HYDROGEL-BASED DELIVERY SYSTEMS FOR TOPICAL ANTIFUNGAL THERAPY: A REVIEW

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Fungal skin infections are a significant global health concern, with a high prevalence, recurrence, and economic burden. Traditional antifungal therapies, such as creams and oral formulations, often suffer from limitations, including poor aqueous solubility, low bioavailability, and the emergence of drug resistance, which can compromise their therapeutic efficacy. In this context, hydrogel-based delivery systems have emerged as a promising approach to address these challenges. Hydrogels offer several advantages, including high drug loading capacity, controlled drug release, improved biocompatibility, and enhanced penetration through the skin barrier. This comprehensive review article provides an in-depth analysis of recent advancements in developing antifungal hydrogels. It explores the various preparation methods. The review also highlights the therapeutic applications of antifungal hydrogels, covering a wide range of fungal skin infections. Furthermore, the article examines the current trends and future perspectives in the field, including the incorporation of novel active pharmaceutical ingredients, the exploration of hybrid systems, and the development of stimuli-responsive hydrogels for enhanced targeting and responsiveness. By synthesizing the latest research and addressing the unmet needs in antifungal therapy, this review aims to provide valuable insights and guidance for researchers and clinicians working towards the development of more effective and patient-centric antifungal treatment approaches.

Keywords: fungal skin infections, hydrogels, antifungal agents, drug delivery system

INTRODUCTION

Skin infections due to fungi are types of infections affecting the surface of the skin, hair, mucous membrane, and skin adnexa. Almost 20-25% global population has been infected by dermatophytes or superficial skin infections.[1] The estimated annual costs related to hospitalized and outpatients with fungal diseases exceeded $7.2 billion in 2017. The total highest cost of any disease of hospitalized patients with *Candida* and *Aspergillus* infections was $2.6 billion and half of outpatients have dermatophyte infections, which bear costs of $802 million.[2] The major causes of fungal diseases are dermatophytes and *Candida*, and these diseases have high prevalence, relapse, and epidemic rates. A warm and humid environment is favorable for fungal growth, and when the human skin is a suitable environment for fungal growth, then dermatomycosis occurs.[3]

Fungal skin and nail infections are a common occurrence, with a significant impact on patients' quality of life. Effective topical or transdermal antifungal therapy is crucial for managing these conditions. Hydrogel-based drug delivery systems offer several advantages for this application, including improved drug solubility, enhanced permeability across the skin barrier, and the potential for controlled and sustained release of antifungal agents.[4-6] Hydrogels are widely used in drug delivery systems. These include the ability of drug release in a pronlonged and controlled way, which maintain a high local concentration of

medicinal preparations in the affected tissues for a prolonged period of time.[7]

To overcome the skin barrier effects, rapidly acting hydrogels are prepared from copolymers of poly(N-isopropylacrylamide) and photo cross-linkable benzophenone.[8] Polyethylene glycol (PEG) based hydrogels are now under recent research due to their self-modification property. PEG-based hydrogels have excellent water permeability. They can also be chemically or biologically modified to alter their properties, such as the degree of crosslinking or hydrophilicity.[9]

In addition to the hydrogel properties, the incorporation of antifungal agents, such as miconazole, can further enhance the therapeutic efficacy of these delivery systems for fungal skin infections. A broad-spectrum antifungal miconazole nitrate is mostly used topically to treat dermatophytosis, superficial mycoses, and *Candida* infections as an oral gel. However, its therapeutic efficacy is reduced because of poor water solubility.[3] Jain *et al*. successfully formulated hydrogel with miconazole loaded solid lipid nanoparticles for topical use that provides prolonged release of miconazole. A broad-spectrum antifungal agent itraconazole is used to treat a wide range of dermatophytes, *e.g. Micosporum*, *Epidermophyton*, and *Trichophyton* spp. For the treatment of *Tinea pedis*, an optimized nonionic surfactant vesicles hydrogel has proved better antifungal activity, as compared to commercial medications.[10] For the treatment of dermatophytosis, sertaconazole – an imidazole anti-fungal agent – is used topically in the form of creams, hydrogels, *etc*. Sertaconazole also has low permeability, like other anti-fungals. Researchers have added 2.5% w/w sertaconazole containing microemulsions to 0.75% w/w Carbopol 940 to formulate a hydrogel of sertaconazole microemulsions. Due to the high permeability of the hydrogel of sertaconazole microemulsions, it increased the skin penetration of sertaconazole, which enhanced the antifungal properties of sertaconazole and decreases the concentration of the drug needed to treat the fungal infection.[11]

