World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Nanogel-based topical delivery systems for antifungal therapy: A narrative review

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World Journal of Biology Pharmacy and Health Sciences, 2026, 26(03), 220-231

Publication history: Received on 01 May 2026; revised on 10 June 2026; accepted on 12 June 2026

Article DOI: https://doi.org/10.30574/wjbphs.2026.26.3.0300

Abstract

Superficial fungal infections affect approximately one in four individuals globally and impose a considerable burden in tropical and subtropical regions. Conventional topical formulations — including creams, ointments, and standard gels — demonstrate limited therapeutic efficacy attributable to inadequate drug penetration, insufficient contact time with the infected skin surface, and poor patient adherence to prescribed treatment regimens.Nanogels, which integrate the penetration-enhancing attributes of nanocarriers within the bioadhesive and aesthetically acceptable framework of hydrogels, offer a delivery platform that is both pharmacologically and practically advantageous for the management of cutaneous fungal disease. This narrative review examines the design, classification, and preparation of antifungal nanogels, with particular focus on miconazole nitrate as a model poorly water-soluble antifungal agent. Characterisation parameters including particle size, zeta potential, entrapment efficiency, rheological behaviour, *In vitro* drug release, and *Ex vivo* skin permeation are discussed in the context of published experimental data. Preclinical evidence consistently demonstrates enhanced antifungal efficacy and improved dermal drug retention relative to conventional formulations. Critical gaps remain before clinical translation can be realised, including scalability challenges, the absence of regulatory guidance specific to topical nanomedicines, long-term stability concerns, and limited data on patient acceptability. Addressing these barriers through rigorous translational research is essential if nanogel technology is to deliver meaningful benefit to the large patient population affected by superficial fungal infections.

Keywords: Nanogel; Miconazole nitrate; Antifungal therapy; Topical drug delivery; Skin penetration; Dermatophytosis; Nanocarriers

1. Introduction

Superficial fungal infections—like ringworm, candida, and pityriasis versicolor—are very common, but often not taken seriously enough. Skin fungal infections are a very common global health issue, particularly in tropical areas where the hot, humid environment causes them to thrive and spread more easily[1,9]. In South Asia, fungal skin infections (dermatophytosis) caused by organisms like Trichophyton rubrum, T. mentagrophytes var. interdigitale, and

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Microsporum canis have become very common—almost like they are always present in many urban and semi-urban areas.Even after people take the usual treatments, the infection often comes back again, meaning the recurrence rate is high [9]. Besides common dermatophytes, Candida and Malassezia also cause many skin infections, and Malassezia is especially difficult to treat because drugs don't easily penetrate the skin and hair follicles where it resides [12]. Topical therapy is the preferred first-line approach for managing uncomplicated superficial fungal infections. treatment durations because it avoids side effects on the liver (hepatotoxicity) that can happen with oral (systemic) antifungal drugs.It reduces drug interactions with other medicines, delivers a high amount of drug directly to the infected area, making it more effective locally, safer and better tolerated when used for a long time [2]. Miconazole nitrate is a commonly used antifungal drug and has been used effectively for many years.It works by blocking enzyme lanosterol 14-α-demethylase required to make ergosterol, which is a key component of the fungal cell membrane. Due to shortage of ergosterol the fungal cell membrane becomes weak and unstable and its structure and function get disrupted [3]. Yet, miconazole nitrate is classified as a BCS Class II drug: practically insoluble in water, with an aqueous solubility below 1 µg/mL and a logP value of approximately 6.0. This extreme lipophilicity of miconazole creates a formulation paradox — while the drug's lipid affinity theoretically aids passive diffusion into the stratum corneum, inadequate aqueous solubility limits its thermodynamic activity within hydrophilic vehicle systems and decrease its bioavailability at the site of infection [10]. Traditional topical products never really solved this problem.Creams and ointments do not spread well into skin folds or nail beds. Plain carbopol gels cannot dissolve much miconazole unless you add too much surfactant, which then irritates the skin and destabilizes the formula. Dusting powders touch the skin only briefly, so they do not work well. And patients often stop treatment as soon as symptoms look better, even though the fungus is still there [4].

These known failures have kept researchers busy for decades looking for better ways to formulate these drugs. Nanocarrier systems like liposomes, transfersomes, solid lipid nanoparticles, and polymeric nanoparticles all work better than standard creams in some ways. But most need special equipment to make, break down over time, or are hard to put on the skin.Nanogels take this a step further. The drug carriers sit inside a hydrogel matrix. This keeps the delivery benefits but also makes the gel stick to skin, stay in place longer, and feel non-greasy—something patients will actually tolerate [7, 22]. This review pulls together what we currently know about nanogels for antifungal skin treatment. It tries to give an honest picture of where the field is now and what practical steps still lie ahead.

