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Expert Opinion

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Drug delivery strategies for improved azole antifungal action

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Background: Azole antifungal agents are the most commonly used antifungals in clinical treatment of both superficial and systemic fungal infections. Many azoles are poorly water soluble, which limits their bioavailability and antifungal effects. *Objective*: To improve the efficacy of azole antifungal drugs by advances in drug delivery. *Methods*: Manipulation of drug formulations and administration routes to improve the antifungal pharmacokinetics with targeted delivery, rapidly followed by sustained release and prolonged retention of high drug concentration localized at the infection site. *Results/conclusion*: Formulation and drug delivery strategies can improve the aqueous wetting and dissolution properties by increasing their chemical potential, stabilizing the drug delivery system and targeting high concentration of the azoles to the infection sites, therefore enhancing the bioavailability and therapeutic efficacy of azole antifungals.

Keywords: azoles, fungal infections, intravenous, oral, pulmonary, topical

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1. Introduction

Fungal infections remain a major healthcare problem. Superficial fungal infections are a major reason for patient visits to dermatologists [1], while the incidence of systemic fungal infections have continued to increase over the last decade within high risk patient groups such as those immunocompromised secondary to chemotherapy and HIV/AIDS, solid organ or hematopoietic stem cell transplant recipients and patients in intensive care units [2].

Antifungal azole drugs are a mainstay in the treatment of fungal infections. Azoles inhibit the fungal cytochrome P450 (CYP) enzyme 14-α-sterol-demethylase, which is involved in ergosterol biosynthesis, an essential molecule of the fungal cell membrane. Many azoles also interact with mammalian P450 isozymes, causing collateral side effects and drug interactions. Clinically, the therapeutic efficacy of an antifungal drug relies not only on its intrinsic antifungal activity, which is usually reflected in the minimum inhibition concentration (MIC) value of the antifungal drug, but also on the bioavailability, that is, penetration and distribution of the drug at the infection site [3], as well as the host's immune response (**Figure 1**). Many azole drugs have low aqueous solubility because of their hydrophobic structures. For example, miconazole, ketoconazole, itraconazole and posaconazole are all very slightly soluble (< 1 μg/ml) or insoluble at neutral pH; whereas the aqueous solubilities of fluconazole and voriconazole are thousands times higher. Generally, low aqueous solubility is associated with low oral bioavailability [4]. This can have a negative impact on antifungal efficacy, side effects, pharmacokinetic variability and the development of drug resistance [5].

Thus, the means to deliver antifungals are critical for effective prophylaxis and treatment of fungal infections. This manuscript summarizes the published drug delivery strategies for improved bioavailability/therapeutic effects of antifungal azole drugs.

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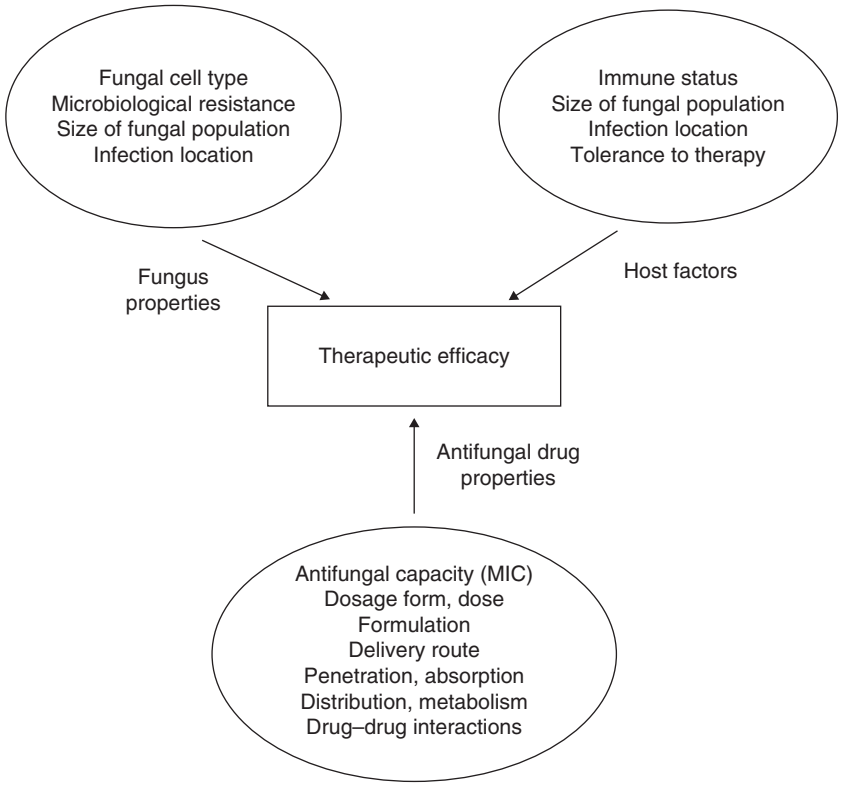

Figure 1. Factors influencing the therapeutic efficacy of antifungal agents.
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2. Medically important antifungal azoles

The azoles are structurally diverse and can be characterized, based on different chemical structures, into two broad groups: the imidazoles and the triazoles. The imidazoles have a two-nitrogen azole ring and are predominantly used in topical preparations for the treatment of superficial fungal infections secondary to adverse effects associated with systemic administration. The names, molecular formula, aqueous solubilities, chemical structures, spectrum of activity and commercially available dosage forms/delivery routes of the imidazole antifungal drugs are summarized in **Table 1**.

Triazole antifungals have three nitrogen atoms in the azole ring (summarized in **Table 2**), and are mainly used for systemic infections [6,7] due to greater affinity for fungal rather than mammalian enzymes, making them safer than the imidazoles for systemic administration [8]. In addition, because of their wider spectrum of antifungal activity and higher potency than the imidazoles, triazole antifungal drugs attract more research on drug delivery strategies.

One of the most widely used triazoles is fluconazole, an orally and intravenously bioavailable agent effective against a wide range of *Candida* infections, including oropharyngeal and esophageal candidiasis in HIV/AIDS patients and invasive candidiasis [9,10]. Fluconazole displays predictable pharmacokinetics with an oral bioavailability greater than 90%. The absorption of fluconazole from the gastrointestinal tract independent of the formulation, gastric acidity, or concomitant food intake [11]. It is not extensively metabolized, and is primarily excreted unchanged in the urine [12]. Fluconazole urine concentrations are 10 times that found in the plasma and it penetrates the cerebrospinal fluid (CSF) well, allowing its use in the treatment of central nervous system and urinary tract fungal infections [13].

Itraconazole is the first marketed orally bioavailable antifungal triazole active against both *Candida* and *Aspergillus* species [14]. Due to its high lipophilicity, approximately 99% of the circulating drug is protein bound and its penetration into CSF and other aqueous body fluids is limited. There is considerable accumulation of the drug in lung, kidney, liver, bone, muscle, skin and nails. Because of its protein binding and retention in the skin and nails, intermittent dosing of itraconazole to treat superficial mycoses is possible [15].

