ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

Transdermal Drug Delivery for Dermatophytosis: A Novel Approach

Ajay[1*]; Dr. Yogendra Singh[2]; Dr. Ashutosh Upadhayay[3]; Prashant Vashisht[4]

[1,2,3,4]School of Pharmaceutical Sciences, MVN University, Palwal-121105, Haryana, India

Corresponding Author: Ajay[1*]

Publication Date: 2026/05/15

Abstract: Dermatophytosis, also called ringworm, is a common fungal infection that affects the skin, hair, and nails. It is mainly caused by fungi such as Trichophyton, Microsporum, and Epidermophyton. The treatments include topical creams and oral antifungal drugs, but these treatments often do not work effectively. This is because the drugs do not penetrate the skin properly, may cause side effects, and the infection often comes back after treatment. To solve these problems, transdermal drug delivery systems (TDDS) provide a new and effective treatment approach for dermatophytosis. Transdermal delivery helps the drug pass through the skin slowly and in a controlled manner, maintaining a sufficient amount of drug at the infected site while reducing unwanted effects on the body. Several noval carriers such as liposomes, niosomes, ethosomes, nanogels, and microneedle-based patches have been developed to improve the penetration and retention of antifungal drugs in the skin. Research studies have shown that these systems provide better drug absorption, longer drug release, and improved patient comfort and compliance. This review highlights the pathophysiology of dermatophytosis, challenges in conventional treatments, and the potential of novel transdermal systems for effective antifungal therapy.

Keywords: *Dermatophytosis, Transdermal Drug Delivery, Antifungal Agents, Nanocarriers, Skin Infection, Controlled Release*.

How to Cite: Ajay; Dr. Yogendra Singh; Dr. Ashutosh Upadhayay; Prashant Vashisht (2026) Transdermal Drug Delivery for Dermatophytosis: A Novel Approach. *International Journal of Innovative Science and Research Technology*, 11(4), 4619-4629. https://doi.org/10.38124/ijisrt/26apr2331

I. INTRODUCTION

Dermatophytosis is the most common superficial fungal infections affecting the skin, hair, and nails. It is primarily caused by dermatophyte fungi such as Trichophyton rubrum, Microsporum gypseum, and Epidermophyton floccosum. These fungi penetrate keratinized tissues and lead to circular, itchy, and scaly lesions, which may cause discomfort. Dermatophytosis has become more common worldwide, especially in tropical and humid regions.(1)

Traditional treatment includes topical formulations like creams and ointments or systemic antifungal drugs such as terbinafine and itraconazole. However, these approaches have poor skin permeability, short duration of action, and local irritation. Additionally, systemic drugs may cause hepatic toxicity and other side effects for their long-term use.(2)

To overcome these challenges, researchers have focused on developing novel drug delivery systems that can enhance drug penetration through the skin barrier and provide sustained release at the target site. Transdermal drug delivery systems (TDDS) offer an effective alternative as they can bypass gastrointestinal degradation, avoid first-pass metabolism, and deliver drugs directly to the infected skin layers. Recent advances in nanotechnology such as liposomes, ethosomes, nanogels, and microneedles, provide better therapeutic outcomes for fungal skin infections.(3)

This review gives a basic overview of dermatophytosis, explains the limitations of traditional antifungal treatments, and highlights transdermal systems as a new and effective method for treating fungal infections.

II. PATHOPHYSIOLOGY

Dermatophytosis is a superficial fungal infection that primarily affects keratinized tissues such as the stratum corneum, hair, and nails. The infection is caused by a group of keratinophilic fungi known as dermatophytes, mainly belonging to three genera: Trichophyton, Microsporum, and Epidermophyton. Among these, Trichophyton rubrum is the most common species responsible for human infections.

The pathogenesis begins when fungal spores (arthroconidia) come into contact with the skin surface. Under favorable conditions such as warmth, humidity, and minor skin trauma, the spores germinate and adhere to the

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

stratum corneum using adhesins and keratinolytic enzymes. These enzymes, including keratinases, proteases, and lipases, degrade keratin and allow the fungi to penetrate into deeper layers of the epidermis.(4)

Once inside the skin, the dermatophytes proliferate and release metabolic products that trigger inflammatory and immune responses. The host's immune reaction plays a key role in determining the severity and persistence of infection. In immunocompetent individuals, the infection often remains superficial, whereas in immunocompromised patients, it may become chronic or extensive.

The infection spreads centrifugally, forming the characteristic circular lesions with an active, red, and scaly border and a clearer center. These lesions are commonly observed on the scalp (tinea capitis), body (tinea corporis), groin (tinea cruris), feet (tinea pedis), and nails (tinea unguium or onychomycosis).(5)

The skin barrier, mainly the stratum corneum, acts as a major obstacle for antifungal drugs. Its lipophilic nature limits the penetration of hydrophilic drugs and large molecules. Therefore, achieving adequate drug concentration at the infection site remains a major challenge in topical therapy. Understanding the pathophysiology of dermatophytosis is crucial for designing effective transdermal delivery systems that can overcome this barrier and ensure better drug diffusion and retention in the infected tissue.(6)

III. CONVENTIONAL TREATMENTS AND THEIR LIMITATIONS

The management of dermatophytosis mainly relies on topical and systemic antifungal therapies. Commonly used antifungal agents include azoles (e.g., clotrimazole, ketoconazole, fluconazole), allylamines (e.g., terbinafine, naftifine), and griseofulvin. These drugs act by disrupting the fungal cell membrane or inhibiting ergosterol synthesis, an essential component of fungal cell walls.(7)

