REVIEW ARTICLE

Nanoparticles as a Tool for Broadening Antifungal Activities

Daniele Fernanda Renzi¹, Laís de Almeida Campos¹, Eduardo Hösel Miranda¹, Rubiana Mara Mainardes¹, Wolf-Rainer Abraham², Diana Fortkamp Grigoletto¹ and Najeh Maissar Khalil^{1,*}

¹Pharmaceutical Nanotechnology Laboratory. Universidade Estadual do Centro-Oeste. Alameda Élio Antonio Dalla Vecchia, 838 - CEP 85040-167, Guarapuava-PR, Brasil; ²Helmholtz Center for Infection Research, Chemical Microbiology, Inhoffenstraße 7, 38124 Braunschweig, Germany

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Abstract: Fungal infections are diseases that are considered neglected although their infection rates have increased worldwide in the last decades. Thus, since the antifungal arsenal is restricted and many strains have shown resistance, new therapeutic alternatives are necessary. Nanoparticles are considered important alternatives to promote drug delivery. In this sense, the objective of the present study was to evaluate the contributions of newly developed nanoparticles to the treatment of fungal infections. Studies have shown that nanoparticles generally improve the biopharmaceutical and pharmacokinetic characteristics of antifungals, which is reflected in a greater pharmacodynamic potential and lower toxicity, as well as the possibility of prolonged action. It also offers the proposition of new routes of administration. Nanotechnology is known to contribute to a new drug delivery system, not only for the control of infectious diseases but for various other diseases as well. In recent years, several studies have emphasized its application in infectious diseases, presenting better alternatives for the treatment of fungal infections.

Keywords: Azoles, echinocandins, fungal infection, nanotechnology, polyenes.

1. INTRODUCTION

Invasive fungal infections, although commonly regarded as neglected diseases, are among the leading causes of morbidity and mortality in hospitalized patients in recent decades, affecting approximately 1 billion people, with 11.5 million life-threatening infections and 1.5 million deaths per year [1, 2, 3, 4].

There are some risk factors associated with these infections, including immunocompromised patients undergoing invasive procedures [5], neonates [6], chemotherapy [7], burns [8], AIDS [9, 10], among others [11, 12]. In addition to these factors, socioeconomic conditions, geographical regions, and cultural habits are also important in the manifestation of these infections [13].

Fungal infections can develop as superficial, cutaneous, subcutaneous, and systemic mycoses, and indi-

viduals living in endemic areas are more susceptible [14, 15]. Endemic mycoses are caused by a group of fungi that share characteristics such as dimorphism and virulence factors that vary according to temperature and environment conditions. They are widespread opportunistic infections mainly in immunocompromised patients, being frequent in tropical and subtropical environments worldwide [16, 17, 18].

Among opportunistic invasive infections, some fungal genera are considered more common, *e.g.* *Candida* sp., *Cryptococcus* sp. and *Aspergillus* sp., each with distinct pathophysiological and treatment characteristics [19, 20, 12].

The demand for antifungals has increased in recent years, mainly due to the increase of immunocompromised patients with secondary diseases [11]. The availability of Class availability of these drugs is known to be restricted and studies have reported the presence of resistant strains [21, 22, 23]. In addition, there is a need for improvement in the pharmacokinetic

*Address correspondence to this author at the Pharmaceutical Nanotechnology Laboratory. Universidade Estadual do Centro-Oeste. Alameda Élio Antonio Dalla Vecchia, 838 - CEP 85040-167, Guarapuava-PR, Brasil; E-mail: najehunicentro@hotmail.com

characteristics of these drugs regarding their toxicity [24, 25].

Nanotechnology has been considered an important strategy to overcome biopharmaceutical, pharmacokinetic, and toxic problems of compounds with antifungal activity [26]. Furthermore, the development of antifungal encapsulation systems allows the controlled release of the drug and can protect the active principle of the gastrointestinal environment, allowing oral administration [27]. Nanoparticles have also shown a synergistic effect with antifungals [28, 29].

Although some studies report the role of nanoparticles in carrying antifungal drugs, they are still restricted. This review brings a broad discussion of the main nanostructured systems that transport compounds with antifungal activity, in order to collaborate in understanding of these systems and the advantages of their therapeutic application, as well as limitations.

2. NANOPARTICLES AS DRUG CARRIERS

Nanoencapsulation of drugs aims particles ranging in size from 1 to 1000 nm [30, 31]. The process of the development and the resulting structure of nanoparticles influences properties and characteristics related to drug release as well as pharmacokinetic and pharmacodynamic aspects can be dissolved. They drug of interest dissolved, adsorbed, or encapsulated in a matrix formed by polymers, proteins, or lipids [32, 33]. The nanoparticles are classified into nanocapsules, systems in which the drug is in a membrane-surrounded cavity, and nanospheres, in which the drug is dispersed in a matrix [34, 35]. In addition, nanoparticles are divided into classes according to their composition. There are ceramic [36], metallic [37], inorganic [38], carbon-based [39], polymeric [40], and lipid-based nanoparticles [41].

The main objective of nanostructured systems is the reduction of undesired effects caused by standard formulations, beyond which the physicochemical and biological properties of these systems enable their use as drug carriers [42, 43]. In the study of Hu *et al.* [44], bortezomib nanoparticles were less toxic to tissues than the free form of bortezomib. In addition, through suitable combinations, nanoparticles can be used with formulations that reduce toxicity, as in the study of Per-everzeva *et al.* [45], in which nanoformulations containing doxorubicin exhibited considerably reduced cardio- and testicular toxicity, compared to a free drug. In oral formulations, nanoparticles protect the drug from degradation due to the acidic pH of the stomach [46].

Nanocarriers have been an important alternative in treating infections. Among the available models, lipid systems stand out for reducing both the pathogenicity of microorganisms and the toxicity in patients [47]. Moreover, it is important to emphasize that the evaluation of the best nanostructured system depends on the demands of each infection [48].

The use of nanoparticles in biomedical applications has shown important results because it allows improvement in the pharmacological aspects of the formulations and decrease in the toxic effects of the compounds, as well as an increase of the release time and stability, and opens the possibilities of various administration routes [49, 50], as oral [51], intravenous [52], pulmonary [53], ocular [54], and topical [55, 56] (Fig. 1).

Fig. (1). Main advantages of using polymeric systems for antifungal administration in *in vivo* models. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

In the last decades, several techniques have been developed to obtain nanoparticles for drug transport purposes [57]. For polymeric nanoparticles, the techniques, in general, can be divided into polymerization of monomers and dispersion of preformed polymers [58, 59]. For the formation of nanoparticles from the polymerization of monomers, there is also the method

of mini- [60], micro- [58], and macroemulsion [61] and interfacial polymerization [62].

For the formation of nanoparticles from polymer dispersion, one can use the techniques of solvent emulsification-evaporation [63, 64], nanoprecipitation [65], solvent homogenization diffusion [66], double emulsion and evaporation [67], double emulsion [68], salting-out [58], dialysis [69], spray drying [70], and supercritical fluid technology [71].

