Expert Opinion

Topical delivery of antifungal agents

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Importance of the field: Superficial fungal infections of skin, hair, nails and the eye are among the most widespread diseases known to man. Topical therapy is the most favored form of treatment for these infections because it lends itself to self-administration, patient compliance, and absence of systemic adverse effects.

Areas covered in this review: The clinical efficacy of antifungal drugs depends on the concentration achieved in cutaneous/ocular tissue, which in turn depends on the molecular mass, route of administration, duration of contact and ability of the compound to penetrate the tissue. Several of these agents have a high molecular mass > 500 Da (such as amphotericin B, natamycin, or ketoconazole), resulting in their poor penetration (even if they are lipophilic in nature). The latter causes relapse infections and requires frequent administration. Packaging these agents into suitable delivery systems can improve the effectiveness of these agents. The usefulness of liposomes/niosomes, lipid emulsions, nanoparticles including solid lipid nanoparticles and microemulsions for development of these agents is discussed.

What the reader will gain: This article aims to discuss limitations to the topical therapy of antifungal agents, and delivery approaches used to enhance their effectiveness.

Take home message: A physicochemical and pharmacokinetic guided approach can help to tailor-make therapeutically effective systems for existing antifungal agents, thus doing away with the need for newer agents, which will save on time, money and manpower.

Keywords: antifungal drugs, lipophilicity, nanoparticles, ocular, skin, topical

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1. Introduction

Fungal infections may be classified as superficial infections affecting the skin, hair, nails or mucous membranes, or systemic, affecting the body as a whole. Subcutaneous infection is largely confined to the subcutaneous tissue and dermis, but may extend to the epidermis as well as deeper, for example, to bone; systemic infections tend to occur more frequently in immunocompromised patients such as those with AIDS. Superficial fungal infections are among the most widespread diseases known to man. They target parts of the body as diverse in form and function as the skin, the nail, the buccal cavity, the eye and the vagina.

2. Skin infections

The most common fungal skin infections are the dermatophytoses, pityriasis versicolor and candidiasis. Other skin fungal infections include: blastomycosis, chromoblastomycosis, mycetoma, mucormycosis, protothecosis and sporotrichosis. Fungal infections that may involve the skin by dissemination include aspergillosis, coccidioidomycosis, cryptococcosis, histoplasmosis and paracoccidioidomycosis. Sometimes the infection may infect mucous membranes, nails, or subcutaneous

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Article highlights.

- The paper provides preliminary information on skin and eye fungal infections and their epidemiology.
- Topical delivery of drug is considered to have various advantages over systemic administration.
- Factors to be considered while fabricating a formulation suitable for topical delivery are log P, molecular mass, structure of biological membrane, and so on.
- Developing topical antifungal formulations offers challenges such as high molecular mass, poor solubility and poor permeation. Proposed new drug delivery systems can enhance bioavailability without compromising stability and antifungal activity.
- New drug delivery systems such as solid lipid nanoparticles, vesicular systems, microemulsion, and so on, are discussed under each antifungal drug.

This box summarizes key points contained in the article.

tissue, and from there can be spread to deeper tissue and disseminate, especially in immunocompromised patients.

Cutaneous fungal infections are common in the US, and causative organisms, that is, dermatophytes, yeasts and non-dermatophyte molds, are in constant competition for their particular environmental niche, often resulting in the emergence of one or more predominant pathogens and displacement of other less competitive species.

Dermatophytes remain the most commonly isolated fungal organisms. Most superficial fungal infections are tineas, and of these the most common are tinea pedis, tinea corporis and tinea cruris [1]. *Trichophyton rubrum* is the most likely agent in these dermatomycoses. *T. rubrum* accounted for 76.2% of all superficial fungal diseases in a representative sample of the US population. With the exception of tinea capitis (in which *Trichophyton tonsurans* was the most likely etiologic agent), *T. rubrum* was the most common dermatophyte isolated in all superficial fungal diseases studied [2].

Dermatophytoses are infections by dermatophytes, a group of fungi that includes soil-dwelling organisms and human and animal pathogens from the genera Trichophyton, Microsporum and Epidermophyton. In the US, dermatophytosis is second only to acne as the most frequently reported skin disease [3]. Infections of nail (onchomycoses) are notoriously difficult to treat [4].

Superficial skin infections can also be commonly caused by *Candida* species, the most common causative agent being *Candida albicans*, although infections with *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis* also occur. Superficial infections caused by Candida spp. include candida vulvovaginitis, intertrigo (skin fold infections), napkin dermatitis, chronic paronychia (nail fold infection) and onchomychosis (nail plate infection). Predisposition factors include antibacterial therapy, skin trauma, diabetes mellitus, pregnancy and immunodeficiency; candidiasis often occurs in patients with HIV infection.

3. Eye infections

Fungal infections of the eye are less common than infections with bacteria or viruses, but are usually severe and may lead to loss of vision. Diagnosis may be delayed owing to gradual onset of symptoms and empirical treatment with antibacterials. Infections may involve the cornea (keratitis), the interior of the eye (endophthalmitis), or the orbit, and may occur following trauma (including surgery) or systemic disseminated infection. According to the World Health Organization, corneal diseases are a major cause of vision loss and blindness, second only to cataracts in overall importance [5]. Fungal keratitis is a devastating disease that is responsible for corneal blindness, the second most common cause of blindness in developing countries [6,7].

Fungi cannot penetrate the intact corneal epithelium and do not enter the cornea from episcleral limbal vessels. They need a penetrating injury or a previous epithelial defect in order to establish a 'foot hold'; however, once within the cornea they are able to proliferate fast. The most common pathogen that invades a pre-existing defect is *Candida*; filamentous fungi are the principal cause of post-traumatic infection. Intrinsic virulence of fungi depends on the fungal substances produced and the host response generated [8]. Most of the ocular fungal infections involve high morbidity. Some of the reasons for this are:

- physical damage by the very presence of fungal organisms
- the infiltrative leukocytic inflammatory response
- secondary damage from fungal toxins and enzymes [8].

Another risk factor (29%) for fungal keratitis in industrialized countries is contact lens wear; *Candida* is the principal cause of keratitis associated with therapeutic contact lenses, and filamentous fungi are the ones associated with refractive contact lens wear. Topical steroid use has definitively been implicated as a cause of increased incidence, development and worsening of fungal keratitis. Other risk factors to be considered are foreign bodies, corneal surgery, chronic keratitis and immunosuppressive diseases. In fact, the physician should have a high level of suspicion if there is a patient with a history of corneal trauma, particularly with plant or soil matter [8]. Previous data report that fungal keratitis is most common in the older population, that is, 51 – 60 years. However, reports [6,9] from Indian subpopulations indicate the younger subgroup of 31 – 40 years (~ 36%), followed by 21 – 30 years (~ 31%) to be the more common age groups involved. Considering that the patients in the age group of 20 – 40 years are often the breadwinners of the family, blindness is of much greater economic consequence in this group. The most common fungi causing eye infections are Aspergillus, Candida and Fusarium; others include Blastomyces, Cryptococcus and Sporothrix. Infection of the orbit usually occurs by spreading from an infection of the paranasal sinus, commonly mucormycosis or aspergillosis.

4. Topical antifungal drug delivery considerations

The treatment of superficial fungal infections may be accomplished with topical antifungal agents and/or with orally administered agents. Fungi often infect the skin surface and subsequently invade the stratum corneum (SC) to avoid being shed from the skin surface by desquamation. Pharmacologic agents applied to the surface of the skin in the form of creams, lotions, or sprays readily penetrate the SC to kill the fungi (fungicidal agents), or at least render them unable to grow or divide (fungistatic agents). Thus, topical therapies work well to rid the skin of topical fungi and yeasts. Safety of therapy is less of a concern for topical medications than oral medications, as serum absorption tends to be minimal with topical dermatophytosis therapy, thus making topical therapy an attractive approach for localized infections. Most adverse events following topical drug application are skin reactions at the application site, which are mild and transient [10], whereas the oral antifungal medications may be associated with severe hepatic toxicity, rare serious skin events such as Stevens–Johnson syndrome, and possible drug–drug interactions resulting from metabolism through the cytochrome P450 system (**Tables 1** and **2**). The latter is particularly important in the elderly or patients on medications metabolized by the cytochrome P450 system.

Also, because skin disease is accessible, it can be treated with locally applied medication, which offers great advantages – exposure to a drug is limited to the affected skin and systemic effects of potentially toxic drugs are minimized.

The topical therapy lends itself to self-administration. Furthermore, the excellent levels of patient compliance and absence of systemic adverse effects make it an attractive approach for treating localized infections. This may be particularly important for long-term systemic administration, which may increase the risk of exposure to drug–drug interactions and other adverse events [11].

Although drugs intended for topical cutaneous administration cover a broad range of therapeutic indications, and have different molecular structures, they retain certain common physicochemical characteristics. Specifically, they are generally highly lipophilic and have poor aqueous solubility; for example, topical antifungals clotrimazole and miconazole have log octanol/water partition coefficients (log P) > 6.0 (**Table 1**). Thus, the molecules partition from the formulation into the lipidic stratum corneum, where they are frequently retained and form a depot. They are then slowly released into the underlying more aqueous membrane layers of viable epidermis and dermis or eliminated by desquamation. The challenge for the formulation scientist is to ensure that the rate and extent of delivery are sufficient to achieve therapeutic local concentrations in a reasonable time frame and provide sustained pharmacological action [11]. The effects of formulation on the rate and extent of drug absorption are much greater with topical drug delivery than with any other route of drug administration [12]. The topical delivery provides a major challenge for optimal therapy, which is the barrier function of the target biologic membrane. Poor drug penetration of skin/nail/cornea limits local bioavailability and drug efficacy. The structures of the SC, corneal, mucosal and nail barriers are certainly different, but collectively they present significant impediments to drug transport. Their barrier function is principally due to their respective epithelial architecture and physicochemical composition. Delivery efficiency and therapeutic effect depend on drug affinity for and diffusion in the membrane and interaction between the formulation excipients and membrane components. Therefore, formulations and drug should be better adapted for traversing a given biologic barrier and may need to be modified for optimum delivery across other membranes. Hence, it is vital to design and develop a formulation system that ensures correct balance between potency and deliverability to obtain therapeutic drug levels at the site of infection [11]. The skin acts as a major target as well as a principal barrier for topical/transdermal drug delivery. The SC plays a crucial role in barrier function for topical drug delivery. Despite major research and development efforts in topical systems and the advantages of these routes, low SC permeability limits the usefulness of topical drug delivery. To overcome this, methods have been assessed to increase permeation. One new method is the use of vesicular systems, such as liposomes and niosomes, whose effectiveness depends on their physicochemical properties.