➢ *Topical Therapy*

Topical formulations such as creams, ointments, gels, and lotions are the first-line treatment for localized infections. They deliver the drug directly to the affected area and minimize systemic exposure. However, their effectiveness is often limited by poor drug penetration through the stratum corneum, frequent reapplication requirements, and short residence time on the skin surface. Many patients also experience local irritation, burning, or allergic reactions due to repeated use of these formulations. Furthermore, noncompliance and incomplete treatment courses frequently result in recurrence or resistance.(8)

➢ *Systemic Therapy*

For extensive or chronic dermatophytosis, oral antifungal agents such as terbinafine, itraconazole, and fluconazole are prescribed. Although systemic therapy ensures deeper tissue penetration, it is associated with several adverse effects including hepatotoxicity, gastrointestinal discomfort, and drug–drug interactions. Long treatment duration and variable bioavailability also limit patient adherence and therapeutic success. Moreover, first-pass metabolism and fluctuating plasma levels often reduce the drug's efficacy.(9)

➢ *Limitations of Conventional Approaches*

The major limitations of conventional antifungal therapy include:

- Inadequate penetration of drugs into deeper skin layers.
- Development of fungal resistance due to subtherapeutic dosing or prolonged use.
- Systemic side effects and poor patient compliance.
- Frequent relapses and long treatment durations.
- Instability of certain antifungal drugs in topical preparations.(10)

These limitations highlight the urgent need for novel drug delivery systems that can overcome the skin barrier, provide sustained drug release, and maintain therapeutic levels at the infection site. Transdermal drug delivery systems (TDDS) offer a promising alternative by enhancing drug permeation, reducing side effects, and improving patient adherence.

IV. OVERVIEW OF TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

The transdermal drug delivery system (TDDS) represents a modern and innovative approach to administering therapeutic agents through the skin, either for systemic circulation or for targeted action at specific sites. Unlike conventional oral or topical therapies, TDDS provides several significant advantages, including controlled and sustained drug release, reduced dosing frequency, minimized fluctuations in plasma drug levels, and improved patient compliance. By bypassing the gastrointestinal tract and first-pass hepatic metabolism, TDDS can enhance the bioavailability of drugs that are otherwise poorly absorbed or extensively metabolized when taken orally.(11)

The skin, as the largest and most accessible organ of the body, offers a convenient and non-invasive route for drug delivery. It allows for both local treatment of superficial conditions, such as dermatophytosis, and systemic therapy for chronic or long-term medical conditions. In the context of dermatophytic infections, TDDS is particularly valuable because it facilitates direct drug penetration into the infected layers of the epidermis and dermis, ensuring higher local drug concentrations while minimizing systemic exposure and adverse effects.(12)

Modern TDDS incorporate advanced formulation technologies, including patches, gels, creams, and nanoparticle-based systems, which are designed to overcome the skin's natural barrier and enhance drug permeation and retention. These systems can be engineered for precise drug release kinetics, ranging from immediate to extended release, providing flexibility in therapy design. Furthermore, TDDS offers improved patient convenience

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

and adherence by eliminating the need for frequent application or oral dosing, reducing the risk of missed doses, and offering a more user-friendly approach for chronic treatments.(13)

Overall, TDDS represents a rational and versatile strategy for drug administration, combining efficacy, safety, and patient-centric benefits, and holds significant potential in improving the management of dermatophytosis and other localized or systemic conditions.

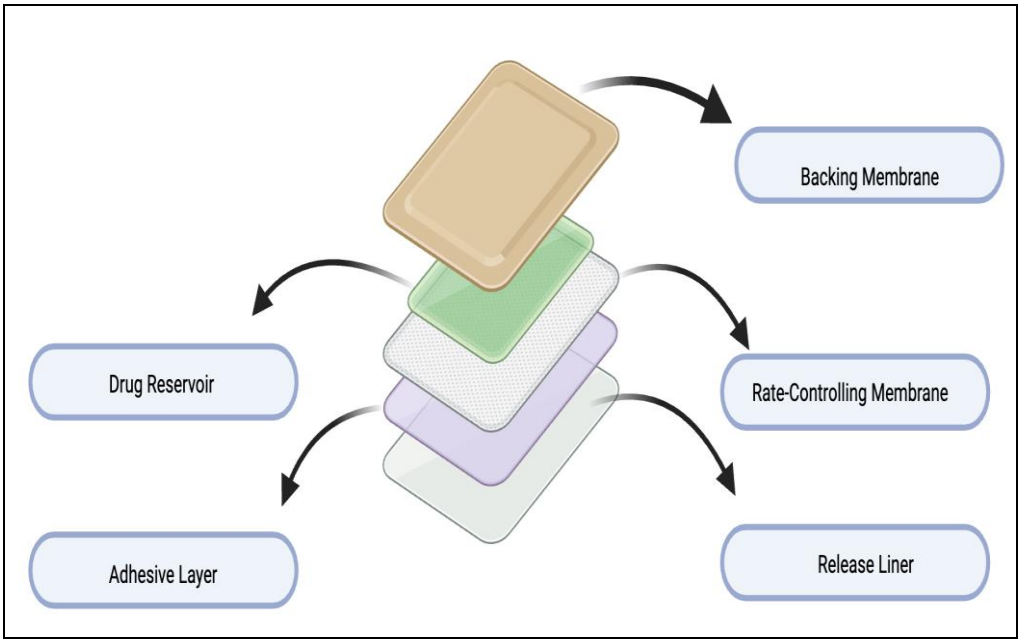

Fig 1 Transdermal Drug Delivery Systems

➢ *Advantages of TDDS*

- Non-invasive and patient-friendly
- Controlled and sustained drug release
- Bypasses first-pass metabolism
- Localized drug action
- Improved safety profile
- Enhanced patient compliance
- Versatility in drug types
- Minimized drug interactions
- Patient convenience and mobility
- Potential for enhanced efficacy(14)

