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ADVANCES IN NANOSTRUCTURED LIPID CARRIER EMBEDDED TRANSDERMAL PATCHES FOR ANTIFUNGAL THERAPY

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1. INTRODUCTION

Fungal infections represent a significant global health concern, affecting millions of individuals annually and contributing substantially to morbidity and mortality, particularly among immunocompromised patients. Fungal pathogens such as *Candida*, *Aspergillus*, *Cryptococcus*, and dermatophyte species are responsible for a wide range of superficial, cutaneous, subcutaneous, and systemic infections.[1] The prevalence of fungal diseases has increased considerably over recent decades due to factors such as prolonged antibiotic use, immunosuppressive therapy, organ transplantation, diabetes mellitus, cancer chemotherapy, and human immunodeficiency virus (HIV) infection. Although superficial fungal infections primarily affect the skin, nails, and mucosal tissues, invasive fungal infections can lead to life-threatening complications with high mortality rates.[2]

Antifungal therapy plays a critical role in the management of fungal infections. Conventional antifungal agents are broadly classified into polyenes, azoles, echinocandins, allylamines, and antimetabolites based on their mechanism of action. These agents exert antifungal activity through disruption of fungal cell membrane integrity, inhibition of ergosterol biosynthesis, interference with fungal cell wall synthesis, or inhibition of nucleic acid synthesis. Commonly used antifungal drugs include amphotericin B, ketoconazole, fluconazole, itraconazole, terbinafine, and clotrimazole. Despite the availability of several antifungal agents, successful treatment remains challenging due to poor drug solubility, limited skin

penetration, systemic toxicity, drug resistance, and inadequate therapeutic concentrations at the target site.[3]

Conventional antifungal dosage forms such as oral tablets, capsules, creams, ointments, and gels possess several limitations that restrict their clinical effectiveness. Oral antifungal therapy often undergoes extensive first-pass metabolism, resulting in variable bioavailability and systemic adverse effects including hepatotoxicity, nephrotoxicity, gastrointestinal irritation, and drug-drug interactions. Moreover, prolonged oral therapy may be required for chronic fungal infections, leading to poor patient compliance and increased risk of antifungal resistance.[4]

Topical antifungal formulations are commonly employed for superficial fungal infections; however, their therapeutic efficacy is frequently limited by inadequate drug penetration through the stratum corneum, short residence time on the skin surface, poor retention at the infection site, and frequent dosing requirements. Conventional topical preparations may also cause skin irritation, instability of active ingredients, and inconsistent drug release profiles. These limitations have necessitated the development of advanced drug delivery systems capable of improving antifungal efficacy while minimizing systemic toxicity and enhancing patient compliance.[3]

Transdermal drug delivery systems (TDDS) have emerged as promising alternatives for the administration of antifungal agents due to their ability to provide controlled and sustained drug release, bypass hepatic first-pass metabolism, reduce systemic side effects, and improve patient adherence. Transdermal patches offer several advantages including non-invasive administration, prolonged therapeutic action, improved bioavailability, and enhanced localization of drugs within skin tissues. However, the highly organized structure of the stratum corneum acts as a major barrier to effective transdermal permeation, particularly for poorly soluble antifungal drugs.[5]

Nanotechnology-based delivery systems have gained considerable attention in overcoming the limitations associated with conventional antifungal formulations and transdermal delivery. Among these, nanostructured lipid carriers (NLCs) have emerged as highly efficient nanocarriers due to their unique structural characteristics, biocompatibility, high drug loading capacity, controlled drug release behavior, and enhanced skin permeation properties. NLCs are second-generation lipid nanoparticles composed of a mixture of solid and liquid lipids

stabilized by surfactants.[6] The imperfect lipid matrix structure of NLCs provides greater drug accommodation and minimizes drug expulsion during storage compared to conventional solid lipid nanoparticles (SLNs).[7]

Embedding NLCs into transdermal patches represents an innovative strategy for improving antifungal therapy. NLC-based transdermal patches can enhance drug solubility, increase skin penetration, prolong drug retention within skin layers, and provide sustained antifungal activity. Additionally, the occlusive properties of lipid nanoparticles improve skin hydration, thereby facilitating enhanced permeation of antifungal agents across the stratum corneum. The integration of nanostructured lipid carriers with transdermal patch technology therefore offers a synergistic platform for effective and targeted antifungal drug delivery.[8]

The present review aims to comprehensively discuss recent advances in nanostructured lipid carrier embedded transdermal patches for antifungal therapy. The review focuses on the formulation principles, physicochemical characteristics, mechanisms of skin permeation, methods of preparation, evaluation parameters, therapeutic applications, and recent research developments associated with NLC-based transdermal systems. Furthermore, the review highlights current challenges, clinical translation barriers, and future prospects for the development of advanced transdermal antifungal delivery platforms.[9]

2. Nanostructured Lipid Carriers (NLCs): Composition and Characteristics

Nanostructured lipid carriers (NLCs) are advanced colloidal drug delivery systems developed as second-generation lipid nanoparticles to overcome the limitations associated with solid lipid nanoparticles (SLNs). NLCs are composed of a blend of solid and liquid lipids stabilized by surfactants, forming a partially crystalline lipid matrix with structural imperfections that enhance drug accommodation and stability. Due to their biocompatibility, controlled drug release behavior, improved drug loading capacity, and enhanced skin permeation properties, NLCs have gained significant attention in transdermal antifungal therapy.[10]

