Nanocarriers of Antifungal Agents

7

Sevgi Güngör and M. Sedef Erdal

Abstract

Fungal infections are still one of the major healthcare problems worldwide. Particularly, the treatment of invasive fungal infections has become more difficult in high-risk patient groups such as AIDS patients, organ transplant recipients, and cancer patients undergoing immunosuppressive chemotherapy. Superficial fungal infections have a less tendency to develop to systemic infection, but they could be serious due to the inefficiency of the treatment. In addition, the controlling of drug release is also important to minimize systemic absorption and to decrease the toxicity of these agents. Therefore, delivery of antifungal agents used for the treatment of superficial and systemic infections has a great impact in terms of both therapeutic aspect and safety. The novel nano-sized drug carriers play a key role to overcome the limitations of conventional dosage forms to improve the efficacy and to ensure safety of the treatment. In the present chapter, the limitations of conventional drug carriers of fungal agents are concisely emphasized, and the impact of nano-sized carriers in delivering antifungal agents has been addressed, paying particular attention toward the studies performed in recent literature.

7.1 Introduction

Nanotechnology has gain great interest in many areas of scientific research during last decades due to its potential benefits. The pharmaceutical field has also taken the advantage of nanotechnology, and the advances in that area have led to the optimization of different types of nano-sized materials for various biomedical applications. In this context, nano-drug delivery systems are increasingly being explored to deliver drugs, cosmetic compounds, or vaccines or for therapeutic purposes. Nano-drug carriers have superiorities of improving aqueous solubility of hydrophobic drugs, controlling/prolonging the drug release, decreasing/minimizing side effects of the drugs such as irritation, keeping the drugs away from environmental factors, and targeting of drugs

S. Güngör (✉) • M.S. Erdal
Faculty of Pharmacy, Department of Pharmaceutical Technology, Istanbul University, 34116 Istanbul, Turkey
e-mail: sgungor@istanbul.edu.tr

A. Basak et al. (eds.), *Recent Trends in Antifungal Agents and Antifungal Therapy*,
DOI 10.1007/978-81-322-2782-3_7

into specific tissues. Therefore, a great range of nanomaterials including colloidal carriers, vesicles, nanocrystalline, and polymeric nanoparticles has been widely investigated, while some of them are already commercially available; there are also some remarkable data which promise a commercialization in the future.

Fungal infections are widely observed and remain as one of the major healthcare problems worldwide. They can be classified as superficial fungal infections which affect the skin, nails, hair, or mucous membranes and systemic infections affecting the whole body. The prevalence and the incidence of either systemic or superficial fungal infections have been increased in the last three decades. Particularly, the treatment of invasive fungal infections has become more difficult in high-risk patient groups such as AIDS patients, organ transplant recipients, and cancer patients undergoing immunosuppressive chemotherapy. Superficial fungal infections have a less tendency to develop to systemic infection, but they could be serious due to the inefficiency of the treatment (Zhang et al. 2007; Kumar et al. 2014).

Overall, it has a great impact to assess the function of the pathogenetic fungi that cause disease in order to choose the most appropriate therapy and antifungal agent in the treatment of fungal infections. Besides, the delivery system of these agents may play a major role for penetration of drugs into target sites of the disease in terms of improving therapeutic aspect and diminishing or preventing the possible adverse effects (Zhang et al. 2007; Kaur and Kakkar 2010).

The antifungal drugs are administered by topical, oral, or parenteral routes. Topical therapy is the most common approach to the management of mucosal and cutaneous fungal infections because of its advantages including targeting of drugs to the site of disease and reducing of systemic side-effect risk of drugs. The conventional dosage formulations including cream, powder, gels, etc. are widely used in the topical treatment of superficial fungal infections. Some adverse reactions may occur at the site of application, but are less than those of systemic agents. However, in some cases topical therapy could lead to side effects like redness, burning, or swelling, which decrease patient compliance. Furthermore, the topical treatment of deep-seated fungal infections like invasive *candidiasis* could be inefficient due to the low penetration capacity of the drug into the target site and inadequate deposition in the skin, resulting in low topical bioavailability. As well as the barrier characteristics of the skin, the physicochemical properties of the drugs including lipophilic character and low aqueous solubility affect the penetration of compounds across the membranes. Noticeably, almost all of antifungal agents currently available in the market are highly lipophilic, and they have poor aqueous solubility, which lead to low release rate of drugs into the skin (Zhang et al. 2007; Kaur and Kakkar 2010; Güngör et al. 2013). Likewise, in case of fungal infection of nail and eye, conventional formulations may show problem of less bioavailability.

Oral treatment of fungal infections is preferred when the disease shows extensive harmful characteristics. But, the main drawbacks of the oral therapy are the serious adverse effects like hepatotoxicity and drug interactions (Kumar et al. 2014). The parenteral administration of antifungal agents in the treatment of systemic infections may also lead to severe toxicity reactions. For example, amphotericin B, a broad antimycotic agent, is widely used in the very serious systemic infections. However, this drug has limitations due to its severe nephrotoxicity, which may lead to kidney failure. Therefore, liposome formulation of amphotericin B for parenteral administration has been first marketed under the name AmBisome in 1990. Then, other products containing lipidic carriers of amphotericin B have come into market in the commercial names of Abelcet® (lipid complex) and Amphotec® (colloidal lipid dispersion). The toxicity of the antifungal agent has been reduced with these liposome-based and submicronic colloidal systems of amphotericin B (Torrado et al. 2008; Kaur and Kakkar 2010). In this context, the formulation of antifungal agents into a suitable delivery system is crucial for either topical or systemic treatment of fungal infections.

The solubility and permeability of drugs, which are affecting parameters for the enhancement of therapeutic efficacy, should be taken into account. The controlling of drug release also has a great impact to minimize systemic absorption and to decrease the toxicity of these agents. Therefore, the development of novel drug delivery systems is a great challenge to overcome the limitations of conventional dosage forms in terms of improving the efficacy and safety of the treatment. For this aim, different nano-sized drug carriers including liposomes, niosomes, ethosomes, microemulsions, nanoparticles, microspheres, and micelles are intensively investigated. Further, they also provide better penetration of drugs into the deep skin to treat invasive fungal infections. Thus, nano-sized carriers could be considered as a promising tool to improve the efficacy and safety of the treatment of fungal infections. Some comprehensive reviews on novel drug delivery approaches for the treatment of fungal infections have already been published (Kaur and Kakkar 2010; Carneiro et al. 2012; Güngör et al. 2013; Madhu et al. 2012). In the present chapter, the limitations of conventional drug carriers of fungal agents are concisely emphasized and the impact of nano-sized carriers in delivering antifungal agents has been addressed paying particular attention toward the studies performed in recent literature.

7.2 Fungal Infections and Current Treatment Options

Fungal infections of the hair, skin, and nails form the most numerous and widespread group of all mycoses. Superficial mycoses are most often caused by dermatophytes and yeasts. Dermatophytes require keratin for growth and therefore cause diseases in body sites where keratin is present. These sites include the skin surface, hair, and nail. Treatment of *dermatophytosis* is often dependent on the clinical setting. Single cutaneous lesions can be adequately treated with a topical antifungal drug, but the treatment of some fungal infections on scalp and nail is often ineffective, and systemic therapy is usually needed to cure these disorders (Ghannoum et al. 2013; Zhang et al. 2007). Yeasts are part of human normal microflora, and invasive infections are observed due to disruption of the barrier or impairment of immune functions. Invasive superficial cutaneous infections include mostly the yeast infections with *Candida* as the absolutely dominating pathogen (Arendrup 2013; Zhang et al. 2007). *Candida albicans* (*C. albicans*) can invade virtually every part of the body including deep organs and tissues as well as superficial sites like skin, nails, and mucous membranes (Randhawa et al. 2015). Most infections due to yeasts respond well to topical treatment, whereas extensive lesions often require oral treatment (Kelly 2012).