Voriconazole is a second-generation synthetic triazole derivative of fluconazole. Its inhibition against the CYP 14-α-demethylase of *C. albicans* and *A. fumigatus* was 1.6 and 160 times greater, respectively, than fluconazole (**Figure 2**) [16]. Additionally, voriconazole also inhibits 24-methylene dihydrolanosterol demethylation of certain yeasts and filamentous fungi, leading to more potent and broader antifungal

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Table 1. Imidazole antifungal drug names, molecular formula, chemical structures, commercially available dosage forms/delivery routes and strength.

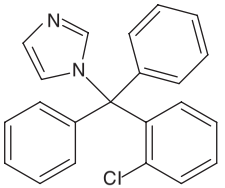
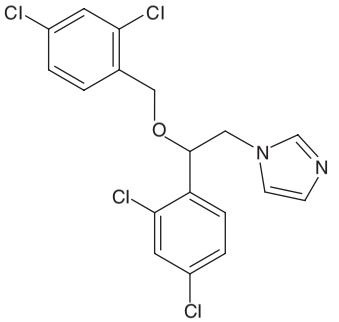
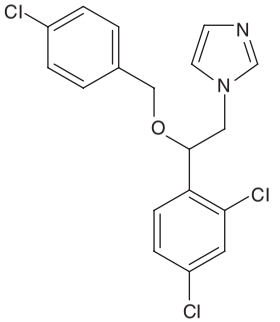
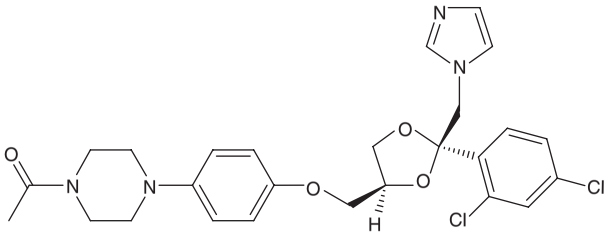
Drug	Molecular formula	Aqueous solubility	Chemical structure	Spectrum of activity	Delivery routes/dosage forms	Strength
Clotrimazole	$C_{22}H_{17}ClN_2$	0.49 µg/ml		Dermatophytes, pathogenic yeasts, filamentous and dimorphic fungi, some gram-positive bacteria	Topical cream Topical solution Vaginal cream Oral Troche/Lozenge	1% 1% 1% 10 mg
Miconazole	$C_{18}H_{14}Cl_4N_2O$	< 1 µg/ml		Dermatophytes, pathogenic yeasts, dimorphic fungi, filamentous fungi including Aspergillus species, some gram-positive bacteria	Vaginal suppository Vaginal cream Topical ointment	100, 200, 1200 mg 2, 4% 0.25%
Econazole	$C_{18}H_{15}Cl_3N_2O$	< 1 mg/ml		Dermatophytes, Candida species, pathogenic yeasts, filamentous fungi, some gram-positive bacteria	Topical cream	1%
Ketoconazole	$C_{26}H_{28}Cl_2N_4O_4$	Insoluble in neutral or slightly acidic solutions		Dermatophytes, pathogenic yeasts, filamentous fungi, dematiaceous fungi	Topical aerosol, foam, Topical gel Topical cream Topical shampoo Oral tablet Oral suspension	2% 2% 2% 1%, 2% 200 mg 100 mg/5 ml

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Table 1. Imidazole antifungal drug names, molecular formula, chemical structures, commercially available dosage forms/delivery routes and strength (continued).

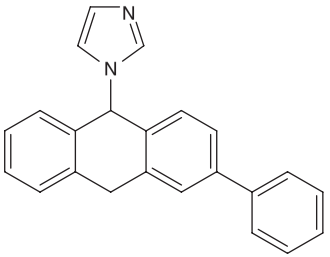
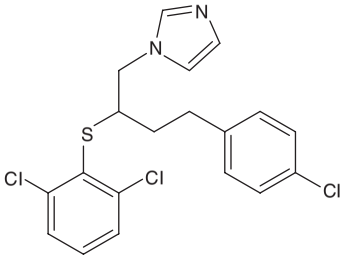
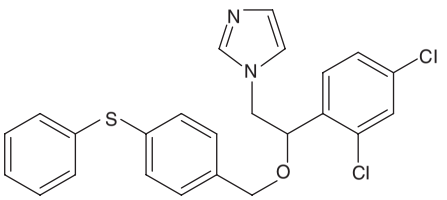
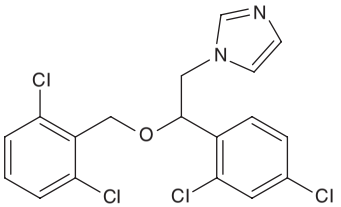
Drug	Molecular formula	Aqueous solubility	Chemical structure	Spectrum of activity	Delivery routes/dosage forms	Strength
Bifonazole	$C_{22}H_{18}N_2$	< 1 µg/ml		Many pathogenic yeasts, dimorphic pathogens, dermatophytes, several pathogenic filamentous fungi		
Butoconazole	$C_{19}H_{17}Cl_3N_2S$	Nitrate salt: 0.26 mg/ml		Clinically important yeasts and dermatophytes (comparable to ketoconazole)	Vaginal cream	2%
Fenticonazole	$C_{24}H_{20}Cl_2N_2OS$	< 0.1 mg/ml		Wide spectrum, most active against dermatophytes	Vaginal ovules Vaginal cream	200, 600, 1000 mg 2%
Isoconazole	$C_{18}H_{14}Cl_4N_2O$			Dermatophytes, pathogenic yeasts, pathogenic filamentous fungi, gram-positive bacteria and trichomonads	Topical cream Vaginal suppository	

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Table 1. Imidazole antifungal drug names, molecular formula, chemical structures, commercially available dosage forms/delivery routes and strength (continued).

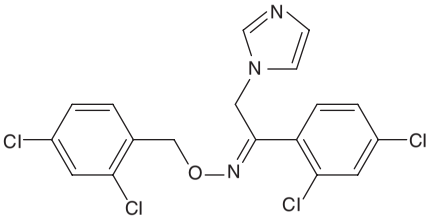
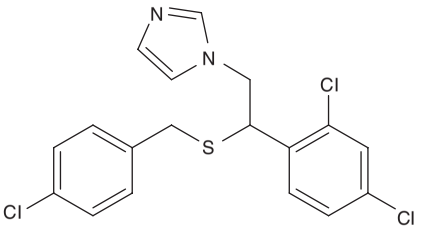
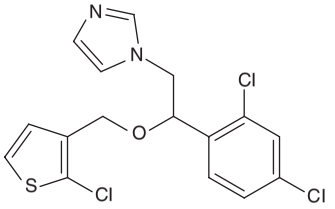
Drug	Molecular formula	Aqueous solubility	Chemical structure	Spectrum of activity	Delivery routes/dosage forms	Strength
Oxiconazole	$C_{18}H_{13}Cl_4N_3O$			Broad spectrum, fungicidal against *A. fumigatus*, *C. neoformans*, *C. albicans*, *T. mentagrophytes*; most active against Mucor and Rhizopus species	Topical cream Topical lotion	EQ 1% base EQ 1% base
Sulconazole	$C_{18}H_{15}Cl_3N_2S$	1.9 mg/ml		Broad spectrum; very active against dermatophytes, active against yeast like fungi, moderately active against Candida and Aspergillus species	Topical cream Topical solution	1% 1%
Tioconazole	$C_{16}H_{13}Cl_3N_2OS$			Pathogenic yeasts, dermatophytes, Aspergillus species, some chlamydia, trichomonads, gram-positive bacteria	Vaginal ointment Topical cream	6.5% 1%

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Table 2. Triazole antifungal drug names, molecular formula, chemical structures, commercially available dosage forms/delivery routes and strength.