The incorporation of antifungal drugs into NLC systems improves solubility, protects drug molecules from degradation, enhances penetration through the stratum corneum, and provides sustained therapeutic action. Furthermore, the occlusive nature of lipid nanoparticles increases skin hydration and facilitates deeper permeation of antifungal agents into infected tissues.[11]

2.1 Structure and Types of NLCs

Nanostructured lipid carriers possess a nanoscale lipid matrix generally ranging from 50 to 500 nm in diameter. Unlike SLNs, which consist entirely of solid lipids, NLCs contain a combination of solid and liquid lipids that create an imperfect crystalline structure. This structural irregularity prevents drug expulsion during storage and significantly increases drug loading efficiency. Based on the internal arrangement of lipids, NLCs are generally classified into three major types.[12]

2.1.1 Imperfect Crystal Type

In this type, mixing of solid and liquid lipids creates imperfections within the crystalline lattice of the solid lipid matrix. These imperfections provide additional spaces for drug incorporation, thereby improving drug loading capacity and minimizing drug leakage during storage.[7]

2.1.2 Amorphous Type

Amorphous NLCs are formulated using special lipids that prevent crystallization of the lipid matrix. The absence of crystalline order reduces the risk of drug expulsion and improves long-term stability of the formulation.[7]

2.1.3 Multiple Type (Oil-in-Fat-in-Water Structure)

This structure consists of tiny oil nanocompartments dispersed within a solid lipid matrix. The presence of liquid lipid droplets enhances drug solubilization and facilitates controlled drug release behavior.[7]

The unique structural characteristics of NLCs contribute to improved therapeutic performance, enhanced skin retention, and better permeation of antifungal drugs across biological barriers.[10]

2.2 Lipid Components and Surfactants

The selection of appropriate lipids and surfactants is critical for the successful formulation of NLCs, as these components influence particle size, drug encapsulation efficiency, stability, and release characteristics.[13]

2.2.1 Solid Lipids

Solid lipids form the structural backbone of NLCs and remain solid at both room and body temperatures. Commonly used solid lipids include, Glyceryl monostearate, Stearic acid, Cetyl

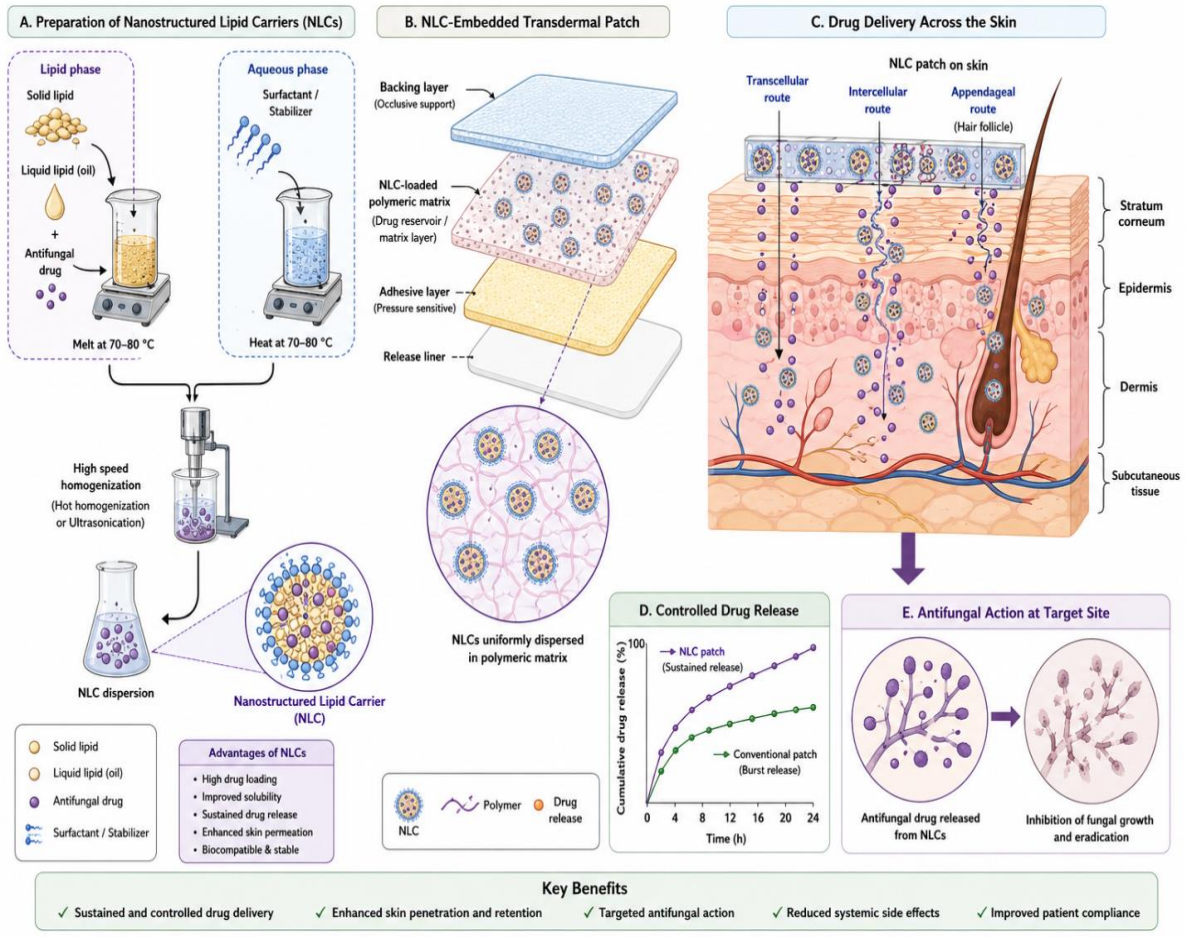
palmitate, Compritol® 888 ATO, Precirol® ATO 5, Beeswax, Carnauba wax These lipids provide structural integrity, controlled drug release, and occlusive properties that improve skin hydration and permeation.[13]