V. STRUCTURE OF SKIN AND ITS ROLE IN DRUG ABSORPTION

The skin is a complex, multi-layered organ that serves as both a protective barrier and a route for drug delivery. It is primarily composed of three main layers: the epidermis, dermis, and hypodermis. The epidermis, the outermost layer, provides the first line of defense against environmental insults, pathogens, and chemical agents. Within the epidermis, the stratum corneum functions as the principal barrier to drug penetration. This layer consists of tightly packed, dead keratinized cells called corneocytes, embedded within a highly organized lipid matrix, often described by the "brick and mortar" model. The corneocytes act as the "bricks," while the lipid layers act as the "mortar," creating a dense structure that limits the passive diffusion of substances through the skin.(15)

Beneath the stratum corneum, the viable epidermis and dermis contain living cells, capillaries, and nerve endings, which are essential for nutrient supply, immune defense, and absorption of drugs that successfully penetrate the outer barrier. The hypodermis, the innermost layer, is composed mainly of adipose tissue and connective tissue, providing cushioning and energy storage. Its vascular network allows drugs that reach this depth to enter systemic circulation.

Drugs can traverse the skin via three main pathways. The transcellular route involves passage directly through corneocytes, requiring drugs to partition through both lipophilic and hydrophilic domains. The intercellular route allows molecules to diffuse between the corneocytes through lipid channels, which is the predominant pathway for lipophilic drugs. The appendageal route involves transport through skin appendages such as hair follicles, sebaceous glands, and sweat glands, providing a minor but strategically important shortcut for larger molecules and hydrophilic compounds.(16)

For effective transdermal drug delivery, a drug must possess specific physicochemical properties. Ideal candidates are typically low molecular weight compounds (usually less than 500 Da), have balanced lipophilicity to penetrate the lipid-rich stratum corneum, and exhibit adequate solubility to diffuse through deeper aqueous layers. Understanding the skin's structure and these transport pathways is critical for designing advanced transdermal systems that can efficiently deliver therapeutic agents, such as antifungal drugs, to target tissues while overcoming the formidable barrier posed by the stratum corneum.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

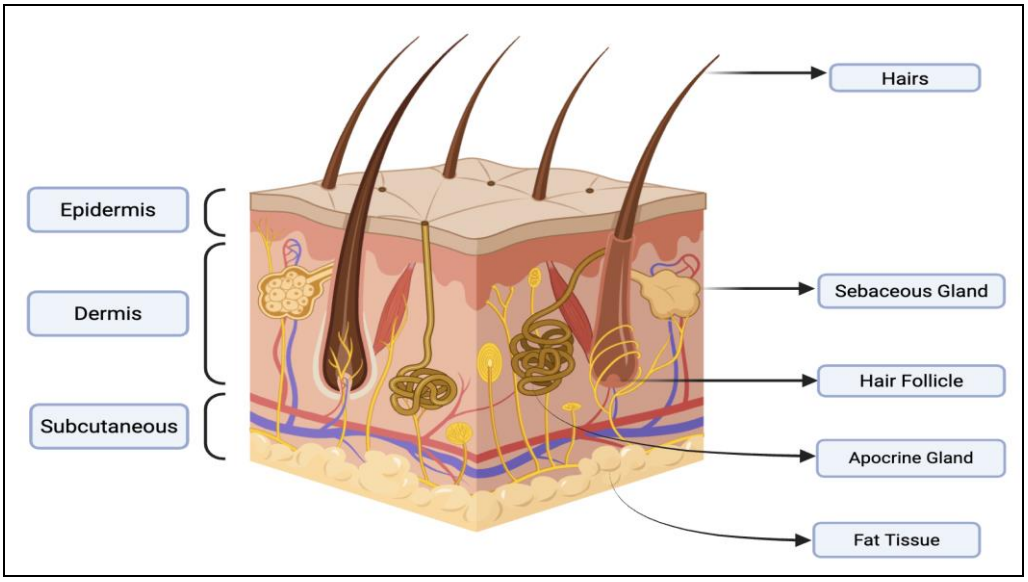

Fig 2 Structure of Human Skin

➢ *Drugs Can Pass Through the Skin Via three Main Pathways:*

- Transcellular route: through the corneocytes.
- Intercellular route: between the cells through lipid channels.
- Appendageal route: through hair follicles and sweat glands.