The nail is one of the skin appendages most prone to fungal invasion; onchomycosis accounts for one-third of all fungal skin infections and half of all nail diseases, and is difficult to manage. The major drawback of existing therapies is the failure to establish and maintain effective drug levels at the site of infection because of the impermeability of the nail plate. Several topical antifungal formulations have been developed (gels, creams, powders, solutions, water- or oil-based lotions). However, they have modest efficacy on account of their low permeability through the nail. Moreover, these dosage forms are easily removed by mechanical contact, for example, rubbing, wiping and washing, which further reduces their efficacy. Water is the principal plasticizer for the nail. Formulations or treatments that improve nail hydration have potential to improve topical therapy for onychomycosis – if a favorable balance between drug delivery and growth conditions for the dermatophytes can be achieved. Studies on the effect of hydration on human skin permeability have shown that diffusivity of water and other materials increases as the tissue becomes more hydrated [13,14].

The main difficulties with topical antifungal treatment of ocular infections are the limited number of preparations, poor ocular penetration and local bioavailability, and drug toxicity (**Figure 1**). Topical drug delivery is complicated by effective removal mechanisms (which operate to keep the ocular surface free from foreign substances) and

Table 1. Some important physicochemical characteristics of various antifungal agents [136].

Group	Generic name	Protein binding	Solubility	$t_{1/2}$ (oral)	Molecular mass (Da)	log P	Drug interactions
Polyene	Nystatin	–	360 mg/l at 24°C	6 h	926.09	0.5	As it is not absorbed from the gut, it is safe for oral use and does not have problems of drug interactions
	Amphotericin B	Highly bound (> 90%) to plasma proteins	750 mg/l at 28°C	15 days follows an initial plasma half-life of ~ 24 h	924.10	0.8	When administered concurrently, the following drugs may interact with amphotericin B: antineoplastic agents, corticosteroids and corticotropin (ACTH), digitalis glycosides, flucytosine, zoles (e.g., ketoconazole, miconazole, clotrimazole, fluconazole, etc.) and other nephrotoxic medications
	Natamycin	–	4100 mg/l at 21°C	–	665.75	1.1	There are no known significant interactions
Azoles (Imidazole)	Clotrimazole	90%	29.84 mg/ml	2 h	344.84	6.1	There is the potential for drug interactions with clotrimazole if taken orally, as it is a potent, specific inhibitor of cytochrome P450 (CYP3A4) oxidase and so may alter the metabolism of other drugs
	Miconazole	92%	0.0111 mg/l at 20°C	20 – 25 h	416.12	6.1	There may be interactions with anticoagulants, phenytoin, terbinafine, some newer atypical antipsychotics, ciclosporin and some statins used to treat hypercholesterolemia
	Ketoconazole	99% (*in vitro* plasma protein binding)	0.0866 mg/l at 25°C	2 h	531.44	4	Concomitant administration of drugs that reduce stomach acidity, such as antimuscarinics, antacids, histamine H_2-receptor antagonists and proton pump inhibitors may reduce absorption of ketoconazole. Ketoconazole is a potent inhibitor of the CYP3A4 enzyme system and may cause increased plasma concentrations of the drugs such as terfenadine, triazolam, oral anticoagulantants, statins and zidovudine. Coadministration of ketoconazole with enzyme-inducing drugs such as rifampicin, isoniazid and phenytoin may reduce plasma concentration of ketoconazole
	Econazole	–	0.00148 mg/ml	–	381.68	5.5	There are no known significant interactions
	Oxiconazole	–	1.91×10^{-3} mg/ml	–	429.13	5.28	No interactions have been reported
	Sulconazole	–	1.9 mg/ml	–	460.77	–	–
	Sertaconazole	> 99% to plasma	0.00638 mg/ml	–	437.77	6.2	–
	Bifonazole	–	0.00246 mg/ml	1 – 2 h	310.39	4.77	–
	Butoconazole	–	0.000818 mg/ml	21 – 24 h	411.78	6.70	There are no known significant interactions

Table 1. Some important physicochemical characteristics of various antifungal agents [136] (continued).

Group	Generic name	Protein binding	Solubility	$t_{1/2}$ (oral)	Molecular mass (Da)	log P	Drug interactions
Azole (Triazole)	Fluconazole	11 – 12%	1 mg/l	30 h (range 20 – 50 h)	306.27	0.4	Potentially significant drug interactions between fluconazole and oral hypoglycemics, coumarin-type anticoagulants, phenytoin, cyclosporine, rifampin, theophylline, terfenadine, cisapride, astemizole, rifabutin, tacrolimus and short-acting benzodiazepines have been observed
	Itraconazole	99.8%	0.000472 mg/l at 25°C	21 h	705.63	6.5	Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, drug interactions with the following drugs are seen: digoxin, carbamazepine, alprazolam, diazepam, cisapride, lovastatin, simvastatin, oral hypoglycemics, indinavir, ritonavir, saquinavir, carbamazepine, isoniazid, rifampin gastric acid suppressors/neutralizers antacids, H_2-receptor antagonists, proton pump inhibitors, clarithromycin and erythromycin
Allylamines	Terbinafine	> 99%	7.38×10^{-4} mg/ml	36 h	291.43	5.9	*In vivo* studies have shown that terbinafine is an inhibitor of the CYP450 2D6 (CYP2D6) isozyme. Coadministration of terbinafine with drugs predominantly metabolized by the CYP2D6 isozyme (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, beta-blockers and monoamine oxidase inhibitors TypeB) Terbinafine decreases the clearance of caffeine by 19% and terbinafine clearance is increased 100% by rifampin, a CYP450 enzyme inducer, and decreased 33% by cimetidine, a CYP450 enzyme inhibitor
	Naftifine		0.000229 mg/ml	Approximately 2 – 3 days following topical administration	287.40	5.4	There are no known significant interactions

Table 1. Some important physicochemical characteristics of various antifungal agents [136] (continued).

Group	Generic name	Protein binding	Solubility	$t_{1/2}$ (oral)	Molecular mass (Da)	log P	Drug interactions
Allylamine-like benzylamine derivatives	Butenafine	–	0.0000756 mg/ml	Following topical application, a biphasic decline of plasma butenafine concentrations was observed with the half-lifes estimated to be 35 h initially and > 150 h terminally	317.47	6.6	–
Hydroxypiridones	Ciclopirox	Protein binding is 94 – 97% following topical administration	1.41 mg/ml	1.7 h for 1% topical solution	207.27	2.3	–
Morpholine derivatives	Amorolfine	–	–	–	317.51	–	–

the barriers operative at the precorneal area. These include the blinking reflex, tear turnover and low corneal permeability [15].

The topically applied ocular drugs have to reach inner parts of the eye to elicit responses. Transcorneal penetration is believed to be the main route for drug absorption. Most ocular drugs seem to penetrate the cornea by diffusion. Paracellular transport (i.e., through intercellular space) and diffusion are the two mechanisms for transport across the cornea. The epithelium and the endothelium are rich in lipids; on the other hand, the stroma has high water content. The epithelium is reported to be the rate-limiting barrier to transcorneal transport. Its barrier function depends favorably on the lipophilicity of the molecules and excludes the macromolecules (r > 10 A). For smaller lipophilic molecules capable of crossing corneal epithelium, stroma and endothelium play a significant role, with endothelium being more important. For macromolecules, the stroma provides a greater barrier than the endothelium [16,17].

One of the major problems of ocular drug delivery is to provide and maintain an adequate concentration of drug in the precorneal area. Rapid nasolacrimal drainage of the instilled drug from tear fluid and non-productive absorption through the conjunctiva may lead to a short duration of action. Tear turnover and drug binding to tear fluid proteins are extra precorneal factors that contribute to the poor ocular bioavailability of many drugs when instilled in the eye in the solution dosage form. The rate of release of drug from the tear fluid to ocular tissues is initially high when instilled as solution, but declines rapidly; this may result in a transient period of overdose and the associated risk of side effects, followed by an extended period of subtherapeutic levels before the next dose is administered. This indicates the need for an ocular drug delivery system that has the convenience of a drop but will serve as a slow release depot [18]. The effects of formulation on the rate and extent of drug absorption are much greater with topical drug delivery than with any other route of drug administration.

Antifungal activity depends on several factors, including the molecular mass and concentration of the drug and the route by which it is administered, the duration of contact with the target ocular tissue, and the ability of the compound to penetrate the eye [19,20]. Compounds with a molecular mass > 500 Da, such as amphotericin B (924.10 Da), natamycin (665.75 Da), or ketoconazole (531.44 Da), barely penetrate an intact corneal epithelium because the force of friction increasingly reduces diffusion [19].

Solubility in lipid-rich tissue is another determinant of diffusion. The ocular penetration of molecules with intermediate molecular masses, such as miconazole (416.12 Da) or fluconazole (306.30 Da), is probably determined by both these factors. Lipophilic compounds, such as itraconazole, easily cross the lipid-rich epithelial and endothelial cell membranes and the blood–aqueous barrier, hydrophilic compounds more easily cross the corneal stroma, and biphasic compounds

Table 2. Proposed mechanisms of action, activity and side effects for various group of antifungal drugs [136].