Techniques using preformed polymers are often prioritized for avoiding toxic waste compared to methods based on polymerization reactions [59]. In addition to these techniques, there are, for example, the flash nanoprecipitation method [72] and ionotropic gelation [73].

For the formation of lipid nanoparticles, the double emulsion method with solvent evaporation [67], solvent diffusion [74], high-pressure homogenization [75], among others, are available. Lipid nanoparticles are widely used in drug delivery systems due to their characteristics, such as lipids present in the formulations are similar to the body's natural lipids. In addition, they have controlled-release, higher bioavailability, lower dose, and higher tissue specificity [76].

In this context, nanoparticles have been developed to improve the characteristics of classical antifungals and molecules with inhibitory activity on the important fungi that cause invasive diseases [55].

3. ANTIFUNGAL CLASSES

The biggest obstacle in developing an effective antifungal is the similarity between the fungal cell and the animal (human) cell. Cholesterol is the main membrane sterol in human cells, while ergosterol is the main sterol in fungal cells, both are very similar [77]. Thus, antifungals aim at targets that differ between these two cell types. Cell wall components, fungal cell membrane, and RNA synthesis are common targets of some commercially available antifungals. Based on their mechanism of action, antifungals can be divided into polyenes, azoles, echinocandins, and those of intracellular action [78].

3.1. Polyenes

Polyenes are considered the oldest class of antifungals, and their main representatives are amphotericin B and nystatin. These antifungals are macrocyclic organic molecules that attach to the double layer of phospholipids in the fungal membrane and the complex formed leads to cell disruption [79, 80, 81]. However, other

mechanisms of this class have also been investigated and described, mainly in relation to amphotericin B which seems to have its mechanism of action associated with the formation of reactive oxygen species (ROS), generally in resistance profile strains [82, 83].

Amphotericin B is the major representative of this class and was isolated around 1955 from a strain of *Streptomyces nodosus* [84]. This drug acts on most yeasts and filamentous fungi, such as *Candida* sp., *Aspergillus* sp., and *Cryptococcus* sp. Produced for intravenous administration, the main reported side effects of amphotericin B in patients are hepatotoxicity and nephrotoxicity [85, 86].

Due to its low solubility in water and in most organic solvents, amphotericin B is not well absorbed in the gastrointestinal tract [87, 88, 89, 90]. Furthermore, this molecule possesses poor stability in gastric juice, which, despite being another disadvantage, is a relatively easily resolved compared to the low solubility [91]. These characteristics were tackled by studies that aim to increase solubility and decrease toxicity, for example through liposome formulations [92, 93, 94].

With respect to pharmacokinetics, about 95% of the amphotericin B is bound to proteins after administration. During the absorption process, higher concentrations of this drug may be found in organs such as the liver and spleen [95, 96]. The elimination half-life of amphotericin B is considered to be slow, taking on average 15 days [97]. The use of the conventional amphotericin B formulation may cause some undesirable effects such as nausea, headache, and chills [98]. These symptoms may be caused by increased prostaglandin production, tumor necrosis factors, and interleukin-1 [99]. One of the benefits of lipid systems is the possible reduction of these mentioned symptoms [100, 101].

Nystatin is a polyene discovered in 1950 and isolated from the Gram-positive bacterium *Streptomyces noursei*. This drug has fungicidal and fungistatic activities and is widely used against infections caused by *C. albicans* [102]. Nystatin can be applied *via* topical creams as well as orally *via* oral suspensions and lozenges [103]. However, it has negligible absorption in the gastrointestinal tract, and high doses can cause nausea and vomiting [104]. Furthermore, nystatin is also able to induce secretion of interleukins and tumor necrosis factor-alpha by binding to Toll-like receptors present in immune cells, triggering a proinflammatory process [105].

Natamycin is a compound naturally produced by the bacterium *Streptomyces natalenses*, first isolated in

1950 [106]. Due to its safety for humans, this drug is widely applied against yeasts and fungi [107]. It has *in vitro* activity against a variety of yeasts and filamentous fungi, such as *Candida* sp., *Epidermophyton* sp., *Microsporum* sp., and *Trichophyton* sp. This drug may also be used in the food industry as a preservative of dairy products [108]. Nevertheless, as previously reported for some antifungal agents, it has also low solubility in most solvents [109].

3.2. Azoles

Azoles are a class of synthetic antifungals that can be divided into imidazoles consisting of ketoconazole, miconazole, and clotrimazole and triazoles comprising itraconazole, fluconazole, voriconazole, and posaconazole. What differs between these two classes basically is the number of nitrogen atoms that form their aromatic rings (Fig. 2) [110].

The mechanism of action is related to the blockade of the 14 α -demethylase enzyme found in cytochrome P-450 in fungal cells, thus, there is no demethylation of the lanosterol precursor to yield ergosterol [111]. As a result, the amount of ergosterol is decreased, thereby altering the flowability of the cell membrane. In addition, azoles can also prevent the transformation of *Candida* sp. into hyphae, which is the pathogenic form of this fungus [112].

Fluconazole has a spectrum of action against *Candida* spp. such as *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and is effective in treating *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Penicillium marneffei*, among others [113, 114, 115]. It can be applied both in oral and parenteral administrations and is generally well absorbed by the gastrointestinal tract

Fig. (2). Structures of antifungals of the polyene and the azole class together with flucytosine and griseofulvine.

due to its hydrophilic properties. It has a low affinity for plasma proteins and is widely distributed throughout the body, including the central nervous system. Its bioavailability is considered excellent and its main side effect is hepatotoxicity [116, 117].

Itraconazole is used in oral and intravenous formulations [118] because it is a highly lipophilic drug [119], with low solubility and high permeability [120]. Following administration, the peak concentration is reached within 2 to 3 hours [121] and the half-life is approximately 24 hours [119]. Effective against strains of *Candida* sp. [122], *Aspergillus* sp. [119, 123], Zygomycetes, dimorphic fungi and causes of chromoblastomycosis, mycetoma, and phaeohyphomycosis [124], this drug has both fungicidal [125] and fungistatic activities [126]. In oral formulations, stomach pH may interfere with the absorption process, which occurs mainly in the proximal small intestine [127]. Itraconazole is a potent inhibitor of cytochrome P-450 and glycoprotein P, making this process the likely mechanism of action in cases of drug interactions [128].

Voriconazole is a broad-spectrum triazole widely used against endemic fungi, for example, *Candida* spp. [129, 130], *Aspergillus* spp. [130], and *Cryptococcus* spp. [129]. This second-generation drug was derived from fluconazole, however, with a higher activity spectrum [131]. It has both fungicidal and fungistatic activities, according to the fungal species in question [132]. It can be found in formulations for oral [133] and intravenous administrations [134]. Voriconazole undergoes hepatic metabolism by P-450 family enzymes, mainly CYP2C19, CYP2C9, and CYP3A4. After this process, the produced inactive metabolites are mostly excreted via the urinary tract and a small percentage through the fecal pathway [135].

