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(Review)

Emergence of Advanced Antifungal-Delivery Approaches for the Treatment of Tinea Pedis

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ABSTRACT

A common fungal infection of the feet known as tinea pedis, which is also known as athlete's foot, significantly lowers quality of life. Its occurrence is caused by dermatophytes, a form of fungus that grows on the dead skin of the feet. Itching, scaling, redness, and skin breaking are among the symptoms that can be brought on by tinea pedis. In extreme circumstances, it may also result in nail infections and painful blisters. Antifungal medications, either systemic or topical, are widely used to treat tinea pedis. In recent years, there has been a surge in interest in developing novel medication delivery systems/strategies for the treatment of tinea pedis. By improving the drug's penetration into the skin and lowering the chance of systemic side effects, these systems seek to increase the safety and efficacy of antifungal therapy. This review has covered the many effective ways to treat tinea pedis, including traditional and state-of-the-art sophisticated delivery techniques. Furthermore, prospective avenues for treatment optimization and recurrence prevention of these severe fungal infections have been emphasized.

Keywords: Tinea pedis; antifungals; advanced drug delivery systems; nanoparticles; microneedles; enhanced efficacy

1. Introduction

Ten percent or more of the world's population suffers from tinea pedis. The late nineteenth and early twentieth centuries, when occlusive shoes gained popularity, are thought to be the time when these illnesses started to spread widely. Men are more likely than women to have tinea pedis, and kids rarely get it [1]. The web space between the fourth and fifth toes is frequently impacted, especially on the lateral toes. Tinea pedis is more likely to occur in those who have a generalized immune weakness, like AIDS or HIV. Tinea pedis is more common in people with a history of atopic dermatitis. Tropical and semitropical areas are more likely to experience such fungal infections, particularly during the summer [2]. The most frequent cause of tinea pedis infection is *Trichophyton rubrum*, however, it can also be caused by *Trichophyton mentagrophytes* and *Epidermophyton floccosum* [3].

In terms of Tinea pedis' pathophysiology, all of the dermatophytes mentioned above require keratin for growth. As a result, when a fungal cell invades the skin, it produces keratinase, an enzyme that feeds on the keratin in the skin's outer layer, causing keratin tissue degradation and skin inflammation. Due to their ability to infect the human skin's deepest layer, these dermatophytes can cause a variety of serious fungal infections (**Figure 1**) [4]. Although tinea pedis has a variety of clinical manifestations, the most typical symptom is a rash/scaled region that spreads from the toes to the soles, heels, and sides of the feet. Even while this fungus is normally not hazardous, it can nevertheless be uncomfortable, may not respond to medication, and may spread to other parts of the body or other individuals. It's also possible for bacteria to spread and secondary infect the affected foot [5].

For the treatment of tinea pedis, ciclopirox, allylamines, imidazoles, and polyenes are the most often utilized antifungal medications. Imidazoles (such as miconazole, clotrimazole, and ketoconazole) prevent the production of ergosterol, which is necessary for the development of the fungal cell membrane. The production of squalene epoxidase, an enzyme necessary for the synthesis of ergosterol, is inhibited by allylamines like terbinafine and naftifine. Amphotericin B and other polyenes that bind to ergosterol break down the fungal cell membrane. The synthesis of fungus nucleic acids and proteins is inhibited by ciclopirox [1,6].

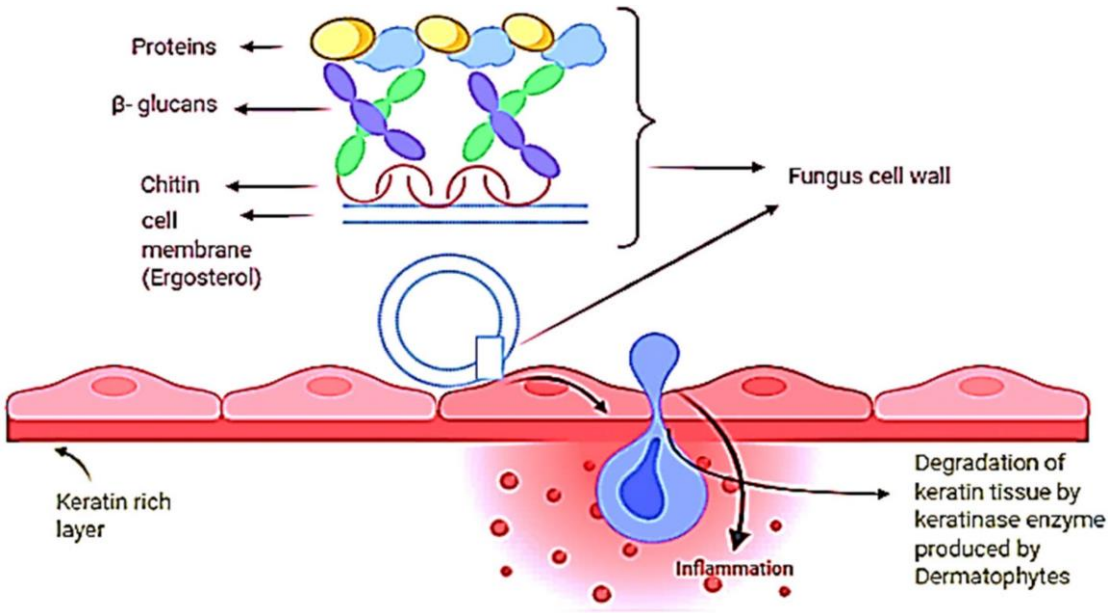

Figure 1. Schematic illustration of Tinea Pedis pathophysiology (dermatophytosis; Figure from Navkiranjeet et al, 2021 [4]).

The classification of several antifungal medications that can be used to treat tinea pedis is displayed in **Figure 2**. Numerous of these recently created antifungal medicines have significant restrictions [7], relating to their pharmacokinetics, drug-drug interactions, physicochemical and biological properties, spectrum of activity, and pharmacodynamic characteristics [6,8].

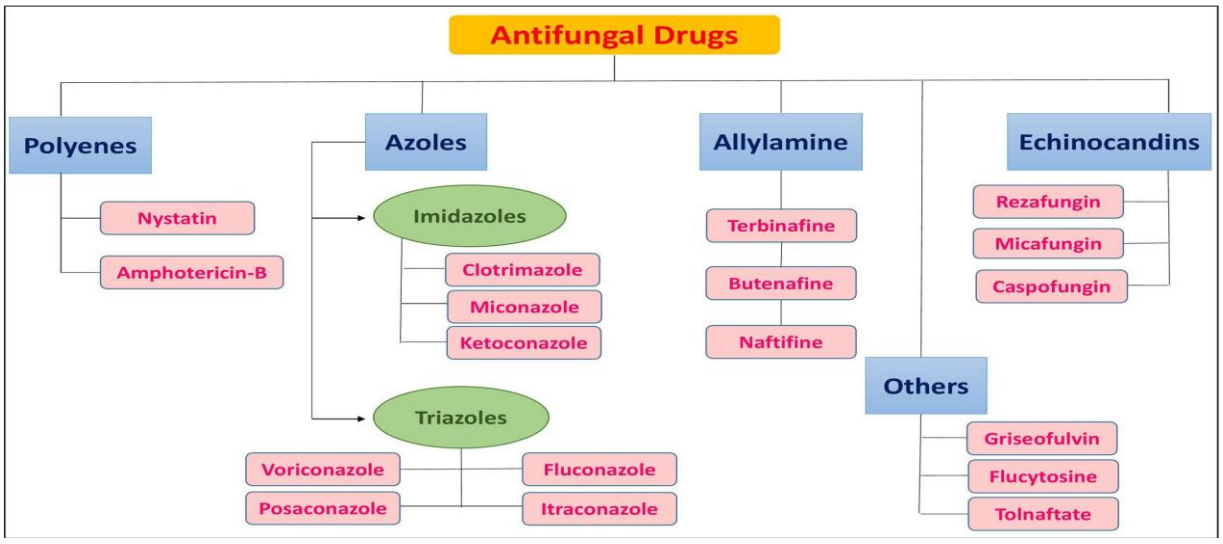

Figure 2. Schematic categorization of antifungals that can be used for tinea pedis treatment (Figure from Mosallam et al, 2022 [9]).