Group	Generic name	Mechanism of action	Activity	Side effects
Polyene	Nystatin	Nystatin interacts with 14-α-demethylase, a cytochrome P450 enzyme necessary for the conversion of lanosterol to ergosterol. This results in inhibition of ergosterol synthesis and increased fungal cellular permeability	Broad spectrum of activity against yeast	Oral: nausea, vomiting diarrhea, irritation, urticaria Topical: irritation
	Amphotericin B	The drug acts by binding to sterols in the cell membrane of susceptible fungi with a resultant change in membrane permeability, allowing leakage of intracellular components	Broad spectrum Good activity against Aspergillus spp. and Candida spp.	Nephrotoxicity (kidney damage) is a major issue and can be severe and/or irreversible. It is much milder when amphotericin B is delivered in liposomes (AmBisome) Electrolyte imbalances (e.g., hypokalemia and hypocalcemia) may also occur
	Natamycin	The drug binds to the sterol moiety of the fungal cell membrane. The polyenesterol complex alters the permeability of the membrane to produce depletion of essential cellular constituents	Broad spectrum	One case of conjunctival chemosis and hyperemia, thought to be allergic in nature, has been reported
Azoles (Imidazole)	Clotrimazole	Clotrimazole interacts with 14-α-demethylase that converts lanosterol to ergosterol, an essential component of the membrane thus inhibits ergosterol synthesis, resulting in increased cellular permeability	Broad spectrum	Oral: gastrointestinal disturbance, mental depression Topical: irritation, burning sensation and contact dermatitis
	Miconazole	Miconazole inhibits 14-α-demethylase, a cytochrome P450 enzyme	Broad spectrum	Oral: nausea, vomiting and diarrhea Topical: mild burning and stinging sensations and minor signs of ocular irritation may be seen occasionally
	Ketoconazole	Ketoconazole inhibits 14-α-demethylase	Broad spectrum	Oral: gastrointestinal disturbances are most frequent; nausea, vomiting, abdominal pain, hepatitis have also been reported Topical: irritation and burning sensation reported
	Econazole	Econazole inhibits 14-α-demethylation of lanosterol	Broad spectrum	Topical: irritation, burning sensation and contact dermatitis
	Oxiconazole	Oxiconazole inhibits ergosterol biosynthesis, which is required for cytoplasmic membrane integrity of fungi	Broad spectrum	Topical side effects incliude pruritus, burning, irritation, erythema, stinging and allergic contact dermatitis and folliculitis, fissuring, maceration rash and nodules
	Sulconazole	Like all imidiazoles, it inhibits 14-α-demethylase	Broad spectrum	Topical: burning, itching, and erythema
	Sertaconazole	Sertaconazole inhibits 14-α-demethylase	Broad spectrum	

Table 2. Proposed mechanisms of action, activity and side effects for various group of antifungal drugs [136] (continued).

Group	Generic name	Mechanism of action	Activity	Side effects
	Bifonazole	Bifonazole works by inhibiting the production of a substance called ergosterol	Kills fungi and yeasts	Topical: local reactions including burning and itching
	Butoconazole	The exact mechanism of the antifungal action of butoconazole is unknown, however, it is presumed to function as other imidazole derivatives by means of inhibition of steroid synthesis	Clinically effective against vaginal infections due to *C. albicans*	Topical: burning and itching
Azole (Triazole)	Fluconazole	Fluconazole inhibits 14-α-demethylase	Broad spectrum Less active against *C. albicans*, *C. glabrata* and *C. krusei*	Oral: abdominal pain, diarrhea, nausea, vomiting, headache, hepatic toxicity Topical: rare but exfoliative cutaneous reactions such as toxic epidermal necrolysis
	Itraconazole	Itraconazole interacts with 14-α-demethylase to convert lanosterol to ergosterol	Broad spectrum	Oral: abdominal pain, nausea, constipation, headache and dizziness; alopecia, edema and hypokalemia on prolonged treatment Topical: temporary blurred vision on instillation, lasting from a few seconds to a few minutes, ocular discomfort, ocular hyperemia and dry eye
Allylamines	Terbinafine	Terbinafine is hypothesized to act by inhibiting squalene epoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes	Broad spectrum	Oral: gastrointestinal disturbances including nausea, vomiting diarrhea and mid-abdominal pain Cutaneous lupus erythematosus and pustulosis, toxic epidermal necrolysis rare Topical: local reactions
	Naftifine	Although the exact mechanism of action against fungi is not known, naftifine appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene 2,3-epoxidase	Broad spectrum	Topical: burning or stinging sensation
Allylamine-like benzylamine derivatives	Butenafine	Like allylamines, butenafine inhibits ergosterol biosynthesis by blocking squalene epoxidation	Mainly active against dermatophytes Active also against *C. albicans*	-

Table 2. Proposed mechanisms of action, activity and side effects for various group of antifungal drugs [136] (continued).

Group	Generic name	Mechanism of action	Activity	Side effects
Hydroxy-piridones	Ciclopirox	Ciclopirox is thought to act through the chelation of polyvalent metal cations, such as Fe^{3+} and Al^{3+}. These cations inhibit many enzymes, including cytochromes, thus disrupting cellular activities such as mitochondrial electron transport processes and energy production	Broad spectrum	Topical: irritation and pruritus
Morpholine derivatives	Amorolfine	Amorolfine inhibits D14 reductase and D7-D8 isomerase, which depletes ergosterol and causes ignosterol to accumulate in the fungal cytoplasmic cell membranes	Broad spectrum	Topical: skin irritation presented as erythema, pruritis and burning sensation

(possessing both the lipid and water solubility) penetrate all corneal layers [21].

Similarly, the efficacy of a topically applied antidermatophytic agent is influenced not only by its antifungal property but also by the ability of the drug molecules to penetrate the keratinized tissue. Drug properties that increase permeability across a given membrane may render the molecule less effective at another biologic tissue; for example, the SC is a lipidic barrier, whereas the keratin-rich nail contains 10-fold less lipid and is perhaps best viewed as a hydrogel with low lipid content. Moreover, the formulation has to be compatible with the biological tissue [11]. The pathogen in superficial fungal skin infections mainly locates in the epidermis. To inhibit fungal growth effectively, the topical formulations must release a proper amount of drug at the target site with penetration through the stratum corneum, in therapeutically effective concentrations [22].

The choice of drug will also depend on the pharmacological response of the drug. Azole drugs such as miconazole, clotrimazole and ketoconazole are fungistatic, limiting the fungal growth. Further, the epidermal turnover to shed the still-living fungus from the skin surface will also monitor the activity of such agents. Allylamines and benzylamines such as terbinafine, naftifine and butenafine are fungicidal, actually killing the fungal organisms. Fungicidal drugs are often preferred over fungistatic drugs for treatment of dermatophytic fungal infections, as treatment times are short. One application daily for 1 week is associated with high cure rates. Furthermore, patients often stop treatments when the skin appears healed, usually after about a week of treatment. If this short-term treatment is stopped, fungi recur more often when fungistatic, rather than fungicidal, drugs have been used [23]. Hence, developing topical antifungal formulations offers difficult challenges in order to get effective antifungal therapy [11].

As many azoles are poorly water soluble, the current commercial products of antifungal azoles for superficial mycosis may not be optimal for successful therapy. New formulations have been reported to optimize their topical delivery and ultimately the antifungal effects (**Figure 2**). Therefore, the goal of new topical antifungal products should be good compliance, which means shortening of the treatment period, high penetration of the drug into horny cell layers, nails and hair, and high affinity to horny cell layers in order to keep a high concentration of the drug within the lesions [24].

5. Different antifungal agents

5.1 Polyenes

The two topical polyenes available in the US are nystatin and amphotericin B. Both work by means of the same mechanism of action, namely by increasing cell membrane permeability by binding to ergosterol. The polyenes are useful in the treatment of cutaneous and mucocutaneous involvement with Candida spp., for which they are fungicidal and fungistatic. However, their use is limited by the fact that they have no significant activity against dermatophytes. The principal

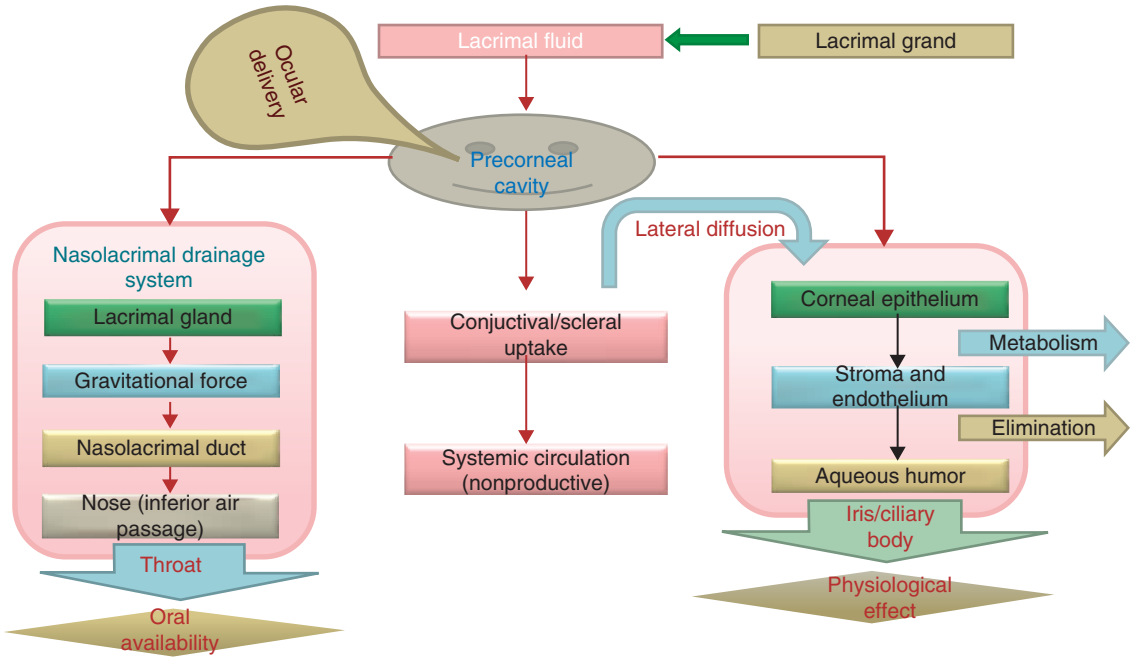

Figure 1. Factors contributing to poor bioavailability of an ophthalmic formulation.

current uses of the topical polyenes include treatment of candidal intertrigo, candidal vaginitis and oral thrush [25]. Natamycin (pimaricin) and amphotericin B are the two polyenes in current use for treatment of ophthalmic mycoses.

5.1.1 *Nystatin*

Nystatin, discovered in 1950, was the first specific antifungal, produced by certain strains of *Streptomyces noursei*. It has both fungistatic and fungicidal activity and a broad spectrum of activity against yeast infections (nystatin has no antidermatophytic properties); it is used to treat *C. albicans*.