2.2.2 Liquid Lipids (Oils)

Liquid lipids are incorporated to create imperfections in the lipid matrix and improve drug solubilization. Commonly used oils include, Oleic acid, Medium-chain triglycerides, Castor oil, Olive oil, Miglio® oils, Sesame oil, Liquid lipids enhance drug loading capacity and contribute to increased flexibility of the nanoparticle matrix.[14]

2.2.3 Surfactants and Stabilizers

Surfactants stabilize the lipid nanoparticles by reducing surface tension and preventing particle aggregation. They also influence skin permeation and formulation stability. Common surfactants include, Tween 80, Poloxamer 188, Span 60, Lecithin, Sodium cholate, Cremophor® RH40 The choice and concentration of surfactants significantly affect particle size distribution, zeta potential, and drug release kinetics.[15]



2.3 Preparation Methods of NLCs

Various formulation techniques have been developed for the preparation of NLCs depending on the physicochemical properties of the drug and formulation requirements.[16]

2.3.1 High-Pressure Homogenization

High-pressure homogenization is one of the most widely used techniques for NLC preparation. In this method, melted lipids containing the drug are dispersed in an aqueous surfactant solution and subjected to high pressure, resulting in nanosized particles. The process may be performed using hot or cold homogenization techniques.[17]

This method offers advantages such as scalability, reproducibility, and solvent-free processing.

2.3.2 Ultrasonication Method

Ultrasonication utilizes ultrasonic energy to reduce particle size and form stable nanoemulsions. The lipid phase and aqueous phase are mixed under high-speed stirring followed by sonication to produce NLC dispersions.[18]

Although simple and cost-effective, this method may lead to particle size variability and possible metal contamination from sonicator probes.

2.3.3 Solvent Emulsification-Evaporation Method

In this technique, lipids are dissolved in organic solvents and emulsified into an aqueous phase containing surfactants. Subsequent solvent evaporation leads to lipid precipitation and nanoparticle formation.[14]

This method is particularly useful for thermosensitive drugs but may involve residual solvent-related concerns.

2.3.4 Microemulsion Technique

A warm microemulsion composed of lipids, surfactants, and water is rapidly dispersed into cold water, resulting in nanoparticle formation due to lipid recrystallization.

This method provides narrow particle size distribution and high encapsulation efficiency.[15]

2.3.5 Melt Emulsification Method

This technique involves melting lipids above their melting point and dispersing them in an aqueous surfactant solution under mechanical stirring. Upon cooling, lipid nanoparticles are

formed.[19]

The method is relatively simple and suitable for large-scale production.

2.4 Physicochemical Properties Influencing Drug Delivery

The therapeutic performance of NLCs is highly dependent on their physicochemical characteristics, which influence drug loading, stability, permeation, and release behavior.[20]

2.4.1 Particle Size and Polydispersity Index (PDI)

Particle size plays a crucial role in transdermal permeation and drug distribution. Smaller nanoparticles possess larger surface area, improved skin contact, and enhanced penetration through the stratum corneum. A low polydispersity index indicates uniform particle size distribution and better formulation stability.[21]

2.4.2 Zeta Potential

Zeta potential reflects the surface charge of nanoparticles and influences colloidal stability. Higher absolute zeta potential values provide electrostatic repulsion between particles, preventing aggregation and improving stability.[22]

2.4.3 Drug Entrapment Efficiency

Entrapment efficiency determines the amount of drug successfully incorporated within the lipid matrix. High entrapment efficiency ensures sustained drug release and improved therapeutic efficacy.[12]

2.4.4 Crystallinity and Lipid Matrix Organization

The degree of lipid crystallinity influences drug loading capacity and release kinetics. Reduced crystallinity and imperfect lipid arrangements facilitate greater drug accommodation and controlled release.[23]

2.4.5 Occlusive Effect and Skin Hydration

NLCs form a lipid film over the skin surface that reduces trans epidermal water loss and enhances hydration of the stratum corneum. Increased hydration loosens the tightly packed lipid structure of the skin barrier, thereby improving drug permeation.[12]

2.4.6 Controlled Drug Release

The lipid matrix of NLCs enables sustained and controlled drug release, maintaining therapeutic drug concentrations over prolonged periods and reducing dosing frequency.