For effective transdermal delivery, a drug must have suitable lipophilicity, low molecular weight, and adequate solubility to cross the stratum corneum and reach deeper skin layers.(17)

➢ *Mechanism of Drug Transport*

The mechanism of drug transport through transdermal drug delivery systems (TDDS) fundamentally relies on passive diffusion, where drug molecules move across the skin layers in response to a concentration gradient between the formulation and the underlying tissues. Under conventional conditions, this process occurs mainly through the stratum corneum—the primary rate-limiting barrier of the skin—via intercellular, transcellular, or appendageal pathways. However, because the stratum corneum is highly resistant to permeation, passive diffusion alone often results in insufficient drug delivery, especially for antifungal agents that need to reach deeper epidermal layers where dermatophytes actively grow.(18)

To address these limitations, modern TDDS incorporate a variety of penetration-enhancement strategies designed to temporarily increase skin permeability and improve drug flux. Technologies such as iontophoresis apply a mild electrical current to drive charged drug molecules across the skin, enhancing their transport without causing tissue damage. Similarly, microneedles create microscopic channels in the skin that bypass the stratum corneum, providing a minimally invasive route for drugs to reach deeper layers directly. In addition, nanocarrier-based systems—including liposomes, solid lipid nanoparticles, polymeric nanoparticles, and nanoemulsions—enhance permeation by interacting with skin lipids, fluidizing the stratum corneum, and improving drug solubility and distribution within skin layers.(19)

These advanced techniques modify the skin barrier in a controlled and reversible manner, ensuring that structural integrity remains intact while enabling greater drug penetration and localized therapeutic action. By combining passive diffusion with these innovative enhancement methods, modern TDDS significantly improve the efficiency and effectiveness of transdermal antifungal therapy, making them a powerful tool in the management of dermatophytosis.

➢ *Tdds in the Treatment of Dermatophytosis*

Transdermal drug delivery systems (TDDS) have gained considerable attention in the treatment of dermatophytosis due to their ability to deliver antifungal agents directly to the infection site with improved penetration and sustained action. In dermatophytic infections, the fungi typically colonize the deeper layers of the stratum corneum, viable epidermis, and sometimes hair follicles—areas that conventional topical preparations often fail to reach adequately. TDDS can overcome this limitation by facilitating controlled and enhanced drug permeation across the skin barrier, ensuring that therapeutic concentrations are maintained within infected tissues for prolonged periods. This targeted and sustained delivery not only enhances the overall clinical response but also reduces the likelihood of incomplete treatment, disease recurrence, and the development of antifungal resistance.(20)

A variety of antifungal agents, including clotrimazole, terbinafine, and ketoconazole, have been successfully incorporated into novel transdermal formulations such as nanoemulsions, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and microneedle-assisted patches. These advanced carriers significantly improve drug solubility and partitioning into the skin, increase residence

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

time at the infection site, and offer better therapeutic performance compared to conventional creams and gels. Furthermore, sustained and controlled release profiles provided by TDDS minimize dosing frequency, enhance patient compliance, and ensure continuous antifungal activity throughout the course of treatment.

Thus, the development and optimization of advanced TDDS present an effective and scientifically sound strategy for improving antifungal therapy in dermatophytosis. By successfully overcoming the formidable skin barrier and enabling precise, site-specific drug deposition, these systems hold strong potential to revolutionize the management of superficial fungal infections and contribute to improved patient outcomes in clinical practice.(21)

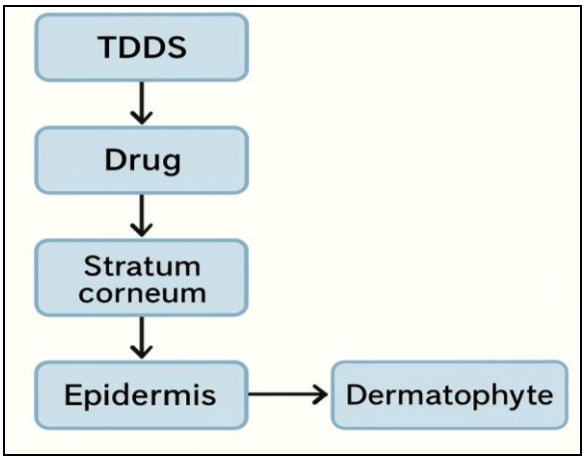

Fig 3 TDDS in the Treatment of Dermatophytosis

VI. NOVEL TRANSDERMAL DELIVERY APPROACHES FOR DERMATOPHYTOSIS

Recent advancements in pharmaceutical technology have enabled the creation of several novel transdermal drug delivery systems (TDDS) specifically engineered to overcome the natural skin barrier and facilitate efficient transport of antifungal agents into deeper epidermal and dermal layers. These advanced delivery platforms—including nanocarriers, vesicular systems, lipid-based nanoparticles, and microneedle-assisted patches—significantly improve key drug properties such as solubility, permeability, chemical stability, and retention at the infection site. By enhancing these parameters, modern TDDS not only ensure higher and more sustained therapeutic concentrations but also reduce dosing frequency, improve patient compliance, and minimize the risk of treatment failure. As a result, these innovative systems hold strong potential to greatly improve the management and clinical outcomes of dermatophytosis.(22)

➢ *Vesicular Drug Delivery Systems*

- *Liposomes*

Liposomes are versatile, nanoscale to microscale vesicular carriers composed of one or more concentric phospholipid bilayers enclosing an aqueous core. Their amphiphilic architecture enables the encapsulation of a wide range of therapeutic molecules, including hydrophilic drugs within the internal aqueous compartment and lipophilic drugs within the lipid bilayers. Because their composition closely mimics natural biological membranes, liposomes exhibit excellent biocompatibility and can interact favorably with skin lipids, particularly those in the stratum corneum. This interaction facilitates enhanced permeation by temporarily disrupting or fluidizing the tightly packed lipid matrix of the stratum corneum, thereby improving the penetration of antifungal agents into deeper skin layers.

