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REVIEW

Fungal diseases: could nanostructured drug delivery systems be a novel paradigm for therapy?

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Abstract: Invasive mycoses are a major problem for immunocompromised individuals and patients in intensive care units. Morbidity and mortality rates of these infections are high because of late diagnosis and delayed treatment. Moreover, the number of available antifungal agents is low, and there are problems with toxicity and resistance. Alternatives for treating invasive fungal infections are necessary. Nanostructured systems could be excellent carriers for antifungal drugs, reducing toxicity and targeting their action. The use of nanostructured systems for antifungal therapy began in the 1990s, with the appearance of lipid formulations of amphotericin B. This review encompasses different antifungal drug delivery systems, such as liposomes, carriers based on solid lipids and nanostructure lipids, polymeric nanoparticles, dendrimers, and others. All these delivery systems have advantages and disadvantages. Main advantages are the improvement in the antifungal properties, such as bioavailability, reduction in toxicity, and target tissue, which facilitates innovative therapeutic techniques. Conversely, a major disadvantage is the high cost of production. In the near future, the use of nanosystems for drug delivery strategies can be used for delivering peptides, including mucoadhesive systems for the treatment of oral and vaginal candidiasis.

Keywords: fungal diseases, antifungal agents, amphotericin B, azoles, nanoparticles, nanotechnology

Fungal diseases

Fungal infections are a growing public health problem, mainly related to the advances of modern medicine in prolonging the lifespan and the quality of life of patients under severe clinical conditions.[1] A range of new broad-spectrum antibiotics made it possible to successfully treat infections of many microorganisms, which had previously been fatal. This resulted in prolonged survival of patients highly susceptible to infection. Thus, fungal infections emerge as leading causes of morbidity and mortality in immunocompromised and intensive care unit patients.[2]

In recent decades, bacteria and fungi have developed considerable resistance to many traditional and modern synthetic drugs.[3] In this context, nanoparticles (NPs) can also overcome the drug resistance mechanisms, related to decreased absorption, increased drug efflux from microbial cells, biofilm formation, or intracellularity.[4] Finally, NPs deliver the highest dose of antimicrobial agents specifically to the site of infection, thus overcoming drug resistance with less adverse effects on the patient.[5]

Pathogenic fungi

Mycoses are among the most difficult global diseases to be controlled. Some conditions can be a predisposition to invasive mycoses, such as immunosuppression, neoplasia, and some chronic diseases. Oral candidiasis and vaginal candidiasis are the most

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common fungal diseases.[6] These superficial mycoses affect 25%–30% of human population.[4] *Candida albicans* is also involved in denture stomatitis pathogenesis, a disease very common in older individuals. Other fungal diseases can be less frequent, but much more severe, such as asthma with fungal sensitization, allergic bronchopulmonary aspergillosis, invasive aspergillosis, chronic pulmonary aspergillosis, pneumocystosis, meningeal cryptococcosis, mucormycoses, or invasive candidiasis.[7] Invasive fungal infections (IFIs) are less predominant, but their morbidity and mortality rates are high, killing about 1.5 million people per year.[8] A total of ten genera of fungi have a high prevalence in infections, including *Aspergillus*, *Candida*, *Cryptococcus*, *Blastomyces*, *Coccidioides*, *Histoplasma*, *Paracoccidioides*, *Penicillium*, *Pneumocystis*, and *Rhizopus*. However, 90% of deaths are caused by *Candida*, *Cryptococcus*, *Aspergillus* and *Pneumocystis*.[8] Bitar et al[9] observed a higher incidence of candidemia (43.4%), followed by *Pneumocystis jirovecii* pneumonia (26.1%), invasive aspergillosis (23.9%), cryptococcosis (5.2%), and mucormycosis (1.5%) in IFIs through a retrospective study conducted in France in 2001–2010. Among fungal infections, candidiasis is the most common fungal infection worldwide[10] and an important cause of morbidity and mortality in bloodstream and other invasive infections among hospitalized patients in many countries of the world.[11] *C. albicans* is the main etiology of candidiasis, but other species, such as *Candida glabrata*, *Candida parapsilosis*, or *Candida krusei*, are emerging as causes of nosocomial infections.[12–14]

Cryptococcus neoformans is the third most common cause of infectious complications in the central nervous system in AIDS patients:[15] 1 million new cases of cryptococcal meningitis occur each year causing ~600,000 deaths.[16] *Aspergillus fumigatus* is the most common cause of invasive mycoses by filamentous fungi, with mortality rates of 40%–90%.[17,18]

Antifungal drugs

Antifungal resistance is an increasing threat for the effective treatment of invasive mycoses, making their therapy difficult, expensive, or even impossible.[10] The current treatment approaches for IFIs are fairly limited and include three main classes of drugs: polyenes (amphotericin B [AmB]), azoles (fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole), and echinocandins (anidulafungin, caspofungin, and mycafungin).[18] To obtain good clinical results in the treatment, early and appropriate treatment is required, but the activity of current antifungal agents is not predictably against emerging yeasts and filamentous fungi and can cause undesirable side effects.[19] Older antifungal agents, such as AmB, despite their toxicity, are very important in the treatment of IFIs as they have a broad-spectrum and low resistance rates.[20]

