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Recent Advancement and Applications of Transdermal Patches having Antifungal Potential

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Abstract:

Most of fungi do not require any human interventions for their propagation, and are not harmful for humans. However, some fungal species are adventitious pathogens are can cause systemic, subcutaneous and superficial infections. There are various synthetic chemical classes with potent antifungal agents. Polyenes, azoles, allylamines, morpholines and some antimetabolite drugs have been used as antifungal agents over decades. Despite the availability of good number of antifungal agents, worldwide emergence of drug resistance against existing antifungal agents is a major challenge for healthcare industry, warranting novel formulations to tackle the situation. Transdermal patches are comparatively novel formulations that can address limitations associated with traditional drug delivery systems. Transdermal patches provide controlled release of drugs, hence can avoid systemic side effects. Transdermal patches offer several advantages over oral antifungal drugs. Oral antifungals are absorbed into systemic circulations and cause numerous side effects. Transdermal patches can also enhance patient adherence to the treatment regimen, as they require less frequent replacement compared to other methods. The review focused on recent innovations and research on antifungal transdermal patches.

Key-words: Fungal infection, Transdermal Patches, Applications

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Introduction

Fungal infections were used to be rare, however, changes in lifestyle and emergence of chemotherapy has now led to increase of fungal infections at alarming rates. People undergoing chemotherapy, recipients of organ transplant and patients of HIV are most susceptible population for fungal infections (Dixon *et al.*, 1996). Most of the infectious fungal species are endemic in tropical areas, but few species may invade other regions with immigrants with long incubation period (Hay, 2006). Vaginal yeast infections, nail infections and ringworms are most common fungal diseases. Some fungal infections may proved to be deadly in hospitalized patients, such as *Candida auris* infections (CDC, 2024).

Current Treatment Approaches

Superficial fungal infections can be easily managed by topical agents such as tolnaftate, undecylenic acid, benzoic acid, ciclopirox olamine and butenafine. Tolnaftate is effective topical agent against infections of *Tinea corporis* and *Tinea cruris* (Tripathi, 2019). Ciclopirox olamine is comparatively a new drug with better effectiveness against *Tinea*

infections. It is also effective against all clinically relevant species of *Candida*, moulds, yeasts and dermatophytes (Sonthalia *et al.*, 2019). A number of antibiotics, antimetabolites, azoles and allylamine drugs are available for management of invasive drug infections. Polyenes represent oldest synthetic antifungals, that are been used from past 7 decades. However, only Amphotericin B and Nystatin are still in use (Chandrasekar, 2011). Echinocandins are semi-synthetic antifungals with good activities against *Candida* and *Aspergilus* species. Azoles are serving mankind in managing fungal infections from over last 40 years. Earlier imidazoles were having limitation for treatment of only superficial fungal treatments, however, trizaoles such as fluconazole and itraconazole have broad range of activity (Allen *et al.*, 2015). Fluconazole still remains a cost-effective drug for treatment of various fungal infections, including cryptococcosis and candidiasis. Itraconazole exhibits good activity against *Aspergillus* species (Zonios & Bennett, 2008). Despite the availability of good number of antifungal agents, worldwide emergence of drug resistance against existing antifungal agents is a major challenge for healthcare industry, warranting novel formulations to tackle the situation (Fisher *et al.*, 2018). Drugs with novel antifungal mechanisms that are currently under clinical trials include Fosmanogepix, Nikkomycin Z, T-2307, Ilicicolin H, AR-12, Acylhydrazones, VL-2397 and Olorofilm. Another challenge associated with conventional antifungal drugs are low efficacy, poor bioavailability and poor stabilities. Novel drug delivery systems such as transdermal patches, liposomal preparations and nanomedicine approaches have been extensively investigated to overcome challenges associated with antifungal drugs (Rao Khadam *et al.*, 2024).

Transdermal Patches

Transdermal patches were introduced to address the limitations of oral drug delivery systems. It consists of an adhesive patch meant for delivering medications in specific doses through skin and into the systemic circulation (Dhiman *et al.*, 2011). First generation transdermal patches include a plastic film dipped in drug solutions, directly applied over skin. The second generation patches resolved the problem of felling off from skin, by using adhesives, that not only serves as a glue for skin, but also hold drugs (Saroha *et al.*, 2011). The third generation patches were designed for delivering its affects to stratum corneum for better delivery of drugs, while also protecting deeper tissues. This was achieved by using microdermabrasion, thermal ablations, microneedles, cavitational ultrasound, electroporation and by use of chemical enhancers (Jatav *et al.*, 2011).