In transdermal and topical delivery, liposomes offer several advantages, including sustained drug release, improved drug solubility, reduced systemic absorption, and enhanced localization of the drug at the site of infection. They can also protect encapsulated drugs from chemical degradation, increasing their stability and therapeutic lifespan. For dermatophytosis, liposome-based formulations have gained significant attention due to their ability to improve cutaneous deposition of antifungal molecules and minimize local irritation.

Several studies have demonstrated the superior performance of liposomal antifungal formulations compared with conventional creams or gels. Liposomal clotrimazole has been shown to provide higher skin retention, prolonged drug residence time, and improved antifungal efficacy. Similarly, liposomal ketoconazole formulations have exhibited enhanced permeability through the stratum corneum, better accumulation in infected tissues, and reduced potential for irritation or sensitization. These enhanced pharmacodynamic properties are largely attributed to the flexible, deformable nature of liposomal vesicles and their capacity to merge with epidermal lipid layers.(23)

Overall, liposomes represent a promising nanocarrier platform for transdermal and topical delivery of antifungal agents used in dermatophytosis. Their ability to modulate permeation pathways, provide controlled release, and improve local drug concentrations makes them a valuable component of novel drug delivery strategies aimed at improving therapeutic outcomes.

- *Niosomes*

Niosomes are vesicular nanocarriers formed from non-ionic surfactants, often stabilized with cholesterol to improve membrane rigidity and entrapment efficiency. Structurally similar to liposomes, niosomes consist of a bilayer arrangement capable of encapsulating both hydrophilic and lipophilic therapeutic agents. However, unlike phospholipid-based liposomes, niosomes exhibit superior chemical stability, reduced susceptibility to oxidative degradation, and lower production costs, making them an economically attractive alternative for large-scale pharmaceutical applications.

The mechanism through which niosomes enhance transdermal and topical delivery involves their ability to interact with and modulate the lipid architecture of the stratum corneum. Upon application, niosomal vesicles can partially disrupt, fluidize, or reorganize the tightly packed

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

lipid domains of the skin barrier, thereby reducing its resistance to permeation. This action facilitates a higher rate of drug diffusion into deeper epidermal and dermal layers while concurrently providing a reservoir effect that supports sustained drug release. Their flexible bilayer structure also allows deformation and improved passage through skin appendages and intercellular pathways.

Niosome-mediated delivery has shown particular promise for antifungal therapy in dermatophytosis. Formulations containing drugs such as terbinafine, fluconazole, and griseofulvin have demonstrated enhanced permeation, increased skin deposition, and improved therapeutic efficacy compared with conventional creams or gels. Studies report that niosomal terbinafine exhibits significantly higher drug retention in infected tissues and prolonged antifungal activity, reducing the need for frequent application. Likewise, niosomal fluconazole formulations have shown improved penetration through the stratum corneum and enhanced bioavailability, which may translate to better clinical outcomes and shorter treatment durations.(24)

Overall, niosomes represent a robust and efficient nanocarrier system for the topical management of dermatophytosis. Their advantages—such as enhanced stability, sustained release behavior, improved skin permeation, and cost-effectiveness—underline their growing relevance in the development of advanced transdermal antifungal delivery systems.

- *Ethosomes*

Ethosomes are advanced, soft vesicular carriers composed of phospholipids, high concentrations of ethanol (typically 20–45%), and water. Their unique composition distinguishes them from conventional liposomes and niosomes, as the presence of ethanol significantly enhances vesicle flexibility and imparts superior skin penetration capabilities. Ethanol, a well-known permeation enhancer, increases the fluidity and disorder of stratum corneum lipids by disrupting the tightly packed lipid bilayers. This leads to a reduction in skin barrier resistance, allowing ethosomal vesicles to penetrate more effectively into deeper epidermal and dermal layers.

The synergistic combination of ethanol and phospholipids results in highly deformable vesicles that can pass through microscopic pathways of the skin with minimal disruption. Ethosomes not only improve drug permeation but also enhance drug loading capacity, stability, and sustained release patterns. These characteristics make ethosomes particularly advantageous for delivering molecules with poor transdermal absorption, low solubility, or limited skin penetration when administered through conventional formulations.

In the context of dermatophytosis, ethosomal drug delivery has shown significant potential. Ethosomal formulations of antifungal agents—such as itraconazole, fluconazole, and ketoconazole—have demonstrated improved cutaneous deposition, enhanced antifungal activity, and superior therapeutic outcomes compared with traditional creams or gels. Studies indicate that ethosomal itraconazole can achieve deeper dermal localization, which is especially important for targeting dermatophytes residing within keratinized tissues. Similarly, ethosomal fluconazole preparations have exhibited greater permeation across the stratum corneum, prolonged drug retention, and more effective reduction of fungal load in infected skin.(25)

Overall, ethosomes represent a highly promising nanocarrier system for the management of dermatophytosis due to their exceptional permeability-enhancing properties, deformability, and ability to deliver therapeutic agents to deeper skin layers. Their incorporation into transdermal drug delivery strategies offers a valuable approach for improving the efficacy of topical antifungal therapy.