2. Conventional antifungal delivery systems

Different topical and oral treatments are used to treat tinea pedis. Topical medications are typically efficient and reasonably priced. However, in some cases, topical antifungal treatments might not be able to completely eradicate dermatophyte fungal species from the keratinous tissue. Relapses and persistent tinea pedis may potentially follow from this consequence. Although systemic medications have the potential to be more effective than topical treatments, there is a higher risk of side effects and drug interactions [1,6].

For many decades, the oral and topical dosing conventional modalities have been used to deliver antifungal medicines. Oral dosage forms, which come in the shape of tablets, solutions, or suspensions, have a number of drawbacks, including the need to administer a higher dose than necessary (due to limited bioavailability), a need for more frequent dosing, a lack of efficacy, and the high probability of developing resistance [10]. Regarding topical delivery, there are numerous forms available for topical antifungal administration that can be employed in the treatment of tinea pedis. Creams are a typical form of topical antifungal medication administration. They are simple to formulate, and use and often penetrate the skin fast. For dry and scaly lesions, creams are frequently employed. Ointments are another popular delivery method because they are greasier and thicker than creams and are typically applied to thickened and dry skin. Gels are applied to weeping, wet sores. They are transparent and typically give the skin a cooling sensation. Gels are frequently applied to body parts like the space between the toes where lotions and ointments might not be appropriate. Sprays are applied to large/broad parts of the body or challenging-to-reach places. They are simple to use and almost immediately absorbed by the skin. Tinea pedis on the soles of the feet is frequently treated using sprays [11]. When treating weeping or moist lesions, solutions can be also employed. The majority of the time, they are applied with a cotton ball or swab, and they swiftly penetrate the skin. Powders are applied to body parts where moisture is a problem, like the space between the toes. Usually, they are used after washing and drying the impacted region [11].

The intensity and location of the illness, as well as the patient's preferences and medical background, all influence the drug delivery method selection. Based on the current conditions specific to each case, a healthcare professional, such as a dermatologist or primary care physician, can suggest the best dosage form or delivery system, in order to ensure the highest rate of recovery and the prevention of recurrence probability, as much as possible.

3. Advanced antifungal delivery systems

Despite the availability of a variety of standard dosage forms for antifungal medications, such as pills, creams, gels, etc., they appeared to be inadequate in addressing the numerous drawbacks of antifungals (such as toxicity, drug-drug interactions, and reduced water solubility of systemic antifungal agents) [6]. To solve these problems, novel delivery approaches are therefore crucially needed. These nanocarriers (NCs) and nanoparticles (NPs) used in sophisticated delivery systems can overcome many of the unfavorable drug features due to their adaptability, multifunctionality, and wide range of capabilities (**Figure 3**) [12,13]. Drug delivery systems that have been rationally designed have the potential to enhance drug performance and get around many of these restrictions [14]. Liposomal Amphotericin-B (L-AmB), AmB colloidal dispersion (ABCD), and AmB lipid complex (ABLC), for instance, exhibited a significant reduction in AmB nephrotoxicity while maintaining its broad range antifungal efficacy [15].

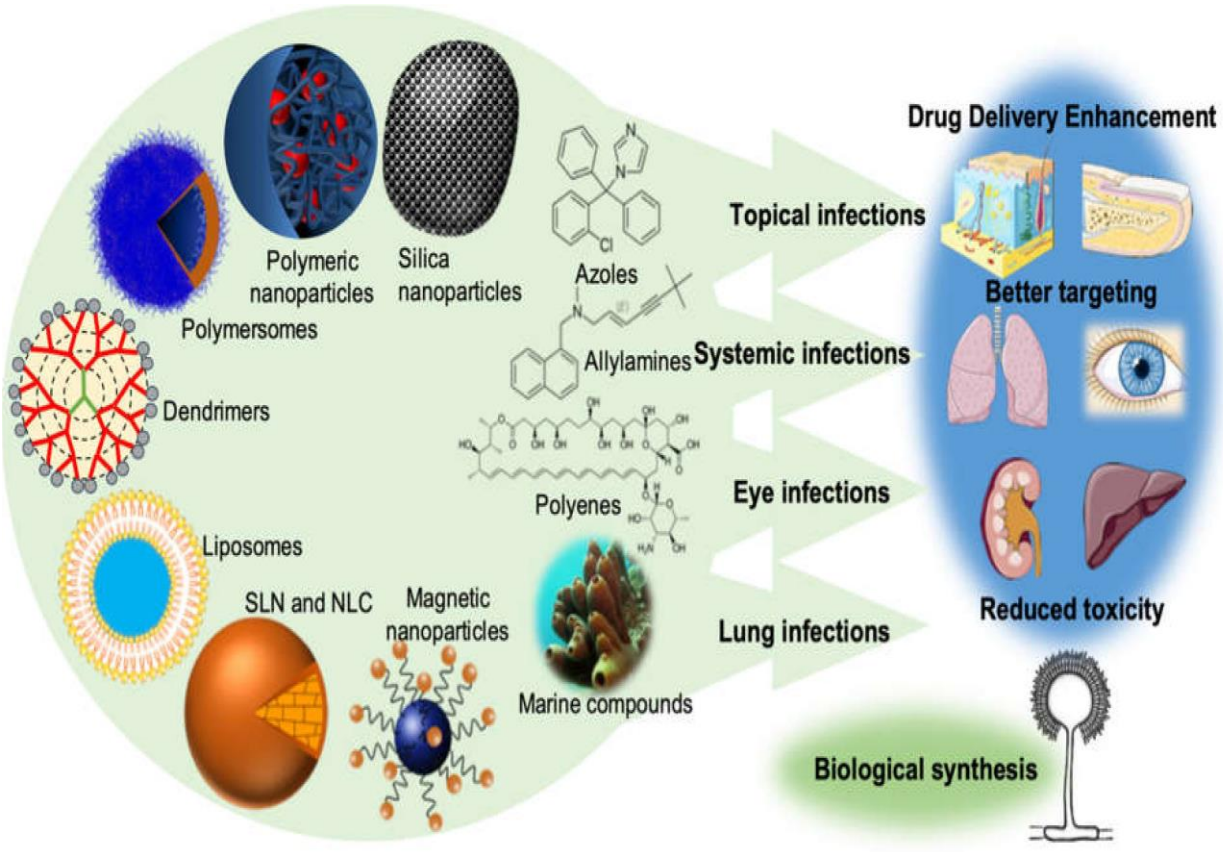

Figure 3. Advanced antifungal delivery systems (Figure from Sousa et al, 2020 [13]).

Phospholipid vesicles (liposomes, transfersomes, ethosomes, and transethosomes; **Figure 4**) and non-phospholipid vesicles (niosomes and spanlastics), as well as polymeric NPs, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and dendrimers, can all be broadly categorized as advanced antifungal delivery systems, based on their composition [13,16]. The emergence in antifungal delivery employing each of these types are covered in the following sections.