It has been used for > 30 years, but primarily as a topical agent because of its toxicity and insolubility. However, a liposomal formulation has been created that might give new promise to intravenous use of this agent [26]. A Phase II study was conducted in which liposomal nystatin 4 mg/kg/day was administered intravenously to 24 patients with definite or probable invasive Aspergillosis who were refractory or intolerant to amphotericin B [27]. A complete response was seen in 5% of evaluated patients, and a partial response was seen in 26% of patients. Dosage reduction was required for nephrotoxicity in 13% of the patients, and 92% were premedicated for chills or respiratory distress after the first infusion, as nystatin administration is associated with these side effects. Dosage was discontinued for severe rigors, chills and hypotension in 8% of the patients enrolled in the study [27].

5.1.2 *Amphotericin B*

Amphotericin B is also a broad spectrum antifungal drug, produced by *Streptomyces nodosus*, active against dermatophytosis and yeast infections. Amphotericin B is invariably fungistatic and occasionally fungicidal, depending on the concentration achieved in serum [28] and the susceptibility of the pathogens; maximum activity is seen at a pH range from 6.0 to 7.5. Amphotericin B has been administered by intravenous, topical, intravitreal and intracameral routes for therapy of ophthalmic mycoses [29,30].

Intravenous amphotericin B continues to be the treatment of choice for invasive fungal infections of the orbit [31,32]. For topical administration, a solution (0.15 – 0.3%) may be freshly prepared with sterile water (amphotericin B precipitates in saline); the preparation must be refrigerated in a dark bottle to reduce the extent and rate of disintegration [29]. Drops may be instilled every 30 – 60 min. The corneal penetration of amphotericin B is reduced in the presence of an intact corneal epithelium [33,34]. An important concern in the topical application of amphotericin B is the possibility of corneal toxicity [35]. Fortunately, the 0.15% solution of amphotericin B in sterile water used in clinical practice appears to be well tolerated. Topical application of 0.5% ointment may cause some conjunctival irritation [29], although a 2% ointment was reported to be well tolerated in therapy of mycotic keratitis [36]. Subconjunctival injection has been reported to lead to severe toxic effects and is no longer recommended. Amphotericin B in solution or as an ointment has been used topically to treat conjunctivitis, scleritis and keratitis [36-38]; it is the treatment of choice for keratitis because of its efficacy against causative Candida spp.

Amphotericin for intravenous administration was originally available only in a conventional colloidal form; liposomal and

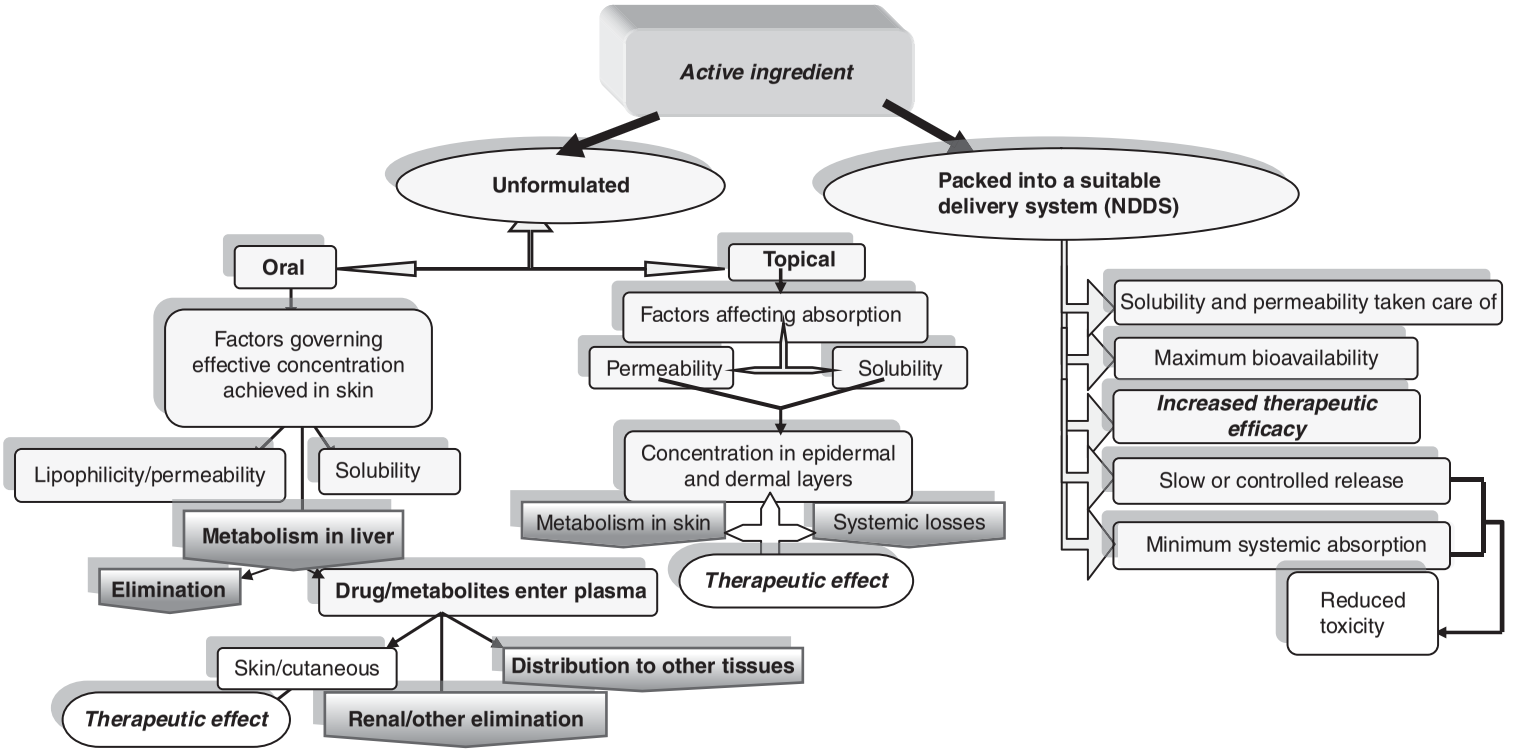

Figure 2. Advantages of drug loaded in a carrier *vis-Á-vis* in a conventional vehicle. Pentagonal boxes represent negative influence.
NDDS: New drug delivery system.

other formulations have now been developed to reduce toxicity. Most of the reported adverse events apply to the conventional form. Three lipid-based formulations of amphotericin available commercially in some countries are: liposomes (e.g., AmBisome, UK); a lipid complex with L-α-dimyristoylphosphatidylglycerol (e.g., Abelcet, UK); and colloidal dispersion with sodium cholesteryl sulfate (e.g., Amphocil, UK) [39]. The aim of reducing the renal toxicity has largely been achieved by these liposomal forms and other complexes of amphotericin, and they are used when conventional amphotericin is contraindicated because of toxicity, especially nephrotoxicity. The liposomal formulation of amphotericin B has allowed the administration of more than five times the doses of the drug with considerable improvement in the safety profile [40,41].

Collagen shields, iontophoresis and pumps have all been used in an attempt to enhance drug delivery to the eye. The use of iontophoresis and pumps has not gained acceptance, and these techniques are difficult to adapt for the eye. However, the collagen shield, which is shaped like a contact lens and is packaged in a dehydrated form and rehydrated before use, has been used to promote corneal epithelial healing and to deliver drugs [21]. The collagen shield has been found to be useful for delivering drugs to the eye because therapeutic levels of medication are delivered reliably with a minimum number of applications. Shields soaked in water-soluble drugs have been found to produce corneal and aqueous levels comparable to those obtained with frequent topical therapy. The prolonged exposure time of medication to the cornea provided by a presoaked shield may produce higher levels in tissue than a single drop that is rapidly carried away by the tears [21].

Amphotericin B-loaded collagen shields have been suggested for the control of *C. albicans*-induced keratomycosis [30]. Delivery of amphotericin B by a collagen shield may improve compliance and ensures a more constant rate of drug delivery in mycotic keratitis [29]. In one study, collagen shields soaked in amphotericin B were found to achieve corneal amphotericin B levels comparable to those achieved by hourly topical administration of drops [42]. In another study, collagen shields presoaked with 0.5% amphotericin B and applied for 1 h/day were found to be as effective as topical applications of 0.15% amphotericin B every hour for 8 h/day in reducing fungal colony counts in experimental *C. albicans* keratitis [43]. Peak levels with collagen shield delivery were found to occur at 1 h and then to fall to achieve a steady-state between 3 and 6 h; however, even at 6 h corneal amphotericin B levels obtained with the collagen shield were still within the therapeutic range. The use of collagen shields, however, may make it difficult for the clinician to perform frequent clinical examinations of the affected eye; improper use may also lead to increased toxicity [42].

5.1.3 Natamycin

Natamycin is a polyene antibiotic produced by the growth of *Streptomyces natalensis*, and is at present the only topical ophthalmic antifungal compound approved by the US Food and Drug Administration. It is reported to have a broad spectrum of activity against various fungi, including species of *Fusarium*, *Aspergillus*, *Acremonium*, *Penicillium*, *Lasiodiplodia* and *Candida* [29,30]. Natamycin is poorly soluble in water. It is stable in a 5% suspension and, in this form, adheres well to the cornea for clinically useful periods [29]. The 5% topical ophthalmic suspension, although viscous, is well tolerated and causes no pain or secondary corneal damage. Natamycin penetrates the cornea and conjunctiva poorly after topical application and effective drug levels are not achieved in either the cornea or the aqueous humor, and it is useful only in the treatment of superficial infection [29]. Thirteen topical applications every 5 min resulted in a drug concentration of ~ 2.5 mg/g cornea in rabbit corneas debrided of epithelium; levels peaked at ~ 10 min after administration. Natamycin is the drug of choice for therapy of mycotic keratitis in many countries [38,44], particularly for keratitis due to filamentous fungi. It has also been used in association with other treatment modalities for therapy of mycotic scleritis [45], conjunctivitis and endophthalmitis; controlled clinical trials are, however, needed to confirm the efficacy of natamycin for these indications.