- *Transfersomes*

Transfersomes are highly deformable, elastic lipid vesicles designed to overcome the limitations of conventional liposomes in transdermal drug delivery. Composed of phospholipids and an edge activator—typically a single-chain surfactant such as sodium cholate, Tween 80, or Span 80—transfersomes possess an exceptionally flexible bilayer that allows them to undergo significant shape deformation. This unique characteristic enables the vesicles to squeeze through intercellular pores and microscopic channels in the stratum corneum that are smaller than their own diameter, without rupturing or compromising vesicle stability.(26)

The mechanism of enhanced penetration by transfersomes relies on the development of a transdermal hydration gradient. When applied to the skin, the surface environment tends to be relatively dry compared with the underlying tissues. Transfersomes respond to this gradient by moving toward areas of higher water content, effectively propelling themselves across the stratum corneum and into deeper epidermal layers. Their ultra-deformable structure further facilitates this movement, allowing them to traverse narrow pathways while maintaining their structural integrity and drug-retaining capacity.

Transferosomes offer several advantages for topical and transdermal drug delivery, including improved skin permeability, enhanced drug loading, reduced irritation, and the ability to target deeper layers without disrupting the natural barrier function of the skin. Their capacity for controlled and sustained release also contributes to prolonged therapeutic activity, reducing dosing frequency and improving patient compliance.(27)

In antifungal therapy, transfersomes have shown promising results, particularly for drugs used in the treatment of dermatophytosis. Transfersomal formulations of clotrimazole have demonstrated superior skin penetration, increased drug accumulation at the site of infection, and extended antifungal activity compared with conventional topical gels or creams. Recent studies report that transfersomal clotrimazole gel provides significantly higher inhibition of dermatophyte growth and achieves deeper

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

tissue localization, which is essential for managing infections involving keratinized structures.(28)

Overall, transfersomes represent a highly effective nanocarrier system for enhancing the transdermal and topical delivery of antifungal agents. Their elastic vesicle architecture, superior permeation capabilities, and ability to deliver drugs to deeper skin layers make them a valuable formulation strategy in the development of advanced therapeutic approaches for dermatophytosis.

➢ *Nanotechnology-Based Carriers*

- *Nanoparticles*

Nanoparticles, including both polymeric and lipid-based systems, have emerged as highly efficient carriers for enhancing the topical and transdermal delivery of antifungal agents. These nanosized particles (typically ranging from 10–500 nm) offer several formulation advantages, such as increased surface area, improved drug solubility, and the ability to modulate release kinetics. Polymeric nanoparticles are commonly prepared from biodegradable polymers such as PLGA, chitosan, or Eudragit, while lipid nanoparticles—comprising solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)—utilize physiologically compatible lipids that enhance skin penetration and stability.

Nanoparticles can encapsulate drugs within their core or adsorb them onto their surface, thereby protecting active molecules from chemical or environmental degradation. This protective function improves the stability of antifungal agents that may otherwise undergo hydrolysis, oxidation, or photodegradation. Additionally, nanoparticles enable sustained and controlled drug release, ensuring prolonged therapeutic concentrations at the infection site and reducing the frequency of application. Their small particle size facilitates efficient permeation into the stratum corneum, where they interact with skin lipids, improving drug diffusion and retention in deeper epidermal layers.(29)

In the management of dermatophytosis, nanoparticles have shown significant potential for enhancing local drug delivery and therapeutic outcomes. Terbinafine-loaded nanoparticles, for instance, have demonstrated superior skin deposition compared with conventional topical formulations, resulting in enhanced antifungal activity and reduced fungal burden. Nanoparticle-based systems not only improve permeation but also prolong drug residence time within infected tissues, enabling more effective targeting of dermatophytes residing in keratinized layers. Similarly, fluconazole, itraconazole, and griseofulvin have been successfully incorporated into nanoparticle carriers, exhibiting improved bioavailability and stronger antifungal effects.(30)

Overall, nanoparticles represent an advanced and highly adaptable drug delivery platform for the treatment of dermatophytosis. Their ability to enhance drug stability, promote sustained release, and significantly increase cutaneous penetration makes them a promising approach for developing next-generation antifungal therapies.

- *Nanogels*

Nanogels are nanoscale, three-dimensional polymeric hydrogel networks capable of absorbing substantial amounts of water while maintaining structural integrity. These soft, highly hydrophilic carriers are synthesized from natural or synthetic polymers—such as chitosan, poly(N-isopropylacrylamide), polyethylene glycol, and polyacrylic acid—and can be engineered with tunable swelling behavior, biodegradability, and drug release characteristics. Their ability to encapsulate both hydrophilic and hydrophobic drugs within the polymeric matrix makes them versatile platforms for topical and transdermal delivery.(31)

One of the primary advantages of nanogels is their excellent skin penetration capability. Their nanoscale dimensions enable them to navigate through the stratum corneum via intercellular gaps, follicular routes, and aqueous channels. Additionally, their soft, deformable nature allows them to adapt to the skin's microenvironment and interact closely with epidermal tissues. These features facilitate enhanced deposition of the drug within infected or inflamed regions, contributing to improved therapeutic efficiency. Nanogels also provide controlled and sustained drug release due to their cross-linked polymeric framework, which gradually releases the entrapped drug in response to stimuli such as temperature, pH, or ionic strength.(32)

In dermatophytosis therapy, nanogels have shown remarkable potential in improving the delivery of antifungal agents. Clotrimazole-loaded nanogels, for example, have demonstrated significantly higher drug retention in infected skin compared with conventional topical formulations. This increased deposition results in prolonged drug residence time, sustained antifungal activity, and more effective fungal clearance. Nanogel formulations also minimize systemic absorption, reducing the risk of adverse effects while enhancing localized action at the site of infection.(33)

Overall, nanogels represent a promising generation of advanced nanocarriers for topical antifungal therapy. Their ability to provide controlled release, enhance skin penetration, improve drug bioavailability, and maintain high drug concentrations within the infection site positions them as valuable candidates in next-generation treatment strategies for dermatophytosis.