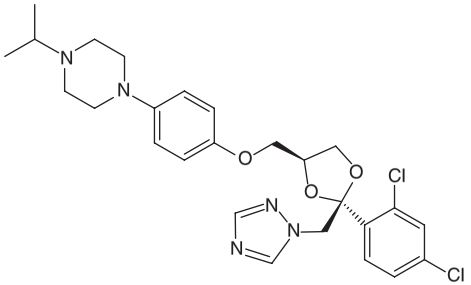
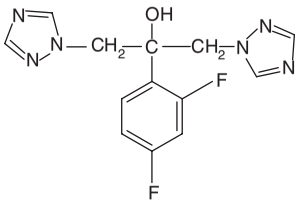
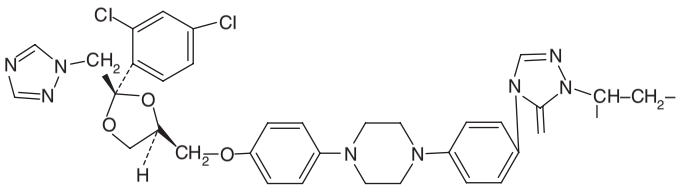
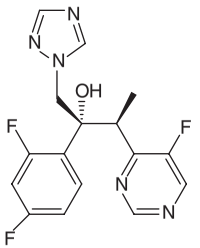
Drug	Molecular formula	Aqueous solubility	Chemical structure	Spectrum of activity	Delivery routes/dosage forms	Strength
Terconazole	$C_{26}H_{31}Cl_2N_5O_3$	< 1 µg/ml		Broad spectrum; active against *Candida albicans*, *C. tropicalis, C. krusei*, *C. parapsilosis*, *C. guilliermondii*, *C. glabrata* and *Trichosporon beigelii*	Vaginal suppository Vaginal cream	80 mg 0.4%, 0.8%
Fluconazole	$C_{13}H_{12}F_2N_6O$	8 mg/ml		Broad spectrum; active against Candida species and *C. neoformans*, less active against dermatophytes, inactive against Aspergillus species	Oral tablets Oral suspension Injectable injection	50, 100, 150, or 200 mg 10 or 40 mg/ml after reconstitution 2 mg/ml in 0.9% NaCl or 5.6% dextrose solution
Itraconazole	$C_{35}H_{38}Cl_2N_8O_4$	6 µg/ml (pH 1) 1 ng/ml (neutral pH)		Broad spectrum; most active against *H. capsulatum*, *A. fumigatus*, *A. flavus*, *Blastomyces dermatitidis*, *C. neoformans*	Oral capsule Oral solutionl Injectable injection	100 mg 10 mg/ml 10 mg/ml
Voriconazole	$C_{16}H_{14}F_3N_5O$	2.7 mg/ml (pH 1.2); 0. 61 mg/ml (neutral pH)		Broad spectrum; active against *C. albicans* and *A. fumigatus*	Oral tablet Injectable i.v. infusion Oral suspension	50, 200 mg 200 mg/vial 200 mg/5 ml

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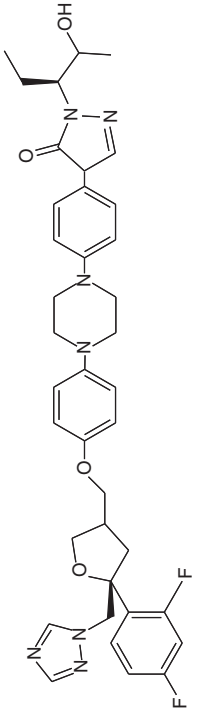
Table 2. Triazole antifungal drug names, molecular formula, chemical structures, commercially available dosage forms/delivery routes and strength (continued).

Drug	Molecular formula	Aqueous solubility	Chemical structure	Spectrum of activity	Delivery routes/dosage forms	Strength
Posaconazole	$C_{37}H_{42}F_2N_8O_4$	< 1 µg/ml		Broad spectrum; active against invasive fungal pathogens, uniquely active against zygomycetes	Oral suspension	40 mg/ml

spectrum activity than fluconazole. Several dosage forms of voriconazole are available under the brand name of VFEND® (Pfizer Inc., NY, USA), including a lyophilized powder for reconstitution to solution for i.v. infusion, film-coated tablets for oral administration and as a powder for oral suspension [17].

The most recently available triazole is posaconazole, a hydroxylated analog of itraconazole, with high permeability (> 10^{-5} cm/s) and low aqueous solubility (< 1 µg/ml). Posaconazole is effective in the treatment of invasive zygomycosis and aspergillosis, including infections in patients with refractory infections or those intolerant to other antifungal therapy [18,19]. Currently posaconazole is clinically available as an immediate-release oral suspension containing 40 mg/ml of the drug formulated with surfactants and suspending agents. However, variable bioavailability is observed when administered on an empty stomach. Absorption of posaconazole from the gastrointestinal tract is saturable and limited when a single high dose (e.g., 800 mg) is administered. Higher plasma concentrations can be achieved when the daily dose is divided into multiple dosing intervals (e.g., 200 mg four times daily or 400 mg twice daily) and administered with food [20]. The main issues concern the lack of an i.v. and tablet formulation, and the fact that the oral suspension must be administered with fatty food two to four times daily to achieve reasonable serum levels [21,22].

3. Topical delivery strategies for antifungal azoles

Superficial fungal skin infections frequently respond to topical antifungal administration, and this modality occupies a prominent position in treating acute lesions and those of limited time of infections [23]. The imidazole antifungals may cause many side effects when administered systemically. Site-directed topical antifungal drug delivery can reduce non-target site toxicities [24]. Therefore, the antifungal imidazoles have mostly been formulated as topical preparations for the treatment of superficial fungal infections.

