeated administration to maintain effective drug concentrations at the infection site.^[22] Skin irritation and allergic reactions are additional concerns associated with traditional topical formulations. Certain excipients, preservatives, surfactants, and penetration enhancers used in creams and ointments may cause redness, itching, burning sensation, dryness, or contact dermatitis, especially in sensitive individuals. Oily ointments may also produce greasy texture, unpleasant appearance, and discomfort, thereby affecting patient acceptance and adherence to therapy.^[31] Another important challenge is the inability of conventional formulations to effectively target fungal biofilms and deeply seated infections. Fungal biofilms act as protective matrices that limit drug penetration and enhance fungal resistance against antifungal agents. Traditional topical dosage forms generally fail to maintain sufficient drug concentration for prolonged periods to effectively disrupt biofilm structures and eradicate resistant fungal cells.^[12] Furthermore, conventional formulations often lack controlled and site-specific drug delivery capabilities. Non-specific drug distribution may lead to drug wastage and insufficient localization of the active agent at the infected tissue. In chronic fungal infections, inadequate drug retention and limited tissue penetration frequently result in incomplete treatment and recurrence.^[2] To overcome these limitations, researchers have increasingly focused on the development of advanced nanotechnology-based topical delivery systems. Nanosponge hydrogel systems have emerged as promising alternatives due to their ability to enhance drug solubility, improve skin permeation, provide sustained release, increase retention time, and minimize irritation. The incorporation of nanosponges into hydrogel matrices offers a synergistic approach for improving topical antifungal therapy and achieving better clinical outcomes.^[32]

1.3 Emergence of Nanosponge Hydrogel Systems

The growing limitations associated with conventional antifungal formulations have accelerated the development of advanced nanotechnology-based drug delivery systems. Among these, nanosponge hydrogel systems have emerged as a promising and innovative approach for enhancing topical and transdermal antifungal therapy. These hybrid systems

combine the unique advantages of nanosponges and hydrogels, offering improved drug solubility, enhanced skin penetration, sustained drug release, prolonged retention time, and reduced systemic toxicity.^[32] Nanosponges are nanosized porous structures composed of biodegradable and biocompatible polymers crosslinked to form three-dimensional networks containing numerous cavities. These cavities can effectively encapsulate both hydrophilic and lipophilic drugs, protecting them from degradation and improving their stability. Due to their porous architecture and high surface area, nanosponges provide controlled and sustained drug release, which is highly beneficial in the treatment of chronic and recurrent fungal infections. Initially, nanosponges were primarily investigated for oral and targeted drug delivery; however, their excellent physicochemical characteristics later expanded their applications into topical and transdermal therapy.^[33] Hydrogels are hydrophilic polymeric systems capable of absorbing and retaining large quantities of water or biological fluids without losing their structural integrity. Hydrogels possess excellent biocompatibility, softness, flexibility, and mucoadhesive properties, making them suitable for dermal applications. Their ability to maintain a moist environment and prolong contact time at the site of application significantly enhances localized drug delivery and patient comfort. However, conventional hydrogels alone may exhibit limited drug loading capacity and uncontrolled drug release for poorly soluble antifungal agents.^[34] The integration of nanosponges into hydrogel matrices has led to the development of nanosponge hydrogel systems, which effectively overcome the individual limitations of both technologies. In these systems, drug-loaded nanosponges are uniformly dispersed within the hydrogel network, enabling efficient drug encapsulation along with prolonged retention at the application site. This dual delivery approach enhances skin permeation and provides sustained therapeutic concentrations of antifungal drugs over extended periods.^[35] The emergence of nanosponge hydrogel systems has been particularly significant in antifungal therapy because many antifungal drugs suffer from poor water solubility, limited permeability, rapid drug elimination, and systemic adverse effects. Nanosponge hydrogels improve the dissolution behavior and bioavailability of antifungal agents while simultaneously reducing dosing frequency and minimizing local irritation. Additionally, their nanoscale size facilitates deeper penetration into infected skin layers and biofilm structures, thereby improving therapeutic efficacy against resistant fungal strains.^[36] Several antifungal drugs including fluconazole, itraconazole, terbinafine, ketoconazole, voriconazole, and amphotericin B have been successfully incorporated into nanosponge hydrogel formulations. Studies have demonstrated that these systems exhibit enhanced antifungal activity, controlled drug release, improved stability, higher entrapment efficiency,

and superior patient compliance compared to conventional topical formulations.^[32] Recent advances in polymer science, crosslinking technologies, and nanofabrication techniques have further accelerated the development of nanosponge hydrogel systems with optimized physicochemical and therapeutic properties. Researchers are also exploring stimuli-responsive and targeted nanosponge hydrogels capable of releasing drugs in response to pH, temperature, or enzymatic changes associated with fungal infections.^[32] Therefore, nanosponge hydrogel systems represent a novel and highly promising platform in antifungal drug delivery. Their multifunctional properties and therapeutic advantages make them attractive candidates for overcoming the challenges associated with conventional antifungal therapy and improving the management of superficial and deep fungal infections.^[11]

1.4 Aim and Scope of the Review

The increasing prevalence of fungal infections and the limitations associated with conventional antifungal therapies have highlighted the urgent need for advanced and more effective drug delivery systems. In recent years, nanosponge hydrogel systems have gained significant attention as promising carriers for antifungal agents due to their ability to improve drug solubility, enhance skin permeation, provide controlled release, and minimize systemic toxicity. These multifunctional delivery systems offer a novel therapeutic approach for overcoming the challenges associated with traditional topical formulations and resistant fungal infections.^[2] The primary aim of this review is to provide a comprehensive overview of nanosponge hydrogel systems and their emerging role in antifungal therapy. The review focuses on the scientific principles, formulation strategies, physicochemical characteristics, and therapeutic potential of nanosponge-loaded hydrogels for the effective management of fungal infections. Special emphasis is placed on the application of these systems in improving topical and transdermal delivery of antifungal drugs.^[37] This review discusses the classification and pathophysiology of fungal infections along with the major challenges encountered in conventional antifungal therapy. It further explores the structural and functional characteristics of nanosponges and hydrogels, including their composition, preparation methods, mechanisms of drug encapsulation, and controlled drug release behavior. Various polymers, crosslinking agents, and fabrication techniques employed in the development of nanosponge hydrogel formulations are also highlighted.^[38] In addition, the review covers important evaluation and characterization parameters such as particle size, zeta potential, drug entrapment efficiency, swelling behavior, rheological properties, *in vitro* drug release, antifungal activity, and stability studies. The therapeutic applications of nanosponge

hydrogel systems for delivering antifungal agents including fluconazole, itraconazole, ketoconazole, terbinafine, amphotericin B, and voriconazole are comprehensively summarized based on recent research findings.^[39] Furthermore, the review addresses the advantages, limitations, and future perspectives of nanosponge hydrogel technology in antifungal drug delivery. Emerging approaches such as stimuli-responsive hydrogels, bio adhesive systems, and targeted nanosponge formulations are also discussed as potential strategies for enhancing therapeutic efficacy and patient compliance.^[32] Overall, this review aims to provide researchers, academicians, and pharmaceutical scientists with an updated understanding of nanosponge hydrogel systems and their growing significance in antifungal therapy. The information presented may contribute to the future design and development of safer, more effective, and patient-friendly antifungal formulations for the management of superficial and systemic fungal infections.^[2]

2. Nanosponge Hydrogel Systems: Composition and Functional Properties

Nanosponge hydrogel systems are advanced hybrid drug delivery platforms designed by incorporating drug-loaded nanosponges into hydrogel matrices. These systems integrate the unique structural and functional advantages of both nanosponges and hydrogels, resulting in improved drug loading, enhanced permeation, prolonged retention, and controlled drug release. Due to their multifunctional properties, nanosponge hydrogels have emerged as highly promising carriers for topical and transdermal antifungal therapy.^[32] Nanosponges are nanosized porous particles generally prepared using biodegradable polymers crosslinked to form a three-dimensional network containing internal cavities. These porous structures are capable of entrapping both hydrophilic and lipophilic drugs within their cavities, thereby improving drug solubility, stability, and bioavailability. The nanoscale size and high surface area of nanosponges facilitate enhanced interaction with biological membranes and infected tissues, enabling efficient localized drug delivery.^[40] Hydrogels, on the other hand, are hydrophilic polymeric networks capable of absorbing large amounts of water or biological fluids while maintaining structural integrity. Their soft, flexible, and biocompatible nature makes them suitable for dermal and mucosal applications. Hydrogels provide prolonged contact time at the site of application, maintain a moist environment, and improve patient comfort and compliance. However, conventional hydrogels may exhibit limitations such as poor loading of hydrophobic drugs and uncontrolled release patterns.^[41] The incorporation of nanosponges into hydrogel matrices combines the beneficial properties of both systems and overcomes their individual limitations. Drug-loaded nanosponges dispersed within the

hydrogel network act as reservoir systems that provide sustained and site-specific drug release. The hydrogel matrix further enhances adhesion to the skin surface, reduces drug leakage, and prolongs residence time, thereby improving therapeutic efficacy against fungal infections.^[35] The composition of nanosponge hydrogel systems generally includes polymers, crosslinking agents, surfactants or stabilizers, solvents, gelling agents, and active pharmaceutical ingredients. Cyclodextrins, ethyl cellulose, polyvinyl alcohol, polymethyl methacrylate, and biodegradable synthetic or natural polymers are commonly used for nanosponge preparation. Crosslinking agents such as carbonyl diimidazole, diphenyl carbonate, and pyromellitic dianhydride help in forming stable porous networks. Hydrogels are usually prepared using natural polymers like chitosan, alginate, xanthan gum, carbopol, and hyaluronic acid or synthetic polymers such as polyethylene glycol and polyvinyl pyrrolidone.^[42] The functional properties of nanosponge hydrogel systems play a crucial role in determining their therapeutic performance. One of the most important properties is controlled and sustained drug release, which helps maintain therapeutic drug concentration at the site of infection for prolonged periods. The porous nanosponge structure enables gradual diffusion of the encapsulated drug, reducing the need for frequent application and improving patient adherence.^[43] Enhanced drug solubility and stability are additional advantages of these systems. Encapsulation within nanosponges protects antifungal agents from environmental degradation caused by heat, oxidation, or light exposure. This is particularly beneficial for poorly water-soluble antifungal drugs such as itraconazole and ketoconazole. Furthermore, nanosponge hydrogels improve skin permeation by increasing the contact surface area and facilitating deeper penetration into infected tissues.^[32] Mucoadhesion and bio adhesion are also important functional characteristics of hydrogel-based systems. These properties allow the formulation to remain attached to the skin or mucosal surface for extended durations, thereby increasing drug retention and therapeutic effectiveness. The hydration capacity and swelling behavior of hydrogels further contribute to controlled drug diffusion and improved patient comfort.^[44] Biocompatibility and reduced toxicity make nanosponge hydrogel systems attractive candidates for antifungal therapy. The use of biodegradable polymers minimizes tissue irritation and adverse reactions, while localized drug delivery reduces systemic exposure and associated side effects. Additionally, the nanoscale size of nanosponges may enhance penetration into fungal biofilms, improving drug access to resistant fungal cells.^[45] Overall, nanosponge hydrogel systems represent a versatile and efficient platform for antifungal drug delivery. Their unique composition and multifunctional properties provide significant advantages over conventional topical