- *Solid Lipid Nanoparticles (SLNS) and Nanostructured Lipid Carriers (NLCS)*

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are advanced lipid-based nanocarrier systems that offer significant advantages for topical and transdermal delivery of antifungal drugs. SLNs are composed of physiologically compatible solid lipids stabilized by surfactants, whereas NLCs are second-generation lipid carriers formed by blending solid lipids with a small proportion of liquid lipids. This combination creates a less-ordered internal structure, which overcomes the limitations of SLNs—such as low drug-loading capacity

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

and potential drug expulsion during storage—thereby enhancing stability and retaining entrapped drugs more efficiently.

Both SLNs and NLCs facilitate improved skin permeation due to their nanoscale size, occlusive properties, and strong interaction with the stratum corneum lipids. These lipid particles form a thin film over the skin surface, reducing transepidermal water loss and increasing skin hydration. The resulting hydration effect loosens the dense lipid structure of the stratum corneum, promoting deeper penetration of encapsulated antifungal agents. Furthermore, the lipid matrix protects drugs from physical and chemical degradation, enhances solubility, and enables controlled or sustained release, ensuring prolonged therapeutic activity at the site of infection.(34)

In the treatment of dermatophytosis, SLNs and NLCs have been successfully employed to improve the delivery and efficacy of several antifungal drugs, including econazole, ketoconazole, clotrimazole, and terbinafine. SLN-based econazole formulations have shown improved drug stability, enhanced retention in skin tissues, and superior antifungal activity compared with conventional creams. Similarly, NLC-based ketoconazole formulations demonstrate higher drug-loading capacity, better permeation through the stratum corneum, and prolonged release, contributing to enhanced local therapeutic effects and reduced dosing frequency.(35)

Overall, SLNs and NLCs represent advanced lipid nanocarriers with significant potential for enhancing antifungal therapy in dermatophytosis. Their ability to improve drug stability, promote deeper penetration, increase drug loading, and provide sustained release makes them highly promising platforms for the development of next-generation topical antifungal formulations.

➢ *Microneedle-Assisted Delivery*

Microneedle-assisted drug delivery represents a novel and minimally invasive technique designed to overcome the limitations imposed by the stratum corneum, the principal barrier to transdermal absorption. Microneedles are micron-sized projections, typically ranging from 50 to 900 µm in height, arranged on a patch-like array. When applied to the skin, these microneedle arrays create transient, microscopic channels that bypass the outermost barrier without reaching the deeper nerve-rich dermal layers. This ensures a painless, bloodless, and highly efficient route for enhancing the transdermal transport of therapeutic agents.(36)

Microneedles can be fabricated from a variety of materials such as silicon, metals, sugars, or biodegradable polymers, and are available in several forms including solid, coated, dissolving, and hydrogel-based designs. Solid microneedles typically pre-treat the skin to improve subsequent drug application, while coated and dissolving microneedles offer the advantage of direct drug incorporation within the needle matrix, enabling precise and targeted delivery. Dissolving microneedles, in particular, have gained significant attention for antifungal therapy due to their ability to release drugs directly into viable epidermal and dermal layers while leaving no biohazardous waste.(37)

In the treatment of dermatophytosis and other superficial fungal infections, microneedle-based systems offer several benefits. The microchannels created by microneedles allow antifungal agents to bypass the highly keratinized stratum corneum—an environment where dermatophytes typically colonize—resulting in enhanced drug penetration and rapid onset of therapeutic action. Furthermore, microneedle patches ensure localized delivery, reducing systemic exposure and minimizing the risk of adverse effects associated with oral antifungal therapy. Studies evaluating antifungal-loaded microneedle patches have demonstrated superior skin permeation, enhanced deposition in infected tissues, and improved therapeutic outcomes compared with conventional topical formulations.(38)

Additionally, microneedle-assisted delivery minimizes irritation and avoids the discomfort associated with traditional intradermal injections. The precise dosing, ease of self-administration, and potential for controlled drug release make microneedle patches an attractive platform for future antifungal therapies. Emerging research highlights their promise for delivering a wide range of antifungal agents—including terbinafine, ketoconazole, and itraconazole—demonstrating their capability to effectively target localized skin infections.(39)

Overall, microneedle-assisted delivery represents an advanced and highly efficient transdermal drug delivery strategy with significant potential to improve the management of superficial fungal infections. Its unique advantages—painless administration, enhanced permeation, rapid therapeutic action, and the ability to deliver drugs directly to affected skin layers—position microneedle technology as a transformative approach in the development of next-generation antifungal treatments.