Overall, the unique composition and physicochemical properties of nanostructured lipid carriers make them highly suitable for transdermal antifungal drug delivery. Their ability to enhance skin permeation, improve drug stability, and provide sustained release has positioned NLCs as promising nanocarriers for advanced antifungal therapy.[10]

3. NLC-Embedded Transdermal Patches for Antifungal Delivery

Nanostructured lipid carrier (NLC)-embedded transdermal patches have emerged as advanced drug delivery systems capable of improving the therapeutic efficacy of antifungal agents. The integration of nanotechnology with transdermal patch systems offers multiple advantages, including enhanced drug solubility, controlled release, improved skin permeation, prolonged therapeutic action, and reduced systemic toxicity. These hybrid delivery systems are particularly beneficial for antifungal drugs that exhibit poor aqueous solubility, limited bioavailability, and inadequate penetration through the stratum corneum.[24]

The incorporation of antifungal-loaded NLCs into polymeric transdermal patches creates a multifunctional platform that combines the permeation-enhancing properties of lipid nanoparticles with the sustained release characteristics of transdermal systems. Such formulations have demonstrated considerable potential in the treatment of superficial and localized fungal infections while improving patient compliance and minimizing adverse effects.[25]

3.1 Principles of Transdermal Patch Systems

Transdermal drug delivery systems (TDDS) are designed to deliver therapeutic agents across the skin into systemic circulation or localized tissues at controlled rates over prolonged periods. These systems provide several advantages over conventional oral and topical dosage forms, including avoidance of first-pass hepatic metabolism, maintenance of steady plasma drug concentrations, reduced dosing frequency, improved patient adherence, and non-invasive administration.[26] A typical transdermal patch consists of several functional layers, including, backing membrane, Drug reservoir or matrix layer, Adhesive layer, Release liner, Permeation enhancers (optional) Depending on drug distribution and release mechanisms, transdermal patches are generally classified into:

3.1.1 Matrix-Type Patches

In matrix systems, the drug is uniformly dispersed within a polymeric matrix that controls drug release through diffusion mechanisms. Matrix patches are simple to formulate, flexible,

and widely employed in antifungal drug delivery.[27]

3.1.2 Reservoir-Type Patches

Reservoir systems contain a drug reservoir enclosed between a backing layer and a rate-controlling membrane. These systems provide precise and sustained drug release but possess more complex fabrication requirements.[28]

3.1.3 Drug-in-Adhesive Systems

In this approach, the drug is incorporated directly into the adhesive layer, simplifying patch design while maintaining effective drug release characteristics. The major challenge in transdermal delivery is overcoming the barrier function of the stratum corneum, which restricts permeation of most therapeutic agents. Nanostructured lipid carriers effectively address this limitation by enhancing drug partitioning into skin layers and facilitating controlled transdermal transport.[20]

3.2 Incorporation of Antifungal Drugs into NLCs

The encapsulation of antifungal agents into NLCs significantly improves their physicochemical and pharmacokinetic properties. Many antifungal drugs, such as ketoconazole, itraconazole, fluconazole, terbinafine, voriconazole, and clotrimazole, exhibit poor aqueous solubility and limited skin permeation. NLCs enhance the solubilization of these lipophilic drugs and provide sustained release behavior.[10]

Antifungal drugs are generally incorporated into NLCs by dissolving or dispersing them within the melted lipid phase during nanoparticle preparation. The drug becomes entrapped within the imperfect lipid matrix formed by the combination of solid and liquid lipids. This encapsulation protects the drug from degradation and enhances stability during storage. The efficiency of drug incorporation depends on several formulation parameters, including, Type of solid and liquid lipids, Drug-lipid compatibility, Surfactant concentration, Preparation method, Lipid crystallinity, Particle size, NLCs improve antifungal therapy through multiple mechanisms, Enhanced drug solubility, Increased skin hydration, Improved penetration into deeper skin layers, Sustained and controlled drug release, Reduced systemic absorption and toxicity, Prolonged retention at the infection site, Additionally, lipid nanoparticles can accumulate within hair follicles and sebaceous glands, which often serve as reservoirs for fungal pathogens. This targeted localization further enhances antifungal efficacy.[3]

3.3 Patch Formulation Approaches and Polymers Used

The successful development of NLC-embedded transdermal patches requires careful selection of polymers, plasticizers, adhesives, and permeation enhancers to achieve optimal mechanical strength, flexibility, adhesiveness, and drug release behavior.[29]

3.3.1 Patch Formulation Approaches

Several fabrication methods are employed for preparing NLC-loaded transdermal patches:

Solvent Casting Method

The solvent casting method is the most commonly used technique for transdermal patch preparation. In this method, polymers are dissolved in suitable solvents, followed by incorporation of NLC dispersions and other excipients. The mixture is cast onto molds or petri dishes and dried to form flexible films.[30]

Hot Melt Extrusion Technique

This solvent-free method involves blending polymers and NLC dispersions under elevated temperatures to produce transdermal films. It offers advantages such as scalability and reduced solvent toxicity.[15]