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and hyaluronic acid or synthetic polymers such as polyethylene glycol and polyvinyl pyrrolidone.^[42] The functional properties of nanosponge hydrogel systems play a crucial role in determining their therapeutic performance. One of the most important properties is controlled and sustained drug release, which helps maintain therapeutic drug concentration at the site of infection for prolonged periods. The porous nanosponge structure enables gradual diffusion of the encapsulated drug, reducing the need for frequent application and improving patient adherence.^[43] Enhanced drug solubility and stability are additional advantages of these systems. Encapsulation within nanosponges protects antifungal agents from environmental degradation caused by heat, oxidation, or light exposure. This is particularly beneficial for poorly water-soluble antifungal drugs such as itraconazole and ketoconazole. Furthermore, nanosponge hydrogels improve skin permeation by increasing the contact surface area and facilitating deeper penetration into infected tissues.^[32] Mucoadhesion and bio adhesion are also important functional characteristics of hydrogel-based systems. These properties allow the formulation to remain attached to the skin or mucosal surface for extended durations, thereby increasing drug retention and therapeutic effectiveness. The hydration capacity and swelling behavior of hydrogels further contribute to controlled drug diffusion and improved patient comfort.^[44] Biocompatibility and reduced toxicity make nanosponge hydrogel systems attractive candidates for antifungal therapy. The use of biodegradable polymers minimizes tissue irritation and adverse reactions, while localized drug delivery reduces systemic exposure and associated side effects. Additionally, the nanoscale size of nanosponges may enhance penetration into fungal biofilms, improving drug access to resistant fungal cells.^[45] Overall, nanosponge hydrogel systems represent a versatile and efficient platform for antifungal drug delivery. Their unique composition and multifunctional properties provide significant advantages over conventional topical formulations and contribute to improved therapeutic outcomes in the treatment of fungal infections.^[2]

2.1 Structure and Characteristics of Nanosponges

Nanosponges are nanosized, highly porous colloidal carriers composed of crosslinked polymeric networks capable of encapsulating a wide variety of therapeutic agents. These nanocarriers possess a three-dimensional architecture containing numerous nanochannels and internal cavities that enable efficient entrapment of both hydrophilic and lipophilic drugs. Due to their unique structural features, nanosponges have gained considerable attention as advanced drug delivery systems for topical, oral, and transdermal applications, particularly in

antifungal therapy.^[46] Structurally, nanosponges are formed through the crosslinking of polymers such as cyclodextrins, ethyl cellulose, polyesters, hyper-crosslinked polystyrenes, and other biodegradable polymers using suitable crosslinking agents. The crosslinking process generates a stable porous network with interconnected cavities that act as reservoirs for drug molecules. These cavities vary in size depending on the type of polymer, degree of crosslinking, and preparation method employed. The porous nature of nanosponges allows high drug loading capacity and controlled release behavior.^[47] The external surface of nanosponges is generally spherical and porous, with particle sizes commonly ranging from 50 to 500 nm. Their nanoscale dimensions provide a large surface area, which enhances interaction with biological membranes and facilitates improved drug permeation through the skin and mucosal tissues. In antifungal therapy, this property contributes to better penetration of antifungal agents into infected tissues and fungal biofilms.^[2] One of the most important structural characteristics of nanosponges is their ability to encapsulate drugs through inclusion complexation, adsorption, or entrapment within the porous matrix. Lipophilic drugs can be effectively incorporated into the hydrophobic cavities, while hydrophilic drugs may interact with the outer hydrophilic regions of the nanosponge structure. This dual encapsulation capability makes nanosponges versatile carriers for various classes of antifungal agents.^[46] Nanosponges exhibit excellent physicochemical stability due to their rigid crosslinked network. They remain stable over a wide range of temperature and pH conditions and protect encapsulated drugs from environmental degradation such as oxidation, hydrolysis, and photodegradation. This enhanced stability significantly improves the shelf life and therapeutic performance of antifungal formulations.^[48] Another important characteristic of nanosponges is their controlled and sustained drug release capability. The porous structure acts as a reservoir system that gradually releases the drug over an extended period through diffusion mechanisms. Drug release profiles can be modified by altering the polymer type, crosslinking density, particle size, and degree of porosity. Sustained release minimizes fluctuations in drug concentration, reduces dosing frequency, and enhances patient compliance.^[49] Nanosponges also demonstrate excellent biocompatibility and low toxicity because they are generally prepared using biodegradable and non-irritant polymers. Their non-toxic nature makes them suitable for prolonged topical application in the treatment of chronic fungal infections. Additionally, their small particle size improves skin adhesion and promotes localized drug delivery with minimal systemic absorption.^[50] The swelling behavior and surface charge of nanosponges further influence their therapeutic performance. Surface charge, commonly measured by zeta potential, affects particle stability and interaction with

biological membranes. Properly optimized zeta potential values help prevent particle aggregation and improve formulation stability. Swelling characteristics contribute to controlled drug diffusion and release kinetics.^[51] Moreover, nanosponges possess high versatility in formulation development. They can be incorporated into various dosage forms such as gels, creams, tablets, capsules, hydrogels, and transdermal systems. In nanosponge hydrogel formulations, nanosponges act as drug reservoirs within the hydrogel matrix, enabling prolonged retention and enhanced antifungal activity at the application site.^[32] Overall, the unique structure and multifunctional characteristics of nanosponges make them highly efficient carriers for antifungal drug delivery. Their porous architecture, high drug loading capacity, controlled release behavior, stability, and biocompatibility contribute significantly to improving the therapeutic efficacy of antifungal agents and overcoming the limitations of conventional formulations.^[11]

2.2 Polymers and Cross-Linking Agents

Polymers and cross-linking agents are the fundamental components involved in the preparation of nanosponge hydrogel systems. The selection of suitable polymers and cross-linkers significantly influences the structural integrity, porosity, drug loading capacity, swelling behavior, stability, and drug release characteristics of the final formulation. In antifungal drug delivery, these materials play a crucial role in enhancing therapeutic efficacy, controlling drug release, and improving biocompatibility.^[52]

2.2.1 Polymers Used in Nanosponge Preparation

Polymers used in nanosponge formulation are generally selected based on their biodegradability, biocompatibility, non-toxicity, and ability to form porous three-dimensional networks. Both natural and synthetic polymers have been widely explored for nanosponge fabrication.^[53]

Cyclodextrins are among the most commonly used polymers in nanosponge systems. Cyclodextrins are cyclic oligosaccharides possessing a hydrophobic internal cavity and hydrophilic outer surface. Their unique structure allows efficient encapsulation of poorly water-soluble antifungal drugs such as itraconazole and ketoconazole. β -Cyclodextrin is particularly preferred because of its suitable cavity size, low toxicity, and cost-effectiveness. Cyclodextrin-based nanosponges exhibit excellent drug entrapment efficiency and controlled release properties.^[54]

Ethyl cellulose is another widely used polymer in nanosponge preparation, especially for topical and controlled-release applications. It is a hydrophobic, biocompatible polymer capable of forming stable porous structures. Ethyl cellulose nanosponges provide sustained drug release and improved skin retention of antifungal agents.^[55]

Other synthetic polymers such as polyvinyl alcohol (PVA), polymethyl methacrylate (PMMA), polycaprolactone (PCL), polyethylene glycol (PEG), and poly (lactic-co-glycolic acid) (PLGA) are also employed in nanosponge fabrication. These polymers contribute to enhanced mechanical strength, improved stability, and controlled drug release behavior.^[56]

Natural polymers including chitosan, alginate, gelatin, xanthan gum, and hyaluronic acid are frequently incorporated because of their biodegradability, mucoadhesive properties, and excellent safety profile. Chitosan is particularly advantageous due to its inherent antifungal and permeation-enhancing properties, making it highly suitable for topical antifungal delivery systems.^[57]

2.2.2 Polymers Used in Hydrogel Formation

Hydrogels are formed using hydrophilic polymers capable of absorbing large quantities of water while maintaining structural integrity. The choice of hydrogel polymer affects viscosity, swelling behavior, spreadability, bio adhesion, and drug diffusion.^[58] Carbopol is one of the most commonly used gelling agents in nanosponge hydrogel formulations due to its excellent viscosity-building and bio adhesive properties. It provides smooth texture, prolonged skin retention, and enhanced stability of topical formulations.^[59]

Hydroxypropyl methylcellulose (HPMC), sodium alginate, poloxamers, polyvinyl pyrrolidone (PVP), and xanthan gum are also extensively utilized in hydrogel preparation. These polymers improve consistency, hydration capacity, and controlled release characteristics. Natural hydrogel-forming polymers such as chitosan and hyaluronic acid additionally enhance wound healing and skin compatibility.^[60]

2.2.3 Cross-Linking Agents

Cross-linking agents are chemical substances responsible for linking polymer chains together to form stable three-dimensional porous networks. The type and concentration of cross-linker greatly influence nanosponge pore size, rigidity, drug entrapment efficiency, and release kinetics.^[53]

Diphenyl carbonate is one of the most frequently used cross-linking agents in cyclodextrin-based nanosponge preparation. It reacts with hydroxyl groups of cyclodextrins to form stable carbonate linkages, generating highly porous nanosponge structures with excellent drug loading capability.^[61]

Carbonyl diimidazole (CDI) is another important cross-linker used for preparing nanosponges with controlled pore size and enhanced stability. Pyromellitic dianhydride, epichlorohydrin, glutaraldehyde, and diisocyanates are also commonly employed depending on the polymer system and intended application.^[62]

In hydrogel systems, cross-linking may occur through physical or chemical methods. Chemical cross-linkers such as glutaraldehyde and genii produce stable hydrogel networks with improved mechanical strength. Physical cross-linking methods involving ionic interactions, hydrogen bonding, or freeze-thaw cycles are preferred in some formulations to minimize toxicity associated with chemical agents.^[42]

2.2.4 Influence of Polymer and Cross-Linker Selection

The properties of nanosponge hydrogel systems are highly dependent on the polymer-to-crosslinker ratio and degree of crosslinking. Increased crosslinking density generally leads to smaller pore size, slower drug release, improved structural rigidity, and enhanced stability. However, excessive crosslinking may reduce drug loading capacity and swelling behavior.^[63]

Similarly, polymer selection influences biocompatibility, permeation, mucoadhesion, and therapeutic performance. Hydrophilic polymers improve swelling and drug diffusion, whereas hydrophobic polymers contribute to sustained release and prolonged retention.^[64] Therefore, careful optimization of polymers and cross-linking agents is essential for developing efficient nanosponge hydrogel systems with desirable physicochemical and therapeutic properties for antifungal drug delivery.^[32]

2.3 Hydrogel Matrices and Formulation Components

Hydrogel matrices are an essential part of nanosponge hydrogel systems and play a significant role in determining the formulation's physicochemical properties, stability, drug release behavior, bio adhesion, and therapeutic effectiveness. Hydrogels are three-dimensional hydrophilic polymeric networks capable of absorbing and retaining large amounts of water or biological fluids while maintaining structural integrity. In antifungal drug

delivery, hydrogel matrices serve as carriers that provide prolonged contact with the infected site, enhance patient comfort, and facilitate controlled drug release.^[65]

The incorporation of drug-loaded nanosponges into hydrogel matrices results in a hybrid delivery system that combines the sustained release properties of nanosponges with the moisturizing and bio adhesive characteristics of hydrogels. Such systems are highly beneficial for topical antifungal therapy because they improve drug retention, skin permeation, and localized therapeutic action while reducing systemic side effects.^[2]

2.3.1 Hydrogel Matrices

Hydrogel matrices are generally prepared using natural, semi-synthetic, or synthetic hydrophilic polymers capable of forming gel-like structures upon hydration. The selection of hydrogel polymer depends on several factors including viscosity, swelling capacity, biocompatibility, mechanical strength, spreadability, and compatibility with the incorporated nanosponges and antifungal drugs.^[66]

Natural Polymers

Natural polymers are widely used because of their biodegradability, biocompatibility, non-toxicity, and mucoadhesive properties.