2. Nanogels: definition and classification

2.1. Definition and Structural Basis

The term "nanogel" refers to a crosslinked, three-dimensional polymeric network that exists at the colloidal scale — typically between 20 and 200 nanometres — and that is swollen by water without dissolving into it [1, 7, 19, 23]. The network may be formed by chemical crosslinking (covalent bonds between polymer chains) or by physical crosslinking (non-covalent interactions such as hydrogen bonding, hydrophobic association, or electrostatic attraction). What makes nanogels different from conventional hydrogels is not merely their size but the biological similar results of that size: at the nanometer scale, these particles can access skin microstructures — particularly the intercellular lipid channels of the stratum corneum, the appendageal openings of hair follicles, and the pores of sweat glands — that are physically not possile to access to macroscale formulations [4, 7, 20]. The interior of the nanogel network can simultaneously accommodate hydrophilic drugs within its aqueous phase and hydrophobic drugs within hydrophobic phase formed by amphiphilic polymer segments and making nanogels inherently versatile as drug carriers across a wide range of physicochemical drug types [13, 24].

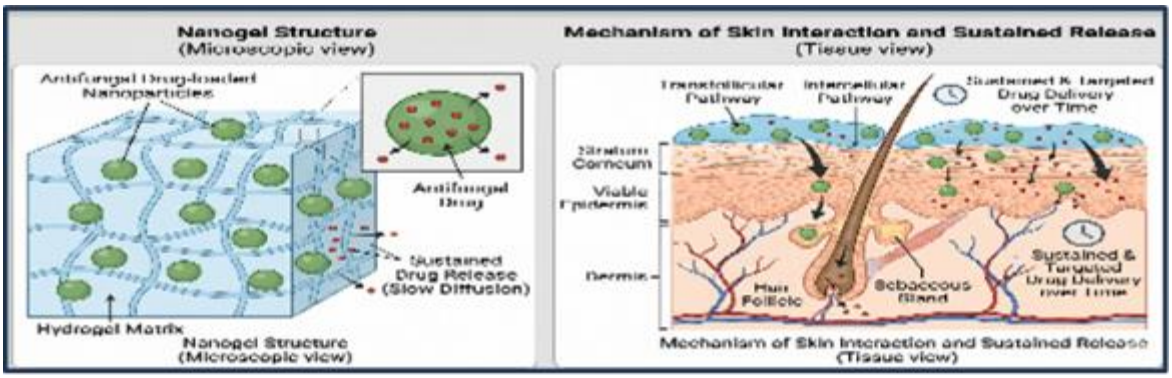

Figure 1 Conceptual Architecture of an Antifungal Nanogel

2.2. Classification Based on Polymer Origin

The first and most fundamental way to make classification of nanogels is according to the origin of their component polymer. Nanogels based on natural polymers are obtained from biopolymers such as chitosan, hyaluronic acid, gelatin, sodium alginate and hydroxypropyl methylcellulose (HPMC). These materials are biodegradable, generally recognized as safe (GRAS) by the major regulatory agencies and have a well-documented safety profile in tropical products. Special attention should be paid to chitosan as it is not only a good nanogel-forming polymer but also exhibits an innate antimicrobial activity due to the presence of protonated amino groups, which can interact and destabilize the negatively charged microbial cell membranes. In this way, chitosan can be considered as a bioactive excipient, which makes a direct contribution to the therapeutic activity of the formulation rather than a mere structural component of the antifungal nanogel. [11, 14, 21, 31, 32].

Synthetic polymer-based nanogels are made by chemical macromolecules such as polyacrylic acid (carbomer), polyethylene glycol (PEG), poly-N-isopropylacrylamide (PNIPAM), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP). These type of polymers offers the formulator precise control over polymer molecular weight, degree of crosslinking, swelling behaviour, and mechanical properties, However, they do not possess natural bioactivity and may raise serious concerns safety and regulatory challenges during long-term topical use. [7, 15] Semi-synthetic or hybrid nanogels integrate both the natural and synthetic polymer components with the intention of achieve the biocompatibility and biological activity of the natural component alongside the tunability and mechanical strength of the synthetic one. Chitosan-Carbopol systems are a very well-studied example of this hybrid model approach: Carbopol contributes gel strength and consistent rheological behaviour and chitosan contributes bio adhesion, skin interaction, and antifungal activity [11]. Such hybrid models have produced some of the most encouraging antifungal nanogel data reported in recent literature.

2.3. Classification Based on Crosslinking Mechanism

Physically crosslinked nanogels are held together by non-covalent intermolecular forces, including hydrogen bonding, hydrophobic association, and electrostatic interactions. These interactions are inherently reversible: they dissociate and reform in response to changes in the surrounding environment. Consequently, fluctuations in temperature, pH, or ionic strength cause the network to swell, contract, or disassemble — the precise mechanism underlying stimuli-responsive drug release. The absence of chemical crosslinking agents simplifies the regulatory safety profile and eliminates the risk of residual toxic reagents within the final formulation. The principal limitation of physical crosslinking is mechanical fragility: shear forces encountered during manufacturing or during topical application can disrupt the network and compromise particle integrity [1, 7]. Chemically crosslinked nanogels are stabilised by covalent bonds formed through free radical polymerization with a bifunctional crosslinking agent, or through condensation reactions between functional groups on adjacent polymer chains that produce imine, ester, or disulfide linkages. Covalently crosslinked networks exhibit superior mechanical robustness, thermal stability, and resistance to deformation, and drug release from these systems follows more predictable, diffusion-controlled kinetics. The regulatory concern associated with chemical crosslinking centres on residual crosslinking agent: unreacted monomer retained after purification carries a toxicity risk, and manufacturers must rigorously validate the purification process to demonstrate that residual levels fall below acceptable thresholds [7, 15].