Recent advances in antifungal chemotherapy with broad-spectrum triazoles and echinocandins provide more effective and less toxic alternatives to conventional polyenes. Despite this, IFI mortality rates remain high, and there is a growing need for new therapeutic options.[21] However, the rate of discovery of antifungal drugs is unlikely to be sufficient for the future demands, since few drugs are currently being discovered. In the early 1990s, two new antifungal drugs were approved by the US Food and Drug Administration (FDA), namely, fluconazole and itraconazole.[22] Still in the 1990s, lipid formulations of AmB, amphotericin B lipid complex (ABLC, in 1995), amphotericin B colloidal dispersion (ABCD, in 1996), and liposomal AmB (L-AmB, in 1997) were all approved. In the 2000s, caspofungin (in 2001) and voriconazole (in 2002)[23] were also approved. Micafungin was the second echinocandin antifungal agent approved by the FDA in 2005 and anidulafungin was the third to be approved in 2006.[24] Posaconazole was approved in 2006 as oral suspension, and in 2013 and 2014 for use in tablets and intravenously, respectively.[22] More recently, in March 2015, the FDA approved isavuconazole[25] (Figure 1).

Given the current panorama of microbial resistance and lack of new drugs, NPs appear to aid in the treatment of various diseases, including mycoses.[26] NPs can be defined as ultradispersed supramolecular structures with submicrometer

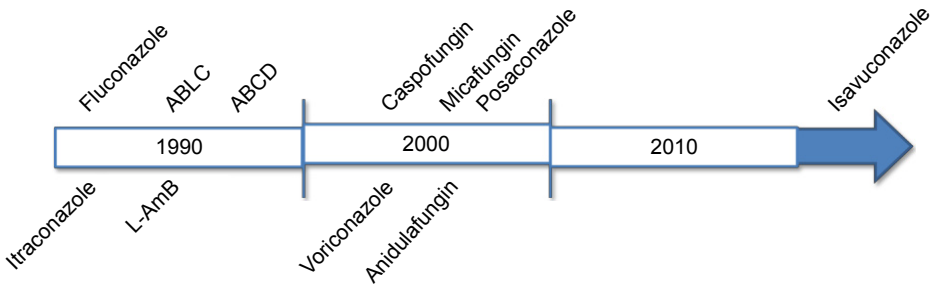

Figure 1 Time course of discovery of antifungal drugs.
Abbreviations: ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion; L-AmB, liposomal amphotericin B.

size ranging from 10 µm to 1,000 µm. The drug may be dissolved, entrapped, encapsulated, or bound to a matrix of NPs, which acts as a reservoir for particulate systems and therefore plays an important role as a drug delivery system for clinical applications, particularly in oncology.[27] Many studies have currently demonstrated the efficacy of antifungal agents incorporated into NPs for combating fungal infections.[6–8] The production of NPs through nanotechnology has revolutionized the delivery of drugs. Today, there is a consensus that nanotechnology represents a miniaturization of objects, as well as the preparation of nanomaterials with physical and chemical properties that drastically differ from those of bulk materials because they are on a nanoscale. Until the early 1970s, the administration of pharmaceutical suspensions intravenously was considered impossible due to the risk of embolism. The current development of suspensions of NPs containing drugs (eg, nanomedicines or nanopharmaceuticals) is the use of NPs for treating, diagnosing, and preventing diseases. Through these, it is possible to increase the therapeutic index of various drugs by improving activity, reducing toxicity, and targeting them selectively toward diseased tissues and cells.

A noteworthy problem in the treatment of many diseases, including invasive mycoses, is the delivery of the drug to the target site, since the conventional drugs have limitations such as restricted efficacy, poor biodistribution, and lack of selectivity. The solution to this problem is the use of a drug delivery control system that can overcome these limitations and drawbacks. The therapy based on a delivery system is important to solve problems, regarding the balance between high drug concentrations and toxic effects. A major technological breakthrough in medicine has been the reduction in the particle size from micrometers to nanometers.[28] Through small dimensions, NPs can target specific sites within the body as cells and tissues are permeable to them. Therefore, NPs can deliver the active drug to sites where conventional drugs do not reach, thus minimizing unwanted side effects. The therapeutic potential of NPs as carriers of drugs depends on their hydrodynamic size, shape, quantity, surface chemistry, route of administration, length of stay in circulation, and reaction with the immune system. Nanostructures exhibit unique physicochemical and biological properties, which makes them a favorable material for biomedical applications.[26,29] Nanoscale structures, or nanosized structures, can be used to carry drugs such as liposomes, synthetic and natural polymers, inorganic and metal NPs, dendrimers, silica, and carbon materials, as well as magnetic NPs (MNPs)[30,31] (Figure 2).

Lipid-associated formulations

Lipid formulations involve the association of an antifungal drug, such as AmB or nystatin, with a lipid delivery system to reduce toxicity.[33,34] Three different lipid formulations of AmB have been introduced in the clinical setting. The lipid composition and molecular structure of these formulations vary considerably with unique pharmacokinetic profiles.