The pathogen in superficial fungal skin infections mainly locates in the epidermis. To effectively inhibit fungal growth, the topical formulations must release a proper amount of drug at the target site with penetration through the stratum corneum [24] in therapeutically effective concentrations [25]. The vehicle composition of a topical delivery system may significantly affect drug release and skin penetration, thereby affecting biological activity [26]. Thermodynamically, i) solubilization of drug in excipient(s) to obviate the rate-limiting phase-to-phase solubilization step; and ii) generation of stable supersaturated systems to enable drug release from the dosage form to the target site [27]. The rate and extent of drug absorption from supersaturated vehicles should be greater than from non-supersaturated vehicles [28]. Since many azoles are poorly water soluble, the current commercial products of antifungal azoles for superficial mycosis may not be optimal for successful therapy. Novel formulations have

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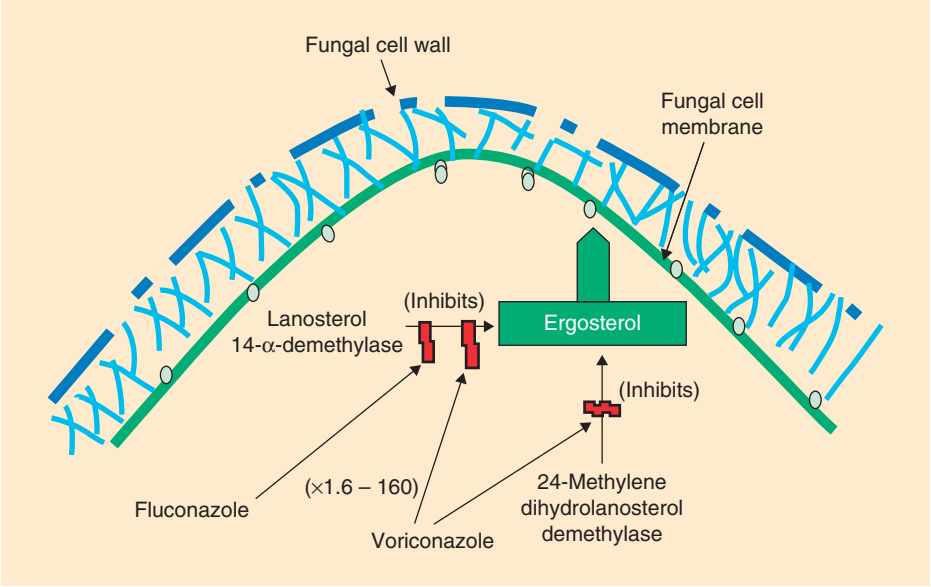

Figure 2. Mechanisms of action of fluconazole and voriconazole.
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been reported to optimize their topical delivery and ultimately the antifungal effects.

3.1 Microemulsions

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 using Brij 96, Capmul and Jojoba oil has been reported to improve the percutaneous absorption of fluconazole through *ex vivo* hairless mouse skin and thereby its antifungal activity, additional to its widest zone of *in vitro* inhibition against *Candida albicans* [29].

Epithelial cells in the skin carry a negative charge on their surface. All epithelia are therefore selective to positively charged solutes [30]. Accordingly, positively charged lipid submicron emulsions of econazole and miconazole nitrate, using surfactants Lipoid E-80, poloxamer 188 and stearylamine (a cationic lipid contributing to the overall positive charge on the oil droplet interface) have been evaluated [31]. The positive-charged submicron emulsions demonstrated enhanced percutaneous absorption of econazole and miconazole nitrate in *ex vivo* hairless rat skin, compared to a negative-charged submicron emulsion. The results indicated that surface-modified emulsion droplets had a significant influence on diffusion of drug through the skin.

3.2 Liposomes

Topical application of liposomes has been shown to enhance the penetration of vesicle-bound drugs into the skin and act as 'drug localizers', with low systemic absorption and sustained drug release locally [32]. 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 to liposomes [33]. Topical application of niosomes behave similar to liposomes *in vivo*, with a prolonged contact time of drug with the applied tissues [34], thus illustrating the potential of drug in niosomes to improve skin penetration and accumulation in the superficial skin strata.

Liposomal clotrimazole (e.g., clotrimazole:egg 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 currently available formulations [35]. The two formulations were then incorporated into a 2% carbopol gel, respectively, 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. Additionally, the liposome and niosome gels were well tolerated. This study suggested alternative formulations for clotrimazole and other antifungal azoles could provide sustained and controlled release of drug for local vaginal therapy.

3.3 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are colloidal carrier systems composed of

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physiological and biodegradable lipids of low toxicity [36]. Both SLN and NLC possess a number of features advantageous for topical application, including protection of labile drugs against chemical degradation, controlled release of the drug, prolonged residence time of formulation in the stratum corneum and targeting of drug to the upper layers of the skin [37]. They were also reported to have occlusive properties as a result of barrier film formation after application [38].

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 stratum corneum and an occlusive effect can increase the amount of the drug penetrating into the mucosa or skin [39]. SLN incorporating clotrimazole [39] and ketoconazole [40], prepared by the hot high pressure homogenization technique, showed high entrapment efficacy (> 50%), sustained release over a 10 h period and considerable physicochemical stability. Likewise, econazole nitrate-loaded SLN has been prepared by o/w high-shear homogenization, with a mean particle size of about 150 nm for topical administration [41]. Applying the SLN incorporated hydrogels onto *ex vivo* porcine stratum corneum, the SLN hydrogels were able to control the drug release through the stratum corneum and the release rate was dependent on the lipid content of the SLN. Moreover, the econazole nitrate-loaded SLN promoted rapid penetration of drug through the stratum corneum of five healthy human subjects after 1 h post-application and improved drug diffusion into the deeper skin layers 3 h after application, compared to a conventional gel containing only econazole nitrate. These results suggested that drug-loaded SLN could be useful for site-specific delivery of antifungal drugs to the skin.

3.4 Bioadhesive lozenges/tablets/creams/films

Miconazole nitrate is widely used in the treatment of oropharyngeal candidiasis. However, the salivary concentration with the use of the commercially available product Daktarin® oral gel with 2% miconazole nitrate (Janssen Pharmaceutica, Beerse, Belgium) has been shown to become subtherapeutic within 30 min [42]. A novel bioadhesive lozenge of miconazole has been described [43]. The lozenge contains two layers; an upper modified-release layer containing miconazole nitrate in spray-dried form formulated with acacia and Cremophor® RH40 (BASF, Germany) to increase miconazole dissolution, and the lower bioadhesive layer containing drum-dried waxy maize starch and Carbopol 980 to facilitate application to the oral mucosa. After applying the lozenge at an upper posterior site in the oral cavity of healthy human volunteers, much more uniform and effective salivary levels of miconazole nitrate were achieved from the lozenge over a prolonged period of time compared to the proprietary oral gel Daktarin.

Bioadhesive effervescent tablets containing ketoconazole were reported for vaginal delivery to overcome gastrointestinal disturbances such as nausea and vomiting associated with orally administered formulations. Sustained release properties were achieved for a vaginal tablet containing carboxymethylcellulose/ketoconazole microcapsules and effervescent granules [44]. Wang *et al.* [45] reported bioadhesive vaginal tablets with first-order release using Carbopol 934P and hydroxypropylcellulose as bioadhesives and effervescence for disintegration. Specifically, 17% of the originally applied drug was retained on the vaginal tissue for up to 24 h after application into the vagina of rats, indicating that sustained release *in vivo* was achieved.