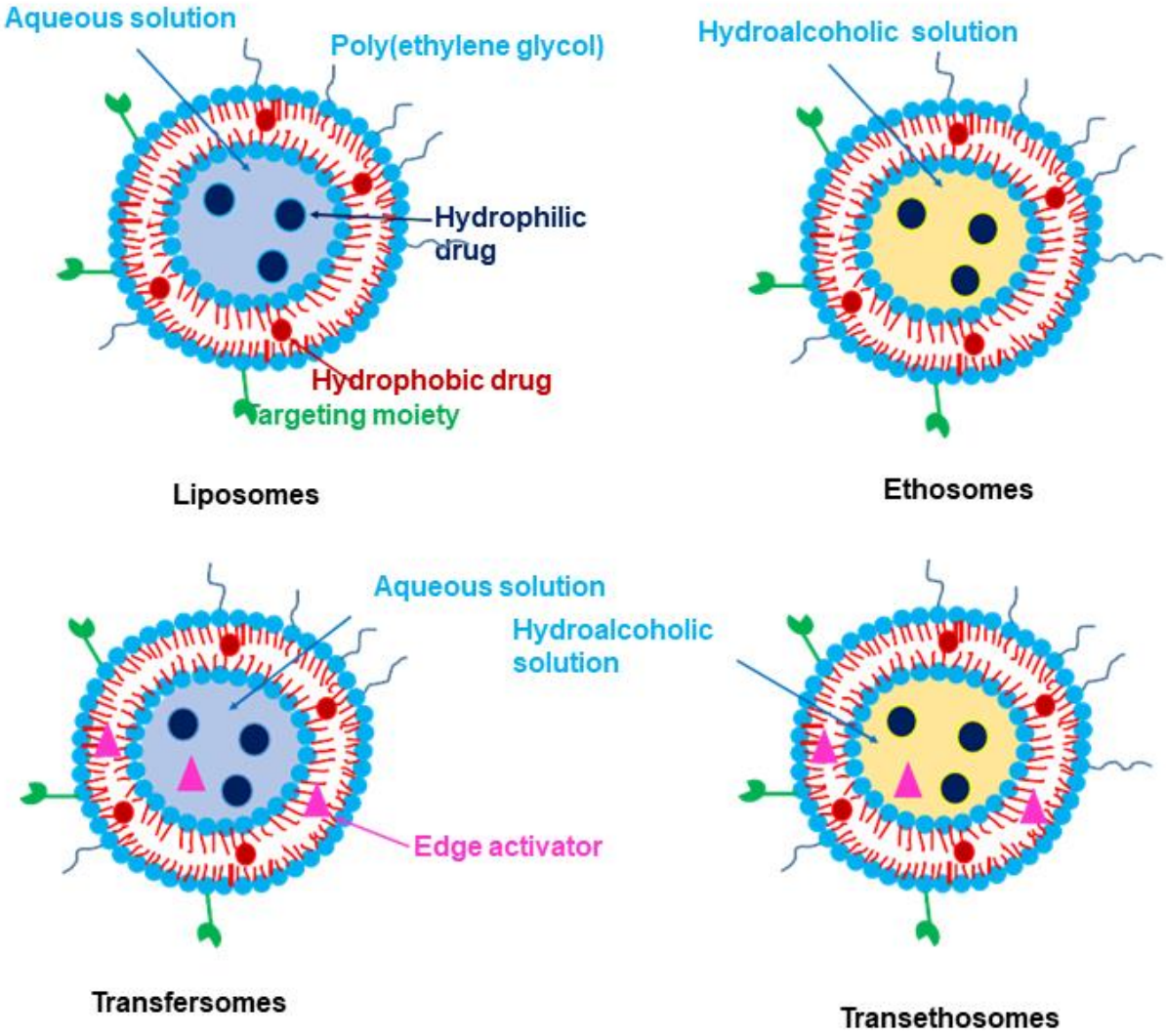

Figure 4. Types of phospholipid-based vesicular systems used in antifungal delivery (Figure from Soliman et al, 2017 [6]).

3.1. Liposomes

Due to drugs-low permeability through the skin barriers, they face a significant barrier when being transported across the skin. This result is explained by the diffusional barrier that exists in the stratum corneum, the top outer layer of the skin [17]. Drug loading into liposomes is one of the most crucial strategies [18]. Sir Alec D. Bingham made the initial discovery of liposomes, which are adaptable vesicular carriers made of phospholipids, in the middle of the 1960s. They are made up of cholesterol and phospholipids that are disseminated in an aqueous phase [19,20]. The phospholipids that are employed to create liposomes have the ability to form liposomal vesicles with a bilayer membrane-like structure. Once they come into contact with the aqueous phase and their concentration crosses the critical micelle concentration, they have the capacity to self-assemble into vesicular structures. Besides phospholipids, cholesterol is one of the key elements of liposomes. It increases the gathering of phospholipid molecules, reduces vesicle agglomeration, and gives the vesicle stiffness so they can tolerate high shear pressures during topical administration [6,17,21]. Liposomes have the ability to localize medications in the skin precisely where they are needed, minimizing drug absorption into the bloodstream and the consequent negative effects [9].

Since 1987, liposomes have been widely used in the cosmeceutical sector. The econazole-loaded liposomal gel (Pevaryl© lipogel) from the Swiss company Cilag was the first commercial formulation of liposomes for topical distribution in the pharmaceutical sector [22]. Antifungals that are either hydrophilic or hydrophobic can both be transported effectively by liposomes when applied topically. They provide a number of benefits for drug distribution across the skin appendages, including depot development at the bioactive site and reduced systemic absorption, which lowers dose and dosing frequency and promotes prolonged drug release, among other more benefits [23]. Only non-rigid deformable vesicles exhibit the greatest penetration enhancement, and differing lipid components have an impact on the penetration enhancement of various formulations. In certain research, the trans-appendageal route was considered for liposomal drug administration and findings revealed that the trans-appendageal route was a very modest element of the transportation network [24]. **Figure 5** depicts the specifics of each of the liposomal mechanisms of skin permeation. In this penetration process, the composition and physicochemical properties of liposomes are crucial. Liposomes' lipid

composition, lamellarity, phase transition temperature, charge, and size, all affect how well they penetrate the skin. [17].

Antifungal delivery via topical liposomal formulations has been extensively studied. The effectiveness of a commercial econazole lipogel (Pevaryl© lipogel) and an econazole cream formulation were examined by Schaller et al. They tested these compositions on both healthy and candidiasis-infected human epidermis. The results showed that Pevaryl© lipogel significantly damaged *C. albicans* blastospores and reduced damage to the human epidermal barrier and econazole buildup in deeper layers of skin. The study showed potential uses of a liposomal carrier for the creation of topical antifungal formulations to treat superficial fungal infections and lessen side effects from standard formulations [25].