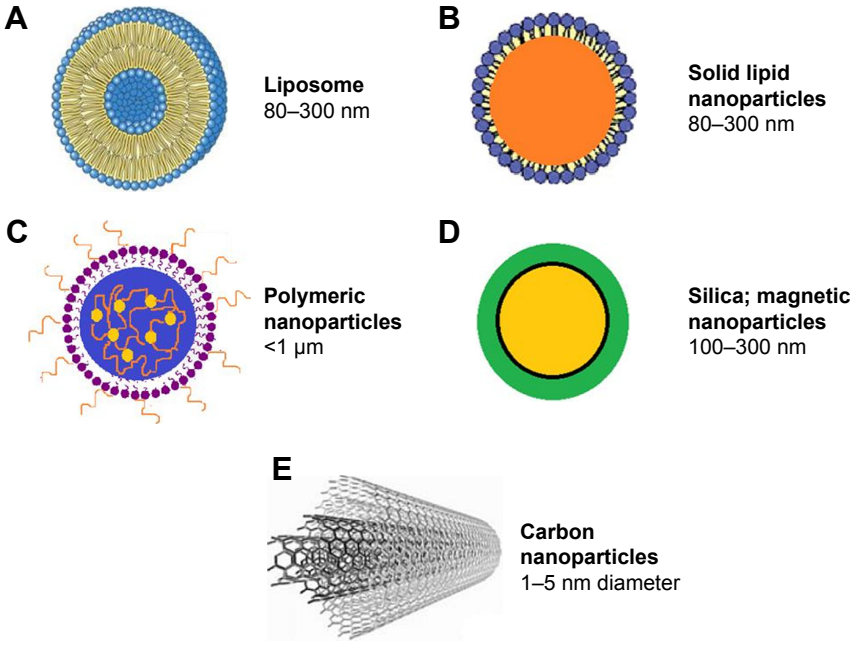

Figure 2 Nanostructured drug delivery systems modified.
Notes: (**A**) Liposome. (**B**) Solid lipid nanporticles. (**C**) Polymeric nanoparticles. (**D**) Silica; magnetic nanoparticles. (**E**) Carbon nanoparticles.

Although there is evidence of the safety of these formulations, the impact of their unique structure and pharmacokinetic differences for specific clinical efficacy is unproven.[35]

AmB deoxycholate (D-AmB) is a polyene macrolide available for clinical use since its initial FDA approval in 1959.[36] AmB is produced through a fermentation process by soil actinomycete *Streptomyces nodosus*. The AmB has broad spectrum of action and has been considered the gold standard of antifungal therapy for many years, despite being associated with a high incidence of adverse effects related to infusion and nephrotoxicity.[36,37] D-AmB still has a place in the antifungal therapy but newer drugs (eg, AmB associated with lipid formulations, fluconazole and voriconazole, or caspofungin and micafungin) are being used as first-line treatment options.[38] Fluconazol represented a major advance in the treatment of invasive candidiasis because of its broad activity, excellent tolerability, and favorable pharmacokinetics. Since its introduction, fluconazole has been widely used for the treatment and prophylaxis of candidiasis, except for those infections caused by *C. krusei*, *C. glabrata*, or other species with reduced susceptibility or resistance to this drug.[39]

Lipid complex and colloidal dispersion

In the late 1990s, almost 40 years after the first formulation of D-AmB, three AmB-based lipid formulations, namely ABLC (Abelcet®), ABCD (Amphotec®), and L-AmB (AmBisome®) were developed to reduce nephrotoxicity without compromising antifungal efficacy.[20,38] ABLC (Abelcet®; The Liposome Company, Princeton, NJ, USA) received initial approval in the UK in April 1995 and was the first lipid-based formulation approved by the FDA in December 1995. ABCD was previously marketed as both Amphocil® and Amphotec® and was initially approved in the UK in 1994 and by the FDA in December 1996.[27] The first lipid-based formulation developed was ABLC by associating AmB with a lipid–drug delivery vehicle. ABLC consists of AmB in complex with two phospholipids at 1:1 drug-to-lipid molar ratio. Both phospholipids, l-α-dimyristoylphosphatidylcholine and l-α-dimyristoylphosphatidylglycerol, are present at 7:3 molar ratio. ABLC is characterized by lipid-stabilized AmB aggregates, which appear as ribbon-like structures, with length ranging from 1.6 nm to 11.1 nm, and because of its size, circulating AmB serum concentrations are lower when compared to D-AmB.[35] ABCD consists of 1:1 molar ratio of AmB and cholesterol sulfate, a highly organized structure formed by a natural metabolite of cholesterol. A noncovalent complex of AmB and cholesteryl sulfate forms a tetramer consisting of a hydrophilic and a hydrophobic part. These add-in spiral arms form a disk-like structure with a diameter of ~122 nm and thickness of 4 nm.[40] Although ABCD reduces the availability of AmB in the kidneys reducing the nephrotoxicity, this drug concentration increases in the endothelial reticulum system,[41,42] as well as the ABLC formulation.[35] Both ABCD and ABLC are quickly endocyted by the endothelial reticulum system and distributed into the tissue.[43] ABLC formulations demonstrated efficacy against fungi such as *Fusarium solani*,[44] *Candida dubliniensis*,[45] *A. fumigatus*,[46] *Aspergillus quadrilineatus*,[47] *C. neoformans*,[48] and *Rhizopus oryzae*.[49] Table 1 lists the activity of ABCL and ABCD formulations against different fungi.

ABCD exhibits dose-limiting, infusion-related toxicities;[35] consequently, the dosages administered should not exceed 3–4 mg/kg/d. ABCD formulation was not effective in the treatment of paracoccidioidomycosis with a dosage of 3 mg/kg/d, the failure of which can possibly be due to dosage, duration, or poor effectiveness of this lipid preparation,[50] although Hanson and Stevens[51] reported in vitro activity against *Paracoccidiodes brasiliensis*. This formulation is not suitable as a prophylactic antifungal agent for neutropenic patients due to adverse effects related to infusion.[52] ABCD was found at high concentrations in the lungs after treatment, which does not happen with L-AmB, thus being a possible alternative for lung infections.[53] The prophylactic use against pulmonary mycoses by AmB nebulization has been reported.[54,55] Other drugs, such as itraconazole, in colloidal dispersion could also be suitable for nebulization.[56]