- **Chitosan** is a cationic polymer with excellent bio adhesive and permeation-enhancing properties. It also exhibits inherent antimicrobial activity and promotes wound healing, making it highly suitable for antifungal formulations.
- **Alginate**, obtained from brown algae, forms hydrogels through ionic crosslinking and provides good swelling behavior and controlled drug release.
- **Xanthan gum, gelatin, and hyaluronic acid** are also commonly utilized due to their moisturizing properties, skin compatibility, and ease of gel formation.^[59]

Semi-Synthetic and Synthetic Polymers

Semi-synthetic and synthetic polymers offer better mechanical strength, reproducibility, and stability compared to natural polymers.^[67]

- **Carbopol** is one of the most extensively used hydrogel-forming polymers because of its high viscosity, excellent spreadability, and strong bio adhesive nature. It produces transparent gels with prolonged retention at the application site.

- **Hydroxypropyl methylcellulose (HPMC)** is frequently employed due to its non-irritant nature and ability to provide sustained drug release.
- **Polyvinyl alcohol (PVA)**, **polyvinyl pyrrolidone (PVP)**, and **poloxamers** are also used to improve gel consistency, flexibility, hydration, and thermoresponsive behavior.^[68]

2.3.2 Formulation Components of Nanosponge Hydrogels

In addition to polymers and nanosponges, nanosponge hydrogel formulations contain several auxiliary components that contribute to stability, texture, drug release, and patient acceptability.^[58]

Drug-Loaded Nanosponges

Drug-loaded nanosponges act as the primary reservoir system within the hydrogel matrix. These porous nanosized particles encapsulate antifungal agents and release them gradually over time. Their incorporation into hydrogels improves drug distribution and enhances penetration into infected skin layers.^[32]

Solvents and Co-Solvents

Solvents are used during formulation preparation to dissolve polymers, drugs, and other excipients. Commonly used solvents include purified water, ethanol, methanol, and acetone. Co-solvents such as propylene glycol and polyethylene glycol improve solubility of poorly water-soluble antifungal drugs and enhance skin permeation.^[69]

Penetration Enhancers

Penetration enhancers facilitate the movement of antifungal drugs through the stratum corneum and improve therapeutic efficacy. Commonly used enhancers include dimethyl sulfoxide (DMSO), oleic acid, propylene glycol, and Tween surfactants. These agents temporarily alter the lipid structure of the skin barrier and increase drug permeation.^[70]

Surfactants and Stabilizers

Surfactants stabilize nanosponge dispersions and improve uniformity within the hydrogel matrix. Nonionic surfactants such as Tween 80 and Span 60 are frequently used because of their low toxicity and compatibility with topical formulations. Stabilizers help prevent aggregation of nanoparticles and improve formulation stability during storage.^[71]

Preservatives and Antioxidants

Preservatives such as methylparaben and propylparaben are added to prevent microbial contamination of hydrogel formulations. Antioxidants including butylated hydroxytoluene (BHT) and ascorbic acid may be incorporated to protect antifungal drugs from oxidative degradation.^[72]

Plasticizers and Humectants

Plasticizers such as glycerol and polyethylene glycol improve flexibility and softness of the hydrogel matrix. Humectants help maintain moisture content and prevent drying of the formulation after application.^[73]

2.3.3 Functional Role of Hydrogel Matrices

Hydrogel matrices provide several functional advantages in antifungal therapy. Their high-water content hydrates the stratum corneum and improves skin permeability, allowing deeper penetration of antifungal agents. The gel network prolongs residence time at the application site and reduces drug leakage, ensuring sustained therapeutic action.^[59] Hydrogels also enhance patient compliance because they are non-greasy, easily spreadable, soothing, and cosmetically acceptable. Furthermore, the moist environment created by hydrogels promotes healing of damaged or infected skin tissues.^[59]

The rheological behavior, swelling capacity, viscosity, and bio adhesion of hydrogel matrices significantly influence drug release and therapeutic performance. Proper optimization of formulation components is therefore essential to achieve stable nanosponge hydrogel systems with desirable physicochemical and antifungal properties.^[32]

Overall, hydrogel matrices and associated formulation components play a critical role in the successful development of nanosponge hydrogel systems for antifungal therapy, contributing to enhanced drug delivery, prolonged release, improved skin retention, and better clinical outcomes.^[74]

2.4 Advantages of Nanosponge-Based Hydrogels

Nanosponge-based hydrogels have emerged as highly promising drug delivery systems in antifungal therapy due to their unique combination of nanotechnology and hydrogel-based delivery mechanisms. These hybrid systems integrate the porous drug-encapsulating capability of nanosponges with the hydrophilic, bio adhesive, and moisturizing characteristics

of hydrogels. As a result, they provide several therapeutic and formulation-related advantages over conventional topical dosage forms such as creams, ointments, and lotions.^[75]

2.4.1 Enhanced Drug Solubility and Bioavailability

One of the major advantages of nanosponge-based hydrogels is their ability to improve the solubility and bioavailability of poorly water-soluble antifungal drugs. Many antifungal agents such as itraconazole, ketoconazole, and voriconazole exhibit limited aqueous solubility, which restricts their therapeutic performance. Nanosponges possess porous internal cavities capable of encapsulating hydrophobic drugs and improving their apparent solubility and dissolution rate. This enhanced solubility contributes to improved drug absorption and therapeutic efficacy.^[54]

2.4.2 Controlled and Sustained Drug Release

Nanosponge hydrogels provide controlled and prolonged drug release due to the reservoir-like porous structure of nanosponges dispersed within the hydrogel matrix. Drug molecules are gradually released through diffusion from the nanosponge cavities into the surrounding hydrogel and subsequently into the skin. Sustained drug release maintains therapeutic drug concentration at the site of infection for extended periods, reduces dosing frequency, and improves patient compliance.^[76]

2.4.3 Improved Skin Penetration and Retention

The nanoscale size of nanosponges increases the surface area available for interaction with the skin, thereby enhancing permeation of antifungal drugs through the stratum corneum. In addition, the hydrogel matrix hydrates the skin and temporarily loosens the tightly packed lipid structure, facilitating deeper drug penetration into infected tissues. The bio adhesive nature of hydrogels further prolongs residence time at the application site, ensuring better drug retention and localized therapeutic action.^[77]

2.4.4 Reduced Systemic Toxicity and Side Effects

Conventional systemic antifungal therapy is often associated with adverse effects such as hepatotoxicity, nephrotoxicity, and gastrointestinal disturbances. Nanosponge-based hydrogels provide localized drug delivery directly to the infected area, thereby minimizing systemic absorption and reducing the risk of systemic toxicity. Controlled drug release also prevents sudden high drug concentrations that may cause irritation or adverse reactions.^[58]

2.4.5 Enhanced Stability of Antifungal Drugs

Encapsulation of antifungal drugs within nanosponges protects them from environmental degradation caused by light, oxidation, hydrolysis, and temperature variations. The rigid crosslinked polymeric network of nanosponges improves the physicochemical stability of labile drugs and increases shelf life. This protective effect is particularly beneficial for antifungal agents sensitive to environmental conditions.^[78]

2.4.6 Improved Patient Compliance and Cosmetic Acceptability

Nanosponge hydrogels are generally non-greasy, smooth, easily spreadable, and cosmetically acceptable compared to conventional ointments and creams. They provide a cooling and soothing sensation upon application and do not leave oily residues on the skin. These characteristics enhance patient comfort and adherence to long-term antifungal therapy.^[2]

2.4.7 Ability to Target Fungal Biofilms

Fungal biofilms are highly resistant structures that limit drug penetration and contribute to chronic infections. Due to their nanosized structure and enhanced permeation capability, nanosponge-based hydrogels can improve penetration into biofilm matrices and deliver antifungal drugs more effectively to resistant fungal cells. Sustained drug release further helps maintain effective drug concentration for prolonged antifungal action.^[65]

2.4.8 High Drug Loading Capacity

The porous architecture and large surface area of nanosponges provide high drug loading capacity for both hydrophilic and lipophilic drugs. This allows efficient incorporation of antifungal agents without significantly affecting formulation stability or texture. Higher drug loading may improve therapeutic effectiveness while reducing formulation volume and dosing frequency.^[79]

2.4.9 Versatility and Formulation Flexibility

Nanosponge-based hydrogels can be formulated using a wide range of natural and synthetic polymers, crosslinkers, and excipients. Their physicochemical properties such as viscosity, swelling behavior, drug release rate, and permeation can be modified according to therapeutic requirements. This versatility makes them suitable for various dermatological and transdermal antifungal applications.^[80]

2.4.10 Biocompatibility and Safety

Most nanosponge hydrogel systems are prepared using biodegradable and biocompatible polymers that exhibit minimal irritation and toxicity. Their safety profile makes them suitable for prolonged topical application, particularly in chronic fungal infections requiring extended treatment duration.^[81]

Overall, nanosponge-based hydrogels offer significant advantages over conventional topical antifungal formulations by enhancing drug solubility, stability, permeation, retention, and controlled release while minimizing toxicity and improving patient compliance. These multifunctional properties make them highly promising platforms for the effective management of superficial and deep fungal infections.^[81]

3. Formulation and Characterization of Nanosponge Hydrogels

The successful development of nanosponge hydrogel systems for antifungal therapy depends on appropriate formulation strategies and comprehensive physicochemical characterization. Formulation parameters such as polymer selection, crosslinking density, drug-to-polymer ratio, solvent system, and hydrogel composition significantly influence the therapeutic performance, stability, drug release profile, and skin permeation behavior of the final product. Characterization studies are essential for evaluating the quality, functionality, and suitability of nanosponge hydrogels for topical antifungal applications.^[82]

The formulation process of nanosponge hydrogels generally involves two major steps: preparation of drug-loaded nanosponges followed by incorporation of the nanosponges into a suitable hydrogel matrix. Various preparation techniques are employed depending on the physicochemical nature of the antifungal drug, polymer characteristics, and intended route of administration.^[83] In the first stage, nanosponges are prepared using polymers such as β -cyclodextrin, ethyl cellulose, polyvinyl alcohol, or biodegradable synthetic polymers along with suitable crosslinking agents. Antifungal drugs are encapsulated within the porous nanosponge structure to improve solubility, stability, and controlled release behavior. The prepared nanosponges are then incorporated into hydrogel matrices composed of polymers such as Carbopol, HPMC, chitosan, alginate, or poloxamers to obtain a stable and bio adhesive topical formulation.^[84]

The formulation variables greatly affect the characteristics of nanosponge hydrogels. The polymer-to-crosslinker ratio influences pore size, drug entrapment efficiency, and release

kinetics. Similarly, hydrogel viscosity and swelling properties determine spreadability, skin retention, and diffusion behavior. Optimization of these formulation parameters is therefore necessary to achieve desired therapeutic performance.^[59]

Characterization of nanosponge hydrogels involves the evaluation of both nanosponge-related properties and hydrogel-specific parameters. Particle size analysis is one of the most important characterization techniques because particle size directly affects skin permeation, stability, and drug release. Nanosponge particle sizes generally range between 50 and 500 nm and are commonly determined using dynamic light scattering techniques.^[53]

Zeta potential measurement is performed to evaluate surface charge and colloidal stability of the nanosponge dispersion. Adequate zeta potential values help prevent particle aggregation and improve formulation stability during storage. Entrapment efficiency and drug loading studies are conducted to determine the amount of antifungal drug successfully encapsulated within the nanosponges. High entrapment efficiency is desirable for improving therapeutic efficacy and minimizing drug wastage.^[85]

Morphological characterization is commonly performed using scanning electron microscopy (SEM), transmission electron microscopy (TEM), or atomic force microscopy (AFM). These techniques provide information regarding the shape, surface texture, porosity, and structural integrity of nanosponges. Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) studies are also conducted to evaluate drug-polymer compatibility, crystallinity, and possible interactions within the formulation.^[86]

Hydrogel characterization includes evaluation of viscosity, pH, spreadability, swelling index, gel strength, and bio adhesive properties. Viscosity plays an important role in determining ease of application and retention at the site of infection. The pH of the formulation should be compatible with skin pH to minimize irritation and ensure patient comfort. Spreadability studies evaluate the ease with which the gel can be applied uniformly over the affected area.^[87]

