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Review Article

Current and Emerging Formulations in Topical Antifungal Therapy: A Comparative Overview

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Abstract

Fungal infections, a widespread issue, affect millions of people worldwide and can range from minor skin diseases to serious, sometimes fatal infections. Traditional topical treatments, such as creams, gels, sprays, and ointments, are popular for treating fungal infections due to their ease of use, fewer adverse effects, and safety. However, they have drawbacks like frequent application, inability to stay on the skin for extended periods, and uneven efficacy. New drug delivery technologies, such as liposomes, nanoparticles, and microemulsions, are transforming the treatment of fungal diseases by improving drug interaction with the skin, enhancing patient comfort, and reducing side effects.

Keywords: Fungal infections, Topical antifungal therapy, Nanotechnology, Therapeutic efficacy.

A. Introduction

Worldwide, fungal infections pose a significant threat in the field of skin disorders. An estimated 40 million people in developing and disadvantaged nations are thought to be afflicted by these illnesses.¹⁻⁴

Three major categories of fungal infections exist: superficial, subcutaneous, and systemic.⁵ Typically, dermatophytes are responsible for superficial infections of keratinized tissues, including hair and nails. On the other hand, *Candida* species are most commonly responsible for infections of the mucus membrane. Subcutaneous infections, which are typically contracted by traumatic inoculation, can be caused by a variety of species. Systemic fungal infections are the most dangerous and potentially fatal. Some regions have endemic systemic fungal diseases, like as the Mississippi valley, where histoplasmosis is prevalent. Systemic infections from commensal and widespread species, particularly *Aspergillus* and *Candida* species, pose a risk for immunocompromised individuals worldwide.⁶

Antifungal chemotherapy is utilized to treat both superficial and deep fungal infections. Several skin layers are frequently affected by fungal infections. Due to its straight access and increased retention rates at the targeted location, topical application of antifungal medications is frequently the most successful strategy for treating significant skin dermatophytes. Additionally, topical delivery helps to minimize systemic toxicity and avoid pre-systemic metabolism⁶⁻⁸. Drugs that go through first-pass metabolism can be effectively administered topically, and this approach is especially helpful for treating fungal infections.⁹

B. Administration of Topical Antifungals

The human skin consists of three layers: dermis, epidermis, and hypodermis, with the stratum corneum, the uppermost layer, being responsible for preventing medication absorption.^{10 11}. Topical drug administration involves drugs permeating skin layers to reach effective concentrations. Factors like the physical and chemical

characteristics of drug molecules and formulations influence their effectiveness. This method prevents systemic adverse effects by limiting medication entry into the circulation¹⁰. Moreover, topical preparations offer better patient compliance due to their non-invasiveness and can be self-administered^{11, 12}. When antifungal drugs are applied topically, they must reach effective concentrations in the living epidermis.

The stratum corneum, a major barrier to cutaneous distribution, has been enhanced through various formulation techniques, including vesicular carriers like liposomes, ethosomes, and niosomes, colloidal drug delivery systems like microemulsions, and lipid-based and polymeric particle carrier systems.^{12, 13}

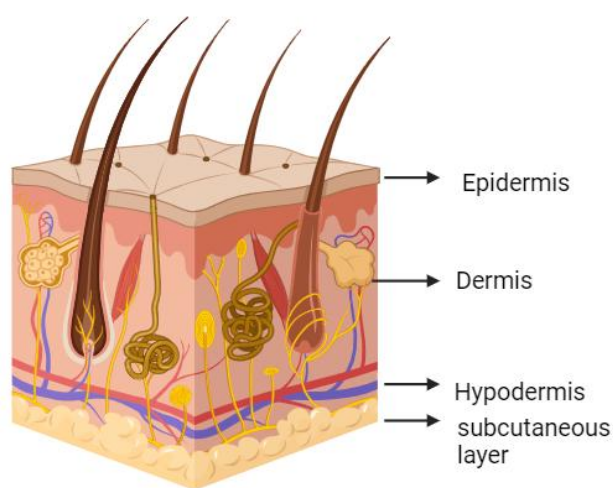


Figure 1: Structure of stratum corneum

C. Mechanism of topical delivery

Topical drug administration for fungal infections uses techniques to maximize effectiveness and reduce systemic exposure. The main challenge is overcoming the skin's barrier, particularly the stratum corneum. Two major routes for medication delivery are transepidermal and transappendageal. Transepidermal occurs through the stratum corneum, while hydrophilic and lipophilic drugs diffuse through corneocytes and intercellular lipid matrices.¹⁴

D. Conventional topical dosage

Antifungal drugs are delivered directly to the affected area using a variety of formulations in conventional topical dose forms to treat fungal infections. Because of their more focused action, fewer systemic adverse effects, and enhanced patient compliance, these formulations are recommended. In antifungal therapy, the most traditional topical dose forms used are:

a) Cream

Creams are emulsions that are semi-solid, easy to apply, and appropriate for a range of skin types. When applied to wet or moist areas, they function well to treat fungal infections of the epidermis

Uses: Because of their moisturizing qualities, they are useful in treating a range of fungal illnesses, such as candidiasis and tinea corporis (ringworm).¹⁵

b) Gels:

They are especially helpful. Gels can improve the way antifungal medications enter the skin.