Liposomes

Liposomes are other type of lipid formulations, consisting of unilamellar or multilamellar layers on the membrane of lipids such as phospholipids, surrounded by aqueous compartment.[60,61] The liposomes can carry hydrophilic drugs in the aqueous core and increase penetration through the lipophilic membranes, as well as lipophilic drugs, which are inserted into the lipid bilayer, increasing their solubility in aqueous body fluids.[68] Liposomes provide a better protection than other lipid formulations against external degradation by enzymes. In addition, they are biocompatible and biodegradable.[62,63]

Conventional liposomes have some limitations, such as little instability and difficult to be stored for long periods and rapid uptake by the RES, thereby decreasing their half-life in circulation.[69] To solve these problems, extensive research has been developed to modify the surface of liposomes, to optimize their size, and to understanding their mechanisms of action. New generation liposomes are characterized by high mechanical stability, ability to induce or to inhibit the

Table 1 Effect of AmB formulations ABLC and ABCD with different fungal species

Disease/microorganism	Treatment systems	Delivery properties	Pharmacokinetic	Category	References
Different fungal species, including *Paracoccidioides brasiliensis*	AmB	ABCD	Not reported	In vitro	51
Fungal sinusitis *Aspergillus quadrilineatus*	AmB	ABCD	Initial dose of 0.5 mg/kg/10 d Increased gradually by 0.5 mg/kg every 3 days until a maximal dose of 2.5 mg/kg	Case study	47
Disseminated cryptococcosis	AmB	ABCD versus D-AmB	0.8 mg/kg	Murine	57
Mucormycosis	AmB	ABCD	Not reported	Case study	58
Liver transplant recipient	AmB	ABCD + ITZ	Not reported	Case study	59
Phaeohyphomycosis	ITZ	ABCD + ITZ	Not reported	Case study	59
Bone marrow transplant patients with invasive fungal infections	AmB	ABCD	7.5 mg/kg	Human	60
Lung transplant recipient with *Fusarium solani* infection	AmB	ABLC	5 mg/kg/d	Case study	44
Immunocompromised patients with candidemia	AmB	ABCD	3.9 mg/kg	Human	61
Meningitis by *Cryptococcus neoformans*	AmB Flucytosine Fluconazole	ABCD	5.0–7.5 mg/kg combined with flucytosine at 20–60 mg/kg/d and fluconazole at 30–40 mg/kg/d	Murine	48
Rhinocerebral mucormycosis	AmB	ABCD	5 mg/kg/d 4 mg/kg/d 6 mg/kg/d	Case study	62
Mucormycosis	AmB	ABLC	5 mg/kg/d	Case study	63
Candida dubliniensis	AmB	ABLC	Not reported	In vitro	45
		ABCD	Not reported	In vitro	45
		L-AmB	Not reported	In vitro	45
Mucormycosis	AmB	ABCD	4.8 mg/kg	Human	60
Invasive aspergillosis	AmB	ABCD	6 mg/kg/d	Human	64
Aspergillus fumigatus	AmB	ABLC	5 mg/kg once daily ×4 days	Rats	46
Lung transplant recipients with invasive aspergillosis	AmB	ABLC	Not reported	Prophylactic use	54
Coccidioidal meningitis by *Coccidioides immitis*	AmB	ABLC versus D-AmB	D-AmB 1 mg/kg ABLC 7.5 mg/kg or 15 mg/kg	Rabbit	65
Cholestatic liver disease and fungal infection	AmB	ABCD	4 mg/kg	Case study	66
Acute myeloblastic leukemia and *Rhizopus oryzae* infection	AmB	ABCD	1×400 mg/d	Case study	49
Liver transplant recipients with invasive fungal infections	AmB	ABCD	Not reported	Prophylactic use	67

Abbreviations: AmB, amphotericin B; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion; D-AmB, AmB deoxycholate; ITZ, itraconazole; L-AmB, liposomal AmB.

immune system, longer bypass, high loading efficiency, ease of interaction with the cell membrane, and increased target specificity. The milestone in the development of the new generation of liposomes is to control drug release.[68]

Indeed, the progress in pharmacology has introduced a number of potent therapeutic agents requiring drug carriers that are selective and bioresponsive. Advances in the technology of liposomes as drug delivery systems include long-circulating liposomes, for example, liposomes prepared with hydrophilic polymers on their surface (eg, polyethylene glycol), reduce both uptake by reticuloendothelial system and toxicity of the encapsulated drug.[64,70] This camouflage allows liposomes to exhibit the abovementioned functions. However, there is the disadvantage of an inhibited cellular absorption, limiting their uptake by macrophages and tumor cells. Hatakeyama et al[71] developed cleavable polyethylene glycol (PEG)-lipids to solve the problem of cellular uptake inhibition, since PEG systems are separated in response to the target tissue microenvironment. The target specificity is achieved by anchoring targeting ligands that bind to the desired receptors.[72] The number of plates or cross-linking lipids controls the rate of drug release from liposomes.[73] Approximately 50 years after the discovery of liposomes, the FDA approved 13 liposome-based products for human

use, which includes one formulation containing AmB for the treatment of fungal infections.[68]