Swelling studies are performed to assess the water absorption capacity of the hydrogel matrix, which influences drug diffusion and release behavior. Bio adhesion studies determine the ability of the formulation to remain attached to the skin or mucosal surface for prolonged

periods. Increased bio adhesion enhances drug retention and improves localized therapeutic action.^[58]

In vitro drug release studies are essential for evaluating the release kinetics of antifungal drugs from nanosponge hydrogels. These studies help determine whether the formulation provides sustained and controlled release over extended durations. Ex vivo skin permeation studies using animal or human skin models are further conducted to assess drug penetration through biological barriers.^[88]

Antifungal activity studies are performed against fungal strains such as *Candida albicans*, *Aspergillus fumigatus*, and dermatophytes to evaluate therapeutic effectiveness. Stability studies under different environmental conditions are also conducted to determine the physical and chemical stability of the formulation during storage.^[89]

Overall, formulation optimization and detailed characterization are critical for the successful development of nanosponge hydrogel systems with enhanced antifungal activity, controlled drug release, improved stability, and superior patient acceptability. These studies provide valuable insights into the therapeutic potential and clinical applicability of nanosponge hydrogels in antifungal therapy.^[32]

3.1 Preparation Methods of Nanosponges

The preparation method used for nanosponge fabrication plays a crucial role in determining the particle size, porosity, drug loading capacity, entrapment efficiency, stability, and release characteristics of the final formulation. Various preparation techniques have been developed depending on the type of polymer, crosslinking agent, physicochemical properties of the drug, and intended therapeutic application. In antifungal drug delivery, the selection of an appropriate preparation method is essential to obtain stable nanosponges with high encapsulation efficiency and controlled drug release behavior.^[46]

The commonly employed preparation methods for nanosponges include solvent method, emulsion solvent diffusion method, ultrasound-assisted synthesis, melt method, quasi-emulsion solvent diffusion technique, and microwave-assisted synthesis.^[46]

3.1.1 Solvent Method

The solvent method is one of the most widely used techniques for nanosponge preparation, particularly for cyclodextrin-based nanosponges. In this method, the polymer is dissolved in a

suitable polar aprotic solvent such as dimethylformamide or dimethyl sulfoxide, followed by the addition of a cross-linking agent under continuous stirring.^[62]

The reaction mixture is heated at a controlled temperature for a specific duration to facilitate crosslinking between the polymer and cross-linker, resulting in the formation of porous nanosponge structures. The prepared nanosponges are then cooled, washed to remove unreacted materials, and dried under vacuum.^[62]

This method offers several advantages including simple processing, good control over crosslinking density, and formation of highly porous nanosponges with high drug loading capacity. However, the use of organic solvents may require extensive purification steps to eliminate solvent residues.^[90]

3.1.2 Emulsion Solvent Diffusion Method

The emulsion solvent diffusion method is commonly used for preparing polymeric nanosponges using hydrophobic polymers such as ethyl cellulose. In this technique, the polymer and drug are dissolved in an organic solvent to form the internal phase, while an aqueous phase containing surfactants or stabilizers is prepared separately.^[91]

The organic phase is slowly added to the aqueous phase under continuous stirring, forming an emulsion. Diffusion and evaporation of the solvent lead to precipitation of the polymer and formation of nanosponge particles. The resulting nanosponges are collected by filtration or centrifugation and subsequently dried.^[92]

This method provides good control over particle size and allows preparation of nanosponges with high encapsulation efficiency. It is particularly suitable for poorly water-soluble antifungal drugs.^[93]

3.1.3 Quasi-Emulsion Solvent Diffusion Method

The quasi-emulsion solvent diffusion method is a modified form of emulsion solvent diffusion and is extensively employed for topical nanosponge formulations. In this method, the drug and polymer are dissolved in an internal organic phase, which is then dispersed into an external aqueous phase containing stabilizers such as polyvinyl alcohol.^[94]

Continuous stirring leads to solvent diffusion from the internal phase into the external phase, resulting in precipitation of polymeric nanosponges. The prepared nanosponges are then filtered, washed, and dried.^[92]

This method is highly advantageous because it produces uniform nanosponge particles with narrow size distribution and excellent drug entrapment efficiency. Additionally, the process is relatively simple and reproducible.^[90]

3.1.4 Ultrasound-Assisted Synthesis

Ultrasound-assisted synthesis is a solvent-free or low-solvent method in which polymer and crosslinking agents are mixed and subjected to ultrasonic irradiation. Ultrasound energy promotes rapid and efficient crosslinking by generating localized high temperature and pressure conditions.^[95]

This technique offers several advantages such as reduced reaction time, improved reaction efficiency, and formation of nanosponges with uniform particle size. It also minimizes the use of toxic organic solvents, making the process more environmentally friendly.^[96]

3.1.5 Melt Method

In the melt method, the polymer and cross-linking agent are mixed and heated above their melting point without using solvents. Continuous stirring facilitates uniform mixing and crosslinking, leading to formation of nanosponge structures. After cooling, the solid mass is crushed, washed, and dried to obtain nanosponges.^[62] The melt method is considered a simple and eco-friendly technique because it avoids the use of organic solvents. However, it may not be suitable for heat-sensitive antifungal drugs due to the elevated processing temperature.^[93]

3.1.6 Microwave-Assisted Synthesis

Microwave-assisted synthesis is an advanced technique that utilizes microwave irradiation to accelerate the crosslinking reaction between polymers and cross-linking agents. Microwave energy provides rapid and uniform heating, resulting in reduced reaction time and improved product yield.^[97] Nanosponges prepared using microwave-assisted synthesis often exhibit uniform particle size, enhanced porosity, and improved drug loading characteristics. This method is considered energy-efficient and suitable for large-scale production.^[98]

3.1.7 Drug Loading into Nanosponges

Drug loading may be performed during or after nanosponge preparation depending on the drug properties and formulation approach. In the loading process, the prepared nanosponges are dispersed in a drug solution and subjected to stirring or sonication to facilitate drug entrapment within the porous cavities. Excess untrapped drug is removed by centrifugation or filtration.^[99] The efficiency of drug loading depends on factors such as polymer type, pore size, drug solubility, crosslinking density, and preparation method.^[100]

3.1.8 Factors Affecting Nanosponge Preparation

Several formulation and process parameters influence the characteristics of prepared nanosponges, including, Type and concentration of polymer, Nature and amount of cross-linking agent, Drug-to-polymer ratio, Solvent selection, stirring speed and duration, Temperature and reaction time, Surfactant concentration, Optimization of these factors is essential for obtaining nanosponges with desirable particle size, porosity, stability, and controlled drug release behavior. Overall, the preparation method significantly affects the physicochemical and therapeutic properties of nanosponges. Appropriate selection and optimization of fabrication techniques are therefore critical for developing effective nanosponge hydrogel systems for antifungal therapy.^[32]

3.2 Incorporation into Hydrogel Systems

The incorporation of drug-loaded nanosponges into hydrogel matrices is a crucial step in the development of nanosponge hydrogel systems for antifungal therapy. This process combines the sustained release and drug encapsulation capabilities of nanosponges with the bio adhesive, hydrating, and skin-compatible properties of hydrogels. The resulting hybrid formulation enhances topical drug delivery, improves residence time at the site of infection, and provides prolonged antifungal activity.^[83]

Hydrogels act as secondary carrier systems that uniformly disperse nanosponge particles within a three-dimensional polymeric network. This dual delivery approach improves formulation stability, facilitates controlled drug release, and enhances patient acceptability compared to conventional topical formulations. Proper incorporation of nanosponges into hydrogels is essential to maintain particle stability, avoid aggregation, and preserve the physicochemical characteristics of both components.^[101]

3.2.1 Selection of Hydrogel Base

The choice of hydrogel polymer significantly influences the viscosity, spreadability, swelling behavior, bio adhesion, and release profile of the final formulation. Hydrophilic polymers capable of forming stable gel matrices are commonly selected for nanosponge incorporation.^[43]

Carbopol is one of the most frequently used gelling agents due to its excellent viscosity-building capacity, transparency, and bio adhesive properties. Hydroxypropyl methylcellulose (HPMC), chitosan, sodium alginate, xanthan gum, polyvinyl alcohol, and poloxamers are also widely employed depending on the desired formulation characteristics.^[102]

The selected hydrogel base should be compatible with the nanosponge system and should not alter the structural integrity or drug release behavior of the encapsulated antifungal agent.

3.2.2 Method of Incorporation

The incorporation process generally involves dispersing the prepared drug-loaded nanosponges into a previously prepared hydrogel base under continuous stirring to ensure uniform distribution. The hydrogel polymer is first hydrated in purified water or suitable solvent and allowed to swell completely to form a homogeneous gel matrix.^[103] After gel formation, nanosponge dispersion is gradually added to the hydrogel under gentle stirring or mechanical mixing. Continuous mixing helps achieve uniform incorporation of nanosponge particles throughout the gel system while preventing particle aggregation. The final formulation is then adjusted for pH, viscosity, and consistency according to topical application requirements.^[75]

In some formulations, sonication may be used during incorporation to improve nanosponge dispersion and maintain particle uniformity within the hydrogel matrix.

3.2.3 Role of Auxiliary Excipients

Various excipients are incorporated during hydrogel formulation to improve stability, texture, and therapeutic performance.

- **Penetration enhancers** such as propylene glycol, ethanol, and oleic acid improve skin permeation of antifungal drugs.
- **Humectants** like glycerol maintain hydration and prevent drying of the gel.

- **Preservatives** such as methylparaben and propylparaben prevent microbial contamination.
- **Surfactants and stabilizers** help maintain uniform dispersion of nanosponges within the hydrogel matrix.
- **Neutralizing agents** such as triethanolamine are used in Carbopol-based gels to adjust pH and achieve optimum gel consistency.

The concentration and compatibility of these excipients must be carefully optimized to avoid instability or irritation.^[104]

3.2.4 Mechanism of Drug Release from Nanosponge Hydrogels

Drug release from nanosponge hydrogel systems generally occurs through a combination of diffusion, swelling, and erosion mechanisms. Initially, water penetrates the hydrogel matrix, causing swelling of the polymer network. The encapsulated antifungal drug then diffuses gradually from the nanosponge cavities into the hydrogel matrix and subsequently into the skin.^[32]

The hydrogel acts as a diffusion barrier that prolongs drug release and maintains sustained therapeutic concentrations at the site of infection. Factors such as nanosponge pore size, hydrogel viscosity, crosslinking density, and polymer composition influence the release kinetics.^[105]

3.2.5 Advantages of Incorporation into Hydrogel Systems

Incorporating nanosponges into hydrogels offers several therapeutic and formulation-related advantages, Improved localization and prolonged retention at the application site, Sustained and controlled antifungal drug release, Enhanced skin hydration and permeation, Reduced drug leakage and systemic absorption, Better spreadability and patient comfort, Increased formulation stability, Enhanced antifungal efficacy against resistant fungal infections. Hydrogels also provide a cooling and soothing effect, which is beneficial in inflammatory fungal conditions associated with itching and irritation.^[35]

3.2.6 Factors Affecting Incorporation Efficiency

Several formulation parameters influence the successful incorporation of nanosponges into hydrogel systems, including, Type and concentration of hydrogel polymer, Viscosity of the gel matrix, Particle size and surface charge of nanosponges, Drug loading capacity, mixing

speed and duration, pH and ionic strength of the formulation, Improper optimization may result in particle aggregation, phase separation, or altered drug release behavior.^[106]

3.2.7 Stability of Nanosponge Hydrogels

The physical and chemical stability of nanosponge hydrogels is essential for maintaining therapeutic effectiveness during storage and application. Stability studies evaluate parameters such as appearance, pH, viscosity, drug content, particle size, and microbial contamination under different environmental conditions.^[107] A stable hydrogel system should maintain uniform nanosponge dispersion without sedimentation or phase separation. Proper packaging and storage conditions further contribute to prolonged shelf life and formulation stability.^[108] The incorporation of nanosponges into hydrogel matrices represents a highly effective strategy for developing advanced topical antifungal delivery systems. This hybrid approach significantly improves drug retention, controlled release, permeation, and patient compliance, making nanosponge hydrogels promising candidates for enhanced antifungal therapy.^[32]