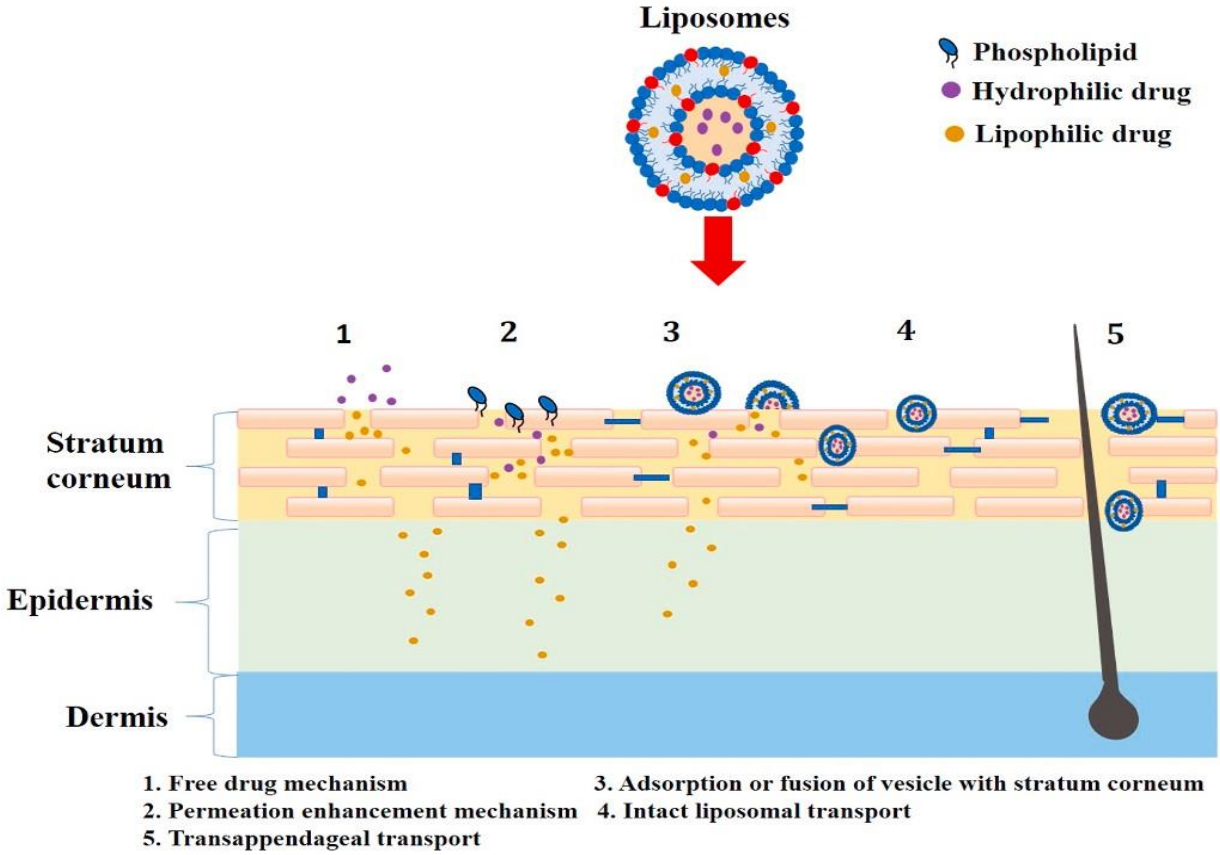

Figure 5. Mechanism of skin permeation of liposomes (Figure from Nene et al, 2021 [17]).

Despite being the first skin-based drug delivery system, liposomes have certain limitations in terms of deeper skin penetration [26]. New vesicular carriers, such as ethosomes,

transethosomes, and transfersomes, which are covered in the sections ahead, were created as a result of the further evolution of the components in liposomal carriers.

3.2. Transfersomes

Gregor Cevc made the initial discovery of transfersomes, which are also known as deformable liposomes, in 1992 [27]. In terms of preparation techniques and structural characteristics, transfersomes and liposomes are almost identical. They are different from liposomes, though, in terms of how easily they may bend and how they penetrate the skin. Edge activators and phospholipids are both added to create these vesicles with increased deformability [28]. Edge activators are single-chain surfactants like dipotassium glycyrrhizinate, sodium cholate, and sodium deoxycholate [28]. The type of edge activators and the ratio of edge activators to phospholipids have an impact on the physicochemical characteristics of transfersomes such as size, entrapment effectiveness, and surface charge. Transfersomes become hard at lower ratios while becoming elastic enough to squish into the skin appendages at higher ratios, which further influences the deformability of the transfersomes [29]. Transfersomes may penetrate the skin through one of two main processes, according to some research. Due to their flexible shape, these vesicles bend and squeeze themselves through the interstitial gaps between the keratinized cells of the SC, according to the first mechanism, suggesting that they transmit through the SC in their intact form. This happens as a result of the skin layers developing a gradient of moisture. Compared to the deeper layers of the epidermis, the SC layer is quite dry. As a result, there is a gradient of moisture between the skin layers [28]. The second mechanism proposes that these vesicles enter the SC and modify intracellular lipids in the skin. This is as a result of the edge activator molecules' ability to improve penetration by lowering the interfacial tension between transfersomes and epidermal lipids [29].

Compared to typical liposomes, transfersomes have a number of advantages, and one of the most significant is their increased flexibility [30]. Various medications' antifungal effects have been enhanced after being loaded into transfersomes. Miconazole nitrate's skin penetration was improved by Qushawy et al. by encapsulating it in transfersomes, which were then placed into the Carbopol 934 gel basis. *In vitro,* permeation tests revealed the miconazole nitrate transfersomal gel had a 1.18-fold higher penetration flux than a commercially available version of the drug (Daktarin® cream) [31]. When compared to Daktarin® cream in a rat model with *C. albicans* infection, optimized transfersomal gel containing miconazole nitrate had greater *in vivo*

antifungal efficacy. The afflicted animal had purple and greyish areas, as well as swelling and inflammation. While transfersomal gel demonstrated normal skin with very little inflammation, the treated rats with Daktarin® cream exhibited the elimination of edema and inflammation but the presence of scars. Transfersomes' enhanced skin penetration compared to the commercial product was credited with the higher antifungal activity of the formulation [31]. Another successful story was for sertaconazole nitrate, which was synthesized as nanovesicular systems (glycerosomes, liposomes, ethosomes, and transfersomes) and compared with the commercial formulation (Dermofix® cream) to target *C. albicans*-related skin fungal infections. When compared to other vesicular formulations, *ex vivo* penetration in rat skin showed the maximum flow for transfersomal formulation. When compared to Dermofix® cream, the transfersomal gel exhibited a 3.5-fold increase in permeation flux up to 6 hours and a 5.5-fold increase after that [32]. Fluorescein diacetate was used to visualize *ex vivo* permeation, and it was discovered that the dispersion of the fluorescent probe was restricted to the epidermis without reaching the dermis layer for transfersomal formation. These findings point to the buildup of drug-containing transfersomes in the epidermal layers, where they serve as reservoirs for prolonged drug release. Thus, among other vesicular carriers, transfersomal gel was chosen for *in vivo* experiments. Sertaconazole-loaded transfersomal gel (below log 1 CFU/mL) showed significantly improved antifungal activity when compared to Dermofix® cream (above log 2 CFU/mL) in *in vivo* antifungal efficacy on fungal infected skin by *C. albicans* [32].

3.3. Ethosomes

Ethosomes are vesicular carriers made of ethanol, phospholipids, and water that are flexible and squishy, as Touitou and other co-workers introduced them in their work [33]. The ethosomes have a higher percentage of ethanol (20–40%) than phospholipids (2–5%), which are present in smaller amounts. Drugs that are either lipophilic or hydrophilic can both be encapsulated. Thin film hydration is typically favored among the preparation techniques due to the use of a significant amount of organic solvents, scalability, ease of use, and production of homogenous vesicles with a high entrapment efficiency [20]. The interaction between the ethanol and the lipids present in the skin causes the vesicular flexibility of ethosomes. Ethanol's ability to lower the temperature at which phospholipids transition from the ordered gel phase to the disordered liquid crystalline phase speeds up the process. Skin traversing is enhanced by high

flexibility and mobility in a liquid crystalline form. Additionally, ethanol helps to dissolve skin lipids, enhancing the entry of ethosomes into the skin's deeper layers [9,17].

Regarding the topical antifungal administration using ethosomes, numerous investigations have been described. Conazole-containing ethosomes and liposomes were created by Verma et al. to treat skin-related fungal infections. The Carbopol-934 gel base was filled with the improved ethosomal preparation. A rat skin *in vitro* permeation investigation found that ethosomal gel of econazole has a 15-fold greater skin permeability flux than liposomal gel. Using Rhodamine red dye, CLSM conducted additional research on the *in vitro* permeation study findings. The CLSM examination revealed that Rhodamine red-loaded ethosomal gel had the highest skin penetration up to the fifth layer of the epidermis. The high level of skin penetration was caused by the inclusion of ethanol in the ethosomal formulation [34]. Amphotericin B-loaded ethosomes were developed by Kaur et al. to test their antifungal effectiveness. *In vitro,* skin permeation on rat skin was tested after the improved formulation was put into a 1.5 percent Carbopol-934P gel base. In comparison to commercialized gel (Fungisome®) and drug solution, the optimised ethosomal gel preparation showed transdermal flux that was 2.7-fold and 9-fold greater, respectively. In comparison to commercial gel (52 µg) and medication solution (23.4 µg), ethosomal gel formulation had the maximum skin deposition (182 µg). To establish skin penetration and deposition of the optimal ethosomal formulation, a CLSM research was conducted. For ethosomal gel, it was discovered that improvements to the fluorescence intensity and depth of skin penetration (240–620 µm) had been confirmed [35].