➢ *Physical and Chemical Enhancement Techniques*

- *Other Approaches Include:*

✓ Iontophoresis: Application of mild electric current to enhance drug permeation.(40)
✓ Sonophoresis: Use of ultrasound waves to increase skin permeability.(41)
✓ Chemical enhancers: Compounds like oleic acid and ethanol that temporarily disrupt the lipid matrix of the stratum corneum.(42)

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

➢ *Summary of Novel Approaches*

Table 1 Summary of Novel Approaches

System	Mechanism	Advantages	Example Drugs
Liposomes	Fusion with skin lipids	Enhanced penetration	Clotrimazole, Ketoconazole
Niosomes	Surfactant-based vesicles	Stable, cost-effective	Terbinafine, Fluconazole
Ethosomes	Ethanol-induced fluidization	Deep dermal delivery	Itraconazole
Transfersomes	Elastic vesicles	Deeper skin transport	Clotrimazole
Nanogels/Nanoparticles	Nano-sized carriers	Controlled release	Clotrimazole, Terbinafine
Microneedles	Micro-channels in skin	Painless targeted delivery	Various antifungals

These novel transdermal approaches collectively represent a promising advancement in the effective treatment of dermatophytosis, addressing limitations of conventional therapies and improving patient compliance.

Table 2 Comparison of Conventional vs Transdermal Delivery

Parameter	Conventional Therapy	Transdermal Delivery
Skin penetration	Poor	Enhanced
Drug retention	Low	High
Systemic toxicity	High (oral drugs)	Minimal
Frequency of application	Multiple times/day	Once daily or sustained
Patient compliance	Low	Improved
Resistance development	Higher	Lower due to targeted delivery
First-pass metabolism	Present	Absent

VII. FUTURE PROSPECTS AND CHALLENGES

Transdermal drug delivery has emerged as a highly promising strategy for the management of dermatophytosis, particularly in cases that are chronic, recurrent, or resistant to conventional therapies. By enabling direct delivery of antifungal agents across the skin barrier, this approach ensures higher drug concentration at the site of infection while minimizing systemic exposure and associated side effects. The incorporation of nanotechnology-based carriers—such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and nanoemulsions—further enhances the therapeutic potential of transdermal systems. These advanced carriers can improve drug solubility, promote deeper skin penetration, and offer controlled or sustained release, thereby reducing dosing frequency and potentially improving patient compliance. Moreover, their targeted delivery capabilities help overcome issues like treatment failures and frequent relapses by maintaining effective drug levels in infected tissues.(43)

Despite these advantages, several challenges limit the widespread application of nanotechnology-enabled transdermal drug delivery for dermatophytosis. Formulation complexity remains a major concern, as the development of stable and uniform nanosystems requires specialized materials, equipment, and optimization processes. Stability issues, including particle aggregation, phase separation, and chemical degradation of active agents, can compromise the efficacy and shelf life of final products. Additionally, regulatory pathways for novel nanocarrier-based formulations are stringent and often require extensive safety, toxicology, and efficacy data, which may prolong development timelines. Manufacturing challenges, such as scalability, batch-to-batch consistency, and cost-effectiveness, further hinder the transition from laboratory research to commercial production. Therefore, continued scientific investigation, well-designed clinical trials, and patient-centric formulation development are essential to address these limitations and successfully bring advanced transdermal antifungal therapies to market.(44)

VIII. CONCLUSION

Transdermal drug delivery systems (TDDS), particularly when integrated with advanced nanocarriers, microneedles, and other emerging penetration-enhancement technologies, offer a transformative approach to managing dermatophytosis. Unlike conventional topical formulations that often fail to sufficiently penetrate the stratum corneum or systemic therapies associated with hepatotoxicity and drug–drug interactions, TDDS enables more precise, localized, and sustained delivery of antifungal agents directly to the infected skin layers. This targeted approach not only improves therapeutic drug concentrations at the site of infection but also minimizes systemic exposure, thereby reducing the risk of adverse effects and enhancing overall patient safety.

The use of nanocarrier systems—such as lipid nanoparticles, polymeric carriers, nanoemulsions, and vesicular systems—further strengthens the potential of transdermal antifungal therapy. These systems can overcome solubility issues of poorly water-soluble antifungal drugs, provide controlled or sustained release, improve skin permeation, and offer enhanced stability. Additionally, microneedle-assisted delivery provides a minimally invasive route to transport drugs across the skin barrier, amplifying the therapeutic outcomes while maintaining patient comfort. Together, these technologies can significantly improve treatment adherence, shorten therapy durations, and decrease recurrence rates, making them highly suitable for chronic or persistent dermatophytic infections.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr2331

However, despite their strong potential, several challenges must be addressed before these advanced systems can transition from research laboratories to widespread clinical use. Key barriers include limited clinical data, scale-up complexity, stability issues, regulatory uncertainties, and high production costs that may limit commercial feasibility. Furthermore, long-term safety studies, patient acceptability assessments, and clear demonstrations of cost-effectiveness are essential to gain regulatory approval and clinician confidence. Therefore, future research should prioritize well-designed in vivo studies, rigorous randomized clinical trials, and innovative manufacturing approaches capable of ensuring reproducibility and large-scale production.

If these scientific, regulatory, and economic challenges are successfully overcome, nanocarrier-based transdermal drug delivery could reshape the therapeutic landscape of dermatophytosis. With continued advancements and focused translational efforts, TDDS holds the potential to offer more effective, safer, and more patient-friendly antifungal treatment options, ultimately contributing to improved clinical outcomes and better quality of life for affected individuals.

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