5.2 Azoles

The first topical imidazole antifungal agent, chlormidazole, was developed in 1959. Since that time, the number of agents in this class that are well tolerated has increased. The azoles can be subdivided into the imidazoles and the triazoles; all azoles work by means of the same mechanism of action, that is, the inhibition of the cytochrome P450-dependent enzyme 14-α-demethylase, an essential enzyme in ergosterol synthesis (**Table 2**). At the minimum inhibitory concentration, these agents are fungistatic, although at 5 – 10 times the minimum inhibitory concentration they do demonstrate fungicidal activity [46]. Members of this class include clotrimazole, econazole, ketoconazole, miconazole, oxiconazole and sulconazole. These agents have broad spectrum activity, including activity against some Gram-positive bacteria. Ketoconazole, sulconazole and oxiconazole require only once-daily application because of their long duration in the superficial layers of the skin. Clotrimazole, miconazole and econazole require twice-daily application.

Some of these agents demonstrate slightly different pharmacokinetic profiles than the older agents. For example, oxiconazole and sulconazole remain in the skin for an extended period of time and may therefore be given in a single daily dose [25]. In the eye, azoles, with the exception of fluconazole, achieve only limited concentrations; they are considered as fungistatics when used in ocular fungal infections [47].

Many azole drugs have low aqueous solubility because of their hydrophobic structures. For example, miconazole, ketoconazole and itraconazole are all very slightly soluble (< 1 μg/ml) or insoluble at neutral pH, whereas the aqueous solubilities of fluconazole are thousands of times higher. Generally, low

aqueous solubility is associated with low oral bioavailability [48]. This can have a negative impact on antifungal efficacy, side effects, pharmacokinetic variability and the development of drug resistance [49]. New drug delivery systems (NDDSs) can improve the antifungal pharmacokinetics with targeted delivery, followed by sustained release and prolonged retention of high drug concentration localized at the infection sites, therefore enhancing the bioavailability and therapeutic efficacy of azole antifungals. The imidazole antifungals may cause many side effects when administered systemically (**Table 2**). Site-directed topical antifungal drug delivery can reduce non-target site toxicities [50]. Therefore, the antifungal imidazoles have mostly been formulated as topical preparations for the treatment of superficial fungal infections. Various patents have been granted dealing with topical delivery of azoles [51,52] and enhancing penetration of these agents [53-56].

5.2.1 *Clotrimazole*

Clotrimazole, an imidazole, is used topically in the treatment of superficial candidiasis and in skin infections of pityriasis versicolor and dermatophytosis. When applied topically clotrimazole penetrates epidermis, but there is little, if any, systemic absorption. Clotrimazole is available topically as a cream, lotion or solution for the treatment of fungal skin infections.

Clotrimazole is widely used for the treatment of mycotic infections of the genitourinary tract. To develop an alternative formulation for the vaginal administration of clotrimazole to provide sustained and controlled release of appropriate drug for local vaginal therapy, liposomes/niosomes were evaluated as delivery vehicles. The ability of the systems to deliver clotrimazole into and through the mucosa was evaluated *in vitro* using rabbit vaginal mucosa with vertical Franz diffusion cells, which showed that the liposome/niosome system increased the total penetration through the vaginal mucosa 1.6/1.5-fold, and the accumulation of clotrimazole into the mucosa was increased 3.1/2.3-fold, respectively, compared with control during 24 h [57].

Topical application of liposomes has been shown to enhance the penetration of vesicle-bound drugs into the skin where they act as 'drug localizers', with low systemic absorption and sustained drug release locally [58]. Niosomes, analogous to liposomes, are closed bilayer structures of self-assembled non-ionic amphiphiles in aqueous media. They have higher chemical stability, intrinsic skin penetration-enhancing properties and a lower cost compared with liposomes [59]. Topical application of niosomes is similar to liposomes *in vivo*, with a prolonged contact time of drug with the applied tissues [60], thus illustrating the potential of drug in niosomes to improve skin penetration and accumulation in the superficial skin strata. Liposomal clotrimazole (e.g., clotrimazole:phospholipid:cholesterol = 2:7:3, molar ratio) and niosomal clotrimazole (e.g., clotrimazole:Span 40: cholesterol = 1:8:2, molar ratio) for vaginal administration were developed to reduce dosing frequency and drug toxicity, which are issues associated with formulations available at present [61]. The two formulations were then incorporated into a 2% carbopol gel as topical preparations. The antifungal efficacies of these formulations were tested *in vivo* using oophorectomized female rats, with intravaginal inoculation of *C. albicans*. The results demonstrated prolonged and enhanced antifungal activity of the liposomal and niosomal formulations, relative to a control drug containing gel and a marketed clotrimazole ointment. Also, the liposome and niosome gels were well tolerated. This study suggested that alternative formulations for clotrimazole and other antifungal azoles could provide sustained and controlled release of drug for local vaginal therapy.

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are colloidal carrier systems composed of physiological and biodegradable lipids of low toxicity [62]. Both SLNs and NLCs possess several features that are advantageous for topical application, including protection of labile drugs against chemical degradation, controlled release of the drug, prolonged residence time of formulation in the SC and targeting of drug to the upper layers of the skin [63]. They were also reported to have occlusive properties as a result of barrier film formation after application [64]. Azole antifungal drugs are good candidates for SLN encapsulation because of their high lipophilicity. Moreover, the small size of lipid particles ensures close contact to the SC and an occlusive effect can increase the amount of drug penetration into the mucosa or skin [65,66]. SLNs incorporating clotrimazole [66], prepared by the hot high-pressure homogenization technique, showed high entrapment efficacy (> 50%), sustained release over a 10 h period and considerable physicochemical stability.

5.2.2 *Miconazole*

Miconazole is available as a solution for intravenous administration; it can also be used for ocular administration as a 1% (10 mg/ml) solution [67] or for subconjunctival administration (5 – 10 mg) [68]. In an experimental rabbit model, aqueous humor levels of 8 µg/ml were noted 1 h after intravenous administration of miconazole (30 mg/kg), levels of 10 µg/ml were noted after subconjunctival injection (10 mg), and levels of 4.5 µg/ml were noted after topical administration (1% solution) every 15 min for 8 doses to corneas with the epithelium debrided [69].

The epithelial cells in the various tissues, including the skin, carry a negative charge on their surface owing to the presence of negatively charged residues of proteins in the outer membrane of the cells and to selective active ion pumps of the membrane. All epithelia are, therefore, selective to positively charged solutes [70]. It is anticipated that a positively charged delivery system that strongly interacts with the cells will result in better permeability of the drug and a prolonged pharmacological effect. Based on these overall results/deductions, submicrometer emulsion was designed for topical delivery with the ultimate objective of enhancing local therapeutic concentration while sustaining the release of the active drug.

Charged submicron emulsions were made using stearylamine or deoxycholic acid to incorporate either econazole or miconazole nitrate, respectively, in positively and negatively charged submicron emulsions. The investigation of the relationship between the physicochemical properties of the vehicles, especially the charge of the emulsion and skin permeation, was conducted *ex vivo* during percutaneous absorption experiments using hairless female rat skin. The results clearly indicated that the surface-modified droplets have a significant influence on the diffusion through the skin, and the positively charged submicron emulsions were found to be more effective in terms of skin penetration of econazole or miconazole nitrate than negatively charged emulsions. The interaction of submicron emulsions with skin depends on several factors, which include the surface electrical charge of the droplets, the emulsion composition, the physiological properties of the skin and the drug. These results suggest that positively charged droplets of submicron emulsions are able to carry efficiently econazole or miconazole into the skin and subsequently promote the penetration of drugs through the skin. The degree of skin binding is probably more important with the positively charged droplets than with the negatively charged droplets as it is known that the skin is negatively charged at neutral pH [71].

Pershing *et al.* [72] investigated differential drug uptake of topical 2% miconazole and 2% ketoconazole from cream formulations into human SC and the results correlated with differential pharmacological activity against *C. albicans* in healthy human subjects. A single 24-h topical equi-dose was applied unoccluded at 4 skin sites on both ventral forearms of 6 human subjects. Topical 2% ketoconazole produced 14-, 10- and 7-fold greater drug concentrations in SC than 2% miconazole at 1, 4 and 8 h, respectively, after a single topical dose. Ketoconazole and miconazole concentrations in the SC were similar 24 h after drug removal. Tape disc extracts from 2% ketoconazole-treated skin sites demonstrated significantly greater bioactivity in the bioassay than 2% miconazole. Increased efficacy of 2% ketoconazole compared with that of 2% miconazole *in vitro* reflected their differential uptake into the SC and inherent pharmacological activity. The inferior miconazole bioactivity per amount of drug in the SC compared with that of ketoconazole is the result of decreased uptake into the SC, its lesser inherent pharmacological activity, and possibly tissue binding of miconazole within SC. The good correlation between the drug uptake into skin and the resulting bioactivity combined with the dose response of pharmacological activity of miconazole against *C. albicans* in the bioassay suggest that improving miconazole uptake into human SC should result in better bioactivity and therefore better clinical efficacy. Another group [73] entrapped miconazole in liposomes and found that liposomes provided a higher penetration and retention in the skin than commercial cream, with the added advantage of localized and controlled delivery of the drug.

SLNs are attracting great attention as new colloidal drug carriers for topical use. The small size and relatively narrow size distribution of SLNs permit site-specific delivery to the skin. SLNs have high affinity to the SC, and therefore an enhanced bioavailability of the encapsulated material, especially the lipophilic molecule, to the skin is achieved. Miconazole nitrate lipid nanoparticles were incorporated in gels for convenient topical application and were evaluated *ex vivo* for skin penetration. With gel containing nanoparticulate dispersion, a greater quantity of drug remained localized in the skin with a lesser amount penetrating into the receptor compartment in comparison with the conventional gel containing free drug [74].

5.2.3 Ketoconazole

Ketoconazole is an imidazole administered topically or by mouth. Ketoconazole, the first successful orally absorbable broad spectrum antifungal azole, is available at present as an oral preparation (200 mg) worldwide. Formulations for ocular or subconjunctival administration are not available, which is unfortunate because experimental studies suggest that concentrations as high as 1391.5 ± 130.0 μg/g can be achieved, particularly after topical administration and to a lesser extent after subconjunctival injection, in the debrided corneal epithelium [75]. Further, the topical application is not associated with significant corneal toxicity [35].

Ketoconazole has been recommended topically and systemically for treating fungal keratitis. To treat keratitis, a high concentration of the antimycotic drug in the cornea and aqueous humor is desired; but ketoconazole is poorly water soluble, so a vehicle is desired to make ketoconazole soluble to administer it in an aqueous eye-drop solution. Thus, Zhang *et al.* [76] combined this drug with cyclodextrins to improve solubility of ketoconazole and evaluated the ocular bioavailability of a ketoconazole solution (ketoconazole complexed with hydroxypropyl-β-cyclodextrin) and suspension. *In vivo* studies showed that ketoconazole solution produced an eightfold increase in bioavailability in the aqueous humor compared with suspension, and a 12-fold increase in bioavailability in cornea over suspension.