Uses: perfect for places with hair or situations when the non-greasy composition is needed. Localized fungal infection can be effectively treated using gels, which can improve penetration¹⁶.

c) Ointments:

Greasy compositions that build a protective layer over the skin, ointments are appropriate for dry, scaly lesions. They improve medicine absorption and effectively preserve moisture.

Uses: Ointments are beneficial for chronic fungal infections because they improve medicine absorption and help preserve moisture, which is best for dry or scaly lesions¹⁷

d) Lotions:

Lotions are fluid solutions that are easily able to cover large areas of skin. They are perfect for treating large lesions or moist locations, like intertriginous regions.

Uses: Ideal for large lesions or moist areas like intertriginous regions (skin folds).¹⁶

e) Nail Lacquers:

Specific formulations, such as nail lacquers (like ciclopirox and amorolfine), are used to treat onychomycosis, which is a fungal infection of the nails. Because they stick to the nail plate, these lacquers offer localized care.

Uses: The antifungal lacquers ciclopirox and amorolfine are frequently used because they efficiently enter the nail and target fungal cells.¹⁸

f) Powders:

To absorb excess moisture and stop fungal powder can be applied to regions that are prone to dampness.

Uses: Beneficial in avoiding fungal infection in body parts that are warm and damp¹⁶

Table 1: Common Antifungal Drug Mechanisms and Targets

Drug	Mechanism	Potential Target	Ref
Miconazole, Fluconazole, Ketoconazole, Imidazole	Inhibit Production of Ergosterol	Cytochrome P450 14 α -Lanosterol Demethylase	19
Terbinafine	Stop The Ergosterol Manufacturing Process	Squalene Epoxidase	20
Tolnaftate	Stop The Ergosterol Manufacturing Process	Squalene Epoxidase	21
Naftifine	Interfere With Sterol Biosynthesis	Squalene 2,3-Epoxidase.	22
Salicylic Acid	Promotes The Exfoliation of The Stratum Corneum	-	23
Tavaborole	Inhibition Of Protein Synthesis in Fungal Cells.	Cytosolic Leucyl-T-RNA Synthetase (Leu RS),	24
Ciclopirox	Chelation Of Metal Ions, Disruption of Essential Cellular Functions,	Catalases And Peroxidases	25
Nystatin	Stop The Ergosterol Manufacturing Process	Squalene Epoxidase	26
Allylamine	Stop The Ergosterol Manufacturing Process	Squalene Epoxidase	27

E. Disadvantages of conventional formulation

- Current dose forms, such as creams, ointments, and patches, have several disadvantages.

a) Patches:

- Occlusive nature obstructs sweat ducts and prevents water evaporation from the skin.
- Can cause skin irritation.
- They are often unsightly, painful to remove, and difficult to apply to curved surfaces.

b) Semisolid formulations (ointments and creams):

- Easily removed by clothing.
- Do not leave a long-lasting effect on the skin.
- Require repeated applications for chronic illnesses like ringworm, athlete's foot, and candidiasis.
- Leave a greasy, sticky residue, reducing patient compliance.
- ❖ A novel dose form is needed to:
 - Minimize application frequency.
 - Maintain extended skin contact.
 - Enhance patient adherence.

Table 2: An outline of new drug delivery methods for several antifungal medications administered subcutaneously.

Name of the drug	Novel drug delivery	Focus	Ref
Miconazole	Liposome	The formulated system exhibited favorable size or stability features and improved permeation qualities in the skin.	28
	Niosomes	He formulated a product that demonstrated a 92.10% drug release within 24 hours, indicating its potential effectiveness in treating topical fungal infections.	29
Fluconazole	Niosomes Liposomes,	Liposomal gel demonstrated a 14.2 times greater comparison of drug accumulation to plain gel, whereas niosomal gel resulted in 3.3 times more accumulation.	30
	Micelles	Micellar formulations may significantly improve the skin's uptake of azole antifungals.	31

