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Review

Nanoparticles as safe and effective delivery systems of antifungal agents: Achievements and challenges

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ABSTRACT

Invasive fungal infections are becoming a major health concern in several groups of patients leading to severe morbidity and mortality. Moreover, cutaneous fungal infections are a major cause of visits to outpatient dermatology clinics. Despite the availability of several effective agents in the antifungal drug arena, their therapeutic outcome is less than optimal due to limitations related to drug physicochemical properties and toxicity. For instance, poor aqueous solubility limits the formulation options and efficacy of several azole antifungal drugs while toxicity limits the benefits of many other drugs. Nanoparticles hold great promise to overcome these limitations due to their ability to enhance drug aqueous solubility, bioavailability and antifungal efficacy. Further, drug incorporation into nanoparticles could greatly reduce its toxicity. Despite these interesting nanoparticle features, there are only few marketed nanoparticle-based antifungal drug formulations. This review sheds light on different classes of nanoparticles used in antifungal drug delivery, such as lipid-based vesicles, polymeric micelles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions and dendrimers with emphasis on their advantages and limitations. Translation of these nanoformulations from the lab to the clinic could be facilitated by focusing the research on overcoming problems related to nanoparticle stability, drug loading and high cost of production and standardization.

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Abbreviations: AmB, amphotericin B; ITZ, itraconazole; SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers; NE, Nanoemulsion; NPs, nanoparticles; AIDS, acquired immune deficiency syndrome; ABLC, AmB lipid complex; UDL, ultradeformable liposomes; DMVs, deformable membrane vesicles; DAS, diallyl sulfide; PLA, poly (lactic acid); PLGA, poly(lactide-co-glycolide); PCL, poly(ε-caprolactone); PACA, poly(alkylcyanoacrylates); PLGA-PLH-PEG, PLGA-*b*-poly(L-histidine)-*b*-poly(ethylene glycol); CDA, *Candida albicans* antibody; HKC, human renal tubular epithelial cell line; TPGS-*b*-PCL-ran-PGA, d-α-tocopheryl PEG 1000 succinate-*b*-poly(ε-caprolactone-ran-glycolide); LMP, low-methoxyl pectin; ALMP, amidated low-methoxyl pectin; HMP, high-methoxyl pectin; RVG29, 29-amino-acid peptide derived from rabies virus glycoprotein peptide; HSA, human serum albumin; CD, cyclodextrin; CAC, critical association concentration; PEG-*b*-PHSA, poly(ethylene oxide)-*b*-poly(*N*-hexyl stearate L-aspartamide); PE-PEG, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-methoxy poly(ethylene glycol); BBB, blood brain barrier; GC-TOS, tocopherol succinate glycol chitosan; PEO–PSO–PEO, poly(ethylene oxide)–poly(styrene oxide)–poly(ethylene oxide); PEG-PmHLA, poly(ethylene glycol)-poly(hexyl-substituted lactides); PCL-*b*-PEG, poly(ε-caprolactone)-*b*-poly(ethylene glycol); PEG-hexPLA, poly(ethylene glycol)-hexyl substituted polylactide; NSCS, *N*-naphthyl-*N*,*O*-succinyl chitosan; TNF-α, tumor necrosis factor-α; IL-12, interleukin-12; RES, reticuloendothelial system; PADRE-PAMAM, peptide conjugated polyamidoamine dendrimer; APC, antigen presenting cells.