One of the latest antifungals introduced is posaconazole. This drug was developed from itraconazole and can be applied as an oral suspension. Posaconazole is effective against various strains, and its action occurs against *Candida* sp., *Cryptococcus* sp., *Aspergillus* sp., melanized, and dimorphic fungi [124, 130]. Its oral bioavailability also depends on stomach pH, and absorption is higher in the presence of fatty foods [136]. Once absorbed, this drug undergoes phase I and II metabolism through the action of P-450 enzymes and the glucuronidation process [137]. Conditions such as diarrhea or concomitant use of some drug classes, such as subtype 2 histamine receptor antagonists [138], may interfere with posaconazole concentrations in blood. Elimination occurs mainly through the fecal pathway [139].

Ketoconazole was the first broad-spectrum antifungal developed against dermatophytes and yeasts [140]. In 1977, its introduction represented a major breakthrough in the class of antifungal drugs [141]. In 1980, it was the only oral antifungal agent to treat systemic infections. However, soon its adverse effects began to become apparent causing this drug to lose its application [131]. In Europe, this drug was withdrawn in 2013 from use due to side effects in patients, especially liver damage [142]. Its use has been indicated in these countries only in very serious cases of infections [141]. In addition, ketoconazole can inhibit several P-450 family enzymes causing an increase of sensitivity of the individual to other drugs [143]. These enzymes are directly related to the biotransformation process, and changes in its function or structure affect this process, harming the organism [144].

Clotrimazole is a synthetic compound widely used in vaginal and skin infections because it has good skin penetration and low systemic absorption [145]. Used to treat infections primarily caused by *C. albicans*, this drug also has activity against Gram-positive bacteria [146].

3.3. Echinocandins

Echinocandins are lipopeptides, more specifically semi-synthetic cyclic hexapeptides with *N*-modified acylated lipid side chains [147]. Although this class of antifungal acts on several classes of yeast *in vitro*, its action *in vivo* is considerable only for *Candida* sp. and *Aspergillus* sp. [148]. They represent the most recent class of antifungals compared to those previously presented. In the last decade, echinocandins have emerged as a first-line antifungal treatment to combat invasive candidiasis [147]. They target the enzyme β -1,3-glucan synthase responsible for the production of the β -1,3-D-glucan present in the fungal cell wall. Inhibition of this enzyme affects membrane integrity and induces fungal cell disruption and subsequent death [149].

The class is represented by caspofungin, micafungin, and anidulafungin (Fig. 3) [148], which are administered only intravenously [150], not orally [147]. Caspofungin and micafungin are metabolized by the liver, while anidulafungin is broken down in the plasma when the macrocyclic ring opens [151].

The spectrum of applications includes the treatment of various diseases caused by *Candida* spp., such as esophageal candidiasis, candidemia, and invasive candidiasis, as well as invasive aspergillosis [149].

Fig. (3). Structures of echinocandins used as antifungals.

3.4. Other Compounds

There is also a class of antifungals that are able to act at the intracellular level, such as griseofulvin, a metabolite of *Penicillium* spp. [152] and flucytosine, a synthetic compound [153]. While griseofulvin acts by interfering with the fungal mitotic spindle and cytoplasmic microtubules [152], flucytosine inhibits the synthesis of nucleic acids and proteins of microorganisms, mainly *Candida* sp. [153].

Flucytosine is a prodrug that, when activated, is transported into cells by cytosine permease [154]. Its administration is by the oral route, where approximately 70% is absorbed, differing in relation to the other classes, by the low binding to plasma proteins and the high solubility in water [155, 156]. In addition, this class of drugs is capable of penetrating to the cerebrospinal, peritoneal, and synovial fluid [155, 157]. The maximum concentration can be reached approximately 1 to 2 hours after administration. It is recommended to keep the plasma concentration between 40–80 $\mu\text{g mL}^{-1}$; elimination occurs mainly in the kidneys through glomerular filtration. Flucytosine therapies generally employ a second antifungal due to the development of fungal resistance [158].

Conventional drugs, despite their considerable efficacy, still offer less than optimal results due to the limitations present in some antifungal classes. Examples include low aqueous solubility and toxicity, which links the active principle to the establishment of new formulations [159, 160, 161].

4. ANTIFUNGAL DRUGS AND TOXICITY

Antifungals can be grouped based on their mechanism of action in the fungal cell [162]. The major problems for the individual who needs this type of treatment are the side effects. Although the fungal cell exhibits some differences to the animal cell, such as the composition of its membrane and cell wall, the similarity between both is still large, which limits specific antifungal sites of action and increases the likelihood of toxicity [163, 78].

Currently available antifungals can be used to treat a range of infections in different parts of the body. During antifungal therapy, one of the main toxic effects reported is hepatotoxicity which may be related to factors including liver disease, physicochemical properties of the antifungal, disease severity, and drug interactions, more often observed for azole derivatives than for echinocandins [164, 165, 166, 167]. These effects

may be considered reversible after discontinuation of treatment and individualized therapy seems to overcome the problems related to toxicity in antifungal use [159].

Flucytosine may cause liver damage during treatment, but this condition may be reversed upon discontinuation of treatment. The exact mechanism is poorly known, but there is an association between dose and side effects, and dose reduction is indicated when necessary [168].

Griseofulvin is related to adverse effects, and animal studies demonstrated that it causes hepatocellular injury, cholestasis, and cirrhosis [169, 170, 171]. A case study of a young patient using griseofulvin and terbinafine reported the appearance of toxic epidermal necrolysis, but the condition could be reversed after discontinuation of treatment [172].

Fluconazole also shows hepatotoxicity, which may be asymptomatic in 5 to 10% of cases, and is dose-dependent. The mechanism causing injuries is poorly understood, but fluconazole appears to involve different enzyme forms from other antifungals due to its low potency as a substrate for hepatic metabolism [164].

A study by Wang *et al.* [167] found that itraconazole provides a higher risk of developing liver damage than other antifungals. Despite elevated liver enzymes, in some cases, no interruption of treatment is required, but patients with some type of liver dysfunction should be monitored during therapy. In the same study, voriconazole showed similar results to itraconazole in relation to the damage caused [167]. At higher concentrations, the risk of liver damage increases and, in some cases, an increase in liver enzymes also occurs. A meta-analysis by Xing *et al.* [173] showed that voriconazole is associated with a higher risk of neurotoxicity, hepatotoxicity, and visual toxicity compared to other antifungals.

Enzymes can be slightly elevated during treatments with posaconazole but resolve after discontinuation of therapy, with fatalities due to liver failure only in a small number of patients with severe underlying diseases. However, common adverse effects include fever, headache, diarrhea, nausea, and vomiting. Severe conditions comprise pulmonary embolism, adrenal insufficiency, and allergic reactions [174].

The echinocandin class offers higher safety even when higher doses are required. There are rarely reports of cardiotoxicity associated with the way the drug was administered. The compounds caspofungin and

micafungin are more likely to develop toxicity when compared to anidulafungin [151].

Nephrotoxicity may also occur due to renal vasoconstriction and subsequent reduction in blood flow caused by some antifungals [175, 176]. Some side effects such as fever and chills, hypotension and hypertension, nausea, vomiting, hypoxia, and hypokalemia may be developed by patients [177]. These adverse effects are associated with proinflammatory cytokines and immunostimulation *via* Toll-like receptors present on the surface of immune cells [178].