Components of a Transdermal Patch

Basic components of a transdermal patch includes a liner, drug reservoir, drug release membrane, contact adhesive and clear backing layer (Wang & Burgess, 2010). Release liner is a protective cover designed to be removed from patch prior to use. It should be compatible with the patch ingredient and should retain on the patch unless it is manually removed. Also, it should not retain any patch adhesive when detached. A reservoir compartment in transdermal patch serves as the storage area for the drug formulation, ensuring a controlled and sustained release of the active pharmaceutical ingredient (API) over time. It can be designed in various forms, such as a gel, liquid, or solid matrix, depending on the specific requirements of the drug and patch. The reservoir is usually enclosed between the drug release membrane and the backing layer, with the release membrane regulating the rate of drug diffusion into the skin. Drug release membrane is the layer that contains the drug, *i.e.,* drug particles are entrapped by release membrane o be released later when applied over skin. They should be flexible enough to move along with movement of patients. A transdermal patch should adhere to the skin to assure the efficacy of formulation. Specialized adhesive materials known as ‘pressure-sensitive adhesive or PSA’ materials are used to provide adhesion of the patch to skin while also allowing drugs to flow through it. PSA are classified into matrix, reservoir or membrane-controlled systems. PSA is an important component of transdermal patches as they affects important attributes such as drug delivery, flux through skin, as well as stability of the patch. A transdermal patch is backed by a backing layer that functions as an impermeable layer preventing the loss of drugs when stored. Backing layers can affect release behaviour and penetration of drug from the patches, and therefore, an important component in formulation of

transdermal patches (Lv *et al.*, 2016).

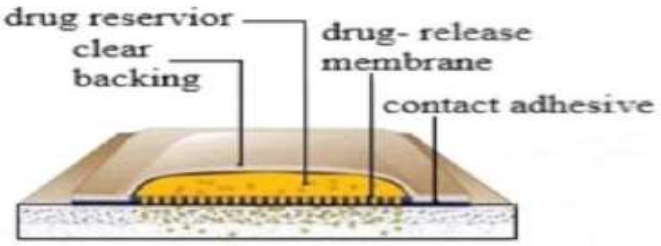

Fig. 1: Components of Transdermal Patches

Anti-Fungal Transdermal Patches Using Synthetic Drugs

Synthetic Antifungals

Antifungal drugs are agents with selectivity for fungal pathogens and have minimal toxicity to host. There are various synthetic chemical classes with potent antifungal agents. Polyenes, azoles, allylamines, morpholines and some antimetabolite drugs have been used as antifungal agents over decades (Dixon & Walsh, 1996). With advancement in technology, a number novel synthetic agents are currently under investigation. Novel synthetic polymer M451 have shown 97.8 to 99% of inhibition against various fungal species, suggesting good candidate for management of plant diseases (Tetz *et al.*, 2023). Zhang *et al.*, (2024) evaluated various novel analogues of azole for antifungal activities, and at least 6 new compounds presented promising results. In another study, 42 novel tetrazole compounds were evaluated for their antifungal activities, out of which, compound namely, '10h' showed best results (Ni *et al.*, 2023). These advancements highlight the potential of synthetic antifungals in overcoming current treatment challenges and expanding therapeutic options.

Development of Antifungal Transdermal Patches

Development of transdermal drugs began in 1980s, to overcome the limitations of oral drugs, such as first pass metabolism. Drugs such as scopolamine, nitrogycerin, clonidine. Oestradiol, fentanyl and nicotine were approved by FDA by year 1991 (Prausnitz & Langer, 2008). Studies for antifungal transdermal patches began in 1990s. Saettone *et al.*, (1991) conducted one of the earliest study for development of an antifungal transdermal patch for delivery of miconazole using topical polyvinyl alcohol matrices. The study pointed out need of good sin adhesive for appropriate delivery of antifungal agents through skin. In another study, different copolymer systems were tested for preparation of monolayer patches for delivery of miconazole drug (Minghetti *et al.*, 1999). Since then a number of synthetic drugs have been studied for delivery using transdermal patches.

Building upon these pioneering efforts, subsequent research has focused on the development of transdermal patches for specific antifungal drugs, optimizing formulations to enhance drug release, skin permeability, and therapeutic efficacy. In a study, Viswanatha *et al.*(2011) developed and evaluated fluconazole transdermal patches using different ratios of hydroxypropyl methyl cellulose and polyvinylpyrrolidone. In another study, Boddeda *et al.*, (2016) developed, evaluated and optimized transdermal patch for delivery of fluconazole drug. They used 2^2 factorial method for development of the patch. Advancements were also made in itraconazole transdermal delivery systems, particularly using nanoparticle technology. In a study, nanoparticles containing itraconazole were developed for transdermal delivery (Passos *et al.*, 2020). In a similar study, itraconazole nanoparticles were incorporated into transdermal patches and were evaluated for their physicochemical and biological characteristics (Rao *et al.*, 2020). Extending antifungal transdermal research, clotrimazole has been widely studied for its therapeutic potential in patch formulations. In a study, clotrimazole transdermal patches were prepared using solvent casting method and evaluated. One patch formulation namely, F1 was considered to be best amongst all patches developed (Joshi *et al.*, 2020). In a similar study, clotrimazole loaded transdermal nail patches were