3.4. Transethosomes

Song and colleagues introduced transethosomes in 2012, which are ethosomal nanocarriers of the second generation with modifications [36]. Transethosomes are made up of phospholipids, an edge activator, and ethanol. They provide a jumble of ethosome and transfersome benefits [37] in addition to higher activity than both ethosomes and transfersomes [36,38]. It was believed that these vesicles' skin penetration criteria combined both the transfersome and ethosome penetration mechanisms [36]. Transethosome skin permeability is influenced by a number of variables, including particle size, edge activator type and concentration, ethanol content, and phospholipid concentration [17]. Ketoconazole was synthesized in four different vesicular carriers, including liposomes, transfersomes, ethosomes, and transethosomes by Guo et al. Higher skin deposition was found for ethosomes,

transfersomes, and transethosomes compared to liposomes in an *in vitro* permeability study in pig skin. Transethosomes were shown to have the maximum skin retention on the epidermis and dermis layer (5.1 folds) after 24 hours of treatment when compared to other vesicular carriers. An *in vivo* skin penetration investigation using rat skin revealed that transethosomes, which accumulated ketoconazole at a greater rate (4.8% of the starting dose) than liposomes, in the deeper layers of the skin. Rhodamine 6G dye was used in a CLSM investigation to demonstrate how these vesicular carriers are delivered to the skin. The dermis layer's fluorescence was noticeably weaker than that of the top layer of skin when using standard liposomes. When compared to liposomes, the transethosomes displayed a 5.5-fold increase in fluorescence intensity. No evidence of irritation or inflammatory cell infiltration was found in the histological analysis. Transethosomes' enhanced skin penetration was found to be responsible for their greater antifungal activity. Transethosomes' skin-enhanced permeability was related to the presence of edge activator and ethanol [39].

3.5. Niosomes

Niosomes are vesicles made of non-ionic surfactants that were developed by L'Oréal in the 1970s [17]. They are made up of charge inducers, hydration mediums, and non-ionic surfactants [40]. The amphiphilic non-ionic surfactants have a hydrophilic head and a hydrophobic tail. The hydrophobic tail is placed in the middle of the hydrophilic head layer, whereas the hydrophilic head is orientated toward the interior and outside of the bilayer. Therefore, medications that are both lipophilic and lipophobic can be combined simultaneously into niosomes [39]. Tweens, spans, and brijs are a few examples of common non-ionic surfactants used in the production of niosomes [41]. In comparison to their ionic cousin, non-ionic surfactants have some advantages, such as lower toxicity, vesicular physicochemical stability, and compatibility [40,42,43]. Cholesterol is also incorporated, which gives the bilayer stiffness and prevents drug leakage from the niosomal vesicle. Niosomes have been studied to administer pharmaceuticals *via* multiple administration routes due to the benefits they offer over liposomes, such as improved physicochemical stability, low production cost, increased penetration through the skin, higher entrapment efficiency, and drug-loading properties [44]. Surfactants promote fluidity, solubilize, and remove lipids from the SC, which both increase permeability across SC. Second, by attaching to and interacting with keratin filaments, they may result in the disruption of corneocytes. By minimising water loss from the epidermis and

increasing skin moisture, the attachment of niosomes to the skin surface alters the SC characteristics. This increase in hydration causes the tightly packed cellular structure to relax [44].

For the treatment of skin-related fungal infections, numerous researches utilizing niosomal formulation have been conducted. To improve its skin penetration, Alomrani et al. created itraconazole (ITZ) loaded niosomes and assessed the antifungal efficacy in cutaneous candidiasis. They investigated the effects of various surfactant types on the physicochemical properties and skin deposition of niosomes that were loaded with ITZ. To investigate the effectiveness of several non-ionic surfactants, an *ex vivo* permeation investigation through rat abdomen skin was conducted. Alomrani et al. assessed the total amount of ITZ deposited on the SC, stripped skin, and receptor fluid. Brij 35-derived niosomes showed less SC permeability than ITZ solution. The underlying cause might be related to Brij 35's higher HLB value (16.92) and larger niosomal size. Due to the lower HLB of Tween 60 and Tween 80 compared to brij and Spans, the niosomes made of Tween 60 and 80 showed good penetration into SC, stripped skin, and a high amount of ITZ was discovered in the receiver compartment. In addition, niosomes containing Tween 65 and Tween 85 (HLB value of 10.5–11) demonstrated enhanced penetration through the SC. Tween 85 was obtained to produce the next-highest amount of SC and stripped skin deposition for ITZ, followed by Span 85. The antifungal efficacy of ITZ niosomes composed of Span 80 mono-alkyl chain (HLB 4.3), Tween 80 mono-alkyl chain (HLB 15), and Tween 85 with tri-alkyl chain, and moderate HLB (11), was also assessed. According to the study's findings, all niosomes had significantly higher antifungal activity than the ITZ solution [17]. Another example regarding the niosomal encapsulation of griseofulvin is worthy to be discussed. In order to distribute griseofulvin topically and combat tinea corporis, Kaseen et al. combined it with niosomal and lipo-sphere gel. On sixteen patients over the course of three weeks, the clinical effectiveness of various formulations was assessed. Niosomal gels had the highest mycological cure rate (80%), followed by liposphere gel with a mycological cure rate of 75%, and griseofulvin plain drug-loaded gel with a mycological cure rate of just about 50% [45].

3.6. Spanlastics

Spanlastics are highly elastic nano vesicular systems made of a non-ionic surfactant and an edge activator [46]. Their target specificity, easiness in formulation, high patient compliance, and chemical stability are only a few of their benefits [47], but when it comes to ocular

administration, they have a modest release profile [48]. Owing to the existence of an edge activator that offers significant flexibility and increases drug permeability, spanlastics may be potential vehicles for the administration of antifungal medications. Abdelbari et al. described the usage of spanlastics as nanovesicles to treat eye fungal infections with clotrimazole [49]. Using the ethanol injection approach, Span 60 with various edge activators was employed to create clotrimazole-loaded spanlastics. A 32 complete factorial design was applied, and the results were analyzed using Design-Expert® software. The optimized formulation was spherical in shape, displayed a sustained *in vitro* release profile, and significantly outperformed clotrimazole suspension in terms of corneal penetration. The greater elasticity of the clotrimazole-loaded spanlastics contributed to their increased corneal permeability. Comparing the optimized formulation to clotrimazole suspension, it had superior antifungal action. The study demonstrated that the release of clotrimazole to treat eye fungal infections using spanlastic vesicles is a promising and practical method.

Luliconazole-loaded spanlastics were created by Alhakamy et al. to increase the medication's antifungal action [50]. The novel imidazole antifungal luciconazole has some drawbacks that limit its use, such as limited solubility and poor skin penetration. By creating spanlastics carrying luciconazole, the study intended to increase the therapeutic effectiveness of the drug. The ethanol injection method was used to manufacture the spanlastics, and a combined mixture-process variable design was used to optimize them. To improve skin penetration and boost effectiveness against fungal infections found in the wounds of experimental animals, the improved formulation was added to a hydrogel. Compared to the medication suspension, it demonstrated much greater antifungal activity and caused no irritation. As a result, luliconazole-loaded spanlastics improved the topical antifungal activity. Another study by Mohanta et al. prepared spanlastics for the delivery of miconazole nitrate to the eyes [9,51]. Various surfactants were used to create formulations using the ethanol injection method. In comparison to the drug's typical niosomes formulation, spanlastics had a greater permeability. The study's findings showed that spanlastics are a more effective delivery system than conventional niosomes for the treatment of fungus infections.