Nephrotoxicity is a condition found in patients using amphotericin B with deoxycholate and is mainly associated with perfusion disorders and morbidity [179]. Hepatotoxicity, in deoxycholate and amphotericin B liposome formulations, is rarer and usually occurs after the administration of cumulative doses. The use of other drugs with hepatotoxic potential together with amphotericin B increases the chances of toxicity [164].

In studies with nystatin, a number of adverse effects have been reported by individuals who have used it. The reports usually mention vomiting, diarrhea, unpleasant taste, abdominal pain, headaches, and rash [180].

A study by França *et al.* [181] evaluated the toxicity of amphotericin B in VERO cell lines. VERO cell lines consist of a mixture of proximal and distal renal tubular cells. The results show that cytotoxicity depended on the time of drug exposure. At concentrations of 15 and 20 µg per ml, the cytotoxicity was higher after 18 hours of exposure. In addition, the possible mechanism of cytotoxic action of amphotericin B is related to damage to VERO cell lysosomes. The protective effect of nanoparticles containing amphotericin B in VERO cell culture and erythrocytes are shown in Fig. (4).

Increased intracellular calcium is related to the toxicity of various pore-forming compounds in the cell, such as amphotericin B, causing cell lysis [151]. Amphotericin B in its standard formulation is highly toxic to VERO cell lines [182]. With the central objective of reducing antifungal-related toxicity, amphotericin B, a standard drug used against various strains, was the first antifungal to be nano-encapsulated [183]. As concluded by Espuelas *et al.* [184] when studying amphotericin B toxicity *in vivo*, nanoparticles show lower toxicity due to a possible reduction in the accumulation of this drug in the kidneys and liver compared to standard

amphotericin B; however, a higher dose is required to ensure the therapeutic effect.

Fig. (4). Protective effect of a nanostructured model containing amphotericin B in VERO and red blood cell culture. (*A higher resolution / colour version of this figure is available in the electronic copy of the article.*)

5. MAIN NANOENCAPSULATED SYSTEMS CONTAINING ANTIFUNGALS

5.1. Amphotericin B

Amphotericin B is considered as one of the main alternatives in the treatment of invasive infections. Commercial amphotericin B nanoforms are available, such as Fungizone sodium deoxycholate micelle and, more recently, lipid preparations such as Abelcet, Ambisome, and Amphocil/Amphotec, which have lower cytotoxicity than intravenous preparations, but still come with high costs and need therapeutic monitoring [23, 185, 186].

In order to overcome limitations such as low water solubility and low absorption in the gastrointestinal tract, Gharib *et al.* [187] studied the development of nanospheres prepared by the spray-dried nanoprecipitation technique and obtained nanoparticles with higher efficacy and lower toxicity, in addition to the lower cost compared to other commercial nanosystems.

Oral delivery systems have been studied with the aim of reducing solubility problems, as well as providing comfort and decreased toxicity in patients [188]. Jain *et al.* [189] developed hybrid amphotericin B, lecithin, and gelatin nanoparticles by the desolvation method. These polymers are biocompatible, biodegradable, and inexpensive. Nanoformulation showed a sustained release profile and decreased hemolytic toxicity in relation to the free drug, but revealed gastrointestinal degradation, indicating the need for system coating. Jain *et al.* [190] characterized the use of bile salt-stabilized chitosan nanoparticles for amphotericin B release. Nanoparticles were obtained by the ionic gelation method, with higher bioavailability, sustained release, increased gastrointestinal stability, and decreased hemolytic toxicity, characterizing a possible alternative for oral delivery of amphotericin B.

Although lipid carriers have increased oral bioavailability, the aggregation state of nanoparticles is still a limitation to some administration routes [89]. Jabri *et al.* [191] developed a hybrid gold and lecithin tragacanta gum nanoparticle system to increase the oral bioavailability of amphotericin B by the solvent diffusion method. The system presented encapsulation efficiency close to 78% and increased oral bioavailability in an animal model. The mucus helped to keep the drugs longer at the administration site, explaining the bioavailability. In addition, topical, nasal, and ocular release systems have also been developed with the same goal of reducing toxicity [192, 193, 194, 195].

Fu *et al.* [196] developed a lipid carrier for amphotericin B with the emulsion evaporation and low-temperature solidification method for ocular administration and keratitis treatment. The system showed sustained *in vitro* release and better bioavailability, as well as the ability to successfully penetrate corneal tissue. Grisin *et al.* [197] developed chitosan and Pluronic chips for mucosal amphotericin B dispersion. The chips increased antifungal activity up to 4 times, possessed mucoadhesive capacity, and may be an alternative for use in hydrogels.

A pulmonary administration route studied by Shirkhani *et al.* [20] associated B-poly (methacrylic acid) (PMA) and anionic hydrogels for amphotericin B nebulization in a prophylactic manner. 99% of *Aspergillus* sp. cells were killed and lung TNF- α was decreased by 90%, which may qualify this hydrogel as an alternative route of administration for prophylactic exposures. In order to direct the tissue distribution of amphotericin B and to avoid toxic effects, Serrano *et al.* [198] developed nanoparticles of *N*-palmitoyl-*N*-monomethyl-*N*,

N-dimethyl-*N,N*-trimethyl chitosan 6-*O*-glycol, and amphotericin B (GCPQ) with similar efficacy to the commercial form Ambisome (parenteral liposomal amphotericin B). GCPQ was able to act on specific organs such as lung, liver, and spleen, showing higher bioavailability and decreased renal exposure.

Despite its wide use in systemic infections, amphotericin B therapy is still restricted in some treatments such as fungal meningitis. Due to its pharmacokinetic characteristics, amphotericin B does not cross the blood-brain barrier [199]. Xu *et al.* [199] developed a nanoformulation that could circumvent this limitation in mice in a meningococcal meningitis model, in addition to reduced cytotoxicity in the liver, kidney, and blood. In the study by Ren *et al.* [52] using nanoprecipitation in poly (lactic acid)-*b*-poly (ethylene glycol) nanoparticles, it was observed that the concentration of the drug in the animals' brain increased, confirming that the formulation was able to cross the blood-brain barrier. In order to improve the distribution of amphotericin B in the central nervous system, Tang *et al.* [200] used a modified transferrin receptor antibody loaded with poly (lactic acid)/ poly (ethylene glycol) (PLA-PEG) to improve the passage of the antifungal through the blood-brain barrier.

Silver nanoparticles have been used in some systems as an alternative to antifungal activity, showing synergistic effects of amphotericin B and antifungal activity against some species of *Candida* sp., *Aspergillus niger*, and *Fusarium culmorum* [201, 202, 203]. Saldanha *et al.* [204] conducted a co-precipitation study with Fe₃O₄ and amphotericin B and tested it in an experimental model of paracoccidioidomycosis. They observed activity similar to free amphotericin, but with reduced adverse effects and number of applications.

In micelles developed by Diaz *et al.* [205], the nanoprecipitation system showed a reduction in red cell toxicity and greater antifungal activity in some *Candida* spp. compared to free amphotericin. The reduction in toxicity was accompanied by the slow release and low aggregation of the nanoparticle. The reduction of toxicity associated with low aggregation was also reported in the study by Chaudhari *et al.* [206].