L-AmB presents significantly lower toxicity compared to other AmB formulations, and it is effective in the treatment of severe invasive mycoses, including mucormycosis,[74] fusariosis,[75] cryptococcal meningitis,[76,77] coccidioidal meningitis,[78,79] blastomycosis,[80] and pulmonary aspergillosis.[81,82] However, in 2013, Ariano et al[83] reported that L-AmB may not be adequate to control lung infections by *Blastomyces dermatitidis*. Al Nakeeb et al[82] found that lipid formulations of AmB can induce dose-dependent reduction in lung injury markers and circulating fungal biomarkers. The recommended therapeutic dosages are 3–6 mg/kg/d.[35] A clinical dose of L-AmB 3 mg/kg/d may cause complete suppression of both galactomannan and levels of 1,3-β-D-glucan in most patients with invasive aspergillosis.[82]

The literature reports some problems associated with administration of L-AmB, such as hepatotoxicity,[84] progressive leukoencephalopathy,[85,86] and also development of lysosomal storage disease.[87] Treatment failures have also been reported.[88,89] The prophylactic use of L-AmB in immunocompromised patients is still a challenge. Mihara et al[90] report that prophylaxis with aerosolized L-AmB was not effective in animal model. Therefore, prospective studies are needed to compare this formulation with triazoles. In addition to AmB, other antifungal agents are carried by liposomal delivery systems, such as nystatin.[33,34] L-AmB could be useful for the treatment of cryptococcosis,[91] including species of *Aspergillus*,[92] *C. dubliniensis*.[45]

L-AmB also has activity against fungal biofilms. Schinabeck et al[94] were the first to describe *Candida* biofilm infection of catheters in animal models treated with L-AmB to block the infection. In addition, L-AmB was effective to eradicate *Candida* biofilm in a continuous catheter flow model,[95] and Ramage et al[96] showed that L-AmB kills *C. albicans* biofilms rapidly and effectively in a dose-dependent manner.

The need to improve treatment outcomes for IFI increased interest in exploring an alternative antifungal strategy. The administration of AmB in aerosol, which has been widely used, to provide the drug directly to the site of infection or fungal colonization, has the potential to maximize their spectrum of activity while minimizing systemic toxicity that is associated with parenteral administration. Aerosol AmB is used (usually as a prophylactic strategy) in high-risk patients.[97] The literature reports few studies regarding delivery systems based on aerosol for fungal infections, including AmB to prevent pulmonary aspergillosis,[98] *C. neoformans*,[89] and *C. albicans*.[99]

Table 2 shows the studies with L-AmB and L-AmB formulations associated with other conventional antifungal drugs for the treatment of IFIs in immunocompromised patients, including studies on in vitro activity of L-AmB against different fungi.

In addition to the liposomal preparation of AmB, there are AmB-polyaggregates with similar efficacy to that of D-AmB and L-AmB in the treatment of a murine-disseminated infection by *C. glabrata*.[120] Souza et al[129] tested an alternative delivery system to D-AmB, the NANO-D-AmB that has antifungal efficacy against *P. brasiliensis* with lower levels of cytotoxicity compared to that of D-AmB formulation both in vivo and in vitro, thus confirming a better delivery of AmB.

NPs based on solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLNs) emerged as a new class of colloidal drug carriers at the beginning of the 1990s, and their application has been widely exploited as drug delivery in the area of pharmaceutics, clinical medicine, and therapy. Polymeric NPs (PNPs) have the advantage of promoting chemical modifications, but there are some limitations such as polymer degradation, high cost, and difficult approval by regulatory authorities.[130] Thus, the attention of several research groups has been focused on an alternative to PNPs, that is, the SLNs.[131] SLNs provide physical stability as incorporated drugs do not suffer degradation, have controlled release, and excellent tolerability. Therefore, they can be used by different routes of administration, such as parenteral,[132] peroral,[133] dermal,[134] ocular,[135] pulmonary,[136] and rectal.[137]

SLNs are a generation of drugs where the liquid lipid (oil) has been replaced by a solid lipid, mainly composed of a dispersed lipid in physiological water or aqueous surfactant solution (Figure 3). Replacement of liquid lipid by solid lipid represents a milestone for drug controlled release because the mobility of the drug within the solid lipid is usually lower than within the liquid oil, which makes this system performance attractive for pharmaceutical products.[131]

The most advanced forms of SLNs are nanostructured lipid carriers (NLCs), lipid–drug conjugates, and polymer lipid hybrid nanoparticles (PLNs). Therefore, NLCs, introduced at the millennium's turn, are made of a solid lipid matrix that traps the liquid lipid in their nanocompartments,[138] which decreases some of the problems associated with SLNs, such as limited drug-loading capacity, expulsion of the drug during storage, suitability of drug release, and physical stability of long-term suspension.[131] Lipid–drug conjugates were developed to increase the drug-loading capacity, whereas PLNs are hybrids of liposome and PNPs developed to carry poorly water-soluble drugs with high encapsulation efficiency and loading capacity and to control the release