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1. Introduction

Fungal diseases of human are in the form of topical infections of the skin and mucous membranes or more seriously, invasive and systemic infections of internal organs (Kim, 2016). Superficial fungal infections are a major reason for patient visits to dermatologists (Pfaller and Wenzel, 2003). It is estimated that around 20–25% of human population suffer from superficial mycoses (Ameen, 2010). In addition, invasive fungal infections are increasingly becoming a significant cause of morbidity and mortality particularly in patients having acquired immune deficiency syndrome (AIDS), hematologic malignancies, severe aplastic anemia, myelodysplasia, immunocompromised patients, organ transplant recipients, premature neonates and the elderly (Vallabhaneni et al., 2016). The death toll resulting from invasive fungal infections is estimated to be one and a half million persons every year (Brown et al., 2012; Kim, 2016). Major advances in the development of new antifungal agents have led to the availability of new generations with improved therapeutic outcomes in these vulnerable groups of patients (Nett and Andes, 2016). Thus, after a lag period of more than 20 years, the first-generation azole drugs, including fluconazole and itraconazole were introduced in the 1990s. This was followed by the introduction of echinocandins (anidulafungin, caspofungin, and mycafungin) and second-generation azole drugs, including voriconazole, posaconazole, and isavuconazole in the 2000s (Nett and Andes, 2016). Despite the improved effectiveness and safety profile of these drugs, invasive fungal infections caused by *Aspergillus* species, Zygomycetes, *Fusarium* spp., *Scedosporium* spp. and non-*albicans Candida* spp. still represent a major risk for vulnerable patients (Walsh et al., 2004). Further, many of these newly developed antifungal agents have important limitations related to their spectrum of activity, physicochemical and biopharmaceutical properties, pharmacokinetics, drug-drug interactions and pharmacodynamic properties (Lewis, 2011).

2. Why do antifungal drugs need delivery systems?

Several antifungal drugs are hydrophobic leading to limited water solubility, poor oral bioavailability and limited formulation approaches (Lewis, 2011). For instance, many commonly used azole antifungal drugs, such as clotrimazole, miconazole, econazole, oxiconazole, tioconazole and sertaconazole are hydrophobic and have poor aqueous solubility (Gupta and Cooper, 2008; Zhang et al., 2010). Toxicity and drug-drug interactions of systemic antifungal agents are other major obstacles that limit their clinical benefits (Ashley et al., 2006). One notorious example of antifungal drug toxicity is amphotericin-B (AmB) where its administration results in dose-limited toxicities, particularly, infusion-related reactions and nephrotoxicity. In addition, AmB augments the nephrotoxicity of many other drugs, such as cyclosporine and aminoglycosides (Churchill and Seely, 1977). Despite the availability of several conventional dosage forms for antifungal drugs including tablets, creams, IV infusions, *etc* they seemed to be ineffective in overcoming these limitations. Therefore, there is a strong need to develop innovative drug delivery systems to address these issues.

Rationally designed drug delivery systems have the ability to improve drug performance and overcome many of these limitations. Indeed, lipid- based formulations of amphotericin-B (AmB), such as AmB lipid complex (ABLC), AmB colloidal dispersion (ABCD) and liposomal AmB (L-AmB) showed a great reduction in AmB nephrotoxicity while maintaining its broad spectrum antifungal activity (Arikan and Rex, 2001). These promising results inspired the utilization of various new drug delivery systems to improve the safety profile of antifungal agents whilst maintaining or enhancing their efficacy. Among many new drug delivery systems currently under active investigation in industry and academia, nanoparticles (NPs) have emerged as an innovative and promising platform able to minimize undesirable drug side effects while maintaining or enhancing its therapeutic efficacy (Zazo et al., 2016; Zhang et al., 2010). By virtue of their versatility, multifunctionality and wide range of properties, NPs can overcome many of the unfavorable drug properties (Fig. 1). Further, NPs could enhance drug penetration through the skin and thus help eradicate deep fungal infections (Mbah et al., 2014). Other attractive features of NPs include sustained drug release, enhanced drug stability, targeting to infected tissue, reduction of off-target side effects, prolongation of residence time in the blood and improved drug efficacy (Chang et al., 2015; Wicki et al., 2015).

The term NPs refers to particles having a dimeter in the range of 1–1000 nm (Petros and DeSimone, 2010; Pinto Reis et al., 2006). However, the terms “nanomaterials” or “nanoscale” are used to describe objects having size in the range of 1–100 nm (Peer et al., 2007; Radomska et al., 2016). For the sake of simplicity in this review, the term NPs will be used for particles having a size in the range of 1–1000 nm and used for drug delivery applications. NPs have different chemical, physical or biological properties compared with their larger-scale counterparts, which make them interesting tools for drug delivery (FDA, 2014).

Progress in the research of cancer diagnosis and therapy using NPs has culminated in the commercialization of many products while many others are undergoing different phases of clinical trials (Chang et al., 2015; Da Silva et al., 2016; Radomska et al., 2016;