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Prospective Nanotechnology-Based Strategies for Enhanced Intra- and Transdermal Delivery of Antifungal Drugs

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Abstract
Topical therapy of superficial fungal infections allows the prevention of systemic side effects and provides drug targeting at the site of disease. However, an appropriate drug concentration in these sites should be provided to ensure the efficacy of such local treatment. The enhancement of intra- and transdermal penetration and accumulation of antifungal drugs is an important aspect here. The present overview is focused on novel nano-based formulations served to improve antimycotic penetration through the skin. Furthermore, it summarizes various approaches towards the stimulation of drug penetration through and into the stratum corneum and hair follicles, which are considered to be promising for the future improvement of superficial antifungal therapy as providing the drug localization and prolonged storage property at the targeted area.

Introduction

Over recent decades, there has been a significant spread of fungal diseases [1, 2]. Dermatophytes are one of the most common etiological agents of skin mycoses [3, 4]. The development of various antifungal agents has already significantly increased the ability to combat skin mycosis. However, the search for new approaches towards the enhancement of antifungal therapy efficiency remains relevant. Over the last decades, the elaboration of different strategies aimed at optimization of the antimycotic action while minimizing the side effects associated with its absorption through the skin [5–9]. Novel drugs and delivery systems that improve the safety of mycosis treatment were proposed [10–13]. It is known that the nature of drug carriers used in topical preparations significantly affects the speed and the depth of drug penetration into and through the skin [14, 15]. Systems such as micelles, liposomes, submicron emulsions, and solid lipid or polymer nanoparticles have been suggested as antifungal carriers with enhanced percutaneous absorption ability [9, 10, 12, 13]. Although due to the skin's barrier functions, their penetration into the healthy intact skin

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remains limited in some cases. These systems can be successfully applied for drug delivery through the damaged skin in order to treat diseases such as atopic dermatitis or superficial mycoses.

Aside from appropriate carrying system development, there are a number of chemical, biochemical, and physical approaches are elaborated in order to improve the efficacy of transdermal drug permeation [16]. Different solvents, surfactants, and peptides may interact with the lipid matrix of the stratum corneum and increase its permeability for drug molecules [17–21]. Various physical methods such as stripping, iontophoresis, ultrasound, intradermal injection and microinjection, and thermal ablation are successfully applied to increase the transdermal delivery of the drug either alone or immobilized into the carriers [16, 22]. This review is focused on the use of different nanoparticles for drug delivery through and into the skin in terms of treatment of fungal infections and on the application of various physical and chemical influences enhancing the transdermal drug penetration that could be adopted for use in antifungal therapy.

Basic Principles of Antifungal Therapy

Etiotropic treatment of fungal infections is based on the usage of systemic or topical antifungal formulations [6, 7]. Systemic therapy is usually applied for the treatment of either deep mycosis or extensive/chronic superficial ones as it may cause systemic toxicity [23]. Systemic antifungals such as Amphotericin B formulations, echinocandins, and triazoles often cause hepatic toxicity [24]. The other common adverse effects include nephrotoxicity, neurotoxicity, haematological side effects, and very rarely, fever, chills, arrhythmia, hypotension, and respiratory distress [25]. Moreover, systemic therapy does not allow for immediate local accumulation of high antifungal drug concentrations.

Common superficial fungal infections are treated with topical medications which provide the accumulation of antifungal drug in skin [8]. Such therapy allows the prevention of the systemic side effects mentioned above. Furthermore, it enables the avoidance of the first-pass liver effect. The main adverse effects caused by the topical antifungals are associated with allergic reactions in skin (dryness, redness, burning, itching, and irritation).

To be effective against superficial fungal infections, an antifungal agent must reach the stratum corneum, hairs or nails to target the pathogen in adequate concentration, and persist at this location long enough to inhibit the fungal pathogen. The achieved intradermal drug concentration depends on administration route, duration of the contact, and ability of the antifungal molecules to penetrate into the tissue [8]. The latter is defined by the molecular weight, viscosity, hydrophobicity, and acidity of the formulation. Although the topical antifungal drugs cover a broad range of therapeutic indications and have various molecular structures, they are generally highly lipophilic and have poor aqueous solubility (e.g., clotrimazole, miconazole, itraconazole, terbinafine, etc.) and therefore capable of penetration into the lipidic stratum corneum [8]. The rate and extent of delivery here should be appropriate to achieve the required local therapeutic concentration. Moreover, large antifungal molecules show poor transdermal penetration, even if they are lipophilic. Poor penetration into the skin limits local bioavailability and drug efficacy and thus causes the relapse of infections and requires frequent administration.