Fungal infections of the oral and vaginal mucosa and eyes are also predominantly associated with *C. albicans* (Melkoumov et al. 2015). A number of effective antifungal agents administered either topically or systemically are available for the management of oral candidiasis. However, antifungal drug resistance and poor patient compliance can impair therapy and lead to chronic relapse of the infections (Munoz et al. 2010). Fungal diseases of vulva and vagina are also superficial infections predominantly caused by *C. albicans* (vulvovaginal candidiasis) (Kasper et al. 2015; Stock 2010). Most cases are accessible to the treatment with local and systemic antifungal agents, and different conventional vaginal formulations (creams, gels, suppositories, powder, ointment, etc.) are available. But these conventional formulations have limited efficacy due to self-cleansing action of vagina, resulting in diminishing residence time of drug on vaginal epithelium (Johal et al. 2014; Stock 2010). Fungal eye infections are less common as compared to infections caused by bacteria or viruses. Various regions of the eye that are attacked by the fungi are cornea and the interior segment of the eye (Kumar et al. 2014).

The main classes of systemic and topical antifungal treatment modalities include the allylamines, the azoles, the polyenes, and the echinocandins (Munoz et al. 2010; Zhang

et al. 2007). A list of antifungal compounds which are approved or under investigation and administrated via oral, intravenous or topical route is given in Table 7.1. The conducted studies using nanocarrier approaches for effective delivery and targeting of these agents are also included.

7.2.1 Allylamine Antifungal Agents

Allylamine antifungals act through inhibiting of an essential enzyme (squalene epoxidase) in the ergosterol biosynthesis pathway of cell membrane formation of fungus. The increased cellular permeability and growth inhibition occurred due to alterations in fungal cellular membranes (Güngör et al. 2013; Kelly 2012).

Terbinafine has a broad-spectrum activity against yeast, fungi, molds, and dermatophytes and is indicated for both oral and topical treatment of mycoses. Topical formulations of terbinafine, such as dermal spray, cream, and film-forming solution, are also effective against tinea versicolor, an infection caused by *Malassezia* sp. Terbinafine is considered the second-line systemic therapy for tinea capitis in children, whereas griseofulvin is considered the first-line systemic therapy (Kelly 2012). Naftifine has been shown to be an effective

Table 7.1 Conventional commercial available dosage forms and nano-based delivery carriers of antifungal drugs investigated in literature

Antifungal compound	Conventional dosage form	Nano-based delivery technology	Reference
Azoles			
Imidazoles			
Clotrimazole	Cream	Micelle solution	Souto et al. (2004)
	Solution	Solid lipid nanoparticle	Bachhav et al. (2011)
	Lotion	Nanostructured lipid carrier	Hashem et al. (2011)
		Ethosome	Maheshwari et al. (2012)
		Transfersome	Basha et al. (2013)
		Microemulsion	Vanić and Škalko-Basnet (2013)
Ketoconazole	Cream	Liposome	Patel et al. (2011)
	Gel	Ethosome	Che et al. (2015)
	Foam	Transfersome	Guo et al. (2015)
	Shampoo	Microemulsion	
	Tablet		
Sertaconazole	Solution	Microemulsion	Sahoo et al. (2014a)
	Cream	Microemulsion-based hydrogel	Sahoo et al. (2014b)
Bifonazole	Solution	Microemulsion-based hydrogel	Sabale and Vora (2012)
	Cream		
	Powder		
Miconazole	Cream	Liposome	Elmoslemany et al. (2012)
	Ointment	Transfersome	Cerdeira et al. (2013)
	Lotion	Nanosuspension	Pandit et al. (2014)
	Solution		
	Powder		
Econazole	Cream	Solid lipid nanoparticle	Sanna et al. (2007)
		Nanostructured lipid carrier	Sharma and Pathak (2011)
		Nanosponge	Verma and Pathak (2012)
		Ethosome	Keshri and Pathak (2013)

(continued)

Table 7.1 (continued)

Antifungal compound	Conventional dosage form	Nano-based delivery technology	Reference
Triazoles			
Fluconazole	Tablet	Microemulsion	Hoeller et al. (2008)
	Oral suspension	Microemulsion-based hydrogel	Bachhav and Patravale (2009)
		Liposome	Bhalaria et al. (2009)
		Liposome gel	Patel et al. (2009)
		Niosome	El-Nesr et al. (2010)
		Ethosome	Gupta et al. (2010)
			Salerno et al. (2010)
			Gupta et al. (2011)
			Schwarz et al. (2011)
			Coneac et al. (2015)
			Oliveira Brito et al. (2015)
Itraconazole	Capsule	Microemulsion	Alomrani et al. (2014)
	Oral suspension	Microemulsion-based hydrogel	Barot et al. (2012a, b)
		Transfersome	Chudasama et al. (2011)
		Nanosuspension	da Fonseca Antunes et al. (2013)
			Kumar and Shishu (2015)
Voriconazole	Oral solution	Nanostructured lipid carrier	El-Hadidy et al. (2012)
	Tablet	Transethosome	Song et al. (2012)
	Intravenous solution	Microemulsion	Song et al. (2014)
Posaconazole	Oral suspension	Nanosizing	Merisko-Liversidge and Liversidge (2011)
Allylamines			
Terbinafine	Tablet	Solid lipid nanoparticle	Barot et al. (2012a, b)
	Solution	Microemulsion	Chen et al. (2012)
	Cream	Liposome	Zhang et al. (2012)
	Spray	Ethosome	Kumar et al. (2014)
	Gel	Transfersome	Tanrıverdi and Özer (2013)
			Koutsoulas et al. (2014)
			Sudhakar et al. (2014)
			Çelebi et al. (2015)
Naftifine	Solution	Niosome gel	Barakat et al. (2009)
	Cream		
	Gel		
Polyenes			
Amphotericin B	Intravenous solution	Liposome gel	Kang et al. (2010)
	Intravenous liposomes	Nanosizing	Randhawa et al. (2015)
Nystatin	Cream	Nanoemulsion	El-Ridy et al. (2011)
	Powder	Niosome	Fernandez-Campos et al. (2012)
	Ointment	Nanosizing	Melkoumov et al. (2015)
	Tablet		
Echinocandins			
Caspofungin	Intravenous lyophilized powder	–	–
Micafungin			
Anidulafungin			

(continued)

Table 7.1 (continued)

Antifungal compound	Conventional dosage form	Nano-based delivery technology	Reference
Other compounds			
Ciclopirox	Cream	Niosome	Shaikh et al. (2010)
	Gel	Liposome gel	Karimunnisa and Atmaram (2013)
	Suspension		
	Shampoo		
	Solution		
Griseofulvin	Tablet	Solid lipid nanoparticle	Aggarwal and Goindi (2012)
		Microemulsion	Aggarwal and Goindi (2013) and Aggarwal et al. (2013)
		Transfersome	

topical allylamine antifungal for the treatment of superficial dermatophytoses (Ghannoum et al. 2013). Cream, gel, and dermal spray formulations of naftifine are available in the market.