The use of nanotechnology also favors the improvement of amphotericin B antifungal activity. Tang *et al.* [200] observed an increase of antifungal activity and survival rate of 95% in animals treated with amphotericin B nanoparticles with anti-*Candida albicans* antibody developed by the solvent evaporation emulsion technique.

Different polymers have been used to make amphotericin B polymeric nanoparticles. Among the polymers, poly lactic-*co*-glycolic acid (PLGA) [207], poly (lactic acid) (PLA) [208], polyethylene glycol (PEG), polycaprolactone (PCL) [209], and chitosan [141] are the most common, being developed by different techniques [210, 200]. The main advantage of using these systems is their biocompatibility and biodegradability [211].

Despite the many efforts to overcome the limitations of administration and adverse effects of amphotericin B, much remains to be understood regarding the distribution and interaction of these systems to ensure their use. However, undoubtedly, they are alternatives that bring improvements in patient therapy and facilitate treatment adherence.

5.2. Voriconazole

Nanostructured systems have shown important results mainly in reducing the undesirable effects of voriconazole administration. In addition to the possibility of sustained-release, which facilitates patient adherence to fungal infection treatments, one of the goals of using nanotechnology is also related to improving the solubility of voriconazole in aqueous media, or allowing new routes of administration [212, 213]. In order to provide new routes of administration for voriconazole besides the oral one, nanotechnology has been explored for ocular [54, 214, 215, 216], pulmonary [53, 217, 218, 219], and nail [220] distribution routes.

Due to the low water solubility of voriconazole, Füredi *et al.* [216] developed lipid-based nanoparticles by high-pressure homogenization for parenteral administration. The nanoparticles obtained had a size of 81.2 nm and encapsulation efficiency close to 70%, allowing doubling of the solubility of voriconazole.

Polymers are an important alternative for the development of nanoparticles with pharmacological interest, mainly for their biodegradable and biocompatible characteristics. Sinha *et al.* [53] encapsulated voriconazole in porous and nonporous PLGA nanoparticles for pulmonary administration. PLGA was also an alternative in the studies by Das *et al.* [218] and Paul *et al.* [219] in nanoparticles for pulmonary release. This alternative is interesting because it allowed prolonged release and better bioavailability, as well as deposition in the lung tissue.

Ocular administration has been stimulated as another route for voriconazole medication, especially in cases of fungal keratitis [215]. Kumar and Sinha [54]

observed sustained release of voriconazole into ocular tissue by the use of solid lipid nanoparticles, offering an alternative for the treatment of fungal keratitis due to good corneal permeation. A thermogel was developed by Cuming *et al.* [215] for ocular release by subconjunctival injection, allowing the reduction of the effects of ocular keratitis in animal models.

Aiming to improve the treatment of ocular keratitis, Huang *et al.* [221] developed hybrid contact lenses based on quaternized chitosan, silver, and graphene oxide through electrostatic interactions. The lens enabled sustained release of voriconazole into corneal tissue and increased antifungal efficacy in an *in vitro* model. Pawar *et al.* [222] developed an ophthalmic gel based on Pluronic F-127 or the combination of Pluronic F-68 and sodium alginate by *in situ* gelation. In addition to the sustained release of voriconazole, decreased toxicity was observed, which may increase patient compliance.

There are still some limitations regarding the treatment of fungal infections with voriconazole. In addition to side effects, variability in pharmacokinetic behavior remains an important limitation to be overcome, which requires pharmacokinetic studies of nanotechnology models.

5.3. Fluconazole

It is one of the most widely used azole antifungals in skin infections and systemic infections, especially in a hospital setting. However, one of the most recent limitations on fluconazole use is the emergence of resistant strains [223, 224, 225]. Among the main administration routes developed for fluconazole delivery, the topical route is used the most [226, 227], however, still existing is the ocular route [228].

In the study by Kelidare *et al.* [229], a lipid carrier system was developed using the ultrasound technique. This carrier was evaluated for activity against *Candida* sp. strains, and a reduction in the MICs of susceptible strains and strains previously resistant to fluconazole was achieved. This demonstrates the potential of studies involving nanotechnology and microorganisms.

5.4. Ketoconazole

To solve absorption-related problems, Modi *et al.* [230] developed chitosan-based mucoadhesive ketoconazole nanoparticles with an average size of 382 nm and approximately 69% mucin binding. The nanoparticles showed prolonged release of the drug even after gastric emptying, proving the success of the study.

Winnicka *et al.* [231] constructed a Bronopol and Carbopol 980-based hydrogel with ketoconazole dendrimers for topical administration, which improved the solubility and *in vitro* release of ketoconazole and increased up to 16-fold the antifungal activity of prepared hydrogels. Martin *et al.* [232] performed a study of gelled castor oil-based organogels using ketoconazole as a model for lipophilic drugs. In the study, encapsulation efficiency was approximately 98% with stability greater than 3 months and particle sizes between 250 and 300 nm. The *in vitro* release profile showed immediate release of the drug due to its rapid diffusion.

Kumar *et al.* [233] evaluated ketoconazole nanoparticles of chitosan and gellan gum for topical administration and observed higher antifungal activity than the free drug in *Aspergillus niger*. The system had an average size of 155 nm and a zeta potential of 32.1 mV. Another alternative for topical administration was developed by Mahtab *et al.* [234] for the nail treatment of onychomycosis, with an average size of 77 nm. In this study, antifungal activity superior to ketoconazole solution was achieved, in addition to increased permeation and safe topical use. In addition to being used in the treatment of onychomycosis and cutaneous mycoses, ketoconazole is also an alternative in the treatment of keratitis. Ahmed and Aljaeid [235] developed a gel with PLGA by *in vitro* gelation and obtained a higher antifungal activity than the free drug.

5.5. Nystatin

Efforts to improve the absorption and permeability characteristics of nystatin have been undertaken [236]. For this, nystatin nanoparticles were developed by Mohammadi *et al.* [237] for the purpose of systemic administration and increased uptake of the drug by microbial cells. The results showed that nystatin and PLA + glucosamide nanoparticles demonstrated appropriate antifungal activity and physicochemical characteristics.

Fernández-Campos *et al.* [238] developed a nanoemulsion for nystatin release in the treatment of oral candidiasis and observed increased antifungal effects. The same group developed a nanoemulsion for topical administration of nystatin and obtained higher absorption than the pharmaceutical form [290]. Another topical release system has been studied by Khalil *et al.* [239], where the objective was to prepare nanoparticles for topical application. Prolonged-release and better efficacy could be obtained in their study.

5.6. Flucytosine

Nanostructured systems have been used to increase flucytosine permeability in different tissues. Salem *et*

al. [217] incorporated flucytosine into gold nanoparticles to increase intraocular penetration and to evaluate the therapeutic efficacy of this topically applied formulation. In addition to intraocular permeation, Salem *et al.* [240] used glutathione to increase flucytosine permeation through the blood-brain barrier, achieving a system with an average size of 100 nm and 70% drug release. Both efforts are promising alternatives for flucytosine release in different tissues. A relationship to some of the nanostructured systems developed in recent years with flucytosine and the main antifungal drugs can be seen in Table 1.