Ketoconazole	Solid lipid nanocarriers (SLNs) and nanostructured lipid carriers (NLCSSs)	SLNs remained stable during storage for three months; however, they deteriorated when exposed to light, whereas NLCSSs successfully stabilized the drug, but the aqueous NLCS dispersion exhibited an increase in size over time.	32
	SLN-Dextran hydrogel	By varying the degree of derivatization or the concentration of the polymer, the prepared system's rheological characteristics could be readily and conveniently altered to maintain a semisolid consistency, a nice texture, and good spreadability, or to remain in the application site when necessary. The system was biocompatible.	33
Clotrimazole	Microemulsion	When compared to traditional cream, the clotrimazole microemulsion-based hydrogel demonstrated superior in vitro antifungal efficacy against <i>Candida albicans</i> and skin retention.	34, 35
	Liposomes, Niosomes	Both niosomal along with liposomal gels exhibited good retention in vaginal tissue and no negative effects on vaginal morphology 24 hours after the treatment.	35
Itraconazole	Niosomes	Both high drug entrapment and good skin penetration were noted in niosomes.	36
	Microemulsion	The topical administration of itraconazole was found to benefit from a microemulsion with a 1.5% w/w drug loading.	37

F. Recent topical anti-fungal drug delivery

a. SLN (solid-lipid nanoparticles)

- Solid lipid nanoparticles (SLNs) are nanoscale carriers that encapsulate active therapeutic substances within a lipid core. These particles are made up of matrices printed with lipids and surfactants. There are two methods to create SLNs: one involves high homogenization techniques, while the other uses microemulsion preparation. Essentially, SLNs are water-in-oil (w/o) emulsions where solid lipids serve as the oil phase.³⁸
- The benefits of SLNs include low potential for toxicity (the lipids used are physiologically similar), making them biocompatible. The small dimensions of the lipid particles enable close interaction with the stratum corneum, enhancing drug intrusion into the dermis and allowing for controlled drug release. Their formulation creates a film over the skin that prevents water loss. Consequently, the skin maintains its hydration and barrier function. Is preserved. The lipid nanoparticles are spherical, giving them excellent lubrication properties that help avoid a limited number of drugs that can be dissolved in suitable lipids.³⁹
- skin irritation and allergic reactions. They possess a high capacity for drug entrapment, and their release kinetics are well-regulated. The active compounds are shielded from Encapsulation-induced degradation. An industrial sterilization process can be applied to a wide variety of formulations. Their stability over the long term is excellent, and bioavailability remains high. However, SLNs do have some drawbacks, such as a limited number of drugs that can be dissolved in suitable lipids.³⁹
- Nanostructured lipid carriers, or NLCSS, are innovative carriers that can effectively deliver drugs directly to the skin. These carriers are made up of a lipid-based structure designed at the nanoscale. Research has demonstrated that NLCs can hold more drugs while ensuring that they stay securely stored.³⁹ NLCs is an effective carrier for drugs used to treat topical skin infections.⁴⁰
- Souto and his team created solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) to deliver clotrimazole topically. These carriers provide a prolonged release of the drug lasting up to 10 hours. Furthermore, the solid lipid nanoparticles have occlusive characteristics, which are beneficial for topical applications^{32, 39}. Both SLNs and NLCs protect the encapsulated drug from photodegradation, providing stability and demonstrating comparable antifungal activity to the marketed product against *Candida albicans*.^{32, 33}
- Sanna and her team showed that SLN formulations significantly improve the absorption of encapsulated econazole nitrate through the stratum corneum, which is typically impermeable, after one hour of application. Furthermore, after three hours, there was a greater penetration of econazole nitrate into the deeper skin layers compared to the reference gel.³³
- While nano-lipid formulations have shown enhanced safety and increased therapeutic efficacy for treating serious fungal infections, several challenges persist. These include low drug payload capacity, irregular particle size and dispersion, insufficient storage stability, high production costs, and challenges in scaling up for clinical use.

b. Liposomes

- A double layer of phospholipids, containing amphiphilic lipids like cholesterol and phospholipids, makes up these spherical vesicles. They can hold a variety of pharmaceuticals, including both fat-soluble and water-soluble ones. Lipophilic medications are embedded in the lipid bilayer, whereas hydrophilic medicines can be contained within their water-filled core.^{41, 42}
- Phospholipids and a range of techniques can be utilized to produce liposomes. A novel class of phospholipid vesicles called deformable or elastic liposomes was created to improve the skin's absorption of antifungal medications. Ultra-deformable liposomes, which are prepared with Tween 80 as an edge activator, have a diameter of 1078 nm, a polydispersity index (PDI) of 0.078, and a zeta potential of -3.0 ± 0.2 mV.
- These liposomes demonstrate a 40-fold enhanced drug accumulation in comparison to Ambisome. Beyond lipid composition, the structure and surface characteristics of liposomes are vital for influencing drug permeability and dermal retention.⁴³
- Current studies to improve antifungal efficacy have demonstrated the great potential of cationic liposomes. With a zeta potential of 40 to 60 mV and a size range of 400 to 500 nm, amphotericin B (amb)-loaded cationic liposomes exhibit superior antifungal activity in comparison to the medication when it is not encapsulated. However, the toxicity associated with the cationic components of these liposomes prevents their clinical use.
- Catalytic liposomes' clinical application is restricted by the toxicity of their cationic constituents. Despite the benefits, stability, drug expulsion, scale-up procedures, and the drug-drug-carrier compatibility complex are the main issues with liposomal formulations.⁴⁴
- Several studies suggest that liposomes effectively target the dermal layer, enhancing the localized action of the drug due to their accumulation and forming a drug reservoir. Furthermore, Studies have been conducted utilizing recreated human skin models to investigate the interactions between liposomes and keratinocytes. The inaugural liposomal topical product, a gel formulation of the antifungal drug ECZ (Pevaryl; Cilag AG, Schaffhausen, Switzerland), was developed in Switzerland in 1994.⁴⁵
- The initial liposomal formulation to hit the market was the antifungal medication Amphotericin B (amb), sold under the brand name ambisome®. This device, which was created in the USA by Nexstar Company, was introduced in 1990 and is now available in a few European nations.²⁷ The application of liposomes to the management of topical fungal infections has been the subject of recent studies. Liposomes are a technique that scientists are especially interested in using to deliver antifungal drugs straight to the skin. To compare the antifungal effectiveness of miconazole