3.3 Physicochemical Characterization

Physicochemical characterization is a critical step in the development of nanosponge hydrogel systems because it provides essential information regarding the structural, morphological, mechanical, and functional properties of the formulation. Comprehensive characterization helps evaluate formulation quality, stability, drug release behavior, and therapeutic suitability for antifungal applications. These studies also ensure reproducibility, safety, and effectiveness of the developed nanosponge hydrogel system.^[32] The physicochemical properties of nanosponge hydrogels are influenced by several formulation parameters including polymer type, crosslinking density, nanosponge size, hydrogel composition, and drug loading efficiency. Therefore, systematic characterization is necessary to optimize formulation performance and achieve desired therapeutic outcomes.^[101]

3.3.1 Particle Size Analysis

Particle size is one of the most important parameters affecting drug release, skin permeation, stability, and therapeutic efficacy of nanosponges. Smaller particles possess larger surface area, resulting in improved interaction with biological membranes and enhanced penetration into infected tissues.^[84] Particle size analysis is commonly performed using dynamic light scattering (DLS), laser diffraction, or nanoparticle tracking analysis techniques. Nanosponge particles generally range between 50 and 500 nm depending on the preparation method and

formulation composition. Uniform particle size distribution is desirable for achieving consistent drug delivery and formulation stability.^[53]

3.3.2 Polydispersity Index (PDI)

Polydispersity index indicates the uniformity of particle size distribution within the nanosponge dispersion. A lower PDI value represents a homogeneous and monodisperse system, whereas higher values indicate broad particle size distribution and possible aggregation.^[96] PDI values below 0.3 are generally considered acceptable for stable nanosponge formulations. Uniform particle distribution contributes to improved reproducibility and therapeutic performance.

3.3.3 Zeta Potential Measurement

Zeta potential is used to determine the surface charge and colloidal stability of nanosponge particles. Adequate surface charge prevents particle aggregation through electrostatic repulsion and improves stability during storage.^[93] Zeta potential is measured using electrophoretic light scattering techniques. Positive or negative zeta potential values greater than ± 20 mV generally indicate good stability of nanosponge dispersions. Surface charge also influences interaction with skin membranes and drug permeation behavior.^[109]

3.3.4 Morphological Characterization

Morphological studies provide information regarding the shape, surface texture, porosity, and structural integrity of nanosponges. These characteristics significantly influence drug loading capacity and release behavior.^[90] Scanning electron microscopy (SEM) is commonly used to examine surface morphology and porous structure of nanosponges. Transmission electron microscopy (TEM) provides detailed information regarding internal structure and particle shape, while atomic force microscopy (AFM) helps evaluate surface topography and roughness.^[110] Nanosponges typically appear spherical or irregularly porous with interconnected cavities capable of entrapping antifungal drugs.

3.3.5 Drug Entrapment Efficiency and Drug Loading

Entrapment efficiency determines the percentage of drug successfully encapsulated within the nanosponge structure relative to the total drug used during formulation. Drug loading capacity indicates the amount of drug present per unit weight of nanosponges.^[96] These parameters are usually determined by separating untrapped drug through centrifugation or filtration followed by spectrophotometric or chromatographic analysis. High entrapment

efficiency is desirable for improving therapeutic efficacy and reducing drug wastage.^[111] Entrapment efficiency depends on factors such as polymer concentration, drug-to-polymer ratio, crosslinking density, and preparation method.

3.3.6 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis is performed to identify functional groups and evaluate possible interactions between the drug, polymer, and other formulation components. This technique helps confirm successful encapsulation and compatibility of antifungal drugs within the nanosponge hydrogel system.^[112] Characteristic peaks corresponding to drug and polymer functional groups are analyzed to detect any chemical incompatibility or structural modifications occurring during formulation.

3.3.7 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry is used to study thermal behavior, crystallinity, and phase transitions of the formulation components. DSC helps determine whether the antifungal drug exists in crystalline or amorphous form after encapsulation.^[113] Reduction or disappearance of characteristic drug melting peaks may indicate successful drug entrapment and conversion into an amorphous state, which can improve solubility and dissolution behavior.

3.3.8 X-Ray Diffraction (XRD) Analysis

XRD studies are conducted to evaluate the crystalline nature of drugs and polymers within the formulation. Sharp diffraction peaks indicate crystalline structure, whereas broad peaks suggest amorphous characteristics.^[114] Encapsulation of antifungal drugs within nanosponges often reduces drug crystallinity, leading to enhanced solubility and bioavailability.

3.3.9 pH Determination

The pH of nanosponge hydrogels is an important parameter for topical application because it affects skin compatibility and formulation stability. The pH should ideally remain close to the physiological skin pH to avoid irritation and discomfort.^[115] pH measurements are generally performed using a digital pH meter under standardized conditions.

3.3.10 Viscosity and Rheological Studies

Viscosity determines the consistency, spreadability, and retention of hydrogel formulations on the skin surface. Rheological studies evaluate flow behavior and mechanical properties of the gel system. Brookfield viscometers or rheometers are commonly used to measure viscosity.

An ideal hydrogel should exhibit pseudoplastic or shear-thinning behavior, allowing easy application and improved retention at the infected site.^[116]

3.3.11 Spreadability Studies

Spreadability studies assess the ease with which the hydrogel can be uniformly applied over the skin surface. Good spreadability improves patient comfort and ensures uniform drug distribution. Spreadability is influenced by viscosity, polymer concentration, and gel consistency.^[59]

3.3.12 Swelling Index and Water Uptake Studies

Swelling studies evaluate the water absorption capacity of the hydrogel matrix. Hydration and swelling influence drug diffusion, release kinetics, and skin hydration. The swelling index is determined by measuring the increase in hydrogel weight after immersion in aqueous media for a specified duration.^[117]

3.3.13 In Vitro Drug Release Studies

In vitro release studies are performed to evaluate the release profile and kinetics of antifungal drugs from nanosponge hydrogels. These studies help determine whether the formulation provides sustained and controlled drug release.^[112] Drug release is commonly studied using Franz diffusion cells or dialysis membrane methods under simulated physiological conditions. Release data are analyzed using kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.^[118]

3.3.14 Ex Vivo Skin Permeation Studies

Ex vivo permeation studies assess the ability of antifungal drugs to penetrate through biological membranes such as animal or human skin. These studies are important for predicting in vivo topical performance. Enhanced permeation indicates improved delivery of antifungal agents into deeper infected tissues.^[119]

3.3.15 Antifungal Activity Studies

Antifungal efficacy of nanosponge hydrogels is evaluated against fungal strains such as *Candida albicans*, *Aspergillus fumigatus*, and dermatophytes using methods such as agar diffusion, broth dilution, or zone of inhibition studies. Improved antifungal activity compared to conventional formulations indicates successful enhancement of drug delivery and therapeutic performance.^[120]

3.3.16 Stability Studies

Stability studies are conducted under different environmental conditions to evaluate physical appearance, pH, viscosity, drug content, particle size, and microbial stability over time. Stable nanosponge hydrogels should maintain uniform consistency, drug content, and therapeutic performance throughout storage. Overall, physicochemical characterization provides critical information regarding the quality, stability, functionality, and therapeutic potential of nanosponge hydrogel systems. These studies are essential for optimization and successful development of effective antifungal formulations with enhanced drug delivery and clinical efficacy.^[32]

3.3.1 Particle Size and Morphology

Particle size and morphology are among the most critical physicochemical parameters in the characterization of nanosponge hydrogel systems. These properties significantly influence drug loading capacity, surface area, stability, skin permeation, drug release behavior, and overall therapeutic efficacy of antifungal formulations. Proper control of particle size and morphology is essential for achieving stable nanosponge systems with enhanced topical drug delivery performance.^[74]

Particle Size of Nanosponges

Particle size refers to the average diameter of nanosponge particles and is generally expressed in nanometers (nm). The particle size of nanosponges commonly ranges between 50 and 500 nm depending on the polymer type, crosslinking density, preparation method, and formulation conditions.^[47] Smaller nanosponge particles possess a larger surface area-to-volume ratio, which enhances interaction with biological membranes and facilitates deeper penetration into infected skin layers. Reduced particle size also improves uniform drug distribution and increases dissolution rate of poorly water-soluble antifungal drugs. In topical antifungal therapy, nanosized particles enhance localization of the drug at the infection site and improve permeation through the stratum corneum.^[110] Particle size additionally affects formulation stability and drug release kinetics. Larger particles may exhibit slower drug release due to longer diffusion pathways, whereas smaller particles generally provide faster and more uniform release profiles. However, excessively small particles may aggregate because of high surface energy, thereby reducing formulation stability. Therefore, optimization of particle size is important for balancing stability and therapeutic performance.^[121] Several formulation and process parameters influence nanosponge particle

size, including, Type and concentration of polymer, Nature of cross-linking agent, Drug-to-polymer ratio, stirring speed and homogenization conditions, Solvent system used, Surfactant concentration, Temperature during preparation, High stirring speed and proper surfactant concentration generally produce smaller and more uniform nanosponge particles.^[62]

Methods for Particle Size Analysis

Particle size analysis is commonly performed using various analytical techniques, including:

Dynamic Light Scattering (DLS)

Dynamic light scattering is the most widely used technique for determining average particle size and particle size distribution of nanosponges. It measures fluctuations in scattered light caused by Brownian motion of particles suspended in liquid media.^[122] DLS provides rapid and accurate measurement of nanoscale particles and is commonly used to determine mean particle diameter and polydispersity index (PDI).

Laser Diffraction

Laser diffraction measures particle size distribution based on light scattering patterns produced by particles. This method is suitable for a wide range of particle sizes and provides detailed information regarding size distribution.^[123]

Nanoparticle Tracking Analysis (NTA)

Nanoparticle tracking analysis visualizes and tracks the movement of individual particles under Brownian motion, enabling accurate determination of particle size distribution and concentration.^[124]

Morphology of Nanosponges

Morphology refers to the shape, surface characteristics, porosity, and structural arrangement of nanosponge particles. Morphological properties play a significant role in determining drug entrapment efficiency, release behavior, and interaction with biological membranes.^[47]

Nanosponges generally exhibit spherical or irregular porous structures with interconnected nanochannels and cavities capable of encapsulating antifungal drugs. Their porous architecture contributes to high surface area and enhanced drug loading capacity.^[46] The surface morphology of nanosponges also influences hydrogel incorporation and stability. Smooth and uniformly porous particles facilitate better dispersion within hydrogel matrices and improve overall formulation consistency.

Techniques for Morphological Characterization

Scanning Electron Microscopy (SEM)

Scanning electron microscopy is widely used to examine the surface morphology and porous structure of nanosponges. SEM provides high-resolution images showing particle shape, surface texture, and pore distribution.^[99] SEM studies often reveal spherical or sponge-like porous structures characteristic of nanosponge formulations.