Furthermore, regardless of the formulation type, the penetration of topical agents in hyperkeratotic lesions is often limited [6, 15]. For this reason, the majority of modern transdermal drugs used in their treatment do not require removal from the infected area after their application.

By this means, the topical antifungal drug delivery provides a major challenge for its optimization. The skin represents a target for the therapy, as well as a principal barrier for transdermal delivery of the topically applied drug.

Penetration Routes of Topically Applied Drugs

Topically applied drugs penetrate through the skin via either transepidermal or transappendageal route. The transepidermal pathway involves the transport of molecules through the stratum corneum, which represents a multilayered and multicellular barrier. It provides a protective barrier function against external actions [16, 26]. Hydrophilic or polar solutes penetrate through corneocytes (intracellular route), while lipophilic or non-polar ones can diffuse via intercellular spaces including continuous lipid matrix. Despite major research and development efforts in topical antifungal delivery systems and their advantages, design of a delivery system allowing one to overcome the limitations associated with transepidermal penetration remains actual.

The alternative, transappendageal delivery route involves cargo permeation via sebaceous and sweat glands, hair funnels, and follicles. The latter can serve as an efficient reservoir extended deep into the skin tissue with systemic drug uptake provided by a dense capillary network of the dermal vasculature [27, 28]. In order to improve the penetration of topically applied drugs through these different skin sites, various transdermal drug delivery systems (nano- and microcarriers) and enhancement strategies (physical, chemical and biochemical enhancers) are elaborated.

Particulate Intra- and Transdermal Delivery Systems

Nano- and micron-sized carriers have been successfully used to increase penetration of drugs or vaccines into the skin, to target them to the specific areas of skin, as well as to control the subsequent drug release in situ. In particulate formulations, drug penetration into skin is governed by physico-chemical properties of the carrier such as size [29], surface area [30], charge [31], pH, and solubility [32], and depends on the chemical composition of the carrier and solvent nature as well [14, 33, 34]. Among these factors, the influences of the size and the charge have been widely studied. Particles of approximately 300–600 nm in size exhibit the deepest penetration into hair follicles, where they can be stored for a significantly longer period than in the stratum corneum [35]. Moreover, the skin penetration and biological activity depend also on the morphology of nanoparticles [36], biological adhesiveness [37], and degradation in vivo [38].

Various carrying systems were proposed for improving the bioavailability, and sustained and controlled release of the loaded drug. Lipid-based particles [39–41] and nanoemulsions [42] are the most well-established ones. The usage of these systems allows the maintaining of the localized therapeutic effect and provides the enhancement of the drug accumulation in different skin sites. Nevertheless, some difficulties arise when liposomes are applied due to their low stability. Biodegradable polymeric [43–45] and inorganic porous [46–49] carriers represent the alternative encapsulation system that allows one to increase the penetration/permeation of drugs throughout the skin appendages. The other approaches proposed for transdermal drug delivery include the use of quantum dots [50], liquid crystalline nanoparticles [51], silk fibroin nanocarriers [52] etc.

Nanocarriers for Intradermal Permeation and Antimycotic Activity Enhancement of Topical Antifungals

Transdermal delivery of nanoparticles has gained a great interest in topical antifungal therapy provided by high drugs penetration rate and controllability of gradual or triggered encapsulated payload release. Active development of various nano- and micron-sized systems for transdermal drug delivery opens up the possibilities for antifungal therapy improvement [53]. Serving as a local (isolated) drug depot and providing a mechanism for controlled release, such systems can deliver high topical concentrations of drugs without pronounced systemic spread [54]. Thus, systems such as polymeric films [55], nano- and microemulsions [56], vesicular carriers [57] (including liposomes [58], ethosomes [59], transethosomes [60], and niosomes [61]), solid lipid [62] and polymeric particles [63], and porous inorganic carriers [64, 65] were proposed and investigated for antifungal agents' penetration promotion.

Ethosomal gel of econazole nitrate was found to have outstanding potential to serve as a topical delivery system, enabling controlled drug release, providing a better antifungal effect. Optimized ethosomes with vesicle size of 202 ± 5 nm and entrapment efficiency of 81% were formulated as Carbopol gels with varied permeation enhancers and compared with liposomal and hydroethanolic gels [66]. Nystatin antifungal activity against *Candida albicans* microorganism was enhanced by its encapsulation into nanostructured lipid carriers as compared to the drug solution and to commercially available Nystatin cream [67].