Layer-by-Layer Assembly

In this advanced approach, multiple polymeric layers containing NLCs are assembled sequentially to achieve controlled and targeted drug release profiles.[31]

Electrospinning Technique

Electrospinning produces nanofibrous transdermal patches with high surface area and enhanced drug release characteristics. NLC incorporation into electrospun fibers further improves skin permeation efficiency.[32]

3.3.2 Polymers Used in NLC-Embedded Patches

Polymers play a critical role in determining the mechanical properties, drug release kinetics, and stability of transdermal patches. Commonly used polymers include, Natural Polymers, Chitosan, Gelatin, Sodium alginate, Pectin, Xanthan gum, Natural polymers exhibit excellent biocompatibility and biodegradability but may possess limited mechanical strength. Synthetic Polymers, Hydroxypropyl methylcellulose (HPMC), Polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Ethyl cellulose, Eudragit® polymers, Carbopol® Synthetic polymers provide better film-forming properties, mechanical stability, and controlled drug

release behavior.[33]

3.3.3 Plasticizers and Permeation Enhancers

Plasticizers such as glycerol, propylene glycol, and polyethylene glycol improve patch flexibility and prevent brittleness. Permeation enhancers including oleic acid, dimethyl sulfoxide (DMSO), ethanol, and terpenes increase skin permeability by disrupting lipid organization within the stratum corneum.[26]

3.4 Drug Release and Skin Permeation Mechanisms

The therapeutic performance of NLC-embedded transdermal patches depends largely on efficient drug release and permeation through the skin barrier.[11]

3.4.1 Controlled Drug Release Mechanisms

Drug release from NLC-loaded patches generally occurs through a combination of, Diffusion from the polymeric matrix, Drug partitioning from lipid nanoparticles, Lipid matrix erosion, Polymer swelling and relaxation.[32]

The lipid matrix of NLCs provides sustained release by gradually releasing the entrapped drug over extended periods. Controlled release maintains therapeutic drug concentrations at the target site while minimizing dosing frequency.[34]

3.4.2 Skin Permeation Mechanisms

Drug permeation across the skin occurs through three primary pathways, Intercellular Pathway, Drug molecules diffuse through the lipid matrix present between corneocytes of the stratum corneum, Transcellular Pathway, Drugs penetrate directly through keratin-filled corneocytes and lipid bilayers, Appendageal Pathway, Hair follicles, sweat glands, and sebaceous glands provide additional routes for nanoparticle penetration and drug deposition. NLCs enhance skin permeation through several mechanisms, Increased contact area with skin surface, Occlusive film formation leading to enhanced skin hydration, Fluidization of stratum corneum lipids, Enhanced drug partitioning into skin tissues, Nanoparticle-mediated follicular targeting, The small particle size and lipid composition of NLCs facilitate close interaction with skin lipids, thereby improving drug transport across biological barriers.[11] Additionally, surfactants present in NLC formulations contribute to permeation enhancement by altering skin lipid organization. Overall, NLC-embedded transdermal patches represent highly promising platforms for advanced antifungal drug delivery. Their ability to provide

controlled release, improved skin penetration, enhanced drug stability, and targeted localization positions them as effective alternatives to conventional antifungal dosage forms.[35]

Drug	Lipid Composition	Polymer Used in Patch	Particle Size (nm)	Entrapment Efficiency (%)	Drug Release Profile	Key Findings
Ketoconazole	Glyceryl monostearate + Oleic acid	HPMC + PVA	145–210	82–91	Sustained release up to 24 h	Enhanced skin permeation and prolonged antifungal activity against Candida albicans
Terbinafine hydrochloride	Compritol® 888 ATO + Miglio®	HPMC + Ethyl cellulose	120–185	85–93	Biphasic release with controlled diffusion	Improved drug retention within skin layers and reduced dosing frequency
Fluconazole	Stearic acid + Castor oil	PVP + Chitosan	160–240	78–88	Sustained release over 24 h	Increased transdermal flux and enhanced antifungal efficacy
Clotrimazole	Cetyl palmitate + Oleic acid	Carbopol® + PVA	130–190	80–95	Controlled release pattern	Superior skin deposition and improved treatment of dermatophytosis
Itraconazole	Precirol® ATO 5 + Olive oil	HPMC + Eudragit® RS100	170–260	84–92	Extended drug release	Enhanced bioavailability and reduced systemic side effects
Voriconazole	Glyceryl behenate + Medium-chain triglycerides	PVA + Sodium alginate	140–225	81–90	Sustained diffusion-controlled release	Improved penetration into deeper skin tissues
Amphotericin B	Stearic acid + Sesame oil	Chitosan + PVP	180–290	75–87	Slow sustained release	Reduced nephrotoxicity and enhanced localized antifungal action
Econazole nitrate	Compritol® + Oleic acid	HPMC + Carbopol®	125–205	83–91	Controlled release for 24 h	Increased antifungal potency and improved skin

						hydration
Miconazole nitrate	Beeswax + Oleic acid	PVA + Ethyl cellulose	150–230	79–89	Sustained release kinetics	Enhanced permeation through stratum corneum and prolonged retention
Luliconazole	Glyceryl monostearate + Caprylic/capric triglycerides	HPMC + Pectin	110–175	88–96	Prolonged release behavior	Improved therapeutic effectiveness against dermatophyte infections