Transmission Electron Microscopy (TEM)

Transmission electron microscopy provides detailed information regarding internal structure, particle size, and morphology at nanoscale resolution. TEM is particularly useful for confirming nanoscale dimensions and evaluating structural uniformity.^[125]

Atomic Force Microscopy (AFM)

Atomic force microscopy evaluates surface topography and roughness by scanning the particle surface using a microscopic probe. AFM provides three-dimensional surface images and detailed structural information.^[126]

Importance in Antifungal Drug Delivery

Particle size and morphology directly affect the therapeutic performance of nanosponge hydrogel systems in antifungal therapy. Optimized nanosponge particles enhance penetration into infected tissues and fungal biofilms, resulting in improved antifungal efficacy. Uniform morphology and appropriate porosity further contribute to controlled drug release and increased drug retention at the site of infection.^[127] Smaller and uniformly distributed nanosponges dispersed within hydrogels provide enhanced stability, better spreadability, and prolonged residence time on the skin surface. Additionally, porous morphology improves encapsulation efficiency and protects antifungal drugs from degradation. Overall, particle size and morphological characterization are essential for evaluating the quality, stability, and functionality of nanosponge hydrogel systems. Proper optimization of these parameters significantly contributes to improved drug delivery, sustained release, and enhanced therapeutic outcomes in antifungal therapy.^[32]

3.3.2 Entrapment Efficiency

Entrapment efficiency is one of the most important characterization parameters in nanosponge hydrogel systems because it determines the amount of antifungal drug successfully encapsulated within the nanosponge structure relative to the total drug used

during formulation. High entrapment efficiency is essential for achieving improved therapeutic efficacy, sustained drug release, enhanced stability, and reduced drug wastage in antifungal drug delivery systems.^[120] Nanosponges possess highly porous three-dimensional structures with interconnected cavities that enable efficient incorporation of both hydrophilic and lipophilic drugs. The extent of drug entrapment within these cavities significantly influences the release profile, bioavailability, and overall performance of the nanosponge hydrogel formulation.^[128]

Definition of Entrapment Efficiency

Entrapment efficiency (EE%) is defined as the percentage of drug encapsulated within the nanosponges compared to the total amount of drug initially added during formulation preparation. Higher entrapment efficiency indicates effective drug incorporation and better utilization of the antifungal agent within the delivery system.^[85]

Methods for Determination of Entrapment Efficiency

Entrapment efficiency is generally determined by separating free untrapped drug from drug-loaded nanosponges followed by quantitative drug analysis.

Centrifugation Method

In this method, nanosponge dispersion is centrifuged at high speed to separate the encapsulated nanosponges from the free drug present in the supernatant. The amount of untrapped drug in the supernatant is measured using analytical techniques such as UV-visible spectrophotometry or high-performance liquid chromatography (HPLC).

The entrapped drug amount is then calculated by subtracting the free drug from the total drug initially used.^[111]

Filtration Method

Filtration techniques using membrane filters may also be employed to separate nanosponges from free drug molecules. The filtrate containing untrapped drug is analyzed for drug concentration.^[130]

Dialysis Method

Dialysis membrane techniques are sometimes used for determining free drug concentration by allowing diffusion of untrapped drug across a semipermeable membrane while retaining the nanosponge particles.^[108]

Factors Affecting Entrapment Efficiency

Several formulation and process-related factors influence the entrapment efficiency of nanosponge systems.

Polymer Type and Concentration

The nature and concentration of polymer significantly affect drug encapsulation. Polymers with higher porosity and suitable affinity for the drug generally provide better entrapment efficiency. Increasing polymer concentration often enhances encapsulation capacity due to the availability of more cavities for drug incorporation.^[131]

Crosslinking Density

Crosslinking density affects pore size and internal structure of nanosponges. Moderate crosslinking improves structural stability and drug entrapment, whereas excessive crosslinking may reduce cavity size and limit drug incorporation.^[54]

Drug-to-Polymer Ratio

An optimum drug-to-polymer ratio is essential for efficient encapsulation. Very high drug concentration may saturate nanosponge cavities and reduce entrapment efficiency due to drug leakage or precipitation.^[90]

Drug Solubility and Physicochemical Properties

Poorly water-soluble lipophilic drugs generally exhibit better encapsulation within hydrophobic nanosponge cavities. Molecular size and drug-polymer compatibility also influence entrapment behavior.

Preparation Method

The fabrication technique used for nanosponge preparation significantly impacts entrapment efficiency. Methods such as quasi-emulsion solvent diffusion and solvent evaporation often produce higher drug loading due to better drug-polymer interaction.^[94]

Stirring Speed and Processing Conditions

Processing variables including stirring speed, temperature, solvent selection, and surfactant concentration influence particle formation and drug incorporation efficiency.

Significance in Nanosponge Hydrogel Systems

Entrapment efficiency directly affects the drug release behavior of nanosponge hydrogels. Formulations with high encapsulation efficiency generally provide prolonged and controlled release because a larger amount of drug remains retained within the porous nanosponge network.^[101]

High drug entrapment also improves stability of antifungal agents by protecting them from hydrolysis, oxidation, and photodegradation. Furthermore, efficient drug encapsulation reduces the risk of burst release and minimizes local irritation associated with sudden high drug concentrations.^[132]

Relationship with Drug Release

Entrapment efficiency and drug release are closely related parameters. Higher drug loading within nanosponges usually results in sustained release profiles because the drug diffuses gradually from internal cavities into the hydrogel matrix and subsequently into the skin.

However, excessively high entrapment may sometimes slow drug release beyond the desired therapeutic range. Therefore, proper optimization is necessary to balance entrapment efficiency and release kinetics.^[73]

Overall, entrapment efficiency is a critical parameter in the characterization of nanosponge hydrogel systems. It provides valuable information regarding drug incorporation capacity, formulation quality, and therapeutic potential. Optimized entrapment efficiency contributes significantly to enhanced antifungal activity, sustained release, improved stability, and better clinical performance of nanosponge-based antifungal formulations.^[32]

3.3.3 Rheological Properties and pH

Rheological properties and pH are important physicochemical parameters in the characterization of nanosponge hydrogel systems intended for topical antifungal therapy. These parameters significantly influence formulation stability, spreadability, skin retention, patient acceptability, and drug release behavior. Proper optimization of rheological characteristics and pH is essential to ensure the safety, effectiveness, and ease of application of nanosponge-based hydrogels.^[133]

Rheological Properties of Nanosponge Hydrogels

Rheology refers to the study of flow and deformation behavior of materials under applied stress. In hydrogel formulations, rheological properties determine viscosity, consistency, spreadability, extrudability, and retention of the formulation at the site of application. These characteristics directly affect patient compliance and therapeutic performance.

An ideal nanosponge hydrogel should possess appropriate viscosity to ensure easy application while remaining sufficiently adhesive to stay at the infected site for prolonged periods. Excessively low viscosity may result in rapid spreading and leakage, whereas very high viscosity may hinder uniform application and patient comfort.^[134]

Viscosity

Viscosity is one of the most important rheological parameters and represents the resistance of the hydrogel to flow. It depends on factors such as polymer concentration, degree of crosslinking, hydration capacity, and nanosponge content within the formulation. Hydrogels prepared using polymers such as Carbopol, HPMC, chitosan, and xanthan gum generally exhibit suitable viscosity for topical applications. Increased polymer concentration usually leads to higher viscosity due to enhanced intermolecular interactions and network formation. Viscosity is commonly measured using Brookfield viscometers or rotational rheometers under controlled temperature conditions. The viscosity profile helps predict formulation stability and performance during storage and application.^[135]

Flow Behavior

Most nanosponge hydrogels exhibit non-Newtonian pseudoplastic or shear-thinning behavior. In pseudoplastic systems, viscosity decreases with increasing shear stress. This behavior is advantageous for topical formulations because the gel becomes less viscous during spreading and regains viscosity after application, thereby improving retention at the application site. Shear-thinning behavior enhances, Ease of application, Uniform spreading over the skin surface, Patient comfort, Stability of the hydrogel matrix, some formulations may also exhibit thixotropic behavior, in which viscosity gradually recovers after removal of shear stress. Thixotropy improves physical stability and prevents phase separation during storage.^[136]

Spreadability and Extrudability

Rheological properties strongly influence spreadability and extrudability of nanosponge hydrogels. Spreadability refers to the ease with which the formulation can be uniformly

distributed over the skin surface, whereas extrudability represents the ease of removing the gel from tubes or containers.^[59]

Hydrogels with optimal rheological behavior provide smooth application, better patient acceptance, and efficient drug distribution at the infected site.

Influence on Drug Release

The viscosity and internal structure of hydrogel matrices affect diffusion of antifungal drugs from the nanosponge system. Highly viscous hydrogels generally retard drug diffusion and prolong release, whereas lower viscosity systems may permit faster drug release.

Thus, rheological optimization is essential for achieving controlled and sustained antifungal drug delivery.^[22]

Factors Affecting Rheological Properties

Several formulation variables influence rheological behavior of nanosponge hydrogels, including, Type and concentration of hydrogel polymer, Crosslinking density, Presence of nanosponges, Water content and hydration level, Temperature, pH of the formulation, Presence of electrolytes or additives, Proper balancing of these factors is necessary to obtain stable and effective hydrogel systems.^[37]

pH of Nanosponge Hydrogels

The pH of topical formulations is another critical parameter because it influences skin compatibility, drug stability, microbial growth, and patient comfort. Human skin generally possesses a slightly acidic pH ranging from 4.5 to 6.5, which helps maintain barrier integrity and normal skin flora.

Nanosponge hydrogels intended for dermal application should ideally possess pH values close to physiological skin pH to minimize irritation, dryness, burning sensation, or allergic reactions.^[112]

Importance of pH in Antifungal Hydrogels

Proper pH maintenance offers several advantages, prevents skin irritation and inflammation, maintains formulation stability, enhances patient acceptability, supports optimum antifungal activity, prevents degradation of pH-sensitive drugs and polymers. Certain antifungal agents

may exhibit altered solubility and stability under highly acidic or alkaline conditions. Therefore, maintaining suitable pH is essential for preserving therapeutic effectiveness.^[28]

Measurement of pH

The pH of nanosponge hydrogels is generally measured using a calibrated digital pH meter. Measurements are performed at room temperature after dispersing the gel in distilled water or buffer solution. Consistent pH values indicate formulation stability and compatibility with skin tissues.^[115]

Factors Affecting pH

Several formulation components influence the pH of nanosponge hydrogels, including, Nature of hydrogel polymer, Type of crosslinking agent, Drug properties, Presence of neutralizers or buffers, Storage conditions In Carbopol-based hydrogels, neutralizing agents such as triethanolamine are commonly added to adjust pH and achieve desired gel consistency.^[104]

Relationship Between Rheology and pH

pH can significantly influence the rheological behavior of hydrogel systems. Certain polymers undergo ionization changes at different pH values, affecting viscosity, swelling, and gel consistency. For example, Carbopol exhibits increased swelling and viscosity at neutral or slightly alkaline pH due to ionization of carboxylic groups.^[138]

Therefore, simultaneous optimization of rheological properties and pH is essential for obtaining stable nanosponge hydrogels with desirable consistency, drug release behavior, and skin compatibility.

Overall, rheological properties and pH are crucial quality attributes of nanosponge hydrogel systems. Proper characterization and optimization of these parameters contribute significantly to formulation stability, patient compliance, controlled drug release, and enhanced therapeutic efficacy in antifungal therapy.^[37]

3.3.4 Stability and Drug Release Studies

Stability and drug release studies are essential components in the characterization of nanosponge hydrogel systems intended for antifungal therapy. These studies provide important information regarding the physicochemical integrity, storage behavior, therapeutic performance, and release kinetics of the formulation. Proper evaluation of stability and drug

release characteristics ensures that nanosponge hydrogels maintain their safety, efficacy, and quality throughout their shelf life and during clinical application.^[106]

Stability Studies

Stability studies are conducted to evaluate the ability of nanosponge hydrogel formulations to maintain their physical, chemical, microbiological, and therapeutic properties under different environmental conditions over time. Stability assessment is important because changes in formulation characteristics may affect drug release, antifungal activity, patient acceptability, and overall therapeutic efficacy.^[139]

Nanosponge hydrogels may undergo instability due to factors such as temperature fluctuations, moisture exposure, oxidation, pH changes, polymer degradation, or particle aggregation. Therefore, systematic stability evaluation is necessary to determine appropriate storage conditions and shelf life.^[106]

Stability Parameters Evaluated

Several physicochemical parameters are monitored during stability studies..