Table 2 Liposomes in fungal diseases

Disease/microorganisms	Treatment	Category	References
Systemic candidiasis	L-AmB	Mouse	100
Hematologic malignancies	L-AmB	Human	93,101
Hematologic malignancies and invasive sino-nasal aspergillosis	L-AmB	Human	102
Candida albicans	L-AmB	In vitro	88
Inhibition of HIV replication	L-AmB	Human	103
Heart transplant and transplant pulmonary	L-AmB	Human	104
Aspergillosis liver transplant	L-AmB	Human	105,106
Lymphoblastic leukemia and fusariosis	L-AmB	Human	107
Rhinocerebral and rhino-orbital mucormycosis	L-AmB	Human	108–110
	L-AmB + micafungin		
Cryptococcus neoformans	Aerosolized L-AmB	Mouse	89
Transplant recipients	L-AmB (AmBisome)	Human	105
Liver transplant and *Rhizopus sinusitis*	L-AmB	Human	111
Blastomycosis	L-AmB	Murine	80
AIDS and cryptococcosis	L-AmB	Human	112
C. albicans	Aerosolized L-AmB	Mouse	98
Cardiac mycetomas	L-AmB + fluconazole	Human	113
Invasive candidiasis	L-AmB + caspofungin	Murine	114
Catheter antifungal lock	L-AmB	Human	115
Exophiala dermatitidis	L-AmB	Murine	116
Fusarium verticillioides	L-AmB + terbinafine	Murine	117
C. albicans biofilm	L-AmB	Rabbit	93
C. albicans biofilm		In vitro	94
C. albicans and bloodstream isolates biofilms		Human	95
Intraventricular cryptococcoma	L-AmB + voriconazole	Case study	118
Kidney transplant	L-AmB	Case study	119
Esophageal histoplasmosis	Itraconazole		
Cerebral aspergillosis by *Aspergillus fumigatus*	L-AmB	Case study	120
Invasive pulmonary aspergillosis	Nebulized L-AmB	Prophylaxis	92
Kidney transplant and mucormycosis (*Rhizopus microsporus*)	L-AmB + posaconazole	Case study	121
Leukemia and pulmonary mucormycoses	L-AmB		122
Hematologic malignancies and IFIs	L-AmB	Prophylaxis	123
Liver transplant and IFIs	L-AmB	Prophylaxis	106
Vertebral infection by *C. albicans*	L-AmB + flucytosine	Case study	124
Disseminated aspergillosis	L-AmB + erythropoietin	Mouse model	125
Invasive aspergillosis by *A. fumigatus*	L-AmB	Rabbit	82
Pulmonary aspergillosis	Nebulized L-AmB	Human	126–128

Abbreviations: *C. albicans, Candida albicans*; L-AmB, liposomal amphotericin B; A. *fumigatus, Aspergillus fumigates*; IFI, invasive fungal infection.

of drugs. Moreover, PLNs show excellent serum stability and a wide spectrum of different target cells.[139,140] The presence of a solid lipid matrix can cause problems in the production of SLNs, since this matrix system is subject to crystallization during its formation, resulting in some drawbacks such as a low encapsulation efficiency and a poor expulsion of the stored drug.[141–143] Table 3 shows some studies on SLN transport systems in antifungal therapy for the therapy of fungal infections. However, scientific evidence on infection treated with the SLN system is scarce.

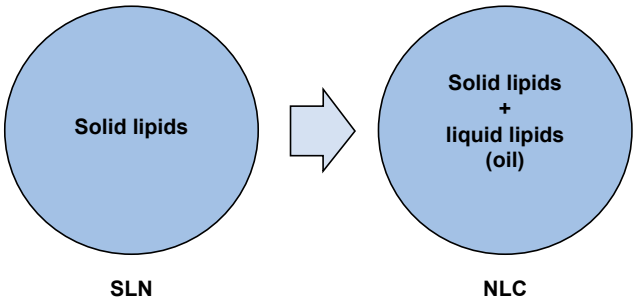

Figure 3 Nanoparticles based on solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs).

NLCs are produced by a lipid mixture of liquid and solid phases with increased content of NPs.[27] Mathpal et al[144] have recently conducted a study using a spraying technique for pulmonary delivery of AmB-NCL and concluded that through this technique the drugs are better distributed throughout the lung tissue. Several antifungal agents were also tested in different SLN and NLC delivery systems, such as itraconazole-loaded SLNs,[130,145] itraconazole-loaded NLC,[146,147] miconazole nitrate-loaded NLC,[148] econazole nitrate-loaded NLC,[149] and voriconazole[150] (Table 3). PNPs and nanosuspensions would present clear advantages over

Table 3 Antifungal drugs-loaded nanoparticles based on solid lipids (SLNs) and nanostructured lipid carriers (NLCs)

Disease/microorganism	Treatment	Delivery systems	Size	Category	References
Candidiasis	Miconazole nitrate (MN)	MN/SLN	206.39±9.37 nm[a]	Rats	152
Cutaneous candidiasis	Fluconazole (FLZ)	SLN/FLZ	178 nm	Rats	153
		NLC/FLZ	134 nm	Rats	153
Fungal vaginal	Clotrimazole (CTZ)	CTZ-NLC-gel	NA	In vitro	154
C. albicans	Miconazole	Encapsulation of miconazole in the NLC	200 nm	In vitro	155
Cutaneous candidiasis	FLZ-loaded SLN	FLZ/SLN	178.9±3.8 nm[a]	In vitro/in vivo	156
C. albicans	SLNs of terbinafine hydrochloride (TH)	SLNs were incorporated into Carbopol gel	300 nm	In vivo	157
Vaginal infection – *C. albicans*	Ketoconazole (KTZ) and CTZ	SLNs based on polyoxyethylene-40 stearate (PEG-40 stearate) for the administration of such as KTZ and CTZ antifungal agents	NA	In vitro	158
Aspergillus flavus	Itraconazole into solid lipid nanoparticles (SLNs) for topical ocular delivery	ITZ/SLNs stearic acid and palmitic acid	139–199 nm (stearic acid) 126–160 nm (palmitic acid)	In vitro	145
Pulmonary aspergillosis	Lipidic nanoparticles of amphotericin B were prepared by spray drying technique using hydroxypropylmethyl-cellulose (HPMC)	AmB/NLC spray drying	600–700 nm	In vivo	144