Mucoadhesive vaginal creams of itraconazole were prepared by homogenization of an aqueous itraconazole/hydroxypropyl-β-cyclodextrin (HPBCD) solution with an oil phase containing paraffin oil, trihydroxystearate and cetyl dimethicone copolyol. These creams retained vaginally in a rabbit model and human clinical studies, in addition to being safe and well tolerated. Furthermore, they were highly effective in reducing or eliminating fungal cultures with few adverse effects due to no systemic absorption [46]. Similarly, addition of a bioadhesive polymer polycarbophil to econazole nitrate vaginal ovules led to a greater frequency of negative culture and reduced recurrence rate after applying for 3 days to women with vaginal candidiasis [47].

Hot melt extrusion (HME) has been shown to be a viable method for preparing drug delivery systems and has benefits over cast film delivery systems in that solvents are unnecessary and with fewer processing steps. Hot-melt extruded bioadhesive films containing ketoconazole (20%), hydroxypropylcellulose and/or poly(ethylene oxide) for treating onychomycosis showed significantly high adhesion force to the 'etched' *ex vivo* human nails and high ketoconazole concentrations in the nails [48]. Likewise, a hydroxypropylcellulose based films containing amorphous itraconazole and α-tocopherol were also reported [49]. Hot-melt extruded bioadhesive film containing antifungal azoles may provide an effective therapy for onychomycosis.

3.5 Nail lacquers

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 a sufficient amount of the antifungal drug could penetrate through the nail barrier to the infection sites. The addition of a penetration enhancer 2-n-nonyl-1,3-dioxolane (18%, v/v) to EcoNail™ (MacroChem, NY, USA) increased econazole content in the ventral/intermediate nail plate and the support bed under the nail 6 and 200 times, respectively, than EcoNail alone, after twice daily application for 14 days to human nails [50].

Likewise, applying fluconazole (1%) solution with 20% urea in a mixture of ethanol and water once daily to 13 patients with onychomycosis, mostly involving the matrix region, resulted in an overall favorable response with four complete resolutions of the condition [51]. Thus,

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incorporation of penetration enhancer in nail lacquers improves the bioavailability and therapeutic action of antifungal azoles.

4. Oral delivery strategies for antifungal azoles

Low bioavailability is associated with oral administration of many azoles due to their low aqueous solubility. There have been a number of reports aimed at enhancing the bioavailability of azole drugs from oral dosage forms basically by increasing drug dissolution rates and apparent solubility.

4.1 Formation of drug/cyclodextrin complexes

Cyclodextrins (CDs) are cyclic oligomers of glucose. Topologically, CDs form a torus that has a hydrophobic interior and a hydrophilic exterior, allowing CD to be dissolved in water where it acts as a host molecule by forming an inclusion complex with a hydrophobic guest molecule. As a result, the dissolution rate, apparent solubility, chemical stability and absorption are affected [52,53].

Several attempts were reported to improve the therapeutic efficacy of miconazole by formation of inclusion complexes with CD and their derivatives [54,55]. Complexes of miconazole with various CDs were prepared by freeze-drying and kneading. The drug/CD complexes had an increased dissolution rate of 28 – 255-fold and a 9 – 55-fold increase in the apparent solubility. Among these, the miconazole/HPBCD complex demonstrated a 2.3-fold increase in oral bioavailability in rats, compared to an aqueous miconazole nitrate particulate suspension [56].

Likewise, complexes of ketoconazole and clotrimazole with various CDs have been investigated [57-60]. Only moderately enhanced oral bioavailability of ketoconazole/HPBCD in mice was reported [54]. Among clotrimazole/CD complexes, the complexation with gamma-CD had greater antifungal activity against *Candida albicans* than the corresponding physical mixture, or clotrimazole alone [61]; Clotrimazole/beta-CD complex showed significantly higher initial plasma concentrations, C_{max} and AUC than did clotrimazole alone, indicating that the drug from the inclusion compound could be more easily absorbed in rats. However, mice that were treated with the clotrimazole/beta-CD showed hepatotoxicity [60].

Compared to the antifungal imidazoles, the greater potency and broader spectrum of activity against invasive fungal pathogens with less toxicity make triazoles more suitable for systemic delivery. Unlike other azoles, fluconazole has relatively high aqueous solubility and is absorbed orally to produce therapeutically effective plasma concentrations. In contrast, the clinical efficacy of itraconazole is limited by its extremely low aqueous solubility (1 ng/ml at neutral pH, approximately 6 μg/ml at pH 1 [62]). Various delivery strategies for itraconazole have been extensively reported to overcome the solubility barrier and enhance its bioavailability.

Itraconazole is commercially available in numerous dosage forms under the brand name Sporanox® (Ortho-McNeil, NJ, USA). The capsule-based oral dosage form is comprised of beads having a sugar core, coated with a mixture of itraconazole and hydroxypropyl-methylcellulose (HPMC), sealed with an outer coating layer. The bioavailability from the oral capsule is low, with considerable intra- and inter-individual variability [63] because this formulation requires an acidic environment and the presence of food for adequate absorption [64]. An alternative oral solution, the itraconazole/HPBCD complex containing 10 mg/ml of itraconazole and 400 mg/ml of HPBCD at a target pH of 2 has also been developed [65]. The use of CD does increase the absorption of itraconazole with a bioavailability of 55%, approximately 30% greater than that observed from the capsule form, and with more consistent plasma concentrations [66]. However, the HPBCD vehicle may cause significant gastrointestinal adverse effects such as nausea, vomiting and diarrhea [54], although no toxicological effect was found in animal tests [67,68].

Other studies have reported efforts to optimize bioavailability, reduce toxicity and achieve more consistent pharmacokinetic parameters. Food intake has been found to influence the pharmacokinetics of Sporanox oral solution, with 30% higher absorption under fasting than under fed conditions [69]. Hydroxybutenyl-β-cyclodextrin (HBenBCD), a chemically modified CD with higher aqueous solubility than HPBCD, has been used to formulate itraconazole complexes, including liquid and lyophilized solid forms [70]. The pharmacokinetic parameters of these itraconazole/HBenBCD complexes were compared with the three commercial Sporanox dosage forms after administration to male Sprague–Dawley rats via oral and i.v. routes. Both the intravenously and orally administered itraconazole/HBenBCD complexes (liquid or solid forms) showed higher bioavailability relative to the corresponding Sporanox formulations. Moreover, no food effects were observed with the itraconazole/HBenBCD solid dosage forms.