Deformable membrane vesicles preparation for topical delivery of griseofulvin as a potential system for dermatophytosis treatment was proposed [68, 69]. The systems based on solid lipid nanoparticles with a controlled release property [70] and nanostructured lipid carrier [71] were formulated for terbinafine hydrochloride. Solid lipid nanoparticles were also applied for Amphotericin B immobilization [72]. Enhanced antifungal activity with low skin irritation was demonstrated as a result of their topical deposition. Dendrimer-based carriers were tested for Amphotericin B delivery showing a high antiparasitic activity in vitro against parasite-infected macrophage cell lines and in vivo on infected mice due to the ability of drug targeting to macrophages [73]. Synergistic fungicidal effect of low-frequency and low-intensity ultrasound combined with a treatment of Amphotericin B-loaded PLGA nanoparticles against *C. albicans* was demonstrated in vitro [74].

Physical and Chemical Strategies to Enhancement of Intra- and Transdermal Drug Delivery

Aside from the development and optimization of antifungal particulate delivery systems, significant efforts are expended on the elaboration of novel approaches to increase skin permeability and therefore to enhance transdermal drug delivery [16]. These strategies can be divided into chemical (usage of special solvents or surfactants), biochemical (the use of metabolic inhibitors), and physical approaches. There are plenty of physical methods, commonly requiring the use of special devices, which allow one to significantly expand the spectrum of drugs that can be administered transdermally (including water-soluble molecules and macromolecules). Such methods include stripping techniques, sono- or iontophoresis, heating, electroporation, mechanical abrasion, thermal ablation, and microneedle usage [22].

The most established and less invasive methods for enhanced drug penetration through the skin barrier involve either removal of outermost skin layer achieved by the peeling tape (tape stripping) or usage of various chemical enhancers, such as dimethylsulphoxide, propylene glycol, ethanol, oleic acid, EDTA, sodium glycocholate and related cholates, Tween 20 (a non-ionic polysorbate surfactant), Brij 35 (polyoxyethylene lauryl ether), saponins, and bile salts [75–77]. Generally, penetration enhancers are small molecules that temporarily soften the bond between the adjacent cells of the corneal epithelium (EDTA) or increase the fluidity of membranes (cholates) [76]. It was demonstrated that chemical enhancers can increase dermal penetration of various antifungal drugs. Thus for example, application of 50% ethanol and 50% isopropyl myristate formulation containing 5% oleic acid significantly enhanced in vivo availability of topical terbinafine [78]. Enhancement of antimycotic delivery using various solvents (dimethyl sulfoxide, methanol), enzymes, hydrogen peroxides, etc. were demonstrated for onychomycosis treatment as well [79, 80].

Moreover, improved skin permeation and accumulation of antifungals (ketoconazole, terbinafine) under combined application of chemical enhancers (essential oils, such as eucalyptus and nigella, or alcohols, such as nerolidol) and carrying vehicles were shown [81–83]. Different pretreatments such as hair plucking [84], hot or cold waxing [85], and cyanoacrylate stripping [86] are used to create channels in the skin before the drug application. In terms of antifungal treatment, the pretreatment techniques are represented by nail drilling proving the formation of tunnels throughout the nail plate to augment delivery and efficacy of topical antifungals to the site of onychomycosis [87].

Ultrasonic treatment (sonophoresis, phonophoresis) is one of the less invasive physical enhancers [88, 89]. It is effectively utilized for enhanced intra- and transdermal delivery of bioactive molecules [90] and particulate systems [47]. Such ultrasonic treatment of skin at frequencies higher than 0.7 MHz gives rise to pressure changes in the medium, forming cavitation bubbles inside the inherent cavities represented by hair follicle shafts and sweat glands [91]. Bubbles oscillation in the follicles push the particle suspension down the follicle. It was shown, that application of 1 MHz ultrasound at a power density of 2 W/cm^2 did not induce adverse effects on rat skin [92]. Prolongation of the enhanced permeability time window allows for the stepwise application of drugs or vaccines [93]. Ultrasonication can also be coupled with other methods. Thus, enhanced transdermal delivery of solid nanoparticles by simultaneous application of ultrasound and various chemical enhancers was demonstrated [94, 95].