Ketoconazole is applied topically as a 2% cream (**Table 3**) for the treatment of candidal or dermatophyte infection of the skin, or in the treatment of pityriasis versicolor, and is applied once or twice daily. A shampoo containing 2% ketoconazole is applied twice weekly in the treatment of seborrhoeic dermatitis or once daily for pityriasis versicolor.

Extina® (Connetics Corporation, USA) is a foam formulation of 2% ketoconazole for the treatment of mycoses and dermatological indications, particularly seborrhoeic dermatitis. The product utilizes Connetics' (USA) proprietary foam drug delivery technology, VersaFoam™. The foam formulation had a twofold higher amount of ketoconazole in the epidermis compared with the cream (Nizoral®, Janssen Pharmaceutica, Belgium) formulation with mild-to-moderate adverse effects, primarily burning and stinging [77].

Microemulsions can improve drug stability and availability because of surfactant solubilization of the drug, and therefore

Table 3. Most commonly available dosage form and dosing frequency of antifungal agents [137].

Drug	Brand name	Strength (%)	Form	Dosing frequency	Manufacturers
Nystatin	Mycostatin	100,000 units nystatin/g	Cream	Twice daily	Westwood-Squibb
	Nilstat	100,000 IU/g	Vaginal cream	Once or twice a day	Zuellig Pharma
Amphotericin B	Fungizone	3%	Cream	2 – 4 times a day	Apothecon
	Abelcet	5 mg/ml	Amphotericin B lipid complex injection	1 mg/kg once a day	Bristol-Myers Squibb
	Ambisome	50 mg/vial	Liposome for injection	1 mg/kg once a day	Gilead Sciences Fujisawa
	Amphotec	50 or 100 mg/vial	Amphotericin B cholesteryl sulfate complex for injection	1 mg/kg once a day	Sequus Pharmaceuticals
Natamycin	Natacyn	5%	Ophthalmic suspension	One drop instilled in the conjunctival sac at hourly or two-hourly intervals	Alcon
Clotrimazole	Lotrimin	1%	Cream	Twice daily	Schering
	Gyne-Lotrimin	1%	Vaginal cream	Once daily	Schering Plough
	Mycelex-G	1%	Vaginal cream	Once daily	Miles
Miconazole	Monistat-IV (also recommended in ocular infection)	10 mg/ml	Intravenous	Twice daily	Janssen
	Micatin	2%	Cream	Twice daily	Pfizer
	Monistat-ermD	2%	Cream	Twice daily	Ortho-McNeil Pharmaceutical
Ketoconazole	Nizoral	200 mg	Tablets	200 mg/day	Janssen
	Nizoral	2%	Cream	Once daily	Janssen
	Xolegel gel (for the topical treatment of seborrheic dermatitis)	2%	Gel	Once daily	Stiefel Laboratories
	Extina (for the topical treatment of seborrheic dermatitis)	2%	Foam	Once daily	Stiefel Laboratories
Econazole	Spectazole	1%	Cream	Twice daily	Ortho
Oxiconazole	Oxistat	1%	Cream	Once daily	Glaxo
Sulconazole	Exelderm	1%	Cream	Once daily	Westwood Squibb
Sertaconazole	Ertaczo	2%	Cream	Twice daily	OrthoNeutrogena
Bifonazole	Canesten	1%	Vaginal cream	Once a day	Bayer

Table 3. Most commonly available dosage form and dosing frequency of antifungal agents [137] (continued).

Drug	Brand name	Strength (%)	Form	Dosing frequency	Manufacturers
Butoconazole	Femstat	2%	Vaginal cream	One full applicator inserted into vagina at bedtime	Procter Syntex
	Gynazole	2%	Vaginal cream		KV Pharmaceutical
Fluconazole	Syscan	0.3%	Eye drops		Torrent
	Flutaur drops	0.3%	Eye drops	2 – 3 times a day	Taurus
	Zocon eye drops	0.3%	Eye drops		FDC
	Flucomet	0.3%	Eye drops		Sun (Milmet)
	Diflucan	50, 100, 150 and 200 mg	Tablets	1 – 2 times a day	Pfizer
Itraconazole	Sporanox	100 mg	Capsules	200 mg once daily	Janssen
Terbinafine	Lamisil	250 mg	Tablets	Once daily for 6 weeks	Patheon Whitby
	Lamisil	1%	Cream	Once or twice a day for 1 – 4 weeks	Novartis
Naftifine	Naftin	1%	Cream	Once or twice a day	Merz Pharmaceuticals
	Naftin	1%	Gel	Twice a day	Merz Pharmaceuticals
Butenafine	Mentax	1%	Cream	1 – 2 times a day	DPT Laboratories
Ciclopirox	Loprox	0.77%	Cream	Twice a day	Hoechst-Marion-Roussel
	Loprox gel	0.77%	Gel	Twice daily	Aventis Pharma
	Ciclopirox Penlac nail lacquer	8%	Topical solution	Once daily	Dermik
Amorolfine	Loceryl nail lacquer	5% w/v	Nail lacquer	Once or twice a week	Galderma

have a significant impact on transdermal delivery. A water-in-oil microemulsion of ketoconazole was prepared using olive oil, water and Labrafil®M 1944 CS and Plurol® Oleique (1:1). The release profiles of ketoconazole from microemulsion and gel formulation were compared and the results showed that release rates from both the formulations did not have significant differences [78].

5.2.4 Econazole

When econazole is applied to skin, absorption is not significant. It is available as a cream, lotion, powder and solution to be applied topically in the treatment of fungal infections. The SC is the target organ of antimycotic treatment, and the improvement of local bioavailability leads to enhanced efficacy of the applied formulation [79]. SLNs and NLCs have been investigated as topical particulate carriers for econazole. Econazole nitrate-loaded SLN has been prepared by oil-in-water high-shear homogenization, with a mean particle size of ~ 150 nm for topical administration [80]. Applying the SLN-incorporated hydrogels onto *ex vivo* porcine SC, the SLN hydrogels were able to control the drug release through the SC and the release rate was dependent on the lipid content of the SLN. Moreover, *in vivo* studies done by a tape stripping technique on five healthy human subjects showed that the econazole nitrate-loaded SLN promoted rapid penetration of drug through the SC 1 h post-application and improved drug diffusion into the deeper skin layers 3 h after application, compared with a conventional gel containing only econazole nitrate. These results suggested that drug-loaded SLNs could be useful for site-specific delivery of antifungal drugs to the skin.

Unlike skin, topical treatment of onychomycosis has been unsatisfactory because of the deep-seated nature of the infection and the ineffective penetration of the deep nail plate by topically applied nail lacquers, a popular dosage form for onychomycosis. A suitable carrier is needed to ensure that a sufficient amount of the antifungal drug penetrates across the nail barrier to the infection sites. The addition of a penetration enhancer 2-*n*-nonyl-1,3-dioxolane (18% v/v) to EcoNail™ (Access Pharmaceuticals, USA) increased econazole content in the ventral/intermediate nail plate and the support bed under the nail 6 and 200 times, respectively, compared with EcoNail™ alone, after twice-daily application for 14 days to human nails [81].

Econazole (2% w/w) liposomal suspension was prepared using an ethanol injection technique and was incorporated into a carbopol gel. The encapsulation efficiency of econazole in liposomes was optimized to > 90% and the mean size of the liposomes was 521 ± 64 nm. The liposomal gel controlled econazole release *in vitro* compared with the liposomal suspension. The liposomal gel proved capable of enhancing drug accumulation at the administration site and retained the drug in mice skin. Liposomes may, therefore, be taken as another useful vehicle for topical drug delivery in the treatment of various skin diseases [82].

5.2.5 Oxiconazole

Oxiconazole is an imidazole antifungal applied topically as a cream, solution, or powder equivalent to oxiconazole 1% in treatment of fungal infections of the skin and as pessaries in treatment of vaginal candidiasis. An *in vivo* study was conducted to assess the nail permeation of oxiconazole from 1% w/v lotion and the effect of co-delivering *N*-acetylcysteine, which functions as a penetration enhancer by breaking down keratin disulfide bonds in the nail [83]. The data showed the effect of *N*-acetylcysteine in promoting oxiconazole penetration into the upper nail layers. The results showed that *N*-acetylcysteine was able to enhance oxiconazole uptake and retention in the upper nail layer. This may be owing to an interaction between the drug and free thiol groups. Although the enhancer had little effect deeper into the nail plate, it has been reported that drug diffusion in the upper layer of the human nail plate is the rate-determining step in nail permeation [84].

5.2.6 Sulconazole

Sulconazole is an imidazole antifungal with activity against dermatophytes, Candida spp. and *Malassezia furfur*. It is slightly soluble in water (1.9 mg/ml) and in order to improve its solubility and hence the bioavailability, β-cyclodextrin-sulconazole nitrate inclusion complexes [85] were synthesized.

It is applied topically as 1% cream (**Table 3**) for the treatment of skin fungal infections. Sulconazole nitrate 1% cream was compared with miconazole nitrate 2% cream in a study involving patients with cutaneous dermatophytosis. Both agents were highly effective, with no statistically significant differences in the parameters studied [86].

5.2.7 Sertaconazole

Sertaconazole is an imidazole used topically in the treatment of superficial candidiasis, dermatiphytosis and pityriasis versicolor. Sertaconazole is a broad spectrum antifungal agent with excellent activity against yeasts, dermatophytes and opportunistic fungi. In addition to this antifungal efficacy, it has a good safety profile, sustained cutaneous retention and low systemic absorption, all of which make it ideal for topical applications. It has been used in Europe to treat a wide variety of skin infections caused by dermatophytes, Candida spp. and *M. furfur* [87] and was approved in the US for the treatment of tinea pedis, which is caused primarily by *Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Epidermophyton floccosum*. Sertaconazole has two primary effects on cell function. First, it inhibits ergosterol synthesis by blockade of the P450-dependent enzyme pathway that catalyzes the methylation of lanosterol to ergosterol, a major constituent of fungal cell wall membranes [88]. Second, it binds directly to non-sterol lipids in the membrane, which interferes with the regulation of the permeability of fungal cell membranes. Inhibition of ergosterol synthesis interferes with fungal cell growth, whereas direct interaction with the membrane produces subsequent leakage of intracellular components,

particularly adenosine triphosphate, thereby contributing to immediate cell death. As a result, sertaconazole is an effective fungicidal and fungistatic agent [89].