7.2.2 Azole Antifungal Agents

Azole antifungals act through selectively inhibiting the synthesis of fungal cell ergosterol, and they alter the permeability of cell membrane by binding with the phospholipids in the fungal cell membrane. The azole antifungal drugs used in the treatment composed of either two or three nitrogens in the azole ring and are thereby classified as imidazoles (e.g., ketoconazole and miconazole, clotrimazole) or triazoles (e.g., itraconazole and fluconazole), respectively (Thompson et al. 2009). Triazoles have a broad range of applications in the treatment of both superficial and systemic fungal infections, and they became standard therapy for invasive candidiasis in the late 1980s (Güngör et al. 2013; Lewis 2010; Sheehan et al. 1999).

The reader is referred to the table to see the conventional dosage formulations of azole antifungals that are currently in therapy. There are a number of licensed azole antifungal drugs; however, fluconazole, itraconazole, posaconazole, and voriconazole are the most frequently used ones in a clinical setting for treatment of systemic fungal infections (Brüggemann et al. 2009).

7.2.3 Polyene Antifungal Agents

The polyene antifungal agents exert their antifungal activity by binding irreversibly to cell membrane ergosterol of fungus. Therefore, the polyenes are fungicidal and have the broadest spectrum of antifungal activity of any of the clinically available agents. These antifungal agents are of amphipathic nature and chemically instable (Flückiger et al. 2006; Güngör et al. 2013; Lewis 2010).

Amphotericin B is the first polyene macrolide antifungal that has been successfully developed into a systemic antifungal agent for the treatment of invasive fungal infections (Adler-Moore and Proffitt 2004). Even though its clinical use is limited by its toxic side effects, amphotericin B remains an important treatment option due to the drug's broad spectrum and minimal cross-resistance with other antifungals. The therapy options already in use include intravenous infusion, lipid complex, colloidal dispersion, and liposomal dispersion of the drug. Parenteral liposomal amphotericin B (Ambiosome) is on the market since 1990, and it has been shown that this preparation demonstrates less nephrotoxicity when compared to amphotericin B lipid complex (Abelcet®) (Kumar et al. 2014). Amphotericin B has very limited aqueous solubility, thus the development of its novel formulations and administration strategies, which take advantage of the drug's unique pharmacokinetic and pharmacodynamic profile, will open

new opportunities for safer and more effective uses of this polyene antifungal (Lewis 2010).

Nystatin is a polyene antifungal drug that has been used in the treatment of cutaneous, vaginal, and oral mucosal fungal infections since the 1950s (El-Ridy et al. 2011). Nystatin has exhibited broad antifungal activity in treating mucocutaneous fungal infections, and its conventional formulations include oral suspension, vaginal ovules, and ointment. The most common adverse effect reported with topical nystatin is allergic contact dermatitis.

7.2.4 Echinocandin Antifungal Agents

Echinocandins destabilize fungal cell walls due to inhibiting of the 1,3-β-glucan synthase complex. They are active against a broad range of *Candida* and *Aspergillus* species (Sable et al. 2008). The Infectious Diseases Society of America has published in 2009 a guideline recommending the use of three echinocandin compounds, namely, caspofungin, micafungin, and anidulafungin as initial therapy for the treatment of candidemia in adults, whereas in Europe only caspofungin and micafungin are indicated for candidemia in pediatric and adult patients (Munoz et al. 2010).

7.2.5 Others (Ciclopirox and Griseofulvin)

Ciclopirox is a synthetic hydroxypyridone derivative having antifungal, antibacterial, and anti-inflammatory activities. Ciclopirox inhibits essential enzymes interfering with fungal mitochondrial electron transport processes and energy production. It is active against many fungi including dermatophytes and yeast (Güngör et al. 2013). The conventional formulations of ciclopirox are dermal and vaginal creams and dermal solutions and sprays.

Griseofulvin is the first agent with antifungal activity and was isolated in 1939 (Sheehan et al. 1999). It is an orally administered antifungal drug and is active against all common dermatophytes and shows fungistatic effect in humans. Griseofulvin is accepted as a safe medication and its adverse effects are common, but mild, including nausea, headache, and urticaria (Kelly 2012).

7.3 Nanocarriers of Antifungal Agents

Numerous types of nano-drug carriers have been developed for the treatment of fungal infections. Overview of novel drug delivery approaches of antifungal agents is briefly shown in Fig. 7.1. The research studies focused on nano-sized carriers as a challenge for the effective treatment of fungal infections have been summarized below.

Vesicular carriers such as liposomes, niosomes, and transfersomes have also been intensively explored for delivering fungal agents in either topical or systemic treatment. Vesicular systems have the advantages of controlling

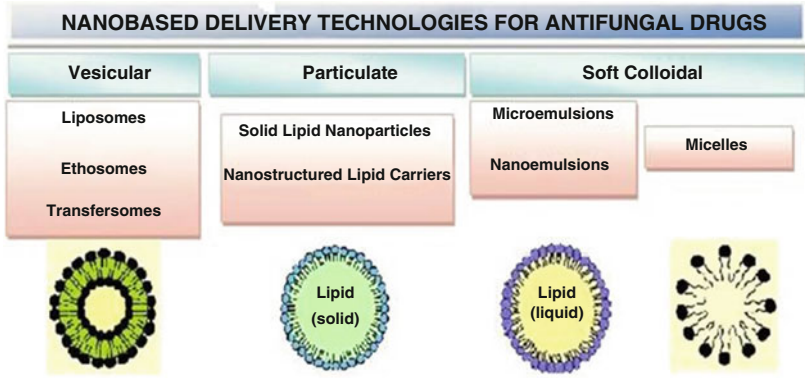

Fig. 7.1 Novel drug delivery technologies of antifungal agents

release rate of the active compound and providing localization of topical delivered drugs in dermal layers. Besides, vesicular systems help to carry drug molecules into systemic circulation to decrease toxicity of drugs (Cevc 1996; Akhtar 2014). At the end of the 1980s, the first liposome dermatological product of econazole nitrate (Pevaryl® Lipogel) had been approved by regulatory authorities, and it was introduced in various countries (Korting et al. 1997). Niosomes are liposomes prepared with nonionic surfactants. They have a potential to overcome the barrier characteristic of skin with the effect of high amount of surfactant in their content (Mahale et al. 2012; Marianecci et al. 2014). Transfersomes are defined as elastic vesicles that can be highly deformed. Classical liposomes have a diameter varying from 200 to 400 nm, which is too large to pass through the skin. On the other hand, transfersomes reach deeper dermal tissues and even the systemic circulation with their elastic and highly deformable characteristics (Benson 2009). Ethosomes contain phospholipids like classical liposomes; however, they contain high concentrations of alcohol in their structure. These carriers improve drug permeation due to the high alcohol content which acts as penetration enhancer as well as disruption of the structure of skin by the phospholipids in their content (Ainbinder et al. 2010; Mbah et al. 2014).

Microemulsions are one of the colloidal carriers studied intensively during the last decades by many scientists to enhance delivery of topical antifungal agents into targeted skin sites. They are thermodynamically stable, optically isotropic, colloidal nanocarriers with a dynamic microstructure that form spontaneously by combining oil, water, surfactant, and a cosurfactant. Microemulsions basically offer increased drug-solubilizing capacity and enhanced drug release and skin penetration. They can modify the diffusional barrier of the skin, which is resulted in enhancement of drug penetration into deeper skin layers compared to conventional formulations. The internal phase of microemulsions can act as a drug reservoir resulting in controlled and sustained drug release (Santos et al. 2008; Neubert 2011; Güngör et al. 2015a, b).