4.2 Solubilization in surfactant systems

Self-emulsifying drug delivery systems (SEDDS) are able to form microemulsions with a droplet size of less than 100 nm in the gastrointestinal tract [71]. SEDDS therefore represent an interesting alternative to traditional oral formulations of lipophilic drugs. Hong *et al.* [72] first reported an itraconazole SEDDS that was formulated with Transcutol, Pluronic L64 and tocopherol acetate. Compared to Sporanox oral capsules, oral administration of the SEDDS formulation demonstrated about four times higher bioavailability in rats fed a fatty diet but no significant changes in bioavailability in animals under fasted condition or fed a normal diet.

Another SEDDS containing itraconazole (itraconazole-GSMP capsule) has been prepared using the excipients Cremophor® (BASF, Germany), HCO® (Nikkol Co., Ltd, Japan) and dl-α-tocopherol, having a mean particle size of 64 nm [73]. The itraconazole–GSMP capsule produced higher values of

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AUC_{0-24} and C_{max} in both the fasted and fed states as compared to those of the Sporanox capsule in healthy human volunteers. Moreover, itraconazole–GSMP capsules demonstrated more reproducible blood–time profiles than Sporanox capsules, with less influence of food on itraconazole absorption. The self-emulsifying formulation may provide an alternative oral dosage form for itraconazole with improved oral bioavailability and reduced food-effect. Despite improved pharmacokinetic profiles of these formulations, which is mainly attributable to the excipients employed, further safety testing is required [74].

In a third study evaluating SEDDS, Park *et al.* [75] prepared a semisolid SEDDS containing itraconazole, oleic acid, polysorbate 80 and co-adjuvant (citric acid) by a hot-melt technique. Compared to Sporanox oral capsules, this itraconazole SEDDS greatly increased dissolution rates in gastric and intestinal media by forming a microemulsion (150 – 250 nm diameter size). Due to the more efficient solubilization, easier dispersibility and higher lymphatic transport, the oral bioavailability of itraconazole from this SEDDS formulation was approximately two times greater than that of Sporanox capsules in rats. The degree of oral bioavailability enhancement using SEDDS is consistent with other studies that evaluated itraconazole SEDDS formulations.

Polymeric nanoparticles have been well established as useful drug carriers for poorly water soluble drugs to improve bioavailability. Poly(lactide-co-glycolide (PLG) or alginate encapsulated clotrimazole and econazole nanoparticles were prepared by a emulsion evaporation nanotechnology [76]. After oral administration to mice, each formulation demonstrated a controlled drug release over 5 – 6 days, in contrast to 3 – 4 h for orally and intravenously administered unencapsulated drugs. Moreover, the relative and absolute bioavailability of each drug were dramatically improved, with significantly prolonged drug retention in the lungs, liver and spleen [77]. Recently, PLG nanoparticles loaded with voriconazole (PNLV), with mean particle size of 130 nm and reduced burst release of drug, showed significantly enhanced antifungal effects in *in vitro* cultures and in infected mice following intragastric administration, in comparison to voriconazole alone. Additionally, renal lesions treated with PNLV were reduced in contrast to those treated with standard voriconazole [78]. These results demonstrate the usefulness of nanotechnology in enhancing oral bioavailability of azole antifungal drugs and suggest promising alternatives for current oral formulations of azoles.

4.3 Solid-state manipulation

Solid dispersion refers to systems in which drug particles are homogeneously distributed throughout a solid matrix. This system provides the possibility of reducing the particle size of drugs to nearly a molecular level in order to transform the drug from the crystalline to partially amorphous morphology. Consequently, solid solution refers to systems in which the drug is molecularly dispersed and no crystal structure of the drug exists (as demonstrated in **Figure 3**) [79]. Due to the higher energy state, the drug in the solid solution/dispersion exhibits higher dissolution rates and higher concentration than its intrinsic solubility, which may generally lead to improved bioavailability.

A example of solid-state manipulation is an itraconazole solid solution formulation (e.g., polyethylene glycol:itraconazole: glycerol:Explotab®:HPMC in a ratio of 2.75:1:0.75:0.25:0.25; Explotab is manufactured by Edward Mendell Co., Inc., NY, USA) prepared by a fusion method followed by quench cooling [80]. This formulation was compared with Sporanox oral capsules in healthy human subjects under fasted and fed conditions. The solid solution formulation showed faster dissolution in simulated gastric fluid than the Sporanox capsules. Additionally, the solid solution itraconazole formulation showed higher AUC and C_{max} values as compared to those of Sporanox under fed conditions, whereas under fasting conditions their AUC values were comparable, although the solid solution of itraconazole had a higher C_{max}(47 versus 32 ng/ml). Recently, an itraconazole ternary solid dispersion (itraconazole/TPGS 1000/PVPVA64) was made by spray drying. This formulation resulted in rapid dissolution with 80% of drug released after 10 min, and the supersaturation was maintained for a hour before precipitation began [81]. However, further studies are needed to assess the *in vivo* performance of this formulation.

HME has also been used to prepare solid solutions/dispersions. The oral bioavailability of three HME-processed solid dispersions of itraconazole (40%, w/w), containing HPMC 2910, Eudragit® E100 (Rohm Pharma, Darmstadt, Germany) or a mixture of Eudragit E100-PVPVA64, was determined in human volunteers and compared to Sporanox capsules [82]. Among the three formulations tested, the mean bioavailability of the itraconazole/HPMC formulation was comparable to that of Sporanox, while the other two were lower. Moreover, an itraconazole melt-extruded tablet was introduced to the Korean market, based on the clinical performance of improved efficacy and safety in the treatment of a hyperkeratotic type of tinea pedis following oral administration of this formulation [83,84].

In a later study [85], engineered micron-sized nanostructured composite particles of amorphous itraconazole, with polyvinylpyrrolidone (PVP) or HPMC as a stabilizer, were melt extruded with poloxamer 407 and poly(ethylene oxide) 200 M to deaggregate and disperse the particles into the hydrophilic polymer matrix. The HME process improved dissolution rates due to better wetting of the itraconazole. The two extruded formulations performed similarly in acidic medium but when the pH was changed from acidic to neutral pH, neither formulation significantly reduced the rate of itraconazole precipitation from supersaturated solution. Moreover, these formulations demonstrated similar pharmacokinetic patterns after oral administration to rats, with markedly higher AUC values than that of animals administered crystalline itraconazole. The *in vitro–in vivo*

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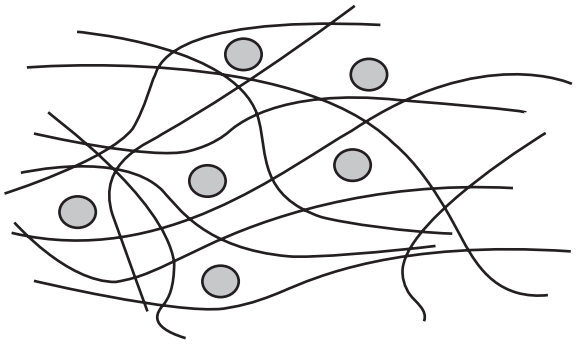

Figure 3. Amorphous solid solution refers to solute (e.g., drug, represented by the small circles) molecules dispersed molecularly and irregularly within the amorphous solvent (e.g., excipient, represented by the tangled lines) as a drug formulation. After dissolution of the excipient(s) in the dissolution medium, the drug is molecularly dispersed, that is present as a supersaturated solution. Molecular dispersion represents a situation of ultimate reduction of drug particle size, and is therefore beneficial to improve the dissolution profiles of poorly water soluble drugs.
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correlation revealed that the high level of supersaturation in the acidic condition led to higher absorption in the stomach, and further suggested that formulations which can maintain supersaturation of itraconazole as the pH is increased to neutral may extend the absorption window in the small intestine.