This comprehensive review article aims to provide an in-depth analysis of the recent advancements in the development of hydrogel-based delivery systems for antifungal therapies. It explores the various preparation methods, the unique properties and performance characteristics of these hydrogel systems, and their therapeutic applications in the management of a wide range of fungal skin infections. Furthermore, the review examines the current trends and future perspectives in the field, including the incorporation of novel active pharmaceutical ingredients, the exploration of hybrid systems, and the development of stimuli-responsive hydrogels for enhanced targeting and responsiveness.

This review focuses on hydrogel-based delivery systems for improved antifungal therapy. The hydrogels discussed include both natural and synthetic polymeric hydrogels. Natural hydrogels, such as those based on polysaccharides like chitosan and alginate, offer advantages like biocompatibility and biodegradability. Synthetic hydrogels, particularly those derived from polyethylene glycol (PEG), provide tunable physical and chemical properties that can be optimized for drug delivery applications. Key characteristics of the hydrogels reviewed include their water permeability, swelling behavior, mechanical strength, and capacity for chemical or biological modification. These hydrogel properties are critical in designing effective topical or transdermal antifungal drug delivery systems.

COMMON SKIN FUNGAL INFECTIONS

Superficial fungal infections of the skin, hair, and nails are among the most prevalent types of fungal diseases worldwide. As illustrated in Figure 1, these infections can be broadly classified according to the depth of penetration of the pathogenic fungi into the skin layers. Infections confined to the stratum corneum, the outermost layer of the epidermis, are considered to be “superficial” fungal infections. Examples include tinea versicolor and some cases of pityriasis versicolor. Infections that penetrate deeper into the epidermis or even the dermis are classified as “cutaneous” mycoses, such as tinea corporis, tinea pedis, and onychomycosis (fungal nail infections).[3] This depth of penetration is a key factor determining the required treatment approach and the efficacy of topical antifungal therapies.

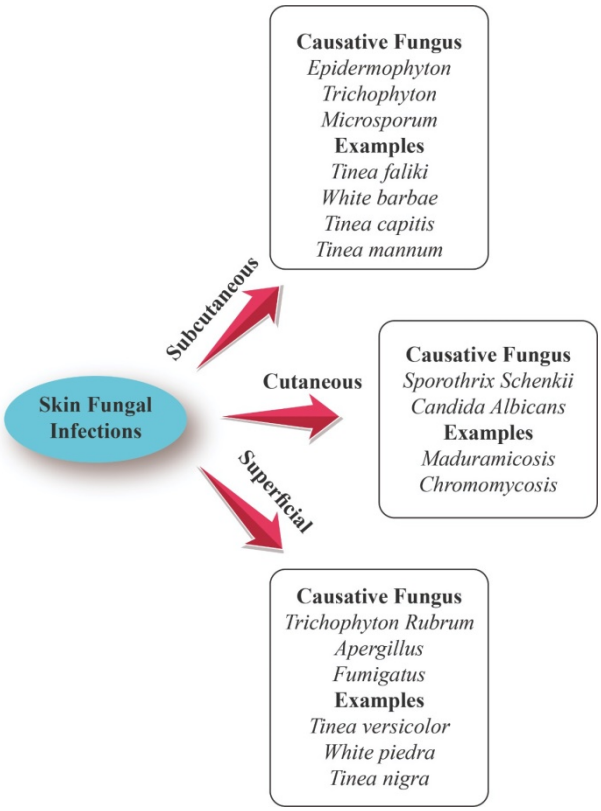

Figure 1: Fungal infections

Dermatophytosis

The agents that cause tinea infections are called as dermatophytes. These are a class of filamentous fungi that cause parasitism and can infect keratinized tissues, including the hair, nails, and stratum corneum of the epidermis.[12] Dermatophytes cause severe itching by triggering a skin inflammatory response that results in erythema and scaling.[13] Tinea has a complex pathogenesis that starts with infectious spores coming into contact with the skin, adhering to surface cells, invading keratin layers by keratinase release, and causing inflammation.[14] The hard keratin is broken down by keratinases into low molecular weight components that dermatophytes can use.[15] Different groupings are used to subcategorize dermatophytes. They are divided into three species: *Microsporum*, *Epidermophyton*, and *Trichophyton*, based on their microscopic traits. They are categorized as anthropophilic species, which only infect humans, zoophilic species, which are mostly harmful to other animals, and geophilic species, which are found in soil, based on their typical habitats.[16]