Solid lipid nanoparticle and nanostructured lipid carrier formulations have also been investigated intensively for the topical treatment of fungal skin infections due to their ability to enhance skin penetration of loaded drugs. While solid lipid nanoparticles are water-in-oil emulsions composed of solids as oil phase and are prepared from solid lipids or from blends of these lipids, nanostructured lipid carriers are new generation lipid particles, and they contain mixtures of different solid lipids blended with liquid oils. The principal advantage of these carriers is their low risk of toxicity (Iqbal et al. 2012; Scalia et al. 2015).

Micelles are colloidal carriers; they are composed of amphiphilic block polymers and characterized by core-shell morphology in nanoscale size. They have been investigated to facilitate the penetration of antifungal drugs for topical delivery via skin. Cutaneous delivery of drugs into micellar carriers, particularly for the treatment of skin diseases, would benefit in terms of improving aqueous solubility of hydrophobic drugs, targeting of drugs into skin layers (Güngör et al. 2015a, b).

The nano-sized carriers reported in current literature to improve delivery of antifungal drugs are summarized in Table 7.1.

7.3.1 Nanocarriers of Allylamine Antifungal Agents

Hydrogels and microemulsion-based gel formulations of terbinafine have been studied to evaluate the efficacy of these formulations for the treatment of fungal infections. In vitro examination of antifungal activity revealed that the Natrosol®-based hydrogel was a good candidate for the topical delivery of terbinafine (Çelebi et al. 2015). In another study, Barot et al. developed a microemulsion-based gel of terbinafine for the treatment of onychomycosis. They have indicated that the developed microemulsion-based gel formulation enhanced penetration and retention of terbinafine into the

human cadaver skin as compared to its commercial cream. This gel formulation of terbinafine showed better activity against *C. albicans* and *Trichophyton rubrum* than the commercial cream (Barot et al. 2012a, b).

To resolve problems of long treatment durations and frequent administration in conventional therapy, solid lipid nanoparticles of terbinafine were developed. The skin of nude mice was used as a barrier membrane, and penetration levels of terbinafine of the formulations designed and its commercial product in the stratum corneum, viable epidermis, and dermis were measured. It was concluded that the application of terbinafine solid lipid particles for 12 h might have an efficacy comparable to that of the commercial topical product (Chen et al. 2012).

The skin permeation of ethosomes, binary ethosomes, and transfersomes of terbinafine was compared under nonocclusive conditions. The results indicated that the binary ethosomes most effectively permitted drug penetration through skin, whereas transfersomes made it easier for the drug to accumulate in the skin. Ethosomes had greater improvement in skin permeation of terbinafine than that of its skin deposition (Zhang et al. 2012).

Nails are skin appendages susceptible to fungal attack, and it is difficult to treat fungal infection of nail by conventional formulations because of the very low permeability of the nail plate (Kumar et al. 2014). Tanrıverdi and Özer prepared terbinafine hydrochloride-loaded liposome and ethosome formulations and performed nail characterization studies to examine the effect of formulations on nail surface. They concluded that vesicular carriers could be served as efficient formulations for ungual application of terbinafine hydrochloride (Tanrıverdi and Özer 2013).

In addition to these studies, liposomal gel formulations of terbinafine and an alcohol-free niosome gel containing naftifine hydrochloride were developed and characterized by various researchers (Barakat et al. 2009; Koutsoulas et al. 2014; Sudhakar et al. 2014).

7.3.2 Nanocarriers of Azole Antifungal Agents

Azole antifungal drugs show numerous drug-drug interactions (Brüggemann et al. 2009). The most significant common drug interactions are drug elevations of cyclosporine, tacrolimus and sirolimus due to most calcium channel blockers and benzodiazepines, many statins and steroids, and warfarin and rifabutin (Zonios and Bennett 2008). Furthermore, the increase in antifungal drug resistance, particularly to azoles, created a strong need for the identification of novel antifungal therapies and drug targets. Several novel vehicles, e.g., microemulsions, vesicular carriers, and lipid particles, have been proposed for the topical application of azole antifungal agents.

7.3.2.1 Imidazoles

Clotrimazole Clotrimazole was first synthesized in the late 1960s and was introduced to markets in 1973. This drug is accepted worldwide for the treatment of common fungal diseases such as vaginal yeast infections and athlete's foot. Microemulsions, ethosomes, and ultradeformable liposomes were formulated and evaluated by various researchers as clotrimazole nanocarriers for dermal, transdermal, vaginal, and ocular delivery (Basha et al. 2013; Maheshwari et al. 2012; Vanić and Škalko-Basnet 2013). The efficacy and tolerability of clotrimazole microemulsion in the treatment of various topical fungal infections were evaluated clinically (Hashem et al. 2011). Ultradeformable carriers showed prolonged ocular delivery of clotrimazole, and their antifungal activity against *C. albicans* was higher than niosomal formulation as well as the drug suspension (Basha et al. 2013). Clotrimazole-loaded solid lipid nanoparticles and nanostructured lipid carriers were prepared by the hot high-pressure homogenization technique to assess the physical stability of these particles, as well as the loading capacity and in vitro release pattern. The results obtained demonstrated the use of the lipid nanoparticles as modified release formulations for clotrimazole (Souto et al. 2004). Aqueous

micelle solutions of several azole antifungals (clotrimazole, econazole nitrate, and fluconazole) were prepared using amphiphilic methoxy-poly (ethylene glycol)-hexyl substituted polylactide block copolymers. The significant increase in skin deposition demonstrated the ability of micelle-type carrier systems to improve cutaneous antifungal drug bioavailability (Bachhav et al. 2011).

Ketoconazole Ketoconazole is a broad-spectrum, systemic antifungal agent. Lipid vesicular systems including conventional liposomes, ethosomes, deformable liposomes, and ethanol-containing deformable liposomes were prepared as nanocarriers for ketoconazole, respectively. Characterization of the vesicles was based on particle size, zeta potential, entrapment efficiency, and transmission electron microscopy. The results demonstrated that ethanol-containing deformable liposomes improved both in vitro and in vivo skin deposition of ketoconazole (Guo et al. 2015). Microemulsion formulations of ketoconazole enhanced percutaneous absorption of the drug, and it has been shown that a microemulsion and cyclodextrin combination enhanced the antifungal activity of the drug in vitro against *Candida parapsilosis* test (Che et al. 2015; Patel et al. 2011).

Sertaconazole Sertaconazole is a broad-spectrum third-generation imidazole derivative that is effective and safe to cure superficial mycoses, such as tineas, candidiasis, and pityriasis versicolor. Microemulsion-based hydrogels for cutaneous delivery of sertaconazole were studied with an objective to increase the solubility and skin permeability of the drug. The results indicated that the microemulsion-based hydrogel studied provided higher antifungal activity against *C. albicans* when compared with commercial cream of sertaconazole (Sahoo et al. 2014a, b).

Bifonazole Bifonazole is a substituted imidazole antifungal agent possessing a broad spectrum of activity in vitro against dermatophytes, molds, and yeasts. It is an effective and well-tolerated treatment for superficial fungal infections of the skin. It has been reported that microemulsion-based hydrogel of bifonazole provided sustained drug release cutaneous application (Sabale and Vora 2012).