6. CO-ENCAPSULATION OF ANTI-FUNGAL

In addition to conventional nanostructured systems, the use of co-encapsulated compounds appears to be a promising alternative as it allows placing two antifungals into one formulation, reducing the dose of each drug used. This concept has been partially put into practice using amphotericin B, rapamycin and 5-fluorocytosine in a nanostructured system. It was observed that the drugs were able to act moderately synergistically against *C. albicans* strains [273].

Some nanomaterials can be used as antifungals as well, *e.g.* silver nanoparticles are naturally effective against microorganisms [274] and chitosan, which can interact with the fungal cell wall and interfere with growth [275]. In the study by Longue *et al.* [224], the combination of fluconazole with silver nanoparticles reduced MIC 16- to 64-fold in *C. albicans* cells. Sun *et al.* [276] observed the synergistic effect of silver nanoparticles combined with antifungals, demonstrating moderate inhibitory action on resistant strains. Silver nanoparticles adhered to the fungal cell membrane, inhibited budding, and promoted the loss of membrane integrity.

Costa *et al.* [277] developed a mucoadhesive system of polymeric nanoparticles for the treatment of vulvovaginal candidiasis with miconazole, farnesol, and chitosan. The system was effective in inhibiting antifungal proliferation and decreasing pathogenicity. Kalita *et al.* [278] co-encapsulated chloramphenicol with lemongrass essential oil in PCL-Pluronic nanocapsules and obtained a significant reduction in cytotoxicity with increased *in vitro* antimicrobial activity against 22 microbial pathogens, including three *Candida* spp. Still in the line of natural products, Svetlichny *et al.* [279] developed solid lipid nanoparticles containing copaiba oil with and without allantoin to evaluate their antifungal activity. They concluded that nanoencapsulation improved the antifungal activity of copaiba oil, which

was enhanced by the presence of allantoin. MICs obtained against *C. krusei*, *C. parapsilosis*, *Trichophyton rubrum*, and *Microsporum canis* were comparable to those of commercial products, offering promising therapies for skin infections.

There are also studies on the formation of micelles containing an antifungal and a compound that adds beneficial properties to the antifungal, as shown in the study of Diezi and Kwon [280]. Here, amphotericin B was co-encapsulated with cholesterol in PEG-phospholipid micelles, meeting the safety and solubility requirements for amphotericin B, causing low *in vitro* hemolysis and reduced toxicity, as well as efficacy against *C. albicans*.

In addition to micelles, there are bifunctional viscous nanovesicles, which range from 130 to 190 nm. Vitonite *et al.* [281] studied resveratrol and gallic acid co-charged nanovesicles to protect the skin against oxidative damage and microorganisms, including *Candida* sp. The authors concluded that if phenols were dispersed in a water/glycerol mixture, the inhibitory effect against *Candida* sp. (in the planktonic state) could be increased.

This demonstrates the potential combining more than one drug in the same nanostructured system. Ideally, studies in this line should be intensified so that new data could be made available, enriching the knowledge about co-encapsulated antifungals.

7. GREEN SYNTHESIS OF NANOPARTICLES

The green synthesis of nanoparticles has gained importance due to the ecological aspect [282, 283], which reduces the use of toxic chemicals, in addition to being, often, a simple and inexpensive process [284]. For this, components from microbial cells [282, 285] and plants [286] can be used, which are sources of potential reducing agents [287]. As an example of green synthesis, we can mention the study by Jogaiah *et al.* [282], who used the extract of the basidiomycete *Ganoderma applanatum* for the synthesis of silver nanoparticles. Nandini *et al.* [285] used the membrane lipids of *Trichoderma* spp. along with Tween 80 for the composition of a nanoemulsion by the ultrasonic emulsification method, and Nayak *et al.* [286] used the extract of the medicinal plant *Dillenia indica*. Sarkar *et al.* [283] used extracts from the plant *Adiantum lunulatum* for the synthesis of copper oxide nanoparticles. Thakur *et al.* [284] synthesized titanium dioxide nanoparticles using the extract of the leaves of the *Azadirachta indica* plant. The use of plant extracts and microorganisms gives nanoparticles several biological activities,

Table 1. Nanostructured systems developed with major antifungals in the last 9 years.

Antifungal Drug	Composition	Method	Route of Administration	Efficiency	Toxicity	Refs.
Voriconazole	Lipids (Stearic acid, Witepsol, Compritol)	High-pressure homogenization	Ocular	Voriconazole effective against strains of <i>C. albicans</i> and <i>A. flavus</i>	-	[216]
Voriconazole	Poly-lactide-co-glycolide	Multiple emulsification	Pulmonary	Better lung deposition	-	[53]
Voriconazole	Lipids (Compritol, Miglyol, gelucire)	Hot and high pressure homogenization	Oral	Voriconazole nanoparticles have higher efficiency against <i>C. albicans</i>	-	[241]
Voriconazole	Precitol, Labrafil	High pressure homogenization	Topical	Increased skin retention and permeation of voriconazole	-	[212]
Voriconazole	Oleic acid, sodium deoxycholate, polyoxyethylene	-	Topical	Microemulsions containing voriconazole for topical administration	-	[213]
Voriconazole	Carbopol 934, stearic acid, Tween 80	Ultrasonication	Ocular	Improved technique used for nanoparticle preparation	-	[214]
Voriconazole	Soy phosphatidylcholine, 1,2-dioleoyl-3-trimethylammonium propane, cholesterol	Thin-film hydration	Ocular	Liposomes with promising topical antifungal action	-	[242]
Voriconazole	Chitosan, silver and graphene oxide	Electrostatic interaction	Ocular	Hydrogel contact lenses with antifungal activity	Mild cationic toxicity in HTCC groups	[221]
Voriconazole	Pluronic F-127, sodium alginate	Gelation <i>in situ</i>	Ocular	Stability and prolonged effect against strains of <i>C. albicans</i> and <i>A. fumigatus</i>	-	[222]
Voriconazole	PLGA, chitosan	Emulsion solvent evaporation	Pulmonary	Better delivery and bioavailability of coated formulations	-	[219]
Voriconazole	Carbopol, methylcellulose, lecithin, and cholesterol	Film hydration	Ocular	Prolonged drug release	-	[243]

(Table 1) contd....