4. Evaluation and Therapeutic Applications

The successful development of nanostructured lipid carrier (NLC)-embedded transdermal patches for antifungal therapy requires comprehensive evaluation of their physicochemical properties, drug release characteristics, permeation efficiency, stability, safety, and therapeutic performance. Proper characterization and evaluation are essential to ensure formulation quality, reproducibility, effectiveness, and patient safety. In recent years, numerous studies have demonstrated that antifungal-loaded NLC transdermal systems exhibit superior drug delivery performance compared to conventional dosage forms due to enhanced skin permeation, sustained drug release, and improved antifungal efficacy.[36]

4.1 Characterization of NLCs and Transdermal Patches

The physicochemical characterization of NLCs and transdermal patches is crucial for understanding their structural properties, stability, and drug delivery behavior.[20]

4.1.1 Particle Size and Polydispersity Index (PDI)

Particle size analysis is one of the most important parameters in evaluating NLC formulations, as it directly influences skin permeation, drug release, and formulation stability. Dynamic light scattering (DLS) is commonly employed to determine particle size and PDI.[15]

Smaller nanoparticles exhibit larger surface area and enhanced interaction with the skin surface, facilitating improved transdermal permeation. A low PDI value indicates uniform particle size distribution and good colloidal stability.[37]

4.1.2 Zeta Potential

Zeta potential measures the surface charge of nanoparticles and provides information

regarding colloidal stability. High absolute zeta potential values prevent nanoparticle aggregation through electrostatic repulsion, thereby improving long-term stability.[38]

Both positive and negative surface charges may influence interactions with skin tissues and permeation characteristics.

4.1.3 Morphological Analysis

Morphological evaluation of NLCs is generally performed using, Transmission electron microscopy (TEM), Scanning electron microscopy (SEM), Atomic force microscopy (AFM), These techniques provide information regarding particle shape, surface characteristics, and structural integrity. NLCs are generally spherical or nearly spherical in morphology.[12]

4.1.4 Entrapment Efficiency and Drug Loading Capacity

Entrapment efficiency indicates the percentage of antifungal drug successfully encapsulated within the lipid matrix, whereas drug loading reflects the amount of drug incorporated relative to total lipid content. High entrapment efficiency is desirable for achieving sustained drug release and effective therapeutic concentrations. These parameters are typically analyzed using ultracentrifugation followed by spectrophotometric or chromatographic quantification techniques.[39]

4.1.5 Thermal and Crystallinity Analysis

Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies are used to evaluate lipid crystallinity, drug-lipid interactions, and polymorphic behavior of NLCs.

Reduced crystallinity and imperfect lipid organization are characteristic features of NLCs that contribute to improved drug incorporation and controlled release properties.[14]

4.1.6 Characterization of Transdermal Patches

Transdermal patches are evaluated for several physicochemical and mechanical properties, including, Thickness uniformity, Weight variation, Folding endurance, Moisture content, Moisture uptake, Tensile strength, Surface pH, Drug content uniformity, Adhesive properties, these parameters ensure patch flexibility, mechanical stability, patient comfort, and uniform drug distribution.[40]

4.2 In Vitro and Ex Vivo Evaluation Studies

Extensive in vitro and ex vivo studies are conducted to evaluate the performance of

antifungal-loaded NLC transdermal systems.[41]

4.2.1 In Vitro Drug Release Studies

In vitro drug release studies are commonly performed using Franz diffusion cells to assess the release profile of antifungal drugs from NLC-loaded patches. The release kinetics depend on several factors, including, Lipid composition, Polymer type, Drug solubility, Nanoparticle size, Patch matrix characteristics NLC-based systems generally exhibit biphasic release behavior consisting of an initial burst release followed by sustained drug release over extended periods. Controlled release helps maintain therapeutic drug levels and reduces dosing frequency.[42]

4.2.2 Ex Vivo Skin Permeation Studies

Ex vivo permeation studies are performed using excised animal or human skin mounted on Franz diffusion cells to evaluate transdermal drug transport. Parameters commonly analyzed include Cumulative drug permeation, Flux, Permeability coefficient, Lag time, Skin retention., LC formulations enhance skin permeation by increasing drug solubilization, improving skin hydration, and interacting with stratum corneum lipids. The nanosized particles facilitate close contact with the skin surface and improve drug deposition within deeper skin layers.[11]

4.2.3 Skin Retention and Deposition Studies

Skin deposition studies determine the amount of drug retained within various skin layers after application of the formulation. Enhanced retention of antifungal drugs within infected tissues contributes to prolonged therapeutic action and improved localized treatment.[43]

4.2.4 Antifungal Activity Studies

The antifungal efficacy of NLC-loaded systems is evaluated against fungal strains such as, Candida albicans, Aspergillus niger, Trichophyton rubrum, Microsporum species Methods such as zone of inhibition assays, minimum inhibitory concentration (MIC) determination, and fungal viability studies are commonly employed. NLC-based formulations frequently demonstrate enhanced antifungal activity compared to conventional formulations due to improved penetration and sustained drug release.[10]