Miconazole Propylene glycol phospholipid vesicles and ultraflexible liposomes have been advocated as deformable lipid carriers for enhanced skin delivery of broad-spectrum imidazole antifungal agent miconazole. The results provided evidence of controlled drug delivery, higher rate of drug transfer across the skin, enhanced skin deposition of miconazole, and better antifungal activity as compared to traditional liposomes and plain drug solution (Elmoslemany et al. 2012; Pandit et al. 2014). Miconazole possesses only slight water solubility, which limits its bioavailability and antifungal efficacy. To increase the dissolution rate of miconazole and itraconazole, the particle size of these compounds was scaled down into nano-size by media milling, respectively. The nanosuspensions obtained had a mean particle size of 210 nm and showed enhanced in vitro performance (Cerdeira et al. 2013).

Econazole Solid lipid nanoparticles and nanostructured lipid carriers of econazole were designed for the treatment of deep-seated fungal infections. In vivo studies demonstrated that solid lipid nanoparticles promoted a rapid penetration of econazole through the stratum corneum and improved the diffusion of the drug in the deeper skin layers (Keshri and Pathak 2013; Sanna et al. 2007). Polymeric nanosponges were prepared as an alternative carrier for targeting econazole to the skin through topical hydrogel formulation (Sharma and Pathak 2011).

7.3.2.2 Triazoles

Fluconazole Fluconazole is a semisynthetic triazole, which is active against numerous yeasts. It remains one of mostly prescribed triazoles due to its good bioavailability and substantially fewer

drug-drug interactions than other triazole compounds. However, systemic treatment with fluconazole can cause adverse effects, including hepatic enzyme elevation and drug interactions (Melkoumov et al. 2015). Microemulsions were investigated for topical delivery of fluconazole and some promising results have been achieved (Hoeller et al. 2008; Brito Oliveira et al. 2015; Patel et al. 2009). One of the major drawbacks of using microemulsions for topical delivery is their liquid nature and their consequently low residence time on the application site. Therefore microemulsion-based hydrogels have gained interest to improve the viscosity of different formulations. Microemulsion-based hydrogels were evaluated as fluconazole delivery systems for the treatment of cutaneous and vaginal mycoses. The small-scale clinical studies indicated that the microemulsion-based gel developed for the vaginal delivery of fluconazole showed faster onset of action than commercial preparation (Bachhav and Patravale 2009; Coneac et al. 2015; Salerno et al. 2010).

Fluconazole-entrapped liposomes and niosomes were prepared and evaluated in terms of in vitro skin permeation and skin retention. Cutaneous accumulation of fluconazole was affected by components and size of the vesicles. Physical stability studies showed superior potentials of lyophilized fluconazole liposomes after reconstitution in comparison with those of a solution product (El-Nesr et al. 2010; Gupta et al. 2011; Schwarz et al. 2011). To improve the stability and overall applicability of the formulations, fluconazole-loaded liposomes and niosomes have been further incorporated into polymer gels. The studies performed in vivo showed that liposomal gel could produce significantly higher drug, a localization in viable skin, compared with its plain gel. The antifungal study also confirmed the maximum therapeutic efficacy of liposomal gel showing its potential for topical delivery of fluconazole with increased accumulation of drug in the skin (Gupta et al. 2010). Bhalaria et al. prepared fluconazole-encapsulated ethosomes and incorporated in a dermatological base to assess the comparative clinical efficacy in the treatment of candidiasis patients. From the clinical evaluation, the novel delivery system developed demonstrated high antifungal activity in comparison to liposomal formulation, marketed formulation, and hydroethanolic solution of the drug (Bhalaria et al. 2009).

Itraconazole Itraconazole is a triazole antifungal agent which may be given orally or intravenously. A microemulsion-based gel of itraconazole was developed for overcoming the shortcomings and adverse effects of currently used therapies. The in vivo evaluation indicated the superiority of microemulsion hydrogel formulation for treating superficial fungal infections than those of its conventional approaches (Kumar and Shishu 2015). Microemulsion-based itraconazole gel was also evaluated for effective treatment of onychomycosis. Ex vivo permeation studies indicated better penetration and retention of itraconazole into nail plate and nail bed models (Barot et al. 2012a, b). Chudasama et al. determined in vitro itraconazole permeation from microemulsion gels across excised rat skin. In vitro antimycotic inhibitory activity of the gels was evaluated with agar cup method and *C. albicans* as a test organism. The results indicated that the microemulsion gel studied showed the widest zone of inhibition and therefore may be a promising vehicle for topical delivery of itraconazole (Chudasama et al. 2011). Deformable liposomes containing hydroxypropyl-β-cyclodextrin enhanced the amount of itraconazole in stratum corneum and deeper skin layers compared to conventional liposomes (Alomrani et al. 2014). Nanosuspensions formulated by ultrasound treatment improved the dissolution behavior of itraconazole (da Fonseca Antunes et al. 2013).

Voriconazole Voriconazole is a second-generation triazole available in both intravenous and oral formulations (Sable et al. 2008). It has revolutionized the treatment of aspergillosis in severely immunocompromised patients, but the use of voriconazole is compromised by complicated pharmacokinetics, notable drug interactions,

and relatively significant adverse events (Zonios and Bennett 2008). Microemulsions as vehicles for topical administration of voriconazole were investigated, and drug-loaded microemulsions were evaluated for their physicochemical characteristics and in vitro permeation studies using guinea pig skin. The presence of permeation enhancers in the formulation favored transdermal rather than dermal delivery of voriconazole (El-Hadidy et al. 2012).

Transethosomes composed of phospholipid, ethanol, water, and edge activator (surfactants) or penetration enhancer (oleic acid) were developed and evaluated for enhanced skin delivery of voriconazole. Transethosomes enhanced both in vitro and in vivo skin deposition of voriconazole in the dermis/epidermis region compared to conventional liposomes, ethosomes, and transfersomes (Song et al. 2012). In order to develop topical preparations of voriconazole for the treatment of mycotic infections of the skin, a nanostructured lipid carrier-based hydrogel formulation was developed and its physical characteristics, in vitro skin permeation, and retention profiles were examined. The in vitro skin permeation study showed that the nanostructured lipid carrier-based hydrogel was superior to conventional cream and microemulsion-based gel formulations of voriconazole. In addition, the formulation developed led to markedly greater accumulation of voriconazole in deeper skin layers as compared with the reference formulations (Song et al. 2014).

Posaconazole Posaconazole, a lipophilic second-generation antifungal triazole, has a significant role for the prophylaxis of invasive fungal infections in severely immunocompromised patients with extended antifungal spectrum, significant activity against the zygomycetes, and apparently, optimal safety profile. Posaconazole is only available as an oral formulation (Brüggemann et al. 2009). Multiple daily dosing, the need for fatty foods for absorption, and the absence of an intravenous formulation restrict its use to selected populations (Zonios and Bennett 2008). There has been consideration of a potential enhancement in solubility with decreasing of the particle size of drugs into nanometer size range. To enhance solubility and the rate of dissolution, posaconazole was nano-sized using wet media milling technology. The mean particle size of the processed crystals had a narrow distribution profile with a mean size of 185 nm (Merisko-Liversidge and Liversidge. 2011).