nitrate (MCZ) loaded into topical liposomes with a traditional cream formulation, a comparative study was carried out.

- Two forms of phosphatidylcholine were utilized for the liposome formulation: unsaturated phosphatidylcholine (PCU) with a 98.0% content and saturated phosphatidylcholine (PCS) with a 97.3% content. According to the study, PCS-made liposomes showed greater skin retention than PCU-made liposomes. The prepared formulations exhibited good size stability and enhanced permeation properties.²⁸

c. Niosomes

- These are non-ionic surfactant-based spherical lipid vesicles²⁶. By interacting with the stratum corneum, they lessen the amount of water lost through the epidermis. The kinds of surfactants utilized, the drug's qualities, and the morphological features of the liposomal preparations all affect how well the skin absorbs things.^{46, 47}
- In these vesicular systems, non-ionic surfactants are typically stabilized by the addition of cholesterol or by using a small amount of anionic surfactants like diacetyl phosphate.⁴⁸
- Niosomes shield encapsulated medicinal compounds from proteolytic enzymes thanks to their sturdy bilayer structure as well as from variations in pH and osmotic pressure, thereby enhancing the stability of the product. However, niosomes have a relatively leaky vasculature compared to liposomes. Notwithstanding their comparable properties, niosomes have some unique advantages over liposomes, such as increased skin penetration, which enables them to be used to treat cutaneous and dermal mycosis. Additionally, they exhibit greater chemical stability, resulting in a longer shelf life and reduced costs.
- Furthermore, niosomes can encapsulate a broad range of medicinal substances because of their special amphiphilic characteristics. By modifying the formulation composition and preparation technique, niosomal preparations' size, shape, fluidity, and surface functionalization can be readily customized⁴⁹. Niosome preparation techniques include ether injection, bubble method, microfluidization, sonication, film hydration, and reverse phase evaporation.⁵⁰
- The main distinction between liposomes and niosomes is that non-ionic surfactants are used in place of phospholipids. Niosomes interact with the stratum corneum (SC) when administered topically, reducing water loss via the epidermis. They can either permeate deeper into the skin layers to form localized depots or be adsorbed on the skin's surface, where the drug's high thermodynamic activity gradient at the interface aids drug permeation.⁵¹
- Significant progress has been achieved by formulation scientists in creating more potent treatment strategies for topical medication delivery. This advancement entails altering earlier techniques to

lessen adverse effects and enhance therapeutic results.

- In this study, an elastic vesicular drug carrier system known as Spanlastics was created to target topically applied drugs to the posterior segment of the eye. This system was formulated using Span 60 and the edge activator Tween 80 in various ratios. The resulting spanlastics were nanosized, elastic in nature, and demonstrated twice the corneal permeation compared to traditional niosomes. After topical application, fluorescent vesicles were observed intact in the vitreous humour and internal eye tissues two hours post-application. These results suggest that spanlastics can effectively deliver drugs to the posterior segment of the eye.⁵²
- Recently, a Carbopol gel containing Griseofulvin niosomes was tested for therapeutic effectiveness against tinea corporis. The results indicated that the niosomal gel of griseofulvin achieved the highest mycological cure rates (approximately 80%) compared to the liposomal gel, which had about 50% cure rates after a treatment period of two weeks.⁵³
- Additionally, griseofulvin was also formulated in a proniosomal gel using Span surfactants (20, 40, 60, and 80). Among these, the proniosomes prepared with Span 40 exhibited the highest entrapment efficiency and the least drug leakage. It was found that the proniosomal gel made with Span 40 demonstrated six times greater skin permeation compared to the plain formulation.⁵⁴

d. Microemulsions

- The microemulsion system is a classic drug delivery method for many antifungal medications, aiming to maximize efficacy while minimizing toxicity. A transparent or translucent mixture of water and oil that is thermodynamically stable is called a microemulsion. It is stabilized by an interfacial film composed of surfactant and co-surfactant molecules, with droplet sizes ranging from 20 to 200 nanometres. This system's interface fluctuates suddenly and continuously.
- Microemulsions possess several favourable properties that make them effective drug delivery tools. Easy creation, optical isotropy, filter sterilization, high surface area (which increases solubilization capacity), and a very small droplet size are some of these. The ability of this mechanism to solubilize hydrophobic medicines and improve topical and systemic availability has led to substantial

research in the pharmaceutical industry. It exhibits quick and efficient skin penetration as well.