2.4. Classification Based on Stimuli-Responsiveness

Temperature-sensitive nanogels are among the most widely investigated and studied stimuli-responsive systems for topical drug delivery. PNIPAM-based polymers exhibit a lower critical solution temperature (LCST) — a threshold point above which they change their swollen hydrophilic state to a compact hydrophobic state, facilitating release of drug from encapsulated state. The LCST of PNIPAM (~32°C) close to normal human skin temperature (~32–34°C) and can be modify by copolymerization, which means a temperature-sensitive nanogel can be designed to release drug upon contact with skin or, more usefully, at sites of infection where local inflammation elevates tissue temperature [7, 15].

pH-sensitive nanogels utilize variations in pH between normal skin (pH 4.5–5.5), inflamed or infected skin, and the nail plate (pH ~7.4) to enable site-specific drug release. Polymers containing ionizable carboxylic or amine groups (Carbopol, chitosan, hyaluronic acid derivatives) swell or contract in response to protonation or deprotonation of these groups, facilitate pH-dependent drug release [7]. This is particularly beneficial for candidiasis and dermatophytosis, where the microenvironment at the site of infection differs from surrounding healthy skin, creating a natural gradient that can be exploited therapeutically.

Redox-sensitive and enzymatically degradable nanogels are among the advanced drug delivery strategies but their clinical application still not widely applicable. Disulfide-crosslinked nanogels break down selectively due to presence of

upraised glutathione level, which can be found in infected or inflamed tissues. Similarly, enzyme-responsive are engineered with specific cleavage sites for proteases or fungal enzymes, which facilitate site-specific drug release [13]. While these approaches are compelling in principle, their clinical translation for topical antifungal therapy is still at an early stage.

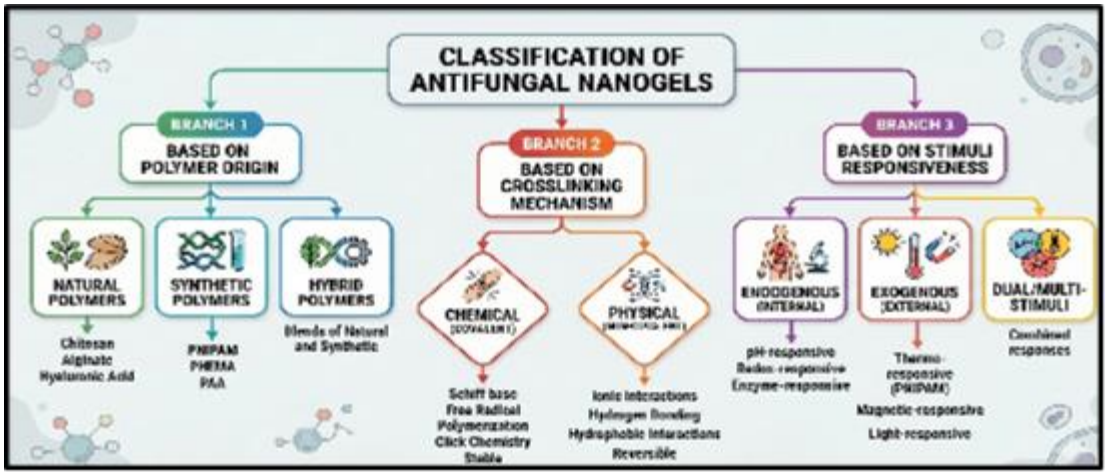

Figure 2 Mechanism of Enhanced Skin Penetration by Nanogels

3. Formulation strategies for antifungal nanogels

3.1. Polymeric Nanoparticle-Based Nanogels

The effective strategic approach of loading an antifungal drug into biodegradable polymeric nanoparticles and dispersing those nanoparticles within a gelling agent has showed consistently promising results. Polymers like PLGA, polylactic acid, ethyl cellulose, and chitosan have been utilized to fabricate nanoparticle cores by techniques like nanoprecipitation, emulsion-diffusion, or ionic gelation. which are then suspended in Carbopol or HPMC gel at concentrations that yield acceptable viscosity for topical use [3, 6]. The polymer matrix provides a sustained, controlled release of drug over extend time period, reducing the required dose frequency of drug for therapeutic effect. The gel base ensures sufficient spreadability and prolonged contact with the infected skin surface. Farooq et al. reported enhanced antifungal efficacy of miconazole-loaded nanogels against *Candida albicans* ATCC 10231, along with improved *In vitro* release behavior and acceptable dermatological tolerance [3].