developed for treatment of Onychomycosis. The prepared patches show potential drug release profile during *in vitro* studies, suggesting need of further studies for establishing the full potential of the formulation (Gaddime *et al.*, 2018). Another antifungal agent that was studied for treatment of onychomycosis is terbinafine. Amichai *et al.*(2010) developed iontophoretic patch for delivery of terbinafine drug. They evaluated and compared the efficacies of terbinafine delivered via conventional topical form and as transdermal patch, and found the latter to be more effective in management of onychomycosis.

Advantages of Antifungal Transdermal Patches over Traditional Delivery Methods

Transdermal patches offer several advantages over oral antifungal drugs. Oral antifungals are absorbed into systemic circulations and causes numerous side effects. These compounds have been reported to have multiple adverse effects including dry lips, alopecia, liver diseases, shortness of breath, cardiovascular irregularities and ocular problems (McManus & Shah, 2019), that can be avoided by using transdermal patch formulations. Oral antifungals are also prone to drug-drug interactions. Gupta *et al.,* 2018 in their work had mentioned numerous drug-drug interaction of oral antifungals and suggested use of topical antifungal formulations for superficial fungal infections if to avoid these interactions. Transdermal patches can also enhance patient adherence to the treatment regimen, as they require less frequent replacement compared to other methods (Patil *et al.*, 2022).Transdermal patches also offers several advantages over traditional topical delivery systems, including antifungal creams and pastes. The former are less messy and can provide sustained release of medications (Peng *et al.*, 2021). Unlike pastes and creams, antifungal transdermal patches only need to be replaced once every few days, improving convenience and compliance (Kumar & Parveen, 2023).

Recent Advances and Studies

Recent years have observed significant advancement in development and investigation on antifungal transdermal patches. The concept of nanotechnology has been incorporated for improvising drug delivery. (Kumar & Parveen, 2023) have recently developed nanoparticles loaded with clotrimazole and incorporated into transdermal patches. *In vitro* and *Ex vivo* studies suggested improved transdermal penetration and hence, higher bioavailability of drug. In a similar study, nanofibers loaded with ketoconazole drug was prepared using electrospinning method, to be used as transdermal patch. These antifungal nanofibers hold significant promise for the development of effective antifungal transdermal patches in the near future (Kadhim & Al-Edresi, 2024).

Microneedle patches have also been explored in recent years for enhancing delivery of antifungal drugs into deeper layers of skin. Arshad *et al.*(2024) developed microneedle patches for delivery of miconazole nitrate lipid nanoparticles. developed patches demonstrated good efficacy against *Candida albicans*, and healing of infected wounds. In another study, microneedle patches were developed for delivery of amphotericin B drug. The biodegradable microneedle patch showed lower cytotoxicity than free drug along with significant fungal inhibition. Study suggested feasibility of microneedle amphotericin B loaded transdermal patches for management of ocular fungal infections in more effective way (Albadr *et al.*, 2022). In a similar study, fluconazole loaded microneedle transdermal patch has shown good potential as ocular patch for treatment of fungal keratitis (Mahfufah *et al.*, 2024).

Electrically-driven drug delivery systems have shown promising potential in delivering antifungal drugs into deep cutaneous tissues. It is a novel strategy for minimal invasive delivery of antifungal drugs for infection eradication (Ghosh *et al.*, 2025). The technique of iontophoresis has been explored for topical delivery of antifungal drug such as Efinaconazole (Nair *et al.*, 2023). In a study, an iontophoresis-assisted transdermal patch was developed for topical delivery of terbinafine drug. Iontophoresis technique showed enhancement of permeation of terbinafine. It was found to be safe and effective technique for treatment of deep antifungal infections. Reverse iontophoresis technique has also been developed as a non-invasive technique for evaluation of bioavailability of topical antifungal agents (Moore *et al.*, 2024).