Pityriasis versicolor

The second most prevalent fungal infection after dermatophytosis is pityriasis versicolor, better known as tinea versicolor. Nondermatophytic fungi are currently becoming major pathogens of superficial mycoses.[17] The yeast species *Malassezia* is the cause of this illness. The most common cause of infections in the microbiology of skin, soft tissue, bone, and joints is *Malassezia globosa*. Skin commensals called *Malassezia* yeasts have the potential to contribute to the pathophysiology of seborrheic dermatitis, dandruff, and Malassezia folliculitis. They could exacerbate psoriasis on the head and neck and atopic dermatitis. These yeasts are lipophilic, and they live naturally on the seborrheic areas of the skin. These organisms grow more easily *in vitro* when oil is added.[18]

Candidiasis

These are group of yeasts that are considered opportunistic and can cause serious infections in immune-compromised persons. Candidiasis is the fourth major nosocomial infection with very high mortality rate.[19] Candida genus comprises of about 200 species, with 15 isolated from infections in humans and animals. Among them about 80% of infections are caused by *Candida albicans*.[20] Typically, candidiasis affects the mucous membranes, hands, fingernails, vaginal and perigenital areas, axillary folds, and the skin

beneath a woman's breasts. Other yeasts (non-*Candida albicans*) that cause candidiasis include *Candida krusei*, *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, and *Candida glabrata*.[21]

Mold infections

Molds are regarded as oppertuinistic and not commonly pathogenic in healthy hosts. People frequently come in contact with them as thier fragments and spores get into the air we breathe.[22] These fungi are known as non-dermatophytic filamentous and can cause similar clinical manifestations as tinea unguium, tinea manuum and tinea pedis, and can be found in feet and toenails. These infections are most common in tropical climates. *Aspergillus niger* is the most common member of this group and others include *Acremonium* sp., *Scopulariopsis brevicaulis*, *Fusarium* sp., *Scytalidium hyalinum* and *Hendersonula toluroidea.*[13]

HYDROGEL-BASED DELIVERY SYSTEMS FOR ANTIFUNGAL THERAPY

Hydrogels, defined as cross-linked polymeric networks capable of absorbing and retaining large amounts of water, have emerged as promising delivery vehicles for topical and transdermal antifungal therapies. These hydrophilic matrices can be formulated from a diverse range of natural and synthetic polymers, each offering distinct advantages in terms of biocompatibility, biodegradability, and functional properties. The preparation of hydrogels for antifungal drug delivery often involves techniques, such as solution casting, *in situ* gelation, and freeze-drying. The choice of the cross-linking method (*e.g*., ionic, covalent, physical) and the degree of cross-linking can significantly impact the hydrogel's swelling behavior, network structure, and drug loading/release properties. Additionally, the incorporation of stimuli-responsive moieties, such as pH-sensitive or thermosensitive groups, can impart triggered drug release capabilities to the hydrogel system. When designing hydrogel-based antifungal formulations, key considerations include the solubility, stability, and permeability of the antifungal agent, as well as the hydrogel's bioadhesive and occlusive properties to enhance skin penetration and retention. The optimization of hydrogel composition and structure is crucial to achieve desirable drug release kinetics, mechanical strength, and compatibility with the target application site.[9] Depending on the nature of the polymers used, hydrogels can be classified into three broad categories: natural, synthetic, and semi-synthetic.

Methods for the preparation of hydrogels

Antifungal hydrogels can be prepared using a variety of methods, depending on the specific polymers and active pharmaceutical ingredients (APIs) involved. Common preparation techniques are described below.

Physical crosslinking

This method involves the use of non-covalent interactions, such as hydrogen bonding, ionic interactions, or hydrophobic interactions, to form the hydrogel network. Examples include the ionic crosslinking of alginate with calcium ions or the thermal gelation of chitosan-based hydrogels.

Chemical crosslinking

In this approach, the hydrogel network is formed through covalent bond formation, typically using crosslinking agents like glutaraldehyde, N,N'-methylenebisacrylamide, or various diisocyanates. This method offers greater control over the mechanical properties and stability of the hydrogel.