Sertaconazole nitrate has been tested with a variety of *in vitro* methods, all of which show fungistatic activity against dermatophytes and fungicidal and fungistatic activity against yeasts [89,90]. Carrillo-Munoz and Tur-Tur [89,90] reported a rank order of potency of terbinafine > sertaconazole > bifonazole against 53 strains of dermatophytes when tested using a broth microdilution method. The MICs of sertaconazole against clinical and laboratory isolates of dermatophytes and candida have been evaluated with both agar and broth dilution MIC methods. Sertaconazole has proved to be among the most potent azoles in the treatment of dermatophytes and candida irrespective of the *in vitro* test method used. When compared with the allylamine drug terbinafine, the MICs of sertaconazole were comparable for dermatophytes and lower for Candida spp. In studies designed to compare the *in vitro* activity of several imidazoles against *C. albicans*, the rank order of fungicidal effect was sertaconazole > miconazole > clotrimazole > ketoconazole. In time–kill curves, sertaconazole produced a 90% fungicidal effect at 8 µg/ml. Ketoconazole was not fungicidal at concentrations as high as 64 µg/ml and did not reach 90% efficacy even after 4 h [91].

5.2.8 *Bifonazole*

Bifonazole is an imidazole antifungal with a broad spectrum of activity; sensitive fungi include dermatophytes, *M. furfur* and Candida spp. It is applied topically in the treatment of fungal skin and nail infections, available as cream, powder, or solution.

5.2.9 *Fluconazole*

Fluconazole and itraconazole belong to a new generation of more potent azoles introduced in the 1980s, known as triazoles. Fluconazole is an antifungal agent with a broad spectrum of activity [92]. Fluconazole is not only effective for deep-seated mycosis caused by Candida, Cryptococcus spp., and so on, but also for superficial infections caused by dermatophytes such as Microsporum and Trichophyton spp. [93]. Fluconazole was found to have extremely potent activity superior to that of ketoconazole in systemic fungal infection models in mice [94] and dermal infection models with *T. mentagrophytes* in guinea-pigs [95]. Oral bioavailability of fluconazole in healthy adult volunteers is > 90%, it is eliminated from plasma with a half-life of ~ 30 h, its pharmacokinetics shows good dose proportionality, and it is mostly excreted in the urine as unchanged drug [96,97]. As fluconazole was evenly distributed throughout the tissues of the body rapidly after administration and because it penetrates readily into skin [96,97], excellent clinical efficacy in the treatment of fungal skin infections is expected following oral administration [98]. After oral dosing (50 mg daily for 12 days or 150 mg once a week for 2 weeks), fluconazole accumulates in eccrine sweat and diffuses rapidly and extensively into the SC. Fluconazole concentration in the skin (SC and epidermis + dermis without SC) is higher than in the serum and its elimination from SC is considerably slower than from serum or plasma [99,100]. The highest concentration is achieved in SC and it is still high 1 week after completion of the treatment. This concentration is much higher than MIC for most dermatophytes [101]. The prolonged skin retention of fluconazole has been attributed to its high affinity to SC owing to an interaction between fluconazole and keratin [102]. However, fluconazole skin distribution after topical administration has been little investigated. Mathy *et al.* [103] reported that fluconazole unbound concentration in dermis, using dermal microdialysis, was higher than the MIC against *C. albicans*.

Dermatophytes generally colonize SC or keratinized adnexa and only very seldom penetrate into the cutis. Various yeasts can also penetrate into non-keratinized epidermis and cutis [104,105]. It is suggested that a high concentration of an antifungal agent is required to show sufficient efficacy against fungal skin infections not only in the SC but also in the epidermis-cutis. Fluconazole transfers to both the SC and epidermis-cutis at high concentrations. It is assumed to diffuse directly into the epidermis-cutis from capillary blood vessels, incorporate into the epidermal basal cells, and migrate to the surface during the normal turnover of keratinocytes, and a major portion of it exists as a non-binding form because of its small extent of binding to corneous keratin. Therefore, fluconazole is considered to be a drug with a favorable pharmacokinetic profile that is suitable for treating both superficial and deep-seated mycosis.

Microemulsions can improve drug stability and availability because of surfactant solubilization of the drug, and therefore have a significant impact on transdermal delivery. For example, a gel microemulsion of fluconazole has been reported to improve the percutaneous absorption of fluconazole as compared with emulsion, emulgel or lipogel [106,107]. A dermally applied microemulsion is expected to penetrate the stratum corneum and to exist intact in the whole horny layer. The drug dissolved in the lipid domain of the microemulsion can directly partition or intercalate into the lipids of SC [108], whereas its hydrophilic domain can hydrate SC so that the active compound can be carried easily through the SC [106].

Considering that vesicular systems intrinsically enhance the permeation of drugs bioactive into the skin and free fatty acids act as penetration enhancers for the bioactives through the stratum corneum [109] and also undergo self-assemblage into vesicles [110], Zakir *et al.* [111] prepared oleic acid vesicles for topical delivery of fluconazole. Oleic acid vesicles were found to provide sustained release and retained the drug in skin epidermis.

As fluconazole is a stable and water-soluble antifungal with low molecular mass, high bioavailability and low toxicity, it can potentially be useful as an ocular agent as well. Orally administered fluconazole was found to penetrate readily all ocular tissues and fluids of Dutch-belted rabbits [112]. After a

single oral dose of 20 mg/kg, the levels achieved were 13.3 ± 1.4 μg/g (cornea), 7.4 ± 0.3 mg/l (aqueous), 9.8 ± 0.9 mg/l (vitreous) and 5.2 ± 0.4 μg/g (choroid and retina); the concentrations in the cornea correlated highly with those in serum. A steady accumulation in both normal corneas and those infected with *C. albicans* was noted when fluconazole was given in a twice-daily divided dose; the presence of inflammation induced by fungal infection did not influence corneal uptake [112].

A biodegradable polymeric scleral implant containing fluconazole was reported to be a promising intravitreal drug delivery system to treat fungal endophthalmitis [113]. Scleral implants loaded with 10, 20 and 30% doses gradually released fluconazole over 4 weeks *in vitro*, whereas those with 50% doses released most of the drug in 1 week; implants with 30% fluconazole that were studied in pigmented rabbits resulted in vitreous concentrations of fluconazole (sustained for 3 weeks) sufficient to inhibit *C. albicans*. In another study [114], intravitreal injection of up to 100 μg of fluconazole per 0.1 ml of vitreous did not produce biomicroscopic, ophthalmoscopic, electroretinographic, or light microscopic evidence of intraocular toxicity, even 8 days after injection.

5.2.10 *Itraconazole*

Itraconazole is synthetic dioxolane triazole, which is well absorbed after oral administration. It is larger than fluconazole, very hydrophobic and > 90% bound to protein in serum [115]. It is highly concentrated in lipid-rich tissue and poorly soluble in aqueous solution, but well absorbed orally, especially when given with a meal or formulated in polyethylene glycol [116]. Itraconazole is generally well tolerated after oral administration; the most common complaint is gastrointestinal upset [117].

Itraconazole accumulates to high levels in keratin and persists in skin for 1 – 4 weeks after stopping treatment because of its lipophilic properties. The major drawback of using itraconazole by the oral route for therapy of ocular fungal infections is its poor availability in ocular tissues including cornea, aqueous humor and vitreous compared with that of fluconazole and ketoconazole.

Attempts have been made to administer itraconazole topically to the eye. In one study, topical 1% itraconazole cream was found to be effective only in non-severe mycotic keratitis [117]. In another study, a 1% suspension of itraconazole, prepared in a commercial isotonic eye-drop formulation containing methylcellulose, borax, boric acid, sodium chloride and potassium chloride, was found to be well tolerated when used for therapy of mycotic keratitis; however, it was not very effective in treating severe mycotic keratitis, perhaps owing to insufficient corneal penetration [118].

Mukherjee *et al.* [119] prepared itraconazole nanoparticles with the aim to improve the therapeutic efficacy and reduction of toxicity of this broad spectrum antifungal agent using lipid (palmitic acid) and surfactants (Pluronic F127 and Tween 40). A prolonged (12 h) *in vitro* drug release profile from nanoparticles was observed. Kinetic analysis of release indicated that nanoparticles formed were matrix in nature, in which itraconazole was dispersed uniformly.

A study investigated liquid crystal cream for delivering itraconazole topically [120]. Ternary water/non-ionic surfactant/oil formulations were used to formulate 1% itraconazole using polyoxyethylene stearyl ether as a surfactant, silicon oil as oil and cetostearyl alcohol as cosurfactant with an aqueous phase consisting of propylene glycol, water and a preservative. After physical characterization, *in vitro* antifungal activity was tested using the agar-cup method and *C. albicans* as a test organism. The liquid crystal cream proved to be efficient for topical itraconazole delivery by displaying the highest inhibition zone diameter as compared with hydroxyethyl gel and glyceryl monostearate cream.

Trey *et al.* [121] explored itraconazole for topical treatment of onchomycosis by using hydroxypropylcellulose (HPC) hot-melt extruded films as an alternative to toxic systemic delivery systems, as orally administered itraconazole leads to patient non-compliance because the patient must take an oral dose of itraconazole 2 – 3 times a day for 3 – 6 months and is associated with serious side effects. Owing to the low solubility of the drug, significant concentrations are stored in fat cells, reducing the amount available for the targeted nail bed [122]. HPC extruded patches were prepared to deliver effectively itraconazole topically to reduce non-target site toxicities by concentrating the dosage directly at the point of infection and providing controlled release of poorly water-soluble drugs.

5.3 Allylamines

Both the allylamines terbinafine and naftifine are very effective against a broad range of dermatophytes and yeasts causing tinea corporis, tinea cruris, tinea pedis, cutaneous candidiasis and pityriasis versicolor, both are well tolerated, rarely causing adverse events such as local irritation or burning at the site of application, and naftifine is found to be associated with anti-inflammatory activity [123].

