

Recent advances in topical formulation carriers of antifungal agents

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ABSTRACT

Fungal infections are amongst the most commonly encountered diseases affecting the skin. Treatment approaches include both topical and oral antifungal agents. The topical route is generally preferred due to the possible side effects of oral medication. Advances in the field of formulation may soon render outdated conventional products such as creams, ointments and gels. Several carrier systems loaded with antifungal drugs have demonstrated promising results in the treatment of skin fungal infections. Examples of these newer carriers include micelles, lipidic systems such as solid lipid nanoparticles and nanostructured lipid carriers, microemulsions and vesicular systems such as liposomes, niosomes, transfersomes, ethosomes, and penetration enhancer vesicles.

Key words: Carriers, formulation, fungal infections, skin

INTRODUCTION

The incidence of cutaneous mycoses is increasing nowadays, especially in immunocompromised patients. They are classified according to the level of tissue invasion into superficial, cutaneous and subcutaneous mycoses.^[1]

Superficial mycoses are caused by fungi that are limited to the outermost layers of the skin such as pityriasis versicolor, tinea nigra, and black/white piedra. When fungal infections extend deeper into the epidermis, they are termed as cutaneous mycoses or dermatomycoses; these can involve the skin appendages as well, such as hair and nails. Unlike superficial mycoses, cutaneous mycoses can induce cellular immune responses causing pathological changes. The fungi causing cutaneous mycoses are

termed dermatophytes, and they usually belong to the following genera: *Microsporum*, *Trichophyton*, and *Epidermophyton*. Examples of the fungal diseases considered as dermatomycoses are tinea corporis, tinea pedis which is the most common form of dermatophytosis, tinea faciei, tinea manuum, tinea cruris, tinea barbae, and tinea capitis.^[2-4]

If the infection further extends into the dermis and the subcutaneous tissue, it is then termed subcutaneous mycosis. The most common type of subcutaneous infection is sporotrichosis, caused by the fungus *Sporothrix schenckii*. Sporotrichosis is characterized by infiltrated nodular or ulcerated lesions on areas exposed to fungal inoculation. Other examples of subcutaneous mycoses include chromomycosis and maduramycosis (or mycetoma).^[5]

Topical agents that are conventionally used for the treatment of skin fungal infections are usually formulated as creams, lotions or gels.^[6] They either exhibit fungicidal or fungistatic actions depending on the agent being delivered. Since the side effects of fungal agents applied topically are less than their oral counterparts, they are the preferred agents.^[7-9] Another advantage of topical formulation is that it avoids

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drug-drug interactions, which are more common in case of oral administration.

A drug must have some specific characteristics to be delivered in the form of a topical preparation for treatment of skin fungal infections; the most important of these is its lipophilic nature. When such a drug is applied on the skin, a depot is formed in the lipidic stratum corneum which releases the drug slowly to the underlying skin layers, that is, epidermis and dermis. Therefore, in order to achieve a topical effect for an antifungal drug, the release rate of this lipophilic drug should be controlled by the formulation in order to achieve high local therapeutic concentration and to provide prolonged pharmacological effect.^[10] Another important consideration is the molecular weight of the drug; this is especially important for antifungal drugs known to exceed 500 Da such as amphotericin B and ketoconazole. These considerations have led to the development of several carriers which were found to improve topical drug delivery by either finding a way into a shunt such as hair follicle, accumulating between corneocytes, and intermingling with skin lipids, or by disintegrating and merging with lipidic layers.^[11,12] Whether their size was in the micrometer or nanometer range, carrier systems were found to impart desirable characteristics to topical formulations of antifungal drugs. Several carrier systems with their corresponding applications in the topical treatment of skin fungal infections will be discussed in this review.