3.2. Transethosomal Nanogels

Transethosomes are among the current most innovative nanocarrier systems developed for dermatological drug delivery effectively. These ultra-deformable lipid vesicles made of bilayer membrane which are modified by incorporation of ethanol and a membrane-softening edge activator — typically a non-ionic or anionic surfactant — which reduces bilayer rigidity allowing the vesicle to squeeze through aqueous channels in the stratum corneum that could be too narrow for conventional liposomes [5, 6]. When these vesicles are dispersed in a gel matrix, the resulting transethosomal nanogel combines the penetration advantage of deformable vesicles with the bioadhesive and rheological properties of the gel. Asghar et al. demonstrated that miconazole nitrate-loaded transethosomal nanogels exhibited significantly higher skin permeation in Franz diffusion studies compared to conventional gels. [5]. while in vivo evaluation by Ahmed et al. in an animal model of tinea infection confirmed that the transethosomal gel produced superior antifungal effects compared to the reference formulation, without any observable skin irritation over the study period [6].

3.3. Lipid Nanoparticle-Based Nanogels

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) utilize a solid lipid matrix to encapsulate and retain poorly water-soluble antifungal drugs such as miconazole nitrate and terbinafine HCl [2, 16, 28, 29]. however, their application as aqueous dispersions is limited because of their low viscosity, which can hinder topical administration. Incorporating in the gel matrix remove this limitation and provide better rheological behaviour for tropical application. The gel matrix provides the physical structure needed for easy and uniform application. The lipid nanoparticles provide sustained biphasic drug release: an initial burst that rapidly saturates the stratum corneum,

followed by slower diffusion-controlled release from the solid lipid core [2]. Lipid encapsulation also provides necessary protection against hydrolytic and oxidative degradation of the drug, a benefit that translates into better chemical stability and a longer product shelf life. Hassan et al. reported improved skin retention and antifungal efficacy of terbinafine-loaded nanogels compared to conventional formulations. [2].

3.4. Chitosan-Carbopol Vesicular Nanogels

Researchers have shown growing interest in carbopol vesicular nanogels for delivering antifungal drugs. These systems combine several useful features in one formulation. Chitosan carries positive charges on its amine groups. These positive charges attract negatively charged surfaces on skin and microbes. This attraction helps the gel stick better and kill fungi more effectively. Carbopol forms the gel base. It is sticky and stays where you put it. So the drug remains at the infection site for a longer time. Lab studies found that these gels release drug slowly over time. They push more drug through the skin. They kill Candida albicans and Trichophyton rubrum better than standard options. Skin irritation was minimal. Other research groups have reported similar results. Their work also shows that chitosan-based nanogels perform better than conventional options [10, 27].

Table 1 Comparative Characteristics of Major Antifungal Nanogel Systems

Nanogel System	Principal Components	Major Functional Advantage	Limitation Addressed	Representative Antifungal Drug
Polymeric nanoparticle nanogel	PLGA/chitosan nanoparticles dispersed in Carbopol or HPMC gel	Sustained drug release with prolonged skin residence	Poor retention and rapid drug loss from conventional gels	Miconazole nitrate
Transethosomal nanogel	Phospholipid vesicles with ethanol and edge activator in gel matrix	Enhanced deformability and deep skin penetration	Inadequate permeation through stratum corneum	Miconazole nitrate
Lipid nanoparticle nanogel	SLNs or NLCs in hydrogel	Improved solubilization and biphasic release	Low aqueous solubility and instability of lipophilic drugs	Terbinafine HCl
Chitosan–Carbopol vesicular nanogel	Chitosan vesicles incorporated into Carbopol gel	Bioadhesion with intrinsic antimicrobial activity	Poor adherence and short contact duration	Voriconazole / Miconazole

4. Characterization of antifungal nanogels

Testing nanogel formulations matters for two reasons. Regulators require it. And you need data to back up any claim that your product works better than existing options. Every test tells you something different. Put them all together and you get a reasonable picture of what will happen once the gel meets actual skin.

4.1. Particle Size and Polydispersity Index (PDI).

Particle size, commonly determined by dynamic light scattering (DLS) method, plays a key role in the performance of topical nanogel systems. Particles within the 50–200 nm range are considered optimal, balancing effective skin penetration with adequate retention at the application site [1, 7]. The polydispersity index (PDI) is a dimensionless measure of the width of the particle size distribution. It should ideally fall below 0.3 which indicating an acceptably uniform population. A narrow size distribution is important for reproducibility and wide PDI values indicate the co-existence of very small and very large particles, that may behave differently in the skin and produce variable drug release profiles. Any PDI above 0.5 is generally considered too heterogeneous for a topical nanogel intended for pharmaceutical development [1, 13].