5.3.1 *Terbinafine*

Terbinafine is an allylamine reported to have a broad spectrum of antifungal activity, which was commercialized in 1995. Terbinafine is administered orally and topically and is generally well tolerated [124]. Terbinafine is fungicidal against dermatophytes and fungistatic against *C. albicans*. Despite studies that seem to demonstrate the effectiveness of terbinafine and butenafine against cutaneous *Candida* infections [125], neither has yet been approved for this indication.

Terbinafine is absorbed well from the gastrointestinal tract. About 40% of the dose undergoes first-pass metabolism. Mean peak plasma concentrations of ~ 1 μg/ml have been reported within 2 h of a single oral dose of 250 mg. Terbinafine is bound extensively to plasma proteins. Terbinafine is distributed into the SC of the skin, the nail plate and hair, where it reaches concentrations considerably higher than

those found in plasma. Less than 5% of a topical dose of terbinafine hydrochloride is absorbed.

In a systemic review by Crawford *et al.* [126] of the oral antifungal agents used to treat dermatophyte onychomycosis, terbinafine appeared to be the most effective therapy for the long-term management of fungally infected toenails. Similarly, in a critical review of long-term efficacy of antifungals in the treatment of toenail onychomycosis, terbinafine was superior to griseofulvin, ketoconazole, fluconazole and itraconazole. De Cuyper and Hindryckx [127] also assessed long-term outcomes in the treatment of toenail onychomycosis. The authors suggested the final assessment at 48 – 52 weeks may overestimate the benefits of treatment because toenails can take up to 12 – 18 months to grow out fully; hence, residual infection and late relapse may be missed. In this assessment, excellent results achieved with terbinafine at 48 weeks were maintained up to and beyond 2 years. Also, failure and relapse rates were much higher in individuals treated with itraconazole compared with terbinafine. These long-term benefits of terbinafine may be related to its primary fungicidal action.

Terbinafine administered orally is one of the most effective treatments for onchomycosis [128], but is found to be associated with various systemic side effects, which include nausea, diarrhea, erythema, pruritus, urticaria, rare cases of severe hepatitis and subacute lupus erythematosus (**Table 2**). Ricketti [129] demonstrated the efficacy and safety of miconazole nitrate 2% (Fungoid®, Pedinol Pharmacal, USA) tincture containing terbinafine tablets (Lamisil®, Novartis, Switzerland) by local application to the nail of onchomycosis patients. The results indicated 53% of nails were cured by the end of the study and no local adverse effects were observed.

On the NDDS front, in 2009 results from a clinical study (Phase II) of a new formulation (terbinafine in Transfersomes®, referred to as TDT-067) for topical treatment of onychomycosis were reported by Celtic Pharma (Bermuda) [130]. Transfersomes have been developed for the non-invasive delivery of agents into or through the skin. Transfersome preparations consist of complex lipid vesicles, which are able to cross the skin permeability barrier, the stratum corneum, driven by the transcutaneous water gradient. TDT-067 is a new, epicutaneously applied (applied directly to the skin) carrier-based dosage form of terbinafine for the treatment of onychomycosis of the toenail and fingernail. This is an open-label study to explore the efficacy and safety of topically applied terbinafine delivered through the Transfersome-targeted delivery technology.

5.3.2 *Naftifine*

Naftifine is an allylamine derivative reported to be fungicidal against dermatophytes and fungistatic against *C. albicans*. Naftifine is applied topically for fungal infections treatment, particularly dermatophytosis and pityriasis versicolor. The allylamines demonstrate a high affinity for the SC because of their lipophilic nature. This probably accounts for the fact that naftifine and terbinafine may be found in the SC at therapeutic levels for up to 1 week after stopping therapy. Naftifine has been noted to have intrinsic anti-inflammatory properties, which are not seen in terbinafine [25].

Naftifine hydrochloride is a synthetic, broad spectrum antifungal agent and is among the first choice drugs for the treatment of dermatophytosis. The problem in formulating naftifine hydrochloride is that the required concentration in the topical preparations exceeds its aqueous solubility. Attempts have been made to formulate the drug as creams, where formulation pH liberates the drug base, which is emulsified as an oil-in-water cream. Alternatively, naftifine hydrochloride has been solubilized using alcohol and Tween 80 and formulated in the form of a hydroalcoholic gel containing 52% (v/v) alcohol. A major concern with such hydroalcoholic products is the clinical implications and consequences of repeated skin exposure to a high alcohol concentration [131].

Ethanol is able to penetrate normal skin within a few minutes through the sweat and sebaceous gland ducts, and transepidermally through the SC. The permeability constant of the human abdominal skin for ethanol is ~ 1.2×10^{-3} cm/h, a value comparable to that of water (1.0×10^{-3} cm/h). Skin alteration as a result of repeated alcohol application has been clinically observed, and includes dryness, desquamation, brown maculae, inhibition of hair growth, erythema, urticaria, papules, vesicles and erosions. Histologically, hyperkeratosis, acanthosis, epithelial atypism and mast cell degranulation were confirmed. Such adverse effects of alcohol are attributed to the carbon atoms of alcohol (C–OH), which yield free radicals leading to fast and violent reactions, especially on vulnerable skin [132]. Barakat *et al.* [131] prepared alcohol-free niosome gel containing 1% naftifine hydrochloride. An alcohol-free controlled delivery hydroxyethylcellulose gel containing 1% (w/w) naftifine hydrochloride was developed. The gel showed good stability and maintained drug delivery over a 12 h study period. The gel contains the drug in both the free form (50%) and niosome-entrapped form (50%) to generate an intended two-phase release profile. Niosomes used in the gel formulation are negatively charged niosomes with 0.15 µm mean diameter, developed in the study. The results suggest the potential usefulness of the niosome gel.

5.4 Allylamine-like benzylamine derivatives

5.4.1 *Butenafine*

Butenafine has a similar structure, mechanism of action and activity to allylamines. It is applied topically as a 1% cream for the treatment of superficial dermatophyte infections.

5.5 Hydroxypiridones

5.5.1 *Ciclopirox*

Ciclopirox has a wide spectrum of antifungal activity. It is applied topically as cream, solution, and powder for treatment of cutaneous candidiasis and other fungal skin infections, namely dermatophytosis and pityriasis versicolor; but ciclopirox 8% nail lacquer is a common topical formulation of ciclopirox for treatment of nail infections. Ciclopirox nail

lacquer is the only nail lacquer approved by the FDA for the treatment of onychomycosis. The lacquer delivery system provides a high concentration gradient for the transfer of the antifungal agent through the nail plate. Daily application to the toenail surface of healthy subjects resulted in good penetration and distribution within all nail layers [133].

In a study done by Hui *et al.* [134], the human nail penetration of ciclopirox was significantly greater with the marketed gel containing 0.77% of ciclopirox than an experimental gel containing 2% of ciclopirox, and a marketed lacquer containing 8% of ciclopirox. In addition, the surface nail contained more unabsorbed drug from the lacquer. Further, the amount of drug penetrating into and through the nail was also greater with the marketed gel, leading to a higher calculated efficacy coefficient for the marketed gel, than with the marketed lacquer or the experimental gel. The formulation plays an important role in the enhancement of ciclopirox permeation into and through the human nail plate, and the concentration of ciclopirox in the formulation was not a factor in determining penetration.

5.6 Morpholine derivatives

5.6.1 *Amorolfine*

Amorolfine is a morpholine derivative type of antifungal, unrelated to the polyenes, azoles, or allylamines. At present, amorolfine is not available in the US. It has activity against dermatophytes, yeasts and filamentous fungi (molds). In the treatment of cutaneous dermatophyte or *Candida* species infection, amorolfine 0.25% cream applied once daily has been found to be effective. The advantage of this medication has been as a topical therapy for onychomycosis. Amorolfine 5% is absorbed through the human nail plate when it is formulated as methylene chloride lacquer; because of the high concentration of the drug in the nail plate forming a reservoir, only application once a week is required. After topical application, systemic absorption of amorolfine is negligible [25].

A study to investigate the release of the drugs from commercial lacquer formulations (amorolfine and ciclopirox) for the treatment of onychomycosis was studied using the online FTIR-ATR technique. Amorolfine appears to be more suitable for drug delivery to human nails because it penetrates into the nails by means of the hydrophilic pathway. Furthermore, amorolfine penetrates very well into fungal cells, owing to the pH value of the nail, as well as the pK_a value of this antimycotic agent and the lipophilic properties of its base form [135].

6. Expert opinion

The clinical efficacy of an antifungal agent depends to a great extent on the concentration achieved in the target ocular/skin tissue. This, in turn, depends on several factors, including the molecular mass and concentration of the drug and the route by which it has been administered, the duration of contact with the target tissue, and the ability of the compound to penetrate the tissue. Frequent topical application is a useful means of achieving therapeutic levels in the tissue, but this is laborious and may cause irritation or other side effects. Various problems and challenges exist and need to be dealt with for the drug to reach the target tissue. Invariably, most of the antifungal agents are poorly water soluble, although most of them are lipophilic (BCS class II). However, a bigger molecular size may at times restrict their intrinsic penetrability. Thus, the NDDS opens new doors for the development of these antifungal agents as ophthalmic/cutaneous formulations. NDDSs give a better chance to repackage and suitably deliver these agents so as to enhance their bioavailability. Use of cyclodextrins, polymers or suitable surfactants can enhance their solubility and entrapment in niosomes, liposomes and microspheres. SLNs, NLCs, microemulsions and emulsions are the other options to improve permeability, and decrease dosage frequency (hence improve compliance) and side effects. This will improve the safety, cost and tolerance to the antifungal therapy. Even though the cost of production may initially make the therapy expensive, a reduced frequency of application can make it a commercially viable venture. Further, for production houses that are utilizing newer technologies for product development, cost will not be an issue.

Moreover, ideal topical antifungal preparations/formulations should:

- be fungicidal instead of fungistatic, as killing of fungi reduces the chances of reinfection
- possess broad spectrum of activity
- provide immediate relief from symptoms
- be patient-compliant with easy application, minimal side effects, if any, and freedom from frequent administration
- provide easy penetration across and good retention in target tissues
- be cost-effective.

For topical administration, properties of the drug agent selected and the site to which the formulation is to be applied influence the development of successful formulation. Hence, an optimized formulation should provide a correct balance between potency, deliverability and effective therapeutic concentration at the target site.

Declaration of interest

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