Need for Novel Drug Delivery Transdermal Patches Using Synthetic Drugs

Challenges with Current Antifungal Therapies

Limitations of traditional drug delivery systems demands development of novel systems to overcome the challenges and improve patient compliance. One of the major limitation of oral antifungals is systemic side effects. One of the most effective antifungal agent for invasive fungal infections is Amphotericin B. However, toxicities associated with the drug limits its use (Girois *et al.*, 2006). Another important class of antifungal drugs used against invasive infections is Azoles. Azoles are often used for prolonged periods of time, but these are also reported to be associated with hormone related side effects and hepatotoxicity (Benitez & Carver, 2019).

Another challenge associated with traditional antifungal drug delivery system is poor patient adherence. Carroll *et al.*(2004) noted poor adherence as an important principle of dermatology. Poor adherence may result in increase in cost of treatment, reduced benefits from treatment and in worst cases, it may even lead to death of patients (Weinberg, 2009). In a prospective exploratory study in patients undergoing treatment for dermatophytosis, over 43% of the patients showed poor adherence just after 6 weeks of treatment (Mukherjee *et al.*, 2021).

Certain infections cannot be treated with conventional therapies. Fungal infections, for example, onychomycosis is very difficult to treat with conventional therapies (Shenoy & Shenoy, 2014). Furthermore, rapid resistance development for most of the conventional antifungal agents is also a concerning issue all over the globe (Fisher *et al.*, 2018). In addition, traditional topical antifungal therapies are often messy and results in patient inconvenience and poor compliance (Kyle & Dahl, 2004). These challenges highlight the urgent need for innovative drug delivery systems like transdermal patches to enhance the efficacy, safety, and patient adherence in antifungal therapy.

Why Transdermal Patches are Promising

Transdermal patches are comparatively novel formulations that can address limitations associated with traditional drug delivery systems. Transdermal patches provide controlled release of drugs, hence can avoid systemic side effects (Patel & Shah, 2018). A recent review suggested only 2% people faced systemic adverse effects of transdermal patches containing diclofenac drug, hence, considered systemic side effects to be rare with transdermal patches (Massey *et al.*, 2010). Another advantage offered by transdermal patches is better patient adherence. There are a number of studies that have suggested better patient adherence to treatment regime with use of transdermal patches. Transdermal patches offer unique advantages that make them promising for drug delivery. They provide a visible reminder of treatment, integrating seamlessly into daily routines and promoting adherence, especially among forgetful patients or caregivers. The visual indication of patch application reassures caregivers that the medication is being administered correctly and allows for quick removal in case of adverse reactions. Additionally, patches minimize the risk of accidental overdose, making them safer for use. This combination of convenience and safety enhances confidence in treatment, potentially allowing for optimized dosing and improved patient outcomes (Small & Dubois, 2007).

As mentioned earlier, some of the diseases that cannot be easily cured by traditional therapies, can actually be cured by use of transdermal patches. Traditional therapies may take as long as 18 months for treatment of onychomycosis, with relapse up to 6.5% of patients (Christenson *et al.*, 2018). Recently studied antifungal patches have shown success as better treatment options in management of onychomycosis. Many natural and synthetic antifungal drugs have shown to be developed into transdermal patches with potential to treat onychomycosis (Etebari *et al.*, 2023; Gaddime *et al.*, 2018). Fungal infections with resistant species is also a threat all over the world. Transdermal patches with ability to deliver high concentration of drugs at local site can be a good solution to overcome the issue (Akhtar *et al.*, 2015). Antifungal microneedle patches facilitate deeper penetration of drug into skin and provide higher bioavailability of antifungals to combat resistant species (Jamaledin *et al.*, 2020).

Conclusion and Future Prospects

The development of antifungal transdermal drug delivery systems (TDDS) is a promising area of research, aiming to address the limitations of traditional antifungal therapies. Nanotechnology integration by employing nanoparticles, such as nanoemulsions and liposomes can significantly enhance solubility and penetration of drugs. There are only few studies that have demonstrated integration of nanosystems in antifungal transdermal patches. However, there are multiple studies suggesting integration of nanosystems in transdermal drug delivery systems, offering advantages such as high antifungal activities, biosafety, better skin diffusion and higher stability. Developing methods to enhance permeation of drugs is crucial for antifungal transdermal patches. Recent years have observed integration of techniques such as microneedle penetration and iontophoresis strategies to enhance drug penetration. Vesicles and microemulgels have also shown potential as penetration enhancers, and further works can be focused on integrating them into antifungal transdermal patches. Research into bioadhesive materials can further improve adhesion of patches to skin. Advancements in bioadhesives can allow better adhesive of patches to most types of skins and during wet and dry conditions. These bioadhesives can be engineered to provide sustained drug release while ensuring comfort and consistent adhesion under varying conditions. As research advances, antifungal transdermal patches hold the potential to revolutionize the treatment of fungal infections, offering safer, more effective and patient-friendly therapeutic options.

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