Table 2 Critical Characterization Parameters of Antifungal Nanogels

Parameter	Ideal/Preferred Range	Pharmaceutical Importance	Analytical Technique
Particle size	50–200 nm	Improves skin penetration and follicular targeting	Dynamic Light Scattering (DLS)
Polydispersity Index (PDI)	< 0.3	Indicates formulation uniformity and reproducibility	DLS
Zeta potential	> +30 mV or < –30 mV	Enhances colloidal stability and prevents aggregation	Electrophoretic mobility analysis
Entrapment efficiency	≥ 70%	Ensures adequate drug incorporation	Centrifugation + UV/HPLC
Rheological profile	Pseudoplastic	Improves spreadability and retention	Rotational rheometry
Drug release pattern	Sustained/non-Fickian	Maintains prolonged therapeutic action	Franz diffusion cell

4.2. Zeta Potential

Zeta potential reflects the surface charge of nanoparticles in dispersion and is widely used as an indicator of colloidal stability and interaction with biological surfaces**.** When particles show zeta potential above +30 mV or below -30 mV, the electrostatic repulsion between them is strong enough. They do not clump together on the shelf [5]. Skin carries a negative charge. Chitosan-based nanogels carry a positive charge. Opposites attract, so these gels stick better and hold the drug in place longer [11, 14]. Negative or neutral nanogels can still stay stable in solution. You just need other tricks, like coating them with PEG to create a physical barrier. But even with these fixes, they usually do not match the adhesion and retention you get from positively charged systems.

4.3. Entrapment Efficiency and Drug Loading.

Entrapment efficiency (EE%) represents the fraction of the total drug successfully incorporated within the nanogel network compare to the initial drug amount used during formulation. Drug Loading (DL%) tells how much drug is present relative to the total carrier (nanogel material**)**; that is, the quantity of drug per unit weight of nanogel. Both parameters are determined by separating unentrapped drug from the nanoparticulate fraction through centrifugation or filtration, followed by quantification of the supernatant or filtrate by UV–Vis spectrophotometry or HPLC [3, 10]. Entrapment efficiency values of 70–80% or above are generally considered acceptable for topical applications. Lower values require the application of greater quantities of formulation to achieve a therapeutically effective dose at the infection site, thereby increasing the excipient load delivered to the skin surface and elevating the risk of local irritation.

4.4. Rheological Characterization

Rheological characterisation evaluates the flow behaviour and viscoelastic properties of the nanogel formulation — parameters that directly govern spreadability, skin contact time, and patient tolerability during application. For topical use, pseudoplastic (shear-thinning) behaviour is the preferred rheological profile. At rest, the formulation should maintain sufficient viscosity to prevent drainage from the application site and to limit transepidermal water evaporation. Upon application of shear during manual spreading, viscosity should decrease to facilitate smooth, uniform coverage of the affected area. Oscillatory rheological measurements yield the storage modulus (G') and loss modulus (G''), which quantify the elastic and viscous components of the formulation's response to applied stress, respectively. A gel-like material is characterised by G' > G'', indicating a predominantly elastic network with adequate structural integrity under conditions of use. For temperature-sensitive nanogels, the sol–gel transition temperature is an additional critical parameter that should correspond closely to the skin surface temperature to ensure in situ gelation upon application [7,10]**.**

4.5. *In vitro* Drug Release

In vitro drug release testing is commonly performed using Franz diffusion cells equipped with synthetic membranes such as cellulose acetate or polycarbonate. It helps to elucidate the mechanism by which the drug is released from the nanogel matrix under simulated physiological conditions. [7, 10]. A dissolution medium is placed in the receptor compartment to replicate the skin's aqueous environment. This medium commonly consists of phosphate buffer (pH

5.5) or a mixture of phosphate buffer and ethanol to maintain sink conditions for drugs with low solubility, including miconazole nitrate. The cumulative amount of drug released over time is measured at regular intervals. The obtained release profile is analysed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine the predominant drug release mechanism. In many nanogels, an n value between 0.45 and 0.89 in the Korsmeyer–Peppas model indicates non-Fickian release. This means that drug release is controlled by both diffusion and swelling, leading to more sustained release than simple diffusion. [10, 13].