- The majority of antifungal medications are lipophilic, including ketoconazole, itraconazole, fluconazole, luliconazole, clotrimazole, econazole, and miconazole. This characteristic makes it challenging to incorporate them into aqueous gels for localized benefits. This problem is solved by creating an oil-in-water microemulsion and adding it to an aqueous gel. By including the medications in the emulsion's oil phase, this arrangement enables a sustained release of the medication when applied topically.⁵⁵
- Microemulsions offer some benefits, including improved drug solubility, low cost, efficient manufacturing procedures, good heat stability, and great permeability. They demonstrate outstanding compatibility with biomaterials, making them suitable delivery systems for both topical and transdermal applications. The combination of oils and surfactants in microemulsion formulations enhances drug permeability across the stratum corneum.⁵⁶⁻⁵⁹
- Several mechanisms have been identified to explain how microemulsions enhance penetration and retention in the dermis. First, the inclusion of a significant amount of either lipophilic or hydrophilic phases improves drug solubility. This enhancement promotes drug partitioning into the skin, as only the dissolved portion of a drug in the vehicle can penetrate the skin effectively.⁶⁰ The enhanced penetration and retention of the drug in microemulsions may result from interactions with the complex lipid layers of the stratum corneum.⁶¹
- A gel that contains a microemulsion of ciclopirox olamine was created to treat vaginal candidiasis. To assess the gel's in vivo antifungal properties, a candidal fungal infection was induced in female rabbits. The microemulsion-based gel demonstrated significant antifungal activity in the rabbits compared to a marketed formulation.(1% clotrimazole gel)⁶². A microemulsion-based gel containing clotrimazole was made and tested for some properties, such as viscosity, droplet size, pH, refractive index, thermodynamic stability, and in vitro antifungal efficacy. Comparing the proposed microemulsion-based hydrogel to traditional cream, it showed much higher in vitro antifungal efficacy against *Candida albicans* and high skin retention. Clinical evaluation of the gel revealed that it was effective in 93.31% of the patients who completed the study.³⁴