4.3 Stability and Safety Assessment

Stability and safety evaluation are critical for ensuring the long-term effectiveness and

clinical acceptability of NLC-embedded transdermal patches.[44]

4.3.1 Stability Studies

Stability studies are conducted under different environmental conditions according to International Council for Harmonization (ICH) guidelines to evaluate changes in, Particle size, Zeta potential, Drug content, Entrapment efficiency, Physical appearance, Drug release profile The presence of liquid lipids within the NLC matrix reduces drug expulsion during storage and improves formulation stability compared to conventional solid lipid nanoparticles.[14]

4.3.2 Skin Irritation and Sensitization Studies

Skin irritation studies are essential to assess the dermatological safety of transdermal formulations. These studies are generally performed using animal models or reconstructed human skin models.[45]

NLC formulations are generally considered safe due to the use of biocompatible lipids and surfactants. However, surfactant concentration, permeation enhancers, and polymer composition may influence skin compatibility.[14]

4.3.3 Cytotoxicity Studies

Cell viability assays such as MTT assays are used to evaluate cytotoxic effects on skin cells and determine formulation safety.

Biocompatible NLC systems exhibit minimal cytotoxicity while maintaining strong antifungal activity.[46]

4.3.4 Microbiological Stability

Microbial contamination and preservation efficacy are also evaluated to ensure product safety during storage and use.[47]

4.4 Therapeutic Effectiveness of Antifungal-Loaded Systems

Numerous studies have demonstrated the superior therapeutic effectiveness of antifungal-loaded NLC transdermal patches compared to conventional formulations. NLC-based systems improve antifungal therapy through, Enhanced drug solubility, increased transdermal permeation, Sustained drug release, Improved skin retention, reduced systemic toxicity, better patient compliance Antifungal-loaded NLC patches have shown promising therapeutic

outcomes in the treatment of superficial fungal infections such as dermatophytosis, candidiasis, and onychomycosis. For example, ketoconazole- and terbinafine-loaded NLC transdermal systems have demonstrated enhanced skin penetration and prolonged antifungal activity compared to conventional creams and gels. Similarly, fluconazole-loaded NLC patches have shown improved drug retention within skin tissues and sustained therapeutic effects.[3] The nanosized lipid carriers facilitate deeper penetration into infected tissues and hair follicles, which often act as reservoirs for fungal pathogens. Furthermore, the occlusive effect of lipid nanoparticles enhances hydration of the stratum corneum and further improves drug permeation. Several experimental studies have also reported reduced dosing frequency and lower incidence of adverse effects with NLC-based systems, highlighting their potential for improved patient adherence and therapeutic outcomes. Overall, the evaluation studies and therapeutic findings strongly support the potential of NLC-embedded transdermal patches as advanced and effective platforms for antifungal drug delivery. Their ability to overcome the limitations of conventional antifungal formulations makes them promising candidates for future clinical applications in fungal infection management.[35]

5. Challenges, Future Perspectives, and Conclusion

5.1 Current Limitations in Formulation and Scale-Up

Despite the significant advances in nanostructured lipid carrier (NLC)-embedded transdermal patches for antifungal therapy, several formulation and manufacturing challenges continue to limit their large-scale industrial application and commercialization. The complexity of nanocarrier-based systems requires careful optimization of formulation variables, processing conditions, and quality control parameters to ensure reproducibility, stability, and therapeutic effectiveness.[48]

One of the major challenges in NLC formulation is maintaining long-term physical and chemical stability. Lipid nanoparticles may undergo aggregation, polymorphic transitions, particle growth, and drug expulsion during storage, which can negatively affect drug release behavior and therapeutic performance. The selection of suitable lipids, surfactants, and stabilizers is therefore critical for maintaining nanoparticle integrity and preventing instability.[49]

Another important limitation is achieving high drug loading efficiency while maintaining nanoparticle stability. Certain antifungal agents exhibit poor compatibility with lipid matrices, leading to low encapsulation efficiency and premature drug leakage. Moreover, the

physicochemical characteristics of antifungal drugs, including molecular weight, lipophilicity, and crystallization tendency, may influence incorporation into NLC systems.[10]

Scale-up of NLC production also presents considerable technical difficulties. Laboratory-scale preparation methods such as ultrasonication and solvent evaporation may not be easily adaptable for industrial manufacturing due to issues related to reproducibility, batch-to-batch variation, energy consumption, and solvent toxicity. Although high-pressure homogenization is considered more suitable for large-scale production, maintaining consistent particle size distribution and formulation uniformity during scale-up remains challenging.[50]

The fabrication of NLC-embedded transdermal patches introduces additional complexities related to polymer selection, mechanical strength, adhesiveness, and drug distribution within the patch matrix. Uniform incorporation of nanoparticles into polymeric films without aggregation is essential to ensure consistent drug release and permeation characteristics.[32]

Furthermore, the high production cost associated with nanotechnology-based formulations may limit accessibility and commercial viability, particularly in resource-limited healthcare settings. Specialized equipment, advanced characterization techniques, and stringent quality control requirements contribute significantly to manufacturing expenses.[51]