3.7. Polymeric nanoparticles

The science of drug delivery has been transformed by polymeric nanoparticles (PNPs) created by the combination of biodegradable and/or biocompatible polymers [52]. PNPs have

proven to be great in enhancing the therapeutic characteristics of drugs while reducing their adverse effects and toxicity [53]. Many PNP-based cytotoxic drug formulations have already entered clinical use, and many more are undergoing various phases of study [6,54,55]. PNPs are divided into three groups based on their design and technique of preparation: nanospheres, nanocapsules, and polymeric micelles (**Figure 6**). A premade polymer can precipitate at the surface of emulsion droplets or polymerize as part of the nanocapsule preparation process. There are numerous ways to deliver nanospheres and nanocapsules (parenteral, oral, topical, etc). They are less costly, simpler to make and store, and much more stable than phospholipid vesicles [56].

Incorporating antifungal medications inside nanospheres and nanocapsules maintained their release, increased their antifungal activity, and decreased their toxicity, according to several studies. Based on the antifungal medication studied, the following examples provide summaries of some of these trials. Itraconazole (ITZ). As a new sustained-release formulation for intravenous delivery, ITZ was added to PLGA nanospheres [57]. To increase AmB's oral bioavailability and lessen any negative effects, it was added to PLGA NPs. A quick initial release phase was followed by a persistent release phase, indicating that AmB release from NPs was biphasic. The NPs had a narrow size range with a diameter of 165 nm. Rats exposed to AmB NPs exhibited less hemolysis and nephrotoxicity than those exposed to Fungizone®. Additionally, the oral bioavailability of NP-loaded AmB was almost eight times greater than that of the marketed drug [58,59].

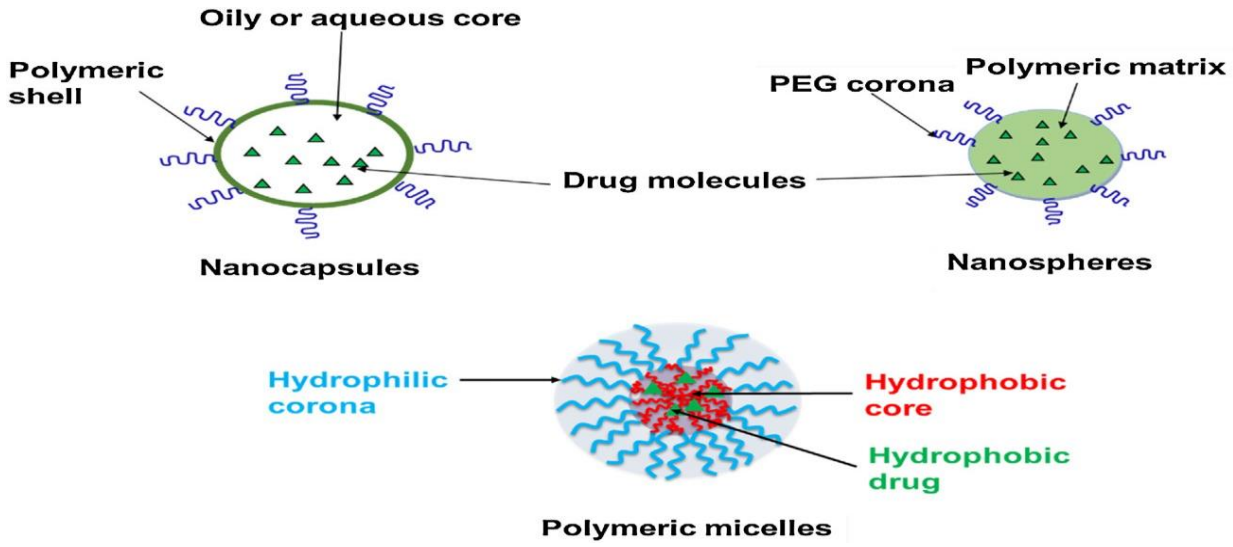

Figure 6. Types of polymeric nanoparticles used for antifungal delivery (Figure from Soliman et al, 2017 [6]).

Amphiphilic block or graft copolymers self-assemble as polymeric micelles in water over their critical association concentration (CAC) [60]. They typically have a core-corona architecture, where the hydrophobic segments of the copolymer make up the core and the hydrophilic portions form the corona. The hydrophilic corona keeps the micelles colloidally stable and water-soluble, decreases their absorption by immune system cells, and extends their blood circulation time. The biodegradability and/or biocompatibility of polymeric micelles, which restrict the *in vivo* immunological reactions, as well as the capacity to carefully regulate micelle size and form by careful management of the hydrophilic/lipophilic balance, are additional appealing characteristics. To help direct medications to specific bodily regions or fluorescent tags to track the fate of the micelle in the body, the micelle corona may be embellished. Due to their tiny size, polymeric micelles were also able to obtain high drug concentrations in tumor and inflammatory tissues [6,61].

Due to its hydrophilicity and biocompatibility, poly(ethylene glycol) (PEG) is the most frequently employed polymer as a hydrophilic micelle corona [62]. Additionally, PEG forms a steric barrier that reduces the binding of opsonin proteins to micelle surfaces, extending the duration that micelles circulate in blood [62]. Due to the substantial dilution that occurs following intravenous administration, polymeric micelles have higher stability against dilution compared to surfactant micelles because they have a lower CAC. The unusual architecture of polymeric micelles, where hydrophobic medicines are integrated into the hydrophobic core leading to a remarkable enhancement in their water solubility, is what spurs interest in them as drug delivery methods [6]. For instance, it was shown that adding curcumin to PEG-PCL-based micelles increased its water solubility by 25,000 times [6,63].

3.8. Solid lipid nanoparticles

The first generation of lipid-based nanoparticles is made up of solid lipid nanoparticles (SLN). They are colloidal in composition and mostly composed of solid lipids, which are biodegradable and of physiological origin. At room temperature, the lipids employed to create nanoparticles are solid and can incorporate both hydrophilic and hydrophobic medications [20,64]. They were created by Müller, Gasco, and Westesen at the beginning of the 1990s to provide advantages of lipid nanoparticles over liposomes and emulsions [65]. The aqueous phase of SLNs is distributed with solid lipids such as triglycerides, fatty acids, partial glycerides, waxes, and steroids ranging from 0.1 to 30% (w/w), which are stabilized by surfactants such as

phospholipids, poloxamers, sorbitan esters, etc. that are typically used in the concentration range of 0.5–5% (w/w) [66]. The typical SLN size is between 50 and 1000 nm [65].

For the delivery of pharmaceuticals and cosmeceuticals via SLN, the topical route continues to be the most common. SLN has several benefits over vesicular carriers, including the ability to shield active substances from chemical deterioration and metabolism following encapsulation, increased loading capacities for lipophilic moieties, regulated release, improved skin penetration, and retention [20]. The adhesiveness of SLN, which enables them to penetrate deeper layers of the skin, is principally responsible for improved skin permeation and retention. The lipid structure and SLN particle size contribute to adhesiveness. The SLN's lipids interact with the SC's lipids, disrupting them, and allowing the SLN to more easily pass through the SC [67]. *In vitro,* SLN skin penetration study was shown by Jensen et al. In this study, it was found that SLN was maintained on the SC, causing a depot to form in the top layers of the skin, which allowed the medication to be released from the reservoir [68]. SLN has been extensively researched to improve the administration of antifungal medications. Clinical trials have also begun for topical antifungal medications with SLN loading. By loading SLN with oxiconazole nitrate and evaluating the results clinically, Mahmoud et al. prepared SLN. This newly created gel system was clinically evaluated in 28 patients (NCT03823040), and the outcomes were contrasted with those obtained using a commercially available version of oxiconazole nitrate (Tinox® cream, Eva Pharma). When compared Tinox® cream, the clinical study demonstrated improved patient compliance with fewer side effects and superior clinical results [69].