Iontophoretic delivery is another effective non-invasive approach for therapeutic drug delivery [96, 97]. Generally, transdermal iontophoresis creates a small electric current (0.1–0.5 mA/cm^2) in the skin to induce transdermal molecular transport, enhancing drug transportation by electrorepulsion and electro-osmosis. At neutral pH, the skin is negatively charged and cation-permselective [98]. Thus, the current passage causes a convective solvent flow from anode to cathode, facilitating cation transport and enabling the enhanced transdermal transport of neutral, polar solutes. Relative electrorepulsion and electro-osmosis effects depend on the physico-chemical and electrical characteristics of the membrane and permanent. In addition, the negative charge of the skin can be reduced, neutralized, or even reversed by the iontophoresis of certain cationic, lipophilic species [99].

Simultaneous application of sonophoresis and iontophoresis is also discussed [100–102]. The synergistic effect of their application is demonstrated for transdermal delivery of various cosmeceutical drugs using a Franz diffusion cell. Such a combined strategy is advantageous as it declines the energy density and thereby reduces the skin irritation [100].

Phono- and iontophoresis were successfully applied for transungual delivery of antimycotics (e.g., terbinafine and ciclopirox) allowing the significant enhancement of their penetration into nail plates [103, 104]. Heating is another physical approach allowing one to improve the delivery profile of topical medicaments [105, 106]. The