Based on the previous study, supersaturated concentrations of itraconazole should be optimally targeted to the small intestine, where there is vastly greater mucosal surface area for drug absorption as compared to the stomach. In a follow-up study, amorphous solid dispersions of itraconazole in an enteric matrix of Eudragit L 100-55 and Carbopol® 974P (B.F. Goodrich, OH, USA) were prepared by HME to prolong supersaturation of itraconazole [86]. Dissolution analysis revealed that the addition of Carbopol 974P to the Eudragit L 100-55 carrier system prolonged the supersaturation levels of itraconazole from the Eudragit L 100-55 matrix following the acidic-to-neutral pH transition. The oral pharmacokinetic study in rats confirmed that the addition of Carbopol 974P substantially reduced the absorption variability seen with the Eudragit L 100-55 carrier only. The 20% Carbopol 974P formulation exhibited a fivefold improvement in oral bioavailability over the earlier study [85]. This study indicated substantial improvements in oral itraconazole can be achieved by intestinal targeting and polymeric stabilization to maximize supersaturation.

5. Intravenous delivery strategies for antifungal azoles

Intravenous delivery of antifungal azoles is appropriate for critically ill patients with invasive fungal infections. However, the high hydrophobicity of azole antifungals presents a significant barrier for developing injectable formulations. A liposomal formulation of itraconazole was initially reported for intravenous administration to modify the pharmacokinetics and enhance concentrations at the site of infection [87]. Itraconazole incorporated into dipalmitoyl-phosphatidylcholine (DPPC) multilamellar liposomes with 80% associated with DPPC, showed higher drug levels in the lung, brain and liver after i.v. administration, as compared to a formulation of itraconazole dissolved in CD. Administration of liposomal itraconazole also led to higher and sustained levels of intact itraconazole in serum. Antifungal efficacy was assessed in murine models infected intravenously with *C. neoformans*, which led to early fatal pneumonia or meningitis. Liposomal itraconazole at 20 mg/kg given intravenously was found to be more effective in improving survival in both models, compared to the same dose of itraconazole in CD or as an oral formulation dissolved in PEG 200 at twice the dose. Furthermore, the i.v. liposomal itraconazole was the only effective treatment in an immunocompromised murine model of pulmonary aspergillosis.

Itraconazole (Sporanox I.V.) has also been solubilized by complexation with HPBCD, which is the same as used in the oral solution. The toxicity and side effects caused by the vehicle limit the maximum applicable dose to 200 mg/50 ml infused twice daily over 1 h. However, this I.V. formulation is no longer commercially available [88].

As an alternative, itraconazole nanosuspensions, which are ultra-fine suspensions of drug nanoparticles stabilized with a surfactant or mixture of surfactants, were produced by high pressure homogenization of aqueous suspensions. In comparative studies with Sporanox I.V., the nanosuspension composition containing itraconazole demonstrated good tolerability and *in vivo* treatment efficacy [89]. Similarly, Rabinow *et al.* [90] reported an i.v. itraconazole nanosuspension produced by a tandem process of microcrystallization followed by homogenization. This new formulation demonstrated reduced peak concentrations with a prolonged half-life and superior survival in an immunocompromised rat model of invasive candidiasis relative to I.V. Sporanox. The itraconazole nanosuspension formulations may enhance their antifungal efficacy with improved tolerability due to distribution of the nanosuspension to organs of the monocyte phagocytic system with sustained release.

A novel itraconazole nanocrystal formulation (NCF) has also been prepared by NanoCrystal® Technology [91], which involves milling larger crystals of itraconazole in the surfactant pluronic-F108, generating physically stable dispersions with 90% of the drug particles less than 335 nm [92]. The pharmacokinetic profiles of intravenously administered both single- and multiple-dose NCF and Sporanox I.V. were comparable in healthy subjects. The itraconazole NCF may therefore provide an alternative to Sporanox I.V. solution, with potentially less toxicity by omitting CD in the formulation.

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Itraconazole injectable emulsions have also been reported. These are made by 'solubilization by emulsification', or referred to as SolEmuls® technology [93]. Since itraconazole is poorly soluble in both the water and oil phases of the emulsion, incorporation is only possible by localizing the drug in the lecithin bilayer at the oil–water interface by homogenization. The maximum loading capacity of the emulsion system was found to be 10 mg/ml, with the mean particle diameter of 220 nm stable over 3 months at room temperature [94].

Nanocapsules, a nanometric colloidal carrier that possesses an oily core surrounded by a polymeric wall with lipophilic and/or hydrophilic surfactants at the interface, have also been applied to azoles due to the ability of nanocapsules to modify the biopharmaceutical properties of lipophilic substances [95]. Nanocapsules containing ^{99m}Technetium-fluconazole, with average diameter of 230 – 360 nm, were found to be stable for 24 h in physiological solutions with or without mouse plasma. The fluconazole nano-capsule formulation may be a suitable and promising i.v. formulation to identify infectious foci and treat dis-seminated candidiasis [96]. However, *in vivo* studies are required for further investigation.

6. Pulmonary delivery strategies for antifungal azoles

Pulmonary delivery of drugs has been used to improve therapeutic efficacy for both local and systemic diseases. In immunocompromised patients, the lungs quite often serve as a primary port of entry into the body and site of infection for many opportunistic fungi, which are associated with high morbidity and mortality [97].

Nanoparticle compositions of itraconazole for deep lung delivery have been designed to achieve sufficient drug concentrations at the infected sites. Particle engineering technologies, including evaporative precipitation of aqueous solution (EPAS) [98], spray freezing into liquid (SFL) [99] and ultra-rapid freezing (URF) [100], have been used to prepare nanostructured particles containing itraconazole. Nebulized colloidal dispersions of these engineered nano-structured itraconazole compositions are suitable for drug delivery to the alveoli [101]. Their bioavailability and *in vivo* antifungal effects have been evaluated in a series of studies.