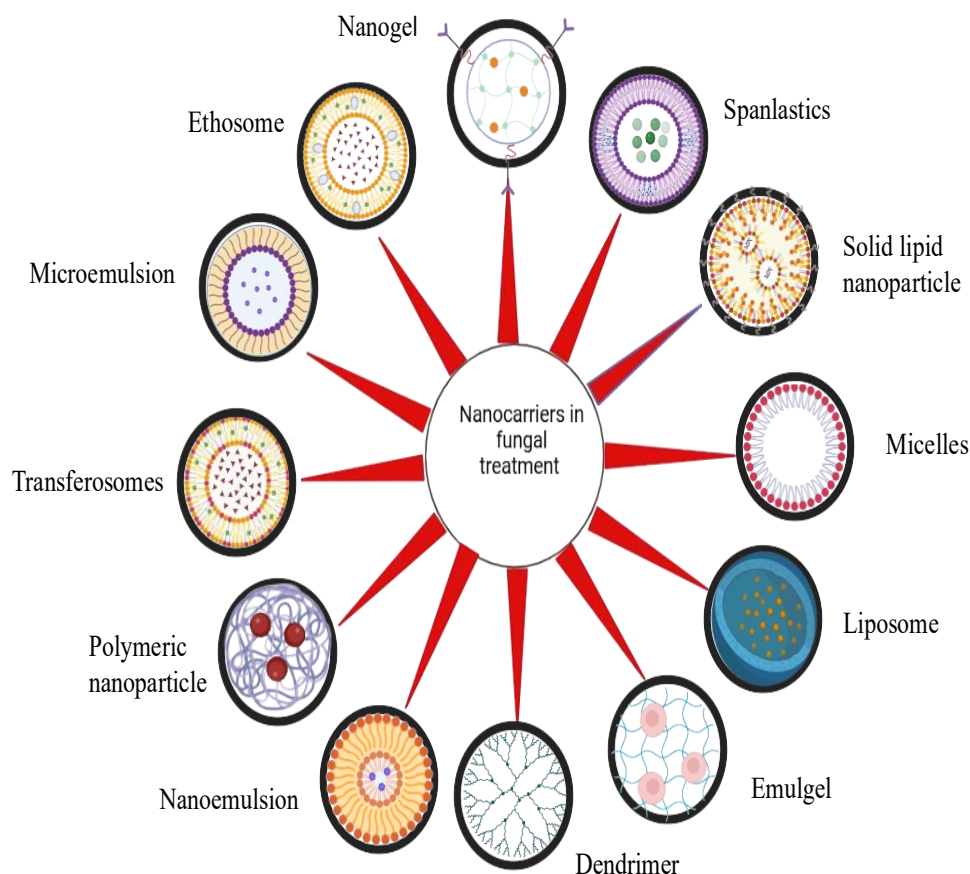


Figure 2: Novel topical anti-fungal drug delivery

e. Nanoemulsion

- Nanoemulsions are emulsified systems characterized by droplets smaller than 1 μm , typically ranging from 20 to 200 nm, and they have low polydispersity. These emulsions appear transparent or translucent to the naked eye and can exist as either oil in water (o/w) or water in oil (w/o), stabilized by a film formed by surfactants and cosurfactants at the interface. However, nanoemulsions are thermodynamically unstable and cannot form spontaneously; they require an input of energy for their production. This energy can be supplied through various dispersion methods (often referred to as brute force) or through physicochemical techniques, such as condensation or low-energy methods⁶³
- These structures are fundamentally nonequilibrium in nature and require energy input for their formation, often originating from an emulsion. Nanoemulsions can be created through high-energy emulsification methods, such as high-pressure homogenization, or through low-energy emulsification that leverages the physicochemical properties of the components involved. The optimization and characterization of topical nanoemulsions designed for various antifungal medications have been extensively explored in the literature. Notably, nanoemulsions maintain physical stability over prolonged storage periods, avoiding issues such as coalescence. However, shearing within high-concentration ranges can expedite their physical

degradation. There is some uncertainty regarding the efficacy of a concentrated nanoemulsion when forced through a nanoporous membrane, such as human skin. The commercially available NB-00X products, which consist of nanoemulsion droplets measuring 200 nm and are based on Nano Stat technology, are primarily utilized for the treatment of herpes labialis.⁴⁵

- Often, topical formulations with nanoemulsions are used to enhance the therapeutic efficacy and tolerability of antifungal medications applied locally. Additionally, these can shield medications from enzymatic and chemical degradation and increase the solubility of poorly soluble drugs, which makes them an excellent topical vector for antifungal medications⁶⁴⁻⁶⁶.
- In 2012, Elosaily combined ethanol, Tween 80, and Labrafil M1944 to create a nanoemulsion. The study's findings showed that, in contrast to the commercially available formulation, the Nanoemulsion (formulations F1 and F8) exhibited larger nanodroplet size, a higher degree of drug release, and stronger antimycotic activity. When compared to the commercial sample, the miconazole-loaded Nanoemulsion demonstrated a greater percentage of zone of inhibition against *Aspergillus niger* and *Candida albicans*.⁶⁷
- Recently, Soriano and colleagues used pig and human skin to assess the skin flux and antifungal effectiveness of a Nanoemulsion loaded with

clotrimazole. The outcome showed that, in comparison to commercial references, the optimized Nanoemulsion offered a sustained release, higher skin penetration, and antifungal efficacies⁶⁸

f. Micelles

- An aggregate of surfactant molecules scattered in a liquid colloid is referred to as a micelle. The formation of an aggregate in an aqueous solution is caused by the hydrophilic head of the surfactant molecule orienting towards the outer solvent and the hydrophobic tails sequestering towards the centre of the micelle⁶⁹
- Micelles have a roughly spherical shape. There may also be other phases, shaped like ellipsoids, cylinders, or bilayers. A micelle's size and shape are determined by the surfactant molecules' molecular geometry as well as the conditions of the solution, including temperature, pH, ionic strengths, and surfactant concentration.⁷⁰
- Micelle formation, a process in soaps, aids in phase behaviour and drug delivery, particularly in topical antifungal medication administration, due to hydrophilic and hydrophobic properties.⁷¹
- Bachhav et al. developed nanometer-sized micelles for treating superficial fungal infections using fluconazole, econazole nitrate, and clotrimazole aqueous micellar solutions. These micelles entrapped econazole nitrate more effectively than commercially available Pevaryl® cream, suggesting a potential role for micelles in enhancing antifungal medication cutaneous bioavailability.³¹

g. Nanogel

- One way to characterize highly cross-linked, nanoscale hydrogel systems is as monomers, which can be ionic or non-ionic, or as co-polymerized systems. Nanogels are found in sizes between 20 and 200 nm. The desire for nanogels as a delivery system is fuelled by their well-known excellent properties¹. Among them are their exceptional thermodynamic stability, high solubility, relatively low viscosity, and ability to withstand a harsh sterilizing process.⁷²
- Despite the low cost of nanogel processing, the most prevalent limitation of nanogel is its inability to easily separate the surfactant and solvent from the final product.^{73, 74}

h. Emulgel

- Emulgel is topical medication delivery systems that incorporate gelled emulsions. These systems combine both an emulsion and a gel, which enhances stability when mixed. Emulgel offers several advantages over both traditional delivery methods and newer vesicular systems. They are emollient, non-staining, water-soluble, greaseless, thixotropic, easily spreadable, and quickly removed, and aesthetically pleasing. These qualities make emulgel ideal for dermatological use.