Physical Appearance

Visual inspection is performed to evaluate color, homogeneity, texture, consistency, phase separation, precipitation, and syneresis of the hydrogel formulation. Stable nanosponge hydrogels should remain smooth, uniform, and free from visible changes during storage.

Particle Size and Zeta Potential

Particle size analysis helps identify nanosponge aggregation or instability over time. Stable formulations maintain relatively constant particle size and surface charge throughout storage.

Zeta potential measurements are also useful in evaluating colloidal stability because reduced surface charge may lead to aggregation and sedimentation.

Drug Content

Drug content analysis determines whether the antifungal drug remains chemically stable within the formulation during storage. Significant reduction in drug content may indicate degradation or leakage from the nanosponge structure.

Drug content is generally analyzed using UV-visible spectrophotometry or high-performance liquid chromatography (HPLC).^[96]

pH Evaluation

Changes in pH may indicate polymer degradation, drug instability, or microbial contamination. The pH of nanosponge hydrogels should remain within acceptable physiological limits to ensure skin compatibility and therapeutic effectiveness.^[106]

Viscosity and Rheological Behavior

Viscosity measurements help determine whether the hydrogel maintains its consistency and spreadability during storage. Significant viscosity changes may affect drug release behavior and patient acceptability.^[140]

Microbial Stability

Microbial contamination studies are important for topical formulations containing high water content. Preservative effectiveness and microbial growth are monitored to ensure product safety.^[141]

Storage Conditions for Stability Studies

Stability studies are generally conducted under various environmental conditions according to regulatory guidelines. Common storage conditions include, refrigerated condition: $4 \pm 2^{\circ}\text{C}$, Room temperature: $25 \pm 2^{\circ}\text{C}$ with 60% relative humidity, Accelerated condition: $40 \pm 2^{\circ}\text{C}$ with 75% relative humidity. The formulations are evaluated periodically over specified time intervals such as 1, 3, 6, and 12 months.^[142]

Importance of Stability in Antifungal Therapy

Stable nanosponge hydrogel systems ensure consistent drug release, prolonged antifungal activity, and patient safety. Enhanced stability is particularly important for antifungal drugs sensitive to light, heat, hydrolysis, or oxidation, such as amphotericin B and itraconazole.^[65] Encapsulation within nanosponges protects antifungal agents from environmental degradation and contributes to improved shelf life and therapeutic performance.

Drug Release Studies

Drug release studies are performed to evaluate the release pattern, kinetics, and diffusion behavior of antifungal drugs from nanosponge hydrogel systems. These studies are critical for

determining whether the formulation provides sustained and controlled drug delivery suitable for prolonged antifungal therapy.^[32]

The release behavior of nanosponge hydrogels is influenced by several factors including nanosponge porosity, polymer composition, crosslinking density, hydrogel viscosity, swelling behavior, and drug-polymer interactions.^[143]

Mechanism of Drug Release

Drug release from nanosponge hydrogels generally occurs through multiple mechanisms including:

Diffusion

Drug molecules diffuse gradually from the porous nanosponge cavities into the surrounding hydrogel matrix and subsequently through the skin.

Swelling-Controlled Release

Hydrogel matrices absorb water and swell, allowing controlled diffusion of the encapsulated antifungal drug.

Erosion Mechanism

In some formulations, gradual erosion or degradation of the hydrogel matrix contributes to drug release. The combined action of these mechanisms provides prolonged and controlled antifungal drug delivery.

Methods for Drug Release Studies

Franz Diffusion Cell Method

The Franz diffusion cell technique is one of the most commonly used methods for evaluating drug release from topical nanosponge hydrogels. The formulation is placed in the donor compartment separated by a dialysis membrane or biological membrane from the receptor compartment containing dissolution medium. Samples are collected at predetermined intervals and analyzed for drug concentration.^[88]

Dialysis Membrane Method

Drug-loaded nanosponge hydrogel is enclosed within a dialysis membrane immersed in dissolution medium under continuous stirring. Drug diffusion through the membrane is monitored over time.^[92]

Release Media Used

Commonly used release media include, Phosphate buffer saline (PBS), Simulated skin fluid, Ethanol-buffer mixtures, Acidic or neutral buffer solutions depending on drug solubility, The release medium should maintain sink conditions throughout the experiment.^[144]

Significance in Antifungal Therapy

Controlled and sustained release of antifungal drugs from nanosponge hydrogels provides several therapeutic advantages, Prolonged antifungal activity, Reduced dosing frequency, Improved patient compliance, better retention at infection site, reduced systemic toxicity, Enhanced treatment of chronic fungal infections, Sustained release also helps maintain therapeutic drug concentration for extended durations, improving effectiveness against fungal biofilms and resistant strains.^[145] Overall, stability and drug release studies are essential for evaluating the quality, reliability, and therapeutic performance of nanosponge hydrogel systems. These studies provide valuable insights into formulation behavior, shelf life, release kinetics, and clinical applicability in antifungal drug delivery.^[32]

4. Therapeutic Applications in Antifungal Therapy

Nanosponge hydrogel systems have emerged as highly promising platforms for the delivery of antifungal agents due to their ability to enhance drug solubility, improve skin penetration, provide controlled release, and reduce systemic toxicity. These advanced delivery systems have demonstrated significant therapeutic potential in the treatment of various superficial and deep fungal infections. By combining the porous drug-encapsulating characteristics of nanosponges with the bio adhesive and hydrating properties of hydrogels, nanosponge hydrogels offer improved localized drug delivery and prolonged antifungal action.^[32]

Fungal infections often require long-term therapy because of poor drug penetration, recurrent infections, and development of fungal resistance. Conventional topical formulations frequently fail to maintain therapeutic drug concentration at the site of infection, leading to incomplete eradication of fungal pathogens. Nanosponge hydrogel systems address these limitations by enhancing retention of antifungal drugs within infected tissues and enabling sustained release over extended durations.^[32]

Several antifungal drugs including fluconazole, itraconazole, ketoconazole, terbinafine, voriconazole, clotrimazole, miconazole, and amphotericin B have been successfully incorporated into nanosponge hydrogel formulations. These systems have shown improved

antifungal efficacy against various fungal pathogens such as *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, and dermatophytes.^[32]

One of the major therapeutic applications of nanosponge hydrogels is in the treatment of superficial fungal infections such as dermatophytosis, cutaneous candidiasis, and tinea infections. The nanosized porous structure of nanosponges enhances drug permeation through the stratum corneum and facilitates deeper penetration into infected skin layers. Simultaneously, the hydrogel matrix prolongs contact time at the application site, resulting in improved therapeutic effectiveness and reduced dosing frequency.^[146]

In the management of cutaneous candidiasis, nanosponge hydrogel formulations containing azole antifungals have demonstrated enhanced retention and sustained antifungal activity against *Candida* species. Improved drug localization helps achieve higher local drug concentration while minimizing systemic exposure and associated adverse effects.^[66]

Nanosponge hydrogels have also shown promising applications in the treatment of nail fungal infections such as onychomycosis. Nail infections are particularly difficult to treat because of the dense keratinized structure of the nail plate, which limits drug penetration. Nanosponge-based systems improve drug permeation through nail tissues and provide prolonged release of antifungal agents, thereby enhancing therapeutic outcomes.^[147]

In addition to skin and nail infections, nanosponge hydrogels are being explored for mucosal antifungal therapy. Bio adhesive hydrogel matrices facilitate prolonged retention on mucosal surfaces, improving localized delivery of antifungal drugs for oral and vaginal candidiasis. Such systems may reduce dosing frequency and improve patient compliance during long-term treatment.^[145]

Another important therapeutic application is the treatment of fungal biofilm-associated infections. Fungal biofilms act as protective matrices that limit penetration of conventional antifungal agents and contribute to chronic and resistant infections. Due to their nanoscale size and enhanced permeation capabilities, nanosponge hydrogels can penetrate biofilm structures more effectively and deliver sustained antifungal concentrations directly to fungal cells. This improves therapeutic efficacy against resistant fungal strains and recurrent infections.^[148]

Nanosponge hydrogels also offer advantages in the delivery of poorly water-soluble antifungal drugs. Encapsulation within nanosponge cavities enhances the apparent solubility and dissolution rate of lipophilic antifungal agents, improving their bioavailability and therapeutic performance. This is particularly beneficial for drugs such as itraconazole and ketoconazole, which exhibit poor aqueous solubility in conventional formulations.^[149]

Controlled and sustained release properties of nanosponge hydrogels further contribute to reduced dosing frequency and improved patient adherence. Continuous release of antifungal drugs maintains therapeutic concentrations at the infection site for prolonged periods, reducing the likelihood of treatment failure and recurrence.^[150]

Recent studies have additionally explored multifunctional nanosponge hydrogel systems incorporating natural antifungal agents, essential oils, and combination therapies to enhance antifungal spectrum and minimize resistance development. Stimuli-responsive nanosponge hydrogels capable of releasing drugs in response to pH or temperature changes are also being investigated as advanced approaches for targeted antifungal therapy.^[11]

Overall, nanosponge hydrogel systems represent highly effective and versatile delivery platforms for antifungal therapy. Their ability to improve drug solubility, permeation, stability, retention, and controlled release makes them promising alternatives to conventional topical antifungal formulations. These systems hold significant potential for improving therapeutic outcomes in superficial, mucosal, nail, and biofilm-associated fungal infections while minimizing toxicity and enhancing patient compliance.^[2]

4.1 Enhanced Skin Permeation and Retention

Enhanced skin permeation and prolonged retention are among the most significant therapeutic advantages of nanosponge hydrogel systems in antifungal drug delivery. Effective treatment of fungal skin infections requires sufficient penetration of antifungal agents through the stratum corneum and prolonged maintenance of therapeutic drug concentration at the infected site. Conventional topical formulations such as creams, lotions, and ointments often exhibit limited skin penetration and poor retention, resulting in inadequate therapeutic efficacy and recurrence of infection. Nanosponge hydrogel systems have been developed to overcome these limitations and improve localized antifungal therapy.^[32]

The stratum corneum acts as the primary barrier to transdermal and topical drug delivery. Its highly organized lipid-rich structure restricts penetration of many antifungal drugs, particularly those with poor aqueous solubility and high molecular weight. Nanosponges, due to their nanoscale size and porous architecture, facilitate closer interaction with the skin surface and improve diffusion of encapsulated antifungal agents into deeper layers of the skin.^[32]

The small particle size of nanosponges significantly increases surface area, enhancing contact with the stratum corneum and promoting better permeation. In addition, the porous structure of nanosponges improves drug solubilization and maintains a high concentration gradient across the skin barrier, which favors enhanced drug diffusion into infected tissues.^[74]

Hydrogel matrices further contribute to improved permeation by hydrating the skin surface. Hydration of the stratum corneum causes swelling and loosening of tightly packed lipid structures, thereby increasing skin permeability. The high-water content of hydrogels creates a moist microenvironment that facilitates diffusion of antifungal drugs through the epidermal layers.^[151]

Several hydrogel polymers such as chitosan, Carbopol, HPMC, and alginate also exhibit bio adhesive properties that prolong the residence time of the formulation on the skin surface. Increased retention at the site of application allows sustained drug release and continuous availability of antifungal agents for extended periods. This prolonged contact improves drug absorption and therapeutic effectiveness while reducing the need for frequent reapplication.^[12]

Penetration enhancers commonly incorporated into nanosponge hydrogels, such as propylene glycol, ethanol, oleic acid, and surfactants, further improve skin permeation by temporarily altering the lipid organization of the stratum corneum. These agents increase drug partitioning into the skin and facilitate deeper penetration of antifungal molecules.^[152]

Enhanced permeation is particularly beneficial in the treatment of chronic fungal infections involving deeper skin layers, nails, or fungal biofilms. Fungal biofilms create protective barriers that reduce penetration of conventional antifungal agents and contribute to drug resistance. Nanosponge hydrogels can penetrate these biofilm structures more effectively due

to their nanosized particles and sustained drug release characteristics, leading to improved antifungal activity.