3.9. Nanostructured lipid carriers

SLN been shown to be quite effective in treating skin-related fungus infections. Poor drug loading capacities, solid-state polymorphism changes that impact the storage stability of SLN, drug leakage during storage, and particle aggregation are some of their drawbacks [70]. To avoid these difficulties and to address the issues with the further modified SLN produced by Müller in 1999, nanostructured lipid carriers (NLC) have been created as the second-generation SLN [17,20]. Caprylic/capric triglycerides, mono-acyl glycerol, lauryl poly oxyglycerides, and other liquid lipids are mixed in different ratios with surfactants (concentration range between 1.5 and 5 % w/v) to make up the heterogeneous lipid matrix that makes up NLC [71]. After SLN synthesis, when the temperature gradually drops to room temperature, the solid lipid crystallizes in the aqueous phase. It's possible that this is a result of the supersaturation brought on by the

lower solubility at ambient temperature. As a result, the lipid matrix is rearranged, which causes drug leakage and restricted drug loading when it transforms into a lower energy form. However, the liquid lipid in NLC prevents crystal development, which lessens the solid lipid matrix's tendency to crystallize. In contrast to SLN, NLC inhibits drug expulsion and instability, which results in higher drug loading [17].

Recently, Na et al. created a film-forming system for dermatophytosis that is embellished with NLC that has been loaded with econazole (ECO-NLC-FFS). The Quality by Design methodology was used to optimize the formulation of econazole-NLC. According to *in vitro* skin permeation research, econazole NLC gel and ECO- NLC-FFS had more skin penetration than the commercially available form of the drug (Ecora® ointment). The skin distribution of formulations containing the dye coumarin–6 was visualized by the use of fluorescence microscopy. Due to increased adherence compared to econazole gel, ECO-NLC-FFS demonstrated a larger fluorescence distribution in the SC than econazole NLC gel formulation. Eight hours after application, ECO-NLC-FFS had a 3.3-fold larger zone of inhibition for *T. rubrum* than Ecora® ointment did as a result of *ex vivo* antifungal activity [72].

3.10. Nanoemulsion

A colloidal dispersion of oil, water, surfactant, and co-surfactant is called a nanoemulsion, which is a transparent or translucent system that is kinetically stable yet thermodynamically unstable [73]. For topical medication administration, nanoemulsion droplet sizes between 50 and 200 nm are preferred [73]. Mini-emulsions, submicron emulsions, and ultrafine emulsions are other names for nanoemulsions. According to their composition, nanoemulsions can be divided into three groups: bi-continuous, water in oil, and oil in water. The nanoemulsion droplets can be categorised as neutral, positive, or negative depending on how charged they are. In comparison to conventional emulsions, nanoemulsions have several benefits, including excellent stability, enhanced interfacial area, and the capacity to increase the solubility of pharmaceuticals, which increases their bioavailability [74]. Lipids from the stratum corneum are extracted as a result of the nanoemulsion droplets' interactions with the SC. This lipid extraction breaks through the SC barrier, enhancing skin penetration. In addition, nanoemulsions cause keratin denaturation, which results in further intracellular penetration [17].

In-depth research has been done on nanoemulsions to improve antifungal medication delivery. Terbinafine HCl-loaded nanoemulsion was created by Karri and colleagues to treat

dermatophytosis brought on by *T. mentagrophytes*. High pressure and high-speed homogenization were used to generate the terbinafine HCl-loaded nanoemulsion, which was then loaded into the carbomer gels known as gel-p and gel-s. Gel-p showed a 1.61-fold increase in permeability compared to gel-s and a 2.5-fold increase compared to Lamisil® cream when tested *in vitro* on hog ear skin. Gel-p and Gel-S effectively treated the dermatophytosis produced by *T. rubrum* in rats after 3 days of topical administration, whereas Lamisil® took 14 days [75]. Amphotericin B loaded nanoemulsion was developed and optimised by Husain et al. The improved nanoemulsion was then added to Carbopol gel at a concentration of 1% w/w. For nanoemulsion loaded into gel and nanoemulsion alone, respectively, *in vitro* penetration in rat skin demonstrated 3.9 and 3.5-fold greater flux compared to drug solution. Rhodamine 123 dye was used in the CLSM test to visualize the skin penetration of the nanoemulsion through the rat skin. The amphotericin B nanoemulsion gel was loaded with the dye. In comparison to the plain dye solution, the fluorescence images for formulations based on nanoemulsions exhibited greater penetration in the SC, epidermis, and dermis areas. Comparing amphotericin B solution in dimethyl sulphoxide to amphotericin B nanoemulsion gel, *in vitro* antifungal activity revealed a 2-fold greater zone of inhibition for the latter over the amphotericin B solution [76].

3.11. Dendrimers

Three-dimensional hyperbranched and globular macromolecules known as dendrimers—from the Greek word "dendron," which means "tree"—have several branching arms extending from a clearly defined central core [77]. Due to its distinctive characteristics, including as structural flexibility, multi-valency, and low polydispersity, dendrimers have a significant promise for the administration of antifungal drugs [77]. Drugs that are hydrophobic can be encapsulated in dendrimer branches to increase their solubility in water. In fact, at pH 7.4, poly(propylene imine) dendrimers increased the solubility of AmB in water by 25 times [6]. Additionally, dendrimer ionised surface groups can be utilized as focal points to attach targeting or imaging moieties or to include ionised medicines through ionic interactions [77]. Given the dearth of research in this area, dendrimers' potential as efficient antifungal drug delivery methods has not yet been fully explored. The majority of these investigations used simple dendrimer modification to build specialized drug delivery systems. Muramyl dipeptide-conjugated poly(propylene imine) dendrimers (MdPPI) targeting macrophages were evaluated for AmB administration [78]. When compared to Fungizone® and AmBisome®, AmB loaded into MdPPI

demonstrated a high macrophage targeting capacity and higher or equal antiparasitic effectiveness against infected J774A.1 macrophage cell lines and infected mice. To improve AmB targeting to antigen-presenting cells, peptide-conjugated polyamidoamine dendrimers (PADRE-PAMAM) were also employed (APC, macrophages and dendritic cells) [79]. According to *in vivo* experiments, PADRE-PAMAM increased AmB's effectiveness by 83 percent and its targeting to APC by ten times, resulting in a decrease in AmB dose and toxicity. Clotrimazole was loaded into generation 2 (G2) and generation 3 (G3) PAMAM dendrimers with amine (PAMAM-NH_2) or hydroxyl surface groups (PAMAM-OH) to increase its aqueous solubility and effectiveness [80]. Compared to PAMAM-OH dendrimers, PAMAM-NH_2 dendrimers demonstrated better drug solubilization. The antifungal activity of drug-loaded PAMAM-NH_2 was 4-32 times more than that of pure drugs, and G2 PAMAM-NH_2 was the most effective dendrimer. Ketoconazole-loaded PAMAM-NH_2 G2 dendrimers showed comparable improvements in medication water solubility and antifungal activity (up to 16-fold) [80].