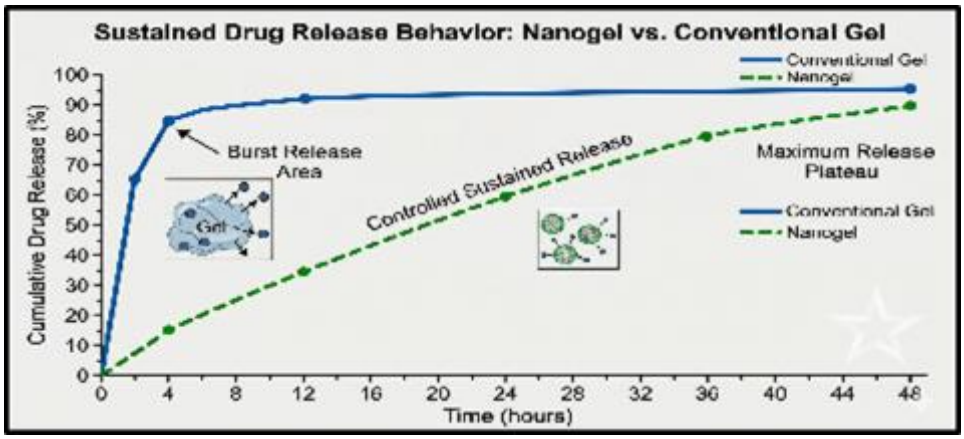

Figure 3 Sustained Drug Release Behavior of Nanogel vs Conventional Gel

4.6. *Ex vivo* Skin Permeation

Ex vivo permeation experiments, conducted with excised skin mounted on Franz diffusion cells, offer greater insight compared to synthetic membrane studies, as they reflect the true diffusional resistance of different skin layers (stratum corneum, epidermis, and dermis). Different skin models, including rat abdominal, porcine ear, and human cadaver skin, have been employed in permeation studies. Among these, porcine ear skin is regarded as the closest model to human skin in terms of follicular density and lipid profile [5, 6]. Drug that crosses the full thickness of the skin into the receptor compartment shows transdermal delivery. Drug that remains within different skin layers, measured by tape stripping and tissue analysis, forms a local depot that is important for antifungal treatment. A formulation that achieves high drug retention within the viable epidermis and dermis with minimal transdermal permeation is considered optimized for topical antifungal use.

4.7. Antifungal Efficacy Testing

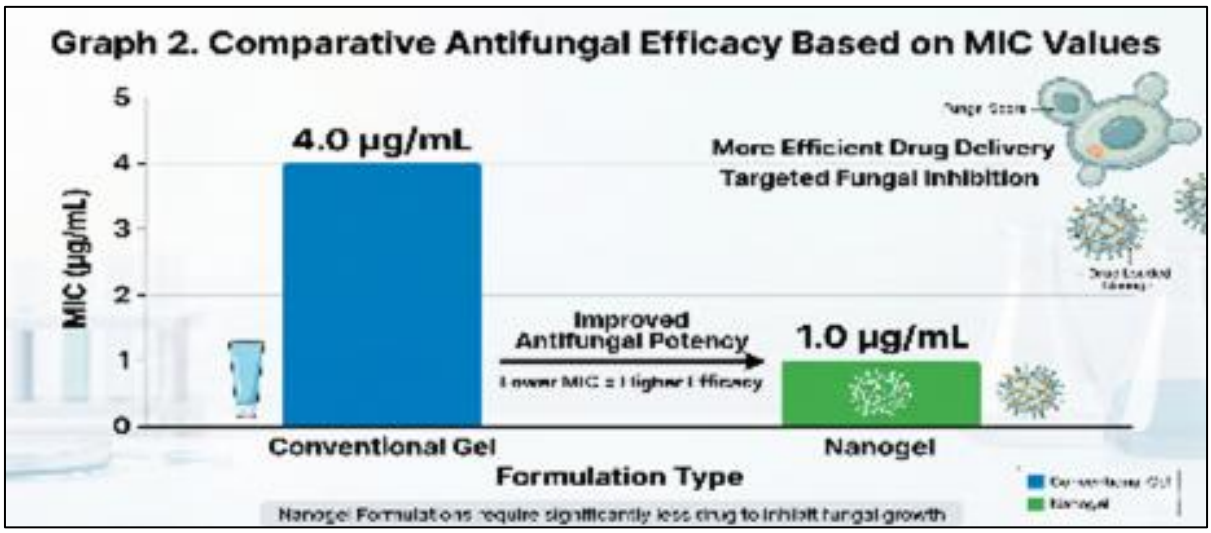

Figure 4 Comparative Antifungal Efficacy Based on MIC Values

Antifungal efficacy *In vitro* is commonly assessed by measuring the minimum inhibitory concentration (MIC) of the formulation against reference organisms, including Candida albicans ATCC 10231 and Trichophyton rubrum ATCC

28188, following broth microdilution protocols as specified in CLSI standards. [3, 11]. Zone of inhibition studies using the agar well diffusion method serves as a complementary approach for evaluating antifungal activity. Comparative MIC analysis should be performed between the nanogel formulation, a plain drug suspension at an equivalent concentration, and a marketed reference product to accurately assess the contribution of the nanogel delivery system.

4.8. Biocompatibility and Skin Safety Evaluation

Safety testing begins in the lab. Researchers run haemolysis tests to check if the gel damages red blood cells. They use MTT assays on skin cells like HaCaT keratinocytes or fibroblasts to see if cells stay alive. They also measure contact angles to judge how well the gel wets and spreads on a surface [8, 12]. For skin irritation, animals like albino rats or rabbits get the gel applied to their skin. The Draize test scores what happens. The skin should show no redness, swelling, or scabbing at the spot where the gel was put. Regulators expect these tests as part of the safety package. Without this data, you cannot move on to human trials.