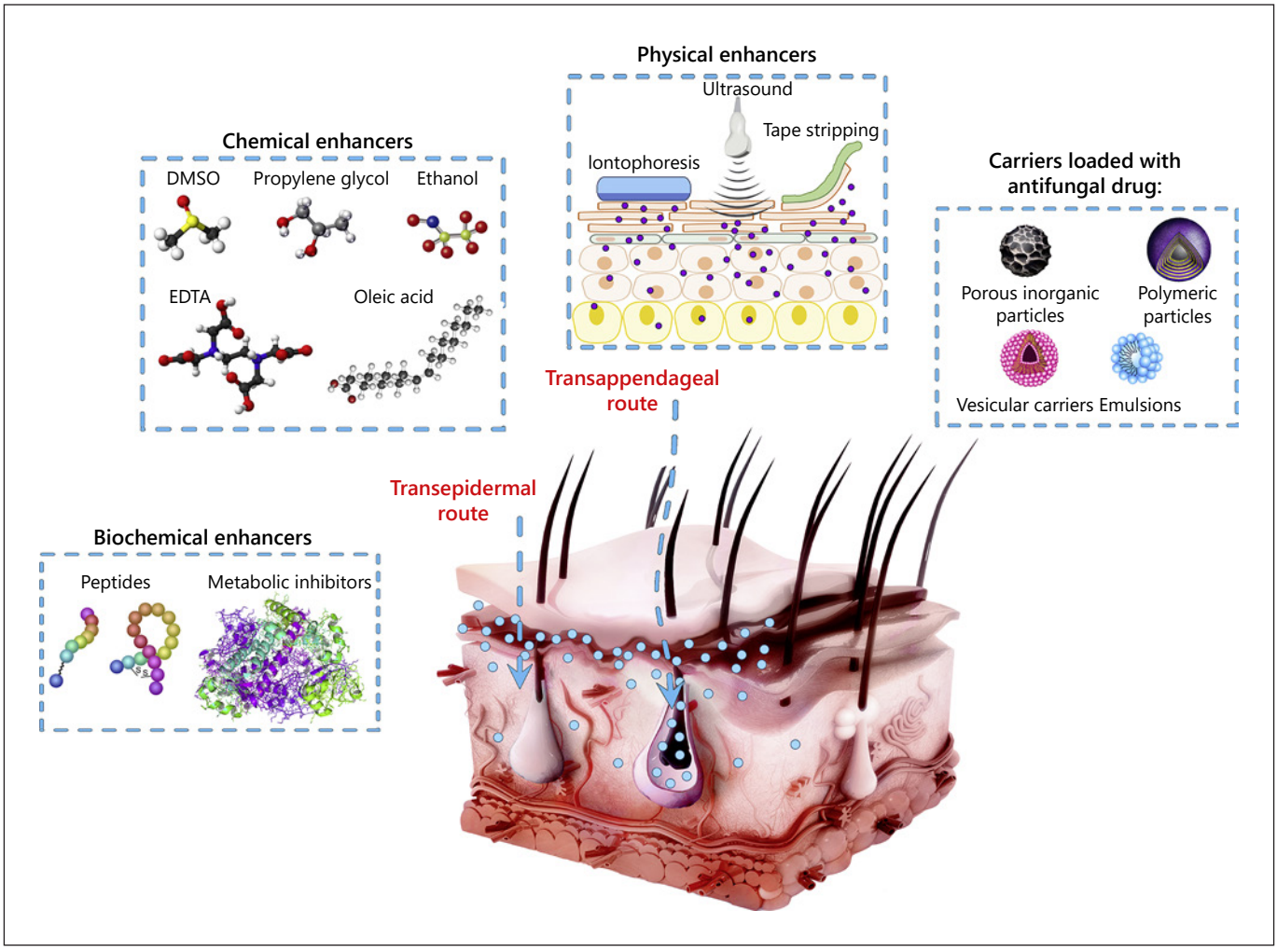

Fig. 1. Promising strategies for enhanced intra- and transdermal delivery of antifungals. Different nanoparticles that are used to deliver antifungal drug through and into the skin, and various physical, chemical, and biochemical enhancers that can be adopted for use in antifungal therapy.

heat-enhanced effect is generally attributed to both an increase in drug diffusion in the vehicle and skin, and to an increase in skin lipid fluidity. Furthermore, the skin temperature rise increases its blood supply that also plays an important role in enhancing the transdermal delivery of a topically applied compound [106].

Microporation is one of the most common invasive physical methods applied for the skin barrier removal. Such a method allows the formation of micropores or even microchannels in the skin by the usage of microneedles fabricated of different materials and geometries [107, 108] or laser and radiofrequency ablations, which allows for further transferring of water-soluble molecules and macromolecules [106, 109], as well as particulate systems [110–114]. Such techniques enable the delivery of much larger molecules with much greater fluxes into the skin than other methods and therefore are extensively developed for delivery of insulin [115], hormones [116], vaccines [117], etc.

Although the formation of micron-scale holes within the stratum corneum is a prospective and successfully applied approach towards the transdermal drug transportation, its adaptation for antifungal treatment of skin appears unpromising as this procedure is invasive. Furthermore, it should be mentioned here that microneedling treatment results in the expression of various genes related to epidermal differentiation, inflammation, and dermal remodelling [118]. Thus, microneedles possess own pharmacological activity which may interact with the antimycotic compound.

Combined application of the most efficient physical methods with various nanocarriers was also investigated demonstrating its superiority in drug penetration enhancement compared to their single use [119]. Thus for example, a particulate drug delivery system based on the use of porous biodegradable carriers appeared beneficial when applied topically together with sonophoresis [47, 120]. Meanwhile, no evidence of systemic toxicity enhancement was indicated. The proposed system provided the transportation of immobilized drug along the entire depth of hair follicles, its intrafollicular accumulation, and prolonged storage. Such an approach was successfully applied for transdermal delivery of griseofulvin antifungal drug as well [65].

Conclusion

Encapsulation of antifungal drugs into various nano- and micron-sized carriers allows for further enhancement of mycosis treatment, particularly therapeutic activity and prolonged effect while enabling triggered release by specific chemical and/or pathophysiologic stimuli. Furthermore, the usage of such systems allows the maintaining of the localized therapeutic effect and provides the enhancement of the drug accumulation in skin. By increasing the efficiency of transdermal delivery of antimycotics, one can enhance its therapeutic efficacy.

In addition, the adaptation of different chemical, biochemical, and physical delivery-enhancing techniques for the use in antifungal treatment renders promising. These methods can allow one to overcome challenging limitations such as low bioavailability of many peroral medicaments and narrow range of choice of the antifungal formulations. Thus for example, plasters, chemical enhancers, iontophoresis, and ultrasonication may open up new perspectives here as they provide the transdermal transportation of low-soluble molecules and macromolecules. The usage of various chemical enhancers, such as dimethylsulphoxide, propylene glycol etc., alone or in combination with physical enhancers is a promising approach to be applied in dermatological practice as well as may provide localization and increased topical concentration of antifungal drug together with prolonged exposure at the targeted site.

Reporting here on the most interesting and prospective, from our point of view, strategies which either aimed at or can be adopted for optimization of topical antifungal drug delivery (Fig. 1), we hope to encourage other researchers to look beyond classical methods and put into practice the novel ones. However, it should be taken into consideration that despite potentially decreased drug toxicity due to increased skin targeting, extensive and accurate chronic toxicity studies should be done before the translation of any novel treatment method to humans.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Investigation and writing – Ekaterina V. Lengert and Yulia I. Svenskaya. Design of the figure – Ekaterina V. Lengert. Conceptualization – Yulia I. Svenskaya. Editing, reviewing, and improving the manuscript – Yulia I. Svenskaya, Ekaterina E. Talnikova, and Valery V. Tuchin. All authors have read and approved the final manuscript.

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