7.3.3 Nanocarriers of Polyene Antifungal Agents

The activity of nano-sized amphotericin B against the growth of *C. albicans* was investigated, and the conventional micro-sized amphotericin B was converted into nano-size (5–20 nm) using a ball milling machine. The results revealed that the antifungal activity of nano-sized drug was two to four times greater than the micro-counterpart. Nano-sized amphotericin B showed an enhanced surface activity by interacting with the walls of Candida yeasts (Randhawa et al. 2015). Kang et al. formulated amphotericin B-loaded cationic liposome gels for topical application and have found this thermosensitive gel to be more stable and less toxic than free amphotericin B for vaginal delivery (Kang et al. 2010).

Nystatin nanoemulsions have been evaluated for topical application. A faster pharmacokinetic release from the nanoemulsion formulation has been recorded than commercial nystatin ointment, and the amount of drug retained in the skin was sufficient to ensure an effective antifungal effect (Fernandez-Campos et al. 2012). In another study performing a comparative evaluation, a nanoparticulate nystatin formulation against a commercial nystatin preparation showed that nanonization of nystatin provides a novel approach to enhancing the efficacy of drug in the treatment of oral candidiasis (Melkoumov et al. 2015).

El-Ridy et al. have been encapsulated nystatin in niosomes to obtain a safe and effective formulation administered parenterally for neutropenic

patients. Nystatin niosomes exerted less nephrotoxicity and hepatotoxicity in vivo, showed higher level of drug in significant organs, and improved efficacy in elimination of the fungal burden in experimental animals infected with *C. albicans* compared with those treated with free nystatin (El-Ridy et al. 2011).

7.3.4 Nanocarriers of Echinocandins

Caspofungin, micafungin, and anidulafungin exist in intravenous form (lyophilized powder for infusion) and are indicated in the management of invasive fungal infections such as esophageal candidiasis and candidemia (Sable et al. 2008). Currently there hasn't been any study published about nano-sized delivery systems of echinocandin antifungal agents. This fact might be due to the relatively big molecular weight of echinocandins (>1000 Da) when compared to conventional small-molecule drug compounds.

7.3.5 Nanocarriers of Ciclopirox and Griseofulvin

Aggarwal et al. developed a microemulsion formulation of griseofulvin intended for the treatment of dermatophytosis. The dermatopharmacokinetics and antifungal activity of the formulation were evaluated on guinea pig model. Treatment of guinea pigs with griseofulvin microemulsion resulted in a complete clinical and mycological cure in 7 days. The formulation was observed to be histopathologically safe and stable (Aggarwal et al. 2013).

Griseofulvin was encapsulated in the deformable membrane vesicles for dermal delivery. The optimized vesicles illustrated remarkably higher drug permeation and skin retention when compared with conventional liposomes. The results indicated that the topical deformable vesicles of griseofulvin could be considered as an alternative to reduce the obstacle of conventional oral formulations (Aggarwal and Goindi 2012). The same researchers optimized griseofulvin-loaded solid lipid nanoparticles by hot microemulsion technique. The cumulative amount of drug permeated through excised mice skin from solid lipid nanoparticles was more than fivefolds as compared to permeation from conventional cream base (Aggarwal and Goindi 2013).

Niosomal vesicular carriers were investigated for dermal delivery of ciclopirox olamine. Deposition of drug into rat skin from niosomal dispersion and niosomal gel formulation was significantly higher than that of solution formulation of ciclopirox olamine and its commercial product. Obtained niosomes possessed sufficient stability on storage (Shaikh et al. 2010). Karimunnisa and Atmaram investigated mucoadhesive liposomal ciclopiroxolamine gel for vaginal use. The gel exhibited good mucoadhesivity to sheep vaginal tissue, and furthermore liposome-entrapped drug displayed good antifungal activity (Karimunnisa and Atmaram 2013).

7.4 Conclusion

Delivery of antifungal agents used for the treatment of superficial and systemic infections has a great impact in terms of both therapeutic aspect and safety. In particular, treatment of deep-seated fungal infections could be inefficient due to poor penetration of drugs into targeted sites, resulting in unsatisfactory bioavailability. In addition, the controlling of drug release is also important to minimize systemic absorption and to decrease the toxicity of these agents. Therefore, novel drug delivery systems play a key role to overcome the limitations of conventional dosage forms to improve the efficacy and to ensure safety of the treatment. So far, optimization of different types of nanocarriers such as liposomes, niosomes, micelles, and transfersomes have been intensively investigated to improve efficiency and safety of antifungal agents. Some liposomal products of antifungal agents are already commercially available. At the end of the 1980s, the first liposome dermatological product (Pevaryl®Lipogel) has come into market. Liposome formulation of amphotericin B for parenteral administration has been first marketed under the name AmBisome in 1990. Still there is a

great effort to optimize novel carriers of antifungal agents. In this context, a considerable amount of research focused on the development of nanocarriers of antifungal drugs, to some extent, has been published.

References

Adler-Moore JP, Proffitt RT (2004) Novel drug delivery systems for antifungal agents. In: Domer JE, Kobayashi GS (eds) The mycota XII human fungal pathogens. Springer, Heidelberg, pp 339–340

Aggarwal N, Goindi S (2012) Preparation and evaluation of antifungal efficacy of griseofulvin loaded deformable membrane vesicles in optimized guinea pig model of Microsporum canis dermatophytosis. Int J Pharm 437(1–2):277–287

Aggarwal N, Goindi S (2013) Preparation and in vivo evaluation of solid lipid nanoparticles of griseofulvin for dermal use. J Biomed Nanotechnol 9(4):564–576

Aggarwal N, Goindi S, Khurana R (2013) Formulation, characterization and evaluation of an optimized microemulsion formulation of griseofulvin for topical application. Colloids Surf B 105:158–166

Ainbinder D, Paolino D, Fresta M et al (2010) Drug delivery applications with ethosomes. J Biomed Nanotechnol 6:558–568

Akhtar N (2014) Vesicles: a recently developed novel carrier for enhanced topical drug delivery. Curr Drug Deliv 11:87–97

Alomrani AH, Shazly GA, Amara AA, Badran MM (2014) Itraconazole-hydroxypropyl-β-cyclodextrin loaded deformable liposomes: in vitro skin penetration studies and antifungal efficacy using Candida albicans as model. Colloids Surf B 121:74–81

Arendrup MC (2013) Candida and candidaemia. Susceptibility and epidemiology. Dan Med J 60(11):B4698

Bachhav YG, Patravale VB (2009) Microemulsion based vaginal gel of fluconazole: formulation, in vitro and in vivo evaluation. Int J Pharm 365(1–2):175–179

Bachhav YG, Mondon K, Kalia YN et al (2011) Novel micelle formulations to increase cutaneous bioavailability of azole antifungals. J Control Release 153 (2):126–132

Barakat HS, Darwish IA, El-Khordagui LK et al (2009) Development of naftifine hydrochloride alcohol-free niosome gel. Drug Dev Ind Pharm 35(5):631–637

Barot BS, Parejiya PB, Patel HK et al (2012a) Microemulsion-based gel of terbinafine for the treatment of onychomycosis: optimization of formulation using D-optimal design. AAPS PharmSciTech 13 (1):184–192

Barot BS, Parejiya PB, Patel HK et al (2012b) Microemulsion-based antifungal gel delivery to nail for the treatment of onychomycosis: formulation, optimization, and efficacy studies. Drug Deliv Transl Res 2(6):463–476

Basha M, Abd El-Alim SH, Shamma RN et al (2013) Design and optimization of surfactant-based nanovesicles for ocular delivery of Clotrimazole. J Liposome Res 23(3):203–210

Benson HA (2009) Elastic liposomes for topical and transdermal drug delivery. Curr Drug Deliv 6:217–226