NOVEL CARRIERS FOR TREATMENT OF SKIN FUNGAL INFECTIONS

Micelles

A micelle is defined as a group of surfactant molecules dispersed in a liquid. In an aqueous solution, micellization occurs due to the mounting of hydrophilic head of surfactant molecules toward water and sequestering of the hydrophobic tails toward the inside.^[13] Micelles were reported to be promising carriers for delivering an antifungal drug topically.^[14]

Bachhav *et al.* developed new aqueous micellar solutions of clotrimazole, econazole nitrate, and fluconazole for the treatment of superficial fungal infections.^[15] The micelles were prepared from novel amphiphilic methoxy poly(ethylene glycol)-hexyl substituted polylactide block copolymers. These micelles, which were in the nanometer range, showed superior entrapment for econazole nitrate. Upon

topical application of the econazole micellar formula compared to the marketed Pevaryl[®] cream on porcine skin, the deposition of econazole was found to be 13-fold higher in the former. This was attributed to the ability of the micellar solution to utilize the follicular penetration pathway. These findings suggest the promising role of micelles in improving the cutaneous bioavailability of the antifungal drug.^[15]

Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles are carriers in which the drug is entrapped within a solid lipid core matrix. Examples of these lipids are triglycerides, diglycerides, monoglycerides, fatty acids, steroids, and waxes.^[16] Nanostructured lipid carriers are the second generation of lipid nanoparticles in which the matrix is composed of a mixture of solid and liquid lipids.^[17] Among the advantages of lipid nanoparticles are that the lipids utilized in their preparation are physiological lipids and that they can be prepared using organic solvent-free methods.^[18] Both solid lipid nanoparticles and nanostructured lipid carriers have been recommended as good carriers for the treatment of topical skin infections, especially for antifungal drugs which are known to be lipophilic, and hence, can be successfully entrapped within the lipidic core of solid lipid nanoparticles or nanostructured lipid carriers.^[19]

Souto *et al.* prepared solid lipid nanoparticles and nanostructured lipid carriers for the topical delivery of clotrimazole.^[20] Both carriers were able to sustain its release for a period of 10 h, with solid lipid nanoparticles displaying occlusive property, which is desirable for topical application in general.^[20] When solid lipid nanoparticles and nanostructured lipid carriers were used as topical carriers for ketoconazole, the latter was found to protect the drug against light degradation, conferring more stability to it and had comparable antifungal activity to the marketed product against *Candida albicans*.^[21,22] Solid lipid nanoparticles of miconazole incorporated in gel form were able to enhance its skin accumulation and uptake as compared to the marketed gel.^[23] Further studies on miconazole solid lipid nanoparticles hydrogel displayed a sustained release for a period of 24 h and a 10-fold better skin retention of the drug compared to the suspension or the hydrogel form (without solid lipid nanoparticles).^[24] Miconazole loaded in solid lipid nanoparticles form was found more efficient in the treatment of candidiasis, and hence, it was

suggested by the authors as a promising formula to provide both quick relief as well as sustained release properties in addition to efficient *in vivo* performance in treating skin fungal infections.^[24] Similarly, solid lipid nanoparticles were able to sustain the release of fluconazole for a period of 24 h and were able to localize the drug in the skin for better topical treatment of fungal infections.^[25] However, nanostructured lipid carriers of fluconazole exhibited more than 3-fold higher retention in the skin compared to solid lipid nanoparticles.^[26] Solid lipid nanoparticles of terbinafine were also found superior to the marketed product, with increased retention of the drug in rat skin. They also decreased the burden of *C. albicans* within a shorter period of time.^[27,28] The amount of terbinafine penetrating deep into the skin and reaching the dermis was higher for solid lipid nanoparticles compared to the marketed Lamisil® cream.^[29] Similar results were obtained with solid lipid nanoparticles of econazole.^[30] Moreover, solid lipid nanoparticles of griseofulvin were shown to exhibit good skin permeation effect as manifested by the complete mycological and clinical cure in *Microsporum canis* infected guinea pigs upon administration of griseofulvin solid lipid nanoparticles gel twice daily for 8 days.^[31]

Solid lipid nanoparticles and nanostructured lipid carriers were generally reported as effective in prolonging release of antifungal drugs and increasing their skin permeation; hence, they are considered amongst the most promising delivery systems.^[32]

Microemulsions

Microemulsions are defined as thermodynamically stable mixtures of oil and water stabilized by surfactants and co-surfactants, with size in the nanometer range. Owing to their ability to solubilize many poorly soluble drugs, microemulsions have been found very promising in the delivery of antifungal drugs which are characterized by their lipophilicity.^[33]