5. Miconazole nitrate: focus on nanogel formulation

Researchers working on antifungal nanogels have consistently centered their attention on miconazole nitrate as a compound of particular interest. No one disputes how clinically valuable this drug is—after all, the WHO still counts it among essential medicines, and virtually every national health system keeps it in their formulary—yet when it comes to squeezing it into water-based topical preparations, its physical and chemical behavior creates genuine headaches for formulators. Because the molecule barely dissolves in water and clings stubbornly to lipids instead, ordinary aqueous gels end up holding only trace quantities of actually dissolved drug. What you mostly find in a standard gel are suspended crystals, and these have to go into solution before any meaningful penetration through the stratum corneum can happen—this dissolution bottleneck ends up choking the amount of active compound that actually reaches where the infection sits. Encapsulating the drug inside nanogels sidesteps that whole dissolution problem: the miconazole nitrate gets tucked into a hydrophobic nanoparticle core or lipid bilayer, already broken down molecularly or locked in an amorphous form rather than sitting there as crystals. Compared to crystalline material, the amorphous version behaves as if it dissolves more readily and shows stronger thermodynamic activity—this steeper chemical potential gradient becomes the engine pushing passive diffusion through the stratum corneum [5, 6]. Several labs, working independently from one another, have reported the same pattern: nanogel versions of miconazole knock down Candida albicans and typical dermatophytes at markedly lower MICs—sometimes needing only a quarter to half the concentration—relative to both raw drug suspensions and off-the-shelf creams, a difference researchers trace back to more drug actually becoming available at the fungal membrane [3, 6, 11, 25, 26].One mechanism that especially matters for scalp ringworm (tinea capitis) and folliculitis involves nanoparticles shuttling drug directly into hair follicles. Follicles punch shortcuts straight through the epidermis, and particles sized between 100 and 300 nm exploit these shunts to slip past an otherwise intact stratum corneum, piling up around the follicle where they build a slow-leak reservoir hugging the hair shaft—exactly where T. tonsurans and M. canis like to set up shop [4, 8].

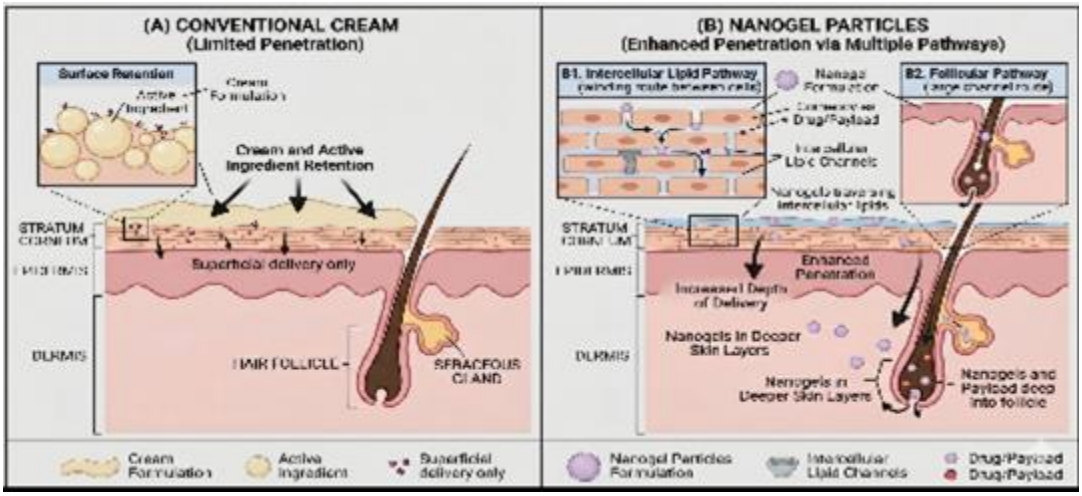

Figure 5 Classification Flowchart of Antifungal Nanogels

Ordinary creams and gels simply cannot tap into this follicular route, which goes some way toward accounting for why nanogels perform markedly better at locations like the scalp, groin, and between toes—areas thick with follicular openings.

6. Nanoparticles in antifungal therapy: broader context

For complete understanding of nanogels requires detail discussion of other nanoparticle systems that have been studied for treating various fungal infections. Researchers have looked closely at silver and zinc oxide nanoparticles. These materials fight fungi without any added drug. They show their effect by oxidative damage, membrane destruction, and enzyme inhibition. These pathways differ from those of conventional antifungals [12,17]. Because of these properties, such nanoparticles are useful in combination treatments. The nanoparticle itself acts as an active agent, not just as a carrier for other drugs. Nami et al. reviewed the use of nanoparticles in antifungal treatment. They noted that nanoparticles enter fungal biofilms more easily than dissolved drugs. Biofilms are dense clusters of fungal cells surrounded by a protective matrix. They resist most standard antifungal agents. Nanoparticles bind to the biofilm matrix through electrostatic and hydrophobic interactions. This helps them enter without depending only on diffusion [12]. Keshwania et al. examined nanocarrier therapies for superficial dermatophyte infections. They found that various nanocarrier designs improved drug retention in the skin. These systems also lowered recurrence rates. Both outcomes were better than those seen with standard topical treatments [8]. Botha et al. discussed nanogels in a wider context of skin therapy. They pointed out that nanogels can carry different drugs and polymers. They can also include components that respond to specific stimuli. Because of this flexibility, nanogels have uses that extend well beyond antifungal treatment [4].