Bhalaria MK, Naik S, Misra AN (2009) Ethosomes: a novel delivery system for antifungal drugs in the treatment of topical fungal diseases. Indian J Exp Biol 47 (5):368–375

Brito Oliveira M, Calixto G, Graminha M et al (2015) Development, characterization, and in vitro biological performance of fluconazole loaded microemulsions for the topical treatment of cutaneous leishmaniasis. Biomed Res Int. doi:10.1155/2015/396894

Brüggemann RJM, Alffenaar JWC, Blijlevens NMA et al (2009) Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis 48:1441–1458

Carneiro G, Aguiar MG, Fernandes AP et al (2012) Drug delivery systems for the topical treatment of cutaneous leishmaniasis. Expert Opin Drug Deliv 9:1083–1097

Çelebi N, Ermiş S, Özkan S (2015) Development of topical hydrogels of terbinafine hydrochloride and evaluation of their antifungal activity. Drug Dev Ind Pharm 41(4):631–639

Cerdeira AM, Mazzotti M, Gander B (2013) Formulation and drying of miconazole and itraconazole nanosuspensions. Int J Pharm 443:209–220

Cevc G (1996) Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery. Crit Rev Ther Drug Carrier Syst 13:257–388

Che J, Wu Z, Shao W et al (2015) Synergetic skin targeting effect of hydroxypropyl-β-cyclodextrin combined with microemulsion for ketoconazole. Eur J Pharm Biopharm. doi:10.1016/j.ejpb.2015.03.028

Chen YC, Liu DZ, Liu JJ et al (2012) Development of terbinafine solid lipid nanoparticles as a topical delivery system. Int J Nanomedicine 7:4409–4418

Chudasama A, Patel V, Nivsarkar M et al (2011) Investigation of microemulsion system for transdermal delivery of itraconazole. J Adv Pharm Technol Res 2(1):30–38

Coneac G, Vlaia V, Olariu I et al (2015) Development and evaluation of new microemulsion-based hydrogel formulations for topical delivery of fluconazole. AAPS PharmSciTech. doi:10.1208/s12249-014-0275-8

da Fonseca Antunes AB, De Geest BG, Vervaet C et al (2013) Solvent-free drug crystal engineering for drug nano- and micro suspensions. Eur J Pharm Sci 48 (1–2):121–129

El-Hadidy GN, Ibrahim HK, Mohamed MI et al (2012) Microemulsions as vehicles for topical administration of voriconazole: formulation and in vitro evaluation. Drug Dev Ind Pharm 38(1):64–72

Elmoslemany RM, Abdallah OY, El-Khordagui LK et al (2012) Propylene glycol liposomes as a topical

delivery system for miconazole nitrate: comparison with conventional liposomes. AAPS PharmSciTech 13(2):723–731
El-Nesr OH, Yahiya SA, El-Gazayerly ON (2010) Effect of formulation design and freeze-drying on properties of fluconazole multilamellar liposomes. Saudi Pharm J J18(4):217–224
El-Ridy MS, Abdelbary A, Essam T et al (2011) Niosomes as a potential drug delivery system for increasing the efficacy and safety of nystatin. Drug Dev Ind Pharm 37(12):1491–1508
Fernández Campos F, Calpena Campmany AC, Rodríguez Delgado G et al (2012) Development and characterization of a novel nystatin-loaded nanoemulsion for the buccal treatment of candidosis: ultrastructural effects and release studies. J Pharm Sci 101(10):3739–3752
Flückiger U, Marchetti O, Bille J, Eggimann P, Zimmerli S, Immof A, Garbino J, Ruef C, Pittet D, Tauber M, Glauser M, Calandra T (2006) Treatment options of invasive fungal infections in adults. Swiss Med Wkly 136:447–463
Ghannoum M, Isham N, Verma A et al (2013) In vitro antifungal activity of naftifine hydrochloride against dermatophytes. Antimicrob Agents Chemother 57 (9):4369–4372
Güngör S, Erdal MS, Aksu B (2013) New formulation strategies in topical antifungal therapy. J Cosm Dermatol Sci Appl 3:56–65
Güngör S, Erdal MS, Güngördük S (2015a) Colloidal carriers in topical treatment of dermatological diseases. In: Naik J (ed) Nano-based drug delivery. IAPC Open Book and Monograph Platform (OBP), Zagreb, pp 391–409
Güngör S, Kahraman E, Özsoy Y (2015b) Polymeric micelles for cutaneous drug delivery. In: Naik J (ed) - Nano-based drug delivery. IAPC Open Book and Monograph Platform (OBP), Zagreb, pp 369–387
Guo F, Wang J, Ma M et al (2015) Skin targeted lipid vesicles as novel nano-carrier of ketoconazole: characterization, in vitro and in vivo evaluation. J Mater Sci Mater Med. doi:10.1007/s10856-015-5487-2
Gupta M, Goyal AK, Paliwal SR et al (2010) Development and characterization of effective topical liposomal system for localized treatment of cutaneous candidiasis. J Liposome Res 20(4):341–350
Gupta M, Vaidya B, Mishra N et al (2011) Effect of surfactants on the characteristics of fluconazole niosomes for enhanced cutaneous delivery. Artif Cells Blood Substit Immobil Biotechnol 39(6):376–384
Hashem FM, Shaker DS, Ghorab MK et al (2011) Formulation, characterization, and clinical evaluation of microemulsion containing clotrimazole for topical delivery. AAPS PharmSciTech 12(3):879–886
Hoeller S, Klang V, Valenta C (2008) Skin-compatible lecithin drug delivery systems for fluconazole: effect of phosphatidylethanolamine and oleic acid on skin permeation. J Pharm Pharmacol 60(5):587–591
Iqbal MA, Md S, Sahni JK et al (2012) Nanostructured lipid carriers system: recent advances in drug delivery. J Drug Target 20:813–830
Johal HS, Garg T, Rath G et al (2014) Advanced topical drug delivery system for the management of vaginal candidiasis. Drug Deliv 24:1–14
Kang JW, Davaa E, Kim YT, Park JS (2010) A new vaginal delivery system of amphotericin B: a dispersion of cationic liposomes in a thermosensitive gel. J Drug Target 18(8):637–644
Karimunnisa S, Atmaram P (2013) Mucoadhesive nanoliposomal formulation for vaginal delivery of an antifungal. Drug Dev Ind Pharm 39(9):1328–1337
Kasper L, Miramón P, Jablonowski N et al (2015) Antifungal activity of clotrimazole against Candida albicans depends on carbon sources, growth phase, and morphology. J Med Microbiol. doi:10.1099/jmm.0.000082
Kaur P, Kakkar S (2010) Topical delivery of antifungal agents. Expert Opin Drug Deliv 7:1303–1327
Kelly BP (2012) Superficial fungal infections. Pediatr Rev 33:22–37
Keshri L, Pathak K (2013) Development of thermodynamically stable nanostructured lipid carrier system using central composite design for zero order permeation of econazole nitrate through epidermis. Pharm Dev Technol 18(3):634–644
Korting HC, Klovekornl W, Klovekorn G (1997) Comparative efficacy and tolerability of econazole liposomal gel 1%, branded econazole conventional cream 1% and generic clotrimazole cream 1% in tinea pedis. Clin Drug Invest 14:286–293
Koutsoulas C, Pippa N, Demetzos C et al (2014) Preparation of liposomal nanoparticles incorporating terbinafine in vitro drug release studies. J Nanosci Nanotechnol 14(6):4529–4533
Kumar N, Shishu (2015) D-optimal experimental approach for designing topical microemulsion of itraconazole: characterization and evaluation of antifungal efficacy against a standardized Tinea pedis infection model in Wistar rats. Eur J Pharm Sci 67:97–112
Kumar L, Verma S, Bhardwaj A, Vaidya S, Vaidya B (2014) Eradication of superficial fungal infections by conventional and novel approaches: a comprehensive review. Artif Cells Nanomed Biotechnol 42(1):32–46
Lewis RE (2010) Polyene antifungal agents. In: ComarúPasqualotto A (ed) Aspergillosis: from diagnosis to prevention. Springer, Heidelberg, pp 281–305
Madhu G, Agrawal U, Vyas S (2012) Nanocarrier-based topical drug delivery for the treatment of skin diseases. Expert Opin Drug Deliv 9:783–804
Mahale NB, Thakkar PD, Mali RG et al (2012) Niosomes: novel sustained release nonionic stable vesicular systems – an overview. Adv Colloid Interf Sci 183–184:46–54
Maheshwari RG, Tekade RK, Sharma PA et al (2012) Ethosomes and ultradeformable liposomes for transdermal delivery of clotrimazole: a comparative assessment. Saudi Pharm J 20(2):161–170
Marianecci C, Di Marzio L, Rinaldi F et al (2014) Niosomes from 80s to present: the state of the art. Adv Colloid Interf Sci 205:187–206
Mbah CC, Builders PF, Attama AA (2014) Nanovesicular carriers as alternative drug delivery systems: ethosomes in focus. Expert Opin Drug Deliv 11:45–59