- Emulgel, with permeation enhancers, can effectively deliver antifungal medications, such as clotrimazole, using two grades of acrylic acid copolymers and jojoba oil for stability and high drug release rates.^{75, 76}
- Emulgel, a combination of gel and emulsion, enhances antifungal composition stability, offers quicker drug release, and doesn't leave residue or a greasy feeling compared to conventional creams or ointments.
- Emulgel works well for adding hydrophobic medications to gel bases that dissolve in water⁷⁷. For instance, adding clotrimazole to an emulgel formulation prepared with HPMC 2910 or Carbopol 934 showed good stability, antifungal efficacy, and physical characteristics.⁷⁸ A formulation was created that combines ϵ -caprolactone and poly (lactic-co-glycolic acid) (PLGA) to encapsulate amphotericin B. This work showed how polymeric nanoparticles can maintain their fungicidal effectiveness while avoiding cytotoxicity.⁷⁹
- The authors found an 84% encapsulation efficiency for amphotericin B, which effectively treats *Candida albicans*, with lower mortality and toxicity compared to the free drug.⁷⁹

i. Ethosomes

- Ethosomes are a subtype of ethanolic liposomes that function as non-invasive delivery vehicles, enabling medications to reach the bloodstream or profoundly penetrate the layers of the skin. These flexible, soft nanovesicles have a special shape that allows them to pass through the skin's natural barrier and distribute medications efficiently.
- For many years, ethosomes have been recognized for their significance in cellular communication and particle transportation. Composed of lipid vesicles, ethosomes contain phospholipids, alcohol (such as ethanol and isopropyl alcohol) in relatively high concentrations, and water.⁸⁰ Vesicle sizes range from 10 nanometres to several micrometres. Deeper distribution and improved penetration inside the lipid bilayer of the skin may be facilitated by the synergistic actions of phospholipids and a high ethanol concentration in formulations.⁸¹
- These are used as drug carriers for antifungal medications such as amphotericin B, fluconazole, and clotrimazole. Ethosomes can be prepared using either a cold method or a hot method.^{63, 64}

j. Dendrimer

- Dendrimers are spherical, branching macromolecules with a tree-like structure, derived from the Greek word "dendron." Tomalia synthesized the first family of dendrimers, with a diameter of one to ten nanometres.^{82, 83}
- Dendrimers are used in various medicinal substances, including antiviral therapies and antibacterial pharmaceuticals. Starpharma, an Australian company, developed Viva Gel, a topical treatment

based on dendrimers, as a vaginal microbicide to prevent the spread of sexually transmitted illnesses.⁸⁴

- Nanoscale structures, with high branching, water solubility, multivalence, well-defined molecular weight, and accessible interior cavities, are highly beneficial as antifungal agents and drug delivery vehicles.^{85, 86}
- The most widely utilized dendrimers for antifungal treatment are polyamidoamine (PAMAM) and polypropylene imine (PPI) dendrimers; however, other kinds have also been described. PAMAM dendrimers containing ketoconazole have been found to increase the drug's antifungal activity, solubility, and in vitro release.⁸⁷

k. Transferosome

- Transferosomes are composed of natural phospholipids, such as phosphatidylcholine, which self-assemble into a lipid bilayer. These bilayers are combined with single-chain surfactants that serve as edge activators. Common edge activators include sodium cholate, Span 80, Tween 80, and dipotassium glycyrrhizinate. The complex lipid bilayer encloses an inner aqueous core, allowing for the incorporation of both hydrophobic and hydrophilic substances. The edge activators help destabilize the lipid bilayer, increasing its fluidity and elasticity, which enables the transferosomes to efficiently cross various transport barriers. Moreover, transferosomes can enhance drug entrapment efficiency, achieving rates of up to 90% for lipophilic drugs.⁸⁸
- They are more flexible and adaptable than traditional liposomes; however, they have demonstrated chemical instability due to a tendency for oxidative degradation, and their formulations are costly.⁸⁹
- In Transfersome® vesicles (TFVs), Steinberg created a topical version of the hydrophobic fungicide terbinafine (TF). In vitro, this formulation's antifungal activity was noticeably higher than that of ordinary TF. According to the study, the fungal endoplasmic reticulum (ER) was more effectively localized and damaged by TFVs. Transferosomes may be able to treat all kinds of fungal illnesses on their own, according to the research.⁹⁰
- Ghannoum et al. Created a liquid spray based on transferosomes to efficiently administer a medicinal medication through the nail bed to treat infections caused by onychomycosis. The minimum inhibitory concentrations (MIC) of the transfersome system ranged from 0.03 to 15 mg/ml, indicating high action against dermatophyte strains.⁹¹
- In a study conducted by Zaky et al., TF-containing transferosomes were created to evaluate skin penetration rates and antifungal efficacy of various vesicular formulations, including mentosomes, transferosomes, and ethosomes, in nonocclusive environments. In comparison to the drug suspension, the ex vivo analysis of the drug-loaded vesicles showed a two- to three-fold increase in penetration rate. To treat fungal infections of the fingernails and