Retention of antifungal drugs within the skin layers is another important factor influencing therapeutic success. Conventional formulations are often rapidly removed by sweating, washing, friction, or skin movements, resulting in reduced drug concentration at the infection site. Nanosponge hydrogels exhibit excellent adhesion and viscosity, allowing prolonged retention and localized drug accumulation within infected tissues.^[146]

The controlled release properties of nanosponges also contribute to sustained retention of therapeutic drug levels. Encapsulated antifungal agents are gradually released from the porous nanosponge cavities into the hydrogel matrix and subsequently into the skin, maintaining prolonged antifungal activity and minimizing fluctuations in drug concentration.

Ex vivo permeation studies and skin retention experiments have demonstrated significantly higher drug deposition and prolonged retention of antifungal agents from nanosponge hydrogel systems compared to conventional topical formulations. Increased skin retention not only improves therapeutic efficacy but also reduces systemic absorption and associated adverse effects.^[153] Enhanced skin permeation and retention collectively result in several clinical advantages, including, Improved delivery of antifungal drugs into deeper infected tissues, Prolonged therapeutic action, Reduced dosing frequency, Better management of resistant fungal infections, Enhanced treatment of fungal biofilms, Reduced systemic toxicity, Improved patient compliance ,overall, nanosponge hydrogel systems provide an efficient strategy for enhancing skin permeation and retention of antifungal agents. Their unique combination of nanoscale drug carriers and bio adhesive hydrogel matrices significantly improves localized antifungal therapy and offers superior therapeutic performance compared to conventional topical formulations.^[2]

4.2 Controlled and Sustained Drug Release

Controlled and sustained drug release is one of the most important therapeutic advantages offered by nanosponge hydrogel systems in antifungal therapy. Conventional topical antifungal formulations often release drugs rapidly after application, leading to an initial burst release followed by a rapid decline in drug concentration below therapeutic levels. Such fluctuations may reduce treatment effectiveness, necessitate frequent application, and contribute to poor patient compliance. Nanosponge hydrogel systems are specifically

designed to overcome these limitations by providing prolonged and regulated release of antifungal agents at the site of infection.^[32]

Nanosponges possess highly porous three-dimensional structures with interconnected nanochannels capable of encapsulating antifungal drugs within their internal cavities. These porous networks act as reservoir systems that gradually release the drug over an extended period through diffusion-controlled mechanisms. The hydrogel matrix surrounding the nanosponges further regulates drug diffusion and prolongs release duration, thereby maintaining sustained therapeutic concentrations at the application site.^[154]

The mechanism of controlled drug release from nanosponge hydrogels generally involves multiple sequential processes. Initially, the hydrogel matrix absorbs water from the surrounding environment and undergoes swelling. Water penetration into the hydrogel facilitates diffusion of the drug from the nanosponge cavities into the hydrated polymer network. The drug subsequently diffuses slowly through the hydrogel matrix and penetrates into the skin layers. This dual diffusion barrier created by both nanosponges and hydrogels contributes to prolonged and controlled release behavior.^[82]

Several formulation factors influence the drug release profile of nanosponge hydrogel systems. The type and concentration of polymer, degree of crosslinking, pore size of nanosponges, hydrogel viscosity, and drug-polymer interactions collectively determine the release kinetics. Increased crosslinking density generally reduces pore size and slows drug diffusion, thereby extending the release duration. Similarly, highly viscous hydrogel matrices retard drug movement and contribute to sustained release.^[155]

Controlled release systems offer significant therapeutic advantages in antifungal therapy. Continuous release of antifungal agents maintains effective drug concentration at the infected site for prolonged periods, ensuring persistent antifungal activity against fungal pathogens. Sustained drug exposure is particularly important in chronic fungal infections and biofilm-associated infections where prolonged therapy is required for complete eradication of fungal cells.^[156]

Nanosponge hydrogels also minimize the burst release phenomenon commonly observed in conventional formulations. Sudden release of large amounts of antifungal drugs may cause

local irritation, toxicity, or rapid depletion of the drug reservoir. Controlled release from nanosponge systems reduces these risks and improves formulation safety and tolerability.^[53]

The sustained release behavior of nanosponge hydrogels contributes to reduced dosing frequency and improved patient adherence. Frequent application of conventional antifungal formulations may be inconvenient for patients and often leads to incomplete treatment. By maintaining prolonged antifungal activity, nanosponge hydrogels reduce the need for repeated administration and improve overall treatment compliance.^[32]

Another important advantage of sustained drug release is enhanced management of fungal biofilms. Biofilms protect fungal cells from conventional antifungal agents by limiting drug penetration and creating resistant microenvironments. Prolonged release of antifungal drugs from nanosponge hydrogels maintains therapeutic concentrations for extended periods, increasing the likelihood of penetrating biofilms and eradicating resistant fungal cells.^[74]

Controlled release additionally reduces systemic absorption and associated adverse effects by localizing drug action primarily at the infected site. This is particularly beneficial for potent antifungal drugs such as amphotericin B and azoles, which may produce systemic toxicity when absorbed in significant amounts.^[22]

Various *in vitro* drug release studies have demonstrated that nanosponge hydrogel formulations provide significantly prolonged release profiles compared to conventional creams and gels. Drug release kinetics are commonly analyzed using mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to understand the release mechanism and diffusion behavior.^[157,158]

4.3 In Vitro, Ex Vivo, and In Vivo Antifungal Studies

In vitro, *ex vivo*, and *in vivo* antifungal studies are essential for evaluating the therapeutic efficacy, permeation behavior, safety, and clinical potential of nanosponge hydrogel systems in antifungal therapy. These studies provide comprehensive information regarding antifungal activity, drug release characteristics, skin penetration, retention, and biological performance of the developed formulations. The combination of these experimental approaches helps establish the effectiveness of nanosponge hydrogels as advanced topical antifungal delivery systems.^[32]

Nanosponge hydrogel formulations have been extensively investigated against various fungal pathogens including *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, *Microsporum gypsum*, and other dermatophytes. Comparative studies with conventional creams, ointments, and gels have demonstrated superior antifungal efficacy and prolonged therapeutic action of nanosponge-based systems.^[2]

4.3.1 In Vitro Antifungal Studies

In vitro studies are laboratory-based investigations performed to evaluate antifungal activity, drug release behavior, and fungal growth inhibition under controlled conditions. These studies are widely used for preliminary assessment of nanosponge hydrogel formulations before animal or clinical studies.^[32]

Antifungal Activity Evaluation

The antifungal efficacy of nanosponge hydrogels is commonly assessed using microbiological techniques such as, Agar diffusion method, Cup-plate method, Disc diffusion assay, Broth dilution method, Minimum inhibitory concentration (MIC) determination, in agar diffusion studies, the formulation is applied to culture media inoculated with fungal strains, and the zone of inhibition is measured after incubation. Larger inhibition zones indicate stronger antifungal activity.^[159]

Broth dilution and MIC studies determine the minimum concentration of antifungal drug required to inhibit visible fungal growth. Nanosponge hydrogel systems often demonstrate lower MIC values compared to conventional formulations due to enhanced drug permeation and sustained release.^[112]

Evaluation Against Fungal Biofilms

Biofilm-associated fungal infections are highly resistant to conventional therapy. In vitro biofilm studies are conducted to assess the ability of nanosponge hydrogels to penetrate and disrupt fungal biofilms.^[32]

The nanoscale size and prolonged release properties of nanosponges facilitate improved drug penetration into biofilm matrices, resulting in enhanced antifungal activity against resistant fungal cells.^[32]

In Vitro Drug Release Studies

In vitro release experiments evaluate the release kinetics and sustained release behavior of antifungal drugs from nanosponge hydrogels. These studies are commonly performed using dialysis membranes or Franz diffusion cells under simulated physiological conditions.

Controlled and prolonged drug release observed in these studies confirms the reservoir function of nanosponges within the hydrogel matrix.^[143]

4.3.2 Ex Vivo Antifungal and Skin Permeation Studies

Ex vivo studies are performed using excised animal or human skin tissues to evaluate drug permeation, retention, and penetration behavior across biological barriers. These studies provide valuable information regarding topical delivery performance under conditions closer to physiological environments.^[160]

Skin Permeation Studies

Franz diffusion cells are commonly used for ex vivo permeation studies. In this method, excised skin is mounted between donor and receptor compartments, and the nanosponge hydrogel formulation is applied to the skin surface. Drug permeation into the receptor medium is measured over time.^[161] Ex vivo studies have demonstrated significantly enhanced permeation of antifungal drugs from nanosponge hydrogels compared to conventional formulations. Improved permeation is attributed to, small particle size of nanosponges, Increased drug solubility, Hydration effect of hydrogels, Presence of penetration enhancers, Sustained release characteristics

Skin Retention Studies

Skin retention studies determine the amount of antifungal drug retained within skin layers after application. Higher drug retention is desirable for localized antifungal therapy because it prolongs therapeutic action and minimizes systemic absorption.^[162] Nanosponge hydrogel systems generally exhibit increased drug deposition within epidermal and dermal tissues due to prolonged contact time and enhanced penetration.^[32]

Histopathological Evaluation

Histopathological studies may be conducted to evaluate skin integrity and irritation after application of nanosponge hydrogels. Tissue sections are examined microscopically for signs of inflammation, edema, irritation, or tissue damage.^[163]

Most nanosponge hydrogel systems prepared using biocompatible polymers show minimal skin irritation and good safety profiles.

4.3.3 In Vivo Antifungal Studies

In vivo studies are performed using animal models to evaluate the therapeutic efficacy, pharmacological performance, toxicity, and safety of nanosponge hydrogel formulations under physiological conditions. These studies provide important preclinical evidence regarding clinical applicability.^[146]

Animal Models for Fungal Infections

Various animal models are used to study topical fungal infections, including, Rat models, Mouse models, Guinea pig models, Rabbit skin infection models, Fungal infections are experimentally induced using fungal strains such as *Candida albicans* or dermatophytes, followed by treatment with nanosponge hydrogel formulations.^[66]

Evaluation Parameters

In vivo antifungal studies evaluate several therapeutic parameters, including, Reduction in fungal burden, Healing of infected lesions, Reduction in inflammation and erythema, Recovery of skin structure, Duration of antifungal effect, Recurrence rate, Nanosponge hydrogels often demonstrate faster healing, greater reduction in fungal growth, and prolonged therapeutic activity compared to conventional topical formulations.^[105]

Pharmacodynamic and Pharmacokinetic Studies

Pharmacodynamic studies evaluate the biological response produced by the formulation, whereas pharmacokinetic studies assess drug absorption, distribution, retention, and elimination.^[164] Localized drug delivery from nanosponge hydrogels generally results in higher skin concentration with lower systemic exposure, thereby reducing toxicity.

Skin Irritation and Toxicity Studies

Safety evaluation is an important aspect of in vivo studies. Skin irritation tests are conducted to assess erythema, edema, allergic reactions, or tissue damage following repeated application. Biodegradable polymers used in nanosponge hydrogels generally provide good biocompatibility and minimal irritation, making them suitable for long-term antifungal therapy.^[32]

Therapeutic Significance of Antifungal Studies

The combined results of in vitro, ex vivo, and in vivo studies demonstrate several therapeutic advantages of nanosponge hydrogel systems, including, Enhanced antifungal efficacy, Improved drug permeation and retention, Sustained and controlled drug release, Better penetration into fungal biofilms, Reduced systemic toxicity, Improved treatment of resistant fungal infections, Enhanced patient compliance, These studies confirm that nanosponge hydrogels are highly promising delivery systems for effective topical antifungal therapy. Overall, in vitro, ex vivo, and in vivo antifungal investigations provide critical evidence regarding the therapeutic potential, safety, and clinical applicability of nanosponge hydrogel systems. Their superior performance compared to conventional formulations supports their growing importance in advanced antifungal drug delivery research.^[32]

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