Note: [a]Data shown as mean ± standard deviation.
Abbreviations: AmB, amphotericin B; *C. albicans*, *Candida albicans*; NA, not available.

lipid formulations, since they have a longer shelf life at room temperature and low production costs.[151]

Polymeric NPs

PNPs are polymeric colloidal systems, which have a diameter <1 μm, in which the drug can be dissolved, coated, encapsulated, or dispersed.[29,159] Polymer degradation, high cost, and difficult approval by regulatory authorities are some of the disadvantages.[131] PNPs are stable in the gastrointestinal environment and protect encapsulated drugs against gastrointestinal pH, degradation enzymes, and efflux pumps, maintaining the stability of the drugs in this unfavorable environment.[160] The use of polymers to form PNPs provides flexibility due to their physicochemical properties (eg, size, surface charge, and hydrophobicity), allowing a controlled drug release. In addition, it is possible to modulate the surface properties or use different polymer conjugates on the surface of PNPs.[161] The possibility to add antibodies, peptides, or small molecules to the polymer surface allows tissue-specific interactions with cell receptors or components.[162] Moreover, PNPs enable the encapsulation of a broad range of therapeutic drugs and molecules, such as DNA and small interfering RNA.[160]

PNPs are classified into two categories: nanospheres and nanocapsules. Nanocapsules are vesicular systems in which the drug is inside an aqueous or oily cavity surrounded by a polymeric membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed in the matrix.[163] These delivery systems have been developed primarily for parenteral, oral, or ocular administration. There are several polymers for preparing PNPs, such as poly-ε-caprolactone,[164] polyacrylamide,[165] polyacrylate,[166] DNA,[167] chitosan,[167–169] and gelatin.[170] After a polymerization reaction, drugs may be immobilized on the surface of the PNPs[171] or encapsulated in their structure during the polymerization processing.[172] The release of the drug may occur by desorption, diffusion, or erosion of PNPs in the target tissue.[29] However, during the storage time, aggregation of NPs can occur and form precipitates. Other chemical stability problems regarding the polymer or other raw materials have been described, which obstruct their industrial applicability.[173]

Inorganic NPs, including gold, iron oxide, silver, or silica, among others, are investigated in preclinical and clinical studies for the treatment, diagnosis, and detection of many diseases. Moreover, many inorganic compounds serving as the material for making NPs have been widely used in clinical practice for several therapeutic applications.[174] One example of therapeutic compounds that act as antibacterial agents is silver ions.[175–177] Inorganic NPs offer diagnostic and therapeutic opportunity that other PNPs or not, cannot offer.[174]

PNPs have some problems arising from residues of organic solvents used in the production process, such as

cytotoxicity of the polymer and complex production for industrial application. In many production processes, the concentration of NPs is low not exceeding 2%,[178] which compromises their use. Thus, the development of solid dosage forms of NPs is a point of interest in research. Examples of antifungal agents and metal particles associated with PNPs used as drug delivery systems are shown in Table 4.

Dendrimers

Dendrimers present synthetic polymeric architectures with low polydispersion and controlled surface features. Dendrimers have three main architectural components, namely, core, dendrons, and surface-active groups.[196,197] There are some ways to connect biologically active compounds to dendrimers: the drug can be encapsulated in the internal structure of the dendrimers[198] or chemically linked or physically adsorbed onto the surface of them.[199] The choice of the immobilization method will depend on the characteristics of the drug.

Several families of dendrimers have been widely studied regarding their use in biomedical sciences. Most well-known dendrimers include polyamidoamines, polypropyleneimines, poly-L-lysines, carbosilanes, and phosphorous dendrimers. Their properties are often not satisfactory because of the high cytotoxicity of the nanomolecules and their low solubility and biocompatibility. Thus, dendrimers are often subjected to various modifications in order to improve their features: dendrimer conjugate with PEG,[200] carbohydrates,[201] or acetyl groups[202] to reduce the cytotoxicity. The compounds bound to dendrimers can improve the surface activity as well as their biological and physical properties. Several specific ligands can be adsorbed, including folic acid,[203] antibodies,[204] target cyclic peptides containing arginine-glycine-aspartic acid,[205] and PEG.[206]