toenails, the TF transfer is considered a potent antifungal treatment against *Aspergillus Niger*.⁹²

l. Spanlastics

- They primarily consist of spans along with edge activators such as tweens and others. Spanlastics are similar to transferosomes and transthesomes, as they all incorporate edge activators. The first reported delivery system based on Spanlastics was developed for the ocular delivery of ketoconazole, utilizing Span 60 and Tween 80 as edge activators.⁵²⁵⁵
- The spanlastics demonstrated a twofold increase higher ocular penetration of ketoconazole as opposed to traditional niosomes. They demonstrated good stability and passed tests for corrosion, genotoxicity, cytotoxicity, and acute and chronic skin and ocular irritation. Furthermore, compared to commercially available eye drops, fluconazole-loaded spanlastics had three times the drug permeability through the pig cornea and were three times smaller than their corresponding niosomes.⁹³
- In order to treat onychomycosis, terbinafine hydrochloride was encapsulated in Span1 60 or 65 Spanlastics that also contained sodium deoxycholate or Tween1 80 as edge activators.⁹⁴
- Spanlastics containing terbinafine demonstrated improved ex vivo permeability through nails compared to a commercial cream. Aside from the later study published in the Journal of Multidisciplinary Healthcare in 2022 (Volume 15), spanlastics have primarily been used for the ocular administration of antifungal agents. Consequently, their potential for both systemic and topical administration of antifungal agents has not yet been fully explored.⁹⁵

m. Microneedle

- These are made to be a painless form of therapy that improves skin function without damaging the epidermis. Numerous methods, such as photolithography, micro shaping, microfabrication, and micro moulding, are used to prepare these. It can help prevent presystemic metabolism, have a quick onset of action, work with a wide range of medications, help people who are afraid of needles, and make administering drugs easier. With the help of this technology, it is possible to get around some of the drawbacks of traditional formulations, such as systemic side effects, poor permeability, low bioavailability of hydrophilic drugs, poor aqueous solubility, and repeated administration.⁹⁶⁻¹⁰⁰

n. Iontophoresis

- This external energy source takes the shape of a direct electrical current applied in iontophoresis. By applying an electric current, iontophoresis increases the penetration of electrically charged drugs into surface tissues.¹⁰¹
- As stated by the fundamental electrical principle that "like charges repel each other and opposite charges attract," Ions can go through the stratum corneum more easily when electrical energy is present. At a

neutral spot on the body's surface, a return electrode opposite the drug's charge is placed, and the drug is applied beneath an electrode with the same charge. The operator then selects a current that is below the patient's threshold for discomfort and allows it to run for the appropriate duration. Because the electrical current attracts opposite charges and repels like ones, it greatly increases the drug's penetration into surface tissues. Iontophoretic treatment requires two traditionally accepted prerequisites: the drug needs to be charged¹⁰²

- Three mechanisms explain how iontophoresis improves transdermal drug delivery: (a) ion-electric field interaction gives an extra force that pushes ions through the skin; (b) electric current flow makes the skin more permeable; and (c) electro-osmosis creates bulk solvent motion that carries ions or neutral species with the solvent stream¹⁰³
- Transdermal iontophoresis has many potential applications, but there are still issues that need to be resolved for successful clinical use" The choice of medications based on skin surface electric potential, which Favors cationic medicines, is one such problem. Second, for long-term use, skin irritation is still a significant problem that needs to be resolved.^{72, 104, 105}

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Conclusion

Advanced drug delivery technologies like liposomes, nanoparticles, microemulsions, and nanogels are replacing traditional topical antifungal treatments. These technologies improve drug penetration, stability, and long-term release, making them viable substitutes for traditional formulations. However, challenges such as large-scale production, cost-effectiveness, long-term stability, and regulatory permissions remain. Future research should focus on refining formulation tactics, enhancing patient adherence, and creating cost-effective production procedures. Despite these advancements, new topical antifungal formulations offer a promising solution to overcome conventional treatments and improve patient outcomes.

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