4. Future Perspectives

4.1. Microneedles

To restore skin function without harming the epidermis, microneedles are intended to be painless therapies. These are made using a variety of processes, including micro shaping, micro molding, and microfabrication. It has a number of potential advantages, such as avoiding pre-systemic metabolism, quick action, suitability for a wide range of medications, reducing needle anxiety, and simplicity in drug administration. With the use of this technique, it is possible to get around problems with traditional formulations such as poor water solubility, limited permeability, low bioavailability of hydrophilic medicines, repeated administration, and systemic side effects [21,81]. Gill and colleagues compared microneedle dimensions to those of normal hypodermic needles to examine the impact on pain. Comparing microneedles of all specifications to traditional hypodermic needles, the discomfort level was much lower (5–40%). The shape of the microneedles, such as their breadth, thickness, and tip angle, had no discernible impact on pain. The number and length of the needles, however, are crucial factors in determining the sensitivity and intensity of the pain. It was discovered that pain intensity was greatly lowered when the density and length of the microneedles were reduced. With a 10-fold increase in microneedle density, the pain score increased by just over a factor of 2. Similar to this, the pain score increased seven times with a threefold increase in microneedle length [21].

The use of microneedles and piezoelectric inkjet dispensing offers the chance to improve drug formulation activity. By using a piezoelectric inkjet printing technique, Boehm and colleagues created biodegradable polymer microneedles that were coated in voriconazole and made of polyglycolic acid. The antifungal potential of the created formulation was compared to that of conventional microneedles against various experimental microorganisms (Candida albicans, Escherichia coli, and Staphylococcus aureus). While unmodified devices proved unsuccessful against the testing strains, the produced microneedles demonstrated higher antifungal effectiveness [21]. Miconazole was effectively loaded onto polymeric microneedles produced from Gantrez® AN 169 BF using piezoelectric inkjet printing technology. Dimethyl sulfoxide was chosen as the solvent in this method to enhance the penetration of the antifungal medication. The created Gantrez® AN 169 BF Microneedles with miconazole in them demonstrated good antifungal ability against *Candida albicans* [82]. Despite solid microneedles being the most basic type for transdermal medication delivery, solid microneedles require skin preparation before use. However, the hollow microneedle has a significant drawback because it allows for a smaller volume of fluid to be infused into the skin. This drawback can be overcome by partially retracting the skin before the medication treatment.

4.2. Electroporation and Iontophoresis

By using sporadic electric pulses that briefly affect the permeability of cell membranes, this biophysical-phenomena improves the transdermal penetration of medications. "Electrochemotherapy" is the process of applying high-voltage electrical pulses to make chemotherapeutics or DNA molecules more permeable to the skin [21]. An especially intriguing alternative to increase medication permeability is electroporation. More recently, Novickij and colleagues studied the effects of fluconazole, terbinafine, and naftifine on the skin penetration of pulsed electric fields (2.5-25 kV cm^{-1}) at a pH range of 3.0-9.0. Higher levels of *C. albicans* inactivation at low pH and greater sensitivity to terbinafine and naftifine, to which the strain was initially resistant, were produced by pulsed electric fields [83]. Although the technology of electroporation has a great deal of potential to increase skin permeability, it is challenging to manipulate the targeted cells and administer treatments to those cells in the post-electroporation stages. Microcapillary electroporation may be used in conjunction with a micropipette to overcome these challenges or it may be combined with a particular physical, chemical, or biological support to increase specificity and therapeutic promise.

Iontophoresis is a technique that uses a low-intensity electric current to let medications penetrate the skin more effectively. In order to improve drug penetration over the skin, the drug is placed under an electrode that has the same charge as the drug. This causes a repulsive force between the like charges. This method is powered by the application of electric potential, which provides it with distinctive characteristics. Consequently, it is appropriate for the controlled dosage form applications [21]. Recently, voriconazole penetration and anti-fungal capabilities were examined by Kalkanci and colleagues using an iontophoresis-assisted fungal keratitis model. The outcome demonstrates that, in comparison to the native medication followed by topical administration, the Iontophoresis-assisted group demonstrated superior antifungal efficacy against the experimental strains of *F. solani* keratitis (4-log reduction) and *C. albicans* keratitis (5-log reduction). Additionally, it was discovered that tissue from animal groups that received iontophoretic treatment had the greatest voriconazole levels [84]. Iontophoresis has also been found to be efficient in removing deep-skin fungal infections when used in conjunction with permeation enhancers. In light of this, Monti and colleagues recently investigated the efficacy of iontophoresis in trans-lingual nystatin permeation with and without permeation enhancers such cetylpyridinium chloride and Polyoxyethylene sorbitan monooleate. The results showed that compared to ordinary iontophoresis, cetylpyridinium chloride, and iontophoresis significantly increased the permeability of the cow hoof membrane to the medication [85]. The selection of medications based on the skin's electric potential, which favors cationic pharmaceuticals, is one of the limitations of transdermal iontophoresis that still has to be overcome for successful clinical applications. Second, a significant problem that must be resolved for long-term usage is skin irritability.

4.3. Concomitant super-adsorbent antifungal socks

Some of the topical antifungals that are now on the market eliminate fungi on keratin without causing significant systemic effects. However, daily treatment is necessary since bathing and dermal cell turnover cause the drug to leave the skin. Once-daily antifungals, allylamine derivative (Lamisil®), and bifonazol (Mycospor®) are examples of often chosen topical treatments. Adverse responses to both drugs have been reported by the Pharmaceuticals and Medical Devices Agency in 1-1.8 percent of users, with contact dermatitis being the most frequent occurrence. For a 4-week course of treatment, topical antifungals have been reported to be successful in 60.2% of patients with tinea pedis; conversely, topical treatment alone has been

ineffective in 50% of the patients. [86]. Treatment for tinea should be applied topically over a period of 4 to 6 weeks. It is important to emphasize the need to completely dry these regions after washing them and to use post-fungal medications as a preventative measure [87]. To underline, there are numerous recurrence prevention strategies required because topical treatment alone is insufficient to alleviate tinea pedis. In addition to pharmacological treatment, the most crucial strategy is to periodically dry the affected area to prevent excessive dampness. From these views, numerous recommendations were made, including how to promote patient compliance and ensure treatment adherence by administering medications in wearable containers like socks [5], so that keep an extended contact with antifungal agents in a convenient way [1]. The purpose of this perspective is to simplify the utilization of a combination of physical qualities (such micro-capillary phenomena) of the super-adsorbent capability of methacrylate-carboxy-methylcellulose derivative with some modifications in order to assist the antifungal effectiveness [88]. Additionally, this viewpoint seeks to improve convenience, compliance, and the required dose of antifungal medications, hence reducing their hepatic adverse effects. It is worthy to mention that the abovementioned novel point of view is still under focus investigations in our laboratories in Egyptian Russian University, which are expected to reveal promising outcomes.

5. Conclusion

According to the aforementioned data collection regarding the delivery of antifungals for the management of tinea pedis, the following important conclusions have been emphasized.

The causative fungal infections, their pathogenesis, as well as categorization of well-known antifungals were detailed. Various effective methods of delivering treatment of tinea pedis have also been mentioned, including conventional and advanced delivery systems, with the challenges that need to be considered in terms of systemic side effects and possible resistance/relapse of infection.

Consequently, advanced drug delivery for these antifungals is raised from this crucial point of view. It is important to note that all of these cutting-edge delivery systems were developed with the goal of improving the efficacy and safety of antifungal therapy by increasing the drug's penetration into the skin and lowering the risk of systemic side effects.

Furthermore, the possible future direction and perspectives in treatment optimization and recurrence prevention of such harsh fungal infection have been briefed comprising microneedles, electroporation, iontophoresis, and concomitant super-adsorbent application within socks.

However, several limitations and challenges have been noted to be associated with the use of advanced delivery systems for the treatment of tinea pedis. Limited clinical research, formulation optimization, regulatory approvals, manufacturing scalability, cost-effectiveness, safety, and stability issues were some of these limitations. Further, focus and effort are needed for maximizing the effectiveness of antifungal drugs alongside minimizing side effects and most importantly, recurrence rates of tinea pedis, for better improvement and enhanced quality of life of people.

Conflict of Interest

The authors declare that they have no competing interests.

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