Initially, a study was conducted to compare the lung deposition of aerosolized itraconazole nanoparticles prepared by the EPAS (itraconazole:poloxamer 407:polysorbate 80 = 1:0.16:0.13 weight ratio, EPAS–itraconazole) and SFL processes (itraconazole:poloxamer 407:polysorbate 80 = 1:0.75:0.75 weight ratio, SFL–itraconazole), respectively [102]. The colloidal dispersions of the two itraconazole compositions (containing 200 mg of itraconazole) were nebulized using a micropump nebulizer and the aerosols were inhaled by mice for 20 min in a non-restricted whole body exposure dosing chamber [103]. The data revealed that irrespective of the nanoparticles containing itraconazole in amorphous (SFL–itraconazole) or crystalline (EPAS–itraconazole) form, lung deposition was similar, which is in agreement with their similar *in vitro* aerodynamic properties.

For both the SFL and EPAS formulations, itraconazole concentrations in the lungs were above 0.5 μg/g wet lung tissue for 24 h after a single inhaled dose. This may be important for therapeutic efficacy as trough concentrations in the blood at this level have been reported to be therapeutically effective [104]. A subsequent multi-dose study was conducted, with a dosing regimen consisting of nebulized SFL–itraconazole aqueous dispersion for 20 min twice daily for up to 12 days, versus oral administration of Sporanox oral solution. The SFL–itraconazole group achieved significantly greater (> 10-fold) lung tissue concentrations and lung levels per unit serum concentration as compared to the Sporanox oral solution group administered three times daily.

In addition, *in vivo* prophylaxis effects of inhaled itraconazole formulations were tested in a murine model of invasive pulmonary aspergillosis in immunocompromised mice inoculated via inhalation with *A. flavus*. Both the aerosolized EPAS–itraconazole and SFL–itraconazole significantly improved survival (up to 60% survival at the end of the study) compared to animals administered the Sporanox oral solution or control (**Figure 4**) [105]. The mice that inhaled SFL–itraconazole had a higher survival rate than those that inhaled EPAS–itraconazole, although the lung deposition levels were similar for both formulations [102]. This may be attributable to the amorphous state of SFL–itraconazole, which enabled supersaturation of itraconazole in the lung lining fluid.

Similar survival results were also observed in immuno-compromised mice inoculated with *A. fumigatus* [106]. Additionally, the SFL–itraconazole treated mice demonstrated minimal invasive disease as assessed by histopathology, in contrast to the extensive damage in the lower airways due to infection of mice in the oral Sporanox and control groups [106]. By enhancing local antifungal delivery and reducing the potential for side effects associated with high dose itraconazole administration, pulmonary delivery of amorphous nanoparticulate itraconazole has the potential to reduce morbidity and mortality for invasive fungal infections [107].

Recently, a novel nanostructured itraconazole solid solution (itraconazole:mannitol:lecithin = 1:0.5:0.2 weight ratio, URF–itraconazole) formulation employing FDA approved excipients for pulmonary delivery was developed by URF technology [108]. Inhalation of nebulized URF–itraconazole aqueous colloidal dispersion (containing 100 mg of itraconazole) for 10 min using the same murine model as used for SFL–itraconazole, produced more than 10-fold higher itraconazole concentration in systemic circulation and significantly enhanced lung deposition. The improved bioavailability was mainly ascribed to the engineered nano-scaled particle size with the primary particles of 30 – 50 nm in diameter, and the lecithin component, which may facilitate penetration of itraconazole through the lung epithelium [109]. These data suggest that a smaller amount of itraconazole may be administered to achieve therapeutic concentrations.

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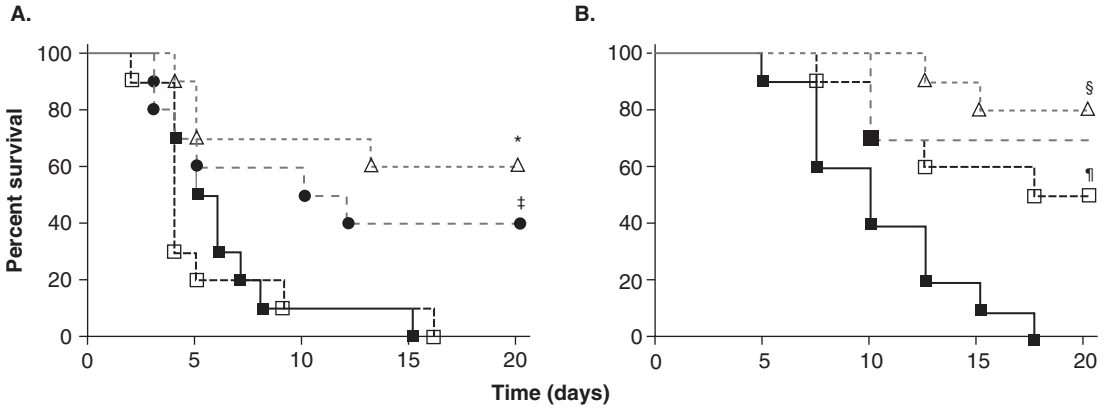

Figure 4. Survival curves for mice (*n* = 10 per group per study arm) that received prophylaxis with aerosolized itraconazole prepared by EPAS (●) and SFL (Δ) or orally administered Sporanox oral liquid (SOL) (□) formulations of itraconazole and controls (■) and challenged with *A. flavus*. A. Long-term survival (day 20). **B.** Acute survival (day 8).

*SFL, $p < 0.005$ versus controls and 0.001 versus SOL.

‡EPAS, p was 0.06 versus controls and 0.04 versus SOL.

§SFL, $p < 0.001$ versus controls.

¶EPAS, $p < 0.05$ versus controls.

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These studies support the concept of treating invasive fungal infections by pulmonary delivery of engineered nanostructured itraconazole formulations [110]. Despite these promising *in vitro* and *in vivo* animal experiments data, no clinical data are available.

7. Conclusion

Antifungal potency and drug bioavailability at the site of infection are key factors in determining the therapeutic efficacy of an antifungal agent. Low aqueous concentrations severely limit azole bioavailability and the therapeutic effectiveness of many members of this class. The low concentration of drug at the infection sites may also induce antifungal resistance to some less susceptible species. There is an unmet need for effective control of tenacious fungal infections and less toxic formulations with better patient compliance.

8. Expert opinion

Novel drug delivery systems are beginning to enhance the clinical efficacy of azole antifungal drugs, but more research is required. The primary factors limiting this effort include the physical and chemical properties of the drug, delivery of therapeutically relevant doses to the site of infection, as well as systemic toxicities associated with these drugs and the excipients used in some formulations, as observed with the Sporanox Oral Liquid. New forms of drug delivery, including administration by inhalation for the targeted treatment of pulmonary fungal infections, as well as advanced oral formulations for use in systemic mycoses, have the potential to enhance the clinical effectiveness of the azoles. However, it is unknown if these advances will reduce adverse effects and systemic toxicities, which currently limit efficacy in many patients with invasive fungal infections. The advances in azole antifungal drug formulations discussed in this review paper are promising. However, many of these data are limited to *in vitro* or animal studies. Further work is needed to translate these findings into the clinical arena in order to benefit patients at risk for or suffering from fungal infections.

Declaration of interest

The authors state no conflicts of interests and have received no payment in the preparation of this manuscript.

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