5.2 Regulatory and Clinical Considerations

The clinical translation of nanocarrier-mediated transdermal antifungal systems requires comprehensive evaluation of their safety, efficacy, quality, and regulatory compliance. Regulatory approval of nanomedicine products remains a complex process due to the unique physicochemical and biological properties of nanoparticles.[52]

One major regulatory concern involves the lack of standardized guidelines specifically designed for nanostructured lipid carrier systems. Conventional pharmaceutical evaluation criteria may not adequately address the complexity of nanoparticle-based formulations. Regulatory agencies therefore require extensive characterization of nanoparticle properties, including particle size, surface charge, morphology, stability, drug release kinetics, and interaction with biological systems.[53]

Safety assessment is another critical aspect of regulatory evaluation. Although NLCs are generally composed of biocompatible and biodegradable lipids, long-term toxicity, skin irritation, immunogenicity, and nanoparticle accumulation within tissues must be thoroughly

investigated. The potential effects of chronic exposure to surfactants, permeation enhancers, and nanomaterials require careful evaluation through preclinical and clinical studies.[54]

Clinical studies evaluating NLC-embedded transdermal patches for antifungal therapy remain relatively limited. Most currently available evidence is based on in vitro and animal studies, whereas large-scale human clinical trials are still lacking. Clinical translation requires well-designed studies assessing therapeutic efficacy, pharmacokinetics, patient compliance, long-term safety, and comparative effectiveness against conventional antifungal therapies.[55]

Additionally, variability in skin physiology among patients, including differences in skin hydration, thickness, disease condition, and permeability, may influence transdermal drug absorption and therapeutic outcomes. Personalized approaches and optimized dosing strategies may therefore be necessary for effective clinical application.[56]

Regulatory considerations also include issues related to product sterilization, packaging, storage conditions, and quality assurance. Establishing standardized manufacturing protocols and quality-by-design approaches will be essential for successful commercialization of NLC-based transdermal antifungal systems.[57]

5.3 Future Trends in Nanocarrier-Mediated Antifungal Therapy

The rapid advancement of nanotechnology and biomaterials science is expected to significantly enhance the future development of antifungal drug delivery systems. Emerging nanocarrier-based approaches aim to improve therapeutic efficiency, targeted delivery, patient compliance, and clinical outcomes while minimizing toxicity and drug resistance.[4]

One promising future trend involves the development of multifunctional and stimuli-responsive nanocarriers capable of responding to environmental triggers such as pH, temperature, enzymes, or fungal metabolites. These smart delivery systems may enable site-specific and controlled release of antifungal agents at infected tissues.[58]

Combination therapy using multiple antifungal agents or synergistic bioactive compounds within a single NLC system also represents an important research direction. Co-delivery strategies may improve antifungal efficacy, reduce resistance development, and enhance therapeutic outcomes against multidrug-resistant fungal pathogens.[10]

Advanced transdermal technologies such as microneedles, iontophoresis, sonophoresis, and

electroporation are increasingly being combined with NLC systems to further improve skin permeation and drug deposition. Microneedle-assisted NLC delivery, in particular, has shown promising potential for overcoming the barrier function of the stratum corneum and enhancing localized antifungal therapy.[20]

The incorporation of natural antifungal agents, herbal extracts, essential oils, and bioactive phytochemicals into lipid nanocarriers is another growing area of interest. Such approaches may provide safer and more biocompatible alternatives to synthetic antifungal drugs.

Nanofibrous transdermal patches fabricated through electrospinning technology are also gaining attention due to their high surface area, flexibility, and ability to provide sustained drug release. Integration of NLCs into electrospun nanofibers may further improve antifungal drug delivery efficiency.[44]

Artificial intelligence (AI) and computational modeling are expected to play an increasingly important role in formulation optimization, prediction of nanoparticle behavior, and personalized antifungal therapy design. These technologies may accelerate the development of highly efficient nanocarrier systems with improved therapeutic performance.[59]

5.4 CONCLUSION

Nanostructured lipid carrier (NLC)-embedded transdermal patches represent an advanced and highly promising approach for antifungal drug delivery. The integration of lipid nanocarriers with transdermal delivery systems offers numerous therapeutic advantages, including enhanced drug solubility, improved skin permeation, sustained drug release, prolonged skin retention, reduced systemic toxicity, and improved patient compliance.

NLCs possess unique structural and physicochemical properties that enable efficient encapsulation and controlled delivery of antifungal agents across the skin barrier. The incorporation of antifungal-loaded NLCs into polymeric transdermal patches further enhances formulation stability, mechanical properties, and therapeutic performance. Experimental studies have consistently demonstrated superior antifungal efficacy of these systems compared to conventional creams, gels, and oral formulations.

Despite these promising outcomes, several challenges related to formulation stability, large-scale production, regulatory approval, and clinical translation remain to be addressed. Continued interdisciplinary research involving pharmaceutical sciences, nanotechnology,

biomaterials engineering, and clinical medicine will be essential for overcoming these limitations and facilitating successful commercialization.

Overall, nanocarrier-mediated transdermal antifungal systems hold significant potential to revolutionize the management of fungal infections. Future advancements in smart nanocarriers, targeted delivery technologies, and personalized medicine approaches are expected to further improve the effectiveness and clinical applicability of NLC-based antifungal therapies.

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