7. Challenges and future perspectives

Table 3 Translational Challenges and Future Directions

Current Challenge	Scientific/Industrial Impact	Proposed Future Strategy
Scale-up variability	Batch inconsistency in particle size and drug loading	Standardized industrial manufacturing protocols
Regulatory uncertainty	Delay in approval pathways	Dedicated nanogel bioequivalence guidelines
Long-term instability	Aggregation and recrystallization	ICH-compliant stability optimization
Poor patient acceptability data	Reduced treatment adherence	Early-stage usability evaluation
Limited targeted delivery	Non-selective drug distribution	Stimuli-responsive smart nanogels

Most preclinical studies on antifungal nanogels report positive findings. Researchers have produced particles in the desired size range. They have achieved entrapment efficiencies over 80% in numerous trials. Skin permeation has improved in measurable ways. MIC values have also dropped. Despite this progress, few products have reached the market. The gap between published research and commercial approval is wide. The reasons for this delay deserve examination. Moving from laboratory to factory scale poses the clearest practical barrier. University labs control every variable: stirring speed, temperature, excipient purity. Industrial settings struggle to match this precision. The result is often variation between batches in particle size and drug loading. Companies have scaled up liposomes and polymeric nanoparticles before. Nanogels are harder. The gel matrix introduces a mixing step that depends on viscosity. Poor control of this step alters particle size distribution [7, 18, 30]. Regulators have not yet finalized clear pathways for approving topical nanomedicines. The USFDA and EMA have published no specific guidance on how to test bioequivalence for nanogels. They have not defined the minimum data needed for approval either. When rules remain unclear, drug companies cannot plan timelines or budgets with confidence. They respond by putting their money elsewhere. However, agreed guidelines will not appear soon [15]. Academic papers often pay little attention to long-term stability. For commercial products, this issue is critical. Published studies typically track stability for weeks or months. Regulators require data for 24 to 36 months under ICH conditions. Accelerated stability studies have shown several problems. Nanoparticles aggregate during storage. Ester-linked polymers hydrolyse. Drugs recrystallize in the gel matrix. Each problem demands careful choice of excipients and packaging [11, 16]. Most published studies ignore patient acceptability. They do not measure how patients feel about texture, spreadability, odor, or residue. Cosmetic elegance matters greatly in dermatology. It drives whether patients continue treatment. Adherence, in turn, determines

whether the treatment works. A nanogel may excel in all laboratory tests. If patients dislike applying it, it will still fail in practice. Researchers should collect patient feedback early in development. Waiting until the end reduces the practical value of their work [4]. One promising direction is combination nanogels. These would carry two drugs with different mechanisms, such as miconazole nitrate and terbinafine. The goal is to overcome resistant strains and prevent new resistance from developing. Theranostic nanogels offer another possibility. They would deliver drug and report treatment response through measurable optical signals — colour changes or fluorescence — enabling real-time monitoring of therapeutic progress at the site of infection [12]. Stimuli-responsive nanogels represent a further direction of considerable interest. Infected skin differs from healthy skin in several measurable ways: local pH is elevated, tissue temperature is increased at sites of inflammation, and the activity of fungal and host-derived enzymes is elevated. Nanogels engineered to detect these microenvironmental signals could release drug selectively at infected sites rather than across the entire application area, representing genuine targeted delivery rather than simply improved bulk penetration. Green synthesis methods deserve attention too. Manufacturers are also looking at plant-based crosslinkers and other sustainable ingredients. These green synthesis approaches address both regulatory demands and public expectations for cleaner drug production [17].

8. Conclusion

Accumulating preclinical evidence demonstrates that nanogel-based delivery systems represent a substantive advance in topical antifungal therapy. By encapsulating poorly water-soluble agents such as miconazole nitrate within nanostructured carriers dispersed in a bioadhesive gel matrix, these formulations address the fundamental solubility and penetration limitations that have constrained the efficacy of conventional topical preparations.Miconazole nitrate has emerged as the most consistently studied model compound in this field, and independently conducted studies converge on the same finding: nanogel formulations achieve superior antifungal efficacy, deeper dermal drug retention, and reduced minimum inhibitory concentrations relative to conventional reference preparations. The preclinical evidence base is now sufficiently mature. Meaningful progress requires engagement with the translational challenges that have thus far constrained the movement of these systems from academic publication to clinical availability: reproducible large-scale manufacture, ICH-compliant long-term stability assessment, resolution of the outstanding regulatory uncertainty surrounding bioequivalence testing for topical nanomedicines, and systematic collection of patient acceptability data. These activities are indispensable preconditions for any nanogel product to reach patients.The global burden of superficial fungal infections — particularly in resource-limited tropical settings where recurrence rates remain high and treatment options remain inadequate — provides clear justification for the sustained, rigorous translational effort this field now requires. The scientific foundation is established; the work ahead is translational, not exploratory, and it is no less essential.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Funding Information

No funding received from any end.

Author Contribution

First author: Conceptualization, Literature Search, Data Curation, Writing – Original Draft.. Second author: Data accumulation. Third author: Design and drafting. Fourth author: Data validation. Corresponding author: Overall validation

Data Availability

Data is available from the corresponding author on request.

Statement of Usage of Artificial Intelligence

Open AI platforms were used for grammatical corrections only.

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