Antifungal Drug	Composition	Method	Route of Administration	Efficiency	Toxicity	Refs.
Voriconazole	Stearic acid, sodium deoxycholate	Emulsification	Pulmonary	Increased deposition and dissolution in the lung	-	[217]
Voriconazole	PLGA	Multiple emulsion by solvent evaporation	Pulmonary	Improved delivery and longer excretion time of nanoparticle formulation	-	[218]
Voriconazole	Compritol, palmitic acid, Poloxamer and soy lecithin, sodium taurocholate	Emulsification/evaporation	Ocular	Development, characterization, and delivery	-	[244]
Fluconazole	Carbopol, precinol, oleic acid, Kolliphor	Lipid suspension by inversion temperature	Topical	Gel with stable, long-acting and located action	-	[245]
Fluconazole	PLGA	Double emulsion solvent diffusion	Oral	Improvement in antifungal activity against <i>C. albicans</i>	Moderate toxicity against VERO cell lines	[246]
Fluconazole	Span 80/60, Tween 80	Ultrasonication	Oral	Solid lipid nanoparticles as a delivery alternative	-	[225]
Fluconazole	Compritol 888 ATO, oleic acid, phosphatidylcholine, and Pluronic F-68	Solvent diffusion	Topical	Carrier, prolonged-release and localized effect	-	[223]
Fluconazole	Oleic acid	Film hydration	Topical	Sustained release and retention of the drug in the deepest part of the skin	-	[227]
Fluconazole	Span 40, Span 60 and Brij 72	Film hydration	Topical	Localized effect, sustained release of drug	-	[247]
Fluconazole	Hyaluronic acid and cholesterol / Tween 80 / Transcutol HP / Maisine 35-1 / Caproyl 90	Hydration of lipid film	Ocular	Increased corneal permeability	No inflammatory response or signs of eye toxicity	[228]
Fluconazole	PCL	Interfacial deposition and high pressure homogenization	Oral	Effective dose reduction of fluconazole and resistance reversal in <i>Candida</i> sp. tested	-	[248]

(Table 1) contd....

Antifungal Drug	Composition	Method	Route of Administration	Efficiency	Toxicity	Refs.
Fluconazole	Compritol 888 ATO, phosphatidylcholine and Pluronic F-68	Solvent diffusion	Topical	Improvement in dermal localization	-	[249]
Fluconazole	PVA	Electrospinning	Topical	Sustained 6-hour drug release and superior activity against <i>C. albicans</i>	Through local application, reduction of systemic toxicity	[250]
Fluconazole	Stearic acid/ Compritol 1,888 ATO, oleic acid and Span 80	Probe ultrasound	-	Effectiveness against <i>Candida</i> sp. with different susceptibilities to conventional fluconazole formulations	-	[229]
Ketoconazole	Carbopol 980, propylene glycol, Tween 80, bronopol, PAMAM-NH ₂ and PAMAM-OH dendrimers generation 2 and generation 3	-	Topical	PAMAM-NH ₂ dendrimers increased the antifungal activity of ketoconazole against strains of <i>Candida</i>	-	[231]
Ketoconazole	Castor oil, HSA, PVA	Hot emulsification	Topical	Better bioavailability	-	[232]
Ketoconazole	-	Ball milling	Oral	Increased efficiency against yeast and biofilms of <i>Candida</i> sp.	-	[188]
Ketoconazole	PLGA, alginate, and chitosan	Freezing by solvent exchange <i>in vitro</i>	Ocular	Good transcorneal permeation and antifungal activity	-	[235]
Ketoconazole	Carbopol Ultrez 21, thio-glycolic acid	Aqueous titration followed by high pressure homogenization	Nail/ Topical	Antifungal effect on <i>Trichophyton rubrum</i> and <i>Candida albicans</i>	Skin irritation and histopathology studies in rat skin showed safe topical use	[234]
Ketoconazole	Chitosan, gellan gum	Electrostatic complexation	Oral	Significantly higher antifungal activity against <i>Aspergillus niger</i>	-	[233]
Nystatin	Emulgade, glycerol monostearate and salty oil	High-pressure homogenization	Oral	-	-	[251]

(Table 1) contd....

Antifungal Drug	Composition	Method	Route of Administration	Efficiency	Toxicity	Refs.
Nystatin	Alginate, chitosan, Poloxamer 407	Emulsification / internal gelation	Topical	Antifungal effect against <i>Candida albicans</i>	Antifungal effect without toxic systemic absorption	[252]
Nystatin	Alginate, chitosan	Emulsification/ internal gelation	Topical	Antifungal effect against <i>Candida albicans</i>	No tissue damage and no presence in the bloodstream	[253]
Nystatin	Sodium alginate, chitosan stearate	Ionotropic complexation	Oral	More localized distribution relative to <i>Leishmania</i> -infected organs (spleen and liver)	Less toxic formulation <i>in vitro</i> and <i>in vivo</i> compared to simple amphotericin B	[254]
Amphotericin B	Ethylene glycol, PEG	Electrostatic and hydrophobic interactions	Oral	Higher antifungal potential	Decreased nephrotoxicity and hemolysis	[255]
Amphotericin B	PLGA, PLGA-PEG	Emulsification solvent evaporation	Oral	Antifungal activity 2x and 10x higher in PLGA-PEG and PLGA nanoparticles than free amphotericin B on <i>C. albicans</i> , being a potential nanocarrier	Decrease in hemolysis toxicity to 2 and 5% compared to free amphotericin B	[207]
Amphotericin B	PLGA	Nanoprecipitation	Oral	Minimum inhibitory concentration lower than free amphotericin B	Activity on red cells 9.5x less toxic compared to free amphotericin B	[187]
Amphotericin B	Polybutylcyanoacrylate, Polysorbate 80, acetic acid, Dextran T-70	Spontaneous anionic polymerization	Oral	Ability to cross the blood-brain barrier. Detection of minor fungal colonies in nanoparticle treated groups in relation to amphotericin B deoxycholate and amphotericin B liposome	Increased animal survival after 7 days of treatment. Reduction of toxicity in liver, kidney, and blood.	[199]
Amphotericin B	Chitosan, lecithin	Ionic gelation	Ocular	approximately 2x higher bioavailability, longer residence time in tissue. Antifungal	-	[256]

(Table 1) contd....

Antifungal Drug	Composition	Method	Route of Administration	Efficiency	Toxicity	Refs.
				activity lower than the commercial formulation, which may be associated with a prolonged-release time of the nanoparticle		
Amphotericin B	TPGS, PLGA	Nanoprecipitation	Oral	Encapsulation efficiency of 85%. Nanoparticles showed increased bioavailability and lower minimum inhibitory concentration compared to free amphotericin on <i>C. albicans</i>	Reduction of red cell toxicity in relation to free amphotericin B	[257]
Amphotericin B	PLGA	Nanoprecipitation	Oral	Higher efficacy compared to commercial formulations of Ambisome or Fungizone that are administered parenterally.	-	[210]
Amphotericin B	PLGA-TPG	Double modified emulsion	Oral	Increased bioavailability and survival of animals. In addition, higher antifungal activity in kidney, liver, lung, and spleen compared to amphotericin B	-	[200]
Amphotericin B	MPEG, PCL	Solvent diffusion	Topical	The system showed improved solubility and efficacy on <i>C. albicans</i> biofilm.	Decreased oral epithelial cell toxicity and increased cell viability <i>in vivo</i>	[258]
Amphotericin B	Campmul PG8, Labrasol and polyethylene glycol	Spontaneous titration	Topical	Antifungal effect against <i>C. albicans</i> and <i>Aspergillus niger</i>	-	[259]
Amphotericin B	PLGA, chitosan	Emulsification solvent evaporation	Oral	Increased release time and amphotericin B-like antifungal activity	Reduction of hemolysis compared to	[192]

(Table 1) contd....