A microemulsion gel developed for topical delivery of fluconazole for the treatment of invasive fungal infections was developed and found very effective in enhancing percutaneous absorption of the drug.^[34] Several researchers further confirmed the ability of microemulsions to increase percutaneous permeability of fluconazole.^[35,36] The same results were obtained with microemulsion formulae of ketoconazole, itraconazole, voriconazole, and econazole.^[37-41] Microemulsion based hydrogel of

clotrimazole exhibited higher skin retention and higher *in vitro* activity against *C. albicans* when compared to the conventional cream.^[42] Furthermore, it demonstrated clinical efficacy when tested in patients suffering from tinea corporis, tinea circinata and tinea pedis with skin involvement of <10% of the total body surface area.^[42] A microemulsion based hydrogel of sertaconazole showed 3-fold higher skin retention than the commercial cream, with higher *in vitro* antifungal activity against *C. albicans*.^[43,44] Amphotericin B was also incorporated in microemulsion form for treatment of invasive fungal infections in which a 2-fold increase in skin retention was obtained with the microemulsion formulation compared to the plain drug solution, with better *in vitro* antifungal activity against *Trichophyton rubrum*.^[45] Moreover, microemulsion formulations of griseofulvin caused complete resolution of dermatophytosis in 7 days.^[46]

Vesicular delivery systems

Vesicles are defined as highly ordered assemblies of one or several concentric lipid bilayers. They are formed when certain amphiphilic molecules such as phospholipids or surfactants are placed in water. They were first reported by Bangham in 1965.^[47] As a topical drug carrier, vesicular systems act as penetration enhancers owing to the penetration of their lipidic components into the stratum corneum leading to alteration in the intercellular lipid matrix. They also serve as depots for localizing and sustaining the release of topically applied compounds.^[48,49] They were reported to reduce the systemic absorption of drugs owing to their high substantivity with the biological membranes.^[50] Several vesicular systems have been prepared and successfully utilized in the treatment of skin fungal infections, among which are liposomes, niosomes, transferosomes, ethosomes, and penetration enhancer vesicles.

Liposomes

Liposomes are vesicles which consist of one or more concentric lipid bilayers separated by water or aqueous buffer compartments, ranging in size from 10 nanometers to 20 micrometers.^[51,52] Liposomes were reported to interact with the skin via several mechanisms. They are either adsorbed onto the skin surface leading to the release of drugs, or penetrate via the lipid-rich channels either intact, or after losing some lipid lamellae; alternatively, they form occlusive films which increase skin hydration and drug penetration into the stratum corneum.^[53,54]

Regarding their applications in fungal infections, a liposomal gel of ketoconazole allowed more drug retention in the skin compared to the gel and cream formulations.^[55] They were also reported to increase both the deposition and skin permeation of fluconazole when compared to controls, and enhance its therapeutic effectiveness against cutaneous candidiasis.^[56,57] Liposomes were also able to effectively decrease fungal colonies when encapsulating ciclopirox olamine.^[58] Prolongation of the action of terbinafine was also suggested by other authors upon encapsulating into liposomal gels.^[59] Liposomes of croconazole too showed excellent activity against different fungal species when compared to miconazole cream as a control.^[60]

Niosomes

Niosomes are similar to liposomes, they only differ in the replacement of phospholipids with non-ionic surfactants.^[61,62] Upon topical application, they interact with the stratum corneum leading to a reduction of transepidermal water loss.^[63] Similar to liposomes, they are either adsorbed on the surface of the skin leading to high thermodynamic activity gradient of the drug at the interface which facilitates drug permeation, or they penetrate into the stratum corneum themselves and act as drug reservoirs.^[64-66]

Regarding their applicability in the treatment of fungal infections, griseofulvin niosomes incorporated in gel showed high mycological cure rates of about 80% in patients suffering from tinea corporis.^[67] Terbinafine hydrochloride niosomes showed efficacy against *Aspergillus niger*.^[68] The action of ketoconazole was prolonged by encapsulating it into niosomes.^[69] Niosomes of itraconazole and miconazole were also found to be effective, proving themselves to be effective carrier systems for antifungal drugs.^[70,71]

Transferosomes

Transferosomes, also termed as ultradeformable or flexible liposomes, have been used as carriers. They are formed of phospholipids and an edge activator; the latter is a surfactant having a high radius of curvature that destabilizes the phospholipid lipid bilayers and increases the deformability of vesicles.^[72,73] In addition to the mechanisms of penetration enhancement proposed for liposomes, transferosomes additionally have the ability to pass to deeper skin layers intact, owing to their deformability, driven by their ability to avoid dry surroundings.