Table 4 Polymeric and other nanoparticles with antifungal activity

Disease/ microorganism	Treatment	Delivery systems/methods/size	Category	References
C. albicans	AmB, 5-fluorocytosine or rapamycin	Encapsulated in 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-methoxy poly(ethylene glycol) (PEG-DSPE) micelles	In vitro	179
C. albicans	AmB	Poly(2-ethyl-2-oxazoline)-block-poly(aspartic acid) (PEOz-b-PAsp)/ micelles	In vitro	180
Paracoccidioides	Peptide	Poly(lactic acid-glycolic acid) (PLGA)	In vitro	181
Cryptococcal meningitis	P10 (PLGA) nanoparticles	Amphotericin B (AmB)-polybutylcyanoacrylate nanoparticles (AmB-PBCA-NPs) modified with polysorbate 80: 69.0±28.6 nm	Mice	182
A. flavus	ITZ and coumarin	ITZ and coumarin-6 loaded polylactic-*co*-glycolic acid-nanoparticles (PLGA-ITZ) and PLGA-C6-NPs): 232 nm, 630 nm and 1,060 nm	In vitro	183
P. brasiliensis	ITZ	PLGA-dimercaptosuccinic acid (DMSA) nanoparticles: 174±86 nm	In vitro	184
A. niger and *Fusarium oxysporum*	Not applicable	Surface-modified sulfur nanoparticles (SNPs)/polyethylene glycol-400 (PEG-400)	In vitro	185
C. albicans	AmB	Poly(epsilon-caprolactone) (PCL) and poly(N,N-dimethylamino-2-ethyl methacrylate) (PDMAEMA), or methoxy polyethylene glycol (PEG)	In vitro	186
C. albicans biofilm	Not applicable	Silicone catheter, polyvinyl chloride (PVC), and glass coated with titanium dioxide (TiO_2) nanoparticles: 70–100 nm	In vitro	187
C. neoformans – meningoencephalitis	AmB	Angiopep-PEG-PE/AmB polymeric micelles	Murine	188
C. albicans, A. fumigatus, and *Trichophyton rubrum*	AmB	Poly(D,L-lactide-*co*-glycolide) (PLGA) nanoparticles (NPs) and nanosuspensions	Mouse	189
Corneal fungal infections (Flu-CNGs)	FLZ	FLZ-loaded chitin nanogels	In vitro	190
A. flavus and *Aspergillus terreus*	Silver nanoparticles	Silver nanoparticle-encapsulated functionalized chitosan was prepared by the phase transfer method	In vitro	191
C. albicans and *C. glabrata*	CTZ	CTZ-loaded cationic nanocapsules using Eudragit® RS100: 144 nm	In vitro	192
C. albicans	CTZ	CLZ-loaded nanovesicular carriers (ocular nanovesicular carrier)	In vitro	193
C. albicans and *C. glabrata* biofilm	Silver nanoparticles	Not applicable	In vitro	176
C. albicans and *C. glabrata*	CTZ	Coconut oil-core nanocapsules prepared from Eudragit® RS100: 200 nm	In vitro	194
C. albicans	Not applicable	Polyethyleneimine (PEI) and PEI-based nanoparticles (nano-PEI)	In vitro	195
C. albicans biofilm	Silver nanoparticles	Not applicable	In vitro	177

Abbreviations: *C. albicans*, *Candida albicans*; AmB, amphotericin B; ITZ, Itraconazole; *A. flavus*, *Aspergillus flavus*; *P. brasiliensis*, *Paracoccidiodes brasiliensis*; *A. niger*, *Aspergillus niger*; *C. neoformans*, *Cryptococcus neoformans*; CTZ, Clotrimazole; *C. glabrata*, *Candida glabrata*.

There are few studies on the antifungal activity enhanced by dendrimers. Polyamidoamine dendrimers were shown to improve the solubility of clotrimazole and enhance its antifungal activity against different species of *Candida*.[207] According to Janiszewska et al,[208] the antifungal activity of dendrimeric lipopeptides causes morphological changes in fungal cells and inhibition of enzyme activity candidal 1,3-β-D-glucan synthase. Staniszewska et al[209] reported in vitro effects of the dendrimer D186 on the virulence factors of *C. albicans*, where there was a reduction in adhesive properties and potential of the pathogenic yeast.

Other delivery systems

The antifungal activity in other delivery systems, such as carbon nanotubes, MNPs, and silica NPs, has been less studied. Carbon nanotubes have been one of the most exploited biomedical applications of NPs in the world. Benincasa et al[210] showed that AmB conjugated to carbon nanotubes presented an excellent activity against clinical isolates of *Candida* spp. The antimicrobial activity against bacteria and fungi (*C. albicans*) was also demonstrated by scanning electron microscopy, showing that microbial cells were wrapped or entrapped by carbon nanotube networks.[211] Reduced graphene oxide nanosheets have antifungal activity against *Aspergillus niger*, *Aspergillus oryzae*, and *Fusarium oxysporum*.[212] In 2014, Ciu et al[213] showed graphene oxide as a novel two-dimensional nanomaterial for applications in health biomedical with antifungal properties and low cost.

Hussein-Al-Ali et al[214] demonstrated the antimicrobial activity of MNPs loaded with ampicillin to form a nanocomposite decreases the activity of *C. albicans*. Niemirowicz et al[215] also reported an inhibition of the growth of *C. albicans* by using MNPs that can be removed from human plasma, blood, serum, and abdominal and cerebrospinal fluids.

Conclusion and future prospects

There is a clear need to find new therapeutic alternatives for IFIs as the number of drugs is reduced and there is an increased resistance to antifungal agents, mainly in emerging fungi such as non-*C. albicans* species. Moreover, many of the current drugs show toxicity. Thus, a major disadvantage of the polyene antifungal agents, such as D-AmB, is their clinically significant toxicity, although the development of lipid formulations of AmB has reduced this problem.[35] Lipid formulations of AmB preserve renal function and survival of critically ill patients suffering from IFIs. However, these formulations are very expensive and are not globally available.[216]

Studies involving nanotechnology and medically important fungi have demonstrated improvements in the antifungal properties, such as bioavailability, toxicity, and target tissue, for some drugs, such as AmB, which can facilitate innovative therapeutic approaches. Nanotechnology offers the possibility of multifunctional systems to meet the many different biological and therapeutic requirements.[85] The ultimate therapeutic goal will be to select a drug that can effectively cure the disease without causing side effects.[217] In the near future, the use of nanosystems for drug delivery can be attractive strategies for delivering peptides, nuclear acids, or drugs.[218] In addition, mucoadhesive systems can promote a more specific targeting and retention of the delivery system in humans, such as mucosal surfaces, gastrointestinal tract, lung, genitourinary tract, nasal, and ocular systems. In combination with excellent technological platforms, nanotechnological strategies can increase the bioavailability of antifungal drugs.[188]

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