Antifungal Drug	Composition	Method	Route of Administration	Efficiency	Toxicity	Refs.
					amphotericin B, which may be associated with obtained slow-release	
Amphotericin B	Poloxamer P407/P188	High-pressure homogenization	Topical	Sustained release and superior antifungal effect than commercial formulation	-	[193]
Amphotericin B	Chitosan	Sulfation	Oral	Chitosan and chitosan sulfated nanoparticles showed a higher antifungal effect on <i>C. glabrata</i> than free amphotericin B	Nanoparticles caused less than 5% blood cell rupture	[260]
Amphotericin B	PCL, PDMAEDA or PEG	Polymerization	Oral	Free amphotericin B-like antifungal activity	Nanoparticles 10x less toxic than the free amphotericin B	[209]
Amphotericin B	Poly-ε-Caprolactone, Chitosan	Nanoprecipitation	Oral	<i>C. parapsilosis</i> susceptible to the developed nanoparticles	Decreased cytotoxicity in erythrocytes and VERO cells	[27]
Amphotericin B	Chitosan	Ionic gelation	Oral	Increased gastrointestinal bioavailability and stability compared to Fungizone	Decreased hemolytic toxicity and nephrotoxicity	[190]
Amphotericin B	Lecithin and gelatin	Desolvation	Oral	Increased stability in the gastrointestinal tract	Significantly lower hemolytic toxicity compared to free drugs Fungizone and Fungisome	[189]
Amphotericin B	PLA-Chitosan	Dialysis	Ocular	-	-	[261]
Amphotericin B	-	Liquid antisolvent precipitation	Oral	Dissolution rate increased by approximately 2x and solubility by 13x	-	[262]

(Table 1) contd....

Antifungal Drug	Composition	Method	Route of Administration	Efficiency	Toxicity	Refs.
Amphotericin B	Fe ₃ O ₄	Ultrasonication	Intravenous	May strengthen brain targeting	Reduction of drug toxicity when injected with magnetic field effect	[263]
Amphotericin B	Chitosan and porphyrin	Complexation	Oral	Higher <i>in vitro</i> and <i>in vivo</i> anti-fungal activity compared to commercial formulation	Hemolytic toxicity suggesting safety in the prepared formulation	[264]
Amphotericin B	Isoprene- β -ethylene polyoxide	Solvent evaporation	Oral	The nanostructure was able to encapsulate lipophilic drugs	-	[265]
Amphotericin B	Silver	-	Oral	Antifungal activity on <i>C. albicans</i> and <i>C. tropicalis</i>	Possible reduction of drug-related toxicity	[201]
Amphotericin B	Fe ₃ O ₄	Coprecipitation	Nasal	Important antifungal activity and reduced number of applications	No clinical, biochemical, genotoxic and histopathological changes were observed	[204]
Amphotericin B	PDMAEMA-B-PCL	Nanoprecipitation	Oral	Antifungal activity against <i>C. albicans</i> , <i>C. krusei</i> and <i>C. glabrata</i>	Toxicity reduction	[205]
Amphotericin B	CGPLAP, Miglyol 812	Nanoprecipitation with spontaneous emulsification	Oral	21-47% encapsulation efficiency	-	[266]
Amphotericin B	PLGA	Double emulsion	Oral	CFU reduction; effective against biofilm	Toxicity reduction	[267]
Amphotericin B	Caprylate / Caprate	High pressure homogenization	Oral	Optimized carriage vehicle	-	[101]
Amphotericin B	Carboxymethyl Carrageenan, Gelatin A	Desolvation	Oral	-	No hemolytic disorder detected	[268]
Amphotericin B	Lecithin, sodium cholate and oleic acid	Solvent diffusion	Oral	-	-	[269]

(Table 1) contd....

Antifungal Drug	Composition	Method	Route of Administration	Efficiency	Toxicity	Refs.
Amphotericin B	Gelatines A and B (GNPs)	Desolvation	Oral	Low cost and safe delivery	No increased hematological toxicity and nephrotoxicity	[270]
Amphotericin B	Compritol 888 ATO, Pre-ciol ATO 5, Pluronic-F68	Solvent diffusion	Topical	Increased permeation and antifungal activity against <i>Trichophyton rubrum</i>	Less skin irritability	[195]
Amphotericin B	PLGA, PLH, PEG	Emulsion solvent evaporation	Pulmonary	Improved bioavailability and antifungal activity	Toxicity reduction	[200]
Amphotericin B	PLA-PEG, Tween 80	Nanoprecipitation	Intravenous	Increased mouse brain drug concentration and therapeutic efficacy	Liver, kidney and blood toxicity reduction	[52]
Amphotericin B	PLA-PEG	Emulsion solvent evaporation	Oral	Controlled release system and stability	-	[208]
Amphotericin B	PLGA	Nanoprecipitation	Oral	Increased efficacy <i>in vivo</i> against <i>A. fumigatus</i>	Toxicity reduction	[271]
Amphotericin B	Stearic acid, PVA 9000	Coacervation	Oral	Increased antifungal activity	-	[272]

which shows an advantage in the agricultural and medical-pharmacological areas [288, 289].

8. TOXICITY OF THE NANOPARTICLES

The nanoparticles have been produced with the objective of increasing the beneficial properties of the encapsulated drug and reducing its toxic and unwanted effects, releasing the drug gradually and, consequently, improving its pharmacokinetics aspects [42, 43]. However, due to their high surface-to-volume ratio, the surface of nanomaterials is very reactive. When nanoparticles are absorbed and exposed to biological fluids, the components of these fluids, such as proteins and biomolecules, tend to associate with the surface of the nanoparticles, causing an interaction at the cellular and molecular levels [291]. Depending on the size, the nanoparticles are absorbed by different organs and tissues. There are also reports of nanoparticles that pass through the blood-brain barrier [291] and cause brain toxicity [293]. In the study by Sohaebuddin *et al.* [294],

it was found that the composition and size of nanomaterials determine cell responses, as well as the type of target cell. However, despite this and many other studies in the area, reports on cell toxicity are still inconsistent [294].

CONCLUSION

The main limitations of antifungals currently available in the market, besides the emergence of resistant strains, are related to the adverse effects caused by them and the available administration routes, which often make patient compliance difficult. Nevertheless, the solubility and degradation characteristics on the gastrointestinal system need to be improved for more efficient oral administration.

In this sense, nanotechnology has been used as a valuable tool for the development of several antifungal release systems, as reported throughout this review. And many of them yielded interesting results regarding

in vitro studies, such as prolonged release, decreased adverse effects, and increased antifungal activity. However, a fact that hinders their therapeutic applications. Although there are reports on the possible toxicity of nanoparticles due to their nanometric size, the advantages of these nanostructured systems are more significant.

Among the commercially available antifungals, amphotericin B, has the best application results in the form of nanoparticles. Nevertheless, therapeutic monitoring of mainly hepatic and renal cytotoxicity is still extremely important, especially in immunocompromised patients.

The co-encapsulation of antifungals system seems to be a strategy of great relevance for patients, due to reduction of the side effects due to the high doses of conventional antifungals.

It is noticeable an urgency of new antifungals. Also, the improvement of the available arsenal is a great strategy to overcome the side and toxic effects, as well as, to secure the efficacy against more resistant strains. Nanostructured systems open a new avenue for antifungal therapeutic.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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