Melkoumov A, Goupil M, Louhichi F et al (2015) Nystatin nanosizing enhances in vitro and in vivo antifungal activity against Candida albicans. J Antimicrob Chemother. doi:10.1093/jac/dkt137

Merisko-Liversidge E, Liversidge GG (2011) Nanosizing for oral and parenteral drug delivery: a perspective on formulating poorly-water soluble compounds using wet media milling technology. Adv Drug Deliv Rev 63:427–440

Munoz P, Guinea J, Rojas L et al (2010) New antifungal agents for the treatment of candidemia. Int J Antimicrob Agents 36:63–69

Neubert RH (2011) Potentials of new nanocarriers for dermal and transdermal drug delivery. Eur J Pharm Biopharm 77:1–2

Pandit J, Garg M, Jain NK (2014) Miconazole nitrate bearing ultraflexible liposomes for the treatment of fungal infection. J Liposome Res 24(2):163–169

Patel MR, Patel RB, Parikh JR et al (2009) Effect of formulation components on the in vitro permeation of microemulsion drug delivery system of fluconazole. AAPS PharmSciTech 10(3):917–923

Patel MR, Patel RB, Parikh JR et al (2011) Investigating effect of microemulsion components: in vitro permeation of ketoconazole. Pharm Dev Technol 16(3):250–258

Randhawa MA, Gondal MA, Al-Zahrani AH et al (2015) Synthesis, morphology and antifungal activity of nano-particulated amphotericin-B, ketoconazole and thymoquinone against Candida albicans yeasts and Candida biofilm. J Environ Sci Health Part A Toxic Hazard Subst Environ Eng 50(2):119–124

Sabale V, Vora S (2012) Formulation and evaluation of microemulsion-based hydrogel for topical delivery. Int J Pharm Invest 2(3):140–149

Sable CA, Strohmeier KM, Chodakewitz JA (2008) Advances in antifungal therapy. Annu Rev Med 59:361–379

Sahoo S, Pani NR, Sahoo SK (2014a) Effect of microemulsion in topical sertaconazole hydrogel: in vitro and in vivo study. Drug Deliv 20:1–8

Sahoo S, Pani NR, Sahoo SK (2014b) Microemulsion based topical hydrogel of sertaconazole: formulation, characterization and evaluation. Colloids Surf B 120:193–199

Salerno C, Carlucci AM, Bregni C (2010) Study of in vitro drug release and percutaneous absorption of fluconazole from topical dosage forms. AAPS PharmSciTech 11(2):986–993

Sanna V, Gavini E, Cossu M et al (2007) Solid lipid nanoparticles (SLN) as carriers for the topical delivery of econazole nitrate: in-vitro characterization, ex-vivo and in-vivo studies. J Pharm Pharmacol 59 (8):1057–1064

Santos P, Watkinson AC, Hadgraft J et al (2008) Application of microemulsions in dermal and transdermal drug delivery. Skin Pharmacol Physiol 21:246–259

Scalia S, Young PM, Traini D (2015) Solid lipid microparticles as an approach to drug delivery. Expert Opin Drug Deliv 12:583–599

Schwarz JC, Kählig H, Matsko NB et al (2011) Decrease of liposomal size and retarding effect on fluconazole skin permeation by lysine derivatives. J Pharm Sci 100 (7):2911–2919

Shaikh KS, Chellampillai B, Pawar AP (2010) Studies on nonionic surfactant bilayer vesicles of ciclopirox olamine. Drug Dev Ind Pharm 36(8):946–953

Sharma R, Pathak K (2011) Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation. Pharm Dev Technol 16(4):367–376

Sheehan DJ, Hitchcock CA, Sibley CM (1999) Current and emerging azole antifungal agents. Clin Microbiol Rev 12(1):40–79

Song CK, Balakrishnan P, Shim CK et al (2012) A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: characterization and in vitro/in vivo evaluation. Colloids Surf B 92:299–304

Song SH, Lee KM, Kang JB et al (2014) Improved skin delivery of voriconazole with a nanostructured lipid carrier-based hydrogel formulation. Chem Pharm Bull 62(8):793–798

Souto EB, Wissing SA, Barbosa CM et al (2004) Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm 278(1):71–77

Stock I (2010) Fungal diseases of vulva and vagina caused by Candida species. Med Monatsschr Pharm 33 (9):324–333

Sudhakar B, Varma JN, Murthy KV (2014) Formulation, characterization and ex vivo studies of terbinafine HCl liposomes for cutaneous delivery. Curr Drug Deliv 11 (4):521–530

Tanrıverdi ST, Özer Ö (2013) Novel topical formulations of Terbinafine-HCl for treatment of onychomycosis. Eur J Pharm Sci 48(4–5):628–636

Thompson GR, Cadena J, Patterson TF (2009) Overview of antifungal agents. Clin Chest Med 30:203–215

Torrado JJ, Espada R, Ballesteros MP et al (2008) Amphotericin B formulations and drug targeting. J Pharm Sci 97:2405–2425

Vanić Ž, Škalko-Basnet N (2013) Nanopharmaceuticals for improved topical vaginal therapy: can they deliver? Eur J Pharm Sci 50(1):29–41

Verma P, Pathak K (2012) Nanosized ethanolic vesicles loaded with econazole nitrate for the treatment of deep fungal infections through topical gel formulation. Nanomedicine 8:489–496

Zhang AY, Camp WL, Elewski BE (2007) Advances in topical and systemic antifungals. Dermatol Clin 25:165–183

Zhang JP, Wei YH, Zhou Y et al (2012) Ethosomes, binary ethosomes and transfersomes of terbinafine hydrochloride: a comparative study. Arch Pharm Res 35(1):109–117

Zonios DI, Bennett JE (2008) Update on azole antifungals. Semin Respir Crit Care Med 29(2):198–210