Transferosomes of griseofulvin were found better than liposomes in the treatment of dermatophytosis, displaying complete mycological cure in 10 days.^[74] They proved themselves as effective carriers for itraconazole as well.^[75] A transferosomal formulation encapsulating amphotericin B was reported to be superior in its skin permeation and its antifungal activity against *Trichophyton rubrum*.^[76] Transferosomal formulations of miconazole showed a higher rate of permeation of the drug into the deeper skin layers.^[77]

Ethosomes

Ethosomes represent another type of deformable vesicles, which contain ethanol instead of edge activator in transferosomes as the penetration enhancer. Ethanol was reported to fluidize the intercellular lipids of the stratum corneum upon topical application and allow the easy penetration of vesicles into deeper skin layers.^[78]

Ethosomes were found superior as carriers of clotrimazole and econazole.^[79,80] They were also reported to be clinically more effective than liposomes and the marketed econazole product against *Candida*.^[81]

Penetration enhancer vesicles

Penetration enhancer containing vesicles are a new elastic vesicular system prepared by penetration enhancers with or without soybean lecithin. Penetration enhancers differ in their chemical structure and properties, the commonly used ones being oleic acid, Transcutol® and Labrasol®.^[82]

Regarding their mechanism of action, penetration enhancer vesicles were reported to penetrate intact down to the epidermis, followed by further penetration to deeper layers owing to the enhancement of bilayers fluidity caused by the penetration enhancer. In addition, the free penetration enhancer exerts a synergistic effect through interaction with skin lipids, which leads to the perturbation of the intercellular skin lipid pathway improving the accumulation of drugs in deeper skin layers.^[83]

We are aware of only one publication on the use of penetration enhancer vesicles in the treatment of skin fungal infections. Oleic acid vesicles loaded with fluconazole were shown to enhance the epidermal accumulation of the drug suggesting their potential for the treatment of deep localized skin fungal infections.^[84]

CONCLUSION

As time progresses, the need to develop new drug formulations increases. Conventional delivery systems, including creams, ointments, and gels are traditionally being used for the treatment of skin fungal infections, even if they are deep seated. Carrier systems have the ability to overcome the immediate drug release caused by these conventional formulations, hence they avoid the possibility of induction of allergic reactions. Moreover, they are especially customized to enhance the penetration of the antifungal agents, leading to more effective treatment of skin fungal infections, especially the deeper ones. These carrier systems are expected to slowly replace the conventional systems as more commercial preparations become available.

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Announcement

IADVL scholarships for attending the XXXVI Symposium of the International Society of Dermatopathology

We are happy to announce 18 grants (6 each for IADVL PLMs, LMs below 35 years, and LMs above 35 years) of Rs. 10,000 each to attend the XXXVI Symposium of the International Society of Dermatopathology, New Delhi (November 19-21, 2015; <http://dermpathindia.org/Symposium/isdp2015-programme.html>).

Only registered delegates presenting a paper/poster who have not obtained any other scholarship from the IADVL and have no other funding source (e.g. conference organizers, state branches, government, ICMR, pharmaceutical company, or institutions) are eligible. Those who have received IADVL Training Fellowships can apply.

Please mail the following to iadvlacademy@gmail.com and iadvlsecretary2014@gmail.com by Tuesday, 15th September, 2015, mentioning 'Application for an IADVL scholarship for the ISDP Symposium' in the subject line:

1. Application form
2. Scanned copy of the declaration
3. Registration receipt
4. Abstract
5. Abstract acceptance letter
6. Brief CV.

The applications will be evaluated by independent judges based on objective criteria (*viz.* academic background, publications, conference participation, awards, and quality of abstract). The results are expected to be declared by Saturday, 10th October. The grant will be disbursed on completion of the conference and submission of proof of attendance.

Please note that those offered scholarships will not be eligible for scholarships again (though they will be eligible for IADVL Training Fellowships).

Dr. Venkataram Mysore
President

Dr. Rashmi Sarkar
Secretary General

Dr. Manas Chatterjee
Chairperson, IADVL Academy

Dr. Ameet Valia
Convener, IADVL Academy