Photopolymerization

Hydrogels can be prepared by *in situ* photopolymerization of monomers or macromers in the presence of a photoinitiator. This technique allows for the production of hydrogels with precise spatial and temporal control, making it suitable for the incorporation of light-sensitive antifungal agents.

Enzymatic crosslinking

Certain enzymes, such as horseradish peroxidase or transglutaminase, can be used to catalyze the formation of covalent bonds between specific functional groups, leading to the development of enzymatically crosslinked hydrogels.

Figure 2 visualizes the interconnectedness and variety of techniques used in the preparation of hydrogels, which are an important class of materials with various applications in fields such as biomedicine, pharmaceuticals, and material science.

Figure 2: Techniques for the preparation of hydrogels

Hydrogels loaded with synthetic antifungal agents

Amphotericin B

Different strategies based on hydrogels have been developed for amphotericin B. For instance, Zumbuehl *et al*. prepared amphotericin B loaded dextran based hydrogels, which they called amphogels. Their product effectively killed *Candida albicans* within 2 hours contact and can be reused for as long as 53 days.[23] Fructan polysacchride based hydrogels have also been developed, providing pore-like structure to encapsulate amphotericin B, which follows diffusion model to release the drug.[24]

Fluconazole

Fluconazole (FLC) is a widely used triazole antifungal agent effective against a broad spectrum of fungal pathogens, including *Candida* and *Cryptococcus* species.[14] FLC exhibits good water solubility, making it a suitable candidate for incorporation into hydrogel delivery systems. Several studies have investigated the use of hydrogels to improve the topical and transdermal delivery of FLC. Polyethylene glycol (PEG) coated fluconazole (FLC) nanoparticles incorporated into carbopol hydrogel showed better release profile and antifungal potential. It followed 1st order release kinetics and super case II transport mechanism. The PEG-coated nanoparticles loaded hydrogel had better antifungal activity than the pure drug containing hydrogel when checked using the agar well diffusion method.[25] In a similar study, Rewak-Soroczynska and co-workers observed better antifungal activity of fluconazole-loaded, 6-anhydro-α-l-galacto-β-d-galactan hydrogels against *Candida* species (*Candida albicans*, *Candida tropicalis* and *Candida glabarata*), *Rhodotorula* species (*Rhodotorula mucilaginosa* and *Rhodotorula rubra*) and *Cryptococcus* species (*Cryptococcus neoformans* and *Cryptococcus gatti*).[26]

Miconazole

Miconazole nitrate loaded cubosome dispersons used as antifungal agents were formulated by the emulsification technique using lipid phase monoolein, nonionic surfactants and polaxamer 407. To formulate cubosomal hydrogels, the optimum formulae were incorporated in carboxymethyl cellulose (CMC) or hydroxypropylmethyl cellulose (HPMC) based hydrogels.[27] The cubosomal hydrogels enhanced the activity of the miconazole nitrate by increasing the penetration through fungal cell wall and inhibiting the synthesis of ergosterol.[28]

Itraconazole

Itraconazole nanomicelles loaded hydrophillic gel was developed to optimize the treatment of superficial fungal disease sporotrichosis. A mortality rate of 5.3% was observed with itraconazole nanomicelles loaded hydrophillic gel

and oral itraconazole, in comparison to 21.3% with oral itraconazole.[29] A formulation of microemulsion based hydrogel for skin use was prepared with benzyl alcohol as an oil and transcutol as surfactant, a mixture of ethanol and phosphatidyl choline (3:2) as a co-surfactant and 0.7% xanthan gum or Carbopol-940 as gelling agent.[30] In another study, a nanoemulsion based hydrogel of itraconazole was developed, which was used transdermally for the treatment of onychomycosis. For the preparation of these hydrogels, an optimized nanoemulsion was preparared using lecithin (surfactant) and sodium cholate (co-surfactant), and was incorporated into a Carbopol-934 (3%) solution.[31] The emulsion solvent diffusion technique was used to prepare the itraconazole loaded nanosponges with different concentrations of ethyl cellulose (polymer), polyvinyl alcohol (surfactant) and dichloromethane (crosslinker). To prepare the hydrogel formulation, the nanosponges were loaded into Carbopol-940 solution. These itraconazole nanosponges loaded hydrogels exhibited improved features, like increased solubility, and drug release.[32] For the treatment of onychomycosis due to *Trichophyton mentagrophytes*, a chitosan nanoparticle based hydrogel was prepared. This hydrogel formulation showed enhanced permeation of loaded lipophilic drugs, like itraconazole and difluorinated curcumin.[33] To enhance the transdermal penetration, liposomal hydrogels were developed using Carbopol. The percent drug released from liposomal hydrogels is ranging from 48.04% to 99.92% in 24 hours.[34] To overcome the low skin permeability of itraconazole, transferosomes based hydrogels of hydroxypropyl methylcellulose (HPMC) were prepared by the thin lipid film hydration technique, using the different surfactants, such as sodium lauryl sulfate (SLS) and sodium deoxycholate (SDC).[35]

Variconazole

To increase the drug absorption at the site of action and to minimize the systemic side effects, variconazole containg microemulsion based hydrogels were formulated as a topical drug delivery system. For the preparation of microemulsion based hydrogels, microemulsions were prepared using benzyl alcohol as an oil, N-methyl-2-pyrrolidone as a surfactant, and an ethanol/phosphatidylcholine mixture (3:2, w/w) as a cosurfactant. These prepared microemulsions were then gellified using Carbopol 940 and xanthan gum as gelling agents.[36] A nanostructured lipid carrier-based hydrogel of variconazole was prepared for the treatment of mycotic skin infections. Nanostructured lipid carriers were formulated by using Precirol ATO5, Labrafil 1944CS, Tween 80 and loaded into Carbopol-940 hydrogel. This nanostructured lipid carrier-based hydrogel provides an alternative treatment for skin infection, such as candidiasis.[37] To prepare smart polymeric vehicles of the antifungal agent variconazole, a crosslinked hydrogel was developed by using chitosan (CS)-graft-poly(N-isopropyl acrylamide) (PNIPAAm) and polyvinyl alcohol (PVA) for topical application.[38] For preparation of variconazole microemulsified hydrogel, the titration technique was used to formulate microemulsified variconazole, which was then added to the carbopol gel.[39] For development of microemulsion based variconazole hydrogels, oleic acid and isopropyl myristate were used as oil phases, and the combination of Tween 20 and Tween 80 as surfactants, and PEG600 as cosurfactant. Carbopol-934 was used to gellify these microemulsions into hydrogels.[40]

Posaconazole

For effective treatment of topical skin fungal infections, a posaconazole microemulsion based hydrogel was developed. Microemulsions were prepared using oleic acid as a oil, Tween 80 as a surfactant and IPA co-surfactant. To formulate the hydrogel, an optimized posaconazole microemulsion was loaded into 1% w/v gel of Carbopol-934.[41] Sodium alginate and chitosan glutamate based cyrogels were formulated by the freeze–thaw technique to achieve enhanced antifungal activity against *Candida parapsilosis*, compared to traditional formulations.[42] The emulsion solvent diffusion method was used to prepare nanosponges of posaconazole by using polyvinyl alcohol (PVA) and dichloromethane. To formulate the hydrogel, posaconazole loaded nanosponges were incorporated into the polymeric gel of Carbopol-934, which showed better topical delivery and prolonged release pattern.[43] To improve patient compliance, achieve sustained drug release and circumvent repeated administration, a posaconazole loaded nanoemulsion based hydrogel was developed in Carbopol-934 that provided better antifungal

activity against *Candida albicans*, compared to other formulations.[44]

Luliconazole

A microemulsion based hydrogel of luliconazole was formulated for better penetration, solubilization and for effective antifugal treatment. Olive oil, with a suitable surfactant and co-surfactant, was used to prepare O/W type microemulsion. To develop the hydrogel, the luliconazole loaded microemulsion was incorporated by stirring into 1% viscous solution of Carbopol-934.[45] For enhanced solubility and dissolution, lulliconazole nanocrystals were prepared, which showed high skin retension and improved antifungal activity. These luliconazole nanocrystals were dispersed into Carbopol-934 for the development of the hydrogel.[46] A novel transungual formulation for the treatment of onychomycosis of nails was developed as an *in situ* gelling thermosensitive hydrogel. This hydrogel was formulated as an aqueous nail lacquer of luliconazole using poloxamer Pluronic F127.[47] In their study, Kapileshwari and co-workers formulated a drug delivery system of luliconazole loaded nanosponges using polyvinyl alcohol and ethyl cellulose polymers. The luliconazole was entrapped in these nanosponges, which acted as a porous nano-carrier system, and improved the permeation rate, retension time and drug availability at the affected skin site. Further, to develop the hydrogel, the nanosponges were incorporated into Carbopol-934 gel.[48] For the transdermal drug delivery and to enhance skin retention and penetration, M. S. Shaikh and co-workers developed a nanosuspension based nanogel of luliconazole by using modified starch esters. The prepared nanosuspensions were loaded into Carbopol-934 gel, which increased the accumulation into human cadaver skin ~3 times that of a standard cream, and proved to be useful to treat resistant fungal stains.[49] A nanoemulsion of luliconazole was optimized using the Box–Behnken statistical design, and a nanoemulgel was prepared by incorporation of these nanoemulsions into Carbopol-934, yielding promising results.[50] By the thin film hydration technique, invasomes of luliconazole were optimized and the hydrogel was developed by incorporating invasomes into Carbopol-934 gel. The obtained hydrogel proved to be a good carier, and an attractive approach to treat fungal infections by enhancing topical delivery.[51] In this latest study, to overcome the challenges of poor solubility and limited skin retention of the drug, nanoporous silica nanoparticles of luliconazole were developed by the sol-gel method, offering a novel strategy for treating cutaneous candidiasis fungal infection.[52]

Sertaconazole

By complex formation with cyclodextrin, a sertaconazole hydrogel was developed to treat *Candida albicans* fungal infections. To overcome the aqueous solubility limitation, the sertaconazole and cyclodextrin complex is a very attractive route with enhanced antifungal activity. A hydrogel of hydroxypropyl-*β*-cyclodextrin (HP-*β*-CD) was prepared by direct crosslinking of methylcellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMCNa), or dextran.[53] For effective treatment of cutaneous fungal infection, a microemulsion based Carbopol-934 hydrogel was prepared. The skin drug retention capacity of the sertaconazole microemulsion based hydrogel was more than three times that of commercial creams, and the hydrogel did not cause any erythema or edema on rabbit skin.[54] A vasicular based hydrogel of sertaconazole was developed for the treatment of dermal fungal infections of deep skin layers. A significant antifungal activity of sertaconazole vasicular based hydrogel was observed with lowest histopathological changes.[55] For the preparation of the sertaconazole nitrate hydrogel, flexisomes of sertaconazole nitrate were incorporated into the gel base, which had high flexibility and enhanced antifungal activity against *Candida albicans*.[56] N. F. Younes and co-workers formulated a sertaconazole nitrate glycerosomes based hydrogel by the thin film hydration technique. This formulation exhibited better deep skin penetration, as well as high local skin accumulation efficiency, which resulted in better fungal control.[57]

Table 1
Summary of antifungal hydrogels

Drug	Optimized formulation	Formulation techniques	Refs
Amphotericin B	Dextran-based hydrogels (amphogels)	Photopolymerization reaction	[23]
Fluconazole	PEG-coated nanoparticle loaded hydrogel	Solvent antisolvent precipitation method	[25]
Fluconazole	6-Anhydro-α-l-Galacto-β-d-Galactan hydrogel	Precipitation method	[26]
Miconazole	Cubosomes based hydrogel	Emulsification of monoglyceride/surfactant mixtures	[27]
Itraconazole	Microemulsion loaded hydrogel	Stirring	[30]
Itraconazole	Nanoemulsion loaded hydrogel	Stirring and ultrasonication	[31]
Itraconazole	Nanosponges loaded hydrogel	Emulsion solvent diffusion method	[32]
Itraconazole	Nanoparticle loaded hydrogel	Stirring	[33]
Itraconazole	Transferosomes loaded hydrogel	Thin lipid film hydration technique	[35]
Variconazole	Microemulsion based hydrogel	Stirring	[36]
Variconazole	Nanostructured lipid carrier-based hydrogel	High-pressure homogenization	[37]
Variconazole	Microemulsion based hydrogel	Water Titration Method	[39]
Variconazole	Polymeric vehicle based hydrogel	Mixing and Freeze–thaw method	[38]
Variconazole	Microemulsion based hydrogel	Water titration method	[40]
Posaconazole	Microemulsion based hydrogel	Stirring	[41]
Posaconazole	Sodium alginate and chitosan glutamate based cyrogels	Freeze–thaw technique	[42]
Luliconazole	Microemulsion based hydrogel	Stirring	[45]
Luliconazole	Thermoresponsive hydrogel	Stirring	[47]
Luliconazole	PVA and ethyl cellulose based naosponges loaded hydrogel	Emulsion solvent diffusion method	[48]
Luliconazole	Nanosuspension based nanogel	Stirring followed by microwave irradiation	[49]
Luliconazole	Nanoemulsion based hydrogel	High-speed homogenization	[50]
Luliconazole	Invosomes loaded hydrogel	Thin-film hydration method	[51]
Luliconazole	Silica based nanoporous nanoparticles loaded hydrogel	Sol−gel method	[52]
Sertaconazole	Microemulsion based hydrogel	stirring followed by ultrasonification	[54]
Sertaconazole	Flexisomes based hydrogel	Rotary evaporation sonication method	[56]
Sertaconazole	Glycerosomes based hydrogel	Thin-film hydration technique	[57]

HYDROGELS LOADED WITH NATURAL PLANT DERIVED EXTRACTS

Plant extracts have come into the research focus as they have shown promise in the treatment of infectious diseases, like fungal infections, since they are inexpensive, easily available and nearly side effect-free.[58]

However, the limited bioavailability of plant extracts often restricts their therapeutic efficacy. Because of their superior ability to load and release plant extracts and their high absorption capacity of exudates, hydrogels hold great promise for use as wound dressings. Pelin *et al.* prepared pullulan/polyvinyl alcohol (P/PVA) based hydrogels by covalent and physical cross-linking technique. Then, a hydroalcoholic extract of *Calendula officinalis* was loaded by a simple post-loading immersion method. The prepared hydrogels showed high extract loading efficiency, owing to hydrogen bonding interactions between the extract and the polymer. They exhibited Fickian diffusion mechanism for drug release. Moreover, these hydrogels showed better antifungal activity against *Candida albicans*.[59] In another study, Aldawsari and co-workers formulated lemongrass-loaded ethyl cellulose nanosponges with a topical hydrogel with an enhanced antifungal effect. Nanosponges were prepared by the emulsion solvent evaporation technique, then these nanosponge dispersions were integrated into 0.4% carbopol hydrogels. The optimized formulation exhibited better drug

loading efficiency and sustained release profile, with greater antifungal activity against *Candida albicans*.[60] In another study, a proanthocyanidin polymer-rich extract of *Commiphora leptophloeos* was incorporated into a hydrogel of chitosan (1.0%) and poloxamer 407 (18%). The prepared formulation showed very good antifungal activity against *Candida albicans* both *in-vitro* and *in-vivo*, compared to the free extract.[61]

Natural hydrogels

Natural polymer-based hydrogels, such as those derived from cellulose, chitosan, alginate, and hyaluronic acid, exhibit excellent biocompatibility and have been extensively explored for antifungal applications. The inherent antimicrobial activity of certain natural polymers, like chitosan, can provide additional therapeutic benefits, when incorporated into hydrogel formulations. Natural hydrogels are derived from renewable sources, such as polysaccharides and proteins, and possess inherent biocompatibility and biodegradability. Examples of natural polymers used in antifungal hydrogels include chitosan, alginate, gelatin, and hyaluronic acid. These polymers often exhibit unique properties, such as antimicrobial activity, wound healing properties, and the ability to promote skin regeneration, which can further enhance the therapeutic efficacy of antifungal agents. Additionally, natural hydrogels can be designed to mimic the extracellular matrix, facilitating better integration with the target tissue and improved drug permeability.

Synthetic hydrogels

Synthetic hydrogels, on the other hand, offer greater versatility in terms of tailoring physicochemical characteristics. Poly(vinyl alcohol), poly(ethylene glycol), and polyacrylic acid are examples of commonly used synthetic polymers that can be chemically or physically cross-linked to form hydrogel networks. Synthetic hydrogels are prepared from non-natural polymers, such as polyacrylic acid, polyethylene glycol, and polyvinyl alcohol. These hydrogels offer a higher degree of design flexibility, allowing for the tailoring of physical, chemical, and mechanical properties to meet specific delivery requirements. Synthetic hydrogels can be engineered to achieve controlled drug release kinetics, enhanced stability, and improved mechanical strength, making them suitable for various antifungal applications. Furthermore, synthetic polymers can be functionalized with specific moieties to enhance drug solubility, target specific fungal pathogens, or trigger responsive drug release.

Semi-synthetic hydrogels

Semi-synthetic hydrogels combine the advantages of both natural and synthetic polymers, offering a balance of biocompatibility, biodegradability, and tunable properties. These hydrogels are typically prepared by the chemical modification of natural polymers, such as the grafting of synthetic polymers onto the natural backbone or the cross-linking of natural polymers with synthetic crosslinkers. Semi-synthetic hydrogels, such as chitosan-g-poly(acrylic acid) and gelatin-based hydrogels, have demonstrated promising results in the delivery of antifungal agents, providing improved mechanical stability, controlled drug release, and enhanced skin penetration.

Regardless of the polymer source, the selection of the appropriate hydrogel system for antifungal delivery is crucial and depends on factors such as the physicochemical properties of the antifungal agent, the target site of action, and the desired drug release kinetics. The unique characteristics of each hydrogel type, including their swelling behavior, network structure, and responsiveness to environmental stimuli, can be exploited to optimize the delivery and therapeutic efficacy of antifungal drugs.

Figure 3 demonstrates how hydrogels can be used as a delivery system to effectively transport and release antifungal drugs onto the skin, providing a targeted treatment for skin fungal infections. The central blue circle represents a hydrogel, which is a water-based, polymeric material. The diagram shows that the drug (represented by red dots) can be loaded into the hydrogel, which can be applied to the skin, where it is released to treat the fungal infection. The smaller blue circle on the right depicts the drug-loaded hydrogel, with the red dots representing the antifungal drug. The arrows indicate the release of the drug from the hydrogel, which can then interact with the skin and treat the skin fungal infection.

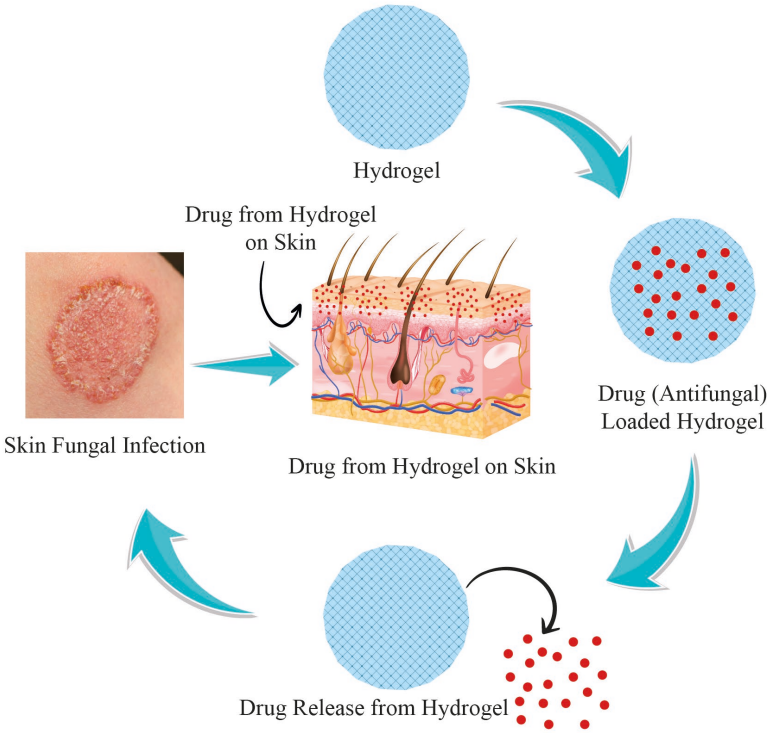

Figure 3: Drug loading onto and drug release from hydrogels to combat skin fungal infections

CONCLUSION

This review has examined the potential of hydrogel-based delivery systems for improved antifungal therapy. Hydrogels, with their unique properties of high water content, biocompatibility, and tunable physicochemical characteristics, have shown promise as versatile platforms for topical and transdermal administration of antifungal agents. The manuscript has provided an overview of the various natural and synthetic polymers that can be utilized to formulate hydrogels for antifungal applications. However, as highlighted in the feedback, the coverage of the hydrogel preparation methods and their influence on the final product characteristics requires more in-depth discussion. Future iterations of the review should dedicate a more comprehensive section to detailing the different hydrogel fabrication techniques, such as solution casting, *in situ* gelation, and freeze-drying, along with how the choice of the cross-linking approach and the degree of cross-linking can impact critical hydrogel properties, like swelling behavior, network